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Chin V, Nagrial A, Sjoquist K, O'Connor CA, Chantrill L, Biankin AV, Scholten RJPM, Yip D

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[Intervention Review]

Chemotherapy and radiotherapy for advanced pancreatic cancer

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ABSTRACT

Background

Pancreatic cancer (PC) is a highly lethal disease with few effective treatment options. Over the past few decades, many anti-cancer therapies have been tested in the locally advanced and metastatic setting, with mixed results. This review attempts to synthesise all the randomised data available to help better inform patient and clinician decision-making when dealing with this difficult disease.

Objectives

To assess the effect of chemotherapy, radiotherapy or both for first-line treatment of advanced pancreatic cancer. Our primary outcome was overall survival, while secondary outcomes include progression-free survival, grade 3/4 adverse events, therapy response and quality of life.

Search methods

We searched for published and unpublished studies in CENTRAL (searched 14 June 2017), Embase (1980 to 14 June 2017), MEDLINE (1946 to 14 June 2017) and CANCERLIT (1999 to 2002) databases. We also handsearched all relevant conference abstracts published up until 14 June 2017.

Selection criteria

All randomised studies assessing overall survival outcomes in patients with advanced pancreatic ductal adenocarcinoma. Chemotherapy and radiotherapy, alone or in combination, were the eligible treatments.

Data collection and analysis

Two review authors independently analysed studies, and a third settled any disputes. We extracted data on overall survival (OS), progression-free survival (PFS), response rates, adverse events (AEs) and quality of life (QoL), and we assessed risk of bias for each study.

Main results

We included 42 studies addressing chemotherapy in 9463 patients with advanced pancreatic cancer. We did not identify any eligible studies on radiotherapy.

We did not find any benefit for chemotherapy over best supportive care. However, two identified studies did not have sufficient data to be included in the analysis, and many of the chemotherapy regimens studied were outdated.

Compared to gemcitabine alone, participants receiving 5FU had worse OS (HR 1.69, 95% CI 1.26 to 2.27, moderate-quality evidence), PFS (HR 1.47, 95% CI 1.12 to 1.92) and QoL. On the other hand, two studies showed FOLFIRINOX was better than gemcitabine for OS (HR 0.51 95% CI 0.43 to 0.60, moderate-quality evidence), PFS (HR 0.46, 95% CI 0.38 to 0.57) and response rates (RR 3.38, 95% CI 2.01 to 5.65), but it increased the rate of side effects. The studies evaluating CO-101, ZD9331 and exatecan did not show benefit or harm when compared with gemcitabine alone.

Giving gemcitabine at a fixed dose rate improved OS (HR 0.79, 95% CI 0.66 to 0.94, high-quality evidence) but increased the rate of side effects when compared with bolus dosing.

When comparing gemcitabine combinations to gemcitabine alone, gemcitabine plus platinum improved PFS (HR 0.80, 95% CI 0.68 to 0.95) and response rates (RR 1.48, 95% CI 1.11 to 1.98) but not OS (HR 0.94, 95% CI 0.81 to 1.08, low-quality evidence). The rate of side effects increased. Gemcitabine plus fluoropyrimidine improved OS (HR 0.88, 95% CI 0.81 to 0.95), PFS (HR 0.79, 95% CI 0.72 to 0.87) and response rates (RR 1.78, 95% CI 1.29 to 2.47, high-quality evidence), but it also increased side effects. Gemcitabine plus topoisomerase inhibitor did not improve survival outcomes but did increase toxicity. One study demonstrated that gemcitabine plus nab-paclitaxel improved OS (HR 0.72, 95% CI 0.62 to 0.84, high-quality evidence), PFS (HR 0.69, 95% CI 0.58 to 0.82) and response rates (RR 3.29, 95% CI 2.24 to 4.84) but increased side effects. Gemcitabine-containing multi-drug combinations (GEMOXEL or cisplatin/epirubicin/5FU/gemcitabine) improved OS (HR 0.55, 95% CI 0.39 to 0.79, low-quality evidence), PFS (HR 0.43, 95% CI 0.30 to 0.62) and QOL.

We did not find any survival advantages when comparing 5FU combinations to 5FU alone.

Authors' conclusions

Combination chemotherapy has recently overtaken the long-standing gemcitabine as the standard of care. FOLFIRINOX and gemcitabine plus nab-paclitaxel are highly efficacious, but our analysis shows that other combination regimens also offer a benefit. Selection of the most appropriate chemotherapy for individual patients still remains difficult, with clinicopathological stratification remaining elusive. Biomarker development is essential to help rationalise treatment selection for patients.

PLAIN LANGUAGE SUMMARY

The effects of anti-cancer therapies on advanced pancreatic cancer

Review question

This review aimed to answer the question, which therapies are the most effective for advanced pancreatic cancer?

Background

Pancreatic cancer (PC) is a serious, often fatal disease, and many people are not diagnosed until they have advanced tumours that cannot be removed with surgery. Symptoms include abdominal pain, weight loss, and yellowing of the skin and eyes. Up until recently, gemcitabine was the standard drug for treating advanced pancreatic cancer, but this gave people only a modest benefit.

Study characteristics

We looked for all studies in people with pancreatic cancer that could not be operated on (locally advanced) or that had already spread beyond the pancreas (metastatic). We found 42 clinical studies involving 9463 participants who were receiving their first therapy for PC. Our search is current to June 2017.

The studies compared one therapy against either best supportive care (symptom management only) or another type of therapy. Studies had to evaluate overall survival (or time to death). The study could be testing either chemotherapy (drugs that kill or slow the growth of cancer cells) or radiotherapy (X-ray treatment). We collected data on survival, tumour response rate, side effects and quality of life. The results of clinical studies addressing targeted/biological therapies, immunotherapies, second-line therapies and local treatments for locally advanced disease will be reported in a separate Cochrane Review.

Key results

This review has shown that in advanced disease, combination chemotherapy with FOLFIRINOX (5-fluorouracil, irinotecan, oxaliplatin combination); GEMOXEL (gemcitabine, oxaliplatin and capecitabine); cisplatin/epirubicin/5FU/gemcitabine; gemcitabine plus nab-paclitaxel; and gemcitabine plus a fluoropyrimidine agent, provide a survival advantage over gemcitabine alone. These combinations do

increase side effects. Gemcitabine given slowly using a fixed rate of infusion may be more effective than giving it in the standard way, which is quickly over 30 minutes.

Quality of the evidence

The quality of the evidence varied greatly amongst comparisons. The highest quality evidence was for gemcitabine versus fixed dose rate gemcitabine and some of the gemcitabine combinations (fluoropyrimidine, topoisomerase, and taxane). We judged the studies for quality using factors like how well they were conducted, how well they reported results and whether they used a placebo.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Anti-cancer therapy versus best supportive care for advanced pancreatic cancer

Anti-cancer therapy versus best supportive care for advanced pancreatic cancer

Person or population: advanced pancreatic cancer
Setting: first-line therapy
Intervention: anti-cancer therapy
Comparison: best supportive care

Outcomes	Anticipated risk of death* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments	Toxicity and QoL
	Risk with best supportive care	Risk with anti-cancer therapy					
Overall survival	Study population		HR 1.08 (0.88 to 1.33)	298 (4 RCTs)	⊕⊕⊕⊖ Moderate[a]	—	The analysis showed that toxicity data were inconsistently reported. Most studies reporting this outcome noted that gastrointestinal adverse events were the most frequent, occurring in between 15% to 31%. 1 study noted haematological toxicity was present in 81.5% of people. 2 out of the 3 studies that analysed QoL demonstrated a benefit with anti-cancer therapy. 1 study showed no difference between the 2 groups.
	707 per 1000	734 per 1000 (660 to 804)					

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR**: hazard ratio; **RCT**: randomised controlled trial.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Confidence interval include both benefit and harm; optimal information size not met.

Summary of findings 2. Various types of chemotherapy versus gemcitabine for advanced pancreatic cancer

Various types of chemotherapy versus gemcitabine for advanced pancreatic cancer

Person or population: advanced pancreatic cancer
Setting: first-line therapy
Intervention: various types of chemotherapy
Comparison: gemcitabine

Outcomes	Anticipated risk of death* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments	Toxicity and QoL
	Risk with gemcitabine	Risk with various types of chemotherapy					
Overall survival - 5FU	Study population		HR 1.69 (1.26 to 2.27)	126 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	Only 1 study	More toxicity was seen in the gemcitabine arm. Clinical benefit was improved in the gemcitabine arm
	825 per 1000	948 per 1000 (889 to 981)					
Overall survival - FOLFIRINOX	Study population		HR 0.51 (0.43 to 0.60)	652 (2 RCTs)	⊕⊕⊕⊖ Moderate[b]	—	More toxicity was seen in the FOLFIRINOX arm. Longer time to degradation of QoL in FOLFIRINOX arm
	794 per 1000	554 per 1000 (494 to 613)					
Overall survival - Fixed dose rate gemcitabine	Study population		HR 0.79 (0.66 to 0.94)	644 (2 RCTs)	⊕⊕⊕⊕ High	—	More toxicity in the fixed-dose rate arm. QoL was not tested
	880 per 1000	812 per 1000 (753 to 863)					
Overall survival - CO-101	Study population		HR 1.07 (0.86 to 1.34)	367 (1 RCT)	⊕⊕⊕⊖ Moderate[c]	Only 1 study	Toxicity was similar in both arms, QoL was not tested
	854 per 1000	872 per 1000 (809 to 924)					
Overall survival - ZD9331	Study population		HR 0.86 (0.42 to 1.76)	55 (1 RCT)	⊕⊕⊕⊖ Moderate[a,c]	Only 1 study	Toxicity was similar in both arms, QoL was not tested
	560 per 1000	506 per 1000 (292 to 764)					
Overall survival - Exatecan	Study population		HR 1.27 (0.96 to 1.68)	339 (1 RCT)	⊕⊕⊕⊖ Moderate[c]	Only 1 study	Toxicity was similar in both arms, QoL was superior in the gemcitabine arm
	776 per 1000	851 per 1000 (763 to 919)					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **HR**: hazard ratio; **RCT**: randomised controlled trial.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Small sample size; optimal information size not met.
[b]Moderate statistical heterogeneity.
[c]Confidence interval includes both benefit and harm.

Summary of findings 3. Gemcitabine combinations versus gemcitabine alone for advanced pancreatic cancer

Gemcitabine combinations versus gemcitabine alone for advanced pancreatic cancer

Person or population: advanced pancreatic cancer
Setting: first-line therapy
Intervention: gemcitabine combinations
Comparison: gemcitabine alone

Outcomes	Anticipated risk of death* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments	Toxicity and QoL
	Risk with gemcitabine alone	Risk with gemcitabine combinations					
Overall survival - Gemcitabine plus platinum agent	Study population 705 per 1000	683 per 1000 (628 to 733)	HR 0.94 (0.81 to 1.08)	1140 (6 RCTs)	⊕⊕⊖⊖ Low[a,b]	—	More toxicity in the combination arm with no differences shown in QoL
Overall survival - Gemcitabine plus fluoropyrimidine	Study population 690 per 1000	648 per 1000 (613 to 679)	HR 0.89 (0.81 to 0.97)	2718 (10 RCTs)	⊕⊕⊕⊕ High	—	More toxicity in the combination arm. 2 studies showed no difference in QoL, 2 studies showed an improved QoL in the combination arm

Overall survival - Gemcitabine plus topoisomerase inhibitor	Study population 800 per 1000 803 per 1000 (753 to 845)	HR 1.01 (0.87 to 1.16)	839 (3 RCTs)	⊕⊕⊕⊕ High	—	More toxicity in the combination arm. In 1 study, QoL was not different between the 2 arms
Overall survival - Gemcitabine plus taxane	Study population 779 per 1000 663 per 1000 (608 to 719)	HR 0.72 (0.62 to 0.84)	861 (1 RCT)	⊕⊕⊕⊕ High	1 study only	More toxicity in the combination arm. QoL not measured
Overall survival - Gemcitabine plus other combinations of chemotherapy	Study population 850 per 1000 648 per 1000 (523 to 777)	HR 0.55 (0.39 to 0.79)	166 (2 RCTs)	⊕⊕⊖⊖ Low[c,d,e]	—	Toxicity measured in 1 study and was not different. QoL was shown to be improved in the combination arms in both studies
Overall survival - Gemcitabine plus other agent(s)	Study population 825 per 1000 748 per 1000 (624 to 853)	HR 0.79 (0.56 to 1.10)	767 (4 RCTs)	⊕⊕⊖⊖ Low[b,f]		There was an increase in anaemia in the combination arm. 2 studies measured QoL and it was similar in both treatment arms

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **HR**: hazard ratio; **RCT**: randomised controlled trial.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Two studies were in abstract form and could not have full assessment completed.
[b]Confidence interval includes both benefit and harm.
[c]One study did not publish sufficient details to make a full assessment.
[d]There was moderate statistical heterogeneity.
[e]Optimal information size not met.
[f]High statistical heterogeneity which is likely due to the difference in agents used in the treatment arms.

Summary of findings 4. Fluoropyrimidine combinations versus fluoropyrimidine alone for advanced pancreatic cancer

Fluoropyrimidine combinations versus fluoropyrimidine alone for advanced pancreatic cancer

Person or population: advanced pancreatic cancer
Setting: first line therapy
Intervention: fluoropyrimidine combinations
Comparison: fluoropyrimidine alone

Outcomes	Anticipated risk of death* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Toxicity and QoL
	Risk with fluoropyrimidine alone	Risk with fluoropyrimidine combinations				
Overall survival	Study population		HR 0.84 (0.61 to 1.15)	491 (4 RCTs)	⊕⊕⊖⊖ Low[a,b]	Toxicity was not different between the 2 treatment arms. QoL was measured in 1 study and showed an improvement in the combination arm
	838 per 1000	783 per 1000 (671 to 877)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR**: hazard ratio; **RCT**: randomised controlled trial.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]High statistical heterogeneity.
[b]Confidence interval includes both benefit and harm.

BACKGROUND

Recently published global cancer statistics show that pancreatic cancer (PC) accounted for 184,400 deaths worldwide in 2012, with the highest incidence in men in high-income countries at 8.6 cases per 100,000 (Torre 2015). In Australia, although PC is relatively uncommon (incidence of 11 per 100,000), it is highly lethal, representing the fourth leading cause of death from cancer (Tracey 2016). The US National Cancer Institute has reported a five-year survival of 21.5% for those with localised disease (www.cancer.gov); however, a review of the Finnish Cancer Registry showed five-year survival of only 4.3% for those with localised disease and an overall five-year survival of 0.2% (Carpelan 2005).

PC is a notoriously insidious cancer, commonly presenting with vague, non-specific symptoms that classically consist of the triad of epigastric abdominal pain, weight loss and jaundice (Howard 1977; Warshaw 1992), which gradually worsen over time. Physical examination is often normal, with the commonest sign of an enlarged liver present in fewer than half of patients (Von Hoff 2005). Thus, most patients have advanced disease when they are diagnosed.

Approximately 10% of early stage pancreatic carcinomas are amenable to curative surgery (Siegel 2013). However, the risk of relapse after surgical resection is still quite high, with only 10% of patients surviving for five years (Conlon 1996; Shahrudin 1997). Although studies have reported a benefit for chemotherapy in advanced disease (Burris 1997; Heinemann 2008; Conroy 2011; Von Hoff 2013), the role of second and subsequent lines of chemotherapy remains controversial (Nagrial 2015). The benefits of radiotherapy, either alone or in combination, as a palliative treatment for advanced or relapsed disease, is uncertain (Sultana 2007). Hammel 2013 tested contemporary chemotherapy and radiotherapy techniques but did not demonstrate a survival benefit in locally advanced disease. Biological therapies are emerging in the treatment of pancreatic cancer and but have yet to find their place in routine clinical practice (Castellanos 2011).

There are other published meta-analyses that look at various aspects covered by this review. Li 2014 analysed eight studies that assessed randomised data using gemcitabine and fluoropyrimidine agents, finding a benefit using gemcitabine plus fluoropyrimidine. Petrelli 2014 analysed 29 studies that assessed gemcitabine monotherapy versus chemotherapy combinations, finding improved outcomes with the chemotherapy combinations. Two studies have used a Bayesian network meta-analysis to perform direct and indirect comparisons of chemotherapy combinations (Chan 2014; Gresham 2014). Chan 2014 concluded that FOLFIRINOX was likely to be the most efficacious regimen in the advanced stage. Two meta-analyses have assessed chemotherapy plus radiotherapy (Bernstein 2014; Chen 2013), both finding a small benefit to adding chemotherapy to radiation; however, neither included the recent study conducted by Hammel 2013.

Anti-cancer therapies in the metastatic setting ideally aim to improve people's quality and length of life, with tolerable side effects. This review will analyse both the anti-cancer effects and the adverse effects of treatments in patients with pancreatic cancer.

Description of the condition

Pancreatic ductal adenocarcinoma (PDAC) is a cancer arising from the ducts in the pancreas gland. It can be localised to the pancreas (local disease), locally advanced (still confined to the area around the pancreas but possibly involving lymph glands or other immediately adjacent structures) or metastatic (with cancer spread to distant areas).

This review includes studies in patients with locally advanced (not amenable to local therapies) or metastatic PC, formally defined as follows (Callery 2009).

1. Locally advanced or unresectable, defined by:
   a. greater than 180° of superior mesenteric vein encasement, any coeliac abutment;
   b. unreconstructable superior mesenteric vein or portal occlusion;
   c. aortic invasion or encasement;
   d. nodal involvement beyond the field of resection.
2. Metastatic, defined by distant sites of disease.

Description of the intervention

Chemotherapy

Chemotherapy encompasses all cytotoxic or antineoplastic drug treatments, intravenous or oral, which work by killing or slowing the growth of cancer cells. Although the schedules differ between therapies, most are given on a four-weekly basis (one cycle) for up to six cycles.

Radiotherapy

Radiation therapy uses X-rays to destroy or injure cancer cells so they cannot multiply (Queensland Cancer Fund 2012). It is given in a number of different ways.

1. External beam radiotherapy: delivered over a number of sessions (fractions) utilising an external radiotherapy source emitting X-rays, gamma rays, electrons or heavy particles.
2. Stereotactic body radiation therapy: a highly conformal (targeted) technique for delivering external beam radiotherapy in a single fraction (stereotactic radiosurgery) or a number of fractions (stereotactic radiotherapy).
3. Brachytherapy: internal radiotherapy utilising a radioactive source placed into or adjacent to the pancreas and administered in a single fraction or number of fractions, given alone or in combination with external beam radiotherapy.
4. Intraoperative radiotherapy: administration of external source radiotherapy or brachytherapy at the time of surgery, given alone or in combination with external beam radiotherapy.

Best supportive care

Best supportive care in advanced disease is defined as anything other than chemotherapy. It may include symptom control by radiotherapy (not to the primary site), palliative surgery, biliary stent insertion, analgesia, blood transfusion, and psychological or social support.

How the intervention might work

The primary goal for all treatments for locally advanced or metastatic pancreatic cancer is to palliate symptoms and improve overall survival (see Appendix 1, 'Glossary of terms'). In general, chemotherapy and radiotherapy can potentially kill cancer cells in the body and reduce the severity of the disease. This can in turn, reduce symptoms and increase survival times. In the advanced setting, chemotherapy and radiotherapy do not offer a cure. Best supportive care is usually administered alongside chemotherapy and radiotherapy, but it can be the sole treatment given to some patients. All anti-cancer therapies can cause side effects, which commonly include fatigue, nausea, vomiting, low blood counts (haemoglobin, white cells and platelets) and diarrhoea. Radiotherapy can cause local pain, skin rash, fatigue, nausea and vomiting.

Why it is important to do this review

Given the poor prognosis of PC, evidence-based clinical decision-making is paramount in guiding patients through treatments. Performing a meta-analysis of studies will ensure that clinicians and patients have a reference to inform their clinical choices.

The meta-analysis published previously in Yip 2009 has been criticised for not using hazard ratios to assess survival (Sultana 2007). This update will use hazard ratios and also assess quality of life.

PC is a notoriously difficult cancer in which to perform clinical studies, and much controversy exists. Although there is evidence in the first line setting that supports the use of FOLFIRINOX (Conroy 2011), gemcitabine plus erlotinib (Moore 2007), gemcitabine plus fluoropyrimidine (Cunningham 2009), or nab-paclitaxel (Von Hoff 2013), questions remain with regard to toxicity, cost and survival benefits. There is conflicting evidence on the place for and schedule of chemoradiation as well as debate about the optimum drug and dose (Kim 2007; Philip 2011).

Previous meta-analyses have had narrow search criteria (Chan 2014; Li 2014; Petrelli 2014), or they have used only phase III randomised data (Gresham 2014). Here, we have attempted to synthesise and organise all available randomised data concerning patients having treatment for advanced pancreas cancer in order to help inform clinical decision-making and guide further research in this area.

OBJECTIVES

To assess the effect of chemotherapy, radiotherapy or both for first-line treatment of advanced pancreatic cancer. Our primary outcome was overall survival, while secondary outcomes include progression-free survival, grade 3/4 adverse events, therapy response and quality of life.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled studies, both published and unpublished, comparing one of the intervention types versus placebo, another intervention type or best supportive care.

Types of participants

People with a diagnosis of pancreatic adenocarcinoma established by either histological or cytological findings (investigations on body tissue or cells). Studies enrolling people with advanced, unresectable or recurrent disease were eligible for inclusion.

Types of interventions

Any type of chemotherapy, radiotherapy or combination of chemotherapy plus radiotherapy versus placebo, no treatment, best supportive care or another chemotherapy and/or radiotherapy treatment regimen.

Best supportive care in advanced disease may include symptom control by radiotherapy (not to the primary site), palliative surgery, biliary stent insertion, analgesia, blood transfusion and psychological or social support.

We looked for interventions falling into the following comparisons.

1. Any chemotherapy treatment versus placebo, no treatment or best supportive care.
2. Any chemotherapy treatment versus any other chemotherapy treatment.
3. Any radiotherapy treatment versus placebo, no treatment or best supportive care.
4. Any radiotherapy treatment versus any other radiotherapy treatment.
5. Any combination of radiotherapy and chemotherapy versus placebo, no treatment or best supportive care.
6. Any combination of radiotherapy and chemotherapy versus any other combination of radiotherapy and chemotherapy.

After searching was complete, the studies were organised into four specific comparisons.

1. Anti-cancer therapy versus best supportive care
2. Various types of chemotherapy versus gemcitabine
3. Gemcitabine combinations versus gemcitabine alone
4. Fluoropyrimidine combinations versus fluoropyrimidines alone

Types of outcome measures

Primary outcomes

Overall survival (OS) - survival until death from any cause

Secondary outcomes

1. Progression-free survival (PFS) - time to progression of disease on a given therapy. This is usually detected by an increase of the size or number of cancer lesions seen on a computer tomography scan (CT) using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria (Nishino 2010).
2. Quality of life (QoL), measured with a validated instrument, such as the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire for cancer patients (QLQ-C30) (eortc.be/qol/).
3. Response rates - this relates to the shrinkage of a cancer in response to therapy and is usually measured on CT scans, with cancer shrinkage defined according to the RECIST criteria (Nishino 2010).

4. Grade 3/4 adverse events - adverse events are defined by the National Cancer Institute (cancer.gov) as an unfavourable and unintended sign or symptom associated with a medical treatment. Severity is graded. Grade 3 is classed as a severe or medically significant event but not immediately life threatening. Hospitalisation is indicated, and the effects limit the patients' ability to self care. Grade 4 is classed as a life-threatening event requiring urgent attention.

Search methods for identification of studies

The authors completed searches to identify all relevant published and unpublished randomised controlled studies. Articles published in any language were eligible for inclusion.

We searched the following electronic databases.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2017; Issue 6), which includes the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group Trials Register, in the Cochrane Library (searched 14 June 2017); Appendix 2.
2. MEDLINE (1946 to 14 June 2017); Appendix 3.
3. EMBASE (1980 to 14 June 2017); Appendix 4.
4. CANCERLIT (1999 to 2002). We did not undertake subsequent searches in CANCERLIT, as the database merged with MEDLINE in 2002.

To identify randomised controlled studies, we applied phases one, two and three of the Cochrane highly sensitive search strategy, as described in the *Cochrane Handbook for Reviews of Interventions* (Higgins 2011).

Electronic searches

We handsearched reference lists from studies and review articles from the electronic searching to identify further relevant studies. We also handsearched published abstracts from the following conference proceedings.

1. American Gastroenterological Association (AGA) (1994 to 2014).
2. American Society of Clinical Oncology (ASCO) (1996 to 2016).
3. American Association of Cancer Research (AACR) (1957 to 2014).
4. American Pancreatic Association (APA) (2001 to 2014).
5. Digestive Disease Week (DDW) (1994 to 2014).
6. European Cancer Conference (ECCO) (1997, 1999, 2001, 2003, 2005, 2007, 2009, 2011, 2013).
7. European Society of Medical Oncology (ESMO) (1998, 2000, 2002, 2004, 2006, 2008, 2010, 2012, 2014).
8. Joint ECCO/ESMO meeting (2009, 2010, 2011, 2013).
9. European Pancreatic Club (EPC) (2000 to 2014).
10. Gastrointestinal Cancers Symposium (2007 to 2015).
11. United European Gastroenterology Week (UEGF) (1960 to 2014).

We searched the following information resources.

1. National Cancer Institute Physician Data Query.
2. UK Co-ordinating Committee on Cancer Research.

We also searched the following study registers.

1. Australian and New Zealand Clinical Trials Registry.
2. National Research Register.
3. Medical Research Council.
4. Clinicaltrials.gov.
5. Current Controlled Trials.
6. Trialscentral.
7. Center Watch.

Searching other resources

We searched the Internet using the Google search engine. In addition, we contacted members of the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group and other experts in the field and ask them to provide details of outstanding clinical studies and any relevant unpublished materials that were known to them.

Data collection and analysis

Selection of studies

We scanned titles of studies from the electronic search, removing duplicates. Two independent review authors (VC and AN) then considered the titles and abstracts to exclude clearly ineligible studies. We retrieved the full text of all remaining records, and two review authors (VC and AN) independently assessed them against inclusion criteria for the review, resolving disagreements with adjudication by a third review author (DY) according to the process outlined in Chapter 7.2.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We documented reasons for excluding studies according to Higgins 2011.

Data extraction and management

Two independent review authors (VC and AN) extracted data, recording the inclusion/exclusion criteria, number of participants and treatment arms for each study. For survival outcomes, we recorded hazard ratios (HRs) for OS and PFS from the published data where possible. If not reported, then we extracted time-to-event data and derived the HRs using the methods described in Tierney 2007. We also extracted median survival times. For response rates and adverse events (AEs), we recorded the number of people who had experienced an event of interest and the total number of people evaluated for that event to determine the risk ratio (RR). We extracted details on QoL in a descriptive fashion as published.

Assessment of risk of bias in included studies

Two review authors used the Cochrane 'Risk of bias' tool to independently assess risk of bias in the studies, with a a third independent review author settling disputes (Higgins 2011).

We summarised the results in a 'Risk of bias summary' graph. We interpreted the results of meta-analyses in light of the findings of the risk of bias assessments.

Measures of treatment effect

For survival data, we used the HR with 95% confidence intervals (CI) and median survival times. For dichotomous data (response rates and grade 3/4 AEs), we used the risk ratio (RR) with a 95% CI. We report quality of life in a descriptive, tabulated fashion.

Unit of analysis issues

For studies that compared more than one treatment arm with a control arm in the same meta-analysis, we divided the number of

participants in the control group by the number of treatment arms. There were no other unit of analysis issues.

Dealing with missing data

When we could not extract data from the text, or when statistics were missing, we attempted to contact the authors of the original article to obtain the necessary information.

Assessment of heterogeneity

We assessed heterogeneity by visual inspection of the forest plots and statistically with the Chi^2 test for homogeneity and the I^2 statistic for inconsistency.

Assessment of reporting biases

Had we included comparisons with more than 10 included studies, we would have constructed funnel plots to assess reporting bias.

Data synthesis

We used the generic inverse variance method for all meta-analyses according to the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Due to the heterogeneity of the interventions and comparators, we used a random-effects model in all instances. We performed all analyses using Review Manager 5 (RevMan 5) software (RevMan 2014), following an intention-to-treat principle when data permitted.

Subgroup analysis and investigation of heterogeneity

We did not perform any subgroup analyses.

Sensitivity analysis

We planned to perform sensitivity analyses by excluding studies at high risk of bias from the meta-analysis, but due to the small number of studies in the various comparisons, we were unable to do so.

Summary of findings table

We created four summary of findings tables describing the primary outcome measure of OS for participants. We included a narrative summary of the toxicity and QoL data in the comments section of the table. We calculated the median 12-month survival rate for the control arm to calculate the assumed risk for each comparison. We used the percentage of people alive at 12 months if it was available, otherwise we extracted the data from the Kaplan-Meier curves. We then applied the summary HR to this rate to give an anticipated effect on the rate of death with the intervention versus the comparator, expressed as number of events per 1000 people. We used the 6-month survival rate if all control arm participants had died by 12 months.

We used the GRADE approach to assess the quality of the body of evidence for the outcome OS as described by the GRADE Working Group and in the GRADE Handbook (Guyatt 2011; Schünemann 2013).

RESULTS

Description of studies

Results of the search

Figure 1 presents the study flow chart. We identified 1304 studies through electronic searches and an additional 80 studies through handsearching. After removing duplicates and studies that were clearly not eligible for inclusion, we assessed 215 full-text articles. Of these, we excluded 155, including 49 that did not meet the inclusion criteria for the review, and 106 that will be reported in a separate Cochrane Review.

Figure 1. 1 Study flow diagram.

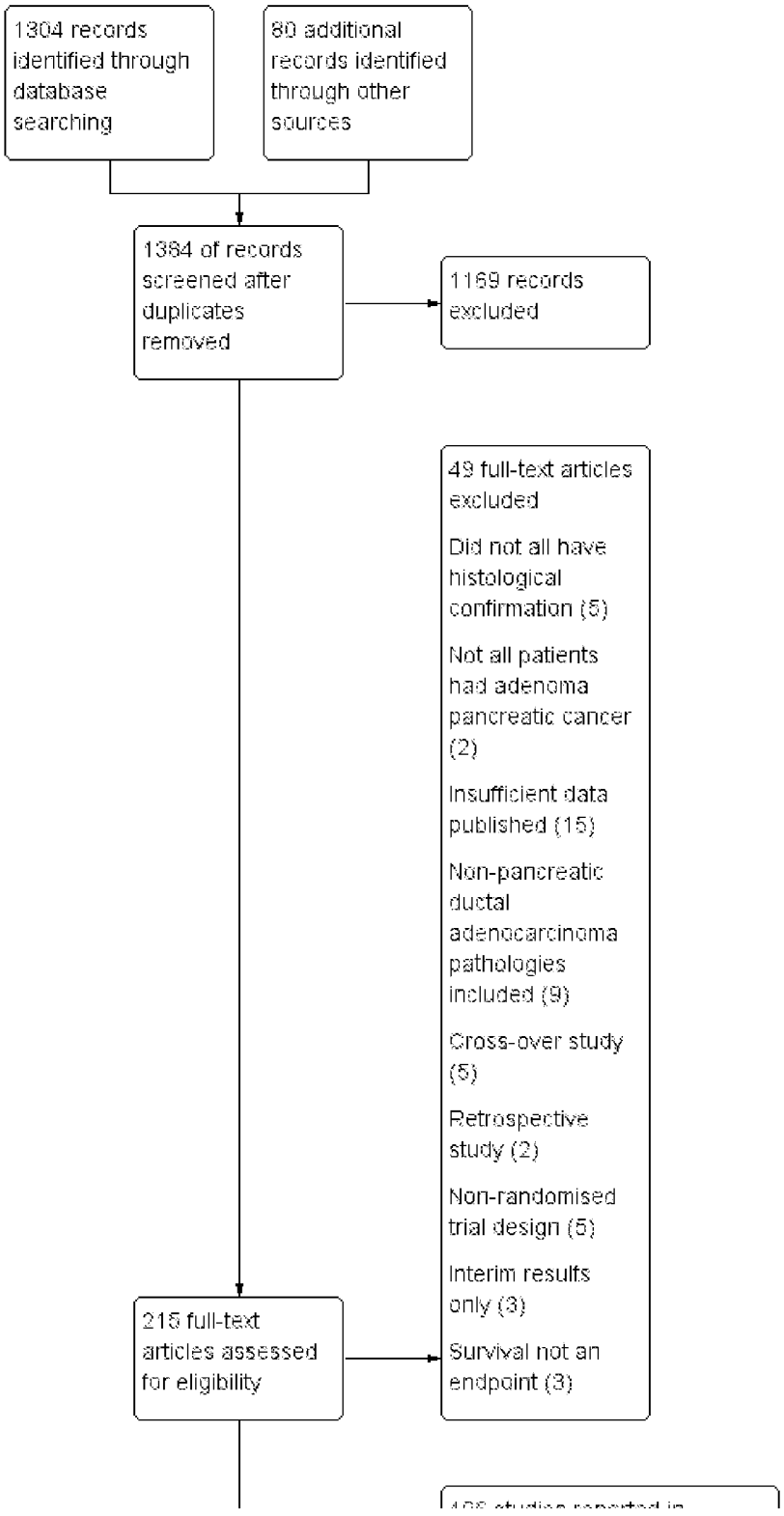
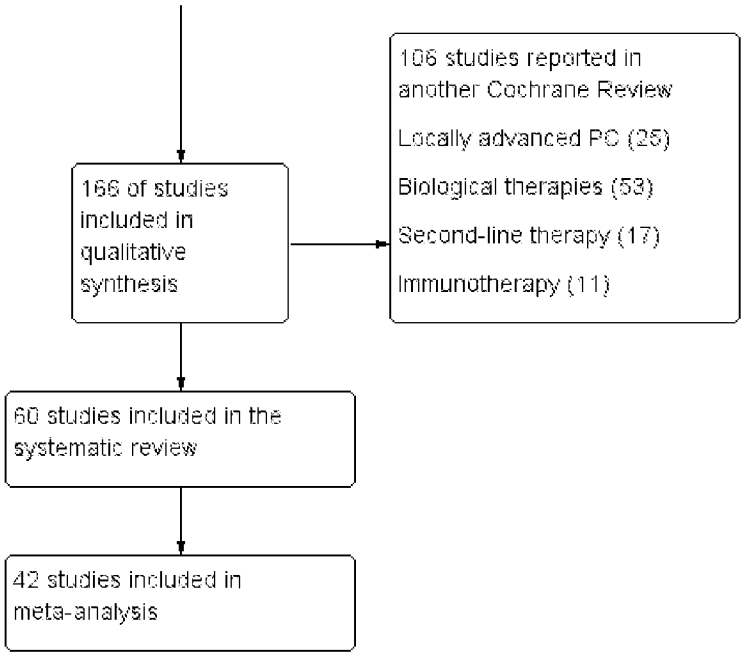


Figure 1. (Continued)



Included studies

The original published protocol had wide inclusion criteria. Due to the large number of studies identified, we decided to split the review. Therefore, we will report studies addressing biological agents, immunotherapy, second-line therapies and local therapies for locally advanced disease separately. This report focuses on studies of either chemotherapy or radiotherapy in the advanced setting only.

We included sixty studies assessing the effects on chemotherapy in advanced PC (Characteristics of included studies). We did not identify any studies that addressed radiotherapy in the advanced setting. Of the included studies, we were able to include 42 with data on 9463 participants in a meta-analysis.

We categorised these studies into five main categories.

1. Any anti-cancer treatment versus best supportive care (6 studies: Andren-Sandberg 1983; Frey 1981; Glimelius 1996; Huguier 2001,Takada 1998; Xinopoulos 2008).
2. Various types of chemotherapy versus gemcitabine (8 studies: Burris 1997; Cheverton 2004; Conroy 2011; Poplin 2009; Poplin 2013; Singhal 2014; Smith 2003; Tempero 2003).
3. Gemcitabine combination versus gemcitabine alone (7 studies addressing platinum plus gemcitabine: Colucci 2002; Colucci 2010; Heinemann 2006; Li 2004; Louvet 2005; Viret 2004; Wang 2002; 10 studies addressing fluoropyrimidine plus gemcitabine: Berlin 2002; Cunningham 2009; Di Costanzo 2005; Herrmann 2007; Lee 2017; Ohkawa 2004; Ozaka 2012; Riess 2005; Scheithauer 2003; Ueno 2013; 3 studies addressing topoisomerase inhibitors plus gemcitabine: Abou-Alfa 2006; Rocha Lima 2004; Stathopoulos 2006; 1 study addressing taxane plus gemcitabine: Von Hoff 2013; 2 studies addressing multi-drug combinations including gemcitabine: Petrioli 2015; Reni 2005; and 4 studies of other agents combined with gemcitabine: Gansauge 2002; Meng 2012; Oettle 2005; Ueno 2013 - EPA study).
4. Fluoropyrimidine-based studies (4 studies: Ducreux 2004; Kovach 1974; Maisey 2002; Moertel 1979).
5. Single studies addressing unique treatment comparisons (13 studies: Afchain 2009; Boeck 2008; Bukowski 1983; Corrie 2017; Hirao 2011; Kelsen 1991; Kulke 2009; Levi 2004; Lohr 2012; Lutz 2005; Moertel 1977; Reni 2012; Topham 1991).

1 Anti-cancer therapy versus best supportive care

Six studies compared a type of anticancer therapy with best supportive care (BSC). Andren-Sandberg 1983 (N = 47) compared 5FU/CCNU plus vincristine (n = 25) versus BSC (n = 22). Frey 1981 included 152 participants with unresectable PC and assessed 5-fluorouracil (5FU) plus chloroethylcyclohexylnitrosurea (CCNU). Glimelius 1996 studied people with advanced PC or biliary tract cancer; of the 53 participants with PC, 29 were given 5FU/LV, with or without etoposide, and 24 received BSC. Huguier 2001 included 45 participants with unresectable PC; the treatment arm was cisplatin plus 5FU plus leucovorin (LV). Takada 1998 included 83 people with unresectable PC; the treatment arm was 5FU plus doxorubicin plus mitomycin C (MMC). Xinopoulos 2008 included 49 people with locally advanced PC; the treatment arm was gemcitabine.

2 Various types of chemotherapy versus gemcitabine

Eight studies compared various types of chemotherapy versus gemcitabine.

2.1 5FU versus gemcitabine

There was one study in this group involving 126 people with symptomatic advanced PC; 63 were given 5FU and 63 gemcitabine chemotherapy (Burris 1997).

2.2 FOLFIRINOX versus gemcitabine

Conroy 2011 tested FOLFIRINOX in 342 people, and Singhal 2014 in 310 people, with metastatic PC.

2.3 CO-101 versus gemcitabine

One study in 367 participants with metastatic PC compared CO-101 (lipid conjugate form of gemcitabine) versus gemcitabine (Poplin 2013).

2.4 ZD9331 versus gemcitabine

One study addressed this comparison (Smith 2003), including 55 participants with locally advanced (LA) or metastatic PC. The treatment arm was ZD9331 (thymidylate synthase inhibitor).

2.5 Fixed-dose rate gemcitabine versus standard infusional gemcitabine

Two studies were available for analysis: Poplin 2009 and Tempero 2003. Both had slightly different schedules: Poplin 2009 involved 824 participants with LA or metastatic PC and compared gemcitabine at 1000 mg/m^2 given over 30 min weekly for 7 out of 8 weeks then 3 out of 4 weeks versus gemcitabine given at 1500 mg/m^2 over 150 min 3 out of 4 weeks. Tempero 2003 involved 92 people with LA or metastatic PC and compared a dose-dense regimen of gemcitabine 2200 mg/m^2 weekly, 3 out of 4 weeks versus gemcitabine 1500 mg/m^2 given at 10 mg/m^2/min, weekly, 3 out of 4 weeks.

2.6 Exatecan (DX-8951f) versus gemcitabine

One study addressed this comparison (Cheverton 2004), including 339 chemotherapy-naive participants with LA or metastatic PC. The treatment arm was exatecan (a hexacyclic, water-soluble, topoisomerase-1 inhibitor).

3 Gemcitabine combination studies

3.1 Gemcitabine plus a platinum agent versus gemcitabine alone

Seven studies compared gemcitabine plus a platinum agent versus gemcitabine alone (Colucci 2002; Colucci 2010; Heinemann 2006; Li 2004; Louvet 2005; Viret 2004; Wang 2002). Louvet 2005 used oxaliplatin, while the rest used cisplatin. All studies had gemcitabine alone as the control arm and gemcitabine plus a platinum agent in the treatment arm. Colucci 2002 (N = 107), Colucci 2010 (N = 400), Heinemann 2006 (N = 195). Li 2004 (N = 46) and Louvet 2005 (N = 326) all included people with LA or metastatic PC, while Viret 2004 (N = 83) and Wang 2002 (N = 42) included participants with stage III/IV PC.

3.2 Gemcitabine plus fluoropyrimidine versus gemcitabine alone

Ten studies compared gemcitabine plus fluoropyrimidine versus gemcitabine alone (Berlin 2002; Cunningham 2009; Di Costanzo 2005; Herrmann 2007; Lee 2017; Ohkawa 2004; Ozaka 2012; Riess 2005; Scheithauer 2003; Ueno 2013).

- Two studies assessed infusional 5FU in 567 participants with with LA/metastatic PC (Di Costanzo 2005; Riess 2005), and one study tested bolus 5FU in 322 participants with unresectable PC (Berlin 2002).
- Four studies used capecitabine in: 533 people with LA/metastatic PC (Cunningham 2009), 319 people with inoperable/metastatic PC (Herrmann 2007), 214 people with LA/metastatic PC (Lee 2017), and 83 people with metastatic PC (Scheithauer 2003).
- Two studies used oral tegafur (S1) in LA/metastatic PC: Ozaka 2012 included 112 participants and Ueno 2013 832. Ueno 2013 was a multi-armed study that compared gemcitabine versus S1 versus gemcitabine plus S1.
- One study assessed tegafur-uracil (UFT) in 19 participants (Ohkawa 2004).

3.3 Gemcitabine plus toposiomerase inhibitor versus gemcitabine alone

Three studies compared gemcitabine plus a toposiomerase inhibitor versus gemcitabine alone in participants with LA or metastatic PC (Abou-Alfa 2006; Rocha Lima 2004; Stathopoulos 2006). Rocha Lima 2004 (N = 360) and Stathopoulos 2006 (N = 130) tested irinotecan, and Abou-Alfa 2006 (N = 349) used exatecan.

3.4 Gemcitabine plus taxane versus gemcitabine alone

Only one study, in 861 participants with metastatic PC, was suitable for analysis (Von Hoff 2013).

3.5 Gemcitabine plus other combinations of chemotherapy versus gemcitabine alone

Two studies assessed gemcitabine plus other combinations of chemotherapy: Petrioli 2015 included 67 people with metastatic PC and combined oxaliplatin plus capecitabine plus gemcitabine (GEMOXEL). Reni 2005 assessed 99 people with LA/metastatic PC and used a combination cisplatin-epirubicin-5FU-gemcitabine.

3.6 Gemcitabine in combination with other agents versus gemcitabine alone

Four studies examined different agents in combination with gemcitabine: Gansauge 2002 looked at 90 participants with unresectable PC and used Ukrain (herbal medicine), Meng 2012 assessed 76 people with unresectable PC and used huachansu (Chinese herbal medicine), Oettle 2005 included 565 people with LA/metastatic PC and used pemetrexed, and Ueno 2013 – EPA study included 66 people with advanced PC and used eicosapentaenoic acid supplement (EPA).

4 Fluoropyrimidine combinations versus fluoropyrimidine alone

Four studies compared fluoropyrimidine combinations versus fluoropyrimidine alone (Ducreux 2004; Kovach 1974; Maisey 2002; Moertel 1979). Ducreux 2004 was a three-armed study in 63 participants with LA or metastatic PC, and Kovach 1974 included 82 participants with unresectable PC and compared 5FU versus bis-chloroethylnitrosurea (BCNU) alone versus 5FU plus BCNU. Maisey 2002 analysed 209 participants with LA or metastatic PC and compared 5FU versus 5FU plus mitomycin C (MMC). Moertel 1979 involved 176 people with metastatic PC and used streptozocin in the treatment arm. We were unable to include Cullinan 1985 and Cullinan 1990 in the meta-analysis, as they were multi-armed studies in which the control arm could not be split.

5 Single studies addressing unique treatment comparisons

Many studies addressed unique comparisons, so we could not group them with other studies.

- Boeck 2008 studied capecitabine plus oxaliplatin (n = 61) versus capecitabine plus gemcitabine (n = 64) versus modified gemcitabine plus oxaliplatin (n = 63).
- Kulke 2009 was a multi-armed study comparing fixed dose rate gemcitabine (n = 64) versus infusional gemcitabine plus cisplatin (n = 66) versus infusional gemcitabine plus docetaxel (n = 65) versus infusional gemcitabine plus irinotecan (n = 60).
- Afchain 2009 compared standard gemcitabine plus oxaliplatin (n = 20) versus a simplified gemcitabine plus oxaliplatin protocol (n = 37).
- Bukowski 1983 compared mitomycin C plus 5FU (MF) (n = 73) versus streptozocin plus MMC plus 5FU (SMF) (n = 72).
- Hirao 2011 looked at gemcitabine given on a three-week schedule (n = 45) versus gemcitabine given on a four-week schedule (n = 45).
- Kelsen 1991 compared streptozocin plus MMC plus 5FU (SMF) (n = 42) versus cisplatin plus ara-C plus caffeine (CAC) (n = 40).
- Levi 2004 studied 5FU given either as a constant or chronomodulated infusion, with (n = 52) versus without (n = 55) cisplatin.
- Lutz 2005 compared gemcitabine plus docetaxel (n = 49) versus cisplatin plus docetaxel (n = 47).
- Moertel 1977 looked at streptozocin plus 5FU (n = 40) versus streptozocin plus cyclophosphamide (n = 48).
- Reni 2012 compared capecitabine plus cisplatin plus gemcitabine plus docetaxel (PDXG) (n = 53) versus capecitabine plus cisplatin plus gemcitabine plus epirubicin (PEXG) (n = 48).
- Finally, Topham 1991 looked at epirubicin (n = 32) versus 5FU plus epirubicin plus MMC (n = 30).

Excluded studies

We excluded 155 studies. Other Cochrane Reviews will cover the 53 studies addressing biological agents, the 11 assessing immunotherapies, the 25 looking at local therapies in locally advanced disease and the 17 focusing on second-line therapies. We excluded the remaining 49 studies for the following reasons.

- Five studies did not mandate histological confirmation in the study protocol (Abdel Wahab 1999; Johnson 2001; Mallinson 1986; Nakai 2012; Palmer 1994).
- Two studies included some participants who did not have advanced stage PC (Andersen 1981; Lygidakis 1995).
- Fifteen studies did not provide sufficient data (Baker 1976; Cohen 2010; GITSG 1985; Kim 2011; Oberic 2011; Queisser 1979; Ramanathan 2011; Sakata 1992; Senzer 2006; Shapiro 2005; Sultana 2009; Sun 2011; Tagliaferri 2013; Trouilloud 2012; Van Cutsem 2013).
- Nine studies included people with non-PDAC histologies (Ducreux 2002; GITSG 1988; Lokich 1979; Mizuno 2013; Moertel 1981; Oster 1986; Schein 1978; Sudo 2014; Takada 1994).
- Five were cross-over studies (Berglund 2010; Dahan 2016; Heinemann 2013 (GUT); Horton 1981; Javle 2011).
- Two were retrospective studies (Nio 2010; Reni 2009).
- Five had a non-randomised study design (Bukowski 1993; Gong 2007; Mitry 2006; Yongxiang 2001; Zemskov 2000).
- Three studies published only interim results (GITSG 1979; Topham 1993; Tuinman 2008).
- Survival was not an endpoint in three studies (Ardalan 1988; Meyer 2008; Schmitz-Winnenthal 2013).

Risk of bias in included studies

Figure 2 and Figure 3 summarise the risk of bias of all included studies. Many studies did not publish sufficient details to make a judgement on selection bias. Of those that did, all were judged to be at a low risk of bias because they used centralised randomisation techniques. Only one study was double-blind and placebo controlled (Meng 2012), and we judged it to be at low risk for performance bias. We assessed the remainder of the studies to be at a high risk of bias. We considered studies that used OS as the primary endpoint to be at a low risk for detection bias (Abou-Alfa 2006; Berlin 2002; Cheverton 2004; Colucci 2010; Conroy 2011; Cullinan 1985; Cullinan 1990; Cunningham 2009; Frey 1981; Gansauge 2002; Glimelius 1996; Heinemann 2006; Herrmann 2007; Huguier 2001; Kulke 2009; Lee 2017; Levi 2004; Li 2004; Lohr 2012; Louvet 2005; Oettle 2005; Poplin 2009; Poplin 2013; Riess 2005; Rocha Lima 2004; Singhal 2014; Smith 2003; Stathopoulos 2006; Takada 1998; Tempero 2003; Ueno 2013; Von Hoff 2013; Xinopoulos 2008). If tumour assessments were needed to assess the primary outcome (e.g. RR or PFS), we assigned a low risk of bias only if an independent reviewer or by a blinded radiologist conducted the assessments (Ducreux 2004; Reni 2005; Reni 2012; Scheithauer 2003). We judged all other studies to be at a high risk of bias. We deemed studies that reported the intention-to-treat population (all participants randomised on the study regardless if they received any treatment or not) to be at a low risk of attrition bias, while we considered studies that did not report all randomised patients to be at a high risk of bias (Bukowski 1983; Cullinan 1985; Ducreux 2004; Kelsen 1991; Louvet 2005; Moertel 1977; Ozaka 2012). We detected selective reporting bias in only two studies (Bukowski 1983; Moertel 1979), the former because only the participants with measurable disease were reported in detail and the latter because the toxicity data were not comprehensively reported.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

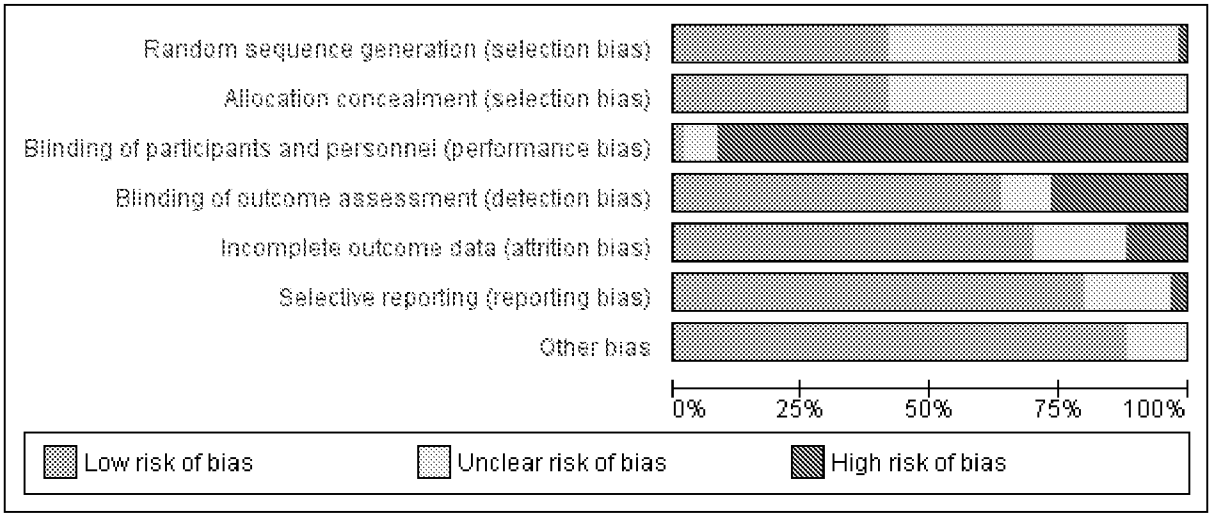
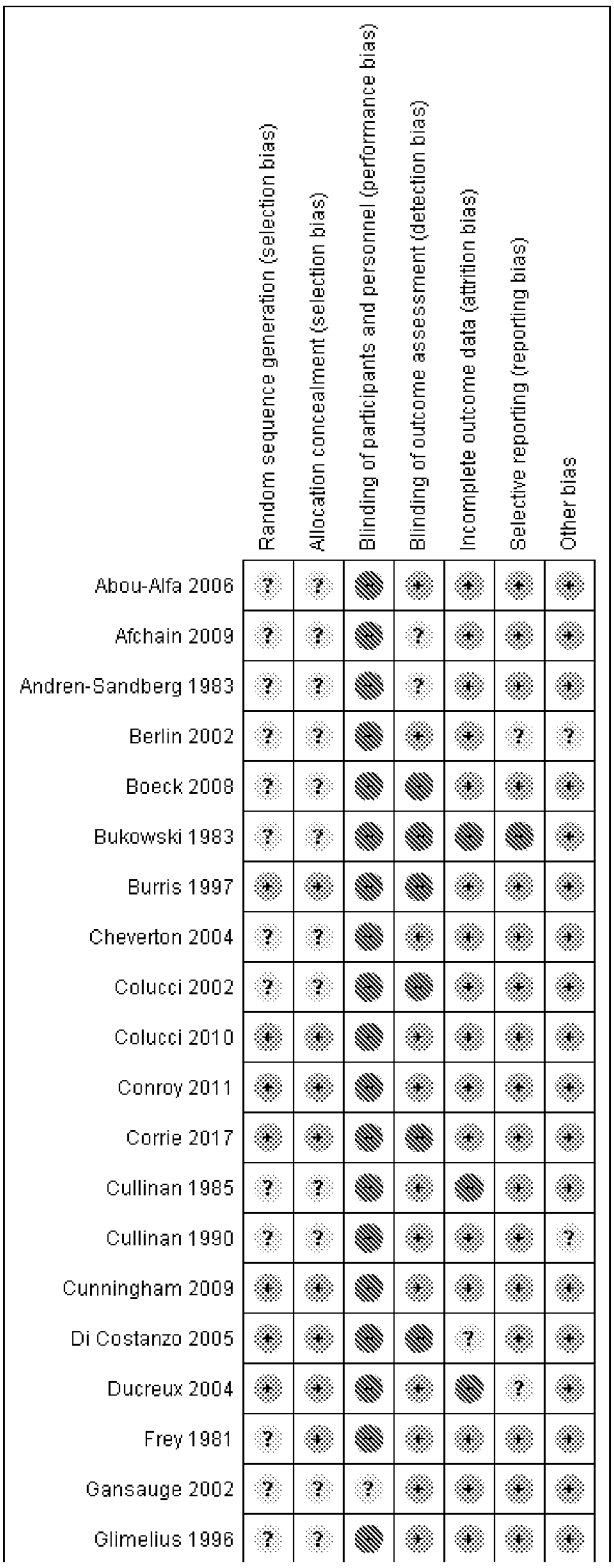


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



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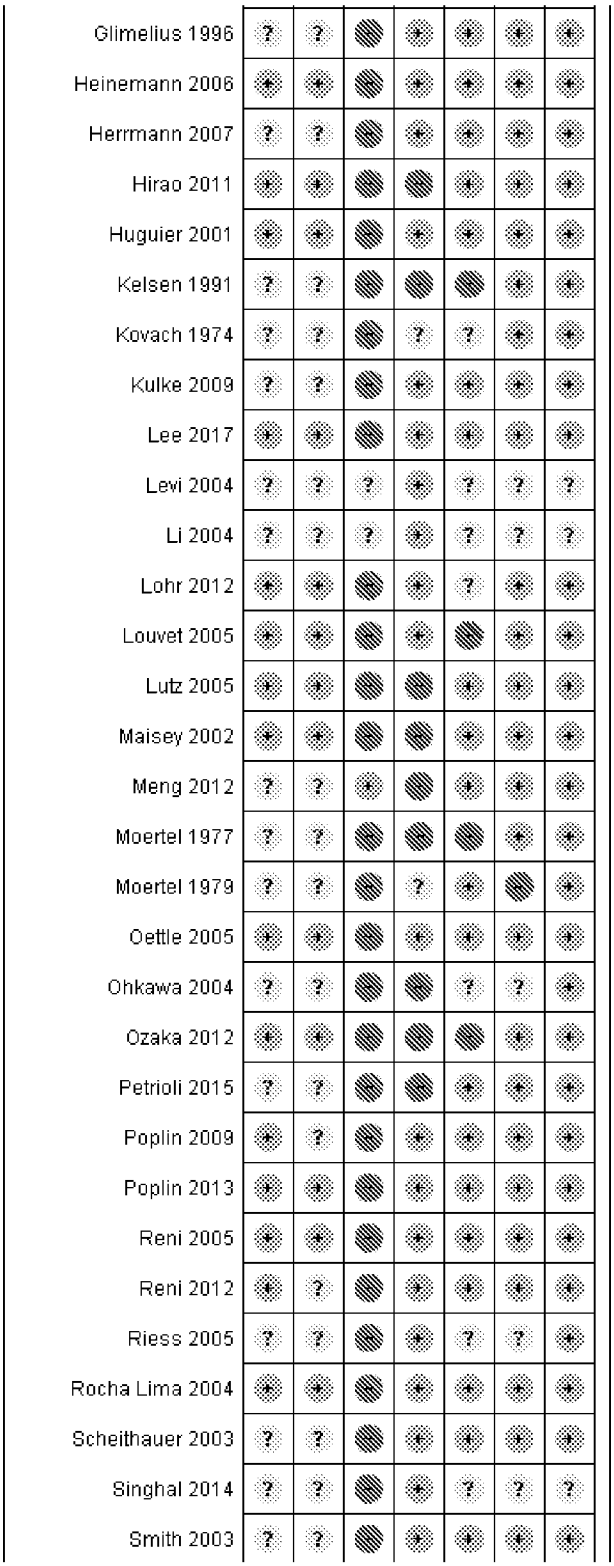

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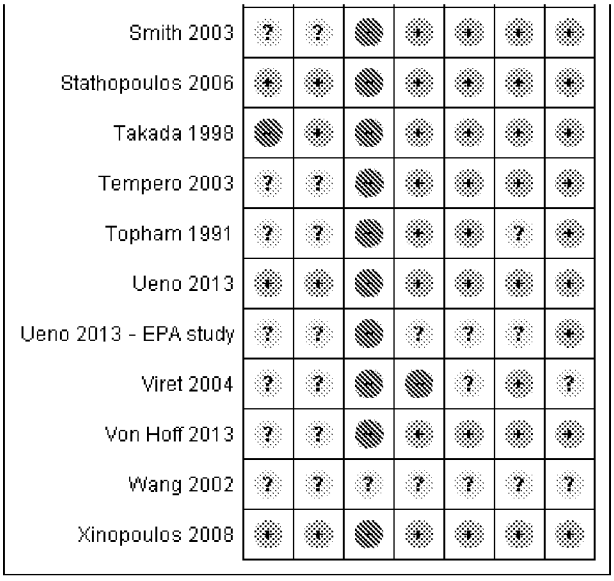

We describe details of the risk of bias of the included studies in the Effects of interventions section.

Effects of interventions

See: **Summary of findings for the main comparison** Anti-cancer therapy versus best supportive care for advanced pancreatic cancer; **Summary of findings 2** Various types of chemotherapy versus gemcitabine for advanced pancreatic cancer; **Summary of findings 3** Gemcitabine combinations versus gemcitabine alone for advanced pancreatic cancer; **Summary of findings 4** Fluoropyrimidine combinations versus fluoropyrimidine alone for advanced pancreatic cancer

1 Anti-cancer therapy versus best supportive care (BSC)

Six studies addressed any anti-cancer therapy versus best supportive care (Andren-Sandberg 1983; Frey 1981; Glimelius 1996; Huguier 2001; Takada 1998; Xinopoulos 2008). The main potential source of bias in these studies came from their non-blinded design; however, we did not feel this significantly affected the results for overall survival (Figure 2; Figure 3). In three studies the risk of selection bias was unclear due to insufficient reporting (Andren-Sandberg 1983; Glimelius 1996; Xinopoulos 2008).

Four of the six studies provided data in sufficient detail to derive hazard ratios (HR) for OS, with 298 people analysed. Pooled data of four studies in 298 people showed an HR of 1.08 (95% CI 0.88 to 1.33; Analysis 1.1). There was no statistical heterogeneity between studies (I^2 = 0%). Median survival ranged from 3.0 to 8.6 months in the anti-cancer therapy group and 2.5 to 7.0 months in the BSC group. The difference in median survival times ranged from 0.9 months in favour of BSC to 3.5 months in favour of anticancer therapy (Table 1).

Three studies reported quality of life (Table 1). Andren-Sandberg 1983 did not find a difference in Karnofsky performance status (KPS) score. In Glimelius 1996, the EORTC QLQ-C30 results favoured the treatment group; however, there was a high rate of dropouts in the later time points. The third study (Xinopoulos 2008) demonstrated a superior QoL (EORTC QLQ-C30) in the gemcitabine group during the first month (P = 0.028), but there was no difference in months two to four, and the BSC group had a superior QoL in months five (P = 0.010) and six (P = 0.0003).

Trials either did not study or did not adequately report PFS and response rates, with the exception of Takada 1998. This study reported complete or partial response in one person in the anti-cancer therapy group versus none in the BSC group.

With respect to adverse effects or toxicity in the anti-cancer therapy group, Frey 1981 reported that 31% of participants experienced at least one toxicity, with the most common being gastrointestinal. Huguier 2001 reported that the most common toxicities were haematological and gastrointestinal (each seen in 15% of people). Takada 1998 showed that the commonest grade 3/4 adverse events (AEs) were anorexia, which occurred in in 15/28 participants and nausea/vomiting, in 5/24 participants. Haematological toxicities were the most common in Xinopoulos 2008, with leucopenia occurring in 81.5% of participants.

2 Various types of chemotherapy versus gemcitabine

Eight studies compared various types of chemotherapy versus gemcitabine (Burris 1997; Cheverton 2004; Conroy 2011; Poplin 2009; Poplin 2013; Singhal 2014; Smith 2003; Tempero 2003), analysing a total of 1844 participants in six treatment subgroups. Due to the heterogeneity of the investigational agents, we did not pool the results. Five studies provided PFS data (Burris 1997; Conroy 2011; Poplin 2009; Singhal 2014; Smith 2003). The main potential source of bias in these studies came from the non-blinded study design. We were unable to comprehensively assess selection bias in some studies (Cheverton 2004; Singhal 2014; Smith 2003; Tempero 2003), and there was a high risk of detection bias noted in Burris 1997, Poplin 2013 and Smith 2003; however, we did not consider that it significantly affected results for overall survival.

2.1 5FU versus gemcitabine

Burris 1997 (N = 126) was the only study to compare 5FU with gemcitabine, showing an HR for OS of 1.69 (95% CI 1.26 to 2.27, P < 0.001; Analysis 2.1). The difference in median survival was 1.3 months in favour of gemcitabine (Table 2). The analysis of PFS showed an HR of 1.47 (95% CI 1.12 to 1.92, P = 0.005; Analysis 2.2). There were better outcomes for both OS and PFS with gemcitabine, and this group also showed more treatment response (0 in the 5FU arm versus 3 in the gemcitabine arm; risk ratio (RR) 0.14, 95% CI 0.01 to 2.71, P = 0.19). On the other hand, the gemcitabine arm showed a higher risk of most types of grade 3/4 toxicity: anaemia (0 in the 5FU arm versus 6 events in the gemcitabine arm: RR 0.08, 95% CI 0.0 to 1.34, P = 0.08; Analysis 2.5); neutropenia (3 events versus 16 events: RR 0.19, 95% CI 0.06 to 0.61, P = 0.006; Analysis 2.6); thrombocytopenia (1 event versus 6 events: RR 0.17, 95% CI 0.02 to 1.34, P = 0.09; Analysis 2.7); and nausea (3 events versus 8 events: RR 0.38, 95% CI 0.10 to 1.35, P = 0.13; Analysis 2.8). Diarrhoea was the exception (3 events in the 5FU arm versus 1 event in the gemcitabine arm: RR 3.00, 95% CI 0.32 to 28.07, P = 0.34; Analysis 2.9). Clinical benefit was superior in the gemcitabine arm compared with the 5FU arm, with a higher clinical benefit response (23.8% versus 4.8%), shorter median time to clinical benefit response (3 weeks versus 7 weeks) and longer duration of clinical benefit response (18 weeks versus 13 weeks) (Table 2).

2.2 FOLFIRINOX versus gemcitabine

Two studies in 652 people assessed the effects of FOLFIRINOX versus gemcitabine (Conroy 2011; Singhal 2014). The FOLFIRINOX group generally outperformed gemcitabine, showing improved OS (HR 0.51, 95% CI 0.43 to 0.60, P < 0.001; I^2 = 29%; Analysis 2.1), longer median survival (4.3 months versus 3.4 months; Table 2), longer PFS (HR 0.46, 95% CI 0.38 to 0.57, N = 652, P < 0.001; I^2 = 0%; Analysis 2.2), longer time to degradation of QoL (HR 0.46, 95% CI 0.35 to 0.61, P < 0.001; I^2 = 0%; Analysis 2.3; Table 2), and more treatment responses (54 responses versus 16 responses: RR 3.38, 95% CI 2.01 to 5.65, P < 0.001; Analysis 2.4). On the other hand, FOLFIRINOX also showed more grade 3/4 haematological toxicity for: anaemia (13 events versus 10 events: RR 1.30, 95% CI 0.59 to 2.88, P = 0.52; Analysis 2.5), neutropenia (75 events versus 35 events: RR 2.14, 95% CI 1.52 to 3.01, P < 0.001: Analysis 2.6), and thrombocytopenia (15 events versus 6 events: RR 2.50, 95% CI 0.99 to 6.29, P = 0.05; Analysis 2.7).

2.3 CO-101 versus gemcitabine

Poplin 2013 tested CO-101 in 367 people. Outcomes were not different for participants in either arm. The HR for OS was 1.07 (95% CI 0.86 to 1.34, P = 0.68; Analysis 2.1). Median survival was similar in both groups, 5.2 months for CO-101 and 6.0 months for gemcitabine (Table 2). The trial did not report PFS. The RR for response was 0.67 (95% CI 0.43 to 1.04, P = 0.08; Analysis 2.4). We could neither prove nor rule out differences in various types of grade 3/4 toxicity (Analysis 2.5; Analysis 2.6; Analysis 2.7).

2.4 ZD9331 versus gemcitabine

Smith 2003 compared ZD9331 versus gemcitabine in 55 people. There was no difference in survival for participants in either arm. The HR for OS was 0.86 (95% CI 0.42 to 1.76, P = 0.68; Analysis 2.1) and for PFS, it was 0.78 (95% CI 0.46 to 1.32, P = 0.36; Analysis 2.2). Median survival was 5.0 months and 3.6 months, respectively (Table 2). The RR for response was 0.42 (95% CI 0.04 to 4.33, P = 0.46, Analysis 2.4). We could neither prove nor rule out differences in various types of grade 3/4 toxicity (Analysis 2.5; Analysis 2.6; Analysis 2.7; Analysis 2.8; Analysis 2.9).

2.5 Fixed dose rate gemcitabine (FDR-gem) versus standard infusional gemcitabine

Two studies assessed the effects of FDR-gem in 644 people (Poplin 2009; Tempero 2003). OS was improved in the FDR-gem group (HR 0.79, 95% CI 0.66 to 0.94, P = 0.009, I^2 = 0%; Analysis 2.1). In the two studies, median survival was 1.3 months and 3.0 months longer in the FDR-gem group (Table 2). Only Poplin 2009 (N = 552) reported PFS, finding no significant difference between groups (HR 0.88, 95% CI 0.77 to 1.01, P = 0.06, Analysis 2.2). There were more responses seen in the FDR-gem group (30 responses versus 19 responses), but this was not significant (RR 1.59, 95% CI 0.91 to 2.79, P = 0.10; Analysis 2.4). Analyses also showed more grade 3/4 toxicity in the FDR-gem group: anaemia (62 events versus 35 events: RR 1.79, 95% CI 1.22 to 2.63, P = 0.003; Analysis 2.5), neutropenia (183 events versus 100 events: RR 1.85, 95% CI 1.53 to 2.23, P < 0.001; Analysis 2.6), thrombocytopenia (107 events versus 39 events: RR 2.77, 95% CI 1.99 to 3.86, P < 0.001; Analysis 2.7), and nausea (37 events versus 25 events: RR 1.52, 95% CI 0.94 to 2.46, P = 0.09; Analysis 2.8). Diarrhoea was the exception (5 events versus 12 events: RR 0.44, 95% CI 0.16 to 1.23, P = 0.12; Analysis 2.9).

2.6 Exatecan (DX-8951f) versus gemcitabine

Cheverton 2004 demonstrated that exatecan had an inferior effect on OS compared with gemcitabine (HR 1.27, 95% CI 0.96 to 1.68, P = 0.093). Median survival in the two respective groups was 5 months versus 6.6 months; 6-month survival rates were 44.1% versus 51.1%; and 12-month survival rates, 17.9% versus 22.1%. There were insufficient data to include this study in the PFS analysis; however, median PFS was 2.8 months versus 4.4 months. Response rates were available in 276 people (1 response versus 10 responses: RR 0.10, 95% CI 0.01 to 0.78, P = 0.03; Analysis 2.4). Toxicity data were available in 330 people and showed that both agents performed similarly for grade 3/4 anaemia (10 events versus 10 events: RR 1.00, 95% CI 0.43 to 2.34, P = 1.00; Analysis 2.5), neutropenia (32 events versus 32 events: RR 1.00, 95% CI 0.64 to 1.55, P = 1.00; Analysis 2.6), thrombocytopenia (12 events versus 16 events: RR 0.75, 95% CI 0.37 to 1.54, P = 0.43; Analysis 2.7) and nausea (7 events versus 4 events: RR 1.75, 95% CI 0.52 to 5.86, P = 0.36; Analysis 2.8). QoL analysis showed that time to worsening of clinical benefit was longer in the gemcitabine arm, with 3.7 months to worsening of pain in the exatecan group versus 7.9 months in the gemcitabine group (P = 0.049). The gemcitabine group also showed a longer time to worsening KPS (3.4 months versus 4.6 months; P = 0.011) and to weight loss (2.3 months versus 3.8 months; P = 0.020). Global and pancreas-specific QoL questionnaires failed to elicit significant differences between the two groups. (Table 2).

3 Gemcitabine combination studies

We identified six subgroups in this comparison, and we pooled results in the subgroups only and not overall.

3.1 Gemcitabine plus a platinum agent versus gemcitabine alone

The HR for OS based on six studies in 1140 participants showed no difference between the treatment groups, 0.94 (95% CI 0.81 to 1.08, P = 0.38; Analysis 3.1). There was some statistical heterogeneity (I^2 = 15%). Four studies in 1015 participants reported PFS and showed

some improvement in the gemcitabine + platinum group, giving an HR of 0.80 (95% CI 0.68 to 0.95, P = 0.01; Analysis 3.2). There was high statistical heterogeneity (I^2 = 46%). The median survival times are listed in Table 3.

All studies (N = 1186) reported response rates favouring the combined treatment arm (100 responses versus 67 responses: RR 1.48, 95% CI 1.11 to 1.98, P = 0.007, I^2 = 0%; Analysis 3.3). Data from all studies (N = 1156) contributed to meta-analyses for grade 3/4 anaemia (62 events in the gemcitabine plus platinum group versus 45 events in the gemcitabine alone group: RR 1.41, 95% CI 0.87 to 2.31, P = 0.17; Analysis 3.4) and neutropenia (122 events versus 97 events: RR 1.34, 95% CI 0.90 to 1.97, P = 0.14; Analysis 3.5), with similar rates between groups. For other adverse events, data in 1110 participants from six studies showed more grade 3/4 AEs in the combination group: thrombocytopenia (78 events versus 35 events: RR 1.96, 95% CI 1.00 to 3.84, P = 0.05; Analysis 3.6) and nausea (52 events versus 22 events: RR 2.28, 95% CI 1.40 to 3.71, P = 0.001; Analysis 3.7), although for diarrhoea, we could not rule out the possibility that these results were due to chance (23 events versus 14 events: RR 1.48, 95% CI 0.62 to 3.53, P = 0.38; Analysis 3.8).

Four studies reported QoL data. Colucci 2010 measured QoL using the EORTC QLQ C30 questionnaires in multiple areas. Scores were from a scale of 0-100. The mean difference (MD) between baseline scores and scores after 4 weeks of treatment were measured. The study did not find a significant MD in global QoL scores between those taking gemcitabine alone (MD 6.20) versus gemcitabine plus platinum (MD 0.09), P = 0.07. Heinemann 2006 found no difference between the treatment groups in either the Spitzer index or pain intensity score, nor did Viret 2004 find any difference in the EORTC-QLQ C30 results between treatment groups. Li 2004 reported finding no difference in clinical benefit but better quality of life outcomes in the gemcitabine alone arm (3.8 months versus 5.6 months in QoL-adjusted life months gained P < 0.001; Table 3).

In the one study that we could not include in the meta-analysis (Li 2004), there were no differences between the control and treatment groups for OS (4.6 months versus 5.6 months) or PFS (2.8 months versus 2.8 months; Table 3).

The main source of bias identified in these studies was their non-blinded study design. There was a high risk of attrition bias in Louvet 2005 and insufficient details in Viret 2004 and Wang 2002 reports to make a comprehensive assessment of risk of bias.

3.2 Gemcitabine plus fluoropyrimidine versus gemcitabine alone

Ten studies reported OS in 2718 participants. A benefit for adding fluoropyrimidine to gemcitabine was detected (HR 0.88, 95% CI 0.81 to 0.95, P = 0.001; Analysis 3.1), with no statistical heterogeneity (I^2 = 0%). Eight studies reported PFS in 2608 participants and abenefit for the combination arm was also shown (HR 0.79, 95% CI 0.72 to 0.87, P < 0.001). There was moderate statistical heterogeneity with an I^2 of 34% (Analysis 3.2). The median survival times ranged from 5.4 months to 8.8 months in the gemcitabine alone group and from 6.7 months to 13.7 months in the combination group (Table 3). Ueno 2013 was a multi-armed study that compared gemcitabine alone versus S1 alone versus gemcitabine plus S1. The analysis in this review includes only the gemcitabine alone and gemcitabine plus S1 arms.

Nine studies reported response rates in 2176 participants. Responses were more common in the combination group (228 responses in the combination group versus 124 responses in the gemcitabine alone group), RR 1.78 (95% CI 1.29 to 2.47, P < 0.001; Analysis 3.3), with high statistical heterogeneity (I^2 = 52%). Eight studies reported grade 3/4 AEs in 2158 participants in the combination group versus the gemcitabine alone group, with the combination treatment group tending to experience more AEs: anaemia (97 events versus 89 events: RR 1.11, 95% CI 0.84 to 1.45, P = 0.47; Analysis 3.4), neutropenia (353 events versus 234 events: RR 1.53, 95% CI 1.34 to 1.74, P < 0.001; Analysis 3.5), thrombocytopenia (122 events versus 81 events: RR 1.48, 95% CI 1.00 to 2.18, P = 0.05; Analysis 3.6), nausea (61 events versus 47 events: RR 1.27, 95% CI 0.87 to 1.84, P = 0.22; Analysis 3.7), and diarrhoea (55 events versus 23 events: RR 2.16, 95% CI 1.34 to 3.47, P = 0.002; Analysis 3.8).

Five studies recorded QoL data. Cunningham 2009 used the Memorial pain assessment card, EORTC QLQ C30 and ESPAC QoL questionnaires. Di Costanzo 2005 recorded mean disturbed days and the mean days the person would like to cancel treatment. Herrmann 2007 used a linear-analogue self-assessment (LASA) indicators for clinical benefit response (CBR). Scheithauer 2003 recorded a combination of pain, KPS and weight, and Ueno 2013 recorded quality adjusted life years (QALYs). Cunningham 2009 did not find any significant differences in QoL between treatment groups. Likewise, Di Costanzo 2005 did not show any differences in QoL outcomes. Herrmann 2007 did not show a difference in either CBR or QoL (measured by LASA); however, in those people who did have a CBR, the duration was longer in the combination arm (9.5 weeks versus 6.5 weeks, P < 0.02). Scheithauer 2003 demonstrated an improvement in pain response and KPS but not weight gain in the combination arm, and Ueno 2013 showed a statistically significant improvement in QALYs in the combination group: 0.401 versus 0.525, P < 0.001 (Table 3).

The main source of bias identified in this comparison was due to the non-blinded study design. The risk of selection bias was unclear in Berlin 2002; Herrmann 2007; Ohkawa 2004; Riess 2005 and Scheithauer 2003, but we did not consider that this significantly affected the results.

3.3 Gemcitabine plus topoisomerase inhibitor versus gemcitabine alone

Three studies reported OS data in 839 participants, giving an HR of 1.01 (95% CI 0.87 to 1.16, P = 0.92; Analysis 3.1), indicating no difference between groups. There was no heterogeneity (I^2 = 0%). Two studies reported similar PFS in 709 participants (HR 0.91, 95% CI 0.78 to 1.07, P = 0.26, I^2 = 0%; Analysis 3.2). The median survival times were very similar between the two groups (Table 3). All studies reported response rates, with data on 729 participants (49 responses in the combined treatment group versus 22 responses in the gemcitabine alone group: RR 1.50, (95% CI 0.92 to 2.46, P = 0.11, I^2 = 0%; Analysis 3.3). The combination arms were shown to be more toxic with data for grade 3/4 AEs in 797 participants: anaemia (41 events versus 37 events: RR 1.09, 95% CI 0.72 to 1.66, P = 0.68; Analysis 3.4), neutropenia (132 events versus 88 events: RR 1.54, 95% CI 1.04 to 2.30, P = 0.03; Analysis 3.5), thrombocytopenia (63 events versus 31 events: RR 2.28, 95% CI 0.97 to 5.36, P = 0.06; Analysis 3.6), nausea (36 events versus 23 events: RR 1.55, 95% CI 0.94 to 2.55, P = 0.09; Analysis 3.7) and diarrhoea (36 events versus 6 events: RR 3.47, 95% CI 0.74 to 16.33, P = 0.12; Analysis 3.8).

Rocha Lima 2004 was the only study to record QoL data (FACT-Hep questionnaire) and reported no significant differences between the two groups (Table 3).

The main source of bias identified in this comparison was due to the non-blinded study design, but we did not consider that this affected the results.

3.4 Gemcitabine plus taxane versus gemcitabine alone

Von Hoff 2013 was the only study in this group, and trialists analysed all 861 participants for OS, PFS and response rate. A benefit in survival outcomes was demonstrated in the combination arm. For OS, the HR was 0.72 (95% CI 0.62 to 0.84; P < 0.001; Analysis 3.1), and for PFS, HR was 0.69 (95% CI 0.58 to 0.82; P < 0.001; Analysis 3.2). The median survival time was 8.5 months in the combination group versus 6.7 months in the gemcitabine control (Table 3). There was a higher response rate in the combination arm (99 responses versus 30 responses: RR 3.29, 95% CI 2.24 to 4.84, P < 0.001; Analysis 3.3). Data on grade 3/4 AEs were available for 793 participants and overall, toxicity was more common in the combination arm: anaemia (53 events versus 48 events: RR 1.06, 95% CI 0.73 to 1.52, P = 0.76; Analysis 3.4), neutropenia (153 events versus 103 events: RR 1.42, 95% CI 1.16 to 1.75, P < 0.001; Analysis 3.5), thrombocytopenia (52 events versus 36 events: RR 1.38, 95% CI 0.93 to 2.07, P = 0.11; Analysis 3.6), neuropathy (70 events versus 3 events: RR 22.35, 95% CI 7.10 to 70.40, P < 0.001; Analysis 3.9) and fatigue (70 events versus 27 events: RR 2.48, 95% CI 1.63 to 3.79, P < 0.001; Analysis 3.10). The studies did not report on QoL.

Corrie 2017 was a unique study that we could not include in this analysis, addressing nab-paclitaxel plus gemcitabine versus the same agents given in a sequential dosing schedule. Here the standard arm had similar results to the nab-paclitaxel plus gemcitabine arm of Von Hoff 2013, with a median survival of 7.9 months, median PFS of 4.0 months and response rate of 33%.

Likewise, we could not include Lohr 2012 in the analysis as it was a multi-armed study. It showed that overall survival for the gemcitabine alone arm was 6.8 months, compared to 8.1 months in combination with liposomal paclitaxel 11 mg/m^2, 8.7 months in combination with liposomal paclitaxel 22 mg/m^2 and 9.3 months in combination with liposomal paclitaxel 44 mg/m^2. When comparing each combination arm with gemcitabine alone the HRs all crossed the line of null effect: for concomitant doses of 11 mg/m^2: HR 0.93 (95% CI 0.60 to 1.43); for 22 mg/m^2: HR 0.69 (95% CI 0.44 to 1.07); and for 44 mg/m^2: HR 0.66 (95% CI 0.43 to 1.03). PFS in the gemcitabine alone group was 2.7 months compared with each of the combination arms: 4.1 months, 4.6 months and 4.4 months (11 mg/m^2, 22 mg/m^2 and 44 mg/m^2, respectively). When comparing each experimental arm with gemcitabine alone for PFS, the HRs were 0.84 (95% CI 0.44 to 1.28), 0.58 (95% CI 0.38 to 0.90) and 0.74 (95% CI 0.49 to 1.13), respectively. The number of responses were similar in all groups (14%, 14%, 14% and 16%, respectively). Neutropenia and fatigue were the commonest AEs and occurred at similar rates across the four groups. The trials did not report QoL. Toxicity was more common in the combination arm with a dose dependent increase in thrombocytopenia, chills and pyrexia.

Although there were insufficient details to make an assessment of selection bias, overall we assessed the study as being at low risk of bias, the main source being due to the non-blinded study design, which we considered to not affect the results.

3.5 Gemcitabine plus other combinations of chemotherapy versus gemcitabine alone

Two studies reported OS data on 166 participants which showed improved survival in the combination group (HR 0.55, 95% CI 0.39 to 0.79, P = 0.001; Analysis 3.1). There was some statistical heterogeneity (I^2 = 24%). Both studies reported PFS and again showed a benefit to the combination arm, with an HR of 0.43 (95% CI 0.30 to 0.62, P < 0.001, I^2 = 17%; Analysis 3.2). Median survival times were only available for Petrioli 2015, who reported that the combined treatment group survived for a median of 11.9 months versus 7.1 months in the gemcitabine alone group (Table 3). Only Petrioli 2015 reported response rates in 67 participants (12 responses versus 6 responses: RR 1.94, 95% CI 0.83 to 4.56, P = 0.13; Analysis 3.3). The same study reported grade 3/4 AEs. Although AEs were more common in the combination arm, the small number of events makes it difficult to assess the real difference between the arms: anaemia (6 events versus 3 events: RR 1.94, 95% CI 0.53 to 7.13, P = 0.32; Analysis 3.4), neutropenia (8 events versus 4 events: RR 1.94, 95% CI 0.65 to 5.83, P = 0.24; Analysis 3.5), thrombocytopenia (10 events versus 5 events: RR 1.94, 95% CI 0.74 to 5.07, P = 0.11; Analysis 3.6) and nausea (5 events versus 0 events: RR 10.69, 95% CI 0.61 to 185.91, P = 0.10; Analysis 3.7).

Both studies reported QoL data. Petrioli 2015 used the EORTC QLQ C30 and McGill Melzack questionnaires, and Reni 2005 used the EORTC-QLQ Pan 26 questionnaire. Petrioli 2015 showed that global QoL was improved in the combined treatment group at two and four months. Reni 2005 stated that the sample size was insufficient to obtain statistical power to detect differences between the control and treatment groups. However, the treatment group had better average emotional functioning, overall QoL, cognitive measures, pain, fatigue, indigestion, dyspnoea, appetite loss and flatulence, while sexual function and body image were better in the control group (Table 3).

Petrioli 2015 did not publish enough data to make a full assessment of selection bias and had a high risk of performance and detection bias. Reni 2005 was a non-blinded study but otherwise had a low risk of bias.

3.6 Gemcitabine plus other agent(s) versus gemcitabine alone

Four studies assessed OS in 767 participants, with no differences in survival detected (HR 0.79, 95% CI 0.56 to 1.10, P = 0.16; I^2 = 62%; Analysis 3.1). Only Meng 2012 reported PFS data in 76 people, with no differences seen, HR 1.05 (95% CI 0.68 to 1.62, P = 0.83; Analysis 3.2). Median survival times in the gemcitabine group ranged from 5.2 months to 9.7 months and in the combination group from 5.2 months to 10.4 months (Table 3). Three studies reported response rates in 691 participants (61 responses versus 22 responses: with RR 3.66, 95% CI 1.04 to 12.82, P = 0.04; Gansauge 2002; Meng 2012; Oettle 2005; Analysis 3.3). Three studies reported haematological toxicity data for grade 3/4 events in 688 participants revealing more anaemia in the combination arm (Meng 2012; Oettle 2005; Ueno 2013 - EPA study): anaemia (49 events versus 12 events: RR 3.58, 95% CI 1.93 to 6.62, P < 0.001; Analysis 3.4), neutropenia (140 events versus 45 events: RR 2.02, 95% CI 0.88 to 4.66, P = 0.10; Analysis 3.5), and thrombocytopenia (55 events versus 23 events: RR 1.41, 95% CI 0.45 to 4.39, P = 0.56; Analysis 3.6). Four studies reported on nausea in 748 participants (17 events versus 11 events: RR 1.25, 95% CI 0.48 to 3.26, P = 0.64; Analysis 3.7).

Two studies reported on QoL: Meng 2012 used the FACT-G and MD Anderson Symptom Inventory questionnaires, and Oettle 2005 used the EORTC QLQ-C30 questionnaire. Meng 2012 did not find a difference in either of the scales used (FACT-G and MD Anderson Symptom Inventory questionnaire) at eight weeks. Oettle 2005 showed that people in the gemcitabine alone group had lower financial difficulties and better physical and cognitive functioning, but the combination arm had lower pain scores. There was no clear trend in QoL scores between the treatment groups, however (Table 3).

There was an unclear risk of selection bias in Gansauge 2002 and Meng 2012 due to insufficient details being published. Ueno 2013 - EPA study did not provide enough details to perform a comprehensive assessment.

4 Fluoropyrimidine combinations versus fluoropyrimidine alone

Four studies reported OS in 491 participants receiving either fluoropyrimidine combinations or fluoropyrimidine alone with no differences in survival detected (HR 0.84, 95% CI 0.61 to 1.15, P = 0.27; Analysis 4.1). There was high statistical heterogeneity with an I^2 of 66%. Ducreux 2004, which studied 5FU with or without oxaliplatin, showed a large benefit in the treatment group in contrast to the other three studies, which did not show much benefit with the combination arms. Only two studies reported PFS in 255 participants, and there were no differences (HR 0.52, 95% CI 0.19 to 1.38, P = 0.19; Analysis 4.2), again, with large statistical heterogeneity (I^2 = 89%). Median survival times ranged from 3.7 months to 6.5 months in the combination group and from 3.4 months to 5.25 months in the 5FU group (Table 4). All four studies reported response rates, but there were no differences between arms (32 responses versus 24 responses: RR 1.18, 95% CI 0.52 to 2.68, P = 0.10; I^2 = 52%; Analysis 4.3). Two studies (N = 255) reported rates of grade 3/4 anaemia, neutropenia, thrombocytopenia, nausea, and diarrhoea (Ducreux 2004; Maisey 2002). There were no significant differences between groups in: anaemia (8 events versus 11 events: RR 0.48, 95% CI 0.06 to 3.62, P = 0.16; Analysis 4.4); neutropenia (7 events versus 0 events: RR 5.70, 95% CI 0.73 to 44.46, P = 0.10; Analysis 4.5); thrombocytopenia (5 events versus 3 events: RR 1.40, 95% CI 0.34 to 5.80, P = 0.65; Analysis 4.6); nausea (7 events versus 5 events, RR 1.06, 95% CI 0.32 to 3.53, P = 0.93; Analysis 4.8); or diarrhoea (6 events versus 6 events: RR 0.92, 95% CI 0.31 to 2.78, P = 0.89; Analysis 4.9). Maisey 2002 reported similar rates of grade 3/4 fatigue in both arms (26 events versus 30 events: RR 0.91, 95% CI 0.58 to 1.43, P = 0.68; Analysis 4.7).

One study recorded QoL data (Maisey 2002), using the EORTC-QLQ C30 questionnaire, which did not demonstrate a difference between the two groups at baseline, 12 weeks or 24 weeks (Table 4).

The main source of bias was in the non-blinded study design. We assessed both Ducreux 2004 and Kovach 1974 as being at high risk of attrition bias, and this may have affected the results.

5 Single studies addressing unique treatment comparisons

Ten studies addressed unique comparisons that could not be categorised under the above-mentioned comparisons (Table 5).

Boeck 2008 showed that capecitabine plus gemcitabine had superior median survival (9.0 months) and response rate (25%) compared with 8.1 months/13% in the capecitabine/oxaliplatin group and 6.9 months/13% in the gemcitabine/oxaliplatin group. Haematological AEs were more common in the gemcitabine-containing regimens.

Kulke 2009 showed a similar OS in all four treatment groups, ranging from 6.4 months to 7.1 months and response rates of 12% to 14%. AEs were similar across treatment arms, with neutropenia and fatigue being the most common.

Afchain 2009 found that a simplified gemcitabine/oxaliplatin regimen was superior to a standard gemcitabine/oxaliplatin regimen with an OS of 7.6 months versus 3.2 months and response rate of 27% versus 10%. Peripheral neuropathy was more common in the simplified arm, however.

Bukowski 1983 did not demonstrate a difference in OS for streptozocin/MMC/5FU (SMF) versus MMC/5FU (18 weeks versus 17 weeks); however, there was an increase in response rate of 34% versus 8%. There was more gastrointestinal and renal toxicity in the SMF arm.

Hirao 2011 showed a slight increase in OS for the three-week schedule of gemcitabine versus the four-week schedule (250 days versus 206 days), but there was a similar response rate (17.1% versus 14.2%). Thrombocytopenia was more common in the four-week schedule.

Kelsen 1991 found that the SMF arm had a longer OS than the cisplatin/ara-C/caffeine arm (10 months versus 5 months), but a similar response rate (10% versus 6%). Nausea and vomiting were more common in the caffeine-containing arm.

Levi 2004 showed that adding cisplatin to 5FU increased OS (8.3 months versus 5.4 months), but there was no difference between the continuous versus the chronomodulated arms (6.1 months versus 6.7 months). Cisplatin increased the rates of haematological AEs, and the chronomodulated regimen increased rates of mucositis.

Lutz 2005 did not demonstrate any striking differences between gemcitabine/docetaxel and cisplatin/docetaxel (OS 7.0 months versus 7.5 months); however, febrile neutropenia was more common in the cisplatin containing arm.

Moertel 1977 showed a slightly increased OS in the streptozocin/5FU arm compared with streptozocin/cyclophosphamide (13 weeks versus 9 weeks), with the cyclophosphamide arm experiencing more haematological AEs.

Reni 2012 showed a similar OS between capecitabine/cisplatin/gemcitabine/docetaxel (PDXG) and capecitabine/cisplatin/gemcitabine/epirubicin (PEXG) (10.7 months versus 11 months); however, there was a higher partial response rate in the PDXG group (58% versus 33%). The PEXG arm had more neutropenia.

Topham 1991 found a slightly higher one-year survival rate in the 5FU/epirubicin/MMC arm compared with epirubicin alone (23.2% versus 15.4%), and the AEs were similar in both arms.

DISCUSSION

Summary of main results

1 Anti-cancer therapy versus best supportive care

We could neither prove nor rule out a survival benefit for anti-cancer therapy versus BSC alone (moderate-quality evidence due to imprecision; Summary of findings for the main comparison). This is in contrast to the previous version of this review, which found a benefit in the odds for death at both 6 months (OR 0.37, 95% CI 0.25 to 0.57, P < 0.001) and 12 months (OR 0.46, 95% CI 0.25 to 0.84, P = 0.01). Due to the new protocol used in this study, we excluded two studies that had featured in the previous review because they included people without histological confirmation (Mallinson 1989; Palmer 1994); this is the likely cause of these discrepant results. The differences in median survival were modest and ranged from 0.9 months in favour of BSC to 3.5 months in favour of anti-cancer therapy (Table 1).

There is evidence for improved QoL with the use of anti-cancer therapy in one study (Glimelius 1996), with Xinopoulos 2008 showing an early benefit that was not sustained after month 5.

Readers should interpret these results with caution, as the included studies span over 30 years, and Xinopoulos 2008 was the only study to use contemporary chemotherapy regimens. As it is unlikely that further studies will be conducted using BSC as the control arm, additional randomised data showing the effects of contemporary chemotherapy over BSC in the first-line setting may never be generated.

2 Various types of chemotherapy versus gemcitabine

The one study addressing gemcitabine versus 5FU chemotherapy, Burris 1997, showed inferior outcomes for OS (HR 1.69; P = 0.004), PFS (HR 1.47; P = 0.005) and QoL with the 5FU arm. Summary of findings 2 shows a rating of moderate-quality evidence due to only one small study being available for analysis. These results demonstrate that using gemcitabine reduces the risk of death by 41% and progression by 32% compared with 5FU therapy. The absolute improvement in OS is modest at just over one month. Gemcitabine may result in more grade 3/4 AEs. There is an improvement in QoL (clinical benefit response).

The analysis of two studies comparing FOLFIRINOX versus gemcitabine demonstrated an improvement in OS (HR 0.51; P < 0.001), PFS (HR 0.46; P < 0.001) and response rate (RR 3.38; P < 0.001) but also significantly more neutropenia and thrombocytopenia (Conroy 2011; Singhal 2014). There was improved QoL. Summary of findings 2 demonstrates the moderate quality of evidence rating based on inconsistency. These results suggest that FOLFIRINOX reduces the risk of death by 49%, reduces the risk of progression by 54% and triples the rate of response compared with gemcitabine. The absolute survival gains are still modest, with OS in the gemcitabine alone arm ranging from 6.8 months to 7.4 months and in the FOLFIRINOX arms between 10.8 months to 11.1 months.

The two studies that assessed the effects of giving gemcitabine at a fixed dose rate showed an improvement in OS (HR 0.79; P = 0.009) but also more haematological toxicity (Poplin 2009; Tempero 2003). Granted, the 'standard' gemcitabine arms differed between the two studies, but the study using a more intense control arm (gemcitabine 2200 mg/m^2 weekly) still found superiority in the FDR-gem arm. Summary of findings 2 details a high quality of evidence rating. This analysis suggests that using FDR-gem reduces the risk of death by 21%; however, the absolute survival gains are again small, with OS in the standard infusional gemcitabine arm ranging from 4.9 months to 5.0 months and in the FDR-gem arm from 6.2 months to 8.0 months.

The studies comparing exatecan, CO-101 and ZD9331 to gemcitabine did not show a survival benefit (Cheverton 2004; Poplin 2013; Smith 2003). None of these studies showed a difference in toxicity and in exatecan, analyses showed QoL to be superior in the gemcitabine arm. We rated each comparison as having moderate-quality evidence due to imprecision (Summary of findings 2).

3 Gemcitabine combination studies

3.1 Gemcitabine plus a platinum agent versus gemcitabine alone

The analysis of seven studies has shown that the combination of gemcitabine with a platinum agent did not significantly improve OS (HR 0.94; P = 0.38) but may improve PFS (HR 0.80; P = 0.01) (Colucci 2002; Colucci 2010; Heinemann 2006; Louvet 2005; Viret 2004; Wang 2002). This equates to a reduction in the risk of progression of 20%. Summary of findings 3 shows that the quality of evidence in this analysis was low, due to two studies being in abstract form and not publishing sufficient data to make a full assessment, along with imprecision. These results are in keeping with the findings of the previous review, which found a benefit in 6-month mortality (OR 0.59, P = 0.001) but not 12-month mortality. We were not able to include all the studies from the previous review (Li 2004 did not publish sufficient data); however, we included two additional studies (Colucci 2010; Viret 2004). The addition of platinum improved response rates but increased thrombocytopenia and nausea. There were no significant differences found in QoL between the control and treatment arms in the people tested. This suggests that while adding platinum increases side effects, this does not translate into a worse QoL. The median survival times were similar in the two groups (Table 3).

3.2 Gemcitabine plus fluoropyrimidine versus gemcitabine alone

The analysis of 10 studies shows that adding a fluoropyrimidine agent can improve OS (HR 0.88; P = 0.001), PFS (0.79; P < 0.001) and response rate (RR 1.78; P < 0.001), but at the cost of increased rates of neutropenia and diarrhoea (Berlin 2002; Cunningham 2009; Di Costanzo 2005; Herrmann 2007; Lee 2017; Ohkawa 2004; Ozaka 2012; Riess 2005; Scheithauer 2003; Ueno 2013). Summary of findings 3 show that the quality of evidence is high. This shows that the addition of 5FU reduces the risk of death by 12%, reduces the risk of progression by 21% and nearly doubles the rate of response, but it also increases toxicity. Two studies did not report any differences in QoL with the addition of a fluoropyrimidine agent; however, two studies did report an improvement, with Scheithauer 2003 showing less pain and Ueno 2013 showing an improvement in QALYs. The previous version of this review did not find significant benefits for adding fluoropyrimidine to gemcitabine; however, that version analysed only 5 studies, compared to the 10 studied here. Because this analysis included both intravenous and oral fluoropyrimidine agents, these results must be interpreted with caution. Moreover, two studies used S1 (Ozaka 2012; Ueno 2013), and one study used UFT (Ohkawa 2004), agents that have not been well studied in non-Asian populations. The absolute improvement

in OS is small, ranging from 5.4 months to 8.8 months in the gemcitabine alone arm and 6.7 months to 13.7 months in the combination arm (Table 3).

3.3 Gemcitabine plus topoisomerase inhibitor versus gemcitabine alone

The analysis of three studies shows that the addition of a topoisomerase inhibitor to gemcitabine does not significantly improve OS (HR 1.01; P = 0.92) or PFS (HR 0.91; P = 0.26) (Abou-Alfa 2006; Rocha Lima 2004; Stathopoulos 2006). Response rates were also not significantly improved (RR 1.50; P = 0.11); however, neutropenia did. Only one study measured QoL and failed to find any differences between the two groups. The median survival times were similar in the two groups (Table 3).

We assessed the quality of evidence as high (Summary of findings 3).

3.4 Gemcitabine plus taxane versus gemcitabine alone

Our search yielded only one study that we could analyse in this category (Von Hoff 2013), and it found that adding nab-paclitaxel to gemcitabine significantly improved OS (HR 0.72; P < 0.001), PFS (HR 0.69; P < 0.001) and response rates (RR 3.29; P < 0.001). Summary of findings 3 show that the quality of evidence is high; however, there is only one study. This demonstrates that the addition of nab-paclitaxel to gemcitabine reduces the risk of death by 28%, reduces the risk of progression by 31% and more than triples the rate of response. There is an increased risk of neutropenia, neuropathy and fatigue, and QoL was not measured. Although there is only one study in this analysis, there was also another study, Corrie 2017, which we could not include; it used gemcitabine plus nab-paclitaxel as the control group and published similar OS, PFS and response data.

3.5 Gemcitabine plus other combinations of chemotherapy versus gemcitabine alone

The two studies analysed showed that combining gemcitabine with multiple other agents improves OS (HR 0.55; P = 0.001) and PFS (HR 0.43; P < 0.001) (Petrioli 2015; Reni 2005). Only one study reported response rates, which were not different between groups. Likewise, one study reported similar incidence of AEs. QoL was improved in both studies. Summary of findings 3 shows the low rating for quality of evidence due to one study not publishing enough data to make a full assessment and because of inconsistency. Given that only one study reported response rates and grade 3/4 AEs, the numbers of events in these analyses are small, and the conclusions that we can draw here are limited. This analysis suggests that the use of combination therapies containing gemcitabine may reduce the risk of death by 45% and reduce the risk of progression by 57%; however, we cannot make any assessment regarding the rates of side effects. There may be an improvement in QoL. Just one study reported median survival times, showing OS in the gemcitabine arm to be 7.1 months compared with 11.9 months in the combination arm (Table 3).

Multi-drug combinations including gemcitabine may be effective in improving survival outcomes, and given the positive results of the Conroy 2011 study, which uses FOLFIRINOX, the findings add weight to the argument that intensive chemotherapy has a place in the treatment of PC.

3.6 Gemcitabine plus other agent(s) versus gemcitabine alone

This group contains studies that did not fall into any of the other pooled analyses. The four studies analysed here are heterogenous in terms of the agents used (Gansauge 2002; Meng 2012; Oettle 2005; Ueno 2013 - EPA study). The analysis shows that OS is not significantly different in the combination arm. Three studies show improved response rates but also increased anaemia. There was high statistical heterogeneity seen in both survival analyses, which is likely to be accounted for by the varied agents used. QoL was not significantly different in the two studies that reported this outcome. Median survival times were longer in the Gansauge 2002 study but otherwise very similar (Table 3).

These data need to be interpreted with caution, as the studies used a wide range of agents. The results for Ukrain in Gansauge 2002 are highly provocative and may warrant further study in larger numbers, supported by a meta-analysis across different cancer types (Ernst 2005). We assessed the quality of evidence as low due to imprecision and inconsistency (Summary of findings 3).

4 Fluoropyrimidine combinations versus fluoropyrimidine alone

This analysis showed that pooling data from studies that added an agent to 5FU did not result in a significant benefit in OS (HR 0.84; P = 0.27) or PFS (0.52; P = 0.19) compared to 5FU alone (Ducreux 2004; Kovach 1974; Maisey 2002; Moertel 1979). However, in these two analyses, there was high statistical heterogeneity (I^2 = 66% and 89%, respectively), likely due to the range of agents tested. Three studies used fairly outdated chemotherapies (BCNU, MMC and streptozocin), whereas one study used oxaliplatin (Ducreux 2004). This study accounts for most of the heterogeneity seen, as it found a statistically significant benefit in both OS and PFS in contrast to the other studies. Response rates were not significantly improved (RR 1.18; P = 0.69), again with high statistical heterogeneity that was mainly due to the Kovach 1974 study, testing BCNU and reporting higher responses in the 5FU alone group. Grade 3/4 AEs were not significantly different between the two groups. Only Maisey 2002 assessed QoL, demonstrating an improvement in dyspnoea.

The conclusions that we can draw from this analysis are limited. It seems that from the results of the Ducreux 2004 study, oxaliplatin plus 5FU is an active combination compared with 5FU alone and does not measurably increase side effects.

The quality of evidence was assessed as low due to imprecision and statistical heterogeneity (Summary of findings 4).

Overall completeness and applicability of evidence

To our knowledge, this review contains a complete review of all the available evidence up until the censor date. We have made every attempt to conduct the analysis in a clinically relevant way in order to fulfil the objective of assisting patients and clinicians in decision-making.

Quality of the evidence

Two review authors independently assessed the risk of bias of the individual studies using the GRADE criteria, and we tabulate this information in Figure 2, Figure 3 and the 'Summary of findings' tables. Only four subgroup comparisons were of high quality, whereas the remainder of the comparisons provided moderate- or low-quality evidence. This was mainly due to inconsistency and

small sample sizes. Given PC is a rare condition which is commonly seen in the elderly, recruiting to clinical studies is incredibly difficult. In addition, recent large scale sequencing studies have revealed the marked genetic heterogeneity in PC, which is likely to contribute to the inconsistent effects seen between studies (Bailey 2016). This should guide future studies and encourage stratified study design.

Potential biases in the review process

In order to reduce the potential biases in the review process, two separate review authors independently evaluated studies and extracted data, resolving disputes with adjudication by a third review author. We did not identify any other potential biases.

Agreements and disagreements with other studies or reviews

Unlike the previous version of this review (Yip 2009), we were unable to replicate the benefit seen for anti-cancer therapy versus best supportive care alone. As discussed in the main text, this was mainly due to the fact we were unable to include all the previously analysed studies due to lack of available time-to-event data.

We have added to the scope and results of the previous review by widening the inclusion criteria and have been able to provide wider recommendations.

AUTHORS' CONCLUSIONS

Implications for practice

Currently there is no way of rationally selecting the 'best' chemotherapy regimen for people with pancreatic cancer. For decades, gemcitabine has been the gold standard; however, there are now several more efficacious options that treating clinicians can consider. The treatment choice must be tailored to the person, taking into account the their performance status and the side effect profiles of the chemotherapy agents. The results of this analysis shows that in advanced pancreas cancer:

1. based on one study, gemcitabine is superior to 5FU alone, reducing the risk of death and progression and improving QoL;
2. compared to gemcitabine alone, multi-drug combinations improve survival outcomes and response rates in PC. FOLFIRINOX, GEMOXEL and gemcitabine/cisplatin/epirubicin and 5FU are active regimens. These data suggest that in people who are fit, multi-drug regimens may be appropriate, but the potential for increased toxicity must be taken into account;
3. gemcitabine given using a fixed dose rate schedule improves overall survival but increases toxicity compared with standard dosing;
4. gemcitabine plus platinum-based chemotherapy does not improve OS but does improve PFS and response rates;
5. gemcitabine plus fluoropyrimidine-based chemotherapy improves survival and response rates, albeit by a small amount;
6. based on one study, gemcitabine plus taxane improves survival outcomes and response rates but increases toxicity.

Implications for research

The results of this analysis suggest that using multi-drug regimens for advanced PC has the potential to improve outcomes. This must be weighed against the increase in toxicity. Currently, there are no effective biomarkers to predict in whom an aggressive approach is warranted, and this should be an area of further research. In addition, this analysis shows that there are many different chemotherapies which are beneficial in this disease, but currently there is no way of rationally selecting the 'best' chemotherapy regimen. Biomarker development has the potential to stratify people early in their disease course, inform clinical study design and avoid exposing people to ineffective chemotherapy.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abou-Alfa 2006

Methods	Randomised phase III trial
Participants	Study was conducted in North America in 349 participants with locally advanced/metastatic pancreatic adenocarcinoma. The mean age in the gemcitabine + exatecan group was 63 years, and the mean age in gemcitabine group 62.3 years. Previous radiotherapy for locally advanced disease was allowed. 174 received gemcitabine. 175 received gemcitabine + exatecan.
Interventions	Gemcitabine: 1000 mg/m² 7/8 weeks, then 3/4 weeks Gemcitabine + exatecan: gemcitabine 1000 mg/m² and exatecan 2 mg/m² days 1 and 8 every 3 weeks
Outcomes	Overall survival Time to progression Safety Quality of life Response rate Progression-free survival
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study

Abou-Alfa 2006 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Overall survival primary endpoint
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported in the results
Other bias	Low risk	No indication of other bias

Afchain 2009

Methods	Randomised phase II study
Participants	Study was conducted in France. 57 participants with metastatic adenocarcinoma without prior chemotherapy or radiotherapy. 20 participants received gemcitabine/oxaliplatin and 37 participants received simplified gemcitabine/oxaliplatin. Mean age was 66.6 years in the gemcitabine/oxaliplatin group and 64.9 years in the simplified gemcitabine/oxaliplatin group.
Interventions	Gemcitabine/oxaliplatin: gemcitabine 1000 mg/m^2 on day 1, oxaliplatin 100 mg/m^2 day 2, every 2 weeks Simplified regimen: gemcitabine 1000 mg/m^2 day 1, oxaliplatin 100 mg/m^2 day 1, every 2 weeks
Outcomes	Progression-free survival Overall survival Response rate
Notes	—

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details published
Incomplete outcome data (attrition bias)	Low risk	All participants included in the efficacy analysis

Afchain 2009 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported in the results
Other bias	Low risk	No indication of other bias

Andren-Sandberg 1983

Methods	Randomised study
Participants	Study was conducted in Sweden. 47 participants with inoperable pancreatic cancer less than 71 years old. 22 received best supportive care and 25 received 5FU + CCNU + vincristine. The mean age was 58 years in the treatment group and 60 years in the best supportive care group.
Interventions	5FU: 500 mg orally days 2-5 CCNU: 40 mg/m^2 orally days 2 + 3 Vincristine: 1 mg/m^2 day 1 Given every 6 weeks
Outcomes	Survival Quality of life
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details published
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported in the results
Other bias	Low risk	No indication of other bias

Berlin 2002

Methods	Randomised phase III trial
Participants	Study was conducted in North America. 322 participants with unresectable pancreatic ductal adenocarcinoma. Were allowed to have received adjuvant gemcitabine if completed > 6 months prior. Were allowed to have received radiotherapy if completed more than 4 weeks prior. 162 received gemcitabine. 160 received gemcitabine + 5-fluorouracil (5FU). The median age in the gemcitabine + 5FU group was 65.8 years and 64.3 years in the gemcitabine group.
Interventions	Gemcitabine 1000 mg/m^2 3/4 weeks Gemcitabine + 5FU: gemcitabine as above + 5FU 600 mg/m^2/week bolus given 3/4 weeks
Outcomes	Overall survival Time to progression Response rate
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in survival analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient details published
Other bias	Unclear risk	No indication of other bias

Boeck 2008

Methods	Randomised phase II trial
Participants	Study was conducted in Germany. 190 participants with advanced pancreatic cancer. 61 received capecitabine + oxaliplatin (CapOx), 64 received capecitabine + gemcitabine (CapGem) and 63 received

Boeck 2008 *(Continued)*

	gemcitabine + oxaliplatin (mGemOx). The median age was 62 years (CapOx), 63 years (CapGem) and 63 years (mGemOx) in the treatment groups.
Interventions	CapOx: capecitabine 1000 mg/m² orally twice daily, days 1-14 every 3 weeks + oxaliplatin 130 mg/m² day 1 CapGem: capecitabine 825 mg/m² orally twice daily, days 1-14 every 3 weeks + gemcitabine 1000 mg/m² days 1 + 8 mGemOx: gemcitabine 1000 mg/m² days 1 + 8 + oxaliplatin 130 mg/m² day 8
Outcomes	Progression-free survival after 3 months Overall survival Overall response rate Clinical benefit response Ca19.9 response
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk for primary endpoint (PFS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat population reported for survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported in the results
Other bias	Low risk	No indication of other bias

Bukowski 1983

Methods	Randomised study
Participants	Study was conducted in North America. 145 participants with inoperable pancreatic adenocarcinoma with no previous chemotherapy or radiotherapy. 73 were given mitomycin C + 5FU (MF), 72 were given streptozocin, mitomycin C and 5FU (SMF). The median age for participants in the SMF arm were 59

Bukowski 1983 *(Continued)*

	years and 59.5 years for those with measurable and non-measurable disease respectively. In the MF arm the median age was 60 years and 62 years for those with measurable and non-measurable disease respectively.
Interventions	MF 'good risk' - mitomycin C 20 mg/m^2 on day 1 + 5FU 1000 mg/m^2 days 1-4 and 29-32 every 56 days MF 'poor risk' - mitomycin C 15 mg/m^2 on day 1 with the same 5FU regimen above SMF 'good risk' - streptozocin 400 mg/m^2 days 1-4 and 29-32, mitomycin C 15 mg/m^2 on day 1 and 5FU 1000 mg/m^2 days 1-4 and 29-32, every 56 days SMF 'poor risk' - mitomycin given at 10 mg/m^2 day 1, with streptozocin and 5FU given as above
Outcomes	Overall survival Performance-free survival Response rate
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Primary outcome measure not stated, no intention-to-treat analysis
Incomplete outcome data (attrition bias) All outcomes	High risk	Only participants with measurable disease were included in survival analysis
Selective reporting (reporting bias)	High risk	Participants with non-measurable disease not comprehensively reported
Other bias	Low risk	No indication of other bias

Burris 1997

Methods	Randomised trial
Participants	Study was conducted in the United States and Canada. 126 participants with advanced, symptomatic pancreas cancer with stabilised pain. 63 received 5-fluorouracil (5FU). 63 received gemcitabine. Median age in the 5FU arm was 61 years and 62 years in the gemcitabine arm.

Burris 1997 *(Continued)*

Interventions	5FU 600 mg/m² weekly Gemcitabine 1000 mg/m² 7/8 weeks then 3/4 weeks
Outcomes	Clinical benefit Response rate Overall survival Progression-free survival Safety
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization of patients with stabilized pain to treatment with either gemcitabine or 5-FU occurred immediately before starting study drug treatment and was performed at a central location"
Allocation concealment (selection bias)	Low risk	"Randomization of patients with stabilized pain to treatment with either gemcitabine or 5-FU occurred immediately before starting study drug treatment and was performed at a central location"
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Treatment was single blind. The study drug was not blinded to the investigator, because a rash was a potential side effect of treatment with both 5-FU and gemcitabine"
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk for the primary endpoint (clinical benefit)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants included in survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported in the results
Other bias	Low risk	No indications of other bias

Cheverton 2004

Methods	Randomised phase III study
Participants	Study was conducted in Europe. 339 participants with locally advanced or metastatic pancreatic cancer and no prior chemotherapy. 170 received gemcitabine. 169 received exatecan. Of these 330 (165 vs 165) received treatment. Median age was not published.
Interventions	Gemcitabine 1000 mg/m² given 3/4 then 7/8 weeks Exatecan 0.5 mg/m² daily for 5 days every 3 weeks

Cheverton 2004 *(Continued)*

Outcomes	Overall survival Response rates Time to tumour progression Quality of life
Notes	Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details published to make an assessment
Allocation concealment (selection bias)	Unclear risk	Insufficient details published to make an assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants included in survival analysis (intention-to-treat population reported).
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported in the results
Other bias	Low risk	No indications of other bias

Colucci 2002

Methods	Randomised phase II trial
Participants	Study was conducted in Italy. 107 participants with locally advanced, metastatic pancreatic ductal adenocarcinoma with measurable disease and no prior therapy. 54 received gemcitabine. 53 received gemcitabine + cisplatin. The median age in the gemcitabine + cisplatin arm was 60 years, and it was 63 years in the gemcitabine alone arm.
Interventions	Gemcitabine 1000 mg/m^2 weekly × 7, then 2 weeks rest. Then 3/4 weeks Gemcitabine + cisplatin: gemcitabine as above. Cisplatin 25 mg/m^2 days 1, 8, 15, 29, 36, 42 then 2 weeks rest. Then gemcitabine and cisplatin days 1, 8, 15 every 4 weeks
Outcomes	Overall response rate Time to progression (assessed at week 7 and then every 2 cycles of treatment) Overall survival

Colucci 2002 *(Continued)*

Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Time to progression was the primary endpoint
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was reported for the primary endpoint
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported in the results
Other bias	Low risk	No indication of other bias

Colucci 2010

Methods	Randomised phase III trial
Participants	Study conducted in Italy. 400 participants with unresectable or metastatic pancreatic ductal adenocarcinoma with no prior chemotherapy. 199 received gemcitabine. 201 received gemcitabine + cisplatin. The median age of participants was 63 years.
Interventions	Gemcitabine: 1000 mg/m^2 7/8 weeks then 3/4 weeks Gemcitabine + cisplatin: gemcitabine as above. Cisplatin 25 mg/m^2 days 1, 8, 15, 29, 36, 42 then 1 week rest. Then cisplatin 25 mg/m^2 days 1, 8, 15 every 4 weeks
Outcomes	Overall survival Progression-free survival Overall response rate Toxicity Clinical benefit Quality of life
Notes	—

Colucci 2010 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned to standard arm or experimental arm in a 1:1 ratio. Telephone random assignment was performed centrally (Clinical Trials Unit, National Cancer Institute, Napoli, Italy), by a computer-driven minimization procedure"
Allocation concealment (selection bias)	Low risk	"Patients were randomly assigned to standard arm or experimental arm in a 1:1 ratio. Telephone random assignment was performed centrally (Clinical Trials Unit, National Cancer Institute, Napoli, Italy), by a computer-driven minimization procedure"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported in the results
Other bias	Low risk	No indication of other bias

Conroy 2011

Methods	Randomised phase II/III study
Participants	Study was conducted in France. 342 participants with measurable, metastatic pancreatic ductal adenocarcinoma and no previous chemotherapy. 171 received gemcitabine. 171 received 5-fluorouracil (5FU) + oxaliplatin + irinotecan (FOLFIRINOX). The median age was 61 in both treatment groups.
Interventions	Gemcitabine 1000 mg/m^2 7/8 weeks then 3/4 weeks FOLFIRINOX: 5FU bolus 400 mg/m^2, 5FU CI 2400 mg/m^2 over 46 hours + leucovorin 400 mg/m^2 + oxaliplatin 85 mg/m^2 + irinotecan 180 mg/m^2 every 2 weeks
Outcomes	Overall survival Progression-free survival Response rate Safety Quality of life
Notes	—

Conroy 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed centrally in a 1:1 ratio with stratification according to center, performance status (0 vs. 1), and primary tumor localization"
Allocation concealment (selection bias)	Low risk	"Randomization was performed centrally in a 1:1 ratio with stratification according to center, performance status (0 vs. 1), and primary tumor localization"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint and other endpoints. "Independent review of CT scans was performed"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All analyses were performed on an intention-to-treat-basis"
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported in the results
Other bias	Low risk	No indications of other bias

Corrie 2017

Methods	Randomised phase II study
Participants	Study was conducted in the UK. 146 participants with metastatic pancreatic adenocarcinoma with no prior treatment. 75 received standard concomitant nab-paclitaxel and gemcitabine and 71 received sequential administration of nab-paclitaxel and gemcitabine. Median age was 66 years.
Interventions	Standard regimen: nab-paclitaxel 125 mg/m^2 and gemcitabine 1000 mg/m^2 given immediately after each other on days 1, 8, 15 of a 4 week cycle Sequential regimen: nab-paclitaxel 125 mg/m^2 on days 1, 8, 15 and gemcitabine 1000 mg/m^2 on days 2, 9, 16 of a 4-week cycle
Outcomes	Progression-free survival Safety Response rate Overall survival Quality of life
Notes	Abstract only

Corrie 2017 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Web based randomisation system with stratified block randomisation
Allocation concealment (selection bias)	Low risk	No evidence of selection bias
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	High for the primary endpoint (PFS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analyses
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported in the results
Other bias	Low risk	None found

Cullinan 1985

Methods	Randomised trial
Participants	Study was conducted in North America. 305 participants with unresectable or metastatic pancreatic or gastric adenocarcinoma. Of the participants with pancreatic cancer, 50 received 5-fluorouracil (5FU), 44 received 5FU + doxorubicin (FA). 50 received 5FU + doxorubicin + mitomycin C (FAM). The majority of participants in the study were between 50 to 69 years old.
Interventions	5FU: 500 mg/m^2 days 1-5 week 1, 4 and 8, then every 5 weeks FA: 5FU 400 mg/m^2 days 1-4 + doxorubicin 40 mg/m^2 day 1 week 1, 4 and 8, then every 5 weeks FAM: 5FU 600 mg/m^2 days 1, 8, 29, 36 + doxorubicin 30 mg/m^2 days 1 and 29 + mitomycin C 10 mg/m^2 day 1, every 8 weeks
Outcomes	Overall survival Progression-free survival Response rate Toxicity Symptom control
Notes	—

Risk of bias

Cullinan 1985 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	High risk	10 participants excluded from survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported in the results
Other bias	Low risk	No indication of other bias

Cullinan 1990

Methods	Randomised phase III trial
Participants	Study was conducted in North America. 187 participants with measurable, metastatic ductal or undifferentiated pancreatic cancer with no prior chemotherapy. 64 received 5-fluorouracil (5FU). 61 received 5FU + cyclophosphamide + methotrexate + vincristine (Mallison regimen). 59 received 5FU + doxorubicin + cisplatin (FAP). Median age for the 5FU, Mallinson and FAP arm was 60, 62 and 62 years respectively.
Interventions	5FU: 500 mg/m^2/day for 5 days every 5 weeks Mallinson: 5FU 270 mg/m^2/day days 1-5 + cyclophosphamide 160 mg/m^2 days 1 + 5 + methotrexate 11 mg/m^2 days 1 + 4 + vincristine 0.7 mg/m^2 days 2 + 5 then maintenance with 5FU 350 mg/m^2 days 1-5 + mitomycin C 3.5 mg/m^2 days 1-5 every 5 weeks FAP: 5FU 300 mg/m^2/day days 1-5 + doxorubicin 40 mg/m^2 day 1 + cisplatin 60 mg/m^2 day 1, every 5 weeks
Outcomes	Overall survival
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details published

Cullinan 1990 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for the primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Survival analysis conducted on all enrolled patients
Selective reporting (reporting bias)	Low risk	Only OS listed specifically as an endpoint in the methods, this is reported on all patients
Other bias	Unclear risk	No indication of other bias

Cunningham 2009

Methods	Randomised phase III trial
Participants	Study was conducted in the UK. 533 participants with locally advanced/metastatic pancreatic ductal adenocarcinoma. 266 received gemcitabine. 267 received gemcitabine + capecitabine. Median age of participants was 62 years.
Interventions	Gemcitabine: 1000 mg/m² 7/8 weeks then 3/4 weeks Gemcitabine + capecitabine: gemcitabine 1000 mg/m² 3/4 weeks + capecitabine 830 mg/m² twice daily orally for 3 weeks then 1 week rest
Outcomes	Overall survival Progression-free survival Overall response rate Toxicity Quality of life Pain
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned to each treatment arm on a 1:1 basis according to a computer-generated variable-size blocked randomization method. Randomization was stratified by performance status (0, 1 versus 2) and extent of disease"

Cunningham 2009 *(Continued)*

Allocation concealment (selection bias)	Low risk	"Patients were randomly assigned to each treatment arm on a 1:1 basis according to a computer-generated variable-size blocked randomization method. Randomization was stratified by performance status (0, 1 versus 2) and extent of disease"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat population reported
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Di Costanzo 2005

Methods	Randomised phase II trial
Participants	Study was conducted in Italy. 94 participants with locally advanced/metastatic pancreatic ductal adenocarcinoma with measurable disease. 48 received gemcitabine. 43 received gemcitabine + 5-fluorouracil (5FU). Median age of participants was 63 years
Interventions	Gemcitabine: 1000 mg/m^2 weekly for 7 weeks then 2 weeks rest, then 3/4 weeks Gemcitabine + 5FU: Gemcitabine as above. 5FU 200 mg/m^2/day for 6 weeks then 2 weeks rest, then 3/4 weeks
Outcomes	Response rate Overall survival Safety Quality of life
Notes	—

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were centrally randomised by the central office of the Italian Oncology Group for Clinical Research (GOIRC) to receive: GEM alone (arm A) or in combination with CI 5-FU (arm B)"

Di Costanzo 2005 *(Continued)*

Allocation concealment (selection bias)	Low risk	"Patients were centrally randomised by the central office of the Italian Oncology Group for Clinical Research (GOIRC) to receive: GEM alone (arm A) or in combination with CI 5-FU (arm B)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk for the primary outcome (response rate)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only patients "evaluable for response" were assessed for the primary endpoint
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Ducreux 2004

Methods	Randomised phase II study
Participants	Study was conducted in France. 63 participants with locally advanced/metastatic pancreatic adenocarcinoma and measurable disease. Were allowed to have had previous 5FU and radiotherapy if more than 3 months prior to randomisation. 17 received oxaliplatin, 31 received 5FU + oxaliplatin and 15 received 5FU alone. The mean age was 57 years.
Interventions	Oxaliplatin: 130 mg/m^2 every 3 weeks 5FU/ oxaliplatin: 5FU 1000 mg/m^2/day, days 1-4 and oxaliplatin as above 5FU alone given as above
Outcomes	Response rate
Notes	The oxaliplatin alone arm was not included in the meta-analysis.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Eligible patients in this open-label study were stratified by center and disease stage (locally advanced versus metastatic) and centralized block randomization was used to assign patients to one of three arms"
Allocation concealment (selection bias)	Low risk	"Eligible patients in this open-label study were stratified by center and disease stage (locally advanced versus metastatic) and centralized block randomization was used to assign patients to one of three arms"
Blinding of participants and personnel (performance bias)	High risk	Non-blinded study

Ducreux 2004 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	External radiologist used to assess tumour response
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 56 participants were evaluable for response, 4 withdrew prior to first assessment and 2 participants had baseline assessments which were old or missing
Selective reporting (reporting bias)	Unclear risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Frey 1981

Methods	Randomised study
Participants	Study was conducted in North America. 152 male participants with unresectable cancer of the pancreas. 65 received 5-fluorouracil (5FU) and CCNU; 87 received best supportive care. The majority of participants were between the age of 50 and 59 years.
Interventions	5FU 9 mg/kg days 1-5 + CCNU 70 mg/m^2 day 1, every 6 weeks
Outcomes	Overall survival Toxicity
Notes	—

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details regarding the method of randomisation provided
Allocation concealment (selection bias)	Low risk	"Assignment of patients to treated or control groups in this multi-institutional trial was made by means of sealed, sequentially numbered envelopes distributed by a statistician from the Follow-up Agency, National Academy of Sciences-National Research Council."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants included in survival analysis

Frey 1981 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indications of other bias

Gansauge 2002

Methods	Randomised phase II trial
Participants	Study was conducted in Germany. 90 participants with unresectable pancreatic adenocarcinoma. 30 received gemcitabine. 30 received Ukrain (NSC-31570). 30 received Ukrain + gemcitabine. The mean age for the gemcitabine, Ukrain and Gemcitabine + Ukrain groups were 63.8, 60.6 and 58.2 respectively.
Interventions	Gemcitabine: 1000 mg/m² 7/8 weeks then 34 weeks Ukrain: 20 mg weekly for 7 weeks, 1 week rest then 3/4 weeks up to 12 cycles Gemcitabine + Ukrain: as above
Outcomes	Overall survival
Notes	This was a multi-armed study. Event rates were not available for the 3 arms. Only the gemcitabine and gemcitabine + Ukrain arms analysed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient details published
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Glimelius 1996

Methods	Randomised study
Participants	Study was conducted in Sweden. 90 participants with non-curable pancreatic or biliary tract cancer. 53 had pancreatic cancer. 29 received 5FU/LV +/- etoposide. 24 received best supportive care. Median age for the chemotherapy and best supportive care arms were 65 and 64 respectively.
Interventions	If participant was > 60 years, then 5FU/LV: 5FU 500 mg/m² + LV 60 mg/m² on days 1 + 2 every 14 days If participant was < 60 years old, then 5FU/LV: 5FU 500 mg/m² + LV 60 mg/m² + etoposide 120 mg/m²
Outcomes	Overall survival Quality of life Objective responses Toxicity
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention to treat analysis reported
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Heinemann 2006

Methods	Randomised phase III trial
Participants	Study was conducted in Germany. 195 participants with locally advanced/metastatic pancreatic adenocarcinoma with measurable disease. Previous radiotherapy was allowed if not on the target lesion. 97 received gemcitabine. 98 received gemcitabine + cisplatin. The median age of the gemcitabine + cisplatin and gemcitabine alone groups was 64 and 66 years respectively.

Heinemann 2006 *(Continued)*

Interventions	Gemcitabine: 1000 mg/m² day 1, 8, 15 every 4 weeks Gemcitabine + cisplatin: gemcitabine as above. Cisplatin 50 mg/m² days 1, 8, 15 every 4 weeks
Outcomes	Overall survival Progression-free survival Response rate Safety Quality of life
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Central random assignment was performed before the start of treatment, and patients were assigned to one of the treatment arms."
Allocation concealment (selection bias)	Low risk	"Central random assignment was performed before the start of treatment, and patients were assigned to one of the treatment arms."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The primary outcome measure was OS, which was determined for all randomly assigned patients from the date of random assignment to the date of death or last contact."
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Herrmann 2007

Methods	Randomised phase III trial
Participants	Study conducted in eight European countries. 319 participants with inoperable/metastatic pancreatic ductal adenocarcinoma. 159 received gemcitabine. 160 received gemcitabine + capecitabine. The median age was not stated.
Interventions	Gemcitabine: 1000 mg/m² 7/8 weeks then 3/4 weeks Capecitabine: 650 mg/m² twice daily orally, days 1-14 every 3 weeks

Herrmann 2007 *(Continued)*

Outcomes	Overall survival Progression-free survival Overall response rate Safety Quality of life
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Likely to be low risk but actual method of randomisation/allocation not stated in publication
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for the primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Intent-to-treat analysis was applied to the analysis of all end points"
Selective reporting (reporting bias)	Low risk	No indication of reporting bias
Other bias	Low risk	No indication of other bias

Hirao 2011

Methods	Randomised phase II trial
Participants	Study was conducted in Japan. 90 participants with unresectable, metastatic pancreatic ductal adenocarcinoma with no prior therapy. 45 received gemcitabine on a 3 week schedule. 45 received gemcitabine on a 4-week schedule. The median age in the 4 week and 3 week schedule was 67 years and 66 years, respectively.
Interventions	3 weeks: gemcitabine 1000 mg/m^2 days 1 and 8 4 weeks: gemcitabine 1000 mg/m^2 days 1, 8 and 15
Outcomes	Compliance rate Overall survival

Hirao 2011 *(Continued)*

	Progression-free survival
	Toxicity
	Response rate
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed centrally, and the random-allocation sequence had been generated previously by a statistician using a computer-generated random code"
Allocation concealment (selection bias)	Low risk	"Randomization was performed centrally, and the random-allocation sequence had been generated previously by a statistician using a computer-generated random code"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk for primary endpoint (compliance rate)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat population included in analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of reporting bias

Huguier 2001

Methods	Randomised study
Participants	Study was conducted in France. 45 participants with unresectable pancreatic ductal adenocarcinoma. 22 received 5-fluorouracil (5FU) + leucovorin (LV) + cisplatin; 23 received best supportive care. The median age of participants was 63.4 years.
Interventions	5FU: 375 mg/m^2/day days 1-5
	LV 200 mg/m^2/day days 1-5
	Cisplatin 15 mg/m^2/day days 1-5
Outcomes	Overall survival
	Side effects

Huguier 2001 *(Continued)*

Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Assignment of patients to chemotherapy or control group used a centralised random permuted block technique"
Allocation concealment (selection bias)	Low risk	"Assignment of patients to chemotherapy or control group used a centralised random permuted block technique"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indications of other bias

Kelsen 1991

Methods	Phase III randomised study
Participants	Study was conducted in North America. 82 participants with advanced pancreatic adenocarcinoma and no prior therapy. 42 received streptozocin, mitomycin C and 5FU (SMF). 50 received cisplatin, cytosine arabinoside and caffeine (CAC). The median age of participants was 59 years.
Interventions	SMF: streptozocin 1 g/m^2 days 1, 8, 29 and 36 + mitomycin C 10 mg/m^2 day 1 + 5FU 600 mg/m^2 days 1, 8 and 36 every 8 weeks CAC: cisplatin 100 mg/m^2 day 1 + cytosine arabinoside 2 g/m^2 two doses day 1 + caffeine 400 mg/m^2 subcutaneous 2 doses day 1
Outcomes	Response
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details published

Kelsen 1991 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk for primary outcome (response rate)
Incomplete outcome data (attrition bias) All outcomes	High risk	Not all participants were assessed for the primary outcome measure
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Kovach 1974

Methods	Randomised study
Participants	Study was conducted in North America. 82 with unresectable pancreatic adenocarcinoma and measurable disease. 31 received 5FU, 21 received 1,3-bis-(2-chloroethyl)-1-nitrosurea (BCNU)and 30 received 5FU + BCNU
Interventions	5FU: 13.5 mg/kg/day for 5 days every 5 weeks BCNU: 50 mg/m^2/day for 5 days every 8 weeks 5FU + carmustine: 5FU 10 mg/kg/day for 5 days and BCNU 40 mg/m^2/day for 5 days every 8 weeks
Outcomes	Not stated
Notes	This is a multi-armed study. Event rates for each arm were not available. Only the 5FU and 5FU + carmustine arms were analysed.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study

Kovach 1978 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Primary outcome measure unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if all participants were included in survival analysis
Selective reporting (reporting bias)	Low risk	No indication of reporting bias
Other bias	Low risk	No indication of other bias

Kulke 2009

Methods	Randomised phase II trial
Participants	Study was conducted in North America. 245 participants with metastatic pancreatic adenocarcinoma. Adjuvant 5-fluorouracil was permitted with completed > 2 weeks prior. 62 received gemcitabine + cisplatin. 58 received gemcitabine. 65 received gemcitabine + docetaxel. 60 received gemcitabine + irinotecan. Median age of participants was 60.5 years.
Interventions	Gemcitabine + cisplatin: gemcitabine 1000 mg/m^2 weekly × 3, cisplatin 50 mg/m^2 days 1 and 15 every 4 weeks. Gemcitabine: 1500 mg/m^2 at 10 mg/m^2/min, weekly × 3, every 4 weeks Gemcitabine + docetaxel: gemcitabine 1000 mg/m^2 weekly × 3, docetaxel 40 mg/m^2 days 1 + 8, every 4 weeks Gemcitbine + irinotecan: gemcitabine 1000 mg/m^2 days 1 and 8, irinotecan 100 mg/m^2 days 1 and 8 every 3 weeks
Outcomes	Overall survival Response rate Time to progression Toxicity
Notes	—

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published. "Patients were randomly assigned to receive one of the following four regimens: gemcitabine/cisplatin (arm A), fixed dose rate gemcitabine (arm B), gemcitabine/docetaxel (arm C), or gemcitabine/irinotecan (arm D)"
Allocation concealment (selection bias)	Unclear risk	Insufficient details published. "Patients were randomly assigned to receive one of the following four regimens: gemcitabine/cisplatin (arm A), fixed dose rate gemcitabine (arm B), gemcitabine/docetaxel (arm C), or gemcitabine/irinotecan (arm D)"

Kulke 2009 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the outcome analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Lee 2017

Methods	Phase III trial
Participants	Study was conducted in Korea. 214 treatment naive participants with locally advanced or metastatic pancreatic adenocarcinoma with ECOG 0-2. 108 participants received gemcitabine + capecitabine and 106 participants received gemcitabine alone. Median age was 54 years years.
Interventions	Gemcitabine 1000 mg/m^2 3/4 weeks Capecitabine 1600 mg/m^2 daily for 3/4 weeks
Outcomes	Overall survival Progression-free survival Overall response rate Disease control rate Toxicity
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"We randomly assigned eligible patients to each treatment arm on a 1:1 basis according to a computer-generated variable-size blocked randomization method."
Allocation concealment (selection bias)	Low risk	"We randomly assigned eligible patients to each treatment arm on a 1:1 basis according to a computer-generated variable-size blocked randomization method."s
Blinding of participants and personnel (performance bias)	High risk	Non-blinded study

Lee 2017 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	None found

Levi 2004

Methods	Randomised study
Participants	Study was conducted in Europe. 107 participants with advanced pancreatic cancer. Factorial design randomised participants to either 5FU given at a constant rate infusion or chronomodulated infusion, with or without cisplatin. Median age of participants was 63 years.
Interventions	5FU: 5 g/m^2 (cycle 1) or 6 g/m^2 (cycle 2) or 6.5 g/m^2 (cycle 3) either at a constant rate infusion or chronomodulated (given between 10 pm and 10 am) Cisplatin: 100 mg/m^2 once per cycle
Outcomes	OS
Notes	Abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient details published
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details published

Levi 2004 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient details published
Other bias	Unclear risk	Insufficient details published

Li 2004

Methods	Randomised study
Participants	Study was conducted in China. 46 participants with metastatic pancreatic adenocarcinoma. 25 received gemcitabine. 21 received gemcitabine + cisplatin
Interventions	Gemcitabine: 1000 mg/m² IV 3/4 weeks Cisplatin: 25 mg/m²/week, 3/4 weeks
Outcomes	Overall survival
Notes	Abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient details published
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details published
Selective reporting (reporting bias)	Unclear risk	Insufficient details published
Other bias	Unclear risk	Insufficient details published

Lohr 2012

Methods	Randomised phase II trial

Lohr 2013 *(Continued)*

Participants	Study was conducted in Europe. 200 participants with locally advanced/unresectable or metastatic pancreatic adenocarcinoma. 50 received gemcitabine. 50 received liposomal-paclitaxel (ET) 11 mg/m^2. 50 received ET 22 mg/m^2. 50 received ET 44 mg/m^2. The median age for the gemcitabine alone, ET 11mg/m^2, ET 22mg/m^2 and ET 44mg/m^2 group was 59.5, 63, 61 and 62.5 years, respectively.
Interventions	Gemcitabine: 1000 mg/m^2 weekly × 7 ET: Dose given twice weekly × 14
Outcomes	Overall survival Progression-free survival Response rate Quality of life Adverse events
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were centrally randomized"
Allocation concealment (selection bias)	Low risk	"Patients were centrally randomized"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	PFS for intention-to-treat population not reported - only the "modified intention to treat" population
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Louvet 2005

Methods	Randomised phase III trial
Participants	Study was conducted in France. 326 participants with unresectable/metastatic pancreatic ductal adenocarcinoma with measurable disease. 156 received gemcitabine. 157 received gemcitabine + oxali-

Louvet 2005 *(Continued)*

	platin. The median age was 60.1 years and 61.3 years in the gemcitabine and gemcitabine + oxaliplatin groups respectively.
Interventions	Gemcitabine 1000 mg/m^2 7/8 weeks then 3/4 weeks Gemcitabine + oxaliplatin: gemcitabine 1000 mg/m^2 day 1 + oxaliplatin 100 mg/m^2 day 2, every 2 weeks
Outcomes	Overall survival Clinical benefit Progression-free survival Safety
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed centrally, and the minimization method was used to balance treatment allocation according to center, stage of disease (locally advanced v metastatic), and PS (0 or 1 v 2)."
Allocation concealment (selection bias)	Low risk	"Randomization was performed centrally, and the minimization method was used to balance treatment allocation according to center, stage of disease (locally advanced v metastatic), and PS (0 or 1 v 2)."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 'per protocol' participants analysed
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Lutz 2005

Methods	Randomised phase II trial
Participants	Study was conducted in Europe. 96 participants with metastatic or locally advanced pancreatic ductal adenocarcinoma with no previous treatment. 49 received gemcitabine + docetaxel. 47 received cisplatin + docetaxel. The median age of participants was 58 years and 59 years in the gemcitabine + docetaxel and cisplatin and docetaxel groups respectively.

Lutz 2005 *(Continued)*

Interventions	Gemcitabine + docetaxel: gemcitabine 800 mg/m² days 1 and 8 + docetaxel 85 mg/m² day 8 every 3 weeks. Cisplatin + docetaxel: cisplatin 75 mg/m² day 1 every 3 weeks
Outcomes	Tumour response Rates of febrile neutropenia Duration of response Progression-free survival Overall survival
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were centrally randomly assigned at the EORTC Data Center, Brussels, Belgium, and stratified using the minimization technique according to institution, performance status (0 v 1), and extent of disease (metastatic v locoregionally advanced)"
Allocation concealment (selection bias)	Low risk	"Patients were centrally randomly assigned at the EORTC Data Center, Brussels, Belgium, and stratified using the minimization technique according to institution, performance status (0 v 1), and extent of disease (metastatic v locoregionally advanced)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk for primary endpoint (tumour response)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat population included in analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Maisey 2002

Methods	Randomised phase III trial
Participants	Study was conducted in the UK. 209 participants with locally advanced/metastatic pancreatic ductal adenocarcinoma. 107 received 5-fluorouracil (5FU). 102 received 5FU + mitomycin C (MMC). The median age of participants was 62 years and 61 years in the 5FU and 5FU + MMC groups respectively.

Maisey 2002 *(Continued)*

Interventions	5FU 300 mg/m²/day via protracted venous infusion (PVI) for 12 weeks. If no progression, another 12 weeks 5FU + MMC: 5FU 300 mg/m²/day + MMC 10 mg/m² every 6 weeks × 4 cycles
Outcomes	Response rate Survival Toxicity QoL
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...patients were randomly assigned to treatment with PVI 5-FU or PVI 5-FU/MMC on a 1:1 basis according to a computer generated randomization code. The patients were randomized centrally in blocks of six and stratified by center"
Allocation concealment (selection bias)	Low risk	"...patients were randomly assigned to treatment with PVI 5-FU or PVI 5-FU/MMC on a 1:1 basis according to a computer generated randomization code. The patients were randomized centrally in blocks of six and stratified by center"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk for primary endpoint (response rate)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Meng 2012

Methods	Randomised, placebo controlled, phase II trial
Participants	Study was conducted in China. 76 participants with unresectable pancreatic adenocarcinoma with measurable disease. 37 received gemcitabine + placebo. 39 received gemcitabine + huachansu. The median age of participants was 60.9 years.
Interventions	Gemcitabine + placebo: 1000 mg/m² 3/4 weeks + saline

Meng 2012 *(Continued)*

	Gemcitabine + huachansu: gemcitabine as above, huachansu 20 mL/m² 5 days per week, 3 weeks on, 1 week off
Outcomes	4 month progression-free survival Overall survival Overall response rate Time to progression Toxicity
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details published - "Patients were randomised using a Bayesian algorithm"
Allocation concealment (selection bias)	Unclear risk	Insufficient details published - "Patients were randomised using a Bayesian algorithm"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk for primary endpoint (PFS at 4 months)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Moertel 1977

Methods	Randomised trial
Participants	Study was conducted in North America. 88 participants with unresectable pancreatic ductal adenocarcinoma with measurable disease. 40 received streptozocin + 5-fluorouracil (5FU). 48 received streptozocin and cyclophosphamide. Most participants were aged between 50 to 59 years old.
Interventions	Streptozocin 500 mg/m² days 1-5 5FU 400 mg/m² days 1-5 every 6 weeks Cyclophosphamide 1000 mg/m² days 1 and 21 every 6 weeks

Moertel 1977 *(Continued)*

Outcomes	Not stated
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Participants who died early or who were unable to continue their assigned treatment were declared to have progressive disease
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 74 participants included in survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Moertel 1979

Methods	Randomised trial
Participants	Study conducted in North American. 176 participants with metastatic pancreatic ductal adenocarcinoma. 89 received 5-fluorouracil (5FU). 87 received 5FU + streptozocin. Details on the age of participants not stated.
Interventions	5FU 450 mg/m^2 days 1-5 every 5 weeks 5FU + streptozocin: 5FU 400 mg/m^2 days 1-5 + streptozocin 400 mg/m^2 days 1-5 every 5 weeks Participants were also randomised +/- spironolactone 50 mg 3 times per day
Outcomes	Survival
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement

Moertel 1979 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details published
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis
Selective reporting (reporting bias)	High risk	Toxicity data scarcely reported
Other bias	Low risk	No indication of other bias

Oettle 2005

Methods	Randomised phase III trial
Participants	Study was conducted in Germany. 565 participants with locally advanced/metastatic pancreatic adenocarcinoma with measurable disease. Radiotherapy permitted if completed > 4 weeks prior. 282 received gemcitabine. 283 received gemcitabine + pemetrexed. The median age of participants was 63 years.
Interventions	Gemcitabine (G): 1000 mg/m^2 3/4 weeks Gemcitabine + pemetrexed (PG): gemcitabine 1250 mg/m^2 days 1 and 8, pemetrexed 500 mg/m^2 day 8, every 21 days
Outcomes	Overall survival Progression-free survival Time to treatment failure Response rate Quality of life
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Eligible patients were randomly assigned using a centralized, automated randomization procedure to either the PG arm or the G arm"

Oettle 2005 *(Continued)*

Allocation concealment (selection bias)	Low risk	"Eligible patients were randomly assigned using a centralized, automated randomization procedure to either the PG arm or the G arm"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Ohkawa 2004

Methods	Randomised trial
Participants	Study was conducted in Japan. 19 participants with advanced pancreatic ductal adenocarcinoma with no previous treatment. 9 received gemcitabine. 10 received gemcitabine + tegafur-uracil (UFT). The median age of participants for the gemcitabine alone and gemcitabine + UFT groups was 58.4 years and 60.5 years respectively.
Interventions	Gemcitabine: 1000 mg/m² 3/4 weeks. UFT 300 mg/day continuous
Outcomes	Response rate Survival time Time to progression
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study

Ohkawa 2004 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk for primary endpoint (response rate)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details published
Selective reporting (reporting bias)	Unclear risk	Insufficient details published
Other bias	Low risk	No indication of other bias

Ozaka 2012

Methods	Randomised phase II trial
Participants	Study was conducted in Japan. 112 participants with locally advanced/metastatic pancreatic ductal adenocarcinoma with measurable disease. 59 received gemcitabine. 53 received gemcitabine + S1. The median age of participants was 64 years.
Interventions	Gemcitabine: 1000 mg/m^2 3/4 weeks Gemcitabine + S1: gemcitabine 1000 mg/m^2 day 1 and 8, S1 80 mg/m^2 twice daily orally, days 1-14 every 3 weeks
Outcomes	Response rate Toxicity Clinical benefit rate Progression-free survival Overall survival
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random assignment was performed centrally by a web-based assistant system (Xexible license assisted data server, JACCRO, Tokyo), using a computer-driven minimization procedure"
Allocation concealment (selection bias)	Low risk	"Random assignment was performed centrally by a web-based assistant system (Xexible license assisted data server, JACCRO, Tokyo), using a computer-driven minimization procedure"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias)	High risk	High risk for primary endpoint (response rate)

Ozaka 2012 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	Intention-to-treat population not reported for PFS
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Petrioli 2015

Methods	Randomised phase II study
Participants	Study was conducted in Italy. 67 participants with metastatic, histologically proven pancreatic cancer and ECOG ≤ 2 and no prior chemotherapy. 33 given gemcitabine alone and 34 given gemcitabine + oxaliplatin + capecitabine (GEMOXEL). The median age of participants in the GEMOXEL and gemcitabine groups was 69 years and 67 years, respectively.
Interventions	Gemcitabine: 1000 mg/m² for 7/8 weeks then days 1, 8 and 15 every 28 days GEMOXEL: gemcitabine 1000 mg/m² days 1, 8, 15 and 22. Oxaliplatin 100 mg/m² day 2, capectiabine 1500 mg/m²/day in 2 divided doses, days 1-14 every 21 days
Outcomes	Disease control rate in per protocol population Safety Progression-free survival Quality of life Overall survival
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk for primary endpoint (disease control rate)

Petrioli 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Poplin 2009

Methods	Randomised phase III trial
Participants	Study was conducted in North America. 824 participants with locally advanced/metastatic pancreatic ductal adenocarcinoma with measurable disease. Were allowed to have had adjuvant radiotherapy if completed more than 4 weeks prior. 275 received standard gemcitabine. 277 received fixed dose rate gemcitabine (FDR). 272 received gemcitabine + oxaliplatin. The median age was 64 years, 61 years and 63 years for the gemcitabine, FDR and gemcitabine + oxaliplatin groups, respectively.
Interventions	Gemcitabine: 1000 mg/m^2 over 30 min 7/8 weeks then 3/4 weeks FDR: gemcitabine 1500 mg/m^2 given over 150 min infusion day 1, 8, 15 every 4 weeks Gemcitabine + oxaliplatin: gemcitabine 1000 mg/m^2 over 100 min day 1 + oxaliplatin 100 mg/m^2 day 2, every 2 weeks
Outcomes	Overall survival Response rate Progression-free survival Symptoms
Notes	Gemcitabine + oxaliplatin arm has not been analysed as the gemcitabine dose schedule is not standard.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned to treatment using a dynamic balancing algorithm that stratified for performance status, 0 to 1 and versus 2, and for locally advanced versus metastatic disease"
Allocation concealment (selection bias)	Unclear risk	"Patients were randomly assigned to treatment using a dynamic balancing algorithm that stratified for performance status, 0 to 1 and versus 2, and for locally advanced versus metastatic disease"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)

Poplin 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat population included in survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Poplin 2013

Methods	Randomised, multicentre, phase II trial
Participants	This was an international study. 367 participants with metastatic pancreatic ductal adenocarcinoma. 185 received gemcitabine. 182 received lipid-drug conjugate of gemcitabine (CO-101). The median age of participants in the low hENT1 group was 62 years, and was 61 years in the high hENT group.
Interventions	Gemcitabine 100 mg/m² 7/8 weeks then 3/4 weeks CO-101 120 mg/m² 3/4 weeks
Outcomes	Overall survival in low hENT1 participants Overall survival Progression-free survival Response rate
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Treatment on the Low hENT1 in Adenocarcinoma of the Pancreas (LEAP) study was randomly assigned (1:1 to gemcitabine or CO-101; Fig 1), and treatment allocation was stratified for Eastern Cooperative Oncology Group (ECOG) performances status (PS; 0 v 1) and geographic location (North America v South America v Australia v Eastern Europe v Western Europe)."
Allocation concealment (selection bias)	Low risk	"Treatment on the Low hENT1 in Adenocarcinoma of the Pancreas (LEAP) study was randomly assigned (1:1 to gemcitabine or CO-101; Fig 1), and treatment allocation was stratified for Eastern Cooperative Oncology Group (ECOG) performances status (PS; 0 v 1) and geographic location (North America v South America v Australia v Eastern Europe v Western Europe)."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)

Poplin 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the analyses
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indications of other bias

Reni 2005

Methods	Randomised phase III trial
Participants	Study was conducted in Italy. 99 participants with locally advanced/metastatic pancreatic adenocarcinoma with measurable disease. 47 received gemcitabine. 52 received cisplatin, epirubicin, gemcitabine and 5-fluorouracil (5FU) (PEGF). The median age of participants was 62 years and 59 years in the PEGF and gemcitabine groups respectively.
Interventions	Gemcitabine: 1000 mg/m² 7/8 weeks then 3/4 weeks PEGF: cisplatin 40 mg/m² day 1, epirubicin 40 mg/m² day 1, gemcitabine 600 mg/m² days 1 and 8, 5FU 200 mg/m²/day every 28 days
Outcomes	Progression-free survival Overall survival Response rate Safety Quality of life
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisationwas done by a secretary at a central location by a phone call. The random-allocation sequence had been generated previously by a statistician (LG) by use of a computer-generated random code."
Allocation concealment (selection bias)	Low risk	"Randomisationwas done by a secretary at a central location by a phone call. The random-allocation sequence had been generated previously by a statistician (LG) by use of a computer-generated random code."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	PFS was primary outcome, but radiologist evaluating progression was blinded.

Reni 2005 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Reni 2012

Methods	Randomised phase II trial
Participants	Study was conducted in Italy. 105 participants with unresectable/metastatic pancreatic ductal adenocarcinoma. 53 participants had capecitabine, cisplatin, gemcitabine and docetaxel (PDXG). 52 participants had capecitabine, epirubicin, cisplatin, gemcitabine (PEXG). The median age of participants was 61 years and 59 years in the PDXG and PEXG arms, respectively.
Interventions	PDXG: capecitabine 1250 mg/m^2 days 1-28, cisplatin 30 mg/m^2 days 1 and 15, gemcitabine 800 mg/m^2 days 1 and 15, docetaxel 25 mg/m^2 days 1 and 15 every 4 weeks PEXG: capecitabine as above, cisplatin as above, gemcitabine as above, epirubicin 30 mg/m^2 days 1 and 15 every 4 weeks
Outcomes	Progression-free survival at 6 months Overall survival Toxicity Response rate
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients fulfilling all inclusion criteria were registered by the attending physician at an independent Contract Research Organization (CRO) that performed randomization on a 1:1 basis to either arm A or B. Patients were stratified according to stage of disease (III vs. IV)"
Allocation concealment (selection bias)	Unclear risk	"Patients fulfilling all inclusion criteria were registered by the attending physician at an independent Contract Research Organization (CRO) that performed randomization on a 1:1 basis to either arm A or B. Patients were stratified according to stage of disease (III vs. IV)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias)	Low risk	PFS primary outcome but radiologists blinded

Reni 2012 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat population included in survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Riess 2005

Methods	Randomised phase III trial
Participants	473 participants with locally advanced/metastatic pancreatic ductal adenocarcinoma with no prior therapy. 238 received gemcitabine. 235 received gemcitabine + 5-fluorouracil (5FU) + folinic acid (FA)
Interventions	Gemcitabine: 1000 mg/m^2 7/8 weeks, then 3/4 weeks Gemcitabine + 5FU + FA: gemcitabine 1000 mg/m^2 + 5FU 750 mg/m^2 as a 24 hour infusion + FA 200 mg/m^2 days 1, 8, 15 every 6 weeks
Outcomes	Overall survival Time to progression Toxicity
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details published
Selective reporting (reporting bias)	Unclear risk	Insufficient details published

Riess 2005 *(Continued)*

Other bias	Low risk	No indication of other bias

Rocha Lima 2004

Methods	Randomised phase III trial
Participants	Study was conducted in North America. 360 participants with locally advanced/metastatic pancreatic adenocarcinoma with measurable disease. Adjuvant radiotherapy and 5-fluorouracil (5FU) were permitted. 180 received gemcitabine. 180 received gemcitabine + irinotecan. The median age of participants was 63.2 years and 60.2 years in the gemcitabine + irinotecan and the gemcitabine alone group, respectively.
Interventions	Gemcitabine: 1000 mg/m² 7/8 weeks then 3/4 weeks Gemcitabine + irinotecan: gemcitabine 1000 mg/m² and irinotecan 100 mg/m² days 1 and 8, every 21 days
Outcomes	Overall survival Quality of life
Notes	—

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were centrally randomly assigned and stratified by ECOG performance status (0, 1, or 2), extent of disease (locally advanced or metastatic), and previous radiotherapy for pancreatic cancer (yes or no)."
Allocation concealment (selection bias)	Low risk	"Patients were centrally randomly assigned and stratified by ECOG performance status (0, 1, or 2), extent of disease (locally advanced or metastatic), and previous radiotherapy for pancreatic cancer (yes or no)."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Scheithauer 2003

Methods	Randomised phase II trial
Participants	Study was conducted in Austria. 83 participants with metastatic pancreatic ductal adenocarcinoma. Adjuvant 5-fluorouracil (5FU) and radiotherapy (RT) was permitted if completed > 6 months prior to randomisation. 42 received gemcitabine. 41 received gemcitabine + capecitabine. The median age of participants was 66 years and 64 years in the gemcitabine alone and the gemcitabine + capecitabine groups respectively.
Interventions	Gemcitabine: 2200 mg/m^2 day 1, every 2 weeks Gemcitabine + capecitabine: gemcitabine as above, capecitabine 2500 mg/m^2/day orally days 1-7 every 2 weeks
Outcomes	Progression-free survival Overall survival Response rate
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details published. "Patients were then assigned to one treatment regimen by the central office located at the University in Vienna"
Allocation concealment (selection bias)	Unclear risk	Insufficient details published. "Patients were then assigned to one treatment regimen by the central office located at the University in Vienna"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	PFS primary endpoint but independently reviewed
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Singhal 2018

Methods	Phase III randomised trial
Participants	310 participants with metastatic PC. Half received FOLFIRINOX and half received gemcitabine. Details on age of participants not published.

Singhal 2014 *(Continued)*

Interventions	FOLFIRINOX: Oxaliplatin 85 mg/m² + irinotecan 180 mg/m² + LV 400 mg/m² + 5FU 400 mg/m² bolus + 5FU 2400 mg/m² as 46 hours continuous infusion every 2 weeks Gemcitabine: 1000 mg/m² days 1, 8, 15 every 28 days
Outcomes	Overall survival Progression-free survival Response rate Quality of life Adverse events
Notes	Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details published
Selective reporting (reporting bias)	Unclear risk	Insufficient details published
Other bias	Unclear risk	Insufficient details published

Smith 2003

Methods	Randomised phase II/III study
Participants	Study was conducted in the UK. 55 participants with locally advanced or metastatic pancreatic adenocarcinoma with no prior treatment. 30 received ZD9331, 25 received gemcitabine alone. The median age of participants was 59.8 years and 60.8 years in the ZD9331 and gemcitabine arms respectively.
Interventions	ZD9331: 130 mg/m² days 1, 8 every 21 days Gemcitabine: 1000 mg/m² weekly, 7/8 weeks, then 3/4 weeks

Smith 2003 *(Continued)*

Outcomes	Tumour response Clinical benefit response PFS OS
Notes	Study supported by Astra Zeneca Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details published - "Patients were then randomised to receive either ZD9331 or gemcitabine and were stratified by centre..."
Allocation concealment (selection bias)	Unclear risk	Insufficient details published - "Patients were then randomised to receive either ZD9331 or gemcitabine and were stratified by centre..."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat population included in survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Stathopoulos 2006

Methods	Randomised phase III trial
Participants	Study was conducted in Greece. 130 participants with locally advanced/metastatic pancreatic adenocarcinoma and no prior therapy. 70 received gemcitabine. 60 received gemcitabine + irinotecan. The median age of participants was 64 years.
Interventions	Gemcitabine: 900 mg/m^2, 3/4 weeks Gemcitabine + irinotecan: gemcitabine 900 mg/m^2 days 1 and 8, irinotecan 300 mg/m^2 day 8, every 3 weeks
Outcomes	Overall survival Response rate Progression-free survival

Stathopoulos 2006 *(Continued)*

	Toxicity
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were centrally randomised by computer at a one-to-one ratio to receive either monotherapy (arm G) with gemcitabine"
Allocation concealment (selection bias)	Low risk	"Patients were centrally randomised by computer at a one-to-one ratio to receive either monotherapy (arm G) with gemcitabine"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed for primary outcome
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Takada 1998

Methods	Randomised study
Participants	Study was conducted in Japan. 83 participants with unresectable pancreatic adenocarcinoma or biliary tract carcinoma, aged < 75 years. Of the participants with pancreatic cancer, 28 received 5-fluorouracil (5FU), doxorubicin and mitomycin C (MMC), and 24 received palliative surgery. The median age in the chemotherapy arm was 62.8 years and was 61.5 years in the palliative surgery arm.
Interventions	5FU 200 mg/m^2 Doxorubicin 15 mg/m^2 MMC 5 mg/m^2 given weekly × 4, then 1 week break. 2 cycles given
Outcomes	Overall survival Response rates Performance status Adverse events

Takada 1998 *(Continued)*

Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Patients were assigned at random to the therapy group or the control group using the envelope method in each facility..."
Allocation concealment (selection bias)	Low risk	"Registration procedures were conducted by telephoning the Study Group Office when the envelope was opened"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants included in survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indications of other bias

Tempero 2003

Methods	Randomised phase II trial
Participants	Study was conducted in North America. 92 participants with locally advanced/metastatic pancreatic ductal adenocarcinoma. 49 received dose-intense gemcitabine. 43 received fixed dose rate infusion gemcitabine (FDR). The median age of participants was 62 years.
Interventions	Dose-intense gemcitabine: 2200 mg/m^2 IV over 30 min given days 1, 8, 15 every 28 days FDR: 1500 mg/m^2 given at 10 mg/m^2/min given days 1, 8, 15 every 28 days.
Outcomes	Time to treatment failure Time to progression Median survival Response rate Toxicity
Notes	—

Risk of bias

Tempero 2003 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details published - "Patients were randomly assigned to the following two treatment arms"
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed for the primary endpoint
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indications of other bias

Topham 1991

Methods	Randomised trial
Participants	Study was conducted in the UK. 62 participants with locally advanced or metastatic pancreatic adenocarcinoma. 32 were given epirubicin alone, 30 were given 5FU + epirubicin + mitomycin C (FEM). No details on the median ages of participants was published.
Interventions	Epirubicin: 100 mg IV every 4 weeks FEM: 5FU 1g IV days 1 and 28, epirubicin 600 mg IV days 1 + 8, mitomycin C 10 mg day 1 every 8 weeks
Outcomes	Not stated
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias)	High risk	Non-blinded study

Topham 1991 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Insufficient details published. Unclear what the primary endpoint was.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat population included in survival analysis
Selective reporting (reporting bias)	Unclear risk	Endpoints not clearly stated in the methods.
Other bias	Low risk	No indication of other bias

Ueno 2013

Methods	Randomised phase III trial
Participants	Study was conducted in Japan. 832 participants with locally advanced/metastatic pancreatic ductal adenocarcinoma, ECOG 0-1. 277 received gemcitabine. 280 received S1. 275 received gemcitabine + S1. Half the patients were under 65 years old and half were 65 years old or more.
Interventions	Gemcitabine: 1000 mg/m² 3/4 weeks S1: orally, twice daily. Body surface area (BSA) < 1.25 m², 80 mg/day; BSA 1.25 m² to 1.5 m², 100 mg/day; BSA > 1.5 m², 120 mg/day. Days 1-28, every 42 days. Gemcitabine + S1: gemcitabine 1000 mg/m² days 1 and 8, S1 (dosing as above), days 1-14 every 21 days
Outcomes	Overall survival Progression-free survival Overall response rate Safety Quality of life
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random assignment was performed centrally with stratification by extent of disease (locally advanced disease v metastatic disease) and institution using the minimization method"
Allocation concealment (selection bias)	Low risk	"Random assignment was performed centrally with stratification by extent of disease (locally advanced disease v metastatic disease) and institution using the minimization method"
Blinding of participants and personnel (performance bias)	High risk	Non-blinded study

Ueno 2013 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Ueno 2013 - EPA study

Methods	Randomised phase II trial
Participants	Study was conducted in Japan. 66 participants with advanced pancreatic adenocarcinoma. 23 received gemcitabine. 43 received gemcitabine + EPA enriched oral supplement. Median ages of participants were not published
Interventions	Gemcitabine: 1000 mg/m² 3/4 weeks Gemcitabine + EPA: gemcitabine as above. EPA 1 tablet orally, daily continuous
Outcomes	1-year survival
Notes	Abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details published
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details published
Selective reporting (reporting bias)	Unclear risk	Insufficient details published

Ueno 2013 – EPA study *(Continued)*

Other bias	Low risk	No indication of other bias

Viret 2004

Methods	Randomised phase II trial
Participants	Study was conducted in France. 83 participants with stage III/IV pancreatic ductal adenocarcinoma. 41 received gemcitabine. 42 received gemcitabine + cisplatin. Median age was 63 years and 61.5 years in the gemcitabine alone and the gemcitabine + cisplatin arms respectively.
Interventions	Gemcitabine 1000 mg/m² 7/8 weeks then 3/4 weeks Gemcitabine + cisplatin: gemcitabine 1000 mg/m² weekly × 3, cisplatin 75 mg/m² day 15 every 4 weeks
Outcomes	Time to treatment failure Toxicity Overall survival Reponse rate Quality of life
Notes	—

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk for primary endpoint (time to treatment failure)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details published
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Unclear risk	Insufficient details published

Von Hoff 2013

Methods	Randomised phase III trial
Participants	This was an international study. 861 participants with metastatic pancreatic ductal adenocarcinoma with measurable disease and no prior therapy. 43 received gemcitabine. 431 received gemcitabine + nab-paclitaxel. The median age of participants was 63 years.
Interventions	Gemcitabine: 1000 mg/m² 7/8 weeks then 3/4 weeks Gemcitabine + nab-paclitaxel: nab-paclitaxel 125 mg/m² followed by gemcitabine 1000 mg/m² days 1, 8, 15 every 4 weeks
Outcomes	Overall survival Progression-free survival Response rate
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Likely to be low, but insufficient details published- "In this international, multicenter, open-label, randomized, phase 3 study, we randomly assigned eligible patients, in a 1:1 ratio"
Allocation concealment (selection bias)	Unclear risk	Likely to be low, but insufficient details published - "In this international, multicenter, open-label, randomized, phase 3 study, we randomly assigned eligible patients, in a 1:1 ratio"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Wang 2002

Methods	Randomised phase III trial
Participants	42 participants with measurable or evaluable stage III/IV pancreatic cancer. 20 received gemcitabine. 22 participants with gemcitabine + cisplatin

Wang 2002 *(Continued)*

Interventions	Gemcitabine 1000 mg/m² 7/8 weeks then 3/4 weeks Gemcitabine + cisplatin: gemcitabine 1000 mg/m² 3/4 weeks + cisplatin 60 mg/m² day 15 every 3 every 4 weeks
Outcomes	Clinical benefit Duration of clinical benefit Duration of response Time to progression Survival Toxicity
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient details published
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details published
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details published
Selective reporting (reporting bias)	Unclear risk	Insufficient details published
Other bias	Unclear risk	Insufficient details published

Xinopoulos 2008

Methods	Randomised study
Participants	Study was conducted in Greece. 49 participants with locally advanced PC with normal liver function tests after biliary stent insertion. 33 received no further treatment after stent insertion, 16 received gemcitabine. Median age of participants not published.
Interventions	Gemcitabine 1000 mg/m² weekly × 3, then 1 week off

Xinopoulos 2008 *(Continued)*

Outcomes	Overall survival Quality of life Requirement for 2nd stent insertion
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients' allocation into the 2 arms was based on a sequence of random binary numbers (i.e.111100111010...) that was developed in a computer based program"
Allocation concealment (selection bias)	Low risk	"Patients' allocation into the 2 arms was based on a sequence of random binary numbers (i.e.111100111010...) that was developed in a computer based program"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indications of other bias

5FU: 5-fluorouracil; **IV**: intravenous; **OS**: overall survival; **PFS**: progression-free survival: **QoL**: quality of life.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abdel Wahab 1999	May include participants who did not have histological confirmation of their tumour. An attempt to contact authors was made
Aigner 1998	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Alberts 2005	Biological agent (addressed in another Cochrane Review)
Andersen 1981	Not all participants had advanced pancreatic cancer.
Ardalan 1988	Survival was not an endpoint.
Astsaturov 2011	Second.line treatment (addressed in another Cochrane Review).

Study	Reason for exclusion
Baker 1976	The survival data of the subgroup of participants with pancreatic cancer are not published separately.
Benavides 2014	Biological agent (addressed in another Cochrane Review)
Benson 2014	Biological agent (addressed in another Cochrane Review)
Benson 2017	Biological agent - addressed in another review
Berglund 2010	Cross-over study.
Bramhall 2001	Biological agent (addressed in another Cochrane Review)
Bramhall 2002	Biological agent (addressed in another Cochrane Review)
Buanes 2009	Immunotherapy (addressed in another Cochrane Review)
Bukowski 1993	Non-randomised study
Burtness 2016	Biological agent (addressed in another Cochrane Review)
Cantore 2004	Second-line treatment (addressed in another Cochrane Review)
Cascinu 2008	Biological agent (addressed in another Cochrane Review)
Cascinu 2013	Biological agent (addressed in another Cochrane Review)
Catenacci 2013	Biological agent (addressed in another Cochrane Review)
Chai 2013	Immunotherapy (addressed in another Cochrane Review)
Chauffert 2008	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Chen 2006	Biological agent (addressed in another Cochrane Review)
Chung 2004	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Chung 2015	Second-line treatment (addressed in another Cochrane Review)
Ciuleanu 2009	Second-line treatment (addressed in another Cochrane Review)
Cohen 2005	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Cohen 2010	Insufficient data published
Dahan 2010	Cross-over study
Daigleish 2015	Immunotherapy (addressed in another Cochrane Review)
Deplanque 2015	Biological agent (addressed in another Cochrane Review)
Ducreux 2002	Contains ampullary cancers
Duffy 2015	Second-line study - addressed in another review (ongoing study)

Study	Reason for exclusion
El-Khoueiry 2012	Biological agent (addressed in another Cochrane Review)
Evans 2014	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Friess 2006	Biological agent (addressed in another Cochrane Review)
Fuchs 2015	Biological agent (addressed in another Cochrane Review)
Fukutomi 2015	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Gill 2014	Second-line treatment (addressed in another Cochrane Review)
Gilliam 2012	Immunotherapy (addressed in another Cochrane Review)
GISTG 1985 (radiotherapy)	Locally advanced study (addressed in another Cochrane Review)
GITSG 1979	Preliminary results only. Included acinar and undifferentiated pathologies
GITSG 1985	Insufficient data published
GITSG 1988	Participants with acinar pathology included
Gong 2007	Non-randomised study
Gonçalves 2012	Biological agent (addressed in another Cochrane Review)
Haas 2015	Biological agent - addressed in another review (ongoing study)
Hammel 2013	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Han 2006	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Hazel 1981	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Heinemann 2013	Biological agent (addressed in another Cochrane Review)
Heinemann 2013 (GUT)	Cross-over study
Herman 2013	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Hingorani 2015	Biological agent - addressed in another review (ongoing study)
Horton 1981	Cross-over study
Hurwitz 2015	Second-line treatment (addressed in another Cochrane Review)
Hurwitz 2015 (JANUS 1)	Biological agent - addressed in another review (ongoing study)
Infante 2013	Biological agent (addressed in another Cochrane Review)
Ioka 2009	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Ioka 2013	Second-line treatment (addressed in another Cochrane Review)
Jacobs 2004	Second-line treatment (addressed in another Cochrane Review)

Study	Reason for exclusion
Javle 2011	Cross-over study
Johnson 2001	Not all participants had a histological diagnosis
Kim 2011	Insufficient data published
Kindler 2008	Biological agent (addressed in another Cochrane Review)
Kindler 2010	Biological agent (addressed in another Cochrane Review)
Kindler 2011	Biological agent (addressed in another Cochrane Review)
Kindler 2012	Biological agent (addressed in another Cochrane Review)
Kindler 2015	Biological agent - addressed in another review
Klaassen 1985	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Ko 2012	Biological agent (addressed in another Cochrane Review)
Ko 2016	Biological agent - addressed in another review
Lasalvia-Prisco 2012	Immunotherapy (addressed in another Cochrane Review)
Le (Ipilimumab) 2013	Second-line treatment (addressed in another Cochrane Review)
Le 2013	Immunotherapy (addressed in another Cochrane Review)
Le 2015	Immunotherapy agent - addressed in another review
Li 2003	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Li 2016	Locally advanced study (address in another Cochrane Review)
Linstadt 1988	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Loehrer 2011	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Lokich 1979	Included participants with acinar pathology
Lygidakis 1995	Not all participants had advanced pancreatic cancer
Mallinson 1980	Not all participants had histologically confirmed pancreatic ductal adenocarcinoma (PDAC)
Meyer 2008	Survival was not an endpoint
Middleton 2014	Immunotherapy (addressed in another Cochrane Review)
Mitry 2006	Non-randomised study
Mizuno 2013	May include adenosquamous participants. An attempt to contact authors was made
Modiano 2012	Biological agent (addressed in another Cochrane Review)
Moertel 1981	Participants with acinar and undifferentiated pathology were included

Study	Reason for exclusion
Moore 2003	Biological agent (addressed in another Cochrane Review)
Moore 2007	Biological agent (addressed in another Cochrane Review)
Mukherjee 2013	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Nakai 2012	Not all participants had histologically confirmed PDAC
Nio 2010	Retrospective study
O'Neil 2015	Biological agent (addressed in another Cochrane Review)
O'Reilly 2013	Biological agent - addressed in another review (ongoing study)
O'Reilly 2015	Second-line study - addressed in another review (ongoing study)
Oberic 2011	Insufficient data published
Oster 1986	Participants with acinar pathology were included
Palmer 1994	Not all participants had a histologically confirmed PDAC
Pandya 2013	Biological agent (addressed in another Cochrane Review)
Pelzer 2011	Second-line treatment (addressed in another Cochrane Review)
Philip 2010	Biological agent (addressed in another Cochrane Review)
Philip 2014	Biological agent (addressed in another Cochrane Review)
Propper 2014	Second-line treatment (addressed in another Cochrane Review)
Queisser 1979	Insufficient information published
Ramanathan 2011	Insufficient data published
Reni 2009	Retrospective analysis
Reni 2013	Second-line treatment (addressed in another Cochrane Review)
Richards 2011	Biological agent (addressed in another Cochrane Review)
Richly 2013	Biological agent (addressed in another Cochrane Review)
Riess 2010	Biological agent (addressed in another Cochrane Review)
Rougier 2013	Biological agent (addressed in another Cochrane Review)
Ryan 2013	Biological agent (addressed in another Cochrane Review)
Saif 2009	Biological agent (addressed in another Cochrane Review)
Sakata 1992	Insufficient information published - pancreas cancer subgroup not reported separately
Schein 1978	Participants with acinar and undifferentiated pathology were included

Study	Reason for exclusion
Schmitz-Winnenthal 2013	Overall survival not an endpoint
Senzer 2006	Insufficient data published
Shapiro 2005	Insufficient data published
Shinchi 2002	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Shinchi 2014	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Spano 2008	Biological agent (addressed in another Cochrane Review)
Strumberg 2013	Biological agent (addressed in another Cochrane Review)
Sudo 2014	Included adenosquamous pathology
Sultana 2009	Insufficient data published
Sun 2011	Insufficient data published
Sunamura 2004	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Tagliaferri 2013	Insufficient data published
Takada 1994	Includes participants with biliary tract cancer. Subgroup analysis of pancreatic cancer participants not available
Topham 1993	Preliminary results only
Trouilloud 2012	Insufficient data published
Tuinman 2008	Interim analysis only. Full results not published
Ulrich-Pur 2003	Second-line treatment (addressed in another Cochrane Review)
Van Cutsem 2004	Biological agent (addressed in another Cochrane Review)
Van Cutsem 2009	Biological agent (addressed in another Cochrane Review)
Van Cutsem 2013	Insufficient data published
Van Cutsem 2014	Biological agent (addressed in another Cochrane Review)
Van Cutsem 2015	Biological agent (addressed in another Cochrane Review)
Von Hoff 1990	Immunotherapy (addressed in another Cochrane Review)
Von Hoff 2014	Second-line treatment (addressed in another Cochrane Review)
Voorthuizen 2006	Biological agent (addressed in another Cochrane Review)
Wagener 2002	Immunotherapy (addressed in another Cochrane Review)
Wang 2000	All participants had locally advanced PC (addressed in another Cochrane Review)

Study	Reason for exclusion
Wang 2004	All participants had locally advanced PC (addressed in another Cochrane Review)
Wang 2015	Biological agent (addressed in another Cochrane Review)
Wiedenmann 2008	Biological agent (addressed in another Cochrane Review)
Wilkowski 2009	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Wolpin 2013	Biological agent (addressed in another Cochrane Review)
Wright 2006	Immunotherapy (addressed in another Cochrane Review)
Yamaue 2015	Biological agent (addressed in another Cochrane Review)
Yongxiang 2001	Non-randomised study
Yoo 2009	Second-line treatment (addressed in another Cochrane Review)
Zemskov 2000	Non-randomised study
Zhang 2007	All participants had locally advanced PC (addressed in another Cochrane Review)

PC: pancreatic cancer; **PDAC**: pancreatic ductal adenocarcinoma.

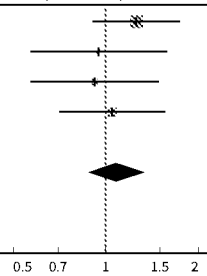
DATA AND ANALYSES

Comparison 1. Anti-cancer therapy versus best supportive care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	4	298	Hazard Ratio (Random, 95% CI)	1.08 [0.88, 1.33]

Analysis 1.1. Comparison 1 Anti-cancer therapy versus best supportive care, Outcome 1 Overall survival.

Study or subgroup	Anti-cancer therapy N	Best supportive care N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
Frey 1981	65	87	0.2 (0.166)		39.31%	1.26[0.91,1.74]
Huguier 2001	22	23	-0.1 (0.261)		15.95%	0.95[0.57,1.58]
Takada 1998	28	24	-0.1 (0.244)		18.15%	0.92[0.57,1.49]
Xinopoulos 2008	16	33	0 (0.202)		26.6%	1.05[0.71,1.56]
Total (95% CI)					**100%**	**1.08[0.88,1.33]**
Heterogeneity: Tau²=0; Chi²=1.55, df=3(P=0.67); I²=0%						
Test for overall effect: Z=0.77(P=0.44)						



Comparison 2. Various types of chemotherapy versus gemcitabine

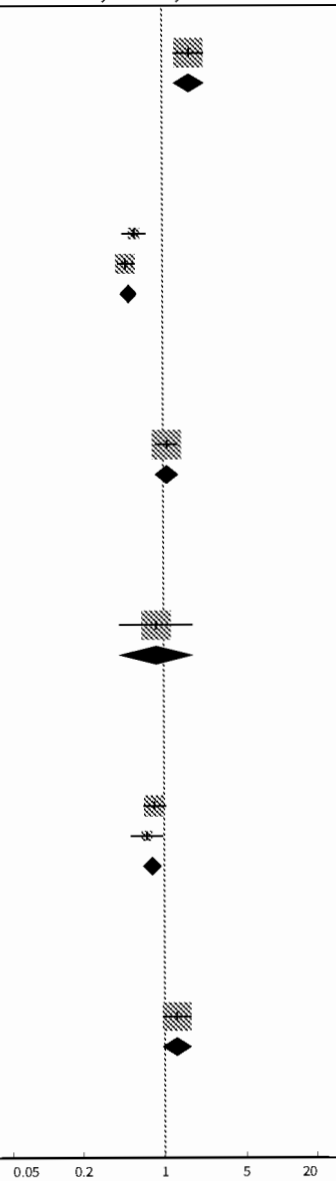
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	8		Hazard Ratio (Random, 95% CI)	Subtotals only
1.1 5-FU	1	126	Hazard Ratio (Random, 95% CI)	1.69 [1.26, 2.27]
1.2 FOLFIRINOX	2	652	Hazard Ratio (Random, 95% CI)	0.51 [0.43, 0.60]
1.3 CO-101	1	367	Hazard Ratio (Random, 95% CI)	1.07 [0.86, 1.34]
1.4 ZD9331	1	55	Hazard Ratio (Random, 95% CI)	0.86 [0.42, 1.76]
1.5 Fixed dose rate gemcitabine	2	644	Hazard Ratio (Random, 95% CI)	0.79 [0.66, 0.94]
1.6 Exatecan	1	339	Hazard Ratio (Random, 95% CI)	1.27 [0.96, 1.68]
2 Progression-free survival	5		Hazard Ratio (Random, 95% CI)	Subtotals only
2.1 5-FU	1	126	Hazard Ratio (Random, 95% CI)	1.47 [1.12, 1.92]
2.2 FOLFIRINOX	2	652	Hazard Ratio (Random, 95% CI)	0.46 [0.38, 0.57]
2.3 ZD9331	1	55	Hazard Ratio (Random, 95% CI)	0.78 [0.46, 1.32]
2.4 Fixed dose rate gemcitabine	1	552	Hazard Ratio (Random, 95% CI)	0.88 [0.77, 1.01]
3 Degradation of QoL at 6 months	2		Hazard Ratio (Random, 95% CI)	0.46 [0.35, 0.61]
4 Response rates	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 5-FU	1	126	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.71]
4.2 FOLFIRINOX	1	342	Risk Ratio (M-H, Random, 95% CI)	3.38 [2.01, 5.65]
4.3 CO-101	1	358	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.43, 1.04]
4.4 ZD9331	1	55	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.04, 4.33]
4.5 Fixed dose rate gemcitabine	2	644	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.91, 2.79]
4.6 Exatecan (DX-8951f)	1	276	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.01, 0.78]
5 Grade 3/4 anaemia	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 5-FU	1	126	Risk Ratio (M-H, Random, 95% CI)	0.08 [0.00, 1.34]
5.2 FOLFIRINOX	1	342	Risk Ratio (M-H, Random, 95% CI)	1.3 [0.59, 2.88]
5.3 CO-101	1	360	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.59, 1.73]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.4 ZD9331	1	55	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.01, 6.58]
5.5 Fixed dose rate gemcitabine	2	644	Risk Ratio (M-H, Random, 95% CI)	1.79 [1.22, 2.63]
5.6 Exatecan	1	330	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.43, 2.34]
6 Grade 3/4 neutropenia	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 5-FU	1	126	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.06, 0.61]
6.2 FOLFIRINOX	1	342	Risk Ratio (M-H, Random, 95% CI)	2.14 [1.52, 3.01]
6.3 CO-101	1	360	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.83, 2.07]
6.4 ZD9331	1	55	Risk Ratio (M-H, Random, 95% CI)	4.17 [0.52, 33.37]
6.5 Fixed dose rate gemcitabine	2	644	Risk Ratio (M-H, Random, 95% CI)	1.85 [1.53, 2.23]
6.6 Exatecan	1	330	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.64, 1.55]
7 Grade 3/4 thrombocytopenia	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 5-FU	1	126	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.34]
7.2 FOLFIRINOX	1	342	Risk Ratio (M-H, Random, 95% CI)	2.5 [0.99, 6.29]
7.3 CO-101	1	360	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.51, 2.34]
7.4 ZD9331	1	55	Risk Ratio (M-H, Random, 95% CI)	3.33 [0.40, 27.94]
7.5 Fixed dose rate gemcitabine	2	644	Risk Ratio (M-H, Random, 95% CI)	2.77 [1.99, 3.86]
7.6 Exatecan	1	330	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.37, 1.54]
8 Grade 3/4 nausea	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 5-FU	1	126	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.10, 1.35]
8.2 ZD9331	1	55	Risk Ratio (M-H, Random, 95% CI)	2.52 [0.11, 59.18]
8.3 Fixed dose rate gemcitabine	2	644	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.94, 2.46]
8.4 Exatecan	1	330	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.52, 5.86]
9 Grade 3/4 diarrhoea	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 5-FU	1	126	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.32, 28.07]

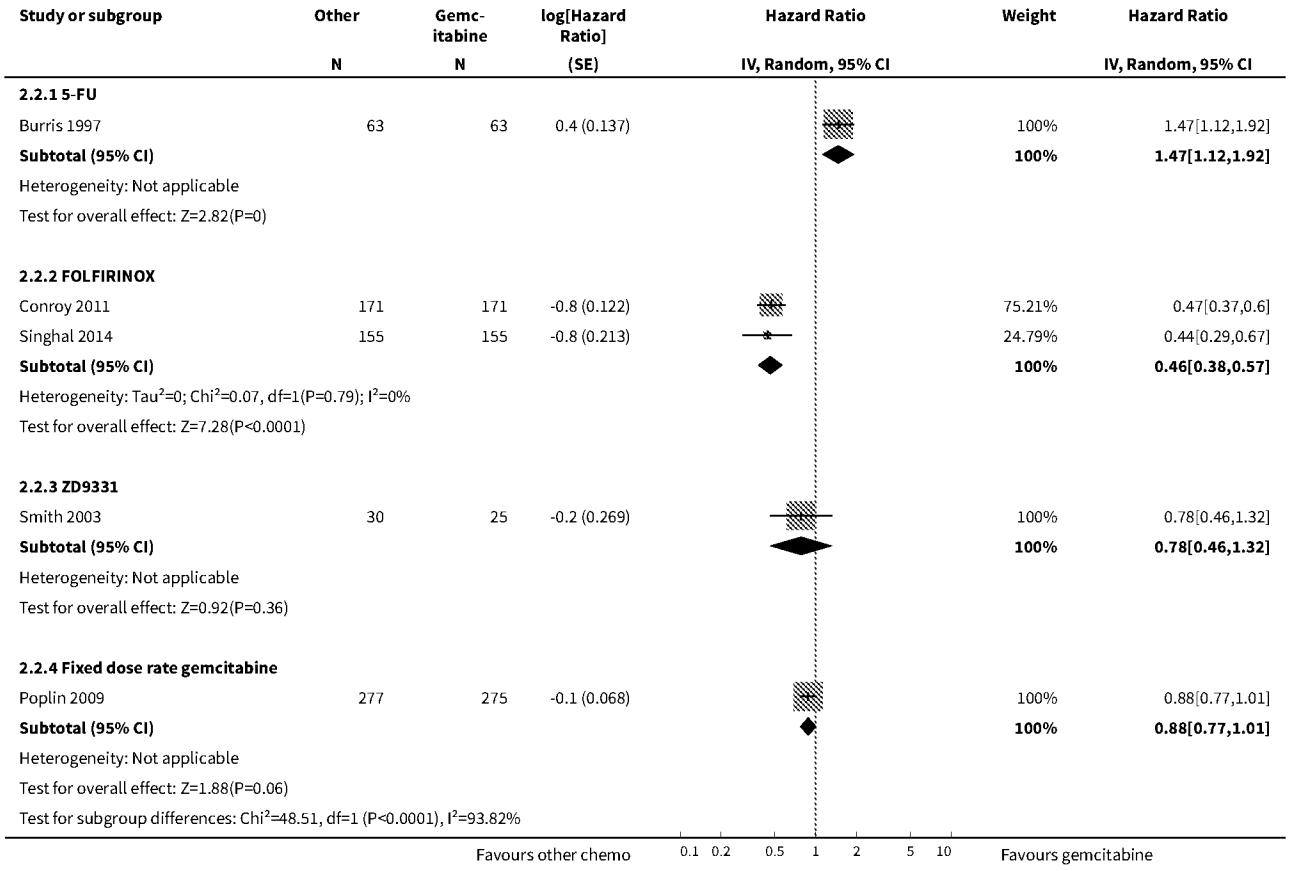
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.2 ZD9331	1	55	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.01, 6.58]
9.3 Fixed dose rate gemcitabine	2	644	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.16, 1.23]

Analysis 2.1. Comparison 2 Various types of chemotherapy versus gemcitabine, Outcome 1 Overall survival.

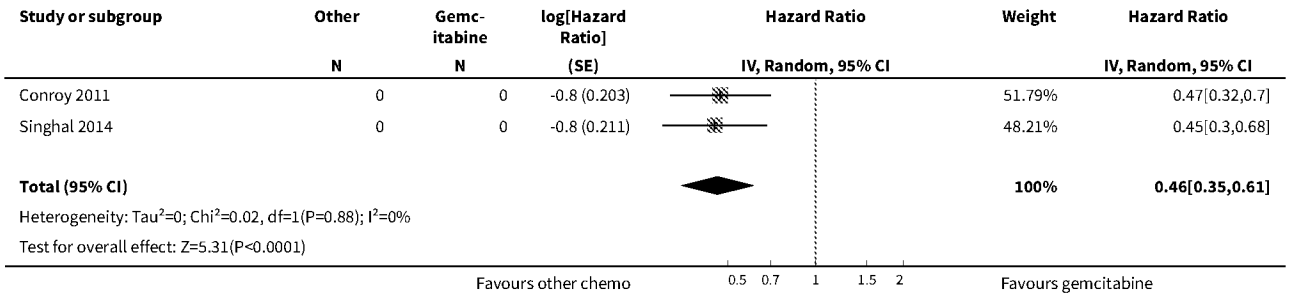
Study or subgroup	Other N	Gemcitabine N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
2.1.1 5-FU						
Burris 1997	63	63	0.5 (0.15)		100%	1.69[1.26,2.27]
Subtotal (95% CI)					**100%**	**1.69[1.26,2.27]**
Heterogeneity: Not applicable						
Test for overall effect: Z=3.52(P=0)						
2.1.2 FOLFIRINOX						
Conroy 2011	171	171	-0.6 (0.121)		36.33%	0.57[0.45,0.72]
Singhal 2014	155	155	-0.7 (0.08)		63.67%	0.48[0.41,0.56]
Subtotal (95% CI)					**100%**	**0.51[0.43,0.6]**
Heterogeneity: Tau^2=0; Chi^2=1.41, df=1(P=0.24); I^2=28.9%						
Test for overall effect: Z=8.12(P<0.0001)						
2.1.3 CO-101						
Poplin 2013	182	185	0.1 (0.115)		100%	1.07[0.86,1.34]
Subtotal (95% CI)					**100%**	**1.07[0.86,1.34]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.61(P=0.54)						
2.1.4 ZD9331						
Smith 2003	30	25	-0.2 (0.366)		100%	0.86[0.42,1.76]
Subtotal (95% CI)					**100%**	**0.86[0.42,1.76]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.41(P=0.68)						
2.1.5 Fixed dose rate gemcitabine						
Poplin 2009	277	275	-0.2 (0.109)		67.88%	0.83[0.67,1.03]
Tempero 2003	43	49	-0.3 (0.159)		32.12%	0.71[0.52,0.97]
Subtotal (95% CI)					**100%**	**0.79[0.66,0.94]**
Heterogeneity: Tau^2=0; Chi^2=0.66, df=1(P=0.42); I^2=0%						
Test for overall effect: Z=2.63(P=0.01)						
2.1.6 Exatecan						
Cheverton 2004	169	170	0.2 (0.142)		100%	1.27[0.96,1.68]
Subtotal (95% CI)					**100%**	**1.27[0.96,1.68]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%						
Test for overall effect: Z=1.68(P=0.09)						
Test for subgroup differences: Chi^2=71.35, df=1 (P<0.0001), I^2=92.99%						



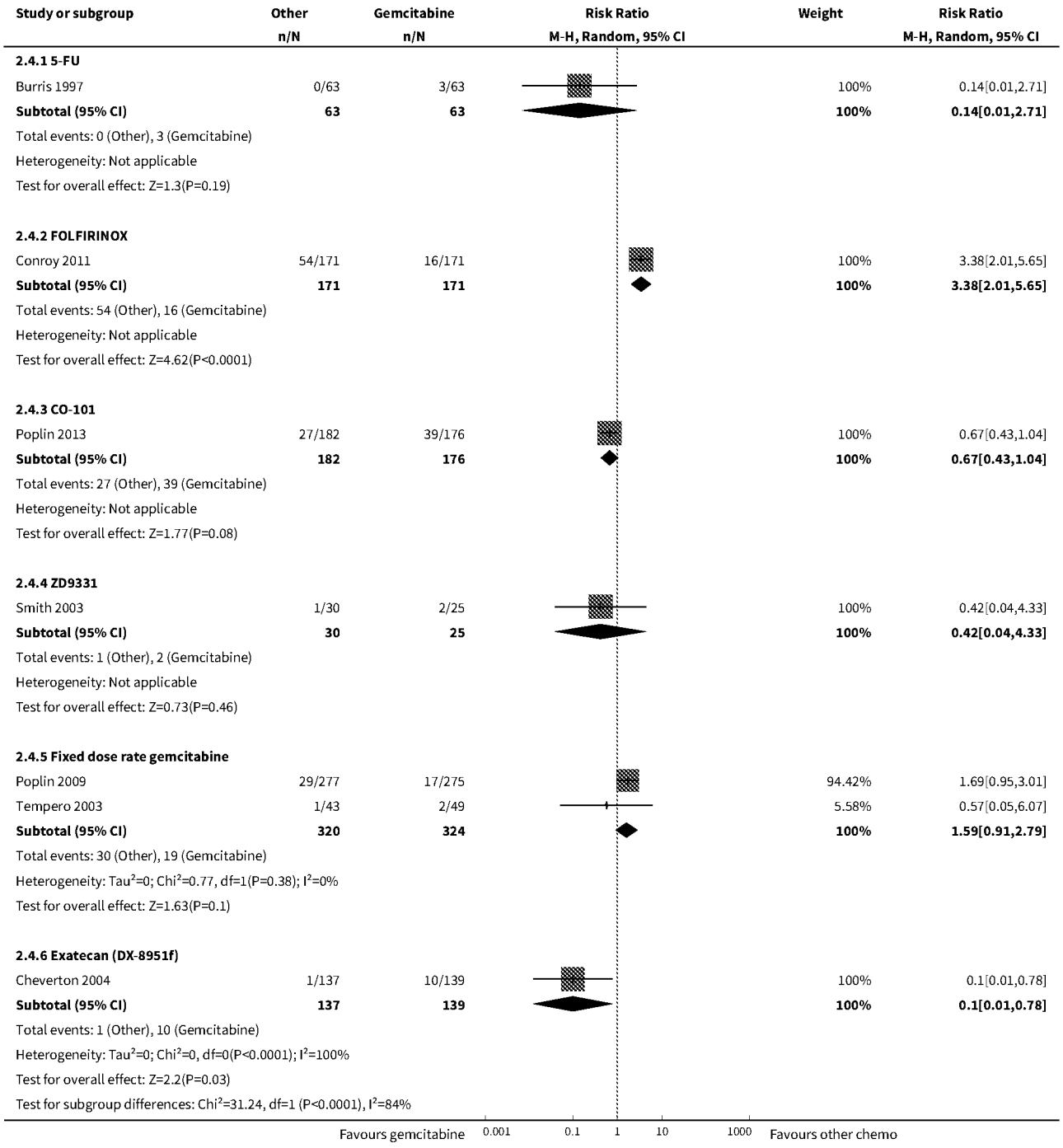
Analysis 2.2. Comparison 2 Various types of chemotherapy versus gemcitabine, Outcome 2 Progression-free survival.



Analysis 2.3. Comparison 2 Various types of chemotherapy versus gemcitabine, Outcome 3 Degradation of QoL at 6 months.

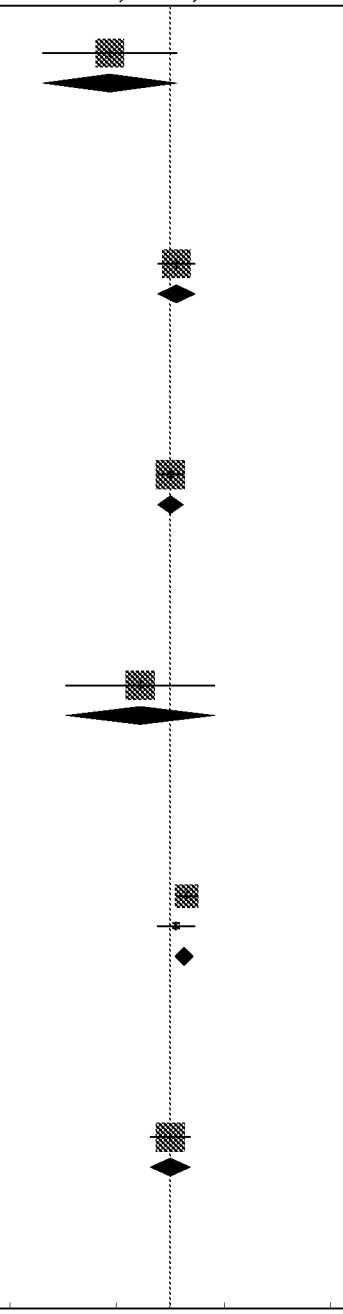


Analysis 2.4. Comparison 2 Various types of chemotherapy versus gemcitabine, Outcome 4 Response rates.



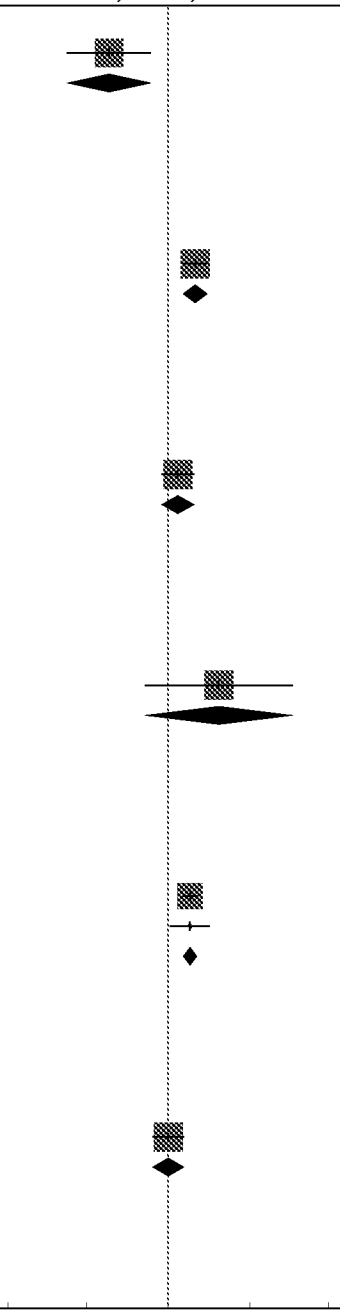
Analysis 2.5. Comparison 2 Various types of chemotherapy versus gemcitabine, Outcome 5 Grade 3/4 anaemia.

Study or subgroup	Other chemotherapy n/N	Gemcitabine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 5-FU					
Burris 1997	0/63	6/63		100%	0.08[0,1.34]
Subtotal (95% CI)	**63**	**63**		**100%**	**0.08[0,1.34]**
Total events: 0 (Other chemotherapy), 6 (Gemcitabine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.76(P=0.08)					
2.5.2 FOLFIRINOX					
Conroy 2011	13/171	10/171		100%	1.3[0.59,2.88]
Subtotal (95% CI)	**171**	**171**		**100%**	**1.3[0.59,2.88]**
Total events: 13 (Other chemotherapy), 10 (Gemcitabine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.65(P=0.52)					
2.5.3 CO-101					
Poplin 2013	23/179	23/181		100%	1.01[0.59,1.73]
Subtotal (95% CI)	**179**	**181**		**100%**	**1.01[0.59,1.73]**
Total events: 23 (Other chemotherapy), 23 (Gemcitabine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.04(P=0.97)					
2.5.4 ZD9331					
Smith 2003	0/30	1/25		100%	0.28[0.01,6.58]
Subtotal (95% CI)	**30**	**25**		**100%**	**0.28[0.01,6.58]**
Total events: 0 (Other chemotherapy), 1 (Gemcitabine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.79(P=0.43)					
2.5.5 Fixed dose rate gemcitabine					
Poplin 2009	52/277	26/275		76.85%	1.99[1.28,3.08]
Tempero 2003	10/43	9/49		23.15%	1.27[0.57,2.82]
Subtotal (95% CI)	**320**	**324**		**100%**	**1.79[1.22,2.63]**
Total events: 62 (Other chemotherapy), 35 (Gemcitabine)					
Heterogeneity: Tau^2=0; Chi^2=0.93, df=1(P=0.33); I^2=0%					
Test for overall effect: Z=2.95(P=0)					
2.5.6 Exatecan					
Cheverton 2004	10/165	10/165		100%	1[0.43,2.34]
Subtotal (95% CI)	**165**	**165**		**100%**	**1[0.43,2.34]**
Total events: 10 (Other chemotherapy), 10 (Gemcitabine)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Chi^2=8.46, df=1 (P=0.13), I^2=40.87%					

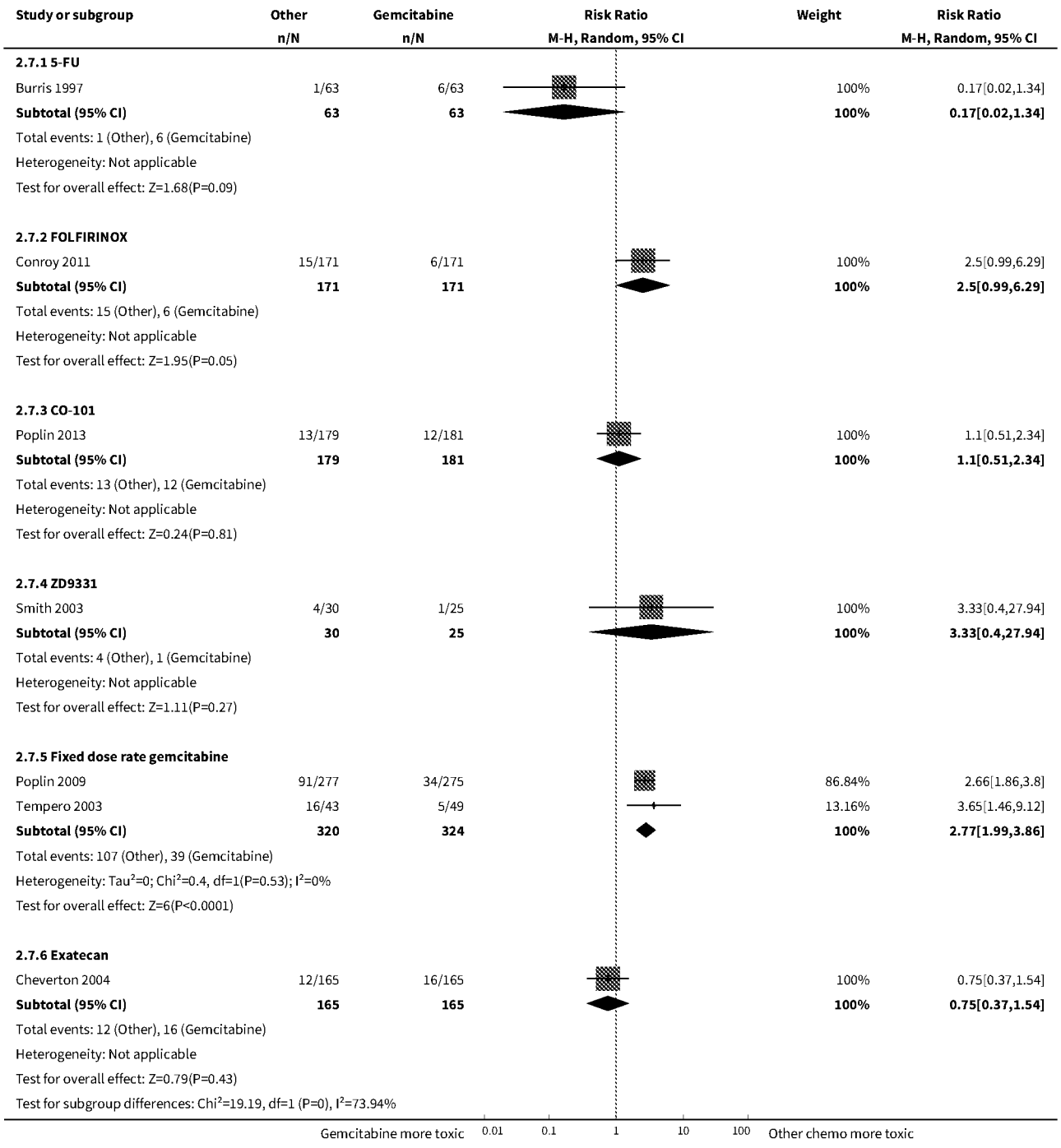


Analysis 2.6. Comparison 2 Various types of chemotherapy versus gemcitabine, Outcome 6 Grade 3/4 neutropenia.

Study or subgroup	Other n/N	Gemcitabine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.6.1 5-FU					
Burris 1997	3/63	16/63		100%	0.19[0.06,0.61]
Subtotal (95% CI)	**63**	**63**		**100%**	**0.19[0.06,0.61]**
Total events: 3 (Other), 16 (Gemcitabine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.77(P=0.01)					
2.6.2 FOLFIRINOX					
Conroy 2011	75/171	35/171		100%	2.14[1.52,3.01]
Subtotal (95% CI)	**171**	**171**		**100%**	**2.14[1.52,3.01]**
Total events: 75 (Other), 35 (Gemcitabine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.38(P<0.0001)					
2.6.3 CO-101					
Poplin 2013	35/179	27/181		100%	1.31[0.83,2.07]
Subtotal (95% CI)	**179**	**181**		**100%**	**1.31[0.83,2.07]**
Total events: 35 (Other), 27 (Gemcitabine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.16(P=0.25)					
2.6.4 ZD9331					
Smith 2003	5/30	1/25		100%	4.17[0.52,33.37]
Subtotal (95% CI)	**30**	**25**		**100%**	**4.17[0.52,33.37]**
Total events: 5 (Other), 1 (Gemcitabine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.34(P=0.18)					
2.6.5 Fixed dose rate gemcitabine					
Poplin 2009	162/277	87/275		88.59%	1.85[1.51,2.26]
Tempero 2003	21/43	13/49		11.41%	1.84[1.05,3.21]
Subtotal (95% CI)	**320**	**324**		**100%**	**1.85[1.53,2.23]**
Total events: 183 (Other), 100 (Gemcitabine)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=6.39(P<0.0001)					
2.6.6 Exatecan					
Cheverton 2004	32/165	32/165		100%	1[0.64,1.55]
Subtotal (95% CI)	**165**	**165**		**100%**	**1[0.64,1.55]**
Total events: 32 (Other), 32 (Gemcitabine)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Chi^2=23.34, df=1 (P=0), I^2=78.57%					

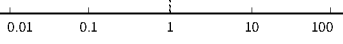


Analysis 2.7. Comparison 2 Various types of chemotherapy versus gemcitabine, Outcome 7 Grade 3/4 thrombocytopenia.



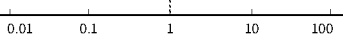
Analysis 2.8. Comparison 2 Various types of chemotherapy versus gemcitabine, Outcome 8 Grade 3/4 nausea.

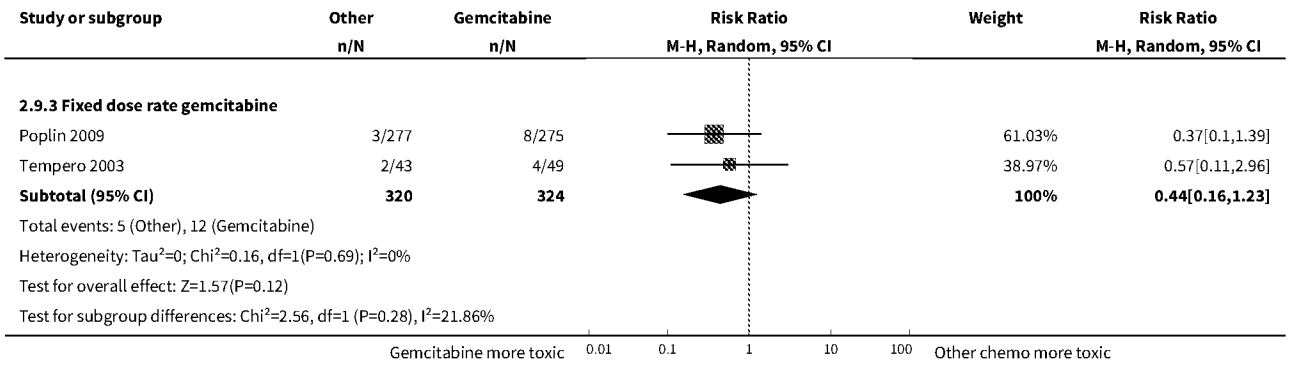
Study or subgroup	Other n/N	Gemcitabine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.8.1 5-FU					
Burris 1997	3/63	8/63		100%	0.38[0.1,1.35]
Subtotal (95% CI)	**63**	**63**		**100%**	**0.38[0.1,1.35]**
Total events: 3 (Other), 8 (Gemcitabine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.5(P=0.13)					
2.8.2 ZD9331					
Smith 2003	1/30	0/25		100%	2.52[0.11,59.18]
Subtotal (95% CI)	**30**	**25**		**100%**	**2.52[0.11,59.18]**
Total events: 1 (Other), 0 (Gemcitabine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.57(P=0.57)					
2.8.3 Fixed dose rate gemcitabine					
Poplin 2009	28/277	18/275		71.45%	1.54[0.87,2.73]
Tempero 2003	9/43	7/49		28.55%	1.47[0.6,3.6]
Subtotal (95% CI)	**320**	**324**		**100%**	**1.52[0.94,2.46]**
Total events: 37 (Other), 25 (Gemcitabine)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.92); I^2=0%					
Test for overall effect: Z=1.71(P=0.09)					
2.8.4 Exatecan					
Cheverton 2004	7/165	4/165		100%	1.75[0.52,5.86]
Subtotal (95% CI)	**165**	**165**		**100%**	**1.75[0.52,5.86]**
Total events: 7 (Other), 4 (Gemcitabine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.91(P=0.36)					
Test for subgroup differences: Chi^2=4.41, df=1 (P=0.22), I^2=31.97%					



Analysis 2.9. Comparison 2 Various types of chemotherapy versus gemcitabine, Outcome 9 Grade 3/4 diarrhoea.

Study or subgroup	Other n/N	Gemcitabine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.9.1 5-FU					
Burris 1997	3/63	1/63		100%	3[0.32,28.07]
Subtotal (95% CI)	**63**	**63**		**100%**	**3[0.32,28.07]**
Total events: 3 (Other), 1 (Gemcitabine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.96(P=0.34)					
2.9.2 ZD9331					
Smith 2003	0/30	1/25		100%	0.28[0.01,6.58]
Subtotal (95% CI)	**30**	**25**		**100%**	**0.28[0.01,6.58]**
Total events: 0 (Other), 1 (Gemcitabine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.79(P=0.43)					





Comparison 3. Gemcitabine combinations versus gemcitabine alone

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Overall survival	26		Hazard Ratio (Random, 95% CI)	Subtotals only
1.1 Gemcitabine plus platinum agent	6	1140	Hazard Ratio (Random, 95% CI)	0.94 [0.81, 1.08]
1.2 Gemcitabine plus fluoropy-rimidine	10	2718	Hazard Ratio (Random, 95% CI)	0.88 [0.81, 0.95]
1.3 Gemcitabine plus topoiso-merase inhibitor	3	839	Hazard Ratio (Random, 95% CI)	1.01 [0.87, 1.16]
1.4 Gemcitabine plus taxane	1	861	Hazard Ratio (Random, 95% CI)	0.72 [0.62, 0.84]
1.5 Gemcitabine plus other combinations of chemothera-py	2	166	Hazard Ratio (Random, 95% CI)	0.55 [0.39, 0.79]
1.6 Gemcitabine plus other agent(s)	4	767	Hazard Ratio (Random, 95% CI)	0.79 [0.56, 1.10]
2 Progression-free survival	18		Hazard Ratio (Random, 95% CI)	Subtotals only
2.1 Gemcitabine plus platinum agent	4	1015	Hazard Ratio (Random, 95% CI)	0.80 [0.68, 0.95]
2.2 Gemcitabine plus fluoropy-rimidine	8	2608	Hazard Ratio (Random, 95% CI)	0.79 [0.72, 0.87]
2.3 Gemcitabine plus topoiso-merase inhibitor	2	709	Hazard Ratio (Random, 95% CI)	0.91 [0.78, 1.07]
2.4 Gemcitabine plus taxane	1	861	Hazard Ratio (Random, 95% CI)	0.69 [0.58, 0.82]

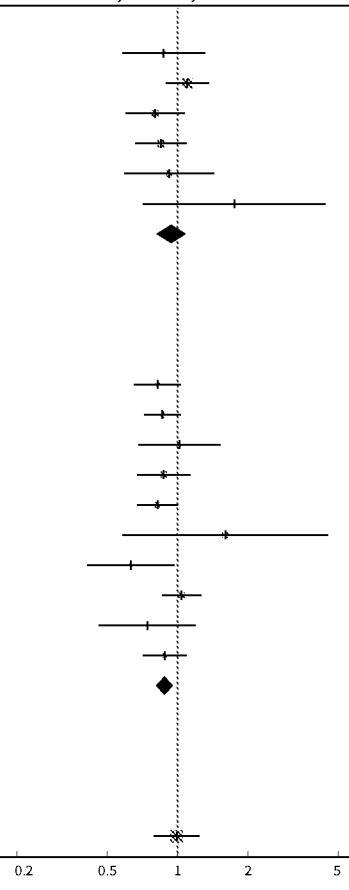
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.5 Gemcitabine plus other combinations of chemotherapy	2	166	Hazard Ratio (Random, 95% CI)	0.43 [0.30, 0.62]
2.6 Gemcitabine plus other agent(s)	1	76	Hazard Ratio (Random, 95% CI)	1.05 [0.68, 1.62]
3 Response rates	24		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Gemcitabine plus platinum agent	7	1186	Risk Ratio (M-H, Random, 95% CI)	1.48 [1.11, 1.98]
3.2 Gemcitabine plus fluoropyrimidine	9	2176	Risk Ratio (M-H, Random, 95% CI)	1.78 [1.29, 2.47]
3.3 Gemcitabine plus topoisomerase inhibitor	3	729	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.92, 2.46]
3.4 Gemcitabine plus taxane	1	861	Risk Ratio (M-H, Random, 95% CI)	3.29 [2.24, 4.84]
3.5 Gemcitabane plus other combinations of chemotherapy	1	67	Risk Ratio (M-H, Random, 95% CI)	1.94 [0.83, 4.56]
3.6 Gemcitabine plus other agent(s)	3	691	Risk Ratio (M-H, Random, 95% CI)	3.66 [1.04, 12.82]
4 Grade 3/4 anaemia	23		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Gemcitabine plus platinum agent	7	1156	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.87, 2.31]
4.2 Gemcitabine plus fluoropyrimidine	8	2158	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.84, 1.45]
4.3 Gemcitabine plus topoisomerase inhibitor	3	797	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.72, 1.66]
4.4 Gemcitabine plus taxane	1	793	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.73, 1.52]
4.5 Gemcitabine plus other combinations of chemotherapy	1	67	Risk Ratio (M-H, Random, 95% CI)	1.94 [0.53, 7.13]
4.6 Gemcitabine plus other agent(s)	3	688	Risk Ratio (M-H, Random, 95% CI)	3.58 [1.93, 6.62]
5 Grade 3/4 neutropenia	23		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Gemcitabine plus platinum agent	6	961	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.90, 1.97]
5.2 Gemcitabine plus fluoropyrimidine	9	2177	Risk Ratio (M-H, Random, 95% CI)	1.53 [1.34, 1.74]

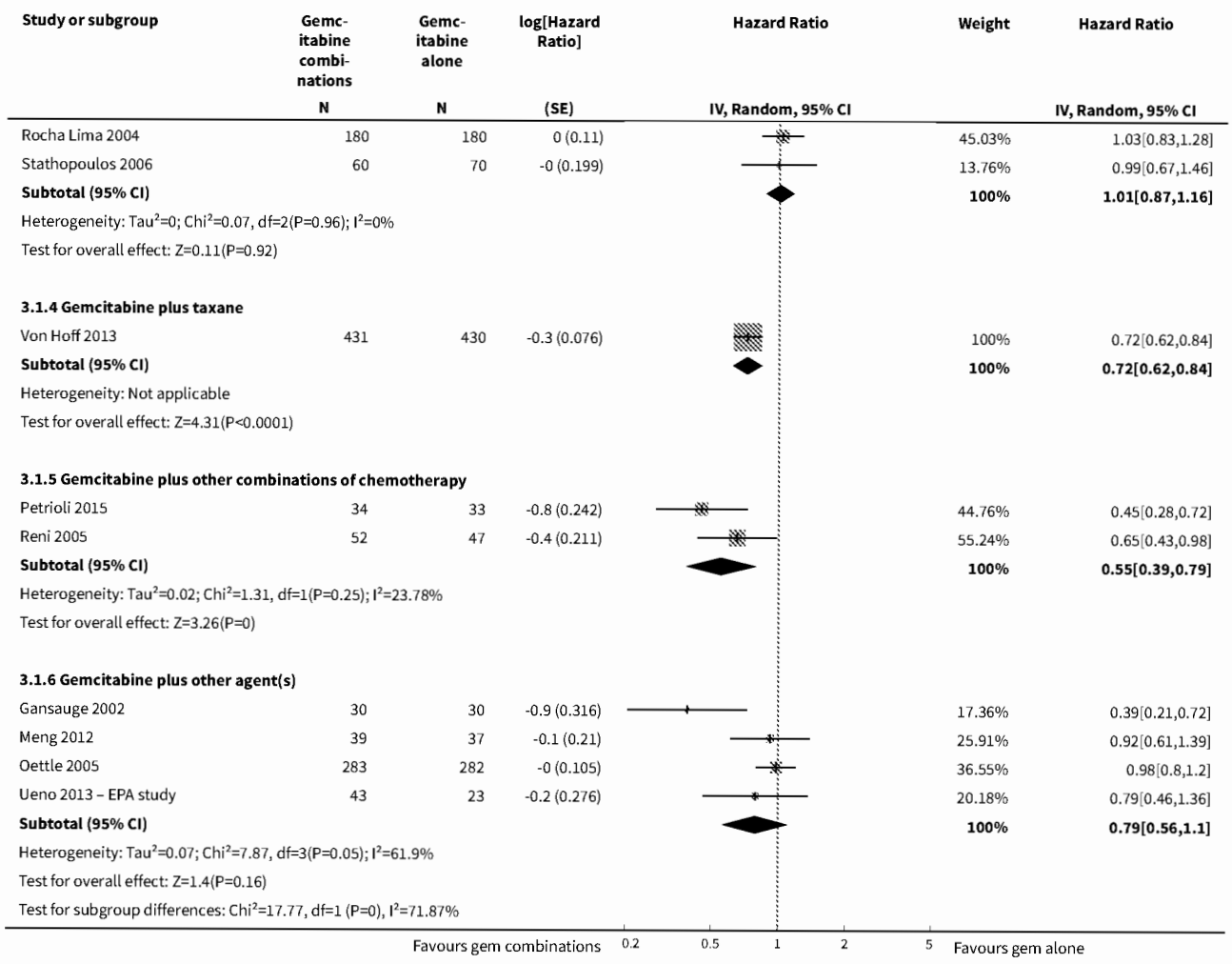
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.3 Gemcitabine plus topoisomerase inhibitor	3	797	Risk Ratio (M-H, Random, 95% CI)	1.54 [1.04, 2.30]
5.4 Gemcitabine plus taxane	1	793	Risk Ratio (M-H, Random, 95% CI)	1.42 [1.16, 1.75]
5.5 Gemcitabine plus other combinations of chemotherapy	1	67	Risk Ratio (M-H, Random, 95% CI)	1.94 [0.65, 5.83]
5.6 Gemcitabine plus other agent(s)	3	688	Risk Ratio (M-H, Random, 95% CI)	2.02 [0.88, 4.66]
6 Grade 3/4 thrombocytopenia	23		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Gemcitabine plus platinum agent	6	1110	Risk Ratio (M-H, Random, 95% CI)	1.96 [1.00, 3.84]
6.2 Gemcitabine plus fluoropyrimidine	9	2177	Risk Ratio (M-H, Random, 95% CI)	1.48 [1.00, 2.18]
6.3 Gemcitabine plus topoisomerase inhibitor	3	797	Risk Ratio (M-H, Random, 95% CI)	2.28 [0.97, 5.36]
6.4 Gemcitabine plus taxane	1	793	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.93, 2.07]
6.5 Gemcitabine plus other combinations of chemotherapy	1	67	Risk Ratio (M-H, Random, 95% CI)	1.94 [0.74, 5.07]
6.6 Gemcitabine plus other agent(s)	3	688	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.45, 4.39]
7 Grade 3/4 nausea	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Gemcitabine plus platinum agent	6	1110	Risk Ratio (M-H, Random, 95% CI)	2.28 [1.40, 3.71]
7.2 Gemcitabine plus fluoropyrimidine	7	2075	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.87, 1.84]
7.3 Gemcitabine plus topoisomerase inhibitor	3	797	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.94, 2.55]
7.4 Gemcitabine plus other combinations of chemotherapy	1	67	Risk Ratio (M-H, Random, 95% CI)	10.69 [0.61, 185.91]
7.5 Gemcitabine plus other agent(s)	4	748	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.48, 3.26]
8 Grade 3/4 diarrhoea	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Gemcitabine plus platinum agent	6	1110	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.62, 3.53]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.2 Gemcitabine plus fluoropyrimidine	8	2087	Risk Ratio (M-H, Random, 95% CI)	2.16 [1.34, 3.47]
8.3 Gemcitabine plus topoisomerase inhibitor	3	797	Risk Ratio (M-H, Random, 95% CI)	3.47 [0.74, 16.33]
9 Grade 3/4 neuropathy	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Gemcitabine plus taxane	1	793	Risk Ratio (M-H, Random, 95% CI)	22.35 [7.10, 70.40]
10 Grade 3/4 fatigue	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Gemcitabine plus taxane	1	793	Risk Ratio (M-H, Random, 95% CI)	2.48 [1.63, 3.79]

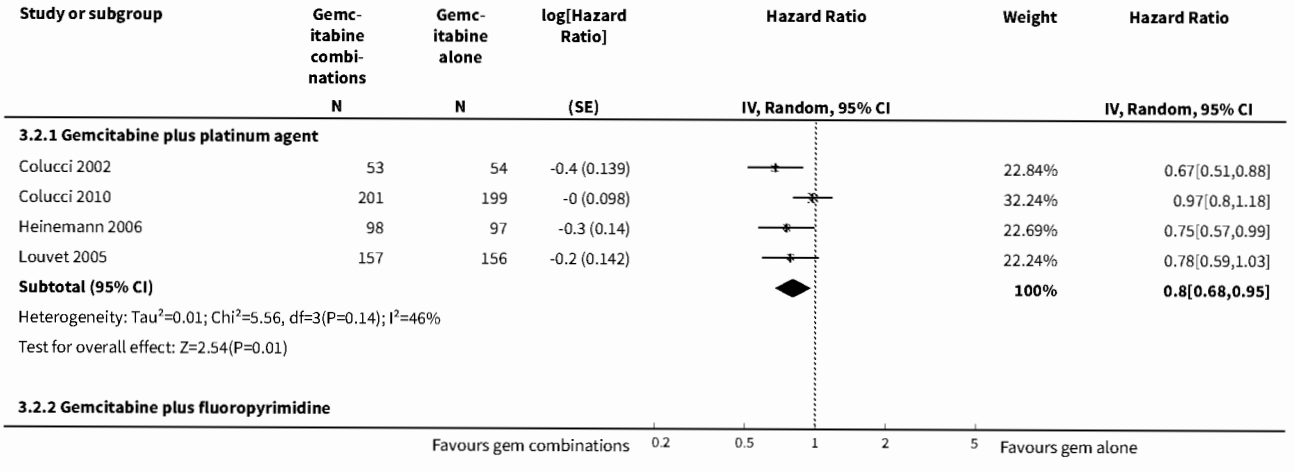
Analysis 3.1. Comparison 3 Gemcitabine combinations versus gemcitabine alone, Outcome 1 Overall survival.

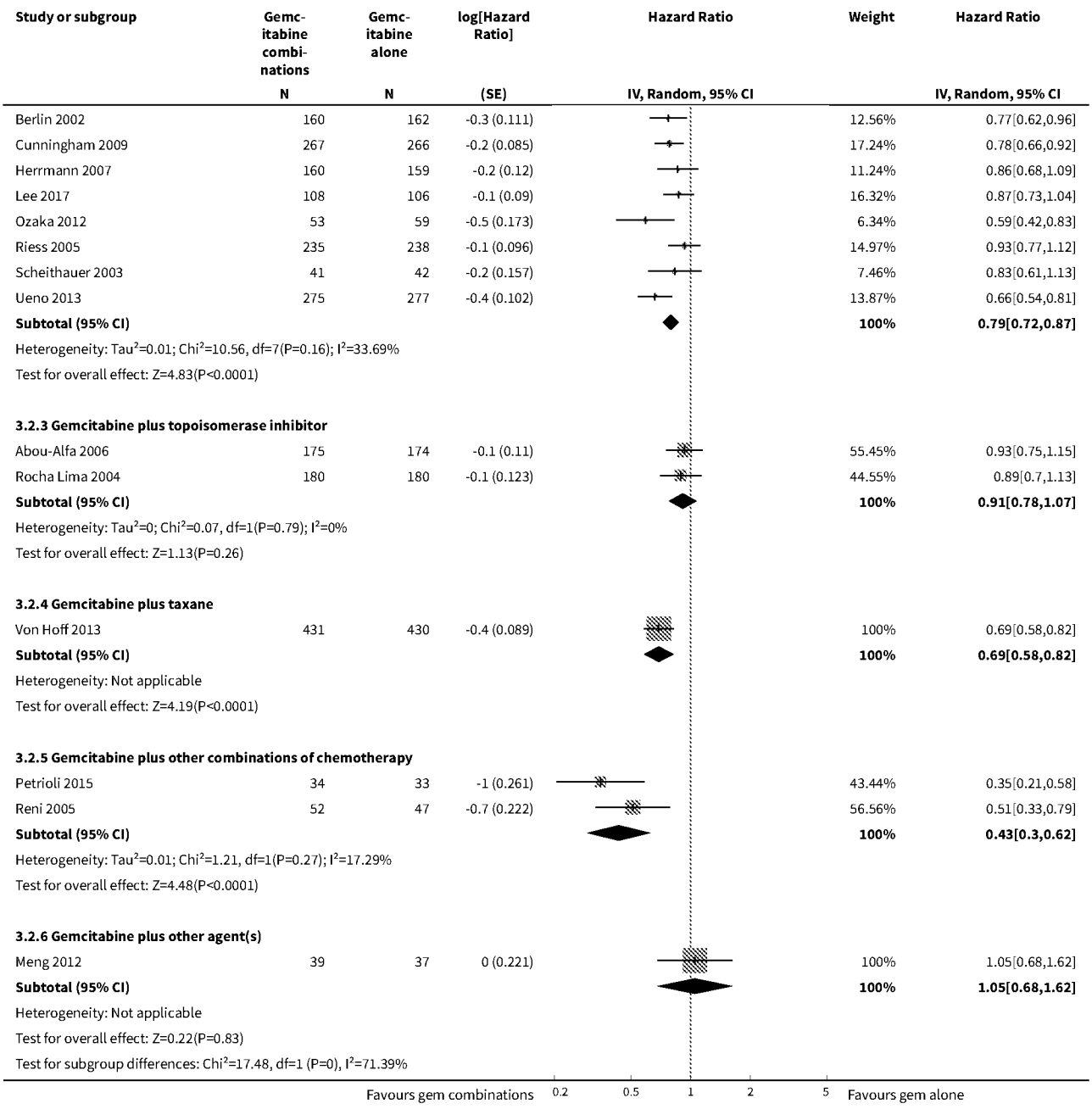
Study or subgroup	Gemcitabine combinations N	Gemcitabine alone N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
3.1.1 Gemcitabine plus platinum agent						
Colucci 2002	53	54	-0.1 (0.207)		11.18%	0.87[0.58,1.31]
Colucci 2010	201	199	0.1 (0.108)		32.07%	1.1[0.89,1.36]
Heinemann 2006	98	97	-0.2 (0.147)		20.14%	0.8[0.6,1.07]
Louvet 2005	157	156	-0.2 (0.129)		24.68%	0.85[0.66,1.09]
Viret 2004	42	41	-0.1 (0.227)		9.47%	0.92[0.59,1.43]
Wang 2002	22	20	0.6 (0.46)		2.46%	1.75[0.71,4.31]
Subtotal (95% CI)					**100%**	**0.94[0.81,1.08]**
Heterogeneity: Tau^2=0; Chi^2=5.9, df=5(P=0.32); I^2=15.23%						
Test for overall effect: Z=0.88(P=0.38)						
3.1.2 Gemcitabine plus fluoropyrimidine						
Berlin 2002	160	162	-0.2 (0.119)		11.91%	0.82[0.65,1.03]
Cunningham 2009	267	266	-0.2 (0.091)		20.34%	0.86[0.72,1.03]
Di Costanzo 2005	43	48	0 (0.207)		3.91%	1.02[0.68,1.53]
Herrmann 2007	160	159	-0.1 (0.133)		9.42%	0.87[0.67,1.13]
Lee 2017	108	106	-0.2 (0.103)		15.74%	0.82[0.67,1]
Ohkawa 2004	10	9	0.5 (0.518)		0.62%	1.6[0.58,4.41]
Ozaka 2012	53	59	-0.5 (0.219)		3.48%	0.63[0.41,0.97]
Riess 2005	235	238	0 (0.097)		17.78%	1.04[0.86,1.26]
Scheithauer 2003	41	42	-0.3 (0.243)		2.84%	0.74[0.46,1.19]
Ueno 2013	275	277	-0.1 (0.11)		13.95%	0.88[0.71,1.09]
Subtotal (95% CI)					**100%**	**0.88[0.81,0.95]**
Heterogeneity: Tau^2=0; Chi^2=8.53, df=9(P=0.48); I^2=0%						
Test for overall effect: Z=3.19(P=0)						
3.1.3 Gemcitabine plus topoisomerase inhibitor						
Abou-Alfa 2006	175	174	-0 (0.115)		41.21%	0.99[0.79,1.24]



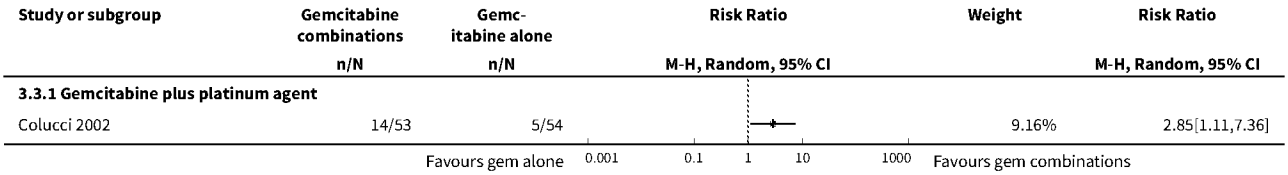


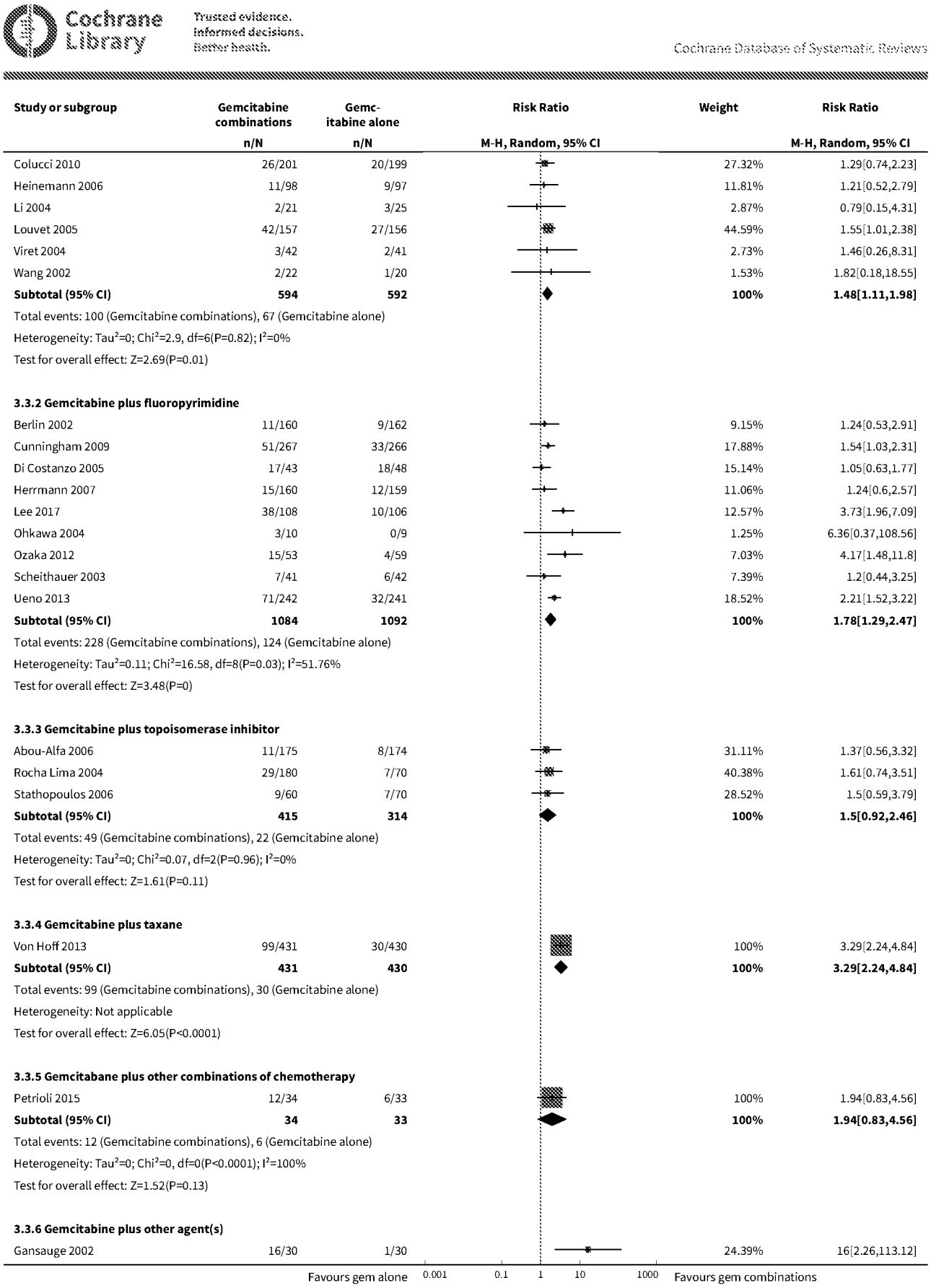
Analysis 3.2. Comparison 3 Gemcitabine combinations versus gemcitabine alone, Outcome 2 Progression-free survival.

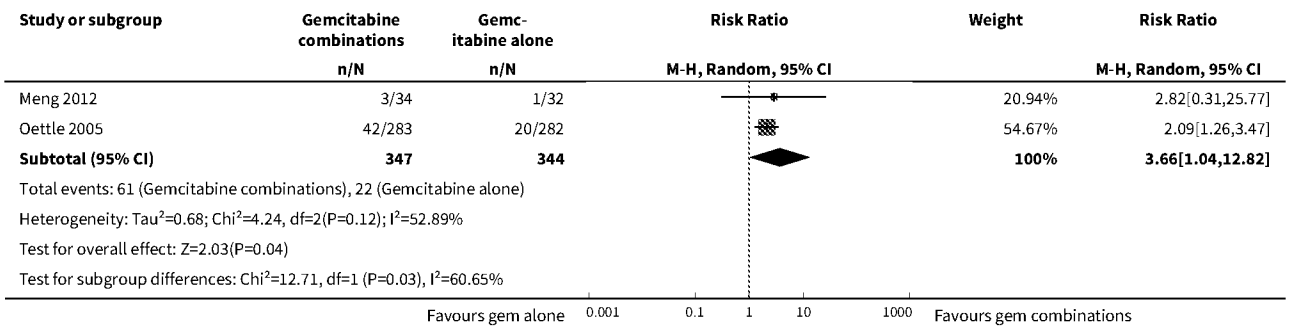




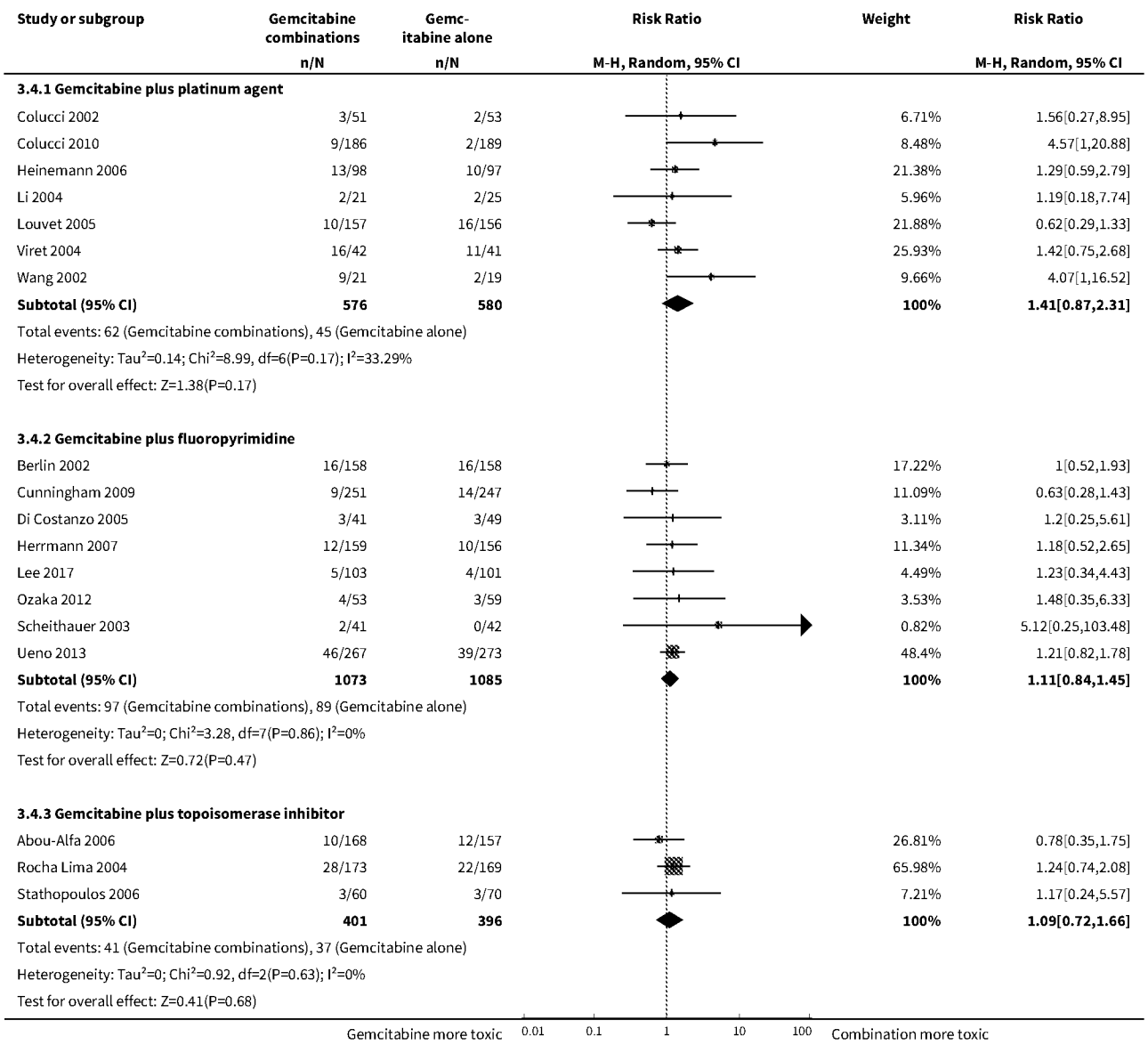
Analysis 3.3. Comparison 3 Gemcitabine combinations versus gemcitabine alone, Outcome 3 Response rates.

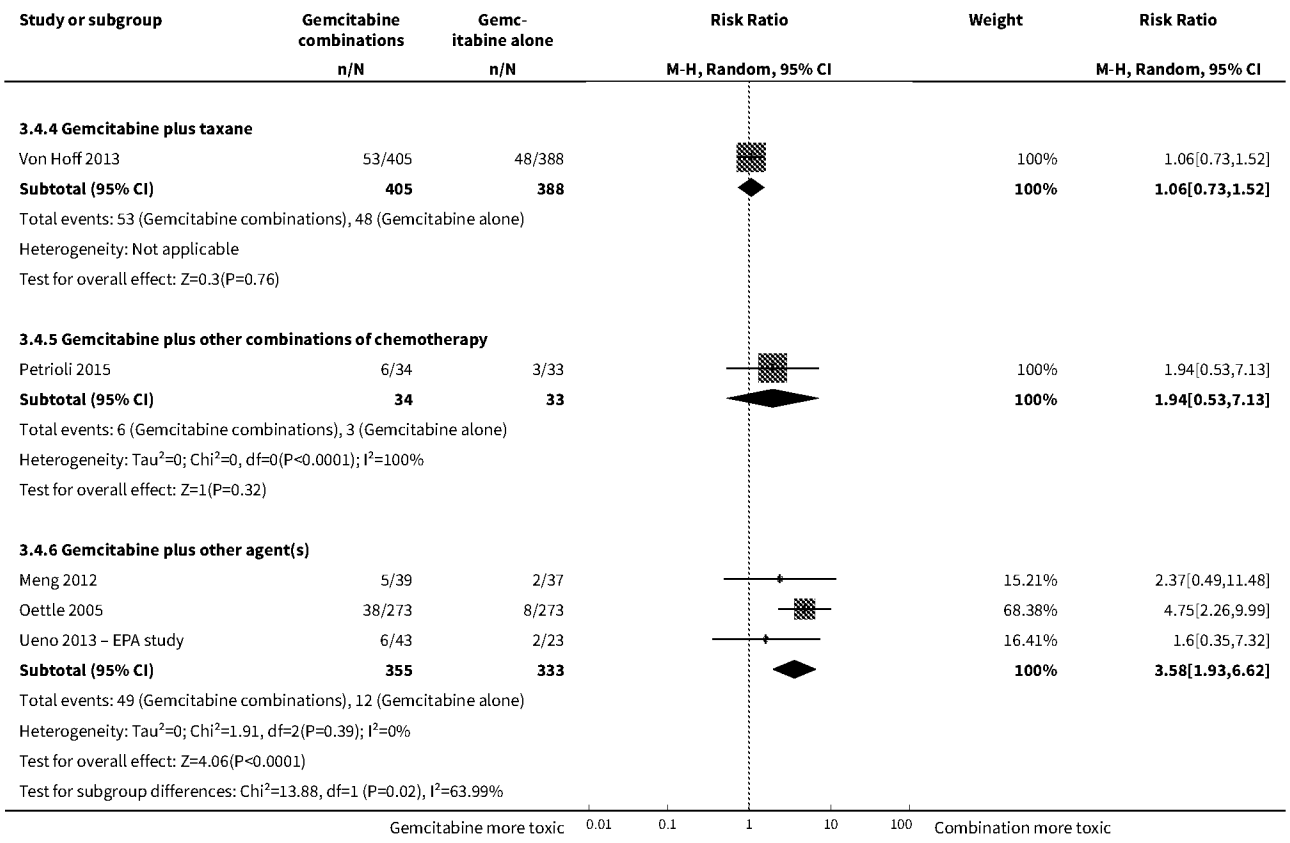




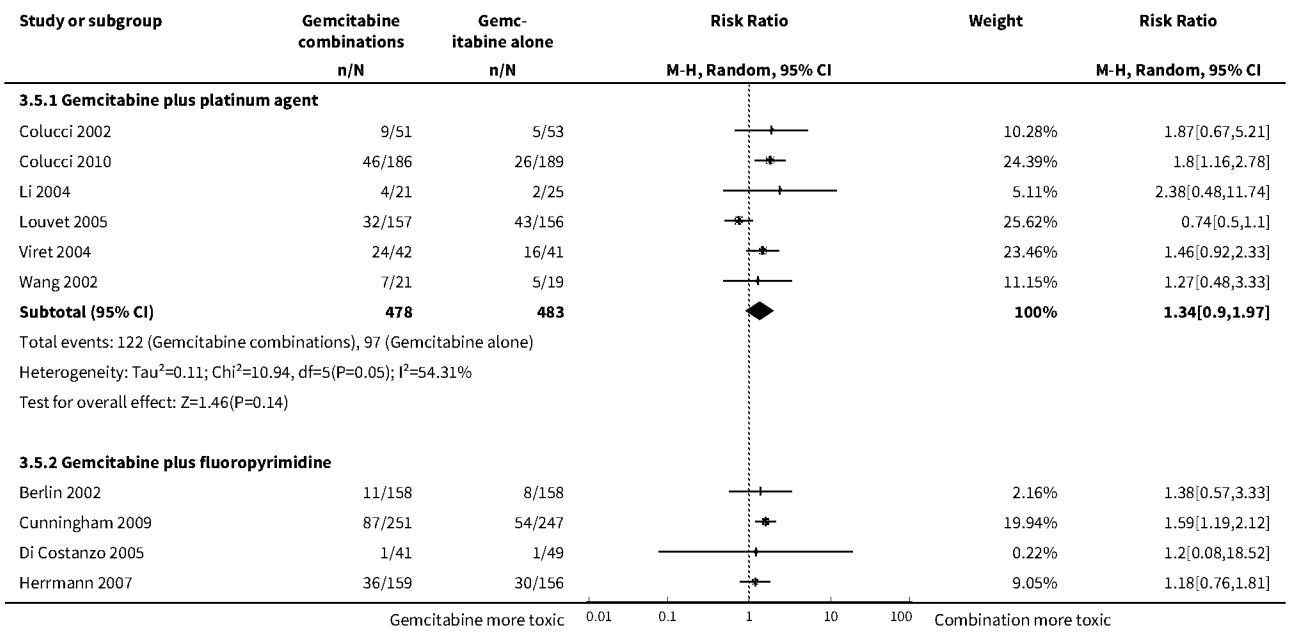


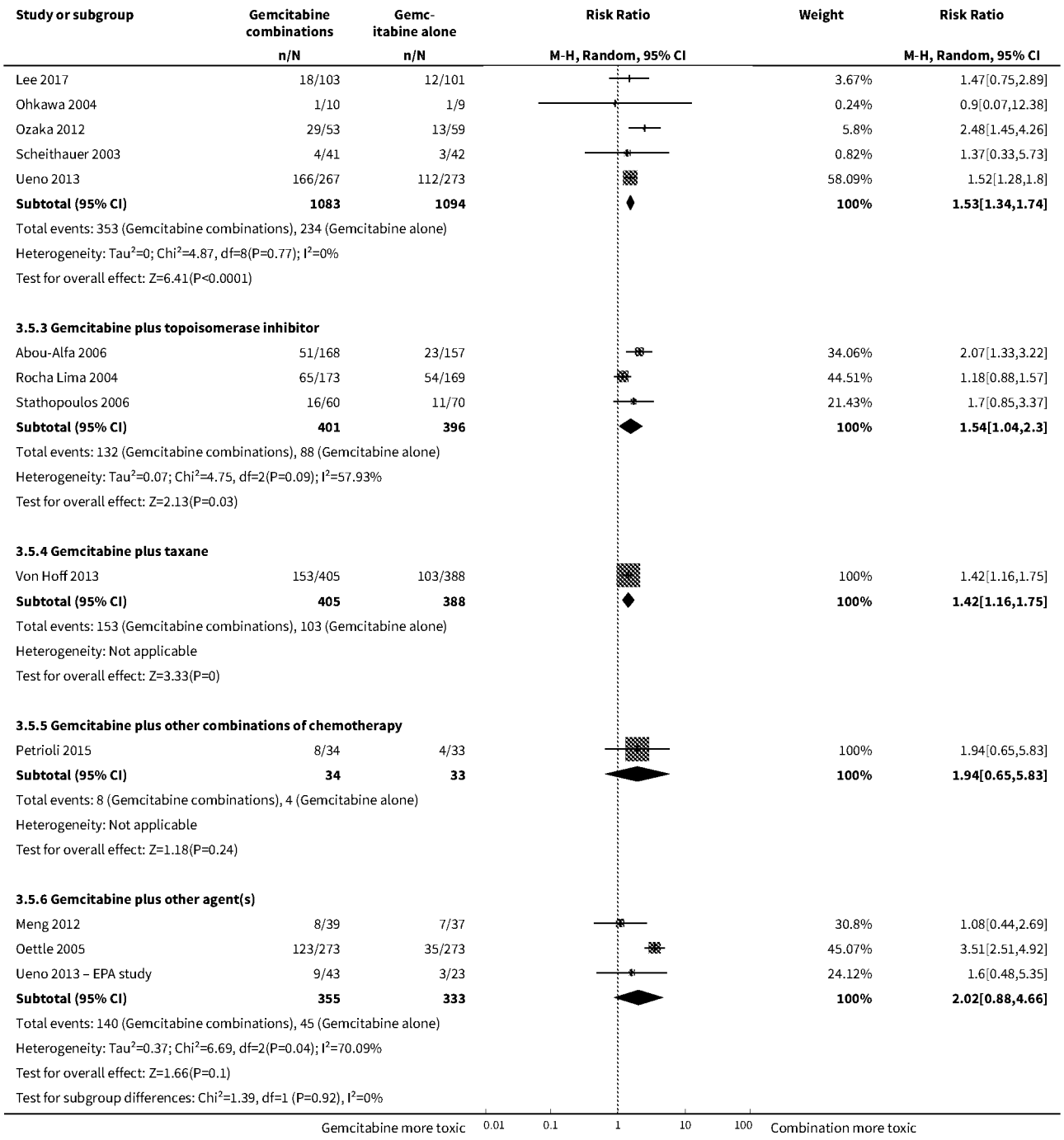
Analysis 3.4. Comparison 3 Gemcitabine combinations versus gemcitabine alone, Outcome 4 Grade 3/4 anaemia.





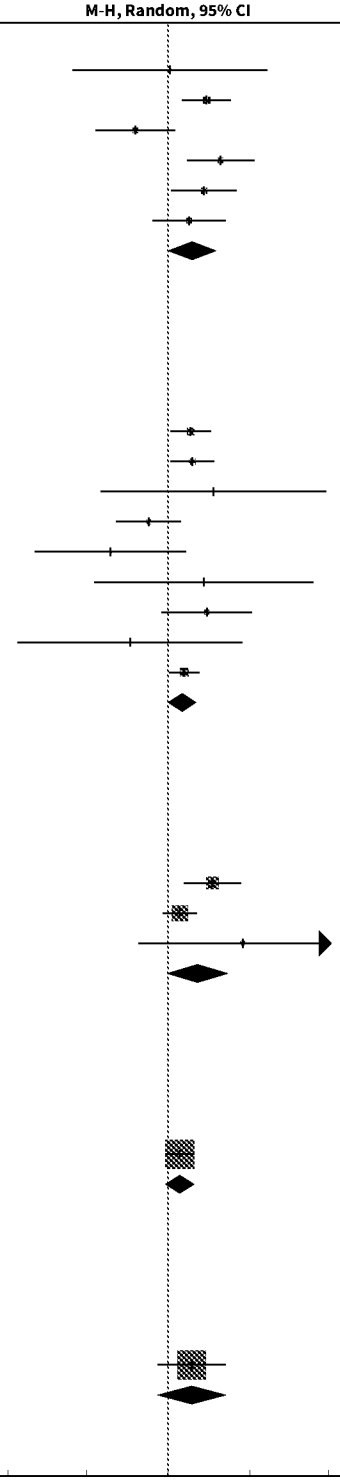
Analysis 3.5. Comparison 3 Gemcitabine combinations versus gemcitabine alone, Outcome 5 Grade 3/4 neutropenia.

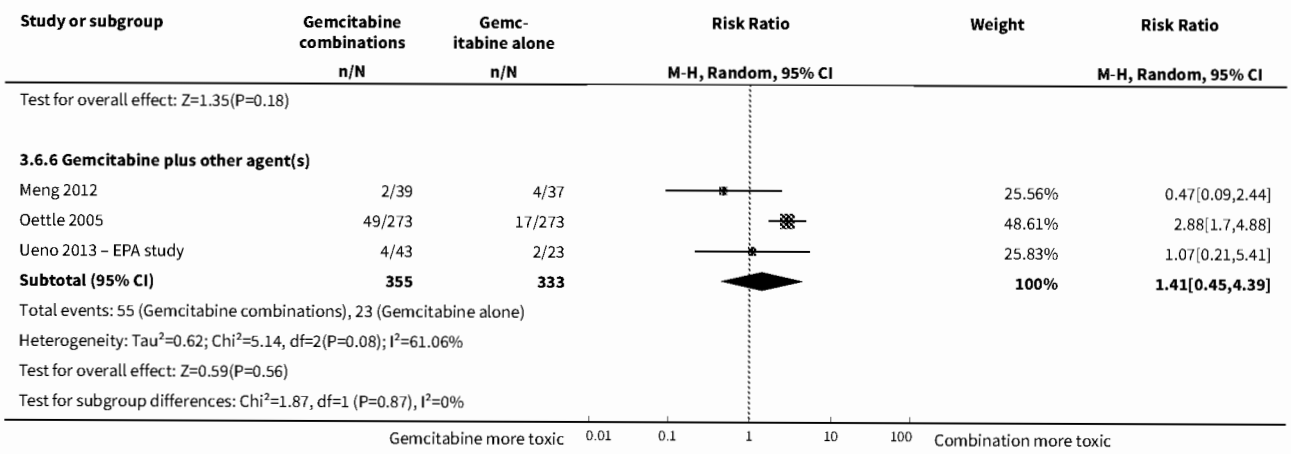




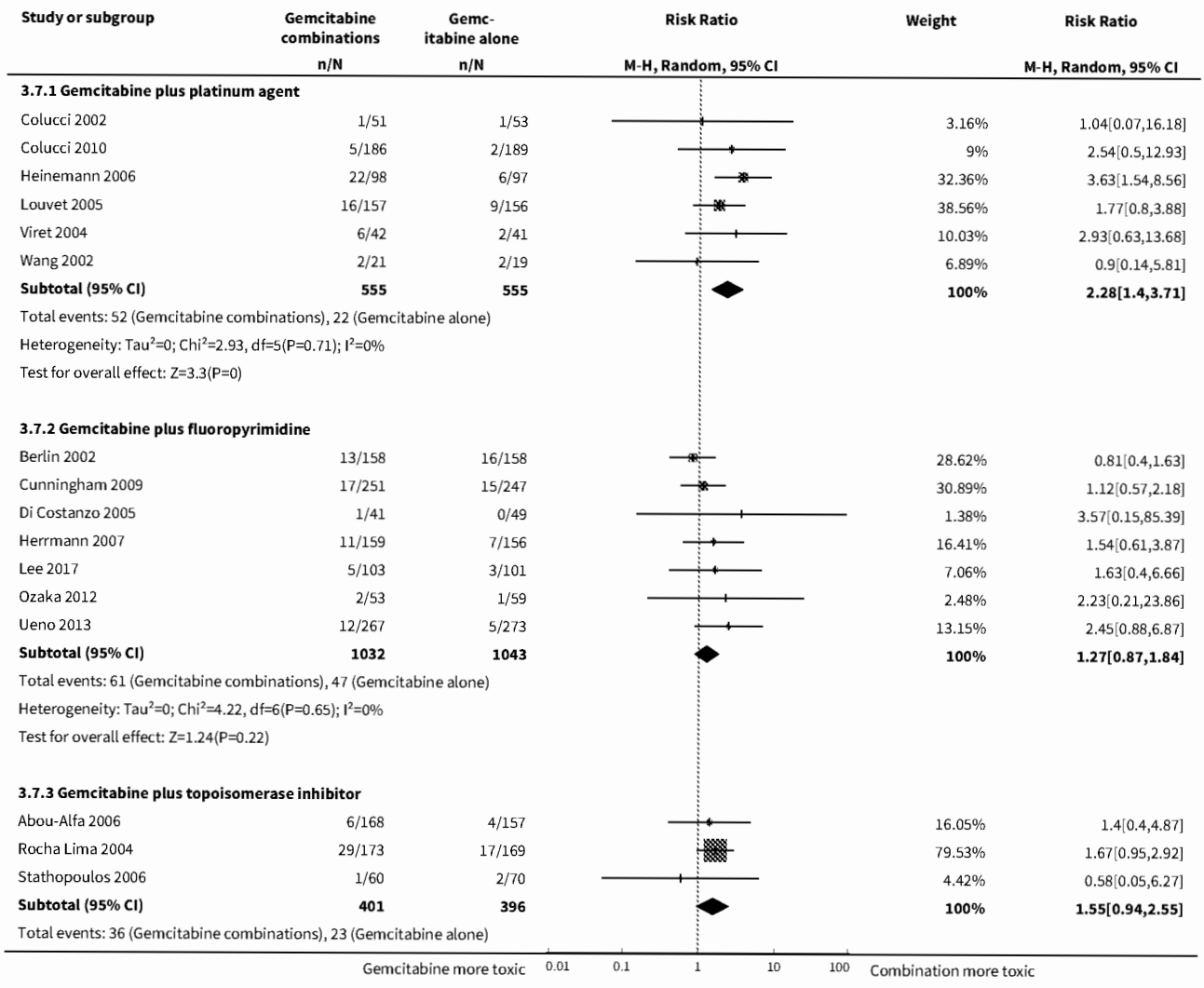
Analysis 3.6. Comparison 3 Gemcitabine combinations versus gemcitabine alone, Outcome 6 Grade 3/4 thrombocytopenia.

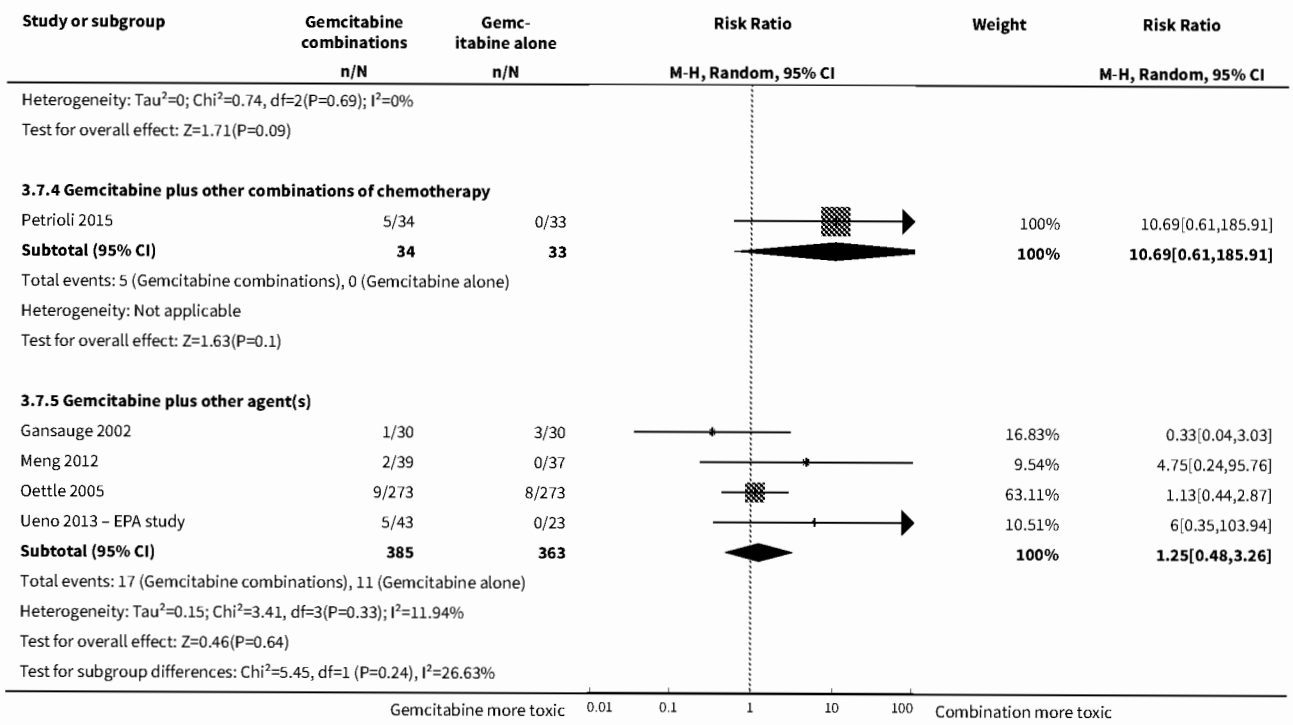
Study or subgroup	Gemcitabine combinations n/N	Gemc-itabine alone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.6.1 Gemcitabine plus platinum agent					
Colucci 2002	1/51	1/53		4.99%	1.04[0.07,16.18]
Colucci 2010	29/186	10/189		22.91%	2.95[1.48,5.87]
Heinemann 2006	4/98	10/97		16.34%	0.4[0.13,1.22]
Louvet 2005	22/157	5/156		18.89%	4.37[1.7,11.25]
Viret 2004	14/42	5/41		19.18%	2.73[1.08,6.9]
Wang 2002	8/21	4/19		17.69%	1.81[0.65,5.06]
Subtotal (95% CI)	**555**	**555**		**100%**	**1.96[1,3.84]**
Total events: 78 (Gemcitabine combinations), 35 (Gemcitabine alone)					
Heterogeneity: Tau^2=0.39; Chi^2=12.28, df=5(P=0.03); I^2=59.28%					
Test for overall effect: Z=1.97(P=0.05)					
3.6.2 Gemcitabine plus fluoropyrimidine					
Berlin 2002	30/158	16/158		22.6%	1.88[1.07,3.3]
Cunningham 2009	28/251	14/247		20.73%	1.97[1.06,3.65]
Di Costanzo 2005	1/41	0/49		1.47%	3.57[0.15,85.39]
Herrmann 2007	7/159	12/156		13%	0.57[0.23,1.42]
Lee 2017	1/103	5/101		3.13%	0.2[0.02,1.65]
Ohkawa 2004	1/10	0/9		1.55%	2.73[0.12,59.57]
Ozaka 2012	8/53	3/59		7.74%	2.97[0.83,10.61]
Scheithauer 2003	0/41	1/42		1.47%	0.34[0.01,8.14]
Ueno 2013	46/267	30/273		28.3%	1.57[1.02,2.41]
Subtotal (95% CI)	**1083**	**1094**		**100%**	**1.48[1,2.18]**
Total events: 122 (Gemcitabine combinations), 81 (Gemcitabine alone)					
Heterogeneity: Tau^2=0.09; Chi^2=11.59, df=8(P=0.17); I^2=30.97%					
Test for overall effect: Z=1.95(P=0.05)					
3.6.3 Gemcitabine plus topoisomerase inhibitor					
Abou-Alfa 2006	26/168	7/157		40.21%	3.47[1.55,7.77]
Rocha Lima 2004	34/173	24/169		52.38%	1.38[0.86,2.23]
Stathopoulos 2006	3/60	0/70		7.41%	8.15[0.43,154.64]
Subtotal (95% CI)	**401**	**396**		**100%**	**2.28[0.97,5.36]**
Total events: 63 (Gemcitabine combinations), 31 (Gemcitabine alone)					
Heterogeneity: Tau^2=0.3; Chi^2=4.86, df=2(P=0.09); I^2=58.86%					
Test for overall effect: Z=1.9(P=0.06)					
3.6.4 Gemcitabine plus taxane					
Von Hoff 2013	52/405	36/388		100%	1.38[0.93,2.07]
Subtotal (95% CI)	**405**	**388**		**100%**	**1.38[0.93,2.07]**
Total events: 52 (Gemcitabine combinations), 36 (Gemcitabine alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.59(P=0.11)					
3.6.5 Gemcitabine plus other combinations of chemotherapy					
Petrioli 2015	10/34	5/33		100%	1.94[0.74,5.07]
Subtotal (95% CI)	**34**	**33**		**100%**	**1.94[0.74,5.07]**
Total events: 10 (Gemcitabine combinations), 5 (Gemcitabine alone)					
Heterogeneity: Not applicable					



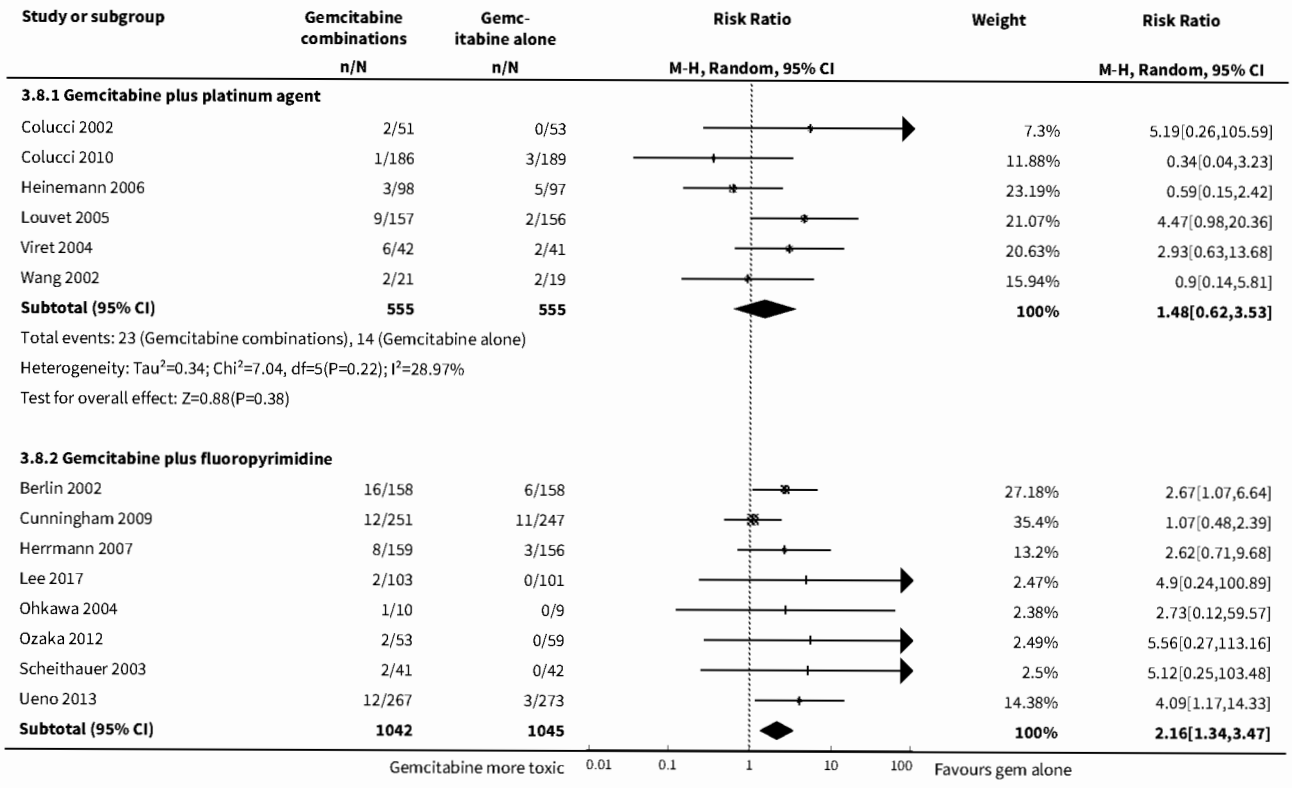


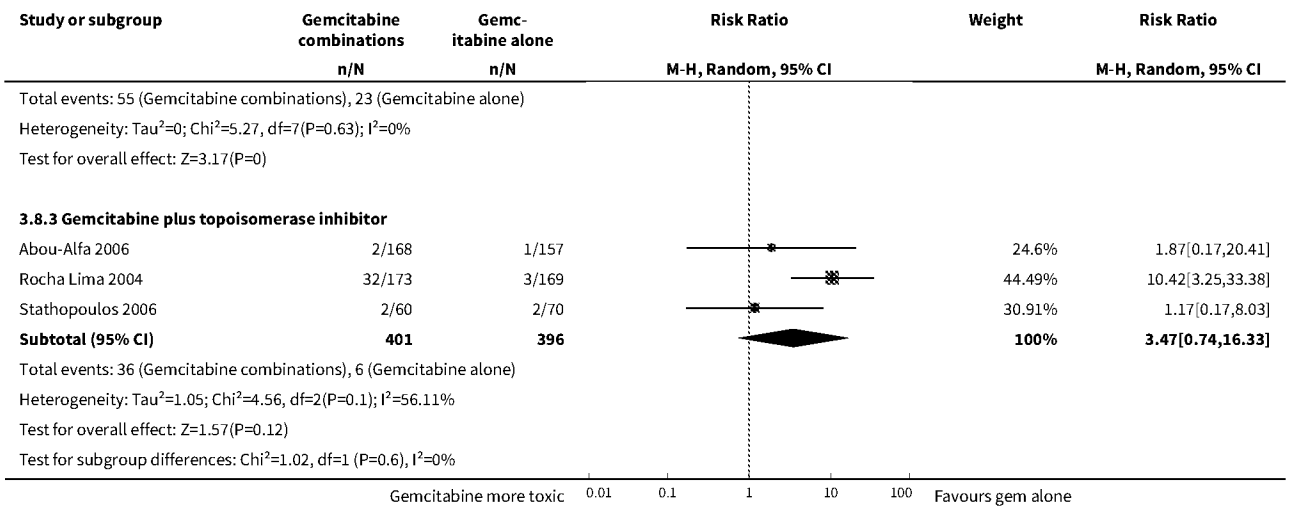
Analysis 3.7. Comparison 3 Gemcitabine combinations versus gemcitabine alone, Outcome 7 Grade 3/4 nausea.



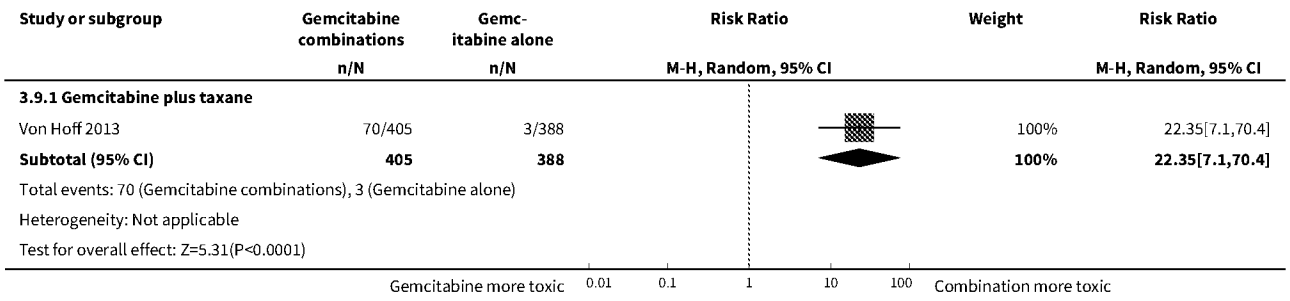


Analysis 3.8. Comparison 3 Gemcitabine combinations versus gemcitabine alone, Outcome 8 Grade 3/4 diarrhoea.

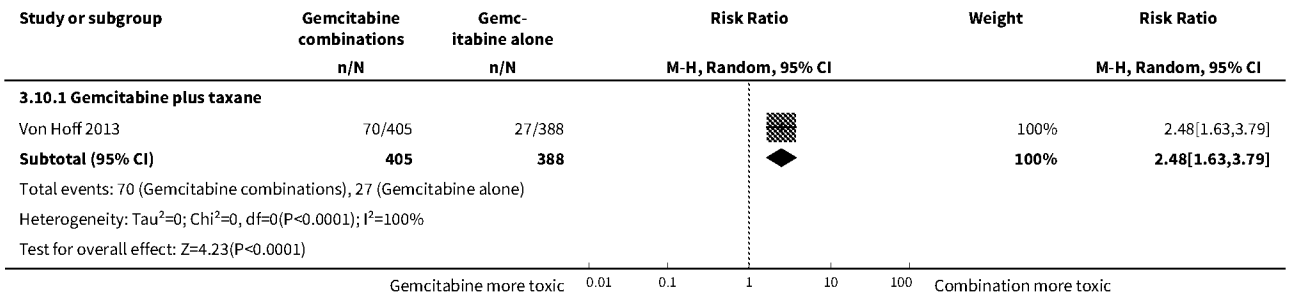




Analysis 3.9. Comparison 3 Gemcitabine combinations versus gemcitabine alone, Outcome 9 Grade 3/4 neuropathy.



Analysis 3.10. Comparison 3 Gemcitabine combinations versus gemcitabine alone, Outcome 10 Grade 3/4 fatigue.

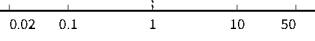


Comparison 4. Fluoropyrimidine combinations versus fluoropyrimidine alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	4	491	Hazard Ratio (Random, 95% CI)	0.84 [0.61, 1.15]
2 Progression-free survival	2	255	Hazard Ratio (Random, 95% CI)	0.52 [0.19, 1.38]
3 Response rates	4	410	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.52, 2.68]
4 Grade 3/4 anaemia	2	255	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.06, 3.62]
5 Grade 3/4 neutropenia	2	255	Risk Ratio (M-H, Random, 95% CI)	5.70 [0.73, 44.46]
6 Grade 3/4 thrombocytopenia	2	255	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.34, 5.80]
7 Grade 3/4 fatigue	1	209	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.43]
8 Grade 3/4 nausea	2	255	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.32, 3.53]
9 Grade 3/4 diarrhoea	2	255	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.31, 2.78]

Analysis 4.1. Comparison 4 Fluoropyrimidine combinations versus fluoropyrimidine alone, Outcome 1 Overall survival.

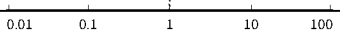
Study or subgroup	5FU combination N	5FU alone N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
Ducreux 2004	31	15	-1 (0.339)		14.85%	0.35[0.18,0.68]
Kovach 1974	30	30	0 (0.254)		20.62%	1.02[0.62,1.68]
Maisey 2002	102	107	-0.1 (0.128)		32.71%	0.9[0.7,1.16]
Moertel 1979	87	89	0 (0.137)		31.82%	1.02[0.78,1.33]
Total (95% CI)					**100%**	**0.84[0.61,1.15]**
Heterogeneity: Tau²=0.07; Chi²=8.83, df=3(P=0.03); I²=66.01%						
Test for overall effect: Z=1.1(P=0.27)						



Favours 5FU combinations | Favours 5FU alone

Analysis 4.2. Comparison 4 Fluoropyrimidine combinations versus fluoropyrimidine alone, Outcome 2 Progression-free survival.

Study or subgroup	5FU combination N	5FU alone N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
Ducreux 2004	31	15	-1.2 (0.321)		45.52%	0.3[0.16,0.56]
Maisey 2002	102	107	-0.2 (0.111)		54.48%	0.82[0.66,1.02]
Total (95% CI)					**100%**	**0.52[0.19,1.38]**
Heterogeneity: Tau²=0.45; Chi²=8.78, df=1(P=0); I²=88.62%						

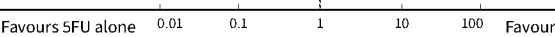


Favours 5FU combinations | Favours 5FU alone

Study or subgroup	5FU combination N	5FU alone N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
Test for overall effect: Z=1.31(P=0.19)						

Analysis 4.3. Comparison 4 Fluoropyrimidine combinations versus fluoropyrimidine alone, Outcome 3 Response rates.

Study or subgroup	5FU combination n/N	5FU alone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Ducreux 2004	3/31	0/15		6.89%	3.5[0.19,63.72]
Kovach 1974	5/31	10/30		30.59%	0.48[0.19,1.25]
Maisey 2002	18/102	9/107		36.1%	2.1[0.99,4.45]
Moertel 1979	6/48	5/46		26.42%	1.15[0.38,3.51]
Total (95% CI)	**212**	**198**		**100%**	**1.18[0.52,2.68]**
Total events: 32 (5FU combination), 24 (5FU alone)					
Heterogeneity: Tau^2=0.33; Chi^2=6.19, df=3(P=0.1); I^2=51.5%					
Test for overall effect: Z=0.4(P=0.69)					

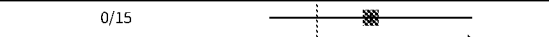


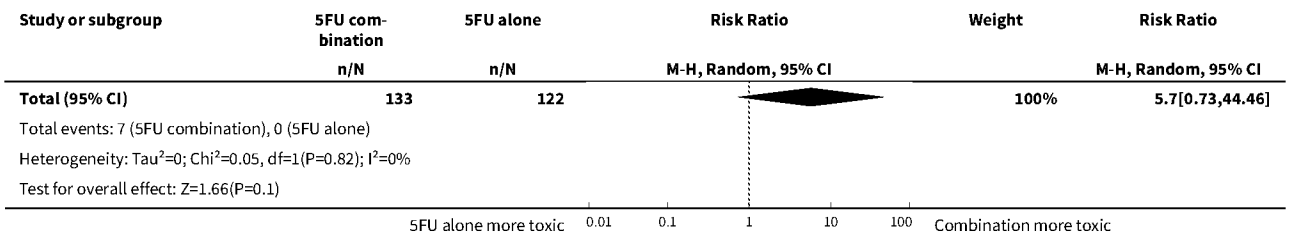
Analysis 4.4. Comparison 4 Fluoropyrimidine combinations versus fluoropyrimidine alone, Outcome 4 Grade 3/4 anaemia.

Study or subgroup	5FU combination n/N	5FU alone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Ducreux 2004	0/31	2/15		29.47%	0.1[0.01,1.96]
Maisey 2002	8/102	9/107		70.53%	0.93[0.37,2.32]
Total (95% CI)	**133**	**122**		**100%**	**0.48[0.06,3.62]**
Total events: 8 (5FU combination), 11 (5FU alone)					
Heterogeneity: Tau^2=1.28; Chi^2=2.02, df=1(P=0.16); I^2=50.4%					
Test for overall effect: Z=0.71(P=0.48)					

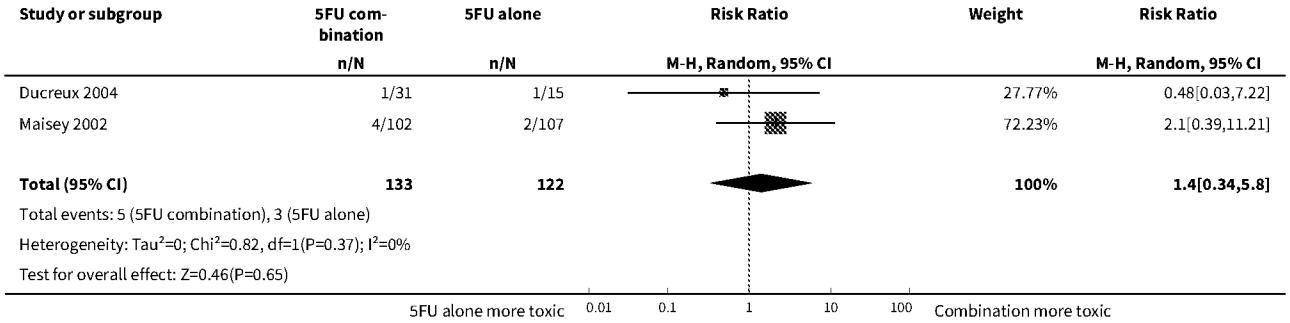
Analysis 4.5. Comparison 4 Fluoropyrimidine combinations versus fluoropyrimidine alone, Outcome 5 Grade 3/4 neutropenia.

Study or subgroup	5FU combination n/N	5FU alone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Ducreux 2004	4/31	0/15		51.57%	4.5[0.26,78.53]
Maisey 2002	3/102	0/107		48.43%	7.34[0.38,140.36]

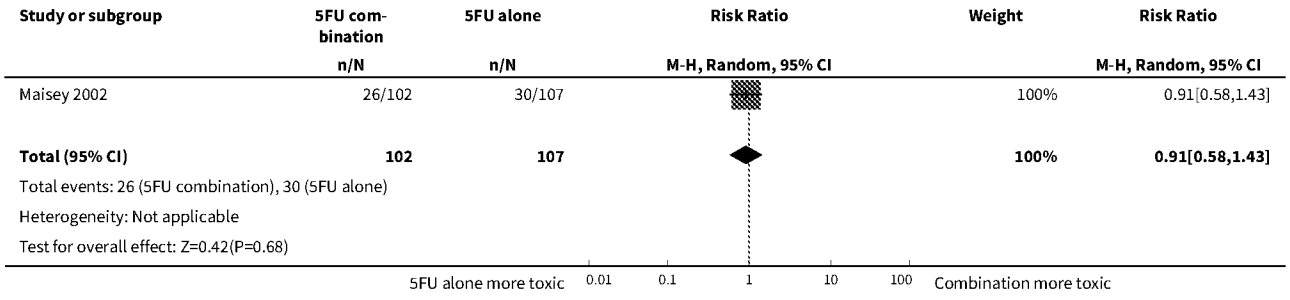




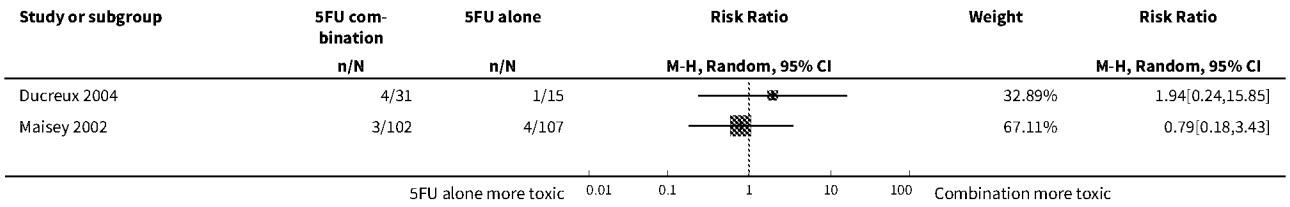
Analysis 4.6. Comparison 4 Fluoropyrimidine combinations versus fluoropyrimidine alone, Outcome 6 Grade 3/4 thrombocytopenia.

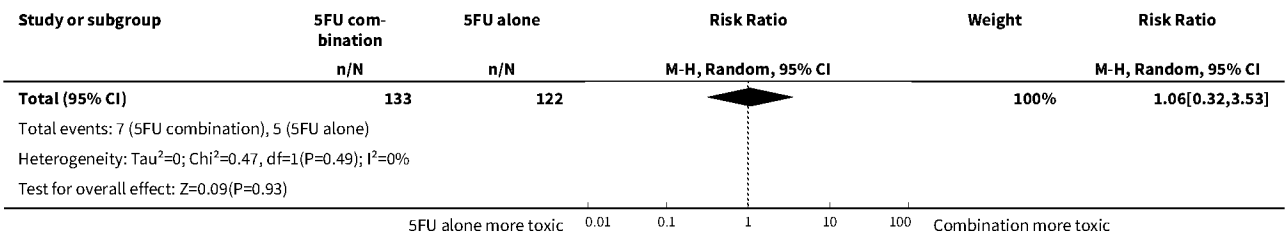


Analysis 4.7. Comparison 4 Fluoropyrimidine combinations versus fluoropyrimidine alone, Outcome 7 Grade 3/4 fatigue.

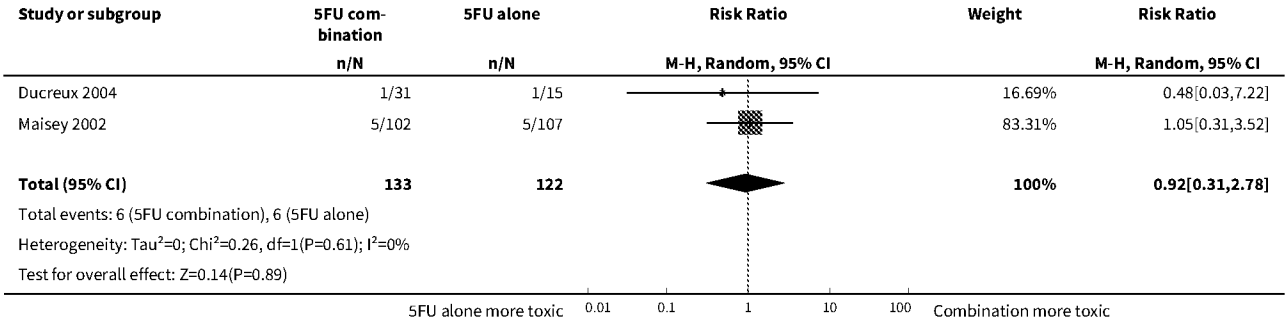


Analysis 4.8. Comparison 4 Fluoropyrimidine combinations versus fluoropyrimidine alone, Outcome 8 Grade 3/4 nausea.





Analysis 4.9. Comparison 4 Fluoropyrimidine combinations versus fluoropyrimidine alone, Outcome 9 Grade 3/4 diarrhoea.



ADDITIONAL TABLES

Table 1. Median survival times and quality of life results of anti-cancer therapy versus best supportive care

Study	Anti-cancer therapy details	Median survival:anti-cancer therapy vs best supportive care (months)	Quality of life
Andren-Sandberg 1983	5FU + CCNU	5 vs 4	No difference in Karnofsky performance status (KPS) score
Frey 1981	5FU + CCNU	3.0 vs 3.9	Not addressed
Glimelius 1996	5FU + LV	6.0 vs 2.5	EORTC QLQ-C30 results favoured the anti-cancer therapy (NB: high rate of dropouts in the later time points)
Huguier 2001	5FU + LV + cisplatin	8.6 vs 7.0	Not addressed
Takada 1998	5FU + doxorubicin + MMC	4.9 vs 5.0	Not addressed
Xinopoulos 2008	Gemcitabine	5.25 vs 5.5	Superior QoL (EORTC QLQ-C30) in the gemcitabine group during the 1st month (P = 0.028), no difference from the 2nd to the 4th month; in the 5th and 6th month superior QoL in the BSC group (P = 0.010 and < 0.001)

5FU: 5-Fluorouracil; **CCNU**: chloroethylcyclohexylnitrosurea; **EORTC QLQ-C30**: European Organisation for Research and Treatment of Cancer quality of life questionnaire for cancer patients; **LV**: leucovorin; **MMC**: 5FU+doxorubicin + mitomycin C

Table 2. Median survival times and quality of life results of various types of chemotherapy versus gemcitabine

Study	Type of other chemotherapy	Median survival:other chemotherapy vs gemcitabine (months)	Quality of life
Burris 1997	5FU	4.4 vs 5.7	Improved clinical benefit 4.8% vs 23.8%. Median time to benefit 7 vs 3 weeks. Duration of benefit 18 vs 13 weeks
Conroy 2011	FOLFIRINOX	11.1 vs 6.8	QLQ-C30: decrease in Global Health Status and QoL scale at 3 months 17% vs 31%; at 6 months 31% vs 66% Median time to definitive deterioration: not reached vs 5.7 months
Singhal 2014	FOLFIRINOX	10.8 vs 7.4	Definitive degradation of QoL at six months: 29% vs 59%
Poplin 2013	CO-101	5.2 vs 6.0	Not addressed
Smith 2003	ZD-9331	5.0 vs 3.6	Not addressed
Poplin 2009	Fixed dose rate gemcitabine 1500 mg/m^2 over 150 min	6.2 vs 4.9	Not addressed
Tempero 2003	Fixed dose rate gemcitabine 1500 mg/m^2 at 10 mg/m^2/min	8.0 vs 5.0	Not addressed
Cheverton 2004	Exatecan (DX-8951f)	5.0 vs 6.6	Time to worsening of clinical benefit was longer in the gemcitabine group. Pain (3.7 vs 7.9 months; P = 0.0493), KPS (3.4 vs 4.6 months; P = 0.0111) and weight (2.3 vs 3.8 months; P = 0.0203). QoL measured with QLQ-C3 and QLQ-PAN26 were similar in the 2 groups

5FU: 5-Fluorouracil; **FOLFIRINOX**: 5-fluorouracil + irinotecan + oxaliplatin; **QoL**: quality of life; **QLQ-C30** and **QLQ-PAN26:** general and pancreatic cancer specific QoL questionnaire.

Table 3. Median survival times and quality of life results of gemcitabine combinations versus gemcitabine alone

Study	Gemcitabine combination details	Median survival:gemcitabine combination vs gemcitabine alone (months)	Quality of life
Platinum combinations			

Table 3. Median survival times and quality of life results of gemcitabine combinations versus gemcitabine alone *(Continued)*

Colucci 2002	Gemcitabine + cisplatin	7.5 vs 5.0	Not addressed
Colucci 2010	Gemcitabine + cisplatin	7.2 vs 8.3	The mean difference from baseline in global QoL (EORTC C30) was not significantly different between the 2 groups: 0.09 (gemcitabine/cisplatin) vs 6.20 (gemcitabine), P = 0.07
Heinemann 2006	Gemcitabine + cisplatin	7.5 vs 6.0	No difference was detected in the 2 groups with either the Spitzer index or the pain intensity score
Li 2004	Gemcitabine + cisplatin	5.6 vs 4.6	Clinical benefit (pain control, performance status, body weight gain) 29% vs 36% (P > 0.05); Quality adjusted life months 3.8 vs 5.6 (P < 0.001)
Louvet 2005	Gemcitabine + oxaliplatin	9.0 vs 7.1	Not addressed
Viret 2004	Gemcitabine + cisplatin	8.0 vs 6.7	Q-TWiST results did not differ significantly between the 2 arms (EORTC C30)
Wang 2002	Gemcitabine + cisplatin	7.2 vs 9.1	Not addressed
Fluoropyrimidine combinations			
Berlin 2002	Gemcitabine + 5FU (weekly)	6.7 vs 5.4	Not addressed
Cunningham 2009	Gemcitabine + capecitabine	7.1 vs 6.2	89% of people completed QoL questionnaires (EORTC QLQ-C30 + ESPAC). No differences seen at baseline between the 2 groups and no differences across treatment groups at 3 or 6 months
Di Costanzo 2005	Gemcitabine + daily 5FU	7.5 vs 7.75	No differences were seen between the 2 groups in mean disturbed days after cycle 1 or 2 or mean of days a person would like to cancel treatment in cycle 1 or 2
Herrmann 2007	Gemcitabine + capecitabine	8.4 vs 7.2	CBR seen in 29% of people in combination arm and 20% of people in gemcitabine arm. Median duration of response 9.5 and 6.5 weeks, respectively (P < 0.02). No differences in QoL as measured by LASA
Lee 2017	Gemcitabine + capecitabine	10.3 vs 7.5	Not addressed
Ohkawa 2004	Gemcitabine + UFT	Not stated	Not addressed
Ozaka 2012	Gemcitabine + S1	13.7 vs 8.0	Not addressed
Riess 2005	Gemcitabine + 5FU (24 hour infusion) + FA	Not stated	Not addressed
Scheithauer 2003	Gemcitabine + capecitabine	9.5 vs 8.2	The gemcitabine + capecitabine arm had an improvement in pain (35.5 vs 20%), KPS (41.9 vs 27%), but not weight (9.7 vs 17%)
Ueno 2013	Gemcitabine + S1	10.1 vs 8.8	The gemcitabine + S1 group showed an improvement in QALYs 0.525 vs 0.401, P < 0.001

Table 3. Median survival times and quality of life results of gemcitabine combinations versus gemcitabine alone *(Continued)*

Topoisomerase combinations			
Abou-Alfa 2006	Gemcitabine + exatecan	6.2 vs 6.7	Not addressed
Rocha Lima 2004	Gemcitabine + irinotecan	6.3 vs 6.5	FACT-Hep questionnaires were completed by 80% of people in irinotecan/gemcitabine group and 73% of the gemcitabine group during the first 30 weeks of the study. There were no differences between the 2 groups.
Stathopoulos 2006	Gemcitabine + irinotecan	6.4 vs 6.5	Not addressed
Taxane combinations			
Von Hoff 2013	Gemcitabine + nab-paclitaxel	8.5 vs 6.7	Not addressed
Other combination chemotherapy including gemcitabine			
Petrioli 2015	Gemcitabine + oxaliplatin + capecitabine (GEMOXEL)	11.9 vs 7.1	The global QoL score was higher in the combination chemotherapy group at 2 months (61 vs 56) and 4 months (72 vs 66)
Reni 2005	Cisplatin/epirubicin/gemcitabine/5FU (PEFG)	Not stated	The EORTC-QLQ Pan 26 questionnaire was done but the sample size was insufficient to obtain adequate statistical power to reliably detect differences between groups for multiple comparisons. People in PEFG group 20% to 44% more likely to have improvement in emotional functioning, overall quality of life, cognitive measures, pain, fatigue, indigestion, dyspnoea, appetite loss and flatulence. However, people in gemcitabine group had better scores for sexual function and body image
Other agents in combination with gemcitabine			
Gansauge 2002	Gemcitabine + Ukrain	10.4 vs 5.2	Not addressed
Meng 2012	Gemcitabine + huachansu	5.2 vs 5.3	No significant differences were seen between the treatment groups with either the FACT-G or MDASI assessments
Oettle 2005	Gemcitabine + pemetrexed	6.2 vs 6.3	People in the gemcitabine group had better financial difficulties score, better physical functioning score and better cognitive functioning score. People in the gemcitabine/pemetrexed group had better pain scores. Performance status improvements was seen in 11.4% of gemcitabine/pemetrexed group and 9.4% of gemcitabine group. Weight gain was seen in 10.2% of gemcitabine/pemetrexed group and 5.7% of gemcitabine group
Ueno 2013 - EPA study	Gemcitabine + EPA	8.2 vs 9.7	Not addressed

5FU: fluorouracil; **CBR**: clinical benefit response; **ESPAC**: European Study Group for Pancreatic Cancer; **EORTC**: European Organisation for Research and Treatment of Cancer; **FACT-G**: Functional Assessment of Cancer Therapy; **FA**: folinic acid; **KPS**: Karnofsky performance status; **LASA**: linear-analog self-assessment indicators; **MDASI**: MD Anderson Symptom Inventory; **QALY**: quality-adjusted life year; **QLQ-C30**: quality of life questionnaire for cancer patients; **QoL**: quality of life; **Q-TWiST**: quality-adjusted time without symptoms or toxicity.

Table 4. Median survival times and quality of life results for fluoropyrimidine combinations versus fluoropyrimidine alone

Study	Fluoropyrimidine combination details	Median survival:fluoropyrimidine combination vs fluoropyrimidine alone (months)	Quality of life
Ducreux 2004	5FU + oxaliplatin	3.7 vs 3.4	Not addressed
Kovach 1974	5FU + BCNU	Not stated	Not addressed
Maisey 2002	5FU + MMC	6.5 vs 5.1	EORTC-QLQ C30 showed that at 24 weeks, global QoL was superior in the combination arm compared to baseline (P = 0.035), and the pain score was also improved (P = 0.048). There was less dyspnoea at 12 weeks in the combination arm when compared to baseline (P = 0.033).
Moertel 1979	5FU + streptozocin	4.5 vs 5.25	Not addressed

5FU: fluorouracil; **BCNU**: bis-chloroethylnitrosourea (carmustine); **EORTC QLQ-C30**: European Organisation for Research and Treatment of Cancer quality of life questionnaire for cancer patients; **MMC**: 5FU+doxorubicin + mitomycin C; **QoL**: quality of life.

Table 5. Results of studies addressing unique treatment comparisons

Study	Treatment arms/no. of participants	Survival outcomes	Response rates	Adverse events	Quality of life
Multi-armed studies					
Boeck 2008	Capecitabine/oxaliplatin (n = 61) versus capecitabine/gemcitabine (n = 64) versus modified gemcitabine/oxaliplatin (n = 63)	OS: 8.1 vs 9.0 v 6.9 months PFS 4.2 vs 5.7 v 3.9 months	PR 13% vs 25% vs 13% SbD: 36% vs 39% vs 43%	Haematological AEs more common in the gemcitabine containing arms	Not studied
Cullinan 1985	5FU (n = 50) versus 5FU/doxorubicin (n = 44) versus 5FU/doxorubicin/mitomycin C (n = 50)	Median survival of 22 weeks in all treatment groups	30% vs 30% vs 7.7%	Haematological AEs more common in the 5FU and 5FU/doxorubicin arm, however the subgroup with PC were not reported separately.	Not studied
Cullinan 1990	5FU (n = 64) versus 5FU/cyclophosphamide/methotrexate 'Mallinson Regimen' (n = 61) versus 5FU/doxorubicin/cisplatin 'FAP' (n = 59)	OS: 3.5 vs 4.5 vs 3.5 months respectively PFS: 2.5 vs 2.5 vs 2.5 months	7% vs 21% vs 15%	More AEs reported in the combination arms compared with 5FU alone	Not studied
Kulke 2009	Gemcitabine (fixed dose rate) (n = 64) versus infusional gemcitabine + cisplatin (n = 66) versus infusional gemcitabine + docetaxel (n = 65) versus infusional gemcitabine + irinotecan (n = 60)	OS: 6.4 vs 6.7 vs 6.4 vs 7.1 months, respectively. Time to progression: 3.3 vs 4.5 vs 4.1 vs 4.0 months	14 vs 12.5 vs 12 vs 14%	Neutropenia and fatigue most common AE and same in all groups	Not studied

Table 5. Results of studies addressing unique treatment comparisons *(Continued)*

Other studies

Afchain 2009	Gemcitabine/oxaliplatin (n = 20) vs simplified gemcitabine/oxaliplatin (n = 37)	OS: 3.2 vs 7.6 months PFS: 2.5 vs 4.0 months	PR: 10% vs 27% SbD: 45% vs 43%	Peripheral neuropathy more common in the simplified GemOx arm	Not studied
Bukowski 1983	Mitomycin C/5FU (MF) (n = 73) vs Streptozocin/mitomycin C/5FU (SMF) (n = 72)	OS: 17 vs 18 weeks	PR: 8% v 34%	More gastrointestinal and renal toxicity in the SMF arm	Not studied
Corrie 2017	Standard nab-paclitaxel and gemcitabine (n = 75) vs sequential nab-paclitaxel and gemcitabine (n = 71)	OS: 7.9 vs 10.1 months (HR 0.88) PFS: 4.0 vs 5.8 months (HR 0.66)	PR: 33% vs 50% SbD: 28% vs 42%	Neutropenia more common in the sequential arm	QoL score dropped by −12.1 points at 24 weeks in the standard arm vs −2.1 in the sequential arm
Hirao 2011	Gemcitabine 3-week schedule (n = 45) vs gemcitabine 4-week schedule (n = 45)	OS: 250 vs 206 days PFS: 114 vs 112 days	17.1% vs 14.2%	Thrombocytopenia more common in the 4-week schedule	Not studied
Kelsen 1991	Streptozocin/mitomycin C/5FU (SMF) (n = 42) vs cisplatin/ara-C/caffeine (CAC) (n = 40)	OS: 10 vs 5 months	10% vs 6%	Nausea and vomiting more common in CAC arm.	Not studied
Levi 2004	5FU constant infusion vs 5FU constant infusion/cisplatin versus 5FU chronomodulated infusion vs 5FU chronomodulated infusion/cisplatin (no cisplatin n = 55, with cisplatin n = 52)	OS: 5.4 vs 8.3 months (no cis vs cis) OS: 6.1 vs 6.7 months (continuous vs chronomodulated) PFS: 2.1 vs 3.2 months	Not reported	Cisplatin increased rates of haematological AEs. Chronomodulated regimen increased rates of mucositis	Not studied
Lutz 2005	Gemcitabine + docetaxel (n = 49) vs cisplatin + docetaxel (n = 47)	OS: 7.0 vs 7.5 months PFS: 3.9 vs 2.8 months	19.4% vs 23.5%	Febile neutropenia more common in the cisplatin/docetaxel arm	Not studied
Moertel 1977	Streptozocin + 5FU (n = 40) vs streptozocin + cyclophosphamide (n = 48)	OS: 13 vs 9 weeks	CR: 3 vs 6 PR: 2 vs 0 SbD: 9 vs 9	Haematological AEs more common in the cyclophosphamide arm	Not studied
Reni 2012	Capecitabine + cisplatin + gemcitabine + docetaxel (PDXG) (n = 53) vs capecitabine + cisplatin + gemcitabine + epirubicin (PEXG) (n = 52)	OS: 10.7 vs 11 months PFS: 7.4 vs 7.6 months	CR: 2 vs 4% PR: 58 vs 33%	Neutropenia more common in the PEXG arm	Not studied

Table 5. Results of studies addressing unique treatment comparisons *(Continued)*

Topham 1991	Epirubicin (n = 32) vs 5FU + epirubicin + mitomycin C (n = 30)	1 year survival rates 15.4 vs 23.2%	8% vs 11%	AEs were similar in both arms	Not studied

5FU: fluorouracil; **AE**: adverse event; **CR**: complete response; **OS**: overall survival; **PC**: pancreatic cancer; **PR**: partial response; **SbD**: stable disease.

APPENDICES

Appendix 1. Glossary of terms

Adenocarcinoma: cancer arising from glandular tissue
Analgesia: medication used to relieve pain
Anti-neoplastic: stopping or preventing the growth and spread of cancerous cells
Antibody: a protein produced to neutralise another protein. In the case of cancer treatment, these proteins block particular cancer pathways
Aortic: the large artery that originates in the heart and supplies the body with blood
Biliary: related to the structures that carry bile (a substance which is produced by the liver and responsible for helping the digestion of fats)
Cobalt source: radioisotope from which radiation is emitted
Coeliac abutment: when tumour touches but does not invade the coeliac vessels, the blood supply around the pancreas
Complete response: when a tumour is no longer seen on imaging in response to treatment
Cytotoxic: chemicals or drugs capable of killing cells
Dyspnoea: difficulty breathing
Epigastric: the top, middle part of the abdomen, the area around the stomach
Flatulence: gas
Insomnia: difficulty sleeping
Jaundice: the yellowing of the skin, whites of of the eyes and mucous membranes due to high levels of bilirubin
Lethal: capable of causing death
Mesenteric vein: one of the two veins responsible for draining the intestines
Neutropenia: low white cell count. Can pre-dispose patients to getting serious infections
Nodal: related to lymph nodes
Palliative: treatment with the intention of improving symptoms, not cure
Partial response: when a tumour shrinks on imaging in response to treatment
Placebo: sham or fake treatment
Portal occlusion: the blockage of the portal vein, a large vein in the abdomen
Resection: surgical removal
Stable disease: when tumour growth stabilises in response to treatment (does not change in size between scans)
Stent: a small tube used to relieve blockages
Thrombocytopenia: low platelet count. Can pre-dispose patients to serious bleeding
Thromboembolic: blood clots in the calf or lung veins
Toxicities: side effects

Appendix 2. CENTRAL search strategy

1. exp Pancreas/
2. (carcin$ or cancer$ or neoplas$ or tumour$ or tumor$ or growth$ or adenocarcin$ or malig$).mp.
3. 1 and 2
4. Carcinoma, Pancreatic Ductal/
5. Pancreatic Neoplasms/
6. or/3-5
7. Antineoplastic Protocols/
8. chemotherap*.tw.
9. Radiotherapy/
10. chemoradiotherap*.tw.
11. chemo-radiotherap*.tw.
12. radiochemotherap*.tw.
13. radio-chemotherap*.tw.

14.Biological Therapy/
15.Immunotherapy, Adoptive/
16.exp Immunotherapy, Active/
17.cetuximab.tw.
18.erlotinib.tw.
19.bevacuzimab.tw.
20.panitumumab.tw.
21.trastuzumab.tw.
22.Protein-Tyrosine Kinases/ai [Antagonists & Inhibitors]
23.tyrosine kinase inhibitor*.tw.
24.interleukins.tw.
25.exp Interleukins/
26.Cancer Vaccines/
27.Antibodies, Monoclonal/
28.exp Interferons/
29.Molecular Targeted Therapy/
30.or/7-29
31.6 and 30

Appendix 3. MEDLINE search strategy

1. exp Pancreas/
2. (carcin$ or cancer$ or neoplas$ or tumour$ or tumor$ or growth$ or adenocarcin$ or malig$).mp.
3. 1 and 2
4. Carcinoma, Pancreatic Ductal/
5. Pancreatic Neoplasms/
6. or/3-5
7. Antineoplastic Protocols/
8. chemotherap*.tw.
9. Radiotherapy/
10.exp Chemoradiotherapy/
11.chemoradiotherap*.tw.
12.chemo-radiotherap*.tw.
13.radiochemotherap*.tw.
14.radio-chemotherap*.tw.
15.Biological Therapy/
16.Immunotherapy, Adoptive/
17.exp Immunotherapy, Active/
18.cetuximab.tw.
19.erlotinib.tw.
20.bevacuzimab.tw.
21.panitumumab.tw.
22.trastuzumab.tw.
23.Protein-Tyrosine Kinases/ai [Antagonists & Inhibitors]
24.tyrosine kinase inhibitor*.tw.
25.interleukins.tw.
26.exp Interleukins/
27.Cancer Vaccines/
28.*Antibodies, Monoclonal/
29.exp Interferons/
30.Molecular Targeted Therapy/
31.or/7-30
32.6 and 31

33.randomized controlled trial.pt.
34.controlled clinical trial.pt.
35.randomized.ab.
36.placebo.ab.
37.clinical trials as topic.sh.
38.randomly.ab.
39.trial.ti.
40.or/33-39
41.exp animals/ not humans.sh.
42.40 not 41
43.32 and 42

Appendix 4. EMBASE search strategy

1. exp Pancreas/
2. (carcin$ or cancer$ or neoplas$ or tumour$ or tumor$ or growth$ or adenocarcin$ or malig$).mp.
3. 1 and 2
4. Carcinoma, Pancreatic Ductal/
5. Pancreatic Neoplasms/
6. or/3-5
7. Cancer chemotherapy/
8. Cancer radiotherapy/
9. exp Chemoradiotherapy/
10.chemoradiotherap*.tw.
11.chemo-radiotherap*.tw.
12.radiochemotherap*.tw.
13.radio-chemotherap*.tw.
14.Biological Therapy/
15.exp Immunotherapy, Active/
16.vaccine/ or cancer vaccine/ or tumor cell vaccine/ or tumor vaccine/
17.active immunization/
18.antineoplastic agent/
19.cetuximab/
20.erlotinib/
21.bevacizumab/
22.panitumumab/
23.trastuzumab/
24.protein tyrosine kinase inhibitor/
25.interleukin derivative/
26.cancer vaccine/
27.monoclonal antibody/
28.exp interferon/
29.immunotherapy/ or adoptive immunotherapy/ or cancer immunization/
30.molecularly targeted therapy/
31.or/7-30
32.6 and 31
33.random:.tw. or placebo:.mp. or double-blind:.tw.
34.32 and 33

HISTORY

Protocol first published: Issue 6, 2013
Review first published: Issue 3, 2018

Date	Event	Description
30 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

VC: protocol design, sourcing articles, reviewer one, data entry, analysis, results, discussion and conclusion, preparation of manuscript.
AN: protocol design, reviewer two, analysis, statistics support, reviewing of manuscript.
KS: protocol design, statistics support, reviewing of manuscript.
CO: protocol design, radiotherapy trials/methodology support, reviewing of manuscript.
LC: protocol design, reviewing of manuscript.
AB: protocol design, reviewing of manuscript.
RS: data analysis and statistical support, reviewing of the manuscript.
DY: author of previous version of this review, protocol design, methodological support, reviewer three, reviewing of manuscript.

DECLARATIONS OF INTEREST

VC: Venessa Chin received scholarship funding from the Research and Education Foundation of the Royal Australasian College of Physicians, Pancare Australia, Sydney Catalyst, National Health and Medical Research Council, and the Garvan Institute of Medical Research for work related to this review.

AN: none known.

KS: Katrin Sjoquist received programme grant funding from the National Health and Medical Research Council for work related to this review. She has received consultancy fees, fees for expert testimony and travel support for work unrelated to this review.

CO: none known.

LC: Lorraine Chantrill is employed (part-time) by NSW Health as a staff specialist in medical oncology and enrolled full-time in PhD studies supported by the Australian Federal Government. She has been paid as an advisory board member in relation to chemotherapy for pancreas cancer and has been paid for formulating educational materials and presentations. She has received grants for the practice of clinical trials in pancreas and other cancers.

AB: Andew Biankin received grant funding from the Cancer Institute NSW for work related to this review. He also received consultancy fees from Celegene and Clovis Oncology for work unrelated to this review. His institution received consultancy fees from Roche for work unrelated to this review.

RS: Rob Scholten's institution has received grant funding from the Belgian Health Care Knowledge Centre for work related to this review. His institution has also received funding from the WHO and World Federation of Haemophilia for travel and consultancy unrelated to this review.

DY: Advisory Board Member, Specialised Therapeutics.

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Internal sources

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  PhD stipend top up for Venessa Chin

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  PhD stipend for Venessa Chin
- Pancare Australia, Australia.

  PhD stipend for Venessa Chin

- Sydney Catalyst, Australia.

PhD stipend for Venessa Chin

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Biological agents, second line therapies, locally advanced PC

The original protocol included studies addressing biological therapies, studies addressing second-line treatment and people with locally advanced disease. We felt that due to the large number of comparisons, the review became unmanageable. We therefore decided to split the review and concentrate on chemotherapy and radiotherapy in the advanced setting. Separate reviews will report on biological and immunological agents, second-line therapies and studies dealing exclusively with people with non-metastatic, locally advanced disease.

Outcomes

The original protocol did not include adverse events, response rates and quality of life as secondary outcomes. Prior to data extraction, the review authors added those as secondary outcomes. We deleted disease-specific survival as a secondary outcome.

Measures of treatment effect

The original protocol stated that fixed-effect model meta-analyses would be used to pool results for survival at 6 months and 12 months. It was never our intention to use 6- and 12-month survival as endpoints in this review. We instead used HRs for overall and progression-free survival. We employed random-effect models for most analyses given the experimental arms were often very different within each comparison.

Dealing with multi-armed studies

In such cases where studies reported the event rates for all arms, we divided the control arm accordingly and entered all arms of the studies into the analysis as appropriate. Where the event rates were not available, if the study had two arms that fell into a subgroup analysis, then we analysed only these two arms. We described any study that we could not analyse in the above two scenarios in table form only.

Number needed to treat (NNT) as a secondary endpoint

We replaced this outcome with GRADE 'Summary of findings' tables.

INDEX TERMS

Medical Subject Headings (MeSH)

Albumins [administration & dosage]; Antineoplastic Combined Chemotherapy Protocols [*therapeutic use]; Cisplatin [administration & dosage]; Deoxycytidine [administration & dosage] [adverse effects] [analogs & derivatives]; Epirubicin [administration & dosage]; Fluorouracil [administration & dosage]; Paclitaxel [administration & dosage]; Pancreatic Neoplasms [*drug therapy] [mortality] [pathology] [radiotherapy]; Pyrimidines [administration & dosage]; Randomized Controlled Trials as Topic; Treatment Outcome

MeSH check words

Humans

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[Articles]

Effects of 5-Fluorouracil and Leucovorin in the Treatment of Pancreatic-Biliary Tract Adenocarcinomas

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Abstract

Adenocarcinomas of the pancreas and biliary tract are highly malignant neoplasms, which are found in the advanced stage. Chemotherapy commonly plays a palliative role in the treatment of pancreatic and biliary tract cancers. 5-Fluorouracil (5-FU) is the most widely studied single agent; the response rate of 5-FU is only 20%. Recently, some reports presented interesting results, in which 5-FU, modulated with levofolinic acid (leucovorin), was active in patients with colorectal cancer. In relation, we performed a phase II study of 5-FU, modulated with leucovorin, in patients affected by advanced pancreatic or biliary tract cancer. Fifty-one patients with nonresectable carcinomas of the pancreas or biliary tract admitted to Korea University Hospital between May 1995 and December 1998 were included in this study. Chemotherapy consisted of leucovorin 25 mg/m^2/day by 2-hour intravenous infusion, followed by 5-FU 375 mg/m^2/day by bolus intravenous infusion, from day 1 to day 5. The treatment was repeated every 3 to 4 weeks. A total of 51 eligible patients with advanced adenocarcinoma of the pancreas or biliary tract were enrolled. Of 23 enrolled patients with pancreatic adenocarcinoma, one patient showed complete remission with a survival duration of 13 months (response duration was 9 months). Three patients had partial responses (PRs) with survival times of 6, 12, and 15 months, respectively. The overall response rate was 17.4% (95% confidence interval [CI], 7.2%-36.2%). The median time of overall survival was 6 months (range: 1-15 months). Of 28 enrolled patients with biliary tract cancer, complete responses were observed in 2 patients (7.1%) with survival time of 14 and 16 months, respectively. Seven patients had PRs with a median survival of 8 months. The overall response rate was 32.1% (95% CI, 20.3%-57.5%). The median time of overall survival was 6 months (range: 1-16 months). The most prominent toxicity was mucositis. Hematologic toxicity was less severe. 5-Fluorouracil in modulation with intravenous leucovorin is well tolerated by patients with stage IV pancreatic adenocarcinoma or biliary tract cancer. Although the response rate for patients with pancreatic adenocarcinoma is not better than that achieved using 5-FU monochemotherapy, the 32.1% overall response rate achieved in patients with biliary tract cancer suggests that 5-FU modulation with leucovorin is active in biliary tract cancer.

Adenocarcinomas of the pancreas and biliary tract are highly malignant neoplasms with an extremely poor prognosis, especially in the advanced stage of the disease. Many patients seeking treatment pancreatic or biliary tract carcinomas are at the advanced stage. At the advanced stage, curative surgery is impossible because of metastasis, and resection is extremely difficult in locally advanced tumors; even after a potentially curative resection, both local and distant failures are common. Thus, chemotherapy often plays a palliative role as a single treatment modality in the treatment of pancreatic or biliary tract cancer.

Only a few single agents have demonstrated substantial activity, and there are no data to suggest that combination regimens are superior to single agents alone. 1-3 5-Fluorouracil is the most widely studied single agent, with a nearly 20% overall response rate. 4,5 The median time of response with 5-FU is brief, usually 3 to 6 months. Because 5-FU is the single most active drug for adenocarcinomas of the pancreas and biliary tract, there has been intense interest in the modulation of 5-FU as has been performed in colorectal cancers. 6-8 Based on these interesting results achieved in the treatment of patients with advanced colorectal carcinoma, we performed a phase II study of 5-FU modulated with leucovorin in a series of patients with advanced pancreatic or biliary tract cancer.

MATERIALS AND METHODS

Patients

Fifty-one patients with nonresectable carcinomas of the pancreas or biliary tract, who were admitted to Korea University Hospital between May 1995 and April 1998, and who fulfilled the following criteria were eligible for this study: 1) those histologically diagnosed as having carcinomas of the pancreas or biliary tract, whose major lesions were not resectable or operable; 2) those with performance status of 0 and 3 and no serious complications; 3) those with baseline laboratory test values of complete blood count (leukocyte count of >=4,000/mm^3 with an absolute neutrophil count >=1,500/mm^3, platelet counts >=120,000/mm^3, hemoglobin >=10 g/dl), liver function test (serum bilirubin <2 mg/dl), and kidney function (serum creatinine <=1.2 mg/dl and blood urea nitrogen <=50 mg/dl) in the normal range; and 4) those with lesions bidimensionally measurable or with assessable disease. Assessable disease was defined as bulky, irregularly shaped, unresectable primary tumor, whose size could be estimated but not be precisely measured bidimensionally.

Treatment

Chemotherapy was administered in the hospital and consisted of leucovorin 25 mg/m^2/day by 2-hour intravenous infusion, followed by 5-FU 375 mg/m^2/day by bolus intravenous infusion, from day 1 to 5. The treatment was repeated every 4 weeks. Chemotherapy was continued until progression of disease or unacceptable toxicity ensued. Doses were reduced (20%) in the cases of grade III oral mucositis or grade IV neutropenia.

Evaluation

After two complete cycles of chemotherapy, patients were restaged. Objective responses were classified according to the World Health Organization criteria. 9 Complete response (CR) was defined as disappearance of all known disease and partial response (PR) as a decrease of greater than 50% in the product of two perpendicular diameters of each measurable lesion. Stable disease was confirmed in cases where there was less than 25% increase in size in one or more of the lesions but less than 50% decrease in total tumor size. To qualify as a response, reduction in tumor dimensions had to last at least 4 weeks. Time to disease progression and survival duration were determined from the first day of treatment.

Statistics

Survival curves were plotted according to the method of Kaplan-Meier, and statistical significance of differences was determined according to Wilcoxon signed-rank test.

RESULTS

A total of 51 eligible patients with advanced adenocarcinoma of the pancreas or biliary tract were enrolled in this clinical trial. The median performance status on the Eastern Cooperative Oncology Group scale was 1, with a range set from 0 to 3. The clinical characteristics of the enrolled patients are presented in Table 1.

TABLE 1. *Characteristics of patients*

	Pancreatic adenocarcinoma	Biliary tract cancer
No. of patients	23	28
Median age (y)	60	57
Range	36–79	41–83
Performance status		
0, 1	7	15
2, 3	16	13
Male/female	15/8	20/8
Previous treatment		
Surgery	1	7
Radiotherapy	1	1
Sites of metastatic disease		
Liver	9	19
Distant lymph nodes	6	6
Peritoneum	2	2
Bone	4	1
Spleen	1	0
Adrenal gland	3	0
Lung	0	4

Table 1. Characteristics of patients

Pancreatic Adenocarcinoma

The 23 enrolled patients had stage IV pancreatic cancer and a median age of 60 years (range, 36-79 years). There were 15 men (65%) and 8 women (35%). The median number of cycles per patient was 2 (range, 1-17 cycles). One patient showed a CR with a survival duration of 13 months (response duration was 9 months). Three patients had a PR with survival duration of 6, 12, and 15 months, respectively. The overall response rate was 17.4% (95% confidence interval, 7.2%-36.2%). Four patients had stable disease (17.4%), and 15 patients (65.2%) had progressive disease (Table 2). The median duration of overall survival was 6 months (Fig. 1).

TABLE 2. *The responses of 5-fluorouracil with leucovorin in pancreatic–biliary tract cancer*

	Pancreatic cancer	Biliary cancer
No. of patients	23	28
Response		
Complete response	1 (4.3%)	2 (7.2%)
Partial response	3 (13.1%)	7 (25.0%)
Stable disease	4 (17.4%)	6 (21.4%)
Progressive disease	15 (65.2%)	13 (46.4%)
Total treatment cycles	74	103
Median	2	2
Median duration of survival (mo)	6	6
Range	1–15	1–16

Table 2. The responses of 5-fluorouracil with leucovorin in pancreatic-biliary tract cancer

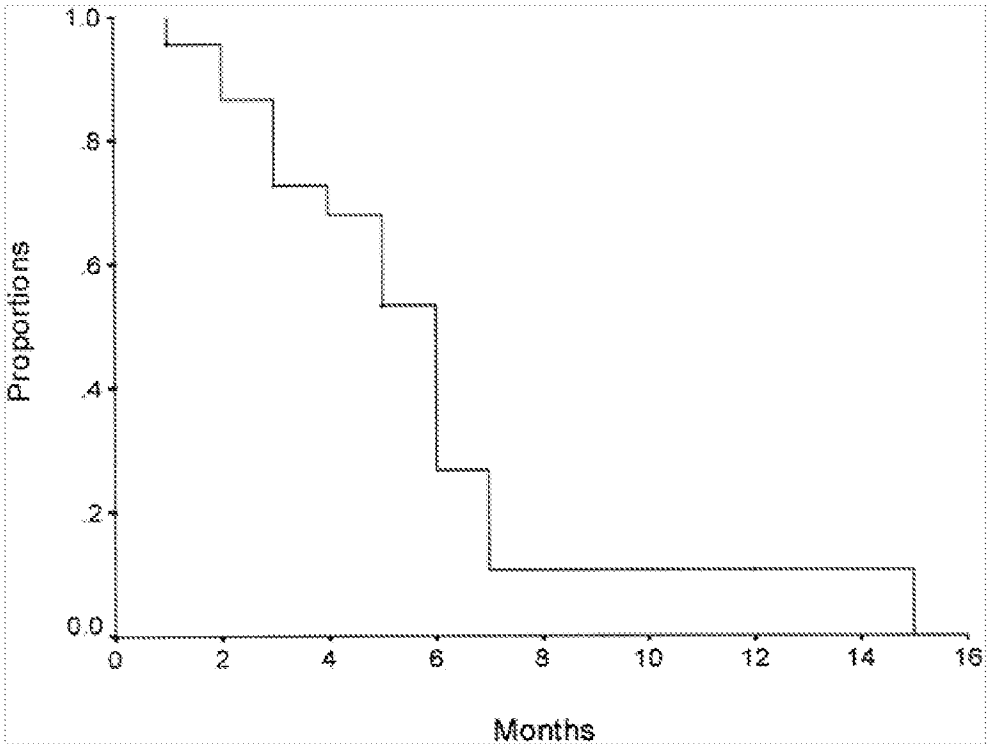

FIG. 1. Survival curve of pancreatic adenocarcinoma (median survival: 6 months).

Biliary Tract Cancer

The 28 enrolled patients had stage IV gallbladder cancer (9 patients) or cholangiocarcinoma (19 patients) and a median age of 57 years (range, 41-83 years). There were 20 men (71%) and 8 women (29%).

Complete responses were recorded in 2 patients (7.1%) with survival durations of 14 and 16 months, respectively. Seven patients had PRs with a median survival duration of 7 months. Stable disease in 6 patients (21%) and progressive disease in 13 patients (46.4%) were observed (Table 2). The overall response rate was 32.1% (95% confidence interval, 20.3%-57.5%). The median duration of survival was 6 months (Fig. 2).

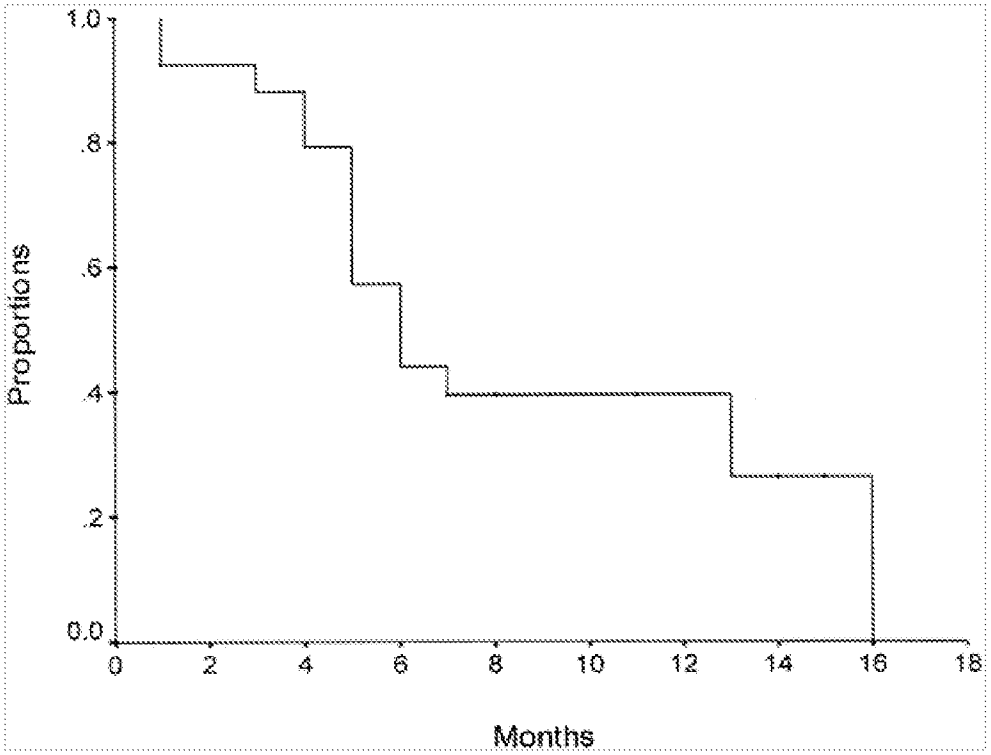

FIG. 2. Survival curve of biliary tract cancer (median survival: 6 months).

in 1 of the 19 evaluable patients with cholangiocarcinoma, a CR was observed, and 4 patients had PRs. Of the 9 patients with gallbladder cancer, one patient had CR and three patients exhibited PRs. The median survival duration of the patients with cholangiocarcinoma was 5 months (range: 1-16 months) and that of patients with gallbladder cancer was 7 months (range: 1-15 months).

Toxicity data are presented in Table 3 for all eligible patients with at least one cycle treatment follow-up. There were no drug toxicity-related deaths. Five patients required dose reductions because of toxicity. The most prominent toxicity was mucositis. Hematologic toxicity was less severe.

TABLE 3. *Toxicities of 5-fluorouracil with leucovorin in pancreatic–biliary tract cancer*

	WHO grade			
	1	2	3	4
Leukopenia	0	4 (8%)	6 (12%)	6 (12%)
Thrombocytopenia	4 (8%)	0	2 (4%)	0
Nausea/vomiting	12 (23%)	8 (16%)	3 (6%)	1 (2%)
Diarrhea	0	3 (6%)	7 (14%)	1 (2%)
Mucositis	3 (6%)	7 (14%)	17 (33%)	0

WHO, World Health Organization.

Table 3. Toxicities of 5-fluorouracil with leucovorin in pancreatic-biliary tract cancerWHO, World Health Organization.

DISCUSSION

To date, there has been no standard combination chemotherapeutic regimen for advanced pancreatic adenocarcinoma and biliary tract cancer, and 5-FU monochemotherapy is still considered the routine palliative treatment for advanced pancreatic carcinomas by many oncologists. 10,11 In the Mayo Clinic experience in 39 patients, the response rate of 5-FU monochemotherapy was 15%. 12

Recently there has been much interest in the possibility of increasing 5-FU activity and therapeutic selectivity by the use of biochemical modulators such as leucovorin and interferons. 6,13 Leucovorin strengthens the binding of the 5-FU active metabolite 5-FdUMP (deoxyuridine monophosphate) to its target enzyme, thymidylate synthase, forming a stable ternary complex that dissociates very slowly. 14 This biochemical interaction increases the fluoropyrimidine cytotoxic activity.

Crown et al. 15 explored the role of high-dose leucovorin (500 mg/m^2/day for 6 days by continuous infusion) with 5-FU (370 mg/m^2/day for 5 days by intravenous bolus) in patients with advanced pancreatic cancer. There were no complete responders or partial responders among 20 evaluable patients. However, there was a modest stable response lasting 4 months. DeCaprio et al. 16 noted a PR in 3 of 42 patients (7%) in patients with advanced pancreatic cancer who were treated with leucovorin (500 mg/m^2 i.v. for 2 hours) with a midinfusion bolus of 5-FU (600 mg/m^2) weekly for 6 of 8 weeks. The median overall survival was 6.2 months.

This study showed one CR and two PRs in 23 patients with pancreatic cancer (overall response rate: 17.3%) treated with 5-FU modulated by leucovorin. The median overall survival was 6 months. Our results show a slightly better response rate than the clinical results mentioned above, but these response rates and overall survival are not superior to those using 5-FU monochemotherapy.

Adenocarcinomas of the biliary tract include cancers that arise from the epithelium of the intrahepatic or extrahepatic bile ducts (cholangiocarcinomas) or from the gallbladder. Most treatment trials of biliary tract cancers have been disappointingly small, and response rates to single or multiagent chemotherapy were less than 25%. The largest study was that reported by Falkson et al., 17 in which 3 of 30 patients responded to 5-FU. The regimen of 5-FU, doxorubicin, and mitomycin (FAM) resulted in four responses in 13 patients (31%). 18 Kajanti and Pyrhonen 19 treated 22 patients who had cancer of the bile duct with a combination of epirubicin, methotrexate, 5-FU, and leucovorin and observed no objective responses. The median survival time was 9 months. Takada et al. 3 performed a multicenter randomized study for comparison of the 5-FU, doxorubicin, and mitomycin regimen with 5-FU alone in the treatment of pancreatic-biliary carcinoma; they concluded that there were no significant differences. Median survival time was 6.2 months in the group treated with the 5-FU, doxorubicin, and mitomycin regimen and 6.0 months in the group treated with 5-FU alone.

Our data showed a 32.1% overall response rate and median overall survival duration of 6 months. These results suggest that 5-FU modulation with leucovorin may be active in biliary tract cancer.

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Key Words: Adenocarcinoma, pancreatic; Biliary tract cancer; 5-FU; Leucovorin; Chemotherapy.

IMAGE GALLERY

Select All

Export Selected to PowerPoint

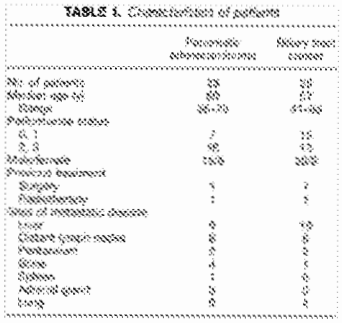

Table 1

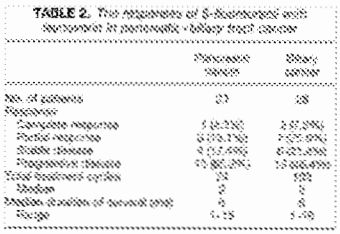

Table 2

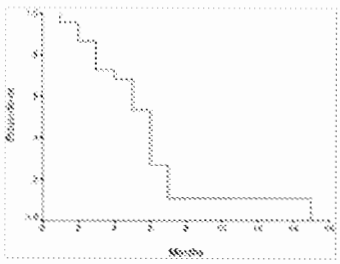

Fig. 1

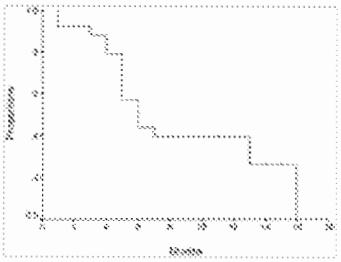

Fig. 2

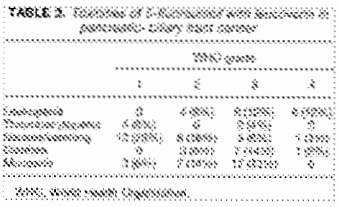

Table 3

Back to Top

Docetaxel and Liposomal Doxorubicin Chemotherapy With Enoxaparin in Patients With Advanced Pancreatic Cancer

ClinicalTrials.gov Identifier: NCT00426127

Recruitment Status : Terminated (Inadequate number of eligible patients)
First Posted : January 24, 2007
Results First Posted : June 2, 2017
Last Update Posted : December 29, 2017

Sponsor:
University of Iowa

Collaborator:
Aventis Pharmaceuticals

Information provided by (Responsible Party):
Daniel Berg, University of Iowa

Study Description

Brief Summary:

The purpose of this study is to assess the effects of the treatment combination of the commercially available chemotherapy drugs, docetaxel and liposomal doxorubicin, and a blood thinner Enoxaparin on pancreatic cancer. The main goal of the study is to find out if this combination chemotherapy and enoxaparin increases the number of individuals whose tumors shrink.

Condition or disease	Intervention/treatment	Phase
Pancreatic Cancer	Drug: Docetaxel Drug: Liposomal Doxorubicin Drug: Enoxaparin	Phase 2

Detailed Description:

The objective of the study is to determine the safety and efficacy of the combination of docetaxel and liposomal doxorubicin chemotherapy combined with enoxaparin in patients with advanced pancreatic cancer.

Docetaxel (TAXOTERE) belongs to the group of anticancer drugs called mitotic inhibitors. Liposomal doxorubicin (Doxil) is an anthracycline, and is thought to prevent nucleic acid synthesis that is needed to make DNA. Enoxaparin (Lovenox) is an anticoagulant. We are interested in combining chemotherapy with the blood thinner enoxaparin because there is a scientific link between blood clotting and malignancy.

This research is being done to improve on currently available chemotherapy treatments for advanced pancreatic cancer. The main goal of the study is to find out if this combination chemotherapy and enoxaparin increases the number of individuals whose tumors shrink. Another purpose of this study is to find out how this study treatment effects blood clotting levels in individuals. We will also determine the incidence of elevated D-dimer and the effect of this regimen on the level of D-dimer, and collect safety data on this regimen.

Study Design

Go to

Study Type :

Interventional (Clinical Trial)

Actual Enrollment :

2 participants

Allocation:

N/A

Intervention Model:

Single Group Assignment

Masking:

None (Open Label)

Primary Purpose:

Treatment

Official Title:

Phase II Trial of Docetaxel and Liposomal Doxorubicin (Doxil) Chemotherapy Combined With Enoxaparin in Patients With Advanced Pancreatic Cancer

Study Start Date :

November 2006

Actual Primary Completion Date :

January 2009

Actual Study Completion Date :

August 2009

Resource links provided by the National Library of Medicine

MedlinePlus related topics: Pancreatic Cancer

Drug Information available for: Doxorubicin Doxorubicin hydrochloride Docetaxel Enoxaparin sodium

Genetic and Rare Diseases Information Center resources: Pancreatic Cancer

U.S. FDA Resources

Arms and Interventions

Go to

Arm	Intervention/treatment
Experimental: Docetaxel and Liposomal Doxorubicin Combined with Enoxaparin Docetaxel 75 mg/m^2 + Doxil 30 mg/m^2 + Enoxaparin 1.5 mg/kg	Drug: Docetaxel Other Name: Taxotere Drug: Liposomal Doxorubicin Other Name: caelyx Drug: Enoxaparin Other Name: Lovenox

Outcome Measures

Go to

Primary Outcome Measures :

1. Tumor Response Measured by CT Scans After Each Set of 3 Cycles of Chemotherapy
   [Time Frame: 9 weeks]

Secondary Outcome Measures :

1. Number of Blood Draws With Incidence of Elevated D-Dimer Measured by Drawing D-Dimer Levels Every Cycle [Time Frame: 3 weeks]

   Incidence of elevated D-Dimer was defined as >.50 as drawn every cycle. Incidence of elevated D-Dimer was tested to determine safety and efficacy of the treatment regimen on patients with advanced pancreatic cancer.

2. Safety and Effect of Chemo Regimen on D-Dimer Measured by Drawing D-Dimer Levels Every Cycle [Time Frame: 3 weeks]

Eligibility Criteria

Go to

Information from the National Library of Medicine

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study:

18 Years and older (Adult, Older Adult)

Sexes Eligible for Study:

All

Accepts Healthy Volunteers:

No

Criteria

Inclusion Criteria:

- Histologically-confirmed pancreatic carcinoma, with at least one lesion measurable by CT scan with a longest diameter of > 10mm, (other than bone) that has either not been previously irradiated, or if previously irradiated, has demonstrated progression since the radiation therapy based on RECIST criteria.
- Locally-advanced unresectable disease or be ineligible for neo-adjuvant therapy (Stage III disease, unresectable and medically unfit for neo-adjuvant treatment or decline chemo radiation treatment) or have metastatic disease.
- 18 years of age or greater. Female patients with child-bearing potential must have a negative pregnancy test at screening. All patients of reproductive potential must agree to practice effective contraception in order to participate in this study for duration of treatment and for 3 months post.
- WBC >3000 cells/mm3 with segments over 1800, hemoglobin >10 g/dl, platelets >150,000 cells/mm3, creatinine <1.5 mg/dl.
- Hepatic function: Total Bilirubin </= ULN. AST and ALT and Alkaline Phosphatase must be within the range allowing for eligibility. In determining eligibility the more abnormal of the two values (AST or ALT) should be used.
- ECOG performance status of </= 2 and an expected survival of at least 3 months.
- Stable neurological status without clinical evidence of CNS metastases and/or stroke. Peripheral neuropathy must be </= Grade 1.

Exclusion Criteria:

- Chemotherapy or radiation therapy within the preceding 4 weeks. Patients must never have had docetaxel or liposomal or regular doxorubicin.
- Spinal/epidural anesthesia and/or catheters for pain management
- New York Heart Association (NYHA) class III or IV congestive heart failure
- Evidence of duodenal erosion from the cancer.
- Heparin or coumadin at the time of enrollment, with the exception of low dose coumadin (1 mg/day or less) administered prophylactically and/or heparin for maintenance of in-dwelling lines or ports.
- Acute DVT or PE on initial evaluation
- History of severe hypersensitivity reaction to docetaxel or other drugs formulated with polysorbate 80
- Pregnant or breast feeding
- Undergone a major surgical procedure, open biopsy, or major traumatic injury less than 4 weeks prior to study entry. Fine needle aspirations or venous access devices are allowed if placed > 7 days before study treatment begins.
- Presence of active or suspected acute or chronic uncontrolled infection, including abscess or fistula
- HIV positive
- History of another malignancy within 5 years prior to study entry, except curatively treated basal cell skin cancer or cervical cancer in situ

- Medical or psychiatric illness that would preclude study or informed consent and/or history of noncompliance to medical regimens or inability or unwillingness to return for all scheduled visits
- Enoxaparin is contraindicated in patients with active major bleeding or who are at high risk for bleeding, in patients with thrombocytopenia associated with a positive in vitro test for anti-platelet antibody in the presence of enoxaparin sodium, or in patients with hypersensitivity to enoxaparin sodium. Patients with known hypersensitivity to heparin or pork products should not be treated with enoxaparin injection or any of its constituents.

Contacts and Locations

Go to

Information from the National Library of Medicine

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): ***NCT00426127***

Locations

United States, Iowa

University of Iowa Hospitals and Clinics
Iowa City, Iowa, United States, 52242

Sponsors and Collaborators

University of Iowa

Aventis Pharmaceuticals

Investigators

Principal Investigator: Daniel J. Berg, MD University of Iowa

More Information

Go to

Additional Information:

Website for Holden Comprehensive Cancer Center at University of Iowa

Responsible Party:

Daniel Berg, Principal Investigator, University of Iowa

ClinicalTrials.gov Identifier:

NCT00426127 History of Changes

Other Study ID Numbers:

200511721

First Posted:

January 24, 2007 Key Record Dates

Results First Posted:

June 2, 2017

Last Update Posted:

December 29, 2017

Last Verified:

December 2017

Individual Participant Data (IPD) Sharing Statement:

Plan to Share IPD:

No

Keywords provided by Daniel Berg, University of Iowa:

Pancreatic

Docetaxel

Doxorubicin

Enoxaparin

Additional relevant MeSH terms:

Pancreatic Neoplasms
Digestive System Neoplasms
Neoplasms by Site
Neoplasms
Endocrine Gland Neoplasms
Digestive System Diseases
Pancreatic Diseases
Endocrine System Diseases
Docetaxel
Doxorubicin
Liposomal doxorubicin
Enoxaparin
Antineoplastic Agents
Tubulin Modulators
Antimitotic Agents
Mitosis Modulators
Molecular Mechanisms of Pharmacological Action
Antibiotics, Antineoplastic
Topoisomerase II Inhibitors
Topoisomerase Inhibitors
Enzyme Inhibitors
Anticoagulants
Fibrinolytic Agents
Fibrin Modulating Agents

Impact of dose reductions on clinical outcomes among patients with metastatic pancreatic cancer treated with liposomal irinotecan in oncology clinics in the US

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BACKGROUND

- In the USA, pancreatic cancer was estimated to be the third leading cause of cancer-related death in 2019, despite comprising only an estimated 3.2% of the total new cancer diagnoses.[1]
- It is estimated that 53% of US patients with pancreatic cancer have metastatic disease at diagnosis.[2]
- Liposomal irinotecan plus 5-fluorouracil and leucovorin received US approval in October 2015 for patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) following progression with gemcitabine-based therapy.[3]
  - The recommended starting dose for liposomal irinotecan is 70 mg/m^2 (irinotecan free base, equivalent to 80 mg/m^2 of irinotecan as the hydrochloride trihydrate).

OBJECTIVE

- The aim of this study was to evaluate the impact of liposomal irinotecan dose reductions on clinical outcomes in patients with mPDAC who were treated in oncology clinics in the USA.

METHODS

Study population

- Patient-level data for adult patients (aged ≥ 18 years) who received a diagnosis of mPDAC were extracted from the Flatiron Health database, a nationwide, US electronic-health-record-derived, deidentified database.
  - Eligible patients were required to have a pathology that was consistent with pancreatic ductal adenocarcinoma and evidence of stage IV, progressive or recurrent disease on or after January 1, 2014.
- Patients were included if they were treated with liposomal irinotecan between November 1, 2015, and January 31, 2019, and if they had initiated treatment at approximately the recommended dose (70 ± 5 mg/m^2).

Liposomal irinotecan dosing

- The dosing data that were assessed included: cumulative dose over the first 6 weeks of treatment; dose reductions (defined as a decrease of ≥ 7 mg/m^2); and duration of treatment (DoT) (defined as time between treatment initiation and the last treatment cycle; no censoring was employed).

Efficacy

- The clinical outcomes that were assessed included: overall survival (OS); and time to treatment failure (TTF) from treatment initiation.
  - Treatment failure was defined as the end of a line of therapy for any reason.

Safety

- Prespecified adverse events (AEs), including anemia, diarrhea, fatigue/asthenia, nausea, neuropathy, neutropenia and thrombocytopenia, were identified directly from the database using diagnostic codes from the International Classification of Diseases and Related Health Problems, 9th and 10th revisions, Clinical Modification.
  - Other prespecified AEs included alanine aminotransferase increased, alkaline phosphatase increased and aspartate aminotransferase increased.
- When laboratory values for these AEs were available, patients were stratified by grade based on the National Cancer Institute Common Terminology Criteria for Adverse Events grading system.

Statistical analyses

- All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).
- Baseline demographics were analyzed by descriptive statistics.
- Kaplan–Meier methods were used to estimate the median OS and TTF from treatment initiation.
- Cox proportional hazards models were used to estimate the differences in survival between subgroups of interest.

RESULTS

Patient demographics and characteristics

- Overall, 257 patients initiated liposomal irinotecan treatment at approximately the recommended dose and were included in these analyses.
  - The patients who were not eligible for these analyses included: 12 who received high-dose treatment (> 75 mg/m^2); 133 who received low-dose treatment (< 65 mg/m^2); and 30 who had missing dose information.
- The median age at study index was 68 years (interquartile range [IQR], 61–73 years) (Table 1).
- Most patients were pretreated, with only 39 of 257 (15.2%) having no previous lines of therapy. Prior gemcitabine-based therapy was reported in 240 of 257 patients (93.4%) (Table 1).

Table 1. Patient demographics and characteristics

	All patients included (N = 257)
Age at index,[a] years	
Mean (SD)	67.2 (8.8)
Median (IQR)	68 (61.0–73.0)
Range	43.0–84.0
Sex, n (%)	
Male	135 (52.5)
Female	122 (47.5)
Stage at diagnosis, n (%)	
Stage IV	142 (55.3)
Other	115 (44.7)
ECOG score, n (%)	
0	37 (14.4)
1	101 (39.3)
≥ 2	45 (17.5)
Missing	74 (28.8)
Previous lines of therapy for metastatic disease, n (%)	
0	39 (15.2)
1	125 (48.6)
≥ 2	93 (36.2)
Prior gemcitabine-based therapy, n (%)	
Yes	240 (93.4)
No	17 (6.6)

[a]The index date was defined as the start date of the initial liposomal irinotecan-containing treatment regimen in the metastatic setting for each patient. ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; SD, standard deviation

Liposomal irinotecan dosing

- Dose reductions were reported in 68 of 257 patients (26.5%).
- The median DoT was 6.1 weeks (IQR, 2.1–15.3 weeks) in all patients and was longer in those with a dose reduction (15.1 weeks) than in those without a dose reduction (4.3 weeks) (Table 2).
- The mean 6-week cumulative dose was 180.0 mg/m^2 (standard deviation, 72.4 mg/m^2) in all patients and was greater in those with a dose reduction (191.8 mg/m^2) than in those without a dose reduction (175.8 mg/m^2) (Table 2).

Clinical outcomes

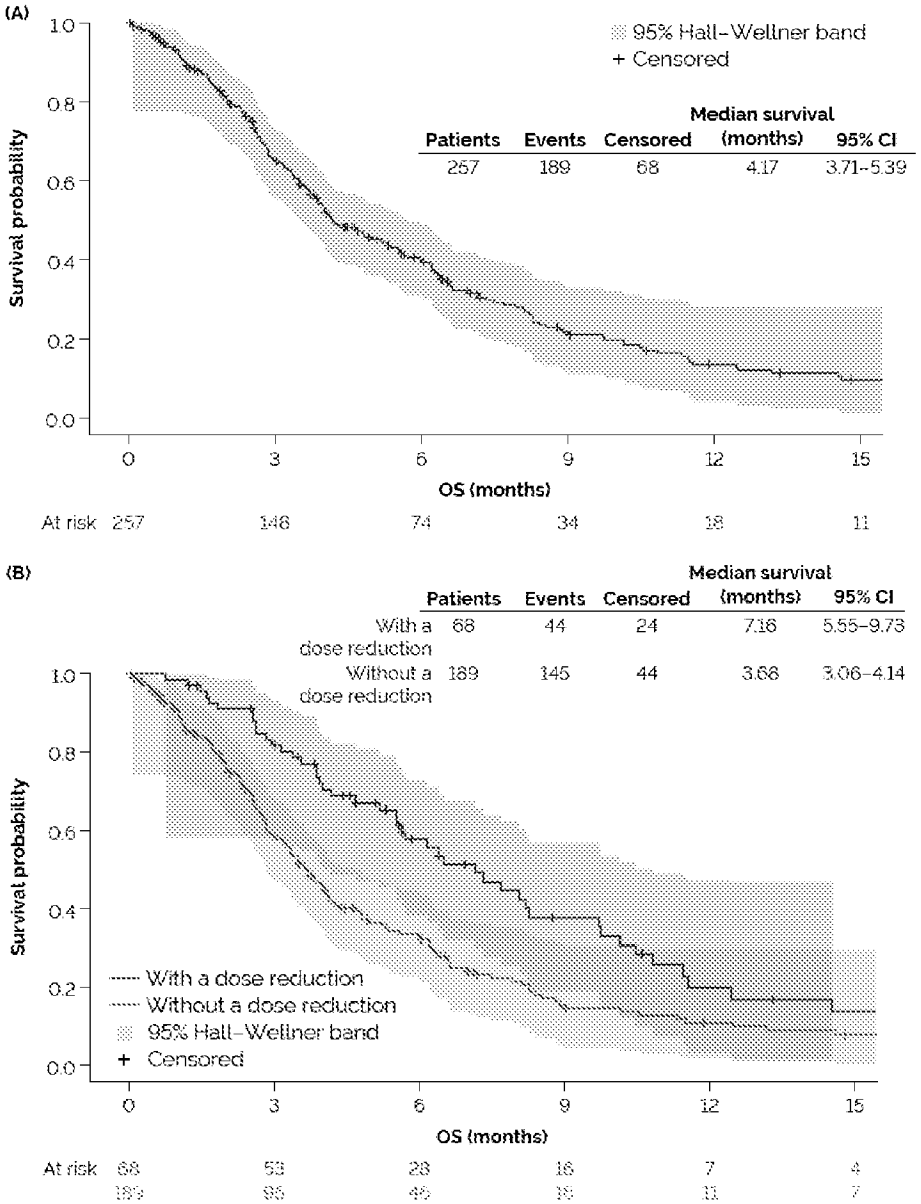
- The median OS and TTF were 4.17 months (95% confidence interval [CI], 3.71–5.39 months) and 1.87 months (95% CI, 1.45–2.50 months), respectively (Figures 1A and 2A).
- The median OS and TTF were longer for patients with a dose reduction (7.16 months and 4.34 months, respectively) than for those without a dose reduction (3.68 months and 1.41 months, respectively) (Figures 1B and 2B); hazard ratio was 0.53 (95% CI, 0.38–0.75) for OS and 0.53 (95% CI, 0.38–0.72) for TTF.

Table 2. Liposomal irinotecan exposure among patients with or without a dose reduction

	Patients with a dose reduction (n = 68)	Patients without a dose reduction (n = 189)
DoT, weeks		
Mean (SD)	17.6 (13.7)	9.2 (14.3)
Median (IQR)	15.1 (7.1–23.0)	4.3 (2.1–12.1)
Range	2.1–65.0	0.1–106.1
Cumulative dose, mg/m²		
Mean (SD)	191.8 (53.2)	175.8 (77.9)
Median (IQR)	191.4 (140.5–216.7)	205.7 (75.0–215.7)
Range	70.2–284.7	65.1–293.0

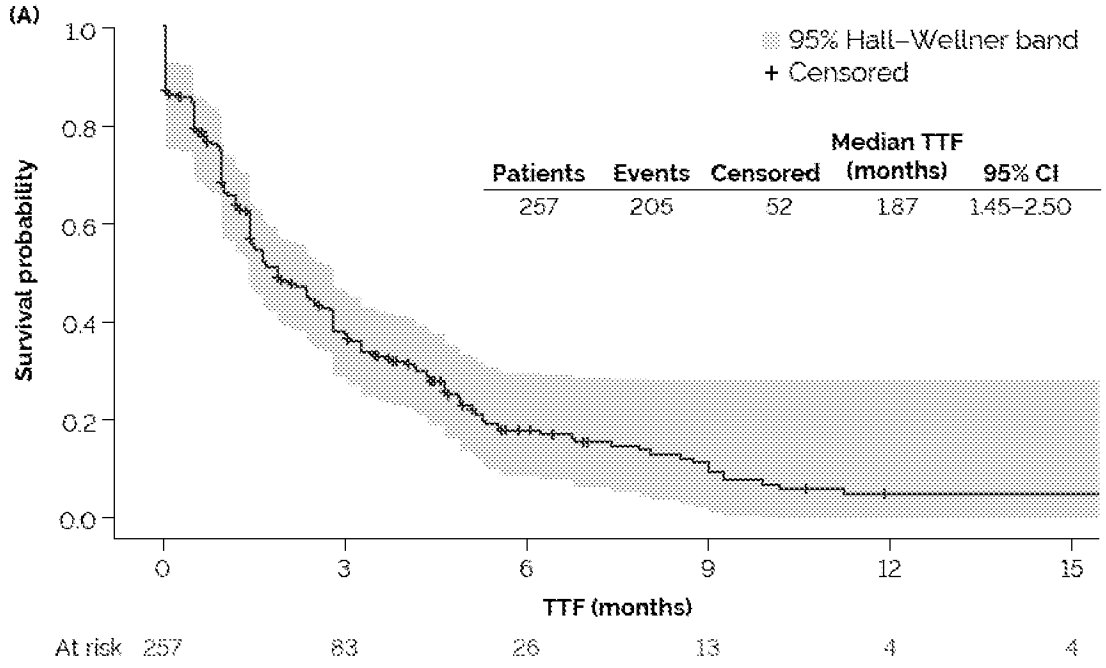
DoT, duration of treatment; IQR, interquartile range; SD, standard deviation.

Figure 1. Kaplan–Meier plots of OS in (A) all patients included and (B) subgroups of patients with or without a dose reduction

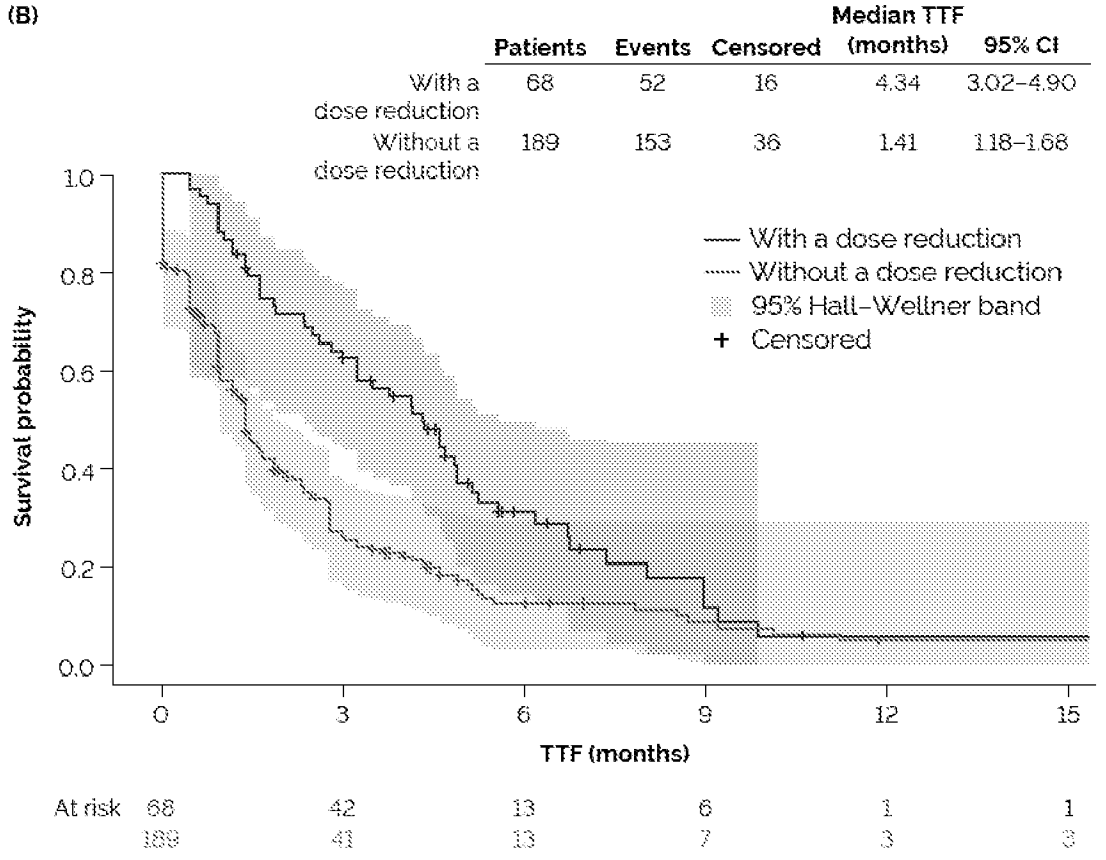


For the OS analyses, patients who died during the study were assigned the 15th day of their month of death, and those who did not die during the study were censored at their last visit or administration date.
CI, confidence interval; OS, overall survival.

Figure 2. Kaplan–Meier plots of TTF in (A) all patients included and (B) subgroups of patients with or without a dose reduction



	Patients	Events	Censored	Median TTF (months)	95% CI
	257	205	52	1.87	1.45–2.50



	Patients	Events	Censored	Median TTF (months)	95% CI
With a dose reduction	68	52	16	4.34	3.02–4.90
Without a dose reduction	189	153	36	1.41	1.18–1.68

CI, confidence interval; TTF, time to treatment failure

Adverse events

- During liposomal irinotecan treatment, prespecified AEs that were identified by diagnosis or laboratory result and were reported in more than 10% of patients included anemia, diarrhea, fatigue/asthenia, neutropenia and thrombocytopenia (Table 3).
- For all AEs identified by laboratory result, at least one patient had a grade 3 or 4 event (Table 3).

Table 3. AEs reported during liposomal irinotecan treatment

	Patients with AE, n (%) (N = 257)
Anemia	
Any	219 (85.2)
Identified by diagnosis code	24 (9.3)
Identified by laboratory result (hemoglobin)	219 (85.2)
Grade 3: < 8.0 g/dL	37 (14.4)
Diarrhea	
Identified by diagnosis code	32 (12.5)
Fatigue/asthenia	
Identified by diagnosis code	40 (15.6)
Nausea	
Identified by diagnosis code	18 (7.0)
Neuropathy	
Identified by diagnosis code	8 (3.1)
Neutropenia	
Any	66 (25.7)
Identified by diagnosis code	19 (7.4)
Identified by laboratory result (neutrophil count)	53 (20.6)
Grade 3: < 1.0–0.5 × 10^9/L	22 (8.6)
Grade 4: < 0.5 × 10^9/L	7 (2.7)
Thrombocytopenia	
Any	96 (37.4)
Identified by diagnosis code	5 (1.9)
Identified by laboratory result (platelet count)	94 (36.6)
Grade 3: < 50.0–25.0 × 10^9/L	9 (3.5)
Grade 4: < 25.0 × 10^9/L	3 (1.2)
ALP increased	
Identified by laboratory result	194 (75.5)
Grade 3: > 5.0–20.0 × ULN	32 (12.5)
Grade 4: > 20.0 × ULN	0 (0)
ALT increased	
Identified by laboratory result	75 (29.2)
Grade 3: > 5.0–20.0 × ULN	5 (1.9)
Grade 4: > 20.0 × ULN	1 (0.4)
AST increased	
Identified by laboratory result	101 (39.3)
Grade 3: > 5.0–20.0 × ULN	8 (3.1)
Grade 4: > 20.0 × ULN	0 (0)

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

Conclusions

- Patients who had dose reduction had longer DoT and higher cumulative dose than those who did not. This suggests that dose reduction is a good option for maintaining patients on treatment without sacrificing treatment benefit.
- Patients in the dose-reduction subgroup also had higher estimated OS and TTF than those without dose reduction. Results are descriptive only, and there may be missing data; the data are not from a prospective, randomized study to compare dose reduction versus no dose reduction. In real-world practice, dose reduction may be affected by both measured and unmeasured confounders (e.g. time since treatment initiation or practice pattern variations). Selection bias will be assessed by evaluating cohort-level baseline characteristics.
- These real-world data are useful for future prospective studies to characterize the impact of liposomal irinotecan dosing on clinical outcomes.

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Conflicts of interest

PC is an employee of Ipsen Biopharmaceuticals, Inc. and holds stock or stock options.
AS and DM are employees of Genesis Research LLC, which received funding for consulting from Ipsen Biopharmaceuticals, Inc.
GK and JK received funding for consulting from Ipsen Biopharmaceuticals, Inc.
RM is an employee of Flatiron Health, which is an independent subsidiary of the Roche group; she reports equity ownership in Flatiron Health and stock ownership in Roche.

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BACKGROUND

OBJECTIVE

METHODS

RESULTS

CONCLUSIONS

H13

PANCREATIC CANCER

Impact of dose reductions on clinical outcomes among patients (pts) with metastatic pancreatic cancer (mPC) treated with liposomal irinotecan (nal-IRI) in oncology clinics in the United States.

Paul Cockrum, Andy Surinach, George P. Kim, Daniel Mercer, Jim M. Koeller, Rebecca A. Miksad

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Abstract Disclosures

Abstract

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Background: The recommended starting dose for nal-IRI is 70mg/m^2 (free base, equivalent to 80 mg/m^2 salt-based dosing). This study evaluates the impact of nal-IRI dose reductions on clinical outcomes. **Methods:** Using the nationwide Flatiron Health electronic health record-derived database, de-identified data were extracted and analyzed for adult mPC pts treated with nal-IRI Jan 2014-Jan 2019 and who initiated treatment at approximately the recommended dose (RD), 70mg/m2 +/- 5mg. Initial dose was derived from structured medication records, prioritizing administrations. The cumulative dose (CD) of nal-IRI over the first six weeks of treatment, the presence of dose reductions (DR) – (a decrease ≥ 7mg/m2), overall survival (OS) from treatment initiation, and duration of treatment (DoT) were assessed. **Results:** 257 mPC pts treated with nal-IRI (median age: 68y, IQR: 61 - 73) were identified initiating therapy at approximately the RD. 26.5% (N = 68) of pts experienced a DR during treatment. Mean 6-week CD was 175.8 mg/m^2(SD: 77.9) among pts with no DR. For pts with DR, mean CD was 191.8 mg/m^2 (53.2). Median DoT was 6.1 wks (IQR: 2.1 – 15.3). Pts that experienced a DR had a longer median DoT: 15.1 wks (7.1 – 23.0) vs 4.3. wks (2.1 – 12.1) for pts with no DR. Overall Median OS (mOS) was 4.2 months (95% CI: 3.7 – 5.4). mOS for DR pts was 7.2 mos (95% CI: 5.5 – 9.7) and 3.7 mos (3.0 – 4.1) for pts who did not experience a DR. **Conclusions:** This real-world analysis suggests that reducing the dose of subsequent administrations of nal-IRI during treatment is associated with pts remaining on therapy longer, experiencing a larger CD, and a with longer OS. Additional

real-world prospective studies are necessary to characterize the impact of nal-IRI dosing on clinical outcomes.

Research Sponsor:

Ipsen Biopharmaceuticals

GASTROINTESTINAL CANCER—GASTROESOPHAGEAL, PANCREATIC, AND HEPATOBILIARY

National Comprehensive Cancer Network (NCCN) category I/FDA-approved metastatic pancreatic adenocarcinoma (mPDAC) treatments in commercially insured patients: An analysis of inpatient (IP) and emergency room (ER) admissions.

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Show Less

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Abstract Disclosures

Abstract

e16739

Background: There are currently four NCCN category 1 systemic regimens approved in the United States for the treatment of mPDAC: FOLFIRINOX (FFX), gemcitabine+nab-paclitaxel (gem+nab-P), gemcitabine monotherapy (gem), and liposomal irinotecan + 5-fluorouracil/leucovorin (5-FU/LV) following progression with gem-based therapy. There is limited real-world research on the IP admissions and ER visit healthcare resource utilization (HRU) of patients receiving these treatments. **Methods:**Using the IQVIA PharMetrics Plus administrative claims database, data were analyzed for adult patients with mPDAC treated with NCCN category 1 regimens in first through fourth line of therapy between January 1, 2014 and May 31, 2019. For each line of therapy, continuous treatment was defined as the time from first administration of a therapy until the last administration. Mean all-cause and mPDAC-related IP admissions, ER visits, inpatient length of stay (LOS) during treatment were assessed. **Results:** Of the 2,731 patients with mPDAC included in the study, 101 (3.7%) were treated with a liposomal irinotecan based regimen, 1,316 (48.2%) were treated with gem+nab-P, 612 (22.4%) with FFX, and 624 (22.8%) with gem in any treatment line. The mean number of IP admissions was 1.2 for liposomal irinotecan treated patients, 1.5 for gem+nab-P, 1.5 for FFX, and 1.2 for gem. Among patients with

at least one IP admission the mean LOS was 4.5 days for liposomal irinotecan, 5.4 days for gem+nab-P, 3.8 for FFX, and 5.1 for gem treated patients. Patients treated with liposomal irinotecan had a mean of 1.3 ER visits during treatment. Gem+nab-P, FFX, and gem-treated patients experienced 1.7, 1.4, and 1.8 mean ER visits, respectively. Mean mPDAC-related IP admissions ranged from 1.1 – 1.5, ER visits ranged from 1.1 – 1.7, and mean LOS ranged from 3.8 – 5.5 days. **Conclusions:** In this descriptive retrospective study patients receiving liposomal irinotecan, across all treatment episodes, generally experienced numerically lower mean IP admissions and ER visits. LOS was similar across all regimens. Further studies are necessary to characterize the IP and ER HRU burden among mPDAC patients treated with approved regimens.

Research Sponsor:

Ipsen

Objectives: To assess the health and economic impact of adding enzalutamide to the Mexican healthcare system versus apalutamide for nmCRPC with high risk of progression. ***Methods:*** A semi-Markov model was built to assess the cost utility of enzalutamide + androgen deprivation therapy (ADT) versus apalutamide + ADT and ADT monotherapy in the Mexican 2018 public payer setting. The model was designed using three health states (nmCRPC; metastatic disease; death) with 1-month cycles and a time horizon of 20 years to represent complete disease history. A 5% discount was applied to costs and outcomes; metastasis-free survival was based on enzalutamide and apalutamide clinical trials. Resource use was estimated from interviews with six top oncologists; costs for drugs, adverse events, laboratory tests, and doctors' visits were obtained from Mexican Institute of Social Security's Diagnostic-Related Groups and unitary costs. Apalutamide cost was assumed as the average of prices in Brazil and the United States, where approved. A budget impact model with a 5-year time horizon was developed to assess the financial impact of adding enzalutamide for the nmCRPC population. Sensitivity analyses were run to assess the robustness of this appraisal. Results are presented in 2018 Mexican pesos. ***Results:*** Total costs were MXN$1.2M for enzalutamide + ADT, MXN$1.4M for apalutamide + ADT, and MXN$11,710 for ADT alone. Enzalutamide was associated with better QALYs than apalutamide + ADT (3.75, 3.27, and 3.00, respectively). Enzalutamide dominated apalutamide and had an ICER of MXN$1.5M versus ADT. Average budget impact of enzalutamide per patient per year was MXN$42,025. Total budget impact in 5 years was MXN$500,231,902, representing 0.434% of the 2018 public budget. ***Conclusions:*** Enzalutamide represents a cost-effective alternative for the Mexican public healthcare system versus apalutamide for the treatment of nmCRPC, while also representing a low budget impact. **FUNDING:** Astellas Pharma Inc. and Medivation LLC, a Pfizer Company **EDITORIAL:** Complete HealthVizion

PCN130
THE COST-EFFECTIVENESS AND BUDGET IMPACT OF EARLY RITUXIMAB USE IN ASYMPTOMATIC FOLLICULAR LYMPHOMA (FL) IN THE US

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Objectives: Patients with asymptomatic follicular lymphoma (FL) can be monitored prior to initiating treatment (watch and wait (WW)) or receive early therapy with rituximab (RTX). RTX delays time to progression, reducing downstream treatment costs and potentially improving patient quality of life. RTX-pvvr, a biosimilar of RTX, has been approved in the US for FL with the potential to reduce treatment costs. This study explored the cost-effectiveness and budget impact of early RTX use (branded and RTX-pvvr) versus WW in the US. ***Methods:*** An area-under-the-curve Markov model was built using time-to-event data from a clinical trial over a lifetime, comparing RTX induction (RI), RTX induction plus maintenance (RIM) and WW for newly-diagnosed asymptomatic FL patients. The model considered five health states: progression-free, symptomatic and asymptomatic progressed disease, transformation and death. The model included up-front RTX treatment costs, three lines of subsequent treatment costs, along with monitoring, adverse event and end of life costs. Outcomes included life years (LYs), quality-adjusted life years (QALYs), progression-free life years (PFLYs) and incremental cost-effectiveness ratios (ICERs). The budget impact model included total and per-member per-month (PMPM) costs over a 5-year time horizon. Scenario analyses included varying transformation assumptions, subsequent treatment costs/market mix and utilities. ***Results:*** In the base case, RI and RIM were dominant treatment options compared to WW for ICER/QALY and ICER/PFLY, with PFLY gains of 1.17 and 3.36, respectively. The use of RTX-pvvr reduced total costs for all treatment arms. A 5% annual uptake of RTX-pvvr reduced the total budget impact, potentially amounting to a $64,925,020 ($-0.003 PMPM) reduction over 5 years for the US population (8,346 eligible patients). Sensitivity and scenario analyses found consistent cost savings; base case trends remained robust. ***Conclusions:*** Early RTX-pvvr use is a dominant treatment option compared to WW in the US, reducing total lifetime FL treatment costs while increasing PFLY and QALYs.

PCN131
COST-EFFECTIVENESS ANALYSIS OF AZACITIDINE VS. DECITABINE IN THE TREATMENT OF MYLODYSPLASTIC SYNDROMES IN CHINA

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Objectives: To assess the cost-effectiveness of azacitidine (AZA) relative to decitabine (DEC) in Chinese patients with the mylodysplastic syndromes (MDS) over a lifetime horizon from the perspective of health care payers. ***Methods:*** A lifetime cohort Markov model was constructed to evaluate the cost-effectiveness of AZA compared with DEC with the 4 health states including MDS with transfusion dependent (MDS+TD), MDS with transfusion independent (MDS+TI), acute myeloid leukemia (AML) and death in 4-week cycles until the death of 95% patients. Model parameters were derived from literature review and expert survey. Cost (2019 ¥/CNY) and outcomes were discounted at 5% annually. One-way sensitivity analysis and probabilistic sensitivity analysis based on 10,000 Monte Carlo simulations were performed. ***Results:*** In the base-case model, the patients treated with AZA were associated with better survival (life years: 3.125 *vs.* 2.536) and more quality-adjusted life years (QALYs) (2.049 vs. 1.621) compared with DEC. And AZA could save total direct medical costs for ¥66,829 compared with DEC. AZA was more effective and less costly compared with DEC. Sensitivity analysis demonstrated robustness of baseline results, with drug acquisition costs being the largest influence factor. The probability that AZA was cost effective comparing with DEC was 82.80% within the threshold of 3 times Chinese GDP per capita/QALYs. ***Conclusions:*** The analysis indicated that the use of AZA in the treatment of MDS is a cost-effective option compared with DEC in the Chinese setting.

PCN133
ECONOMIC EVALUATION OF EPIDERMAL GROWTH FACTOR RECEPTOR - TYROSINE KINASE INHIBITOR (EGFR-TKI) DRUGS IN NON-SMALL CELL LUNG CANCER (NSCLC) TREATMENT: A SYSTEMATIC REVIEW OF RECENT STUDIES

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Objectives: Epidermal Growth Factor Receptor - Tyrosine Kinase Inhibitor (EGFR-TKI) drugs are indicated for non-small cell lung cancer (NSCLC) with EGFR mutations. In this study we reviewed the recent works conducting economic evaluation of EGFR-TKI drugs. ***Methods:*** A systematic literature search was performed in MEDLINE, Embase and Cochrane Central databases. Only the studies on gefitinib, erlotinib, afatinib, osimertinib, dacomitinib or icotinib in NSCLC that performed cost effectiveness (CEA), cost benefit (CBA) or budget impact (BIA) analysis, and were published between 2014 to 2019 met the inclusion criteria. ***Results:*** Among total 168 retrieved articles 17 were duplicates, and 126 did not fulfill the inclusion criteria in abstract review. Out of remaining 25 studies 21 (19 CEA + 2 BIA) were selected for final synthesis after full text review. Among these 21 studies, 3 performed evaluation from only US health-system perspective, 3 from US and non-US perspective and 15 from only non-US perspective. From US payer's perspective, one study found 1st line erlotinib to be cost effective (ICER: $61,809 vs afatinib), and three studies found osimertinib to be not cost effective as either 1st line (vs 1st generation EGFR-TKIs) or 2nd line (vs chemotherapy) treatment of NSCLC. The acquisition cost of osimertinib was identified as the major factor affecting CE in sensitivity analysis of all three studies. Two BIA analysis conducted from a US private health plan's perspective found erlotinib and afatinib to increase a plan's per person per month expenditure by $0.013 and $0.0001 respectively in the first year. Non-US studies provided varied results in respective context. ***Conclusions:*** We found that relatively new EGFR-TKI osimertinib is not cost effective in US healthcare setting due to its high cost. Additionally, the estimated budget impact of several other EGFR-TKI drugs for US health plans was not substantial.

PCN134
AN EXAMINATION OF QUALITY METRICS: INPATIENT AND EMERGENCY DEPARTMENT BURDEN OF COMMERCIALLY INSURED TREATED METASTATIC PANCREATIC CANCER (MPC) PATIENTS IN THE UNITED STATES (US)

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Objectives: Medical expenditures for cancer are expected to increase 27% in 2020 relative to 2010. This study examined inpatient and ER admissions and associated costs to describe key cost drivers for mPC patients. ***Methods:*** IQVIA PharMetrics Plus administrative claims database data were used to identify and analyze adult patients with mPC treated between January 1, 2014 and May 31, 2019. Patients were required to have continuous health coverage for ≥ 6 months prior to and ≥ 3 months after the first treatment date post-metastatic diagnosis with no treatment using NCCN guideline-recommended chemotherapy within 60 days prior to index date. Mean all-cause per patient costs were assessed for inpatient and ER admissions during treatment. Treatment regimens included were: FOLFIRI, FOLFOX, FOLFIRINOX, gem-citabine+nab-paclitaxel (gem+nab-P), and liposomal irinotecan (lip-IRI). ***Results:*** 2,731 mPC patients (median age: 59y; IQR 54-64) were included. Among patients treated in any line, 101 (3.7%) were treated with lip-IRI, 1,316 (48.2%) were treated with gem+nab-P, 612 (22.4%) with FOLFIRINOX, 281 (10.3%) with FOLFOX, and 208 (7.6%) with FOLFIRI. Mean all-cause inpatient admissions costs per patient were lowest for patients receiving lip-IRI compared to other included regimens (FOLFIRI-$12,667, FOLFOX-$11,393, FOLFIRINOX-$13,872, gem+nab-P-$13,246, lip-IRI-$8,220). Similarly, mean all-cause ER admissions costs per patient were lowest for patients receiving lip-IRI compared to other included regimens (FOLFIRI-$697, FOLFOX-$773, FOLFIRINOX-$1,348, gem+nab-P-$1,052, lip-IRI-$644). ***Conclusions:*** This claims analysis found that mean all-cause costs for inpatient and ER visits during treatment were highest for those receiving FOLFIRINOX and gem+nab-P, and lowest for those receiving lip-IRI. Further studies are needed to understand the impact of treatment on inpatient and ER costs among treated mPC patients.

systematic literature review (SLR) was conducted in August 2019. Database searching using pre-determined search strategies was conducted in EMBASE, Medline, Medline (R) In-Process search strategy (via Embase.com) and the Cochrane library. In addition, grey literature search was performed. No treatment or date of publication restrictions were applied. A comprehensive quality assessment of each study identified was conducted using pre-defined guidelines. ***Results:*** Of the initial 55 references, 11 met the economic evaluation criteria. The SLR identified six UK HTA appraisals, of which 4 assessed daratumumab against other interventions for the treatment of rrMM, one assessed ixazomib in combination with lenalidomide+dexamethasone in patients with at least one prior therapy and one re-assessed lenalidomide+dexamethasone in patients with one prior regimen of bortezomib. Five published studies in RRMM were also retrieved. Most references reported a partitioned survival model in a cost-utility analysis with a time horizon ranging from 15 years to a lifetime. Most studies were in patients with disease refractory to a proteasome inhibitor and an immunomodulatory agent or in patients who received atleast one line of prior therapy. ***Conclusions:*** Most economic evaluations assessed treatments used early in the MM pathway and applied partitioned survival models. No evaluations were retrieved in later stages of the disease (i.e. 5th line and beyond). Additional economic analyses need to be conducted for therapies addressing an unmet need once all therapeutic options have been exhausted.

PCN166
IMPACT OF COLORECTAL CANCER SCREENING IN THE FRAMEWORK OF UNIVERSAL HEALTH COVERAGE (UHC)

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Objectives: Estimate the health impact and the economic costs of the implementation of screening for CRC with fecal occult blood test in the Argentine public health system ***Methods:*** Markov model that simulates the evolution in 50 years of a population cohort exposed to the risk of developing CRC in two analysis scenarios: "IFOBT screening" and "Non-existence of screening". The natural history of the disease was simulated by ten health states based on information from scientific publications. The medical costs associated with the detection and treatment of polyps and cancer were estimated using public bidding prices from the Ministry of Health.The time horizon is 50 years and a 3% annual discount rate is used for costs and outcomes measured in QALYs. ***Results:*** According to our simulation, during the first five years of the screening implementation, an increase in the CRC incidence is observed. Reached the tenth year of implementation, the number of high-risk polyps and cases of CRC decrease by 40% and 50% respectively. In turn, the decrease in the risk of dying from CRC for people who participate in screening is 28%. Finally, the screening strategy with TiSOMF is an effective cost since the cost per AVAC of the intervention is USD 349 (incremental cost USD 120 and incremental AVAC 0.35), while the Argentine GDP per capita in dollars for the year 2018 was USD 11,645, that is, the RCEI is sufficiently lower than the national GDP per capita (0.03 GDP PC). ***Conclusions:*** The implementation of screening with IFOBT is a cost effective intervention compared to the current situation.In the screening scenario, 90% of the expenditure is destined to the treatment of advanced CRC, while in the scenario with the same proportion, it is allocated to instances of prevention and early detection with an impact on hope and quality of life.

PCN167
AN INTEGRATED DELIVERY NETWORK FOCUS ON COST DRIVERS IN CHEMOTHERAPY: THE ECONOMIC BURDEN OF NEUTROPENIA AND INPATIENT ADMISSIONS AMONG COMMERCIALLY INSURED METASTATIC PANCREATIC CANCER PATIENTS (MPC)

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Objectives: Pancreatic ductal adenocarcinoma is the third leading cause of cancer-related death in the US. Hospitalizations related to neutropenia are a substantial economic burden among cancer patients. This analysis assessed inpatient costs and rates of neutropenia for mPC patients enrolled in US commercial health plans. ***Methods:*** Using the IQVIA PharMetrics Plus administrative claims database, data were obtained for adult patients with mPC treated between January 1, 2014 and May 31, 2019. Treatment regimens included were: FOLFIRI, FOLFOX, FOLFIRINOX, gemcitabine+nab-paclitaxel (gem+nab-P), and liposomal irinotecan-based treatment (lip-IRI). Patients were required to have continuous health coverage for ≥ 6 months prior to and ≥ 3 months after the first treatment date post-metastatic diagnosis. All-cause inpatient per patient costs (PPC) during treatment were calculated and adjusted to 2019 US dollars. The proportions of patients with neutropenia during treatment were assessed by treatment group. ***Results:*** 2,731 mPC patients were identified (median age: 59y; IQR 54-64). Of these patients, 1,699 (62.2%) received second line treatment, 809 (29.6%) third line and 363 (13.2%) fourth line. Among patients treated in any line, 101 (3.7%) were treated with lip-IRI, 1,316 (48.2%) were treated with gem+nab-P, 612 (22.4%) with FOLRINOX, 281 (10.3%) with FOLFOX, and 208 (7.6%) with FOLFIRI. All-cause inpatient PPC were $8,220 for lip-IRI, $13,246 for gem+nab-P, $13,872 for FOLFIRINOX, $11,393 for FOLFOX, and $12,667 for FOLFIRI. Neutropenia was reported in 12% of patients receiving lip-IRI, 24% receiving gem-nab-p, 32% receiving FOLFIRINOX, and in 19% of patients receiving FOLFOX or FOLFIRI. ***Conclusions:*** In this study mPC patients receiving lip-IRI experienced lower inpatient PPC and fewer neutropenia events during treatment than other common regimens. Further studies are needed to understand the impact of mPC treatment on neutropenia and inpatient admissions in the real-world.

PCN168
MEDICAL RESOURCE UTILIZATION (MRU) OF APALUTAMIDE (APA) PLUS ANDROGEN DEPRIVATION THERAPY (ADT) IN NON-METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (NMCRPC) AND METASTATIC CASTRATION-SENSITIVE PROSTATE CANCER (MCSPC): RESULTS FROM SPARTAN AND TITAN

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Objectives: In nmCRPC and mCSPC, treatment with APA+ADT demonstrated significant clinical benefit versus placebo + ADT (ADT alone) in the SPARTAN and TITAN trials. APA+ADT was shown to be generally well tolerated with a safety profile similar to that of ADT alone. It is important to understand the impact of apalutamide on MRU; therefore, this analysis aimed to assess this across both studies. ***Methods:*** MRU data collected from SPARTAN and TITAN based on first interim analyses were obtained and analyzed. MRU types included emergency department and outpatient visits, hospitalizations, and others beyond those mandated within the trials. The median follow-up was slightly different for each study (20.3 months in SPARTAN and 22.7 months in TITAN). To correct for the different treatment durations across both groups, MRU types were analyzed by treatment cycle. A maximum of 45 cycles were available for the analysis in SPARTAN, and 13 cycles for TITAN. ***Results:*** In SPARTAN, there were 803 and 398 evaluable patients at baseline, and 4 and 0 evaluable patients at cycle 45 for APA+ADT and ADT alone, respectively. In TITAN, there were 524 and 527 evaluable patients at baseline, decreasing to 433 and 386 patients at cycle 13 for APA+ADT and ADT alone, respectively. MRU was low in all trial groups over the treatment cycles with no apparent differences seen between the APA+ADT and ADT alone groups in either study. In SPARTAN, the average probability of being hospitalized over all cycles was 3.3% for APA+ADT and 5.2% for ADT alone. The probability of hospitalizations in TITAN was 0.9% for both groups. Average emergency department visits in both groups was less than 1.3% in SPARTAN and less than 0.5% in TITAN. ***Conclusions:*** The addition of APA to ADT does not increase MRU, indicating that this addition does not impact tolerability of the treatment regimen.

PCN169
COST BY OUTCOMES ANALYSIS OF BLINATUMOMAB AND INOTUZUMAB OZOGAMICIN FOR ACUTE LYMPHOBLASTIC LEUKEMIA FROM THE BRAZILIAN PRIVATE HEALTHCARE PERSPECTIVE

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Objectives: To estimate treatment costs of novel therapies blinatumomab and inotuzumab ozogamicin in the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) from the Brazilian private healthcare perspective. ***Methods:*** Treatment costs associated with blinatumomab, a bispecific T-cell engager (BiTE®) antibody construct, and inotuzumab ozogamicin, a CD22 monoclonal antibody were compared. For each therapy, the median number of treatment cycles from its pivotal phase III clinical trial was used as treatment duration. Treatment costs were estimated for the modeled treatment duration considering therapy-specific dosing schedules and mean body surface area for Brazilian adult men/ women. Drug prices were based on December 2019 Brazilian list prices with 18% state tax (PF 18%). No vial sharing was assumed. Total treatment costs, cost per median overall survival (OS) and cost per complete response (CR) were compared. ***Results:*** Total treatment costs ranged from 585,601 to 1,054,081 BRL for inotuzumab ozogamicin depending on the mean body surface area (BSA) and treatment response; for blinatumomab the treatment cost presented up to 47% lower than inotuzumab ozogamicin (561,294 BRL) and the treatment cost didn't vary for blinatumomab once for adult patients with weight greater than or equal to 45kg is considered a fixed-dose. In terms of cost per median OS blinatumomab presented up to 56% lower than inotuzumab ozogamicin (60,354 BRL versus 80,037-136,894 BRL). Similarly, the cost per achieved CR was lower for blinatumomab (1,521,123 BRL) than that for inotuzumab ozogamicin (1,839,660 – 3,146,510 BRL). ***Conclusions:*** Results of the present analysis indicate that blinatumomab might be associated with considerably lower treatment costs. When cost analysis included efficacy data, blinatumomab presented lower cost per median OS and cost per CR than inotuzumab ozogamicin from the Brazilian private healthcare perspective.

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EFS ID:	42013985
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Confirmation Number:	5137
Title of Invention:	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin
First Named Inventor/Applicant Name:	Eliel Bayever
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Application Number	15809815
Filing Date	2017-11-10
First Named Inventor	Eliel Bayever
Art Unit	1612
Examiner Name	Celeste A. RONEY
Attorney Docket Number	01208-0007-01US

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	Application Number	15809815
	Filing Date	2017-11-10
	First Named Inventor	Eliel Bayever
	Art Unit	1612
	Examiner Name	Celeste A. RONEY
	Attorney Docket Number	01208-0007-01US

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15809815
	Filing Date	2017-11-10
	First Named Inventor	Eliel Bayever
	Art Unit	1612
	Examiner Name	Celeste A. RONEY
	Attorney Docket Number	01208-0007-01US

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	Examiner Name	Celeste A. RONEY
	Attorney Docket Number	01208-0007-01US

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	Art Unit	1612
	Examiner Name	Celeste A. RONEY
	Attorney Docket Number	01208-0007-01US

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TIME COURSE OF SELECTED TREATMENT EMERGENT ADVERSE EVENTS (TEAES) IN NAPOLI-1: A PHASE 3 STUDY OF NAL-IRI (MM-398) + 5-FLUOROURACIL AND LEUCOVORIN (5-FU/LV) VS 5-FU/LV IN METASTATIC PANCREATIC CANCER (MPAC) PREVIOUSLY TREATED WITH GEMCITABINE-BASED THERAPY

Date
08 Oct 2016

Session
Poster Display

Presenters
Richard Hubner

Citation
Annals of Oncology (2016) 27 (6): 207-242. 10.1093/annonc/mdw371

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Abstract 3832

Background

Liposomal irinotecan (nal-IRI) plus 5-FU/LV is approved in the US for patients (pts) with mPAC previously treated with gemcitabine-based therapy. Primary analysis from NAPOLI-1 (NCT01494506) showed a significant median survival advantage for nal-IRI + 5-FU/LV vs 5-FU/LV (6.1 vs. 4.2 mo; HR 0.67; 95% CI 0.49-0.92; P = 0.012; Wang-Gillam et al, Lancet, 2016). The most common TEAEs included diarrhea, vomiting, nausea, decreased appetite, fatigue, neutropenia, and anemia. Here we report incidence and prevalence of selected TEAEs over time in NAPOLI-1.

Methods

Pts were randomly assigned to nal-IRI + 5-FU/LV, nal-IRI, or 5-FU/LV. In this post hoc analysis (data cutoff, Feb 14, 2014), incidence (ie, first occurrence) and prevalence (ie, first occurrence, ongoing event, or recurrence) of selected TEAEs were analyzed by treatment period (first 6 wk [period 1], second 6 wk [period 2], and beyond second 6 wk [period 3]). Denominators for percentages were the number of pts in the risk set during each period (for incidence: pts still on treatment without a previous event; for prevalence: all safety-evaluable pts).

Results

398 pts were treated with nal-IRI + 5-FU/LV (n = 117), nal-IRI (n = 147), or 5-FU/LV (n = 134). In the nal-IRI + 5-FU/LV arm, most first occurrences of neutropenia, diarrhea, nausea, and vomiting were during the first 6 wk of treatment, with incidence and severity generally decreasing thereafter (Table). Similarly, prevalence and severity were highest in the first 6 wk and tended to decrease over time. Similar trends were observed in the nal-IRI and 5-FU/LV arms.

Incidence, %	nal-IRI + 5-FU/LV			nal-IRI			5-FU/LV		
	Period			Period			Period		
	1	2	3	1	2	3	1	2	3
Neutropenia grade	n = 117	n = 73	n = 34	n = 147	n = 95	n = 48	n = 134	n = 111	n = 43
1	1	3	3	1	2	0	1	0	0
2	8	3	3	8	3	0	1	2	2
3	14	4	9	5	1	0	2	0	0

Incidence, %	nal-IRI + 5-FU/LV			nal-IRI			5-FU/LV		
	Period			Period			Period		
	1	2	3	1	2	3	1	2	3
1	21	4	0	25	11	18	15	5	6
2	17	12	4	20	7	9	2	1	0
3	12	0	4	16	4	0	2	1	3
4	0	0	0	1	0	0	0	0	0
5	0	0	0	1	0	0	0	0	0
Nausea grade	n = 117	n = 56	n = 28	n = 147	n = 53	n = 25	n = 134	n = 87	n = 26
1	21	5	7	23	4	8	19	4	12
2	16	0	7	27	4	8	5	4	4
3	7	2	0	5	2	0	2	2	0
4	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0
Vomiting grade	n = 117	n = 61	n = 35	n = 147	n = 61	n = 28	n = 134	n = 89	n = 29
1	19	5	11	27	2	7	16	2	4
2	14	0	9	10	3	4	5	1	4
3	10	0	3	12	2	0	1	1	4
4	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0

Conclusions

Neutropenia, diarrhea, nausea, and vomiting typically first occur early during the course of treatment with nal-IRI + 5-FU/LV and tend to decrease in incidence and severity thereafter.

Clinical trial identification

NCT01494506

Legal entity responsible for the study

Merrimack Pharmaceuticals, Inc..

Funding

Merrimack Pharmaceuticals, Inc.

Disclosure

L.T. Chen: 1. Merrimack/ NAPOLI-1 study Steering Committee Member, uncompensated 2. Baxalta/ Advisory Meeting, honorarium 3. PharmaEngine/ Consultant, honorarium. J.T. Siveke: 1. Baxalta/ Ad Board, honoraria. A. Dean: Merrimack/ Investigator meeting, travel grant. D. Cunningham: Amgen, AstraZeneca, Bayer, Celgene, MedImmune, Merck Serono, Merrimack, Sanofi: research funding to my institution. J-F. Blanc: Baxalta, honoraria. F. Braiteh: Merrimack, institutional research funding.

K. Mamlouk: Merrimack, employee and stock. B. Belanger: Merrimack, employee. F. de Jong: Baxalta, employee and stock. D.D. von Hoff: Merrimack/ Clinical trial. A. Wang-Gillam: 1. Merrimack/ Ad Board 2. Newlink/ Ad Board 3. Pfizer/ Ad Board. All other authors have declared no conflicts of interest.

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10 Oct 2015

ZUMA-3: A phase 1/2 multi-center study evaluation the safety and efficacy of KTE-C19 anti-CD19 CAR T cells in adult patients with relapsed/refractory B precursor acute lymphoblastic leukemia (R/R ALL)

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(R/R MCL)

Presenter: Michael Wang Session: Poster Display

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Presenter: Maria Teresa Martinez Session: Poster display

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Abstract

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03 Oct 2015

Wait times for diagnosis and treatment of lung cancer: a single centre experience

Presenter: Catherine Labbe Session: Poster Display

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Abstract

741P Prognostic value of baseline neutrophil-to-lymphocyte ratio for predicting clinical outcome in metastatic pancreatic ductal adenocarcinoma (mPDAC) patients treated with liposomal irinotecan (nal-IRI) + 5-fluorouracil and leucovorin (5-FU/LV) vs 5-FU/LV alone

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Background: Elevated baseline neutrophil-to-lymphocyte ratio (NLR), a marker of subclinical inflammation, is associated with poor survival in several malignancies including mPDAC. Here we report the association of NLR with overall survival (OS) and progression-free survival (PFS) in a post-hoc analysis of the NAPOLI-1 trial (NCT01494506), that demonstrated improved survival with nal-IRI + 5-FU/LV vs 5-FU/LV for treatment of mPDAC patients (pts) after disease progression following gemcitabine-based therapy

Methods: Pts treated with nal-IRI + 5-FU/LV or 5-FU/LV and available baseline NLR data were included (data cutoff: Nov 16, 2015). OS and PFS were assessed in pts with high (>5) or low (≤5) baseline NLR in individual and pooled treatment arms.

Results: Baseline NLR was available for 221 pts: 116/117 nal-IRI + 5-FU/LV pts and 105/105 5-FU/LV pts. In the pooled treatment arms, pts with NLR≤5 had significantly better OS compared to pts with NLR >5 (6.2 vs 3.7 months, HR = 0.7, p = 0.02). Interestingly, this improvement in OS in pts with low vs high NLR was significant in the nal-IRI+5-FU/LV arm (8.4 vs 4.3 months, HR = 0.5, p=0.001), but not in the 5-FU/LV arm (4.8 vs 3.1 months, HR = 0.9, p=0.6). Similarly, PFS was significantly higher in pts with NLR≤5 vs NLR >5 in the pooled treatment arms (2.7 vs 1.4 months, HR = 0.7, p=0.05), and the nal-IRI+5-FU/LV arm (4.2 vs 1.4 months, HR = 0.5, p=0.002), but not the 5-FU/LV arm (1.5 vs 1.4 months, HR = 1.1, p=0.6).

Conclusions: Data from these exploratory analyses are consistent with previous reports on the prognostic value of baseline NLR in mPDAC, and extend it to the post-gemcitabine setting. Median OS and PFS were improved in pts with low vs high baseline NLR in the nal-IRI+5-FU/LV arm but not in the 5-FU/LV arm. Clinical implications of these data remain to be determined.

Clinical trial identification: NCT01494506

Legal entity responsible for the study: Merrimack Pharmaceuticals, Inc.

Funding: Ipsen Biopharmaceuticals, Inc

Disclosure: R.A. Hubner: Consulting for Celgene, BTG, Baxalta. Speakers' Bureau for Abbott, Ipsen. L-T. Chen: Consulting for ONO, Eli Lilly, MSD, PharmaEngine, Merrimack, TTY, Syncore, Five Prime, Novartis. Research funding from Novartis, GSK, TTY, Polaris. G. Bodoky: Honoraria from Servier, Roche, Bayer, Pfizer, Janssen, Novartis, Lilly. Advisory board of Bayer, Roche, Pfizer, Janssen, Novartis, Lilly, Taiho, Nordic. D. Cunningham: Research funding from Amgen, Astrazeneca, Bayer, Celgene, Merrimack, Medimmune, Merck Serono, Sanofi. J.T. Siveke: Research funding from Celgene, BMS, 4SC, Novartis, Boehringer. Consultant for Merrimack, Baxalta, Celgene, Eli Lilly. F.S. Braiteh: Consulting and speaking fees from Ipsen. F.A. de Jong: Employee and stockholder of Shire. B. Belanger, R. Walls, P.D. Mody: Employee of Ipsen Biopharmaceuticals, Inc. D.D. von Hoff: Research funding from Merrimack. A. Wang-Gillam: Research funding from Newlink, Astrazeneca, Biomed Valley, Eli Lilly, Abbvie, Verastem, Precision Biologics. Consulting for Merrimack, Pfizer, Newlink. All other authors have declared no conflicts of interest.

Table: 741P

	Pooled treatment arms		nal-IRI + 5FU/LV		5FU/LV	
Baseline NLR	≤5 (n = 155)	>5 (n = 66)	≤5 (n = 82)	>5 (n = 34)	≤5 (n = 73)	>5 (n = 32)
Median[1] OS, months (95% CI)	6.2 (5.2 - 7.6)	3.7 (3.1 - 4.4)	8.4 (6.1 - 10.2)	4.3 (3.4 - 4.7)	4.8 (3.6 - 6.1)	3.1 (1.9 - 4.2)
HR[2]	0.7		0.5		0.9	
95% CI	0.5 - 0.9		0.3 - 0.8		0.6 - 1.4	
p[3]	0.02		0.001		0.6	
Median[1] PFS, months (95% CI)	2.7 (2.4 - 3.3)	1.4 (1.4 - 1.6)	4.2 (3.1 - 5.6)	1.4 (1.4 - 2.8)	1.5 (1.4 - 2.6)	1.4 (1.3 - 1.9)
HR[2]	0.7		0.5		1.1	
95% CI	0.5 - 1.0		0.3 - 0.8		0.8 - 1.8	
p[3]	0.05		0.007		0.6	

[1]Medians reflect Kaplan-Meier estimates.

[2]Hazard ratios (HRs) reflect Cox regression analysis.

[3]Two-sided p-value < 0.05 considered statistically significant in these exploratory analyses.

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orals

O – 004 Effects of nal-IRI (MM-398) ± 5-fluorouracil on quality of life (QoL) in NAPOLI-1: a phase 3 study in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) previously treated with gemcitabine

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Introduction: Patients with mPDAC frequently experience a significant symptom burden. This in turn negatively impacts their QoL. Nal-IRI, a nanoliposomal formulation of irinotecan, was evaluated with or without 5-FU/LV vs 5-FU/LV in a randomized phase 3 study in patients with mPDAC previously treated with gemcitabine-based therapy (NAPOLI-1). Results showed nal-IRI + 5-FU/LV significantly improved overall survival compared with 5-FU/LV (6.1 vs 4.2 months; unstratified hazard ratio 0.67; $P = 0.012$) (Wang-Gillam et al., *Lancet.* 2016). QoL was a secondary endpoint of the study.

Methods: QoL was assessed using the European Organization for Research and Treatment of Cancer quality-of-life core questionnaire (EORTC-QLQ-C30), which includes functional scales (physical, role, cognitive, emotional, and social); symptom scales (appetite loss, constipation, diarrhea, dyspnea, fatigue, insomnia, nausea and vomiting, and pain); and a global health and quality-of-life scale. Patients were to complete the questionnaire at treatment start, every 6 weeks, and 30 days post-follow-up visit. The population analyzed included all patients who provided baseline and at ≥1 subsequent EORTC-QLQ-C30 assessment. Linear transformations were applied to the raw scores to produce reported scores in the 0-100 range. In the responder analysis, patients were classified as *improved* (≥10% increase in scale of breadth at a post-baseline time point and remained above baseline for ≥6 weeks), *worsened* (did not meet improvement criteria and died, or had ≥10% decrease from baseline in scale of breadth at a post-baseline time point), or *stable* (did not meet criteria for improvement or worsening) for each subscale. Pairwise treatment group comparisons on response classification were performed for each subscale using Cochran-Mantel-Haenszel testing adjusted for multiplicity with a Benjamini-Hochberg correction to control false discovery rate at 0.05 level for the 15 comparisons.

Results: A total of 154 patients (nal-IRI + 5-FU/LV, n = 71; 5-FU/LV, n = 83) comprised the population for this analysis of which 69% (49/71) of patients in the nal-IRI + 5-FU group and 53% (44/83) in the 5-FU/LV group had evaluable data at 12 weeks. At baseline, median Global Health Status scores were near the midpoint of the scoring range, median Functional Scale scores were high, and Symptom Scale scores were low, with baseline values similar between groups. The observed median change in score at 12 weeks was 0 for both treatment groups for Global Health Status and for the following subscale scores: role functioning, emotional functioning, cognitive functioning, social functioning, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. For subscale scores for which the median change was not 0 (nal-IRI + 5-FU/LV: physical functioning and fatigue), the between-group differences were not substantial. Additionally, there were no significant differences in the proportion of patients classified as improved, worsened, or stable between the treatment groups. Across subscales, adjusted P values for the comparisons were >0.05 (NS).

Conclusion: In NAPOLI-1, evaluable nal-IRI + 5-FU/LV-treated patients with data through 12 weeks tended to maintain baseline QoL over 12 weeks, and there were no significant differences versus the 5-FU/LV-treated patients in QoL response despite the addition of a second cytotoxic agent. These results are limited by the small number of patients and variability in QoL subscale scores.

Expanded analyses of NAPOLI-1: Phase 3 study of nal-IRI (MM-398), with or without 5-fluorouracil (5FU) and leucovorin (LV), versus 5-fluorouracil and leucovorin (5FU/LV), in metastatic pancreatic cancer (mPAC) previously treated with gemcitabine-based therapy

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Background

Nal-IRI is a nanoliposomal encapsulation of irinotecan. OS in the ITT-population was significantly longer with nal-IRI+5FU/LV over 5FU/LV alone (median OS for nal-IRI+5FU/LV was 6.1m (95%CI=4.8-8.9m; N=117) vs 4.2m (95%CI=3.3-5.3m; N=119) for 5FU/LV (unstratified HR=0.67; 95%CI=0.49-0.92; log-rank test p=0.011). Most

frequent grade 3+ AEs included neutropenia, fatigue, and GI-effects (diarrhea and vomiting).[1] Expanded, pre-specified analyses of the Phase-3 study have been presented.[2]

Method

Patients with mPAC (n=417) previously treated with gemcitabine-based therapy, were randomized 1:1:1 in an open-label study to receive: (A) Nal-IRI (120mg/m^2 IV over 90min) q3w; (B) 5FU (2,000mg/m^2 over 24h) plus racemic LV (200mg/m^2 over 30min) x4w followed by 2w rest; or (C) combination of nal-IRI (80mg/m^2 IV over 90min) prior to 5FU (2,400mg/m^2 over 46h) and racemic LV (400mg/m^2 over 30min) q2w. The primary endpoint was OS. The Intent to Treat (ITT)-population included all randomized patients; the Per Protocol (PP)-population included patients who received at least 80% of the target dose in the first 6 weeks and did not violate any inclusion/exclusion criteria.

Results

Analysis of the PP-populations confirmed the favorable OS, which was also reflected by the PFS, ORR and CA19-9 levels, of the combination nal-IRI+5FU/LV over the control 5FU/LV arm. Median OS in the PP-population for nal-IRI+5FU/LV-arm was 8.9m (95%CI=6.4-10.5m; N=66) vs 5.1m (95%CI=4.0-7.2m; N=71) for 5FU/LV (unstratified HR=0.57; 95%CI=0.37-0.88; log-rank test p=0.011). The nal-IRI-monotherapy arm did not show a statistically significant improvement in OS compared with the control arm. Analysis of subgroups, based on pretreatment characteristics including stage at diagnosis, time since initial histological diagnosis, prior lines of therapy, time since last prior therapy, and CA19-9, consistently favored OS for the nal-IRI+5FU/LV arm over the 5FU/LV arm.

Conclusion

Expanded analysis of the PP-population and sensitivity analyses support the favorability of nal-IRI+5FU/LV over 5FU/LV, with a manageable safety profile. Clinical trial information: NCT01494506.[3]

GASTROINTESTINAL (NONCOLORECTAL) CANCER

A randomized phase II study of FOLFOX or FOLFIRI.3 as second-line therapy in patients with advanced pancreatic cancer previously treated with gemcitabine-based chemotherapy

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Abstract

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Background: Only few clinical trials have been conducted in patients with advanced pancreatic cancer after failure of first-line gemcitabine-based chemotherapy. We conducted a randomized phase II trial of modified FOLFOX vs. modified FOLFIRI.3 as second-line regimen for the patients with gemcitabine refractory pancreatic cancer (NCT00786006). **Methods:** Patients with advanced pancreatic adenocarcinoma previously treated with gemcitabine were randomly assigned to FOLFOX or FOLFIRI.3 stratifying by age (≤ 65 vs. >65), performance status (0–1 vs. 2) and prior response to gemcitabine (PR/SD vs. PD). FOIFIRI.3 regimen consisted of Irinotecan 70 mg/m^2 (over 60 min) D1, leucovorin 400 mg/m^2 (over 2h) D1, 5-FU 2000 mg/m^2 (over 46 hours) from D1, then irinotecan 70 mg/m^2 (over 60 min) at the end of the 5-FU infusion every two week. FOLFOX regimen is composed of oxaliplatin 85 mg/m^2(over 120 min) D1, LV 400 mg/m^2 D1, 5-FU 2,000 mg/m^2 (over 46 hours) every two week. The primary end-point was 6-month overall survival (P_0=20%) and Simon-Wittes-Ellenberg design was used to calculate the sample size (29 evaluable patients for each treatment arm). **Results:** From January 2007 to December 2008, sixty patients were enrolled and randomized to FOLFOX (N=30) or FOLFIRI.3 (N=30). Baseline characteristics were well balanced between each arm; median age 56 (35–60) vs. 56 yo (37–73); ECOG PS 0/1/2, 5/24/1 vs. 5/25/0; prior response to gemcitabine-based chemotherapy PR/SD/PD 10/13/7 vs. 10/11/9. With a median follow-up period of 6.0 months (95% CI, 4.7–7.3) the median overall survival was 4.0 months in both group (HR=0.95, 95% CI 0.52–1.75) with 6-month survival rates of 25% and 20%, respectively. The median PFS was 1.4 months for FOLFOX and 1.9 months for FOLFIRI.3 (HR=1.11, 95% CI, 0.64–1.92). Disease control (PR+SD) was achieved in 20% (5/25 in FOLFOX) and 28% (7/25 in FOLFIRI.3) of patients with measurable

disease. The incidences of grade 3/4 toxicities were similar in both groups. **Conclusions:** Both FOLFOX and FOLFIRI.3 were tolerated with manageable toxicity, offering modest activity as second-line treatment of patients with advanced or metastatic pancreatic cancer, previously treated with gemcitabine.

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Improving the Toxicity of Irinotecan/5-FU/ Leucovorin: A 21-Day Schedule

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Irinotecan (CPT-11, Camptosar) is one of the new generation ofchemotherapeutic agents that has activity in advanced colorectal cancer.It has antitumor efficacy as a single agent, and also has beencombined with fluorouracil (5-FU) and leucovorin (IFL) to treat thesepatients. Randomized studies have confirmed the superiority of IFL to5-FU and leucovorin alone with regard to patient survival, time toprogression, and tumor response rate. The optimal schedule for combiningthese agents remains uncertain, but in the United States, theschedule of IFL weekly for 4 consecutive weeks repeated every 6 weeks,according to the schedule reported by Saltz et al, has been widely used,although with some toxicity (especially myelosuppression and diarrhea).In an attempt to improve the tolerability of IFL, some haveadvocated modifying the schedule of IFL to weekly for 2 weeks, withrepeated cycles every 21 days. Twenty-three patients with advancedcolorectal cancer have been treated on this schedule at a single institution.Therapy was well tolerated, with 35% of patients experiencinggrade 3/4 neutropenia, two of whom had episodes of febrile neutropenia,and 9% with grade 3/4 diarrhea. The median relative dose intensityof irinotecan administered in the first 18 patients treated with thisregimen was 94%. These data support the hypothesis that modifying theschedule of administration of IFL improves the tolerability and abilityto deliver the regimen, but must be confirmed by randomized prospectivestudies, which may also attempt to evaluate the role of bolus 5-FUin the treatment of advanced colorectal cancer.

ABSTRACT: Irinotecan (CPT-11, Camptosar) is one of the new generation ofchemotherapeutic agents that has activity in advanced colorectal cancer.It has antitumor efficacy as a single agent, and also has beencombined with fluorouracil (5-FU) and leucovorin (IFL) to treat thesepatients. Randomized studies have confirmed the superiority of IFL to5-FU and leucovorin alone with regard to patient survival, time toprogression, and tumor response rate. The optimal schedule for combiningthese agents remains uncertain, but in the United States, theschedule of IFL weekly for 4 consecutive weeks repeated every 6 weeks,according to the schedule reported by Saltz et al, has been widely used,although

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Irinotecan (CPT-11, Camptosar) isa semisynthetic derivative ofcamptothecin sodium, which itselfis the active extract from the bark ofthe Chinese/Tibetan deciduous tree*Camptotheca acuminata* (Nyssaceaefamily). Although early developmentof this camptothecin was stymied bythe toxicity of the compound, in particularmyelosuppression and hemorrhagiccystitis, irinotecan has beenmuch better tolerated, with the primarytoxicities being myelosuppressionand diarrhea.[1] Subsequent studiesin humans have demonstrated thatirinotecan has activity in a number ofmalignancies, including colorectal,[2,3] gastroesophageal,[4-6] pancreatic,[7] lung,[8,9] breast,[10] andgynecologic cancers.[11,12] In theUnite States, irinotecan is currentlyindicated for use in patients with advancedcolorectal cancer.In 1998, two studies proved thebenefit of irinotecan in patients withadvanced colorectal cancer that hadprogressed despite prior therapy withthe then-standard therapy, fluorouracil(5-FU). Cunningham et al[13] reportedthat salvage irinotecan (n = 189) at300 to 350 mg/m^2 intravenously (IV)every 3 weeks significantly increased1-year survival in comparison to supportivecare alone (n = 90): 36.2%compared to 13.8%. In the same patientpopulation, Rougier et al[14] randomized267 patients to 300 mg/m^{2}of irinotecan every 3 weeks or infusional5-FU. Again, the 1-year andmedian survivals were increased inpatients treated with irinotecan(n = 133), at 45% and 10.8 months vs32% and 8.5 months, respectively.[14]Other studies confirmed that irinotecanhas antitumor activity in patientswithout previous chemotherapy for metastaticcolorectal cancer.[2,3,15,16] Asa result, irinotecan has become widelyaccepted for use in patients withmetastatic colorectal cancer.

Irinotecan and 5-FUBased on the differing mechanismsof activity of the two most active antineoplasticagents in colorectal and othergastrointestinal cancers, thesedrugs-irinotecan and 5-FU-havebeen administered together. A numberof methods of combining irinotecanand 5-FU with leucovorin (IFL)have been evaluated, but the optimalcombination and schedule remain uncertain(Table 1). Given the multitudeof 5-FU treatment schedules usedaround the world, this is not surprising.However, the most widely usedcombinations of irinotecan and 5-FUare based upon a bolus administrationof therapy.In a phase I study, Saltz et al[17]combined irinotecan, 5-FU, and leucovorin in a weekly for 4 weeks

schedule,with cycles repeated every 6weeks (therapy administered on days1, 8, 15, and 22 every 42 days). Sequentialescalations of 5-FU, thenirinotecan, were performed, and thedoses recommended for further evaluationwere 125 mg/m^2 of irinotecaninfused IV over 90 minutes, 500 mg/m^2 of 5-FU by bolus, and 20 mg/m^2 ofleucovorin by IV bolus. The primarydose-limiting toxicity was neutropenia,although diarrhea was common. [17]Furthering the evaluation of thispromising combination, Saltz et al[18]reported a study of 683 patients whowere randomized to either weekly IFLwith this schedule (n = 231), 5-FUand leucovorin on the Mayo clinicschedule (n = 226), or irinotecan at125 mg/m^2 IV for 4 consecutive weeks(n = 226), again followed by a 2-weekbreak. This study demonstrated a significantsuperiority of IFL in medianprogression-free survival, objectiveresponse rate, and median survival. Inparticular, therapy with IFL resultedin a 36% decrease in risk of progression, and a 22% decrease in risk ofdeath in comparison to the previousstandard therapy, 5-FU and leucovorin.[18]The so-called de Gramont regimenhas been an accepted standard combinationof 5-FU and leucovorin for advancedcolorectal cancer inFrance.[19] A simplified version ofthis regimen, with the 5-FU administeredas a 400 mg/m^2 IV bolus, followedby a 46-hour continuousinfusion at 2,400 to 3,000 mg/m^2, every2 weeks, has been combined with180 mg/m^2 irinotecan on the first dayof therapy (FOLFIRI), in a study reportedby Andre et al.[20] As salvagetherapy, limited antitumor activity wasnoted. In 33 treated patients, two (6%)patients had partial responses and 20experienced stabilization of disease.Therapy was well tolerated, with 15%of patients experiencing severe vomitingand myelosuppression, and severediarrhea seen in 12%.[20]The popular German ArbeitsgemeinschaftInternische Onkologie(AIO) schedule of high-dose 5-FUadministered as a 24-hour infusion weekly has also been combined withirinotecan. Vanhoefer et al[21] deliveredthe full dose of 5-FU (2,600 mg/m^2 weekly) and leucovorin (500 mg/m^2) with 80 mg/m^2 of irinotecan. Thedose-limiting toxicity was severe diarrhea;however, myelosuppressionwas not a significant problem.[21]Other researchers have evaluatedfurther combinations of the agents.Falcone et al[22] combined a 48-hourcontinuous infusion of 5-FU (3,500mg/m^2) with irinotecan in 33 patients,evaluating irinotecan both precedingand following 5-FU. Cycles prior to5-FU and leucovorin permitted a higherdose of irinotecan administration(recommending a dose of 350 mg/m^2)in this combination, with less toxicityoverall than the reverse schedule. Severeneutropenia was noted in 22% ofpatients, and grade 3/4 diarrhea in4%.[22] In a phase I study in 42 patientswith metastatic colon cancer,Kakolyris et al[23] combined a 4-daycontinuous infusion of 5-FU withirinotecan immediately afterwards.The doses recommended for subsequentevaluation were 600 mg/m^2/dand 350 mg/m^2, respectively. At thesedoses, 20% of 25 cycles reported grade3/4 neutropenia, and dose-limitingtoxicities were noted in two of sixpatients: severe neutropenia with severediarrhea, and neutropenic fever.[23]Capecitabine (Xeloda), an oral fluoropyrimidine,was found to have superioractivity and less toxicity incomparison to bolus 5-FU and leucovorinadministered on the Mayo clinicschedule.[24,25] Because of its easeof administration and good toxicityprofile, capecitabine has been combinedwith irinotecan, with promisingresults.

Several schedules have beenevaluated. Cassata et al[26] combined1,000 mg/m^2 of capecitabine twicedaily for 14 days with irinotecan, withthe latter administered either as 300mg/m^2 on day 1 or 150 mg/m^2 on days1 and 8 of each 21-day treatment cycle.Both schedules were fairly welltolerated, and active in the first-linetreatment setting (71% overall response[15/21]).[26]Others have evaluated similarschedules and slightly lower irinotecandoses yielding similar findingswith regard to efficacy, as well as asuggestion of somewhat better toxicityprofiles.[27,28]. On the formerschedule, Delord et al[29] used 250mg/m^2 of irinotecan on day 1 of treatment,and reported grade 3 neutropeniain two of seven patients, and grade3 diarrhea in one patient. As part of arandomized phase II study, Jordan etal[30] treated advanced colorectal cancerpatients with irinotecan at 100 mg/m^2 on days 1 and 8 of each 21-daytreatment cycle. Severe diarrhea wasreported in three and severe neutropeniain two of the 28 patients. However,two patients died from neutropenicsepsis with diarrhea and pulmonaryembolism, respectively.[30]Despite evaluations of these variousschedules, the preferred combinationof irinotecan and 5-FU remainsuncertain. The schedules that havebeen the most intensely evaluated todate are the weekly IFL schedule, andirinotecan in combination with somevariation of the bimonthly de Gramontschedule.

IFL as First-Line Therapyin Colorectal Cancer

Efficacy

The superior antitumor activity ofIFL in comparison to 5-FU and leucovorinadministered by the Mayo or deGramont schedules, as well as irinotecanalone in patients with metastaticcolorectal cancer with no priorchemotherapy for metastatic disease,was established by two reports publishedin 2000. The first by Saltz etal,[18] in the *New England Journal ofMedicine* as described above, demonstratedsuperior response, time to progression,and survival with theaddition of irinotecan to 5-FU andleucovorin in comparison to irinotecanalone, or 5-FU and leucovorinadministered according to the Mayoclinic schedule.Similarly, Douillard et al[31] randomized387 patients to one of two 5-FU/leucovorin treatment regimens (deGramont schedule with this schedule[288 patients] or AIO schedule [97patients] at the investigator's discretion)with or without irinotecan. Irinotecanwas administered at either 180mg/m^2 IV on day 1 of therapy every 2 weeks with the de Gramont schedule,or 80 mg/m^2 IV weekly. Again, irinotecansignificantly increased the responserate ($P < .005$), time toprogression ($P < .001$), and mediansurvival ($P < .031$) in comparison topatients treated with 5-FU and leucovorinalone, regardless of the scheduleemployed.[31]With these studies demonstratingthe efficacy of IFL, this combinationsubsequently became the standard initialtherapy for patients with metastaticcolorectal cancer. Although thepreferred combination was uncertain,in the United States the weekly schedulewas most widely used, in part becauseof the ease of administration.However, subsequent reports haveraised concerns about the tolerabilityof this schedule.

Toxicity

Not surprisingly, the toxicity profileof IFL depends in great part onthe schedule of 5-FU administeredwith irinotecan (Table 2). The weeklyIFL toxicities reported by Saltz etal[18] in the phase III study were primarilymyelosuppression, with 53.8%of patients experiencing grade 3/4 neutropenia,and neutropenic fevers in7.1%. Severe or life-

threatening diarrheawas also a prominent toxicity,occurring in 22.7% of patients, andgrade 3/4 nausea/vomiting in 9.7%.Overall though, therapy was consideredto be well tolerated, with only 2(0.9%) of 225 patients dying as a consequenceof therapy.[18]With the combination of the deGramont schedule of 5-FU and leucovorinwith irinotecan administeredevery other week, grade 3/4 neutropeniaremained the most common toxicity,occurring in 46.2% of patients,with neutropenic fever in 5.5% of patients.Severe diarrhea occurred in13.1% of patients, and grade 3/4 nausea/vomiting in about 3% of patients.When combined with 5-FU and leu-

covorin administered on the AIOschedule, IFL resulted in somewhatmore toxicity, including severe diarrheain 44.4% and vomiting in 11.1%of the 54 patients treated. Grade 3/4neutropenia was reported in 28.8%,and febrile neutropenia in 9.3%.[31]This difference in toxicities amongthese regimens was most likely a consequenceof the 5-FU/leucovorinschedule employed, and the resultantdifference in irinotecan schedule.Again, the regimens appeared to havea similar efficacy, despite the differencein toxicity.With the combination of irinotecan,5-FU, and leucovorin becomingthe standard therapy for patients withmetastatic colorectal cancer, its use inthe late 1990s and early 21st centuryescalated dramatically. In the UnitedStates, the weekly regimen of IFL,the so-called Saltz regimen, had becomethe predominant schedule employedbecause of the relative ease ofadministration, which did not requirethe placement of prolonged venousaccess. However, dramatic reportsfrom two Intergroup studies-Cancerand Leukemia Group B (CALGB)89803 and North Central CancerTreatment Group (NCCTG) 9741-evaluating the efficacy of this scheduleof IFL in the respective adjuvantand metastatic settings have led torenewed concerns about the tolerabilityof this regimen (Table 3).In April 2001, the External DataMonitoring Committee for NCCTG9741 reported deaths within the first60 days of study entry in 13 (4.5%) of289 patients. A subsequent review ofthe CALGB study found that 16(2.5%) of 635 patients treated withIFL also died within 60 days of initiatingtreatment. Of interest, the initialreport of IFL in a phase III studynoted that 0.9% of 225 patients diedfrom drug-related causes, comparedto 1.4% of 219 patients treated withbolus 5-FU/leucovorin on the MayoClinic schedule. The deaths that occurredon this study were later reviewed,and the 60-day mortality, thesame yardstick applied to the Intergroupstudies, revealed rates of 6.7%with IFL and 7.3% with 5-FU/leucovorin.[32]An independent review of thesedeaths attributed them to "gastrointestinalsyndrome," including diarrhea,nausea, vomiting, abdominal crampingleading to dehydration and electrolyteabnormalities, and often in thesetting of neutropenia, fever, or infection;or "vascular syndrome," includingmyocardial infarction, pulmonaryembolism, or cerebrovascular accidents.The gastrointestinal syndromewas felt to cause, exacerbate, or contributeto the deaths of 12 patientsin the CALGB study and 6 in theNCCTG study. The vascular syndromewas believed to cause or contributeto the deaths of five patients inthe CALGB study and three in theNCCTG study.The panel found that the medianage of the patients treated with IFLwho died was 69.5 years in CALGB89803 and

65 years in NCCTG 9741,older than the median ages of patientstypically enrolled in studies of colorectalcancer. A number of recommendationswere made by this expertpanel, including close monitoring ofpatients treated with IFL, especiallyolder patients, and an aggressive approachto the treatment of diarrheaand abdominal cramping, includingaggressive use of antibiotics in patients with diarrhea and neutropenia.[33]In addition to the concerns aboutthe toxicities of weekly IFL, anotherdifficulty of the regimen is that severetoxicities occurred despite a relativelylow dose intensity ofchemotherapy. In particular, great difficultywas encountered in administeringweeks 3 and 4 of chemotherapybecause of myelosuppression and diarrhea.As a result, the median relativedose intensities (calculated bydividing the actual dose of the agentdelivered by the intended dose of theagent) of irinotecan and 5-FU were72% and 71%, respectively.[18]

21-Day Schedule

Considering the difficulties of dosedelivery and toxicity in weekly IFLaccording to the Saltz schedule, whichappeared to be cumulative within acycle, one manner of improving thetherapeutic index of weekly IFL wouldseem to be to create a break after thesecond week of therapy, prior to resumingIFL. To evaluate this hypothesis,23 patients have been treated withweekly IFL at the Lombardi CancerCenter at Georgetown UniversityMedical Center. However, therapywas administered on days 1 and 8every 21 days. For patients who were75 years or older, the initial dose ofirinotecan was 100 mg/m^2. Theplanned dose intensity of this schedulewould be identical to the Saltzschedule of IFL.The patient population was similarto other studies of patients with ad-

vancedcolorectal cancer (Table 4).However, none of the patients hadreceived prior chemotherapy. All patientshad a good performance status(Eastern Cooperative Oncology Group0 or 1). The median age of the populationwas 57 years, encompassing arange of ages from 38 to 77; two patientswere 75 years or older. Fourteenof the patients were males. Fifteenof the patients were given chemotherapyas adjuvant treatment. Only eightof these patients received therapy astreatment for measurable metastaticdisease. One patient has received 6weeks of therapy and is not yet evaluablefor response. Three of the otherseven had stable disease, and four hadprogression of disease on their follow-up evaluation.This schedule was well tolerated,with grade 3/4 neutropenia occurringin eight (35%) patients, and severediarrhea in only two (9%). Two patientsexperienced one episode eachof febrile neutropenia with the firstcycle of therapy, but tolerated furthertreatment with IFL on the 21-dayschedule after a 25% dose reduction.No other grade 3/4 toxicities werenoted (Table 5).Supporting these data that demonstratethe tolerability of this scheduleof IFL was the ability to deliver thetherapy. In the first 18 patients treatedwith this schedule, the median relativedose intensities, calculated by thesame method as Saltz et al,[18] ofirinotecan and 5-FU were 94% and 92% (Table 6). Half of these patientsreceived therapy without requiring anydose modifications. Full doses wereadministered in 104 of 141 cycles,with a 10% dose reduction occurringin 26 cycles (18.4%), and 25% and50% dose reductions in 9 and 2 cycles,respectively.These results, especially with regardto the ability to deliver a

highdose intensity of the regimen with asimple modification of the scheduleof administration, support the hypothesisthat altering the schedule of therapywill improve the therapeutic indexof IFL. However, because of the potentiallyconfounding differences betweenstudy populations, thecomparison of median relative doseintensity between these two studygroups requires confirmation in a prospectiverandomized study. Furthermore,the change in the schedule maynot be the only, or primary, reason forthe ability to deliver such a high proportionof the intended dose.In particular, the patient populationmust be considered to be favorable.First, the median age of thetreated patients was 57 years, withonly two patients being over 75, andthus may be considered inadequatelyrepresentative of the population ofpatients with advanced colorectal cancer.Moreover, as many of the patientswho were treated in this programhad only a high risk for disease recurrence,and essentially received adjuvanttherapy, they may have been a"healthier" population overall. Theantitumor activity and tolerability ofthe 21-day schedule of IFL, then, canonly be assessed in the context of aprospective randomized trial.

Future DirectionsAt the 2002 meeting of the AmericanSociety of Clinical Oncology,Goldberg et al[34] reported the preliminaryresults of NCCTG 9741. Atotal of 795 patients with advancedcolorectal cancer were randomized toweekly IFL using the Saltz scheduleas the control arm, or oxaliplatin(Eloxatin), 5-FU, and leucovorin onthe de Gramont schedule (FOLFOX4), or a combination of irinotecan andoxaliplatin every 3 weeks. The medianprogression-free survival and medianoverall survival weresignificantly longer for patients treatedwith FOLFOX 4 than IFL on theSaltz schedule, at 8.8 vs 6.9 months,and 18.6 compared to 14.1 months,respectively.[34]As a result of these findings, theUS Food and Drug Administrationapproved oxaliplatin in August 2002for use in combination with infusional5-FU and leucovorin for the treatmentof patients with advancedcolorectal cancer. An additional questionis whether oxaliplatin-based chemotherapywill become the newstandard first-line therapy for patientswith metastatic colorectal cancer.Irinotecan, oxaliplatin, and 5-FU possessactivity in advanced colorectalcancer, and should be made availableto all. However, the appropriate combinationand best sequence of theseagents will need to be elucidated, including the optimal method of administering5-FU (ie, bolus, infusional, ororal) (Figure 1).Finally, the potential role of thetargeted therapies, such as the epidermalgrowth factor receptor (EGFR) antagonistsincluding erbitux (C-225),[35]gefitinib (ZD1839, Iressa), and OSI-774 (Tarceva), and vascular endothelialgrowth factor antagonistsincluding bevacizumab,[36] are beingevaluated. About 70% of patientswith colorectal cancer have tumorsthat overexpress EGFR, making thisa promising target for intervention.Preliminary studies have suggestedthat the combination of irinotecan anderbitux has activity in patients withmetastatic colorectal cancer. The precisecontribution of erbitux in thiscombination, as well as the optimalmethod of combining chemotherapyand these targeted therapies, also remainunknown [35].With a plethora of other potentialtargets and agents against these targetsbeing identified and developed, avariety of options may be availablefor patients in

the future, offering anopportunity to tailor therapy to thepatient, maximize activity, and minimizetoxicity. A modification of theweekly bolus IFL, altering the scheduleto administer therapy on days 1and 8 every 21 days, may improve thetherapeutic index of IFL and allowphysicians to continue offering patientsa relatively easily delivered and effective chemotherapy regimen, andencourage investigators to explore theregimen as a backbone to further studyof new agents and combinations inthe treatment of advanced colorectalcancer.

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The author(s) have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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Presentation of proteins encapsulated in sterically stabilized liposomes by dendritic cells initiates CD8+ T-cell responses in vivo

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Liposomes have been proposed as a vehicle to deliver proteins to antigen-presenting cells (APC), such as dendritic cells (DC), to stimulate strong T cell–mediated immune responses. Unfortunately, because of their instability in vivo and their rapid uptake by cells of the mononuclear phagocyte system on intravenous administration, most types of conventional liposomes lack clinical applicability. In contrast, sterically stabilized liposomes (SL) have increased in vivo stability. It is shown that both immature and mature DC take up SL into neutral or mildly acidic compartments distinct from endocytic vacuoles. These DC presented SL-encapsulated protein to both CD4+ and CD8+ T cells in vitro. Although CD4+ T-cell responses were comparable to those induced by soluble protein, CD8+ T-cell proliferation was up to 300-fold stronger when DC had been pulsed with SL-encapsulated ovalbumin. DC processed SL-encapsulated antigen through a TAP-dependent mechanism. Immunization of mice with SL-encapsulated ovalbumin led to antigen presentation by DC in vivo and stimulated greater CD8+ T-cell responses than immunization with soluble protein or with conventional or positively charged liposomes carrying ovalbumin. Therefore, the application of SL-encapsulated antigens offers a novel effective, safe vaccine approach if a combination of CD8+ and CD4+ T-cell responses is desired (ie, in anti-viral or anti-tumor immunity). (Blood. 2000;96:3505-3513)

Introduction

One of the major obstacles in vaccine research is the fact that protein antigens are usually poorly presented on major histocompatibility class I molecules and therefore fail to induce strong CD8+ T-cell responses. To overcome this problem, liposomes have been proposed as antigen-delivery vehicles (reviewed in [1,2]). Unfortunately, the antigen delivery potential of conventional liposomes in vivo is limited because of their rapid elimination from the peripheral circulation by resident macrophages (MΦ) of the mononuclear phagocyte system (MPS), leading to their lysosomal localization in liver and spleen.[3,4] The rate of liposome clearance strongly depends on several physical parameters, including the size and surface charge of the liposomes.[5-8]

A new type of liposome, sterically stabilized liposomes (SL), contains large molecules, such as polyethylene glycol (PEG), in its membrane and is, therefore, less efficiently taken up by myelomonocytic cells than conventional liposomes.[9,10] PEG interferes with the binding of serum proteins to the liposome surface and the subsequent adhesion of SL to cells of the MPS, considerably reducing the clearance of SL, irrespective of their surface charge.[8,11] As a result, SL exhibit a serum half-life up to approximately 48 hours in humans and animal models,[12,13] compared to only a few hours for conventional liposomes. In addition to their prolonged circulation, they can extravasate to the skin or to sites of trauma (inflammation, tumors) that are characterized by capillary leakage.[12,14]

Based on their biologic stability and their unique distribution, SL may prove to be more effective than other forms of liposomes in delivering antigens to antigen-presenting cells (APC), such as immature dendritic cells (DC), residing in the periphery of the body. Once immature DC pick up antigens, they migrate to the regional lymph nodes (LN).[15,16] On arrival in the LN, they display a mature phenotype and present antigens to lymphocytes, efficiently activating naive and memory T-cell and B-cell responses.[16] Recent advances in cell culture technology have facilitated the generation of large numbers of immature and mature DC from precursor cells in the peripheral blood. Ex vivo–generated antigen-pulsed DC are being investigated for their possible immunostimulating or immunotherapeutic value.

Because of the potential advantages of SL in immunization strategies, we examined the impact of combining SL with potent antigen-presenting DC. We documented the uptake and intracellular processing of SL by immature and mature DC and the capacity of DC to present SL-encapsulated antigens in vitro and in vivo. We observed that SL are taken up and processed by both immature and mature DC into neutral intracellular sites, most likely the cytoplasm. Although CD4+ T cells are activated by DC presenting SL-encapsulated proteins, there is much more efficient presentation of SL-encapsulated protein antigen by DC to CD8+ T cells in vitro and in vivo. This far exceeded the CD8+ T cell–responses induced by soluble protein or antigen encapsulated in conventional or positively charged liposomes. In addition, in vivo antigen-presenting activity to CD8+ T cells after subcutaneous injection of SL-encapsulated antigen was exclusively confined to the CD11c+ DC subset. Therefore, these results encourage the development of immunization strategies using SL-encapsulated proteins.

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Materials and methods

Culture media

DC were generated in RPMI 1640 (Celigro, Fisher Scientific, Springfield, NJ), supplemented with 2 mmol/L L-glutamine (GIBCO-BRL Life Technologies, Grand Island, NY), 50 μmol/L 2-mercaptoethanol (2-ME; Sigma Chemical, St. Louis, MO), 10 mmol/L HEPES (GIBCO-BRL), penicillin (100 U/mL)–streptomycin (100 μg/mL) (GIBCO-BRL), and 1% human plasma (heparinized). To generate MΦ, RPMI 1640 was supplemented with 2 mmol/L L-glutamine, 50 μmol/L 2-ME, 10 mmol/L HEPES, penicillin (100 U/mL)–streptomycin (100 μg/mL), 10% fetal bovine serum (BioWhittaker, Walkersville, MD), and 2.5% autologous human serum.

Medium for mouse cells was RPMI 1640, supplemented with 2 mmol/L L-glutamine, 50 μmol/L 2-ME, penicillin (100 U/mL)–streptomycin (100 μg/mL), and 5% fetal calf serum (Atlanta Biologicals, Norcross, GA).

Cells

Human DC and T cells. Peripheral human blood was collected in heparinized syringes. Peripheral blood mononuclear cells (PBMC) were separated by centrifugation on Ficoll-Hypaque (Amersham Pharmacia AB, Uppsala, Sweden). T cells were removed by incubation with neuraminidase (Calbiochem-Behring, La Jolla, CA)-treated sheep red blood cells and subsequent centrifugation on Ficoll-Hypaque, or by adherence at 8×10^6 cells/well in a 6-well tray (Falcon, Lincoln Park, NY) for 1 hour at 37°C. T cell-depleted populations were then cultured for 7 days in the presence of 100 U/mL IL-4 (R&D Systems, Minneapolis, MN) and 1000 U/mL granulocyte-macrophage colony-stimulating factor (GM-CSF) (Immunex, Seattle, WA) to generate immature DC. To generate mature DC, 50% of the medium was substituted by monocyte-conditioned medium (MCM) on day 7, and cells were cultured for another 2 days.[17] MCM was generated as previously described[18] with minor modifications. Briefly, immunoglobulin-coated bacteriologic dishes (Falcon) were prepared by the addition of 4 mL of 100 μg/mL phosphate-buffered saline (PBS) human γ-globulin (Bayer, Elkhart, IN) and incubated for 10 minutes at room temperature. The dishes were washed 4 times with PBS, 9×10^7 PBMC were added in 10 mL medium, and the dishes were incubated for 1 hour at 37°C. All nonadherent cells were removed, fresh medium was added, and the medium was collected after incubation for 24 hours at 37°C, filtered, and frozen before use.

The phenotype of DC was routinely monitored by FACS using anti-HLA-DR-fluorescein isothiocyanate (FITC) (Becton Dickinson Immunocytometry Systems [BDIS], San Jose, CA) versus anti-CD25-phycoerythrin (PE; BDIS), CD83-PE (Coulter, Miami, FL), CD86-PE (PharMingen, San Diego, CA), and CD14-PE (BDIS). Immature DC typically were HLA-DR^{++}, CD86^{+++}, CD14^{weak}, and CD83$^{-/weak}$, whereas mature DC were HLA-DR^{+++}, CD86^{++++}, CD25^{++}, CD83^{++}, and CD14^{-}.

For some experiments DC were separated into immature CD83^{-} and mature CD83^{+} cells by cell sorting using a FACStar^{PLUS} (Becton Dickinson, Mountainview, CA) after incubation with unconjugated anti-CD83 (Coulter), followed by incubation with goat-antimouse FITC (Cappel Labs, Organon Teknika, Durham, NC). T cells were either used as bulk T cells or stained with anti-CD4-PE and anti-CD8-PE and sorted into CD4^{-} and CD8^{-} small cells.

Human MΦ. MΦ were prepared by the plastic adherence method as previously described.[19] Briefly, PBMC were cultured at 4 to 8×10^6 cells/mL in 1.5 mL/well in a 24-well flat-bottom tray. Supernatant containing nonadherent cells was aspirated at day 2, and 2 mL fresh medium was added. After another 3 days, remaining nonadherent cells were gently washed off, and the medium was replaced by fresh medium. MΦ was harvested and used after 7 to 9 days of culture. They were HLA-DR^{+}, CD86^{++}, CD14^{++}, and CD83^{-}.

Mouse DC. Mouse bone marrow–derived DC (BmDC) were generated from C57/BL6 mice (Jackson Laboratory, Bar Harbor, ME) or were transporter-associated with antigen-processing TAP1, knock-out (*TAP1*$^{-/-}$) mice[20] (kindly provided by Dr Jiri Treka, Memorial Sloan Kettering Cancer Institute, New York, NY) following a standard protocol.[21] Briefly, bone marrow cells were cultured in the presence of GM-CSF (100 U/mL) for 6 days, with intermittent feeding. At day 6, immature DC were harvested and recultured in GM-CSF–containing medium in new 6-well trays in 3- to 4-mL medium at 1×10^6 cells/mL for another 48 hours to allow further maturation.

Mouse CD8^{+} T cells. To obtain ovalbumin (OVA)-specific T cells, single-cell suspensions of LN and spleens were prepared from 6- to 8-week-old, OVA-specific T-cell receptor transgenic mice (OT-1) with a T-cell specificity for an octamer peptide from OVA (OVA$_{257-264}$) in the context of H-2K^{b}.[22] To remove non-T cells, the cells were incubated with antibodies directed against MHC class II (clone M5/114; ATCC), B220 (clone RA3-6B2; ATCC), and macrophages (clone F4/80; ATCC) on ice for 30 minutes. Cells were washed 3 times with medium and incubated with goat-anti-rat immunoglobulin Dynabeads (Dynal, Oslo, Norway) for an additional 30 minutes at 4°C. Non-T cells were removed by applying a magnetic field, and remaining T cells were collected. The population comprised 95% T cells (CD8α^{+}, CD3^{+}, MHC-II^{-}) as confirmed by FACS (all antibodies were from PharMingen).

Preparation of liposomes

Cholesterol was obtained from Sigma, and PEG-PE, POPC, and DOTAP/DOPE (1:1) were obtained from Avanti (Avanti Polar Lipids, Alabaster, AL). The membrane lipid composition of SL was cholesterol:POPC:PEG-PE (2:3:0.3 mol ratio), that of conventional liposomes was cholesterol:POPC (2:3 mol ratio), and that of positively charged liposomes was DOTAP:DOPE (1:1 mol ratio). Liposomes of 100-nm diameter were prepared as previously described.[23,24] Briefly, thin films of lipid were prepared by rotor evaporation of the above lipid mixtures (50 μmol total phospholipid) in a round-bottom glass flask. The lipid films were hydrated with 1 mL solution containing tetanus toxoid (TT) (Statens Seruminstitut, Copenhagen, Denmark) or OVA (Sigma) at a concentration of 1 mg/mL or 2 mg/mL, respectively, and the flask was rotated slowly for 2 hours at 55°C. The formed liposomes were extruded 20 times through polycarbonate filters of decreasing diameters (0.6, 0.2, 0.1 μm) using a Mini Extruder (Avanti Polar Lipids). The liposomes were then separated from nonencapsulated antigen by size-exclusion chromatography (2 passages on a 15 × 1.5 cm column of Sepharose 4B [Sigma]). The concentration of encapsulated antigen was determined by subjecting liposomes (5, 10, 30 μL) to SDS-PAGE electrophoresis in parallel with known amounts of antigen (0.5, 1, 2.5, 5 μg) and visualizing the protein by Coomassie blue staining. The density of the bands was determined by gel scanning and densitometry analysis using the Alpha Imager 2000 (Alpha Innotech, San Leandro, CA). Encapsulation of the pH-sensitive, water-soluble fluorescent probe (HPTS; Molecular Probes, Eugene, OR), was performed as previously described.[25-27]

Incubation of DC and MΦ with fluorescent liposomes

DC and MΦ were plated in 96-well and 24-well flat bottom trays (Linbro; ICN Biomedicals, Aurora, OH) at 10^5 cells/well. Various concentrations (100-500 μmol/L) of SL containing HPTS were added to triplicate wells for different lengths of time (up to 48 hours) at 37°C. No cell toxicity was observed for the highest SL concentration and the maximum incubation period. Cells were harvested and washed 3 times in DPBS containing 5 mmol/L glucose (Sigma). Cell numbers were determined, and cells were resuspended at 10^6 cells/mL in DPBS containing 5 mmol/L glucose and plated in 96-well round-bottom trays (Linbro) at 10^5 cells/well. Plates were centrifuged to concentrate the cells in the center of the wells, and the fluorescence intensity (counts per second) associated with the cell pellet was recorded at 405 and 450 nm using a Biolumin 960 (Molecular Dynamics, Sunnyvale, CA). The fluorescence associated with the same number of cells incubated with empty SL (autofluorescence) was subtracted from that associated with cells incubated with HPTS-containing SL (HPTS-SL). To obtain information on the pH of the site occupied by SL, indicating the intracellular fate of SL, the fluorescence emission ratio at excitation wavelengths of 450 and 405 nm was determined as previously described.[25,26] At these 2 excitation wavelengths, the fluorescence emission spectrum from HPTS exhibits 2 peaks. The intensity of the former peak is highly susceptible to the pH and becomes 0 at pH values below 6.0. In

contrast, the intensity of the latter peak at 405 nm slightly increases when the pH decreases below 6.0. When most of the SL associated with the cells are located in cellular compartments whose pH is greater than 6.0 on the cell surface or the cytoplasm or in early endosomes, the 450 nm/405 nm fluorescence ratio is greater than 1. In contrast, when most SL are located in intracellular vacuoles whose pH is less than 6.0, such as lysosomes, the 450 nm/405 nm fluorescence ratio is less than 1. Therefore, by monitoring the 450 nm/405 nm fluorescence ratio, the intracellular fate of SL can be estimated for each cell type used.

The uptake of HPTS-SL by DC was visualized as follows. Cells were incubated with HPTS-SL as described above. In some experiments acridine orange (Aldrich, Milwaukee, WI) was added at 2 μg/mL for the last 30 minutes of incubation.[28] After they were washed extensively to eliminate free SL, cells were mounted on glass slides and covered with a coverslip. Slides were monitored using an Olympus BH2 series microscope (Olympus, Melville, NY) equipped with a reflective light fluorescence attachment. Two standard excitation filter cubes were used, one exciting in a violet band (350-410 nm) and the other at a narrower blue excitation (450-490 nm), and photographs were taken.[25,26] Uptake of HPTS-SL by MΦ was visualized as for DC, except that during MΦ preparation, the cells were allowed to differentiate directly onto glass coverslips.

Confocal immunofluorescence microscopy

Immature and mature DC were incubated with HPTS-SL for 24 hours, SL were washed out, and cells were seeded in serum-free RPMI into poly L-lysine (Sigma)–coated Lab Tek (Nunc, Naperville, IL) tissue culture chambers.[29] After the cells were attached to the slides (1-2–hour incubation at 37°C), the cells were fixed with 4% paraformaldehyde/PBS (wt/vol) for 20 minutes at room temperature and permeabilized for 15 minutes at room temperature by incubation with permeabilization buffer—RPMI containing 10% normal goat serum (Gibco), 0.05% saponin (Sigma), and 10 mmol/L glycine (Sigma). Thereafter, cells were incubated for 45 minutes at room temperature with antibodies against CD71 (transferrin receptor), CD107a (lysosomal-associated membrane protein 1 [LAMP-1]), HLA-DR, or isotype controls (all obtained from PharMingen), respectively. After 2 washes with permeabilization buffer, cells were incubated for 45 minutes with Texas red-labeled goat-antimouse secondary reagents (Jackson ImmunoResearch, West Grove, PA), mounted with aquamount (PolyScience, Niles, IL), and examined by confocal laser scanning microscopy (Zeiss, Oberkochen, Germany).

TT-specific proliferation assays

DC were cultured for 24 hours in the presence of SL-encapsulated TT (TT-SL) or soluble TT (sTT) at a concentration of 2 μg/mL or empty control liposomes (based on lipid concentration). The antigen was washed out, and 10^4 DC were cocultured with 10^5 syngeneic T cells in a 96-well flat-bottom tray. Where indicated, DC at a range of doses were cultured with 10^5 syngeneic T cells in the presence of 0.2 to 2 μg/mL of sTT, TT-SL, or empty SL, respectively. Proliferation was measured on day 5 by measuring the incorporation of (^{3}H)-thymidine (^{3}H-TdR) at a concentration of 1 μCi/well during the last 8 hours of culture.

OVA-specific proliferation assays

Mouse BmDC at day 7 were cultured for 12 hours in the presence of SL-encapsulated OVA (OVA-SL; OVA concentration, 10 μg/mL), empty SL (based on lipid concentration), or 10 μg/mL soluble OVA (sOVA). Nonadherent, pulsed DC were then harvested, washed 3 times, and cocultured in graded doses with 3×10^5 CD8$^+$ T cells/well in 96-well flat-bottom trays overnight. T-cell proliferation was assayed by adding ^{3}H-TdR (1 μCi/well) to the cultures after 36 hours, and incorporation of radioactivity during the final 12 hours of culture was determined by scintillation counting.

In vivo immunization with OVA

Two C57Bl/6 mice were injected subcutaneously with 8 μg OVA total into the hindfoot pads. They received OVA-SL, OVA in positively charged liposomes, OVA in nonstabilized (conventional) liposomes, OVA as soluble protein, or OVA as soluble protein mixed with empty SL (based on the lipid concentration of OVA-SL). In addition, 2 animals received empty SL only based on the lipid concentration. After 5 days, all animals were boosted with the same antigen preparation received initially. Five days later, popliteal and inguinal LN were removed. The LN cell suspensions of the 2 animals from each group were pooled, and the CD8$^+$ T cells were purified by magnetic beading. Then 2.5×10^5 CD8$^+$ T cells were incubated with 1.5×10^4 to 3×10^4 BmDC that had been incubated with OVA-SL (10 μg/mL) for 12 hours, and T-cell proliferation was measured in a standard proliferation assay (see above).

To elucidate which type of APC presents SL-encapsulated antigen in vivo, draining and nondraining LN from mice injected subcutaneously with 10 μg OVA-SL were removed 3 days after injection. T and B cells were removed from single-cell suspensions by magnetic beading using anti-murine CD5 and CD19 Dynabeads (Dynal), respectively, and resultant populations were separated into CD11c$^+$ and CD11c$^-$ fractions using antimurine CD11c magnetic beads (Miltenyi Biotec, Auburn, CA). These cells were applied in graded doses as APCs to 3×10^5 T cells from OT-I mice without further addition of antigen, and T-cell proliferation was determined on day 3 (as above).

Results

Uptake and compartmentalization of fluorescently labeled SL by DC and MΦ

To appreciate the interactions of SL with DC, we first measured the uptake and intracellular localization of fluorescent SL using fluorometric techniques.[25,26] DC (both immature and mature) were compared to MΦ because the latter are known to phagocytose very efficiently. Table 1 demonstrates typical results after a 24-hour incubation of cells with HPTS-SL. Similar results were obtained at 3 hours and 48 hours (data not shown). DC took up considerable amounts of SL but less (lower fluorescence intensity) and more slowly than MΦ. In addition, determination of the 450 nm/405 nm fluorescence ratio indicated that both immature and mature DC processed SL to cellular sites with a neutral or mildly acidic pH, whereas MΦ processed them into compartments with acidic pH.

The potentials of mature and immature DC to take up SL-encapsulated antigens were more precisely compared. Immature DC were cultured for 18 hours in MCM, and cells were separated into CD83$^-$ immature and CD83$^+$ mature DC. When these populations were incubated with HPTS-SL for 24 hours, SL were taken up equally well by both CD83$^-$ and CD83$^+$ DC (Table 2).

The fate of SL in DC versus MΦ could be visualized by incubation of the cells with HPTS-SL and staining with acridine orange, which accumulates in and stains acidic intracellular compartments.[30] Analysis using fluorescent microscopy revealed

Table 1. Uptake of fluorescently labeled, sterically stabilized liposomes by macrophages and by immature and mature dendritic cells

	405 nm	450 nm	450 nm/405 nm
MΦ	33 277*	5313	0.15
Immature DC	3071	5955	1.9
Mature DC	1095	1483	1.35

MΦ (d 9), immature DC (d 9, cultured in GM-CSF and IL-4 only), mature DC (d 9, cultured in MCM for the final 2 d) were incubated with HPTS-containing SL for 24 h at 37°C. HPTS-SL were washed out, and the fluorescence intensity was measured at excitation wavelengths of 405 and 450 nm. Data demonstrate 1 of 3 experiments yielding similar results.

*Fluorescence intensity in counts/sec

Table 2. Uptake of fluorescently labeled, sterically stabilized liposomes by CD83+ and CD83− dendritic cells

	405 nm	450 nm	450 nm/405 nm
CD83+	8383*	21 701	2.6
CD83−	7826	24 108	3.0

Immature DC were cultured for 18 h in MCM and sorted into CD83+ and CD83− cells. Cells were incubated with HPTS-containing SL for 24 h at 37°C and washed, and the fluorescence intensity was measured at excitation wavelengths of 405 and 450 nm. Data demonstrate 1 of 2 experiments yielding similar results.

*Fluorescence intensity in counts/sec.

that in MΦ, HPTS-SL, and acridine orange were colocalized (Figure 1A) and that most HPTS fluorescence was invisible at 490 nm (Figure 1B), indicating that most of the SL were in acidic lysosomal compartments. In contrast, in both mature (Figure 1C-D) and immature DC (Figure 1E-F), acridine orange and SL could be clearly distinguished in separate intracellular locations, and the HPTS fluorescence intensities at both 405 and 490 nm were comparable. Thus, the results confirmed our previous findings that DC process SL into sites with neutral or mildly acidic pH.

Confocal microscopy was performed to more accurately localize where SL were stored in DC. After incubation with HPTS-SL, cells were stained with monoclonal antibodies against different cellular antigens such as the transferrin receptor and the macrophage mannose receptor (used to visualize early endosomal compartments), LAMP-1 (to visualize late endosomal and early lysosomal compartments), and HLA-DR (to visualize MHC class II compartments) (Figure 2). These studies showed that SL were not colocalized with any of these known cellular compartments. Hence, most of the liposome content was either located in the cytoplasm or in a previously unidentified neutral compartment, and only small amounts gained access to the lysosomal pathway.

Presentation of SL-encapsulated antigen by DC to CD4+ T cells

To test whether any SL-encapsulated antigen went into the lysosomal pathway of DC to be processed and presented to CD4+ T cells, DC were generated from PBMC from human donors known to be responsive to TT. Mature DC were pulsed for 24 hours with TT-SL or sTT (2 μg TT/mL) and cultured with syngeneic T cells, and the TT-specific proliferative responses were measured. As shown in Figure 3, mature DC were able to present both SL-encapsulated TT and soluble protein to T cells, mediating comparable T-cell proliferative responses. When similar assays were set up with bulk T cells, sorted CD4- or CD8-depleted cells, only CD8-depleted or bulk T cells proliferated (data not shown).

Because both immature and mature DC take up similar amounts of SL (Table 2), the capacities of immature and mature DC to present SL-encapsulated antigen to CD4+ T cells were compared. Immature DC were cultured for 18 hours in MCM, sorted into CD83+ and CD83− DC, and cultured with syngeneic T cells in the presence of TT-SL (2 μg TT/mL) or empty control liposomes. Both CD83+ and CD83− DC presented antigen to T cells without considerable differences (Table 3).

To further investigate whether lower antigen concentrations or DC:T cell ratios might reveal more subtle differences between DC pulsed with soluble antigen versus SL-encapsulated TT, mature and immature DC were cocultured in graded doses with T cells in the presence of 2 or 0.02 μg/mL soluble or encapsulated TT. Figure 4 demonstrates that the capacity of immature and mature DC to process and present soluble protein to CD4+ T cells was greater than that obtained using TT-SL, particularly at low antigen concentrations and lower DC:T cell ratios. Therefore, even though only small amounts of SL-encapsulated protein reach the lysosomal pathway of DC, they can be presented to CD4+ T cells.

Preferential stimulation of CD8+ T-cell proliferation by SL-encapsulated antigen

Although modest quantities of SL-encapsulated antigen reaching the lysosomes can be presented to CD4+ T cells (Figures 3, 4, Table 3), the predominance of SL in the cytoplasm of DC suggests that this might favor the activation of CD8+ T cells. We examined this in proliferation assays using CD8+ T cells from OVA TCR-transgenic mice and antigen-pulsed BmDC. Mature DC were incubated with 10 μg OVA/mL as OVA-SL or as soluble OVA versus empty SL (based on lipid concentration) as a control. When these populations were incubated with 3×10^5 CD8+ T cells, OVA-SL–pulsed DC stimulated T-cell proliferation to a much greater extent (up to 300-fold) than DC pulsed with comparable amounts of nonencapsulated, soluble protein (Figure 5). To confirm that SL-encapsulated protein was presented on MHC class I molecules through a TAP-dependent pathway, BmDC from normal and *TAP1*(−/−) mice were pulsed with OVA-SL or empty SL and cultured in graded doses with

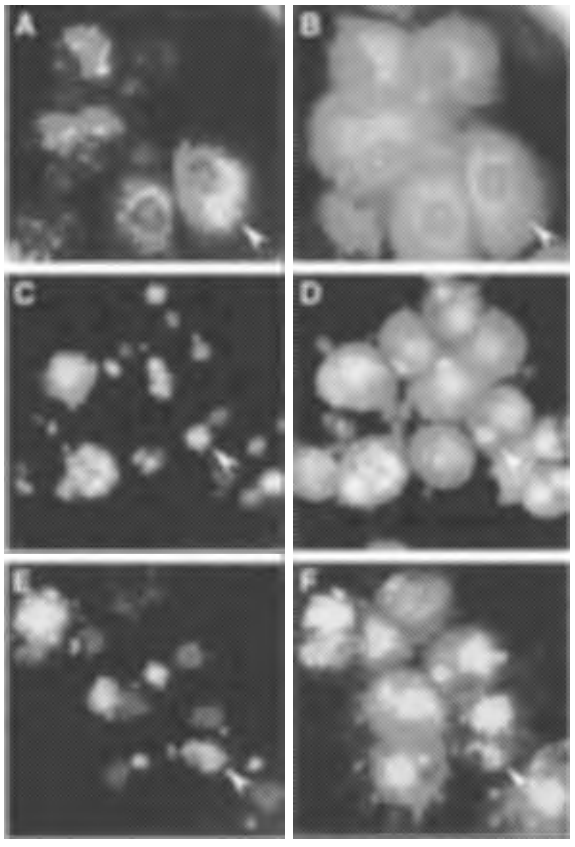

Figure 1. Uptake of HPTS-SL and acridine orange by human MΦ (A, B), mature DC (C, D), and immature DC (E, F). Cells were incubated with HPTS-SL for 24 hours, and acridine orange was added for the last 30 minutes of culture. Cells were washed and mounted on a glass slide, and photographs were taken under a fluorescence microscope at an excitation of 350 nm to 410 nm (left) and 450 nm to 490 nm (right), respectively (magnification, 400×). Arrowheads highlight HPTS-SL in each panel; note that in MΦ most of the HPTS-SL are colocalized with acridine orange and not visible at 450 nm to 490 nm, whereas SL in DC are separated from acridine orange and visible at both wavelengths.

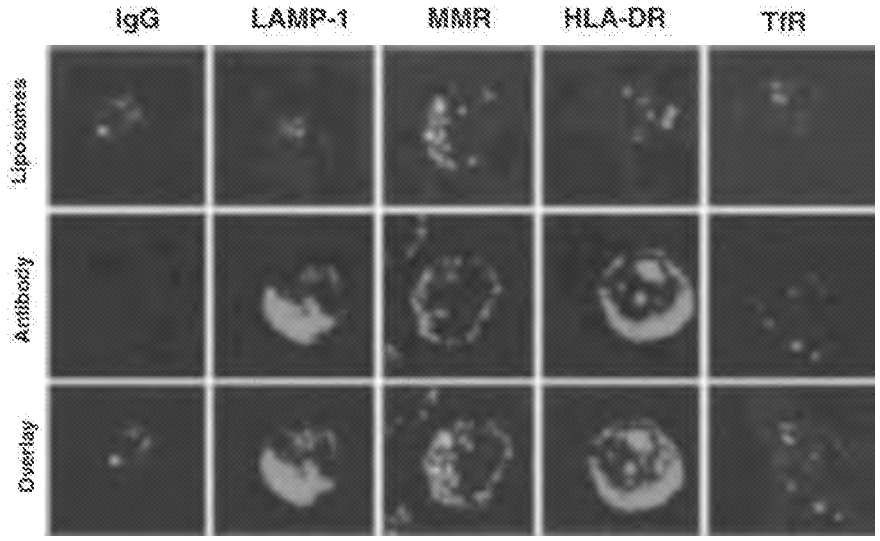

Figure 2. Non-colocalization of HPTS-SL with various cellular compartments in DC. Human DC were incubated with HPTS-SL for 24 hours. After incubation, SL were washed out, and cells were mounted on slides and stained intracellularly (for details, see "Materials and methods") with control IgG or antibodies against LAMP-1, the macrophage mannose receptor (MMR), MHC class II (HLA-DR), and the transferrin receptor (TfR). Results are shown as HPTS-SL only (excitation for green, top), antibody staining (excitation for red, middle), and the computerized overlay of these pictures (bottom). Yellow in the bottom panels indicates colocalization of green and red (magnification, 1000×).

3×10^5 $CD8^+$ T cells from OVA TCR-transgenic mice. *TAP1*(−/−) mice have been shown to lack antigen presentation on MHC class I.[20] Figure 6 demonstrates that mature BmDC from *TAP1*(−/−) mice stimulated T-cell proliferation much less efficiently than wild-type DC, proving the importance of the presence of TAP molecules for delivering SL-encapsulated antigens to the MHC class I pathway.

Superior induction of $CD8^+$ T-cell responses in vivo with SL-encapsulated protein

To elucidate how these in vitro findings would relate in vivo, we compared SL with soluble antigen and with other liposome formulations that have been used previously to induce $CD8^+$ T-cell responses in naive animals.[31-36] Mice were immunized with OVA-SL, OVA encapsulated in positively charged liposomes, conventional liposomes, or soluble OVA. Each mouse received 2 subcutaneous doses of 8 μg OVA at 5-day intervals. On day 10, $CD8^+$ T cells were prepared from the draining LN and cultured with OVA-SL–loaded BmDC, which induce $CD8^+$ T-cell responses (Figures 5, 6). Although OVA in positively charged liposomes was more efficient than that in conventional liposomes (and both were better than soluble protein) at eliciting OVA-specific $CD8^+$ T-cell–mediated immune responses (Figure 7), immunization with OVA-SL induced the strongest $CD8^+$ T-cell proliferative response. Control animals, immunized with soluble OVA and empty SL, exhibited responses similar to those induced with soluble OVA alone (Figure 7). This demonstrates that the encapsulation of antigen is mandatory and excludes nonspecific adjuvant effects by SL. Hence, SL are more potent than other liposome formulations or soluble protein at directing antigen to the APCs for the induction of $CD8^+$ T-cell responses in vivo.

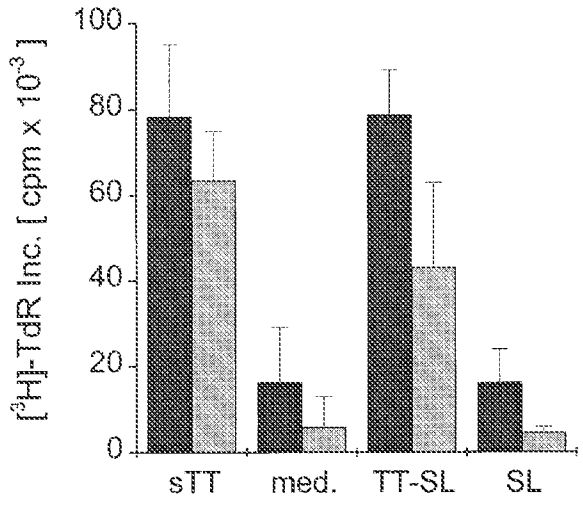

Figure 3. $CD4^+$ T-cell proliferation induced by presentation of SL-encapsulated tetanus toxoid. Mature human DC were pulsed with either soluble (sTT) or encapsulated tetanus toxoid (TT-SL) at 2.0 μg/mL for 24 hours. DC cultured in medium alone (med.) or pulsed with empty SL (SL, based on lipid concentration) were included as controls. Antigen was washed out, and DC were cocultured with 1×10^5 syngeneic T cells in a ratio of 1:10 (dark gray bars) or 1:30 (light gray bars). T-cell proliferation was monitored by measuring the uptake of thymidine, and mean cpm × 10^{-3} ± SEM of triplicate cultures from a representative experiment are shown.

Lymph node DC present SL-encapsulated antigen in vivo after subcutaneous immunization

Mice were injected subcutaneously with OVA-SL, and cell suspensions were obtained after 3 days from the draining and the nondraining LN to investigate which APCs would present SL-encapsulated antigens in situ. Here, soluble protein was not included because at the applied doses (ie, 8-10 μg/mouse), it did not yield $CD8^+$ T-cell–mediated immune responses in the previous experiments (Figure 7). Because DC are known to express high levels of CD11c, $CD11c^+$, and $CD11c^-$, cells were separated from the LN cells by magnetic sorting. $CD11c^+$ versus $CD11c^-$ cells

Table 3. Tetanus toxoid–specific T-cell proliferation induced by immature ($CD83^-$) or mature ($CD83^+$) dendritic cells

		Experiment 1		Experiment 2	
	DC:T-cell ratio	TT-SL	Empty SL	TT-SL	Empty SL
$CD83^+$	1:10	51 751	17 933	27 522	5752
	1:30	ND	ND	19 457	3116
$CD83^-$	1:10	41 121	23 879	13 893	1783
	1:30	ND	ND	16 734	1642

Immature DC were generated and treated with MCM for 18 h. Cells were stained with anti-CD83 and FITC-conjugated goat-antimouse immunoglobulin and were sorted into $CD83^+$ and $CD83^-$ fractions. DC were immediately transferred to 96-well flat-bottom trays, and 1×10^5 syngeneic T cells and TT-containing SL or empty SL were added. Mean cpm × 10^{-3} of triplicate cultures is shown.

ND, not determined.

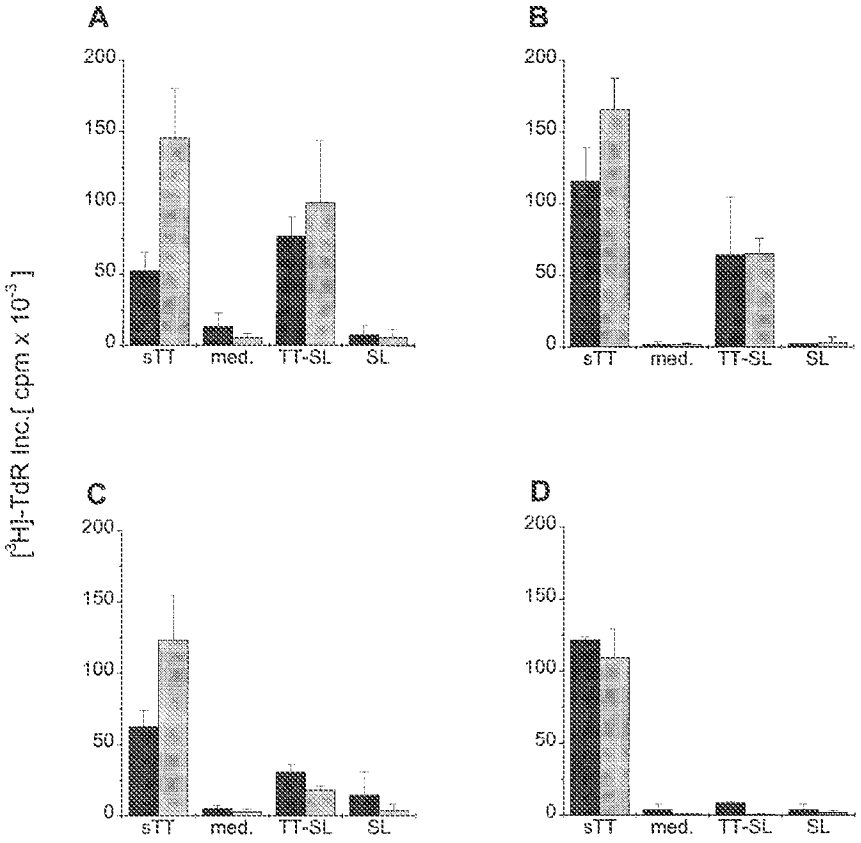

Figure 4. Presentation of graded doses of sTT or TT-SL by DC at different DC:T-cell ratios. Mature (A, C) and immature (B, D) human DC were generated and added in a ratio of 1:10 (dark gray bars) or 1:30 (light gray bars) to 1×10^5 syngeneic T cells. Antigens (sTT or TT-SL) were directly added to the wells at 2.0 (A, B) or 0.02 (C, D) μg/mL. DC:T cell cocultures without antigen (med.) or pulsed with empty SL (SL, based on lipid concentration) were controls. T-cell proliferation was assessed by measuring the uptake of thymidine (as in Figure 3).

were used to stimulate $CD8^+$ T cells from OT-1 mice. Only $CD11c^+$ cells from draining LN of injected mice induced significant proliferative responses (Figure 8). $CD11c^-$ cells stimulated negligible responses comparable to those induced by $CD11c^+$ or $CD11c^-$ cells isolated from the nondraining LN. Therefore, after subcutaneous injection of SL-encapsulated antigens, DC are efficiently targeted and can present the encapsulated protein to $CD8^+$ T cells.

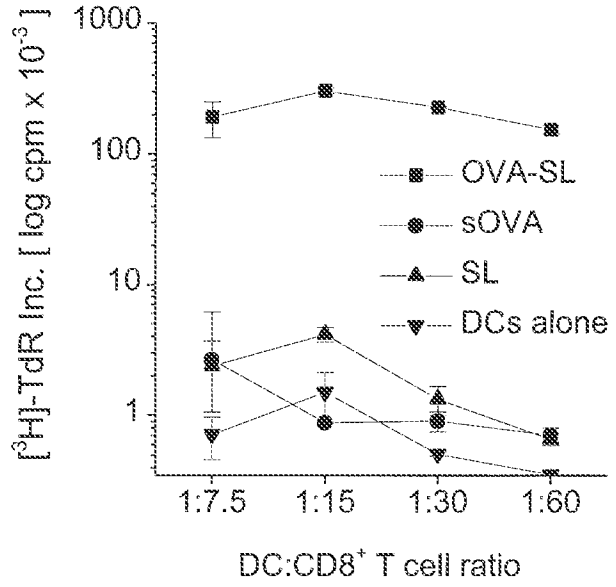

Figure 5. Superior stimulation of $CD8^+$ T cells by SL-encapsulated antigen. Mouse GmDC were generated and transferred to new wells on day 6. On day 7, antigens (OVA-SL or sOVA) were added at 10 μg/mL, and DC pulsed with empty SL (based on lipid concentration) or cultured in medium alone were controls. On day 8, cells were harvested, washed, and added in graded doses to 3×10^5 $CD8^+$ T cells from OT-1 mice (OVA TCR-transgenic mice). After 24 hours T-cell proliferation was assayed by thymidine incorporation, and mean log cpm×10^{-3} ± SEM of triplicate cultures from a representative experiment are shown.

Discussion

Presentation of protein antigen on MHC class I molecules is known to be difficult to achieve unless the antigen is specifically targeted to the MHC class I processing machinery.[37-39] As a consequence, we investigated whether the encapsulation of proteins in a new type of liposomes (SL) would lead to increased $CD8^+$ T-cell stimulation, and we studied the interaction of SL with potent antigen-presenting DC. Both immature and mature DC took up SL into intracellular sites with neutral or only mildly acidic pH. In contrast, MΦ captured more SL than DC and processed them to acidic cellular compartments, most likely lysosomes. Lysosomal location of conventional liposomes has been reported for the murine MΦ cell line J774.[26] Interestingly, immature and mature DC did not differ considerably with respect to the uptake of SL, indicating that SL may enter both types of DC by similar means. This is of particular importance because the maturation of DC is generally accompanied by down-regulation of their phagocytic and antigen-processing capabilities and elevated T-cell stimulatory capacity.[40] This implies that although an immature phenotype of DC is required for successful loading of DC with soluble antigen, immunization strategies based on SL-pulsed DC may be independent of the status of DC maturation. This may be critical in vitro because immature DC are known to revert to monocytes after the withdrawal of cytokines, whereas mature DC are more stable and exhibit much stronger T-cell stimulatory capacity.[15,16]

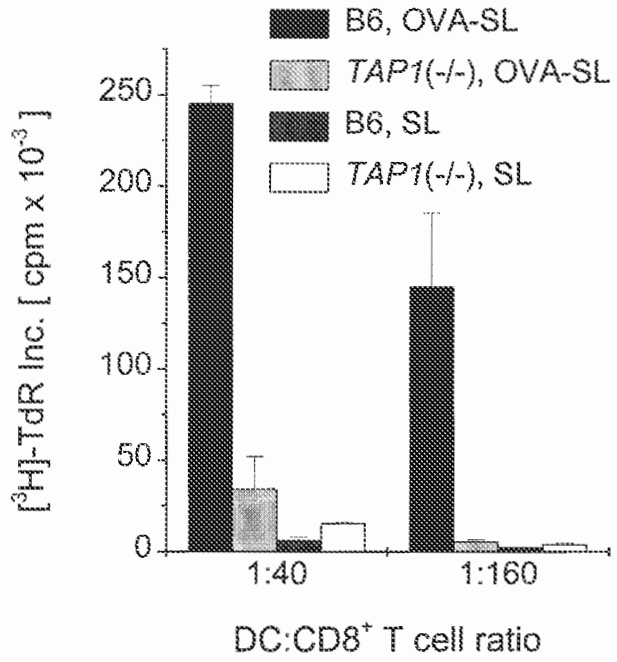

Figure 6. Abrogation of presentation of SL-encapsulated OVA in *TAP1*(−/−) mice. Mouse BmDC were generated from wild-type (B6) and *TAP1*(−/−) mice, and cells were transferred to new wells on day 6. OVA-SL at 10 μg/mL or empty SL were added on day 7. On day 8, cells were harvested, washed, and added in graded doses to 3×10^5 $CD8^+$ T cells from OT-1 mice. After 24 hours, T-cell proliferation was assayed by thymidine uptake, and mean cpm×10^{-3} ± SEM of triplicate cultures from a representative experiment are shown.

Confocal microscopy revealed that fluorescently labeled SL did not colocalize with any of the known endosomal, lysosomal, or MHC class II compartments. Therefore, SL were targeted to an otherwise unidentified cellular compartment with neutral pH, most likely the cytoplasm of the DC. A mildly acidic yet endocytic antigen-retention compartment in immature DC has been described.[41] However, this compartment stained positive for LAMP-1 and MHC class II and is, therefore, distinct from the one in which SL localize in both immature and mature human DC (Figure 2). On the other hand, Rodriguez et al[42] recently described a membrane transport pathway linking the lumen of endocytic compartments and the cytoplasm. This mechanism, which is restricted to DC and enables small proteins (3-20 kd) to escape into the cytoplasm, could more likely account for the observed differences between DC and MΦ in intracellular locations of SL.

Interestingly, our findings demonstrate that SL-encapsulated antigens ingested by DC can be readily presented to both $CD4^+$ (Figures 3, 4; Table 3) and $CD8^+$ T cells (Figures 5-8). However, because our initial observations suggested that only small amounts of SL were retained in the lysosomal pathway, the comparable stimulation of $CD4^+$ T cells by both sTT and TT-SL at a dose of 2 μg/mL TT by immature and mature DC was an unexpected finding (Figure 3). Of note, when the antigen concentration was decreased or lower DC:T cell ratios were used, the responses induced by TT-SL–bearing DC were considerably smaller, indicating that too little antigen had reached the MHC class II pathway to induce significant T-cell proliferation under these more limiting conditions.

In stark contrast, SL-encapsulated protein was efficiently targeted to the MHC class I processing/presenting pathway. As little as 10 μg/mL SL-encapsulated OVA induced strong stimulation of $CD8^+$ T-cell proliferation, whereas much higher concentrations (up to 10 mg/mL) of soluble protein are usually required for successful in vitro priming (unpublished observations and Watts[37]). The limited ability of mature murine DC to capture exogenous soluble protein antigen and present it to $CD8^+$ T cells has been described.[39] The lack of antigen presentation by DC generated from *TAP1*(−/−) mice confirmed that SL-encapsulated antigen gained access to the MHC class I pathway through the TAP transporter of mature DC. This is much like the TAP-dependent pathways identified for the presentation of exogenous antigen.[37]

Similarly, efficient TAP-dependent antigen presentation of liposome-encapsulated hen egg lysozyme by DC has been reported.[43,44] However, here the liposomes were targeted to Fc receptors or MHC class I and II molecules, and immature DC were used. Recent studies by Regnault et al[38] highlighted an alternative route of delivery of protein antigens into DC. Very low concentrations of immunocomplexed antigens were efficiently picked up and presented by DC to $CD8^+$ T cells in a TAP-dependent fashion. Interestingly, the uptake of immunocomplexed antigen was very much reduced in mature DC. This most likely reflects the decreased expression or function of Fc receptors on mature DC (vs immature DC), which are required for binding and uptake of immunocomplexed antigen. This was not the case in the present study—both immature and mature DC took up and presented SL-encapsulated antigen equally well. Our experiments suggest that targeting either immature or mature DC with SL-encapsulated antigen may represent a reliable way to induce potent antigen-specific $CD8^+$ and $CD4^+$ T cell responses in vivo. In fact, in vivo studies described herein documented that subcutaneous injected SL-encapsulated

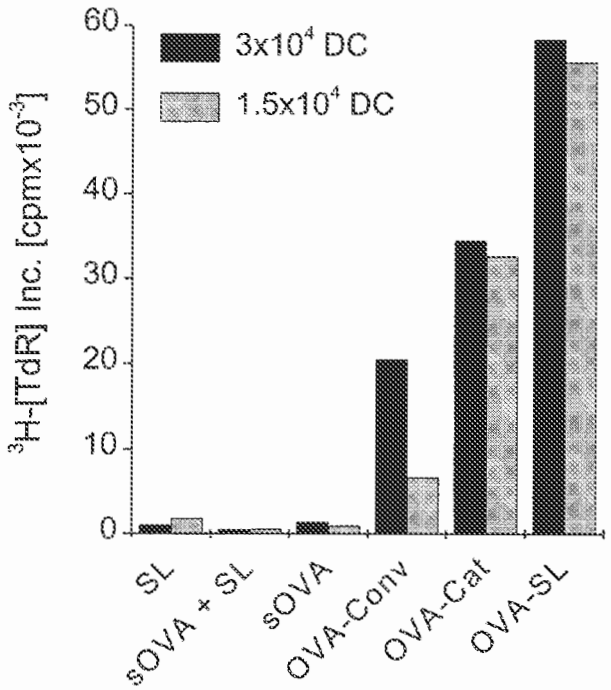

Figure 7. Preferential induction of $CD8^+$ T-cell responses by SL-encapsulated antigen in vivo. Two mice were injected subcutaneously in the hindfoot pads with OVA-SL, OVA in positively charged liposomes (OVA-Cat), OVA in nonstabilized (conventional) liposomes (OVA-Conv), OVA as soluble protein (sOVA), OVA as soluble protein mixed with empty SL (based on the lipid concentration of OVA-SL) (sOVA + SL), or empty SL (SL). All animals immunized with OVA received a total of 8 μg OVA, and the amount of empty SL injected was based on the lipid concentration of OVA-SL. All animals were boosted on day 5 with the same antigen preparation received initially, and 5 days later draining LN were removed. The LN cell suspensions of the 2 animals from each group were pooled, and the $CD8^+$ T cells were purified magnetically. Then 2.5×10^5 $CD8^+$ T cells were incubated with 3×10^4 or 1.5×10^4 BmDC, respectively, that had been incubated with OVA-SL (10 μg/mL) for 12 hours. T-cell proliferation was measured after 4 days, and mean cpm × 10^{-3} from a representative experiment is shown.

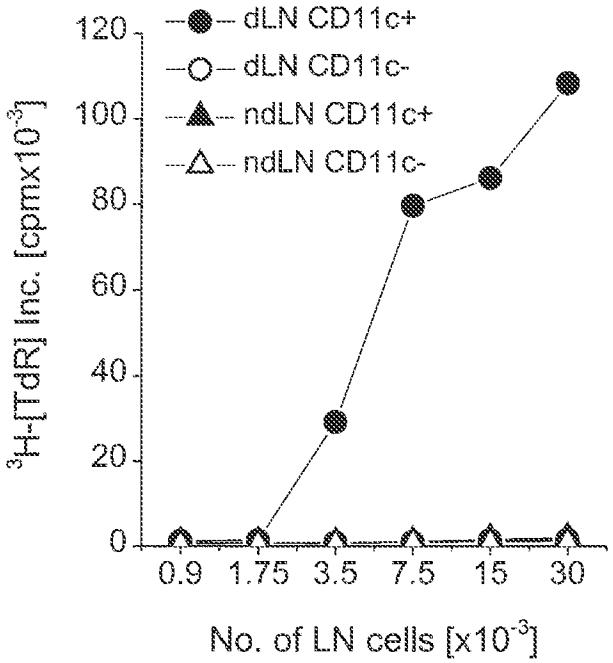

Figure 8. DC are the APCs involved in presentation of SL-encapsulated antigen in vivo. Two mice were injected with 10 μg OVA-SL subcutaneously. Draining LN (dLN) and nondraining LN (ndLN) were removed 3 days later. Single-cell suspensions from LN were pooled, separated magnetically into CD11c$^+$ and CD11c$^-$ fractions, and applied in graded doses to 3 × 10^5 CD8$^+$ T cells from OT-1 mice. After 24 hours, T-cell proliferation was assayed by thymidine incorporation. Mean cpm×10^{-3} from a representative experiment (1 of 2) are shown.

protein targets and is efficiently presented by CD11c$^+$ DC to activate antigen-specific CD8$^+$ T cells (Figure 8).

The interaction of various forms of liposomes with DC has been described. Zheng et al[33] recently reported that loading of human immature DC with HIV proteins by positively charged liposomes leads to an increased stimulation of HIV-specific cytotoxic T lymphocyte responses than with cells pulsed with protein alone. Rouse et al[45,46] have demonstrated the ability of murine DC loaded with protein antigen in conventional liposomes to induce primary cytotoxic T lymphocyte responses. In addition, the authors showed evidence that after intravenous injection, the liposomes primarily were taken up by MΦ, which then handed over the antigen to DC.[47] To compare these different types of liposomes to SL for their potential to induce CD8$^+$ T-cell responses in mice in vivo, we chose the subcutaneous route for its clinical relevance and injected OVA in the various liposome formulations at about 10- to 25-fold lower doses than used in previous studies. We observed that under these conditions, the greatest (up to 3-fold) CD8$^+$ T-cell stimulation was induced by SL-encapsulated antigen, whereas soluble protein at the chosen dose of OVA did not cause any CD8$^+$ T-cell stimulation.

In conclusion, these studies demonstrate that SL represent a safe and effective means to deliver protein antigens to potent antigen-presenting DC for the induction of CD4$^+$ and, most notably, CD8$^+$ T-cell responses. In particular, SL-encapsulated antigen is efficiently presented to CD4$^+$ T cells, which might be critical in helping to stimulate and maintain CD8$^+$ T-cell responses.[48] Therefore, SL are of great interest for future vaccine studies, and experiments elucidating the impact of various adjuvants and the induction of other T-cell functions such as cytokine secretion, cytotoxicity, and protection against microbial pathogens, are under way in our laboratories.

Acknowledgment

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Presentation of proteins encapsulated in sterically stabilized liposomes by dendritic cells initiates CD8 $^{+}$ T-cell responses in vivo

Ralf Ignatius, Karsten Mahnke, Miguel Rivera, Keelung Hong, Frank Isdell, Ralph M. Steinman, Melissa Pope and Leonidas Stamatatos

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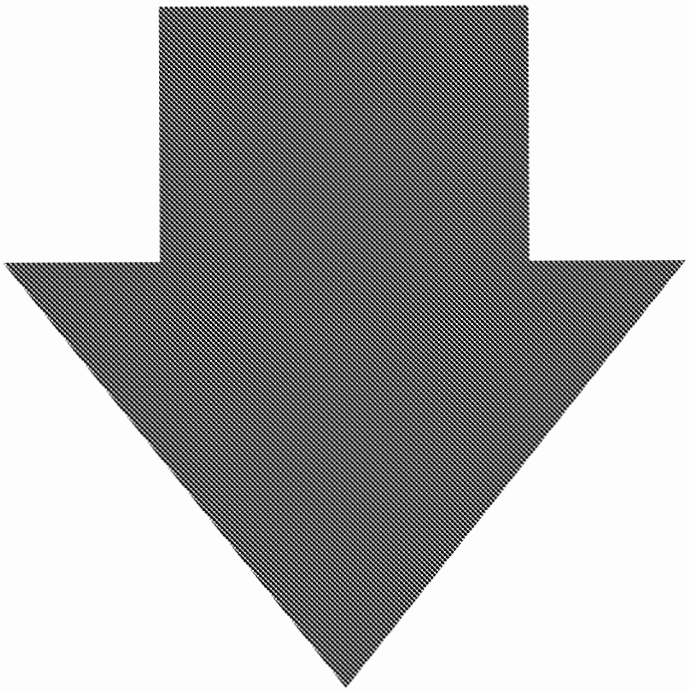

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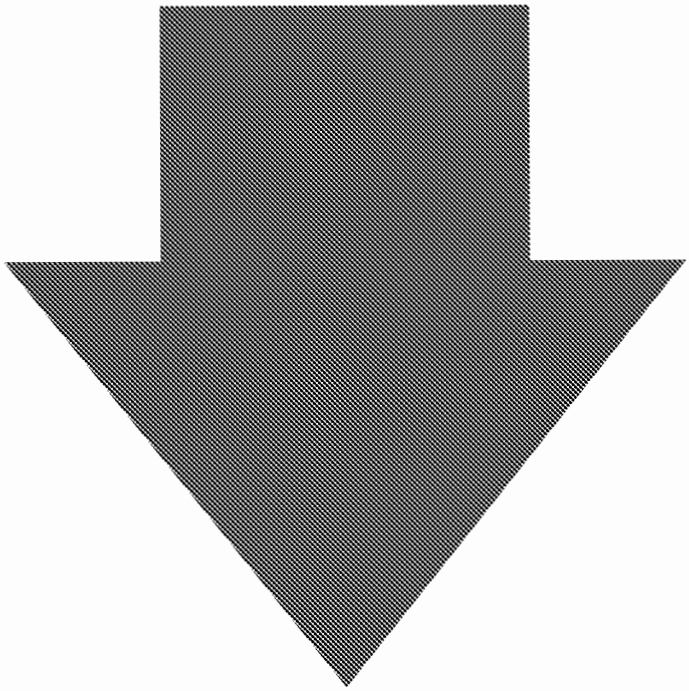

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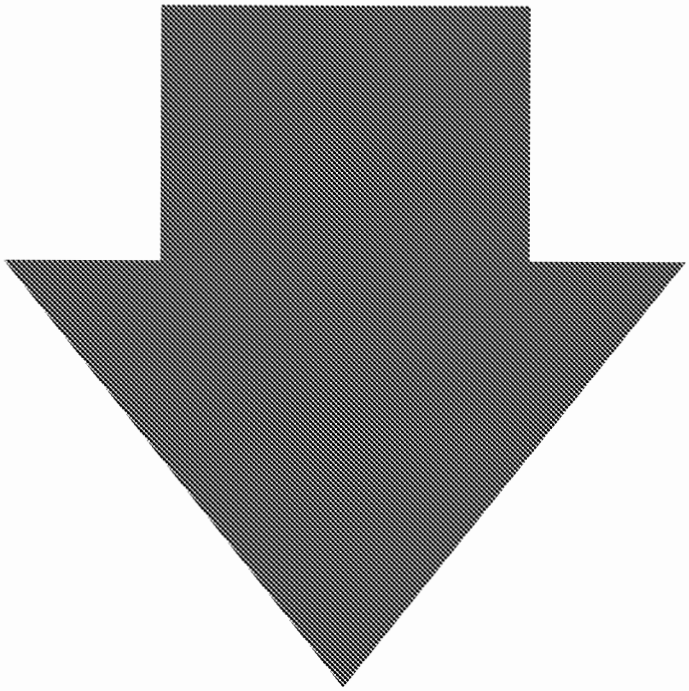

SUMMARY AND COMMENT | ONCOLOGY AND HEMATOLOGY

PRACTICE CHANGING

December 8, 2015

Nanoliposomal Irinotecan Effective for Pancreatic

David H. Ilson, MD, PhD

Associate Editor
NEJM JOURNAL WATCH ONCOLOGY AND HEMATOLOGY

Cancer

David H. Ilson, MD, PhD reviewing Wang-Gillam A et al. Lancet 2015 Nov 20

Adding nanoliposomal irinotecan to 5-fluorouracil and folinic acid significantly improved overall survival in patients with gemcitabine-refractory disease.

Progress has been made in the treatment of patients with advanced pancreatic cancer, with combination chemotherapy modestly improving overall survival compared with single-agent gemcitabine. However, after FOLFIRINOX or gemcitabine-based first-line chemotherapy, there is no standard second-line chemotherapy.

Investigators now report results of the NAPOLI-1 trial, an industry-sponsored, global, open-label, randomized phase III study of nanoliposomal-encapsulated irinotecan in 417 patients with pancreatic cancer who experienced disease progression with gemcitabine-based chemotherapy. Patients were randomized to receive nanoliposomal irinotecan monotherapy; 5-fluorouracil (5-FU) plus folinic acid; or nanoliposomal irinotecan followed by folinic acid and 5-FU. Results were as follows:

- Median overall survival (OS; the primary endpoint) was improved with nanoliposomal irinotecan, 5-FU, and folinic acid combination therapy versus 5-FU and folinic acid (6.1 vs. 4.2 months; hazard ratio, 0.67; *P*=0.012).
- OS was similar with nanoliposomal irinotecan monotherapy or 5-FU and folinic acid (4.9 and 4.2 months, respectively).
- Progression-free survival was superior with nanoliposomal irinotecan combination therapy versus 5-FU and folinic acid (3.1 vs. 1.5 months; HR, 0.56; *P*=0.0001).
- Response rates were superior with nanoliposomal irinotecan combination therapy (16%) and nanoliposomal irinotecan monotherapy (6%) versus 5-FU and folinic acid (1%).

Grade 3 or 4 toxicities, including diarrhea, vomiting, fatigue, and neutropenia, were greater with nanoliposomal irinotecan combination therapy than with 5-FU and folinic acid. Patients homozygous for the *UGT1A1*28* allele, a potential marker for greater irinotecan toxicity, received nanoliposomal irinotecan at a lower dose, but this accounted for only 5% to 6% of patients, and 30% to 40% of these tolerated a planned dose escalation of nanoliposomal irinotecan.

COMMENT

In patients with gemcitabine-refractory pancreatic cancer, the combination of nanoliposomal irinotecan plus infusional 5-FU and folinic acid improved survival versus 5-FU and folinic acid. This combination represents a new care standard in this setting. Whether this novel irinotecan formulation offers any advantage over conventional irinotecan, however, is

unclear. Also, this therapy likely has no role after disease progression on FOLFIRINOX, which contains infusional 5-FU and irinotecan.

EDITOR DISCLOSURES AT TIME OF PUBLICATION

Disclosures for David H. Ilson, MD, PhD at time of publication

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132P

Liposomal irinotecan (nal-IRI) plus 5-fluorouracil/levoleucovorin (5 FU/LV) vs 5-FU/LV in Japanese patients (pts) with gemcitabine-refractory metastatic pancreatic cancer (mPAC)

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INTRODUCATION

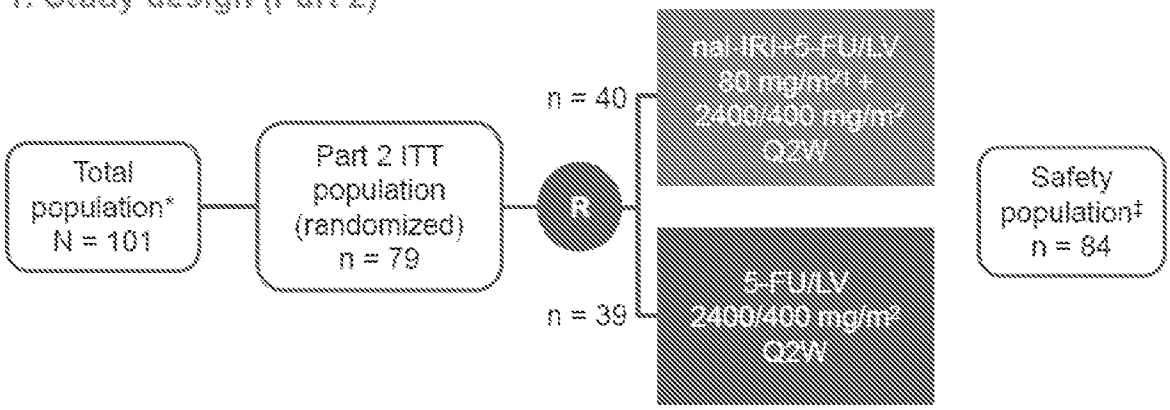
- Pancreatic cancer is the 6th most common cancer and 4th leading cause of cancer-related death in Japan, with 43,000 cases and 37,000 deaths in 2018.[1]
- Most patients are diagnosed with metastatic disease, reducing the possibility of curative treatment.[2]
- The effectiveness of the liposomal irinotecan + 5-fluorouracil/leucovorin (nal-IRI+5-FU/LV) combination versus 5-FU/LV in patients with metastatic pancreatic cancer (mPAC) that progressed on gemcitabine-based therapy was demonstrated in NAPOLI-1, a global phase 3 trial (mOS 6.1 vs 4.2 months, HR 0.67, p = 0.012; mPFS [investigator assessed] 3.1 vs 1.5 months, HR 0.56, p = 0.0001).[3]
- The results from the NAPOLI-1 trial led to the recommendation of nal-IRI+5-FU/LV as an option in the second-line setting for patients with mPAC with disease progression after treatment with gemcitabine-based or fluoropyrimidine-based therapy (if no prior irinotecan).[2, 4–6]
- The aim of this study was to determine the efficacy and safety profile of the NAPOLI-1 regimen in Japanese patients (registered at Clinicaltrials.gov, identifier: NCT02697058).

METHODS

- This was a prospective, open-label, randomized, multicenter phase 2 study in Japanese patients with mPAC that progressed or recurred following prior gemcitabine-based therapy.
- The study was conducted in two parts:
  - Part 1 to confirm tolerability and characterize pharmacokinetics (PK) of nal-IRI+5-FU/LV.
  - Part 2 to further assess the safety of the combination, analyze the PK of nal-IRI in combination with 5-FU/LV, and compare efficacy of nal-IRI+5-FU/LV with 5-FU/LV following a review of all safety data by the Independent Data Monitoring Committee. Part 2 data are presented here.
- In this study, the active isomer calcium levoleucovorin was used in place of the leucovorin used in the NAPOLI-1 trial.

- Patients were randomized 1:1 between the two arms (nal-IRI+5-FULV and 5-FU/LV), and stratified by:
  - Karnofsky Performance Status (KPS; 70 and 80 vs ≥90).
  - Baseline albumin levels (≥4.0 g/dL vs <4.0 g/dL).

Figure 1. Study design (Part 2)



*Total population includes patients in Parts 1 and 2, and patients failing screening. †Dose based on irinotecan hydrochloride trihydrate (salt base). ‡Safety population includes patients who received nal-IRI+5-FU/LV in Part 1 (n = 6) and excludes one patient randomized to the 5-FU/LV arm who was subsequently found to be in conflict with the exclusion criteria prior to receiving the study drug. Patients homozygous for *UGT1A1*28* or *UGT1A1*6* alleles, or heterozygous for received a starting dose of 60 mg/m² irinotecan . ITT, intention to treat; Q2W, two weekly; R, randomization

Key inclusion criteria

- Confirmed mPAC with ≥1 measurable metastatic lesion by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- Documented progression on gemcitabine-based therapy.
- Age ≥20.

Primary endpoint

- Progression-free survival (PFS) in Part 2, defined as the time from randomization to first documented disease progression based on the independent central review board's assessment using RECIST v1.1 or death due to any cause, whichever occurred first.

Secondary endpoints

- PFS (based on investigator assessment), overall survival (OS), time to treatment failure (TTF), carbohydrate antigen 19-9 (CA 19-9) response, objective response rate (ORR) and disease control rate (DCR) per RECIST 1.1, quality of life (QoL) and safety outcomes.

RESULTS

PATIENT CHARACTERISTICS

- Patient characteristics and demographics are shown in **Table 1**.
  - Patients in the nal-IRI+5-FU/LV arm were more likely to have KPS <100, hepatic lesions at baseline and stage IV disease at diagnosis.
  - The UGT1A1 status was similar for patients in both arms.
  - More patients in the 5-FU/LV arm received post-study anticancer therapy.

Table 1. Patient demographics and baseline characteristics in the ITT population

	nal-IRI+5-FU/LV (n = 40)	5-FU/LV (n = 39)
Sex, n (%)		
Female	16 (40)	19 (49)
Male	24 (60)	20 (51)
Median age, years (min–max)	67.0 (39–83)	69.0 (36–78)
Ethnicity, n (%)		
Asian (Japanese)	40 (100)	39 (100)
Baseline KPS, n (%)		
100	6 (15)	10 (26)
90	28 (70)	24 (62)
80	5 (13)	5 (13)
70	1 (2.3)	0
Baseline CA 19-9		
Median (IU/mL)	1419.4	1283.3
Evaluable for response, n (%)†	28 (70)	28 (72)
UGT1A1 status		
Homozygous for *UGT1A1*28*	0	1 (3)
Homozygous for *UGT1A1*6*	2 (5)	2 (5)
Heterozygous for both *UGT1A1*28* and *UGT1A1*6*	1 (3)	0
Baseline albumin, n (%)		
<4.0 g/dL	31 (78)	30 (77)
≥4.0 g/dL	9 (23)	9 (23)
Median (g/dL)	37.0	38.0
Hepatic lesions at baseline, n (%)‡	25 (63)	20 (51)
Prior anticancer therapy, n (%)§		
Gemcitabine-containing	40 (100)	38 (97)
Fluorouracil-containing (S-1)	8 (20)	14 (36)
Fluorouracil-containing (5-FU)	0	1 (3)
Platinum-containing (oxaliplatin)	1 (3)	0
Irinotecan-containing	0	0
Investigational agents	0	3 (8)
Other	38 (95)	34 (87)
Post-study anticancer therapy, n (%)§		
Received ≥1 post-study anticancer therapy	22 (55)	28 (72)
Gemcitabine-containing	6 (15)	9 (23)
Fluorouracil-containing (S-1)	12 (30)	7 (18)
Fluorouracil-containing (5-FU)	15 (38)	23 (59)
Platinum-containing (oxaliplatin)	13 (33)	25 (64)
Irinotecan-containing	9 (23)	19 (49)
Investigational agents	0	0
Other	4 (10)	7 (18)
Not recorded	18 (45)	11 (28)
Median time from last study drug exposure to first post-study anticancer therapy, weeks (1st and 3rd quartiles)	3.1 (2.9–4.7)	2.6 (2.1–3.1)
Median time since initial diagnosis, months (1st and 3rd quartiles)	7.2 (4.2–14.0)	10.8 (6.9–20.8)

†Only patients with a recorded pre-treatment CA 19-9 value were included. ‡Lesion locations were defined according to Response Evaluation Criteria in Solid Tumors v1.1. §Column values may add up to ≥100% as patients could have received more than one prior line of therapy or more than one post-study anticancer therapy, resulting in their inclusion in multiple categories. CA 19-9, carbohydrate antigen 19-9; KPS, Karnofsky performance status; min, minimum; max, maximum.

EFFICACY ASSESSMENT

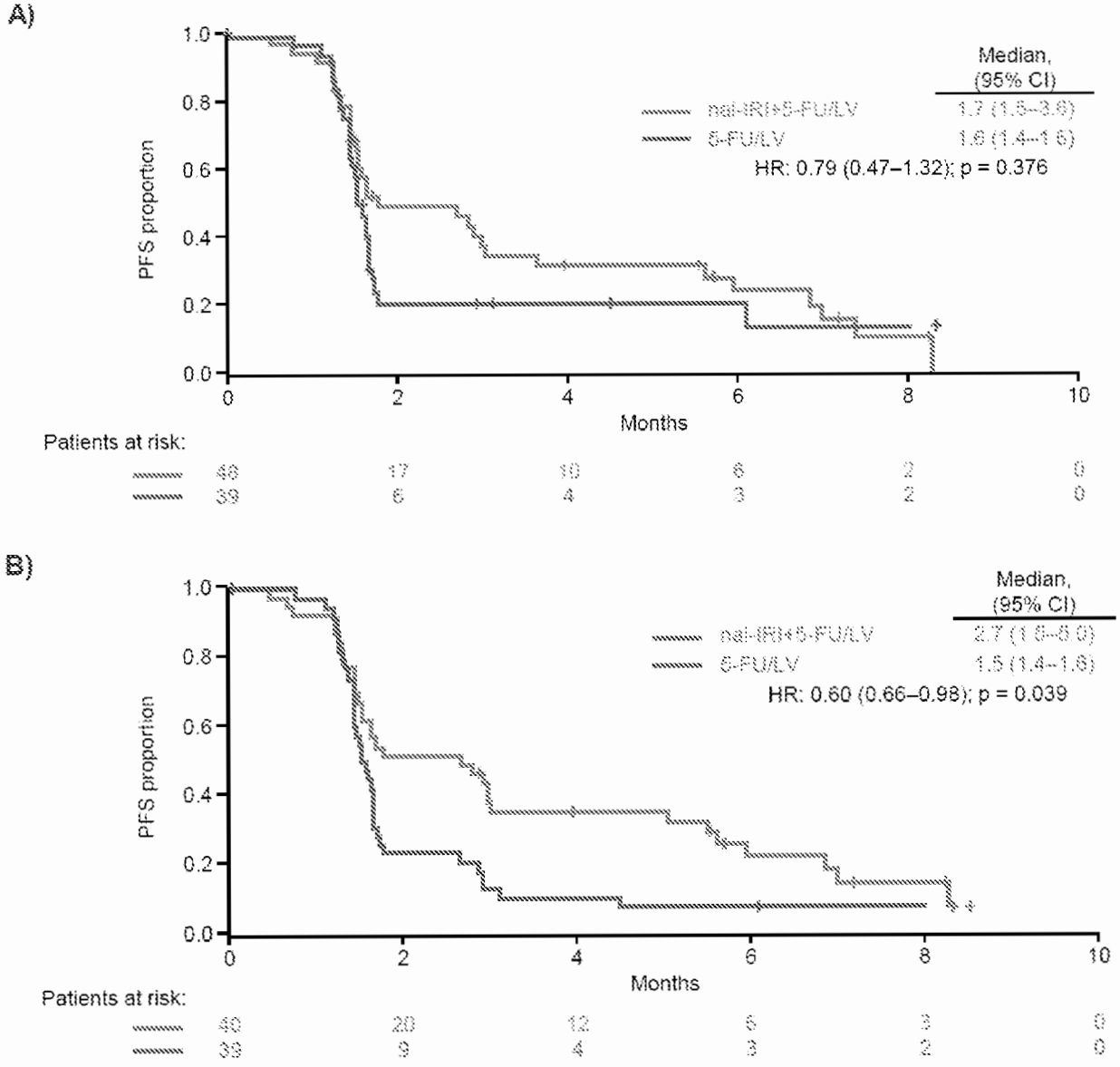
Primary endpoint

- Treatment with nal-IRI+5-FU/LV resulted in a median PFS of 1.7 months vs 1.6 months for 5-FU/LV based on independent assessment (**Figure 2A**).

Secondary endpoints

- Treatment with nal-IRI+5-FU/LV resulted in a median PFS of 2.7 months vs 1.5 months for 5-FU/LV based on investigator assessment (**Figure 2B**).
- Median OS was 6.3 months in the nal-IRI+5-FU/LV arm but not reached in the 5-FU/LV control arm (**Table 2**).
- ORR was significantly improved with nal-IRI+5-FU/LV vs 5-FU/LV treatment (**Table 2**).

Figure 2. Progression-free survival in the ITT population by A) independent assessment and B) investigator assessment



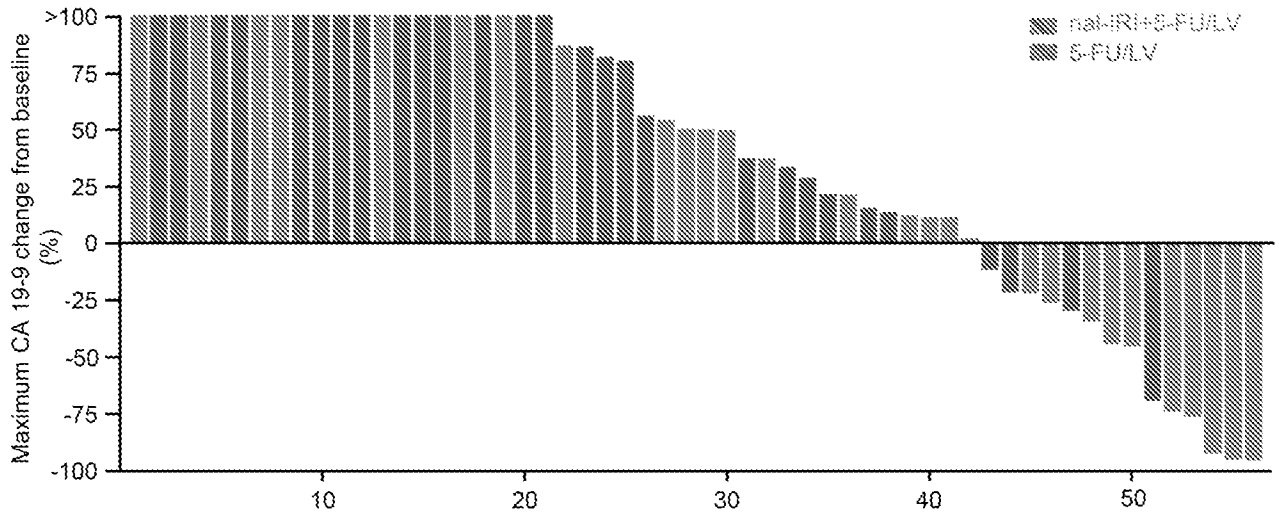
Tick marks indicate censoring points. CI, confidence interval; HR, unstratified hazard ratio; ITT, intention-to-treat.

Table 2: Additional efficacy outcomes in the ITT population		
	nal-IRI+5-FU/LV (n = 40)	**5-FU/LV (n = 39)**
Median OS, months (95% CI)	6.3 (5.2–NR)	NR (6.1–NR)
HR* (95% CI), p value†	1.67 (0.88–3.16), 0.110	
Median TTF, months (95% CI)	1.7 (1.5–2.2)	1.5 (1.4–1.6)
HR* (95% CI), p value†	0.70 (0.44–1.12), 0.134	
Best overall response (independent assessment)‡, n (%)	40 (100)	39 (100)
CR	2 (5)	0
PR	5 (12.5)	0
SD	14 (35)	10 (26)
PD	19 (48)	27 (69)
Non-CR/non-PD	0	0
NE	0	2 (5)
ORR	7 (18)	0
Rate difference (95% CI), p value§	17.5 (5.7–29.3), 0.012	
Disease control rate,¶ n (%)	8 (20)	2 (5)
Rate difference (95% CI), p value§	14.9 (0.7–29.1), 0.087	

*HR from unstratified Cox proportional hazards modelling. †Two-sided p value from log-rank test. ‡Best overall response was defined according to Response Evaluation Criteria in Solid Tumors v1.1 and reviewed by an independent central review board. §Two-sided p value from Fisher's exact test. ¶Disease control was defined as subjects with a best overall response of unconfirmed CR, PR or SD lasting ≥24 weeks following the start of first study drug. CA 19-9, carbohydrate antigen 19-9; CI, confidence interval; HR, hazard ratio; NR, not reached; ORR, objective response rate (CR + PR) OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTF, time to treatment failure.

- TTF was comparable between treatment arms (**Table 2**).
- More patients in the nal-IRI+5-FU/LV arm achieved a CA 19-9 response vs the 5-FU/LV arm, although this was not statistically significant (**Figure 3**).
- In a *post-hoc* sensitivity analysis to evaluate impact of post-treatment therapy, censoring survival at the start of post-study gemcitabine-based or FOLFIRINOX regimens, median OS for nal-IRI+5-FU/LV was 6.2 vs 6.7 months for 5-FU/LV (HR 1.11, 95% CI 0.49–2.49).

Figure 3. Change from baseline in CA 19-9 tumor marker response (TMRE population)



CA 19-9, carbohydrate antigen 19-9; TMRE, tumor marker response evaluable.

- QoL was maintained with nal-IRI+5-FU/LV despite added cytotoxic agent burden on the patient (data not shown).

SAFETY OUTCOMES

Treatment exposure

- Patients receiving nal-IRI+5-FU/LV had a higher mean number of treatment cycles and a longer time on treatment vs patients receiving 5-FU/LV (**Table 3**).

Table 3: Treatment duration and exposure in the nal-IRI+5-FU/LV and 5-FU/LV treatment arms (safety population)

	nal-IRI+5-FU/LV (n = 46)	5-FU/LV (n = 38)
Number of treatment cycles received		
Mean (SD)	6.7 (5.7)	4.9 (4.1)
Median (1st and 3rd quartiles)	3.5 (3.0, 11.0)	3.5 (3.0, 4.0)
Minimum time on treatment, n (%)		
≥6 weeks	35 (76)	32 (84)
≥12 weeks	19 (41)	9 (24)
≥18 weeks	15 (33)	4 (11)
Relative dose intensity (%), mean (SD)*		
nal-IRI	92 (13)	n/a
5-FU	91 (12)	99 (4)
Duration of exposure (weeks), mean (SD)†		
nal-IRI	15.1 (13)	n/a
5-FU	15.0 (13)	10.2 (9)

The safety population comprised patients who received ≥1 dose of study drug during study Part 1 or 2. *Relative dose intensity = (actual dose intensity/planned dose intensity) × 100. †Duration of exposure is the total duration (start date of last dose – start date of first dose + 14)/7. n/a, not applicable; SD, standard deviation.

Treatment-emergent adverse events

- Overall, treatment-emergent adverse events (TEAEs) were myelosuppressive or gastrointestinal in nature and more frequent with nal-IRI+5-FU/LV vs 5-FU/LV (**Table 4**).

Table 4: Grade ≥3 TEAEs in both treatment arms (safety population)

n (%)	nal-IRI+5-FU/LV (n = 46)	5-FU/LV (n = 38)
Any grade ≥3 TEAE*	36 (78)	14 (37)
Neutrophil count decreased	17 (37)	1 (3)
White blood cell count decreased	9 (20)	0
Diarrhea	8 (17)	1 (3)
Hyponatremia	4 (9)	0
Neutropenia	4 (9)	0
Anemia	3 (9)	1 (3)
Cholangitis	3 (7)	0
Gamma-glutamyl transferase increased	3 (7)	0
Hypokalemia	3 (7)	0
Lymphocyte count decreased	1 (2)	3 (8)
Tumor pain	0	2 (5)
Decreased appetite	0	1 (3)
Fatigue	1 (2)	1 (3)
Febrile neutropenia	1 (2)	0
Nausea	1 (2)	1 (3)

*TEAE: an AE with an onset date or a pre-existing AE worsening following the first dose of study drug through to 30 days after the last dose of study drug. AEs were coded according to MedDRA version 18.1.
AE, adverse event; TEAE, treatment-emergent adverse event.

- TEAEs of any grade leading to dose modifications were more frequent in patients in the nal-IRI+5-FU/LV arm vs the 5-FU/LV arm (**Table 5**), with 72% vs 16% being treatment related.
- nal-IRI+5-FU/LV was withdrawn in 5 patients due to treatment-related AEs.
- None of the four TEAEs with fatal outcome were study drug-related (**Table 5**).

Table 5: TEAEs (any grade) resulting in dose delay, dose reduction (≥5% of patients in either treatment arm) or treatment discontinuation (≥2% of patients in either treatment arm) (safety population)

	nal-IRI+5-FU/LV (n = 46)	5-FU/LV (n = 38)
Patients with TEAE* leading to any dose modification,† n (%)	35 (76)	12 (32)
Dose delay‡	32 (70)	11 (29)
Dose reduction§	23 (50)	3 (8)
Treatment discontinuation	10 (22)	0 (0)
Dose delay, n (%)		
White blood cell count decreased	21 (46)	2 (5)
Neutrophil count decreased	20 (44)	1 (3)
Diarrhea	5 (11)	0
Neutropenia	4 (9)	0
Constipation	0	2 (5)
Platelet count decreased	0	2 (5)
Dose reduction, n (%)		
Neutrophil count decreased	11 (24)	0
Diarrhea	8 (17)	1 (3)
White blood cell count decreased	7 (15)	0
Neutropenia	3 (7)	0
Treatment discontinuation, n (%)		
Pancreatic carcinoma	2 (4)	0
Anemia	1 (2)	0
Cerebral infarction	1 (2)	0
Diarrhea	1 (2)	0
Infection	1 (2)	0
Myalgia	1 (2)	0
Neutropenia	1 (2)	0
Neutrophil count decreased	1 (2)	0
Pleural effusion	1 (2)	0
White blood cell count decreased	1 (2)	0
Patients with any TEAEs leading to death, n (%)	4 (9)	2 (5)
Pancreatic carcinoma	3 (7)	2 (5)
Infection	1 (2)	0
TEAEs leading to death (all causes) related to study drug, n (%)	0	0

*TEAE: an AE with an onset date or a pre-existing AE worsening following the first dose of study drug to 30 days after the last dose of study drug. AEs were coded according to MedDRA version 18.1. †Dose modification: Dose reduction, interruption or withdrawal. ‡Dose delay: Infusion interrupted. §Dose reduction: Dose decreased or slowing infusion rate. AE, adverse event; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Treatment with nal-IRI+5-FU/LV resulted in clinically meaningful and statistically significant gains in investigator-assessed PFS in Japanese patients that had progressed or recurred following gemcitabine-based therapy and who received nal-IRI+5-FU/LV vs 5-FU/LV.
  - Independently-assessed PFS was also increased (not statistically significant), and improvements in PFS were consistent with the NAPOLI-1 trial.[2]
- Improved OS outcomes for patients receiving 5-FU/LV vs nal-IRI+5-FU/LV may have been influenced by post-study anticancer therapies, as suggested by a post-hoc analysis censoring survival for post-study anticancer therapy; although the study was not powered to determine this.
- The addition of nal-IRI to 5-FU/LV had no impact on QoL, despite the added cytotoxic burden on the patients.
- No new or unexpected safety signals were identified in the Japanese patient population
- These data are comparable to prior experience in the NAPOLI-1 trial and support the use of the regimen in a Japanese patient population.[3]

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Liposomal irinotecan (nal-IRI) plus 5-fluorouracil/leucovorin (5-FU/LV) vs 5-FU/LV in advanced pancreatic cancer: Interaction between prognostic factors and treatment

INTRODUCTION

METHODS

RESULTS

CONCLUSIONS

132P Liposomal irinotecan (nal-IRI) plus 5-fluorouracil/leucovorin (5-FU/LV) vs 5-FU/LV in Japanese patients (pts) with gemcitabine-refractory metastatic pancreatic cancer (mPAC)

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Background: In the NAPOLI-1 phase 3 trial, nal-IRI+5-FU/LV significantly increased median PFS (mPFS) vs 5-FU/LV (3.1 vs 1.5 months [mo], unstratified HR = 0.56, P = 0.0001) in pts with mPAC that progressed on prior gemcitabine-based therapy. This randomised phase 2 trial evaluated nalIRI+5FU/LV vs 5-FU/LV in Japanese pts with gemcitabine-refractory mPAC (NCT02697058).

Table: 132P

	nal-IRI+5-FU/LV n = 40	5-FU/LV n = 39
PFS, mo (investigator assessed)		
Median	2.7	1.5
95% CI	1.5–5.0	1.4–1.6
HR	0.60	
95% CI	0.37–0.98	
P-value	0.039	
PFS, mo (independently assessed)		
Median	1.7	1.6
95% CI	1.5–3.6	1.4–1.6
HR	0.79	
95% CI	0.47–1.32	
P-value	0.376	
Best overall response, n (%)	40 (100.0)	39 (100.0)
ORR	8 (20.0)	1 (2.6)
P-value	0.029	
Disease control rate, n (%)	8 (20.0)	2 (5.1)
P-value	0.037	
OS, mo		
Median	6.3	NR
95% CI	5.2–NR	6.1–NR
HR	1.67	
95% CI	0.88–3.16	
P-value	0.110	
TTF, mo		
Median	1.7	1.5
95% CI	1.5–2.2	1.4–1.6
HR	0.70	
95% CI	0.44–1.12	
P-value	0.134	
CA19-9 response rate,n/evaluable population (%)	5/28 (17.9)	1/38 (3.6)
P-value	0.193	

Methods: This study assessed nal-IRI+5-FU/LV tolerability as per the NAPOLI-1 dosing regimen (Part 1), and safety and efficacy (Part 2). Part 2 outcomes are reported. Pts were randomised 1:1 and stratified by KPS (70 and 80 vs ≥ 90) and baseline albumin (≥4.0 g/dL vs < 4.0 g/dL). Primary endpoint was PFS; secondary endpoints were ORR, DCR, OS, TTF, CA19 response and QoL. The ITT population comprised all pts randomised.

Results: Differences in pt baseline characteristics were noted in the nal-IRI+5-FU/LV (n = 40/79) vs 5FU/LV (n = 39/79) arms, e.g. hepatic lesions (63% vs 51%), stage IV disease at diagnosis (78% vs 51%), and post-study anticancer therapy (55% vs 72%). Efficacy results are shown in the table. Investigator-assessed mPFS increase with nal-IRI+5-FU/LV was clinically meaningful and statistically significant vs 5-FU/LV (2.7 vs 1.5 mo, P = 0.039). Independently-assessed mPFS showed a similar trend (1.7 vs 1.6 mo, P = 0.376). mOS was 6.3 mo with nal-IRI+5-FU/LV and not reached with 5-FU/LV. DCR, TTF, CA19-9 and ORR response increased, ORR significantly, with nalIRI+5-FU/LV vs 5-FU/LV. The most commonly reported grade ≥3 TEAEs with nal-IRI+5-FU/LV vs 5-FU/LV were decreased neutrophil count (37% vs 3%), decreased white blood cell count (20% vs 0) and diarrhoea (17% vs 3%).

Conclusions: Treatment with nal-IRI+5-FU/LV was associated with clinically meaningful and statistically significant gains in investigator-assessed mPFS and ORR vs 5-FU/LV in Japanese patients, with no new or unexpected safety signals in this population.

Clinical trial identification: NCT02697058.

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Disclosure: All authors have declared no conflicts of interest.

271P **Target therapy treatment patterns on advanced gastrointestinal stromal tumor (GIST) patients: a nation-wide cohort study in Taiwan**

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Background: Imatinib and sunitinib are two reimbursed targeted therapies for advanced GIST in Taiwan. A national-wide study was performed to evaluate the targeted therapies in GIST treatment among Taiwanese population.

Methods: We conducted a nationwide retrospective cohort study based on data from the National Health Insurance Research Database (NHIRD) between January 2005 and December 2010. All 1186 patients enrolled had histology-confirmed GIST with first-line imatinib (400mg qd) and follow-up more than one year. We estimated recurrence-free survival (RFS), progression-free survival (PFS), and overall survival (OS) probabilities with the Kaplan-Meier method. The proportional hazards assumption was verified by tests of correlations with time and examination of residual plots, and only variables that were deemed statistically significant were included in the final Cox model.

Results: With a median follow-up for surviving patients of 42 months, the median PFS of the cohort was 31 months since first-line imatinib. Cox proportional hazards multivariate analysis demonstrated directly switching to sunitinib was significant (hazard ratio: 0.77, 95% CI: 0.55-1.08; $p < 0.001$) prognostic factor for post-imatinib OS (59 months vs. 47 months). The whole cohort was divided into three groups. Group A ($n = 585$) had complete surgical resection and began imatinib treatment once recurrence confirmed. Group B ($n = 419$) received imatinib therapy within 3 months after operation. Group C ($n = 182$) was patients who were considered as unsuitable for operation. The median RFS of Group A was 16 months (95% CI 15-18) and the median OS after complete resection was 84 months. The cohort also demonstrated that PFS and OS of switching to sunitinib were longer than that with imatinib dose escalation after switching.

Conclusions: Taiwanese advanced GIST patients who failed first-line treatment still gained benefit from either imatinib dose escalation or a switch to sunitinib. Significant improvement in PFS using sunitinib directly as switch maintenance in advanced GIST.

Clinical trial indentification: In 1995, Taiwan launched a single-payer National Health Insurance program, and as of 2007, 22.60 million of Taiwan's 22.96 million population were enrolled in this program. Each year, the Bureau of National Health Insurance, Taiwan, collects data, including registration files and original claim data for reimbursement, from the National Health Insurance, and sorts it into data files. These data files are de-identified by scrambling the identification codes of patients, medical institutions and physicians and sent to the National Health Research Institutes, Taiwan, to form the original files of the NHIRD. Therefore, these files contain all the records of individuals enrolled in the National Health Insurance program, and they are available for research purposes only.

Legal entity responsible for the study: Taipei Medical University

Funding: Pfizer Limited, Taiwan Division

Disclosure: All authors have declared no conflicts of interest.

272P **Meta-analysis of intracorporeal or extracorporeal anastomosis after laparoscopic total gastrectomy for gastric cancer: Which is better?**

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Background: Totally laparoscopic total gastrectomy (TLTG) is still uncommon because of the difficult of esophago-jejunostomy technique laparoscopically which almost depends on surgeon. So far, the benefit as well as the reality of TLTG is under controversial. The aim of this study was to determine the useful extent of this procedure.

Methods: The literature on comparative studies of TLTG versus LATG up to now were extensively retrieved from database PubMed, Cochrane library, EMBASE. The operation times, blood loss, time to flatus, time to first oral intake, postoperative hospital stay, postoperative complications especially anastomosis leakage and anastomosis stenosis were analyzed. The statistical analysis was performed with STATa 13.0 software.

Results: Nine studies met the inclusion criteria for meta-analysis. Odds ratios (ORs) and weighted mean differences (WMDs) were calculated with 95% confidence intervals (CIs) to evaluate the effect of TLTG. Compare to LATG, TLTG experienced less blood loss [weighted mean difference (WMD)=-16.25 ml, 95% confidence interval (CI: -29.25,-3.25, $p = 0.270$)], smaller incision length (WMD= -2.74, 95% CI:-4.60, -0.89;$p<0.01$). Bowl recovery was similar between 2 groups and overall length of hospital stay was equal (WMD=-0.28,95% CI -0.76, 0.20, $p = 0.761$). The complication profile was similar with equality in anastomosis leakage (WMD=0.83;95% CI:0.36,1.90;$p=0.686$) and stricture (WMD=0.98;95%CI:0.44,2.18;$p= 0.847$) as well as bleeding (WMD=1.55;95%CI:0.45,5.35;$p=0.745$). No inferiority in the number of retrieved lymph node (WMD=1.41;95% CI:-0.45,3.28; $p = 0.296$) as well as proximal margin (WMD=0.11,95%CI: -0.11,0.33; $p = 0.346$) was noticed.

Conclusions: TLTG is shown by this meta-analysis to be efficient and safe in the short term outcome. Future studies should evaluate oncological outcomes with adequate long-term follow-up, preferably in randomized trials.

Legal entity responsible for the study: National Cancer Center-Korea

Funding: National Cancer Center-Korea

Disclosure: All authors have declared no conflicts of interest.

273P **Cisplatin in combination with pemetrexed in the treatment of patients for advanced malignant peritoneal mesothelioma: Retrospective study of 21 cases**

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Background: Malignant peritoneal mesothelioma (PM) is a relatively rare disease accounting for 10% of all mesotheliomas that occur in the mesothelial cells of the pleura, peritoneum, pericardium, and tunica vaginalis testis, and its prognosis is poor. A standard therapy for malignant PM has not been established. Conventional therapies are employed for malignant PM in clinical settings, however, the treatment outcomes are unknown. This was a retrospective study to evaluate the effects of primary chemotherapy of CDDP + PEM on patients with PM.

Methods: Twenty-one subjects who were pathologically and definitively diagnosed with PM and received 2 or more cycles of first-line combination chemotherapy of CDDP + PEM were included in this study. Treatment outcome was assessed using CT images based on RECIST. FDG-PET images obtained before and after the treatment were used for cases that were difficult to assess based on CT findings.

Results: The median age of the patients was 60.6 years (32–76 years), and 13 men and 8 women were included. Histological types included 20 epithelial and 1 biphasic types while clinical conditions included 5 cases of ascites retention, 6 mass forming, and 10 mixed types. In assessment of tumor reduction effects, 2, 9, and 5 subjects achieved a CR (10%), PR (42%), and a SD (24%), respectively, and PFS and MST were 10.1 and 16.7 months, respectively. Epithelial and ascites retention predicted favorable outcome of chemotherapy.

Conclusions: While PM is generally considered an extremely treatment-resistant malignant tumor, classical first-line therapy of CDDP + PEM allowed us to demonstrate a response rate of 52% and PFS of 10 months or longer. Although this was a retrospective study, these results are more favorable than those observed for patients with primary mesothelioma in the pleura. Therefore, first-line systemic chemotherapy of CDDP + PEM can be considered effective for patients with PM.

Legal entity responsible for the study: Hyogo College of Medicine

Funding: Hyogo College of Medicine

Disclosure: All authors have declared no conflicts of interest.

274TiP **A randomized phase 2 study of nanoliposomal irinotecan (nal-IRI, BAX2398)-containing regimen in Japanese patients with metastatic pancreatic adenocarcinoma (mPAC)**

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Background: The global, phase 3 study (NAPOLI-1) demonstrated that nal-IRI, a liposomal formulation of irinotecan (BAX2398, MM-398), in combination with 5-FU/LV significantly improved overall survival (OS) in patients with mPAC previously treated with gemcitabine-based therapy compared with 5-FU/LV (6.1 vs 4.2 months; unstratified hazard ratio 0.67; [95% CI 0.49–0.92; P = .012]). The most frequent ≥ grade 3 adverse events in the nal-IRI + 5-FU/LV–treated patients were neutropenia

(27%), diarrhea (13%), vomiting (11%), and fatigue (14%) (Wang-Gillam A. Lancet. 2016).

Trial design: The ongoing open-label, phase 2 study (ClinicalTrials.gov, NCT02697058) is designed to evaluate the safety, PK, and efficacy of nal-IRI+5-FU/calcium levofolinate in Japanese patients with mPAC that progressed or recurred after prior gemcitabine-based therapy. This 2 part study involves a safety run-in (part 1) and a randomized, open-label study (part 2). Key eligibility criteria include: age ≥20 years; pathologically confirmed pancreatic cancer; metastatic disease with at least 1 measurable lesion as defined by RECIST v1.1 guidelines; documented disease progression after prior gemcitabine-containing therapy; KPS ≥70; no known metastases to the central nervous system; and adequate hematologic, hepatic, and renal functions. The primary objectives of part 1 are to assess the safety and tolerability of nal-IRI+5-FU/calcium levofolinate and to characterize the PK of nal-IRI in at least 6 patients. In part 2, an additional 74 patients will be randomly assigned 1:1 to nal-IRI+5-FU/calcium levofolinate alone (arm A) or 5-FU/calcium levofolinate (arm B) with progression-free survival as the primary objective. Secondary objectives of part 2 include characterization of PK and safety, and between-arm comparison of objective response rate, OS, time to treatment failure, disease control rate, CA19-9 response, and patient-reported outcomes using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire core module (EORTC-QLQ-C30) and patient diary. This study is currently recruiting patients at 16 sites in Japan.

Legal entity responsible for the study: Shire Japan KK

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ABSTRACT BOOK

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Adverse Events in Patients with Metastatic Pancreatic Cancer Receiving Liposomal Irinotecan: Understanding the Occurrence and How Management Affects Patient Outcomes

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Background

- Pancreatic cancer is the third leading cause of cancer-associated mortality in the US; however, it represents only 3.2% of new cancer diagnoses. Despite surgery, locoregional therapy, chemotherapy, and molecular therapies, the 5-year survival rate is only 8.2%.[1]
- Liposomal irinotecan (nal-IRI) is a liposomal formulation of irinotecan, a topoisomerase I inhibitor, for intravenous use.[2,3]
  - nal-IRI is approved in the US, EU, and other countries in combination with 5-fluorouracil and leucovorin (5-FU/LV) for the treatment of adult patients with metastatic pancreatic cancer after disease progression following gemcitabine-based therapy.[4]
- Primary results from the NAPOLI-1 clinical trial (NCT01494506) demonstrated a survival benefit of nal-IRI+5-FU/LV in patients with metastatic pancreatic cancer previously treated with gemcitabine-based therapy.[5]
  - Median overall survival (OS) was 6.1 months for nal-IRI+5-FU/LV compared with 4.2 months for 5-FU/LV alone (unstratified hazard ratio [HR]: 0.67; 95% confidence interval [CI]: 0.49–0.92; P=0.012). OS in patients receiving nal-IRI monotherapy was similar to that of patients receiving 5-FU/LV (4.9 vs 4.2 months; unstratified HR, 0.99 [95% CI, 0.77–1.28]; P=0.94).[5]
  - nal-IRI+5-FU/LV had a manageable safety profile in NAPOLI-1; the most commonly occurring grade 3 or 4 treatment-emergent adverse events (TEAEs) included neutropenia (27%), diarrhea (13%), vomiting (11%), and fatigue (14%).[5]
- The NAPOLI-1 protocol allowed up to 2 dose reductions for nal-IRI and 5-FU, as well as a dosing delay of up to 3 weeks to allow for recovery from toxicity-related TEAEs.[4,5]
- Oncology nurses play an important role in instructing those receiving nal-IRI+5-FU/LV therapy including proactive planning for potential side effects, management of toxicity-related TEAEs, when to seek help for TEAEs, and educating patients about possible outcomes of dosing modifications to manage TEAEs.

Purpose

- To assess the timing of common TEAEs and whether the recommended dose modifications for TEAEs influenced patient outcomes in NAPOLI-1.

Methods

Study Design

- NAPOLI-1 was a large (N=417), global, phase 3 clinical trial that evaluated nal-IRI alone and in combination with 5-FU/LV, compared with 5-FU/LV alone, in patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy. The study methods have been previously described in detail.[5]
  - Patients were initially randomly assigned to nal-IRI monotherapy or 5-FU/LV (protocol version 1).
    - The nal-IRI dose: 120 mg/m^2 every 3 weeks (expressed as irinotecan HCl salt, equivalent to 100 mg/m^2 irinotecan free base per the USPI)
    - The 5-FU/LV dose: 2000 mg/m^2 5-FU and 200 mg/m^2 LV, weekly for the first 4 weeks of each 6-week cycle
  - After 63 patients were enrolled, a third treatment arm was added: combination nal IRI+5-FU/LV (protocol version 2).
    - 80 mg/m^2 every 2 weeks (expressed as irinotecan HCL salt, equivalent to 70 mg/m^2 irinotecan free base per the USPI) + 2400 mg/m^2 5-FU and 400 mg/m^2 LV
- Treatment was continued until disease progression or unacceptable toxicity.
- The primary endpoint was OS, with key secondary endpoints including progression-free survival (PFS), objective response rate, and safety.

Dose Modifications

- Dosing could be delayed for up to 3 weeks to allow for recovery from TEAEs. If the time required for recovery from toxicity exceeded 3 weeks, study treatment was generally discontinued.
- In general, for patients not homozygous for the UGT1A1*28 allele, dose reductions were not required for AEs ≤grade 2.
- For grade 3/4 AEs in patients not homozygous for the UGT1A1*28 allele:
  - nal-IRI+5-FU/LV arm: Reduce nal-IRI dose to 60 mg/m² (expressed as irinotecan HCl salt, equivalent to 50 mg/m² irinotecan free base) for the first occurrence and to 50 mg/m² (expressed as irinotecan HCL salt, equivalent to 43 mg/m² irinotecan free base) for the second occurrence.

Post hoc Analysis: Timing of Common TEAEs

- A post hoc analysis of patients in NAPOLI-1 was conducted (data cutoff, February 14, 2014) to analyze the incidence and prevalence of selected TEAEs analyzed over 3 time periods (Weeks 1–6, Weeks 6–12, and Week 12 to the end of the study period).
  - The treatment-emergent period for AEs is from time of first administration of study drug to 30 days after administration of the last dose of study drug.
  - Incidence was used as a measure of the first occurrence of a TEAE within a specified time interval; the numerator was the number of patients reporting the TEAE of interest for the first time during the period, and the denominator was the number of patients still on treatment during that period who had not yet experienced the TEAE of interest.
  - Prevalence was used as a measure of the ongoing frequency of the TEAE of interest within a specified time interval; the numerator included all patients who were experiencing the TEAE of interest during the period, and the denominator included all patients who were evaluable for safety for that period.

Post hoc Analysis: Impact of Dose Modification on Patient Outcomes

- A separate exploratory post hoc analysis of patients in NAPOLI-1was conducted to examine the impact on patient outcomes when a dose reduction or dose delay for nal-IRI in the nal-IRI+5-FU/LV arm was required to manage TEAEs within the first 6 weeks of the study.
  - To evaluate the impact of a dose modification (ie, a delay or dose reduction) on patient outcomes, OS was compared within the nal-IRI+5-FU/LV arm and with the 5-FU/LV arm.
  - All comparisons were made using the population cohort of patients randomized to receive either 5-FU/LV or nal-IRI+5-FU/LV and who enrolled under protocol version 2.
  - OS was calculated using the Kaplan-Meier method.
  - Hazard ratios (HRs) were calculated to assess the impact of dose modifications or delays used to manage TEAEs on OS in the individual and pooled treatment arms.
    - HRs were estimated by Cox regression analysis.
    - Fisher's exact test was used for comparisons.
    - All P values that were calculated were descriptive in nature.

Results

Patient Characteristics

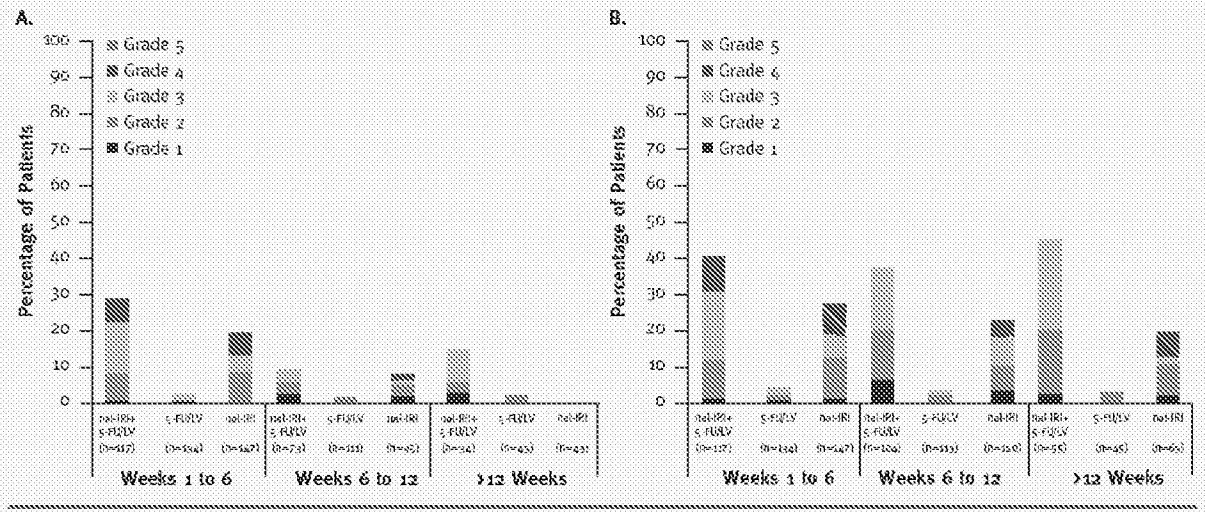
- A total of 417 patients were enrolled from 76 sites in 14 countries between January 2012 and September 2013.
- Patient demographic and baseline characteristics were well balanced across the treatment arms.

Timing of Common TEAEs

Incidence and Prevalence of Any-Grade TEAEs by Time Period

- In the nal-IRI+5-FU/LV arm, the incidence of neutropenia was highest during the first 6 weeks of treatment, with lower incidence in subsequent periods; in some cases, the first occurrence of grade 3 neutropenia occurred at >12 weeks (Figure 1A).
- Prevalence of neutropenia increased slightly from Weeks 1–6 to >12 weeks, but grade 4 neutropenia resolved within 6 weeks (Figure 1B).

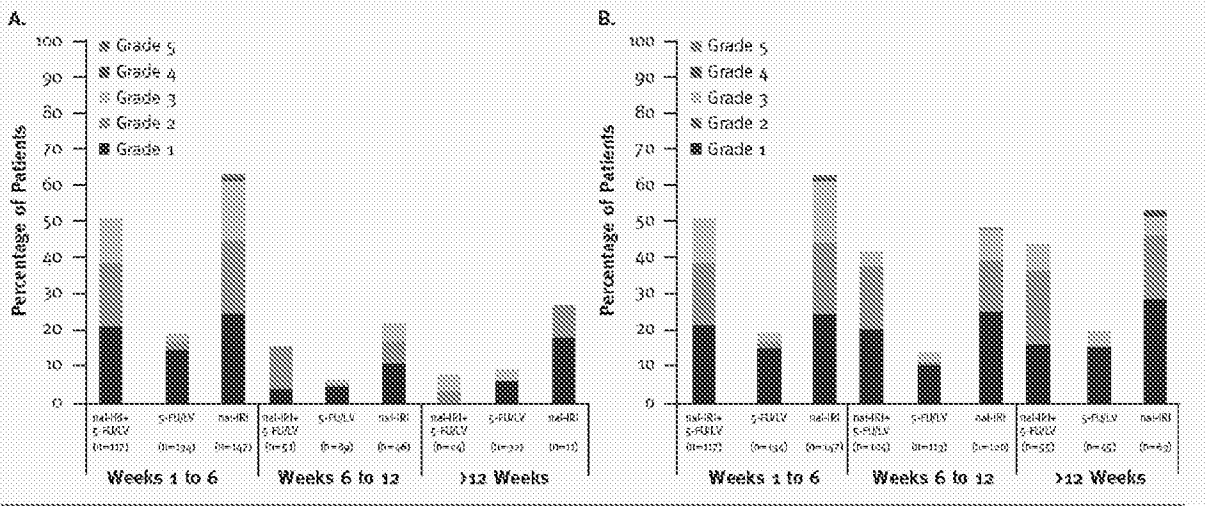
Figure 1. Incidence[a] (A) and Prevalence[b] (B) of All-Grade Neutropenia[c] Over Time by Treatment Arm



[a]Percentage of patients with newly occurring adverse events in that time frame.
[b]Percentage of patients experiencing the adverse event in that time frame.
[c]Neutropenia encompasses agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutropenic sepsis, decreased neutrophil count, and pancytopenia.

- The incidence of diarrhea in the nal-IRI+5-FU/LV arm was highest during Weeks 1–6 and decreased over time, though it tended to persist throughout the treatment course based on relatively stable prevalence. However, the majority of persisting events were ≤grade 2, and the proportion of patients with discontinuation due to diarrhea was low (1.7%) (Figure 2).

Figure 2. Incidence[a] (A) and Prevalence[b] (B) of All-Grade Diarrhea Over Time by Treatment Arm



[a]Percentage of patients with newly occurring adverse events in that time frame.
[b]Percentage of patients experiencing the adverse event in that time frame.

- Nausea and vomiting showed a similar pattern in the nal-IRI+5-FU/LV arm, with the incidence of both TEAEs being highest in Weeks 1–6 and decreasing over time; the prevalence decreased from Weeks 1–6 to >12 weeks, suggesting a short duration and low recurrence for these TEAEs (Figures 3 and 4).

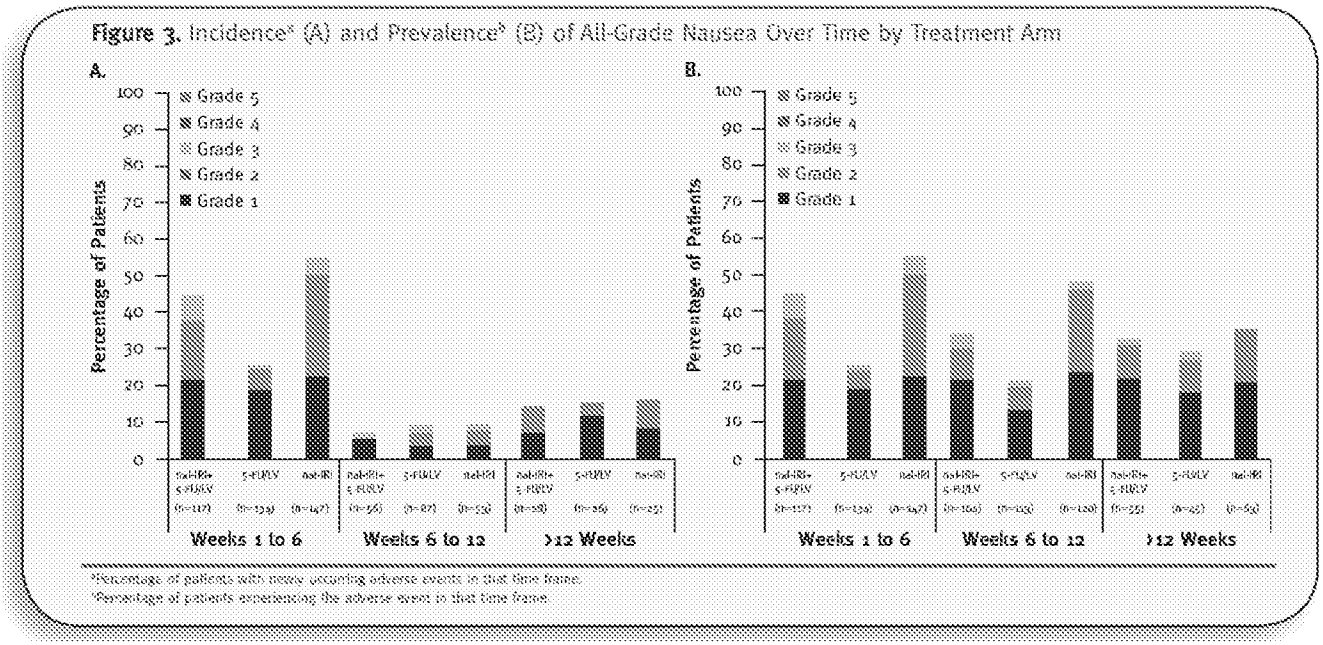


Figure 3. Incidence[a] (A) and Prevalence[b] (B) of All-Grade Nausea Over Time by Treatment Arm

[a]Percentage of patients with newly occurring adverse events in that time frame.
[b]Percentage of patients experiencing the adverse event in that time frame.

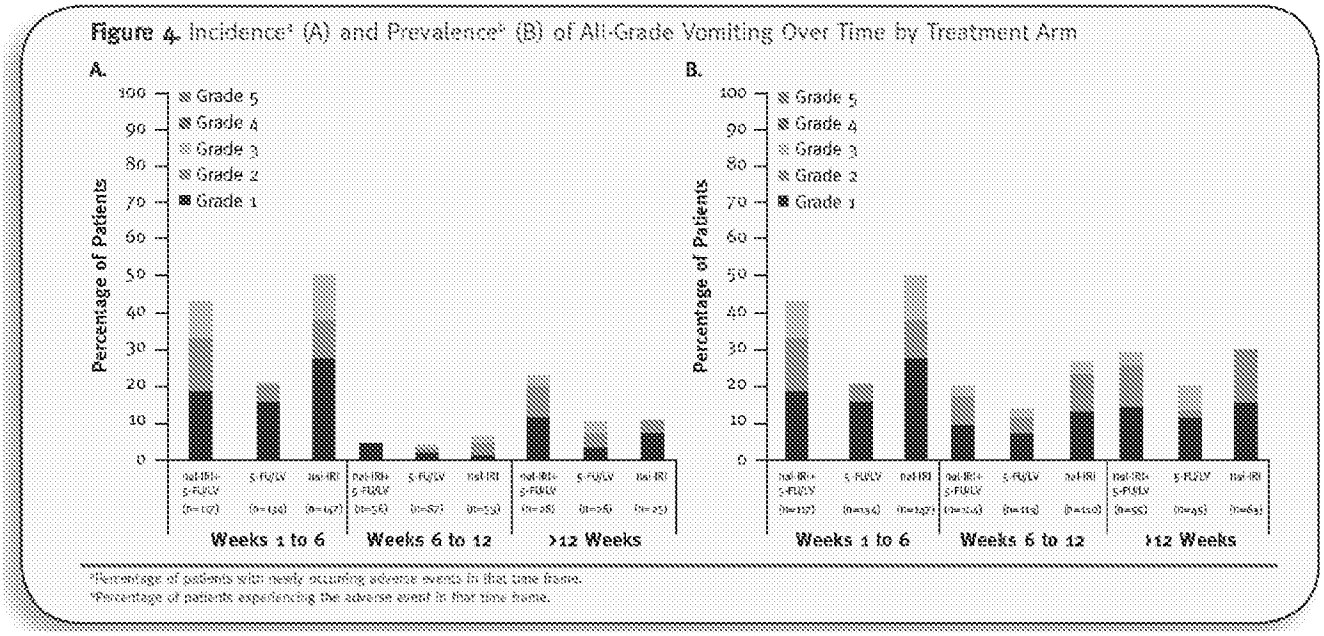


Figure 4. Incidence[a] (A) and Prevalence[b] (B) of All-Grade Vomiting Over Time by Treatment Arm

[a]Percentage of patients with newly occurring adverse events in that time frame.
[b]Percentage of patients experiencing the adverse event in that time frame.

- In the nal-IRI+5-FU/LV arm, 1 patient in Weeks 1–6 and 1 patient at >12 weeks experienced grade 3 febrile neutropenia, and 1 patient in Weeks 1–6 experienced grade 3 neutropenic sepsis; these were managed by dose reduction and/or delay.
- In the nal-IRI monotherapy arm, 5 patients experienced febrile neutropenia in Weeks 1–6 (4 with grade 3 and 1 with grade 4), and 1 experienced grade 3 febrile neutropenia in Weeks 6–12; these were managed by dose reduction and/or delay.
- No patients in the 5-FU/LV monotherapy arm experienced febrile neutropenia.

Duration of TEAEs

- Across treatment arms, the median duration of TEAEs ranged from 2 to 18 days and was typically within the range of 5 to 14 days, whether for any grade or for ≥grade 3 (Table 1).

Table 4. Duration of Treatment-Emergent Adverse Events (TEAEs) in Days[a]

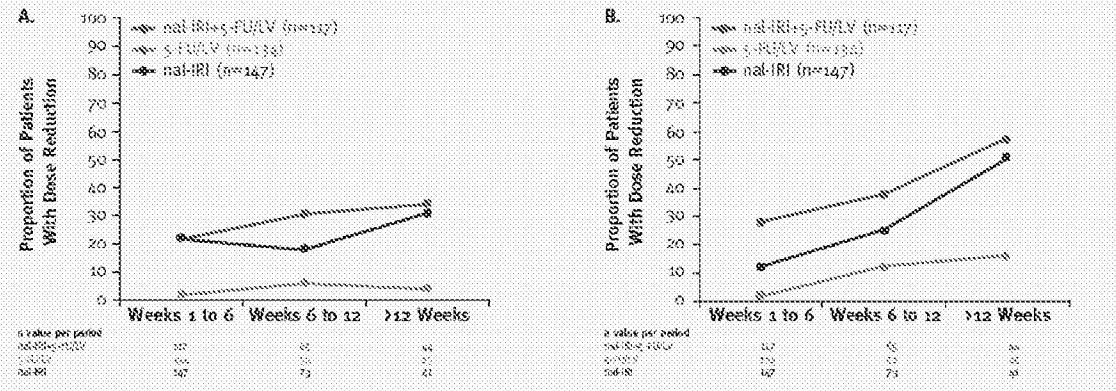
TEAE, days median (25th percentile, 75th percentile)[b]	nal-IRI+5-FU/LV (n=147) Any	nal-IRI+5-FU/LV (n=147) Grade ≥3	5-FU/LV (n=135) Any	5-FU/LV (n=135) Grade ≥3	nal-IRI (n=147) Any	nal-IRI (n=147) Grade ≥3
Diarrhea	6 (3, 19)	8 (5, 17)	3 (2, 11)	6 (2, 11)	8 (3, 16)	10 (7, 15)
Nausea	11 (5, 42)	10 (6, 14)	6 (2, 53)	8 (5, 11)	14 (5, 58)	7 (4, 10)
Vomiting	5 (2, 17)	10 (7, 13)	2 (1, 9)	4 (2, 9)	4 (2, 12)	7 (3, 14)
Neutropenia[c]	9 (8, 15)	9 (8, 15)	8 (8, 13)	18 (15, 21)	8 (7, 15)	10 (7, 19)
Neutropenic fever/sepsis[c]	8 (5, 11)	6 (4, 10)	13 (13, 13)	--	7 (6, 10)	7 (6, 7)

[a]For events without end date, duration is censored at the earliest of death date, last study drug + 30 days.
[b]Median and quartiles from Kaplan-Meier estimation.
[c]Neutropenia and neutropenic fever/sepsis are based on umbrella terms.

Impact of Dose Reductions or Dose Delays on TEAEs

- The proportion of patients with dose reductions or delays increased over the course of treatment in the nal-IRI+5-FU/LV arm (Figure 5).
- It is possible that dose reductions and delays may have contributed to the observed decrease in the incidence and severity of TEAEs over time.
  - The 25th percentile and median time to first dose reduction were 36 and 70 days, respectively, for nal-IRI+5-FU/LV, not applicable for 5-FU/LV, and 33 and 86 days for nal-IRI.
  - The 25th percentile and median time to first dose delay were 29 and 50 days, respectively, for nal-IRI+5-FU/LV, 429 and 429 days for 5-FU/LV, and 50 and 103 days for nal-IRI.

Figure 5. Dose Modifications Over Time by Treatment Arm Based on Dose Reduction (A) or Dose Delay (B)



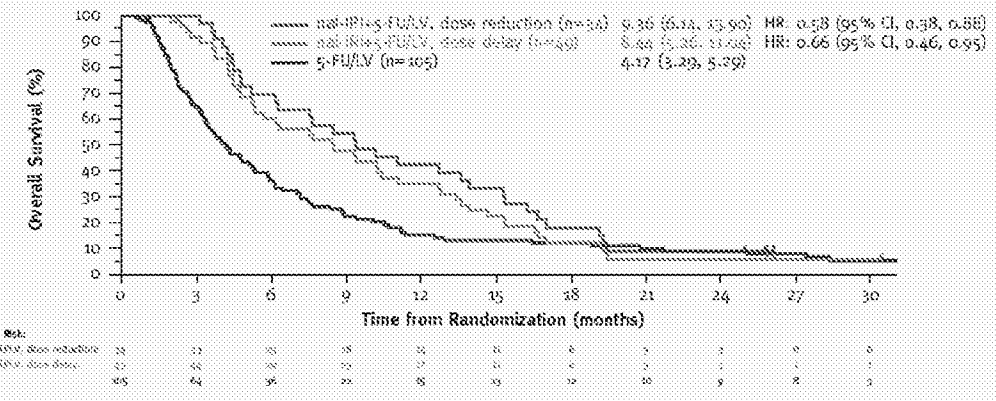
Denominators for the dose-modification figures reflect the numbers of patients who received study drug during the period. 5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan.

Impact of Dose Modification on Patient Outcomes

Overall Survival

- In the between-treatment arm analysis, which assessed the impact of dose delays or dose reductions in the first 6 weeks of treatment on OS between the nal-IRI+5-FU/LV and the 5-FU/LV arms, OS was greater in the nal-IRI+5-FU/LV treatment arm, regardless of whether the modification was a delay or a dose reduction (Figure 6).

Figure 6. Impact of nal-IRI Dose Delay or Dose Reduction During the First 6 Weeks of Treatment on Overall Survival



5-FU, 5-fluorouracil; CI, confidence interval; HR, hazard ratio; LV, leucovorin; nal-IRI, liposomal irinotecan.
OS analysis includes all patients randomized after implementation of a protocol amendment that added the nal-IRI+5-FU/LV combination arm.

Discussion & Limitations

- Diarrhea, vomiting, nausea, decreased appetite, fatigue, neutropenia, and anemia were the most common TEAEs reported, and they occurred more frequently in the nal-IRI+5-FU/LV arm versus the 5-FU/LV arm.
- In patients receiving nal-IRI+5-FU/LV, most first occurrences of neutropenia, diarrhea, nausea, and vomiting happened during the first 6 weeks of treatment, with incidence and severity generally decreasing thereafter.
- The prevalence and severity were also highest in the first 6 weeks, tending to decrease over time.
- The difference in OS between the nal-IRI+5-FU/LV and 5-FU/LV arms remained significantly different when dose delays (8.4 vs 4.2 months, HR=0.66 [0.48, 0.94]) or dose reductions (8.4 vs 4.2 months, HR=0.58 [0.35, 0.88]) during Weeks 1–6 were considered.
  - A limitation of the post hoc survival analysis was the inclusion of patients who had rapid clinical progression or who withdrew early due to adverse events. A future analysis will restrict the non-dose-modification group to per-protocol patients (defined as patients receiving ≥80% of protocol-defined treatment during the first 6 weeks of treatment).

Innovation

- These results suggest that TEAEs occur most frequently during the first 6 weeks of nal-IRI+5-FU/LV therapy and can typically be managed using TEAE management strategies and recommended dosing modifications described in the PI, while maintaining efficacy.[4]
- This knowledge is vital for oncology nurses caring for patients who receive this therapy for pancreatic cancer so they can provide informed education and coaching to these patients for the management of toxicity-related TEAEs.
- Patients can be empowered by this information as they consider their goals and treatment decisions.

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This presentation was sponsored by Ipsen

Adverse Events in Patients with Metastatic Pancreatic Cancer Receiving Liposomal Irinotecan: Understanding the Occurrence and How Management Affects Patient Outcomes

Background

Purpose

Methods

Results

Discussion & Limitations

Innovation

1: Adverse Events in Patients with Metastatic Pancreatic Cancer Receiving Liposomal Irinotecan: Understanding the Occurrence and How Management Affects Patient Outcomes

Thursday, May 17, 2018
01:45 PM - 02:45 PM
Walter E. Washington Convention Center - Level 2 Concourse

Significance & Background: In the phase III NAPOLI-1 trial (NCT01494506), liposomal irinotecan in combination with 5-fluorouracil/leucovorin (nal-IRI+5-FU/LV) improved overall survival (OS) vs 5-FU/LV (6.1 vs 4.2 months, hazard ratio [HR]=0.67, P=0.012) in patients with metastatic adenocarcinoma of the pancreas (mPDAC) previously treated with gemcitabine-based therapy. The prescribing information for nal-IRI has detailed recommendations for dose modifications for adverse event (AE) management. Nurses, as part of the interdisciplinary team, serve as patient advocates educating oncology patients regarding the incidence and management of AEs. Purpose: To assess the timing of common AEs and whether recommended dose modifications for AEs influence patient outcomes. Interventions: The first occurrence (incidence) of selected AEs by treatment period (Weeks 1-6, 7-12, and >12) and the number of patients experiencing the AE during each period (prevalence) were analyzed. A separate analysis examined the effect on OS of dose delays or reductions for AEs occurring during the first 6 weeks of the study. Delays were defined as delays in dosing >3 days from target dosing date and dose reductions were reductions in dose from initial administered dose. Median OS was based on Kaplan-Meier estimates and Cox regression analysis was used to calculate HRs. Evaluation: Diarrhea, vomiting, nausea, decreased appetite, fatigue, neutropenia, and anemia were the most common AEs reported, and they occurred more frequently in the nal-IRI+5-FU/LV arm vs 5-FU/LV arm. In patients receiving nal-IRI+5-FU/LV, most first occurrences of neutropenia, diarrhea, nausea, and vomiting happened during the first 6 weeks of treatment, with the incidence and severity generally decreasing thereafter. The prevalence and severity were also highest in the first 6 weeks, tending to decrease over time. The difference in OS between the nal-IRI+5-FU/LV and 5-FU/LV arm remained significantly different when dose delays (8.4 vs 4.2 months HR=0.66 [0.46, 0.94]) or dose reductions (9.4 vs 4.2 months, HR=0.58 [0.38, 0.88]) during Weeks 1-6 were considered. Discussion/Innovation: These results suggest that AEs occur most frequently during the first 6 weeks of nal-IRI+5-FU/LV therapy and can typically be managed using recommended dosing modifications and AE management strategies while maintaining efficacy. This knowledge is vital for oncology nurses who educate, coach, and manage symptoms of those receiving this second-line therapy for mPDAC. Patients can be empowered by this information as they consider their goals and treatment decisions.

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EDITORIAL

Optimal Second Line Treatment Options for Gemcitabine Refractory Advanced Pancreatic Cancer Patients. Can We Establish Standard of Care with Available Data?

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Introduction

Since the birth of fluorouracil (5-FU) 50 years ago, we have made only incremental changes in clinical outcomes in pancreatic cancer. Gemcitabine remains to be the only standard of care in advanced pancreatic cancer since mid-1990s [1]. Numerous trials which enrolled thousands of patients failed to improve the outcome significantly beyond gemcitabine. At present time, data set in 2nd line setting is grossly limited. One reason is that most advanced pancreatic cancer patients who progress on their 1st line treatment are often poor candidates for clinical trials due to their worsening performance status. Lack of active agents seen in number of trials in 1st line is another limitation in advancing agents in 2nd line setting. The change of this rather dark landscape in 1st line setting is suggested by two recent large randomized phase III trials in advanced pancreatic cancer showing that addition of capecitabine or erlotinib to gemcitabine render superiority to single-agent gemcitabine [2, 3].

There is growing evidence supporting benefit of chemotherapy after gemcitabine failure in selected patients with good performance status (Tables 1 and 2) [4]. In order to establish a much needed effective 2nd line treatment options for advanced pancreatic cancer, we need cooperative efforts among

Table 1. Published monotherapy options in second-line treatment of pancreatic cancer.

Single agent treatment	Disease control rate (CR, PR, and SD)	Progression free survival	Survival data (mOS)	P value	Number of patients
Capecitabine [10]	DCR: 37%	2.2 months	7.5 months since start of capecitabine treatment	N/A	37
Oxaliplatin [16]	Clinical benefit RR: 28%; SD: 17%	2 months	N/A	N/A	18
Irinotecan [20]	DCR: 57%	4 months	N/A	N/A	21
Raltitrexed [22]	DCR: 37%	2.5 months	4.3 months	N/A	19
Rubitecan [25]	DCR: 28%	58 days	108 days	N/A	198
Paclitaxel [28]	DCR: 42%	N/A	18 weeks	N/A	14
Pemetrexed [29]	DCR: 23%	7 weeks	20 weeks	N/A	52
Erlotinib [32]	DCR: 38%	1 month	N/A	N/A	13

CR: complete response; DCR: disease control rate; mOS: median overall survival; PR: partial response; SD: stable disease
N/A: not available

institutions and community practices in enrolling gemcitabine refractory patients in clinical trials.

Cytotoxic Agents

Fluoropyrimidine

Single agent 5-FU has shown benefit over best supportive care in number of clinical trials in advanced pancreatic cancer and has been the standard of care for approximately 40 years until mid 1990's when gemcitabine emerged as the new standard [1]. Response rates with 5-FU alone with or without leucovorin (LV) in various infusional modes in 1st line settings have been modest. Currently, there is no data supporting the use of 5-FU/LV alone in gemcitabine refractory advanced pancreatic cancer patients.

Table 2. Published combination therapy options in second-line treatment of pancreatic cancer

Combination regimen	Disease control rate (CR, PR, and SD)	Progression free survival	Survival data	P value	Number of patients
Oxaliplatin/folinic acid/5-FU (OFF) 24h *versus* best supportive care (BSC) [5]	N/A	N/A	Median survival time of 2nd line therapy: 21 weeks (OFF) *versus* 10 weeks (BSC)	0.0077	46
Oxaliplatin plus 5-FU (OXFU) [6]	DCR: 17% (0% ORR; 17% SD)	0.9 months	1.3 months from the start of 2nd-line therapy	N/A	18
Folfox 4 [7] [a]	DCR: 52%	4 months	mOS: 6.7 months	N/A	42
5-FU/LV/oxaliplatin [8]	DCR: 53%	22 weeks	mOS: 25 weeks	N/A	30
Capecitabine plus oxaliplatin (XELOX) [11]	DCR: 25%	N/A	6-month median survival rate: 48%	N/A	36
Capecitabine and docetaxel [12]	DCR: 83% (12.5% of PR)	N/A	N/A	N/A	24
Capecitabine plus celecoxib (CapCel) [13]	DCR: 30%	11 weeks	mOS :16 weeks	N/A	23
Celecoxib plus infusional 5-FU [14]	DCR: 12%	8 weeks	mOS: 15 weeks	N/A	17
Gemcitabine plus oxaliplatin (GEMOX) [17]	DCR: 57%	4.2 months	mOS: 6 months	N/A	31
Oxaliplatin and irinotecan [18]	DCR: 33%	4.1 months	mOS: 5.9 months	N/A	30
Gemcitabine and cisplatin combination with regional hyperthermia [19]	DCR: 70%	8 months	1-year EFS: 32%	N/A	12
Irinotecan plus raltitrexed [22]	DCR: 48% ORR: 16%	4 months	mOS:6.5 months	N/A	19
5-FU, folinic acid, and irinotecan (FOLFIRI 3) [23] [b]	DCR: 65% ORR: 37.5%	5.6 months	mOS: 12.1 months 1-year survival: 51%	N/A	43
Docetaxel plus gefitinib [26]	DCR: 19%	2.1 days	mOS: 2.9	N/A	26
Docetaxel plus gefitinib [27]	Study stopped due to lack of efficacy	N/A	N/A	N/A	15
Capecitabine plus erlotinib [33]	ORR: 10%	3.4months	mOS: 6.5 months	N/A	30

CR: complete response; DCR: disease control rate; EFS: event free survival; mOS: median overall survival; ORR: objective response rate; PR: partial response; SD: stable disease

N/A: not available

[a] Folfox 4 regimen: oxaliplatin administered on day 1 at the dose of 85 mg/m^2 as a 2-h infusion, concurrently with folinic acid 200 mg/m^2/day, followed by bolus 5-FU 400 mg/m^2 and a 22-h infusion of 5-FU 600 mg/m^2 for two consecutive days

[b] FOLFIRI 3 regimen: irinotecan 90 mg/m^2 as a 60-min infusion on day 1, leucovorin 400 mg/m^2 as a 2-h infusion on day 1, followed by 5-FU 2,000 mg/m^2 as a 46-h infusion and irinotecan 90 mg/m^2, repeated on day 3, at the end of the 5-FU infusion, every 2 weeks

Clinical trials including phase III randomized trial proving that patients with refractory advanced pancreatic cancer benefit from salvage chemotherapy with 5-FU based regimen [5, 6]. Various combinations of 5-FU/LV/oxaliplatin were tested in advanced pancreatic cancer patients after gemcitabine failure and have shown promising disease control rates. A chemotherapy protocol consisting of oxaliplatin, 5-FU, and folinic acid (Folfox 4; oxaliplatin administered on day 1 at the dose of 85 mg/m^2 as a 2-h infusion, concurrently with folinic acid 200 mg/m^2/day, followed by bolus 5-FU 400 mg/m^2 and a 22-h infusion of 5-FU 600 mg/m^2 for two consecutive days) appears to be the most active regimen of this combination resulting in 52% disease control rates and 4 months progression free survival (Tables 1 and 2) [7, 8].

Capecitabine is an oral fluoropyrimidine which was tested in 1st line setting with clinical benefit response rate of 24%, suggesting possible role of capecitabine as a salvage therapy after gemcitabine failure [9]. Capecitabine as monotherapy or in combination with oxaliplatin (XELOX) has shown encouraging disease control rates in gemcitabine refractory patients [10, 11]. Capecitabine and docetaxel combination is also an active 2nd line treatment option with 71% of patients maintaining stable disease for 2 or more cycles (Tables 1 and 2) [12].

Lately, a novel combination of capecitabine plus celecoxib resulted in modest activity in 2nd line setting of advanced pancreatic cancer [13]. Celecoxib was also combined with protracted intravenous 5-FU in gemcitabine refractory advanced pancreatic cancer patients and shown modest activity suggesting synergy between fluoropyrimidine and celecoxib [14]. S-1 is a fourth generation oral fluoropyrimidine with a potential activity in pancreatic cancer in second line setting and needs further investigation (Tables 1 and 2) [15].

Platinum

Single agent oxaliplatin rendered a clinical response in 28% of advanced pancreatic cancer who progressed on gemcitabine [16]. Oxaliplatin in combination with 5-FU and capecitabine is a reasonable 2nd line treatment option in advanced pancreatic cancer as described in above section. Gemcitabine plus oxaliplatin (GEMOX) showed activity in 2nd line setting after gemcitabine failure. GEMOX regimen showed approximately 57% disease control rates with median time to progression of 4 months in a study by Demols *et al.* [17]. Cantore *et al.* also reported 20% clinical response rates with duration of 7.2 months using a combination of oxaliplatin and irinotecan in gemcitabine refractory advanced pancreatic cancer patients [18]. Gemcitabine and cisplatin combination with regional hyperthermia was evaluated in advanced pancreatic cancer patients after gemcitabine failure. This regimen, at interim analysis which was presented in the 2006 American Society of Clinical Oncology (ASCO) meeting, showed a potential although only 12 patients were evaluated at the time [19].

Topoisomerase Inhibitors

Irinotecan monotherapy is active as a 2nd line treatment of gemcitabine refractory advanced pancreatic cancer patients. Fifty-seven percent of patients had disease control with median time to progression of 4 months [20]. Preclinical study suggesting that pemetrexed and irinotecan may have synergistic activity in pancreatic cancer, and this regimen should be evaluated in 2nd line settings [21]. Irinotecan plus raltitrexed in gemcitabine refractory advanced pancreatic cancer patients resulted in an objective response rate of 16% and clinical benefit response of 29% [22]. Combination of 5-FU, folinic acid, and irinotecan (FOLFIRI) was tested in 1st line setting with promising activity and due to this regimen's lack of cross-resistance with gemcitabine based 1st line treatment options, FOLFIRI may emerge as a reasonable 2nd line option in selected patients with good performance status [23]. Rubitecan is an orally active camptothecin derivative, and it has shown a moderate activity as a salvage therapy in heavily pretreated patients with advanced pancreatic cancer [24, 25].

Taxane

Docetaxel has been used in 1st and 2nd line setting in combination with irinotecan and biological agents. Ignatiadis *et al.* evaluated docetaxel/gefitinib combination as 2nd line treatment in patients with advanced pancreatic cancer after gemcitabine failure. Conclusion of this study was that the regimen, although safe, has no activity as salvage treatment for advanced pancreatic cancer after failure of gemcitabine-based chemotherapy [26]. Another study presented in the 2007 ASCO meeting confirmed inactivity of this combination [27].
Single agent weekly paclitaxel in 2nd and 3rd line setting after gemcitabine failure in a small study by Oettle *et al.* showed a modest activity. Paclitaxel monotherapy may be considered to be an additional treatment option in gemcitabine refractory pancreatic cancer [28].

Antimetabolites

Pemetrexed is a novel multitargeted antifolate that targets enzymes involved in folate metabolism. In a phase II trial with 52 patients who had progression of disease on gemcitabine, single agent pemetrexed resulted in a 3-month survival rate of 75%, disease control rate of 23% with time to progression of 7 weeks and decrease of CA 19-9 levels by more than 50% in 23% of treated patients [29].

Biological Agents

Vascular Endothelial Growth Factor (VEGF) Inhibition

Agents inhibiting VEGF pathways have been largely disappointing in 1st line setting thus far. Bevacizumab in combination with gemcitabine in randomized phase III clinical trial and sorafenib in a small pilot study have failed to show the superiority over gemcitabine monotherapy [30, 31]. Other combination regimen and novel agents should be investigated in 2nd line setting taking advantage of relatively low toxicity profile of these agents. Our experience in treating other cancer types with bevacizumab suggests that perhaps gemcitabine is not the ideal agent to combine bevacizumab with. Folfox, 5-FU, capecitabine, paclitaxel, and irinotecan have shown synergistic anti-tumor activities in randomized clinical trials, and these approaches should be further investigated in advanced pancreatic cancer.

Epidermal Growth Factor Receptor (EGFR)

Erlotinib monotherapy in 2nd line setting was tested in a small study with 13 patients evaluated. In this study 5 patients had disease control with time to progression of 1 month suggesting that erlotinib is an option for gemcitabine refractory patients with minimal toxicity [32].
Capecitabine plus erlotinib in gemcitabine refractory pancreatic cancer rendered an objective response rate of 10% with median progression free survival of 3.4 months in a recent trial of 30 patients. This study noted no association between clinical outcome and *EGFR* mutational status although the sample was small [33]. It would be interesting to see if patients with K-*ras* wild type gene would benefit more from erlotinib in 2nd line setting and should be investigated in future clinical trials. Docetaxel/gefitinib is not active in 2nd line as described in previous section [26, 27].
Docetaxel plus irinotecan plus cetuximab showed a promising activity as a non-gemcitabine containing regimen and can potentially be use in 2nd line setting as well [34].

Hormonal Therapies

Tamoxifen monotherapy and octreotide monotherapy showed minimal activity in multiple clinical trials. Tamoxifen did not render survival advantage over placebo in clinical trials and octreotide in combination with 5-FU failed to show any benefit [35, 36, 37, 38]. Based upon these negative trials in 1st line setting, it is unlikely that these agents would have any benefit in 2nd line setting.

Future Direction

Lack of attention to 2nd line treatment strategy in advanced pancreatic cancer is due to the fact that we still do not have 1st line option that renders true survival benefit; therefore,

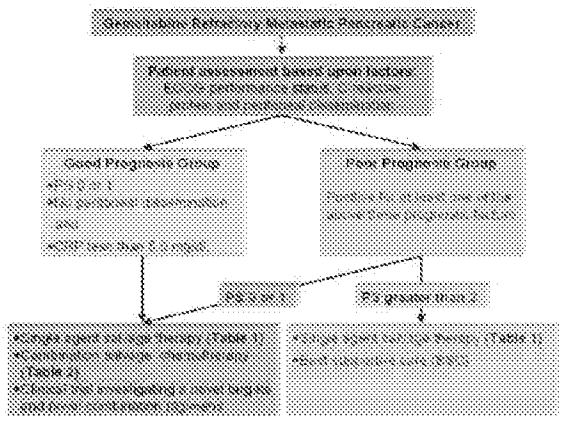

Figure 1. Proposed selection guideline for second-line therapy after gemcitabine failure [43].

development of novel therapeutic agents should be an obvious area of our focus in the future. However, it is equally important that we improve study design and be more rigorous in scrutinizing phase II data before moving forward with large phase III randomized trials that require enormous resources. One solution would be more frequent implementation of randomized phase II trials to test agents with encouraging activities before undertaking phase III trials.

Patient selection and individualized medicine has been the area of increased interest since human genome project was completed. While it is still at a very early stage and it would take years before we can see clinical application, pharmacogenomics in pancreatic cancer is an important area to watch. There are various preclinical studies investigating polymorphisms and expression levels of genes associated with gemcitabine sensitivity and/or resistance [39]. Given the fact that the cost of sequencing has drastically come down, genotyping patients enrolled in large phase III trials in pancreatic cancer for genotyping should also be a routine practice in order to investigate genotype-phenotype association with significant statistical power in the future [40].

Presence of circulating tumor cells correlates with prognosis and can predict how patient will respond to chemotherapy in breast cancer patients [41]. Research of circulating tumor cells in pancreatic cancer is very limited [42]. Reliable biomarkers such as circulating tumor cells that predict treatment response or outcome earlier than traditional imaging methods will enable oncologists to change treatment regimen before the worsening performance status prohibit us from salvage treatment.

Selected advanced pancreatic cancer patients with good performance status should be considered for 2nd line chemotherapy after 1st line gemcitabine failure [4, 5]. With better patient selection, we can improve clinical outcomes of advanced pancreatic cancer in 2nd line settings. Prospective clinical trials investigating clinical outcomes in association with published prognostic factors such as performance status, C-reactive protein, and peritoneal dissemination may improve patient selection for 2nd line treatment (Figure 1) [43].

Conclusion

Current data set on treatment options in 2nd line setting after gemcitabine failure is scattered and scant. We need to establish the standard of care for this rising group of patients. We can achieve this goal by better understanding of the disease, development of novel agents, and concerted effort to enroll patients in rationally designed clinical trials. Emerging science and technology may further guide us to develop individualized treatment algorithm for advanced pancreatic cancer patients which will spare advanced pancreatic cancer patients from inactive 1st line treatment.

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Keywords Pancreatic Neoplasms; Salvage Therapy; Treatment Failure

Abbreviations ASCO: American Society of Clinical Oncology; LV: leucovorin

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ORIGINAL ARTICLE

Second-line chemotherapy with Capecitabine (Xeloda) and Docetaxel (Taxotere) in previously treated, unresectable adenocarcinoma of pancreas: the final results of a phase II trial

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Abstract
Purpose To investigate the efficacy and toxicity of the doceraxel and capecitabine combination in patients with previously treated, unresectable adenocarcinoma of the pancreas.
Patients and Methods Patients with pancreatic adenocarcinoma, pre-treated with gemcitabine-based chemotherapy, were treated with capecitabine (800 mg/m^2 orally, twice a day for 14 days) and docetaxel (75 mg/m^2 i.v. on day1), every 3 weeks. The primary end-point was overall response rate (RR).
Results Thirty-one patients were enrolled in the study; 93.6% of them had a performance status (PS) of 0–1 and 96.8% had stage IV disease. Patients received a median of 4 cycles/patient, and the main reason for treatment discontinuation was disease progression. Partial response was observed in three (9.7%) patients, stable disease in seven (22.6%) (disease control rate: 32.3%, 95% CI: 15.80–48.71%) and disease progression in 21 (67.6%). The median progression-free survival (PFS) was 2.4 months (95% CI: 1.6–3.13) and the median overall survival (OS) was 6.3 months (95% CI: 3.38–9.23); the estimated 1-year survival rate was 14.7%. Grade III/IV neutropenia occurred in 10 (32.2%) patients and febrile neutropenia in one patient. Other severe non-hematologic toxicities were mild and manageable. After 2 chemotherapy cycles, pain control occurred in 20% of patients and stabilization of body weight in 40%.
Conclusion The combination of doceraxel/capecitabine may confer good disease control associated with improvement of quality of life as second-line chemotherapy in patients with metastatic pancreatic cancer.

Keywords Capecitabine · Docetaxel · Phase II trial · Pancreas

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Introduction

Adenocarcinoma of the pancreas is responsible for almost 6% of cancer-related deaths [1]. For all patients combined, the 1- and 5-year relative survival rates for this disease are only 24 and 5%, respectively. Up to 60% of patients have advanced pancreatic cancer at the time of diagnosis. The median survival of patients with locally advanced disease is 6–10 months, and for patients with metastatic disease, 3–6 months [2].

Fixed dose rate gemcitabine [3], or combination chemotherapy of gemcitabine with other cytotoxic agents such as oxaliplatin [4], or cisplatin [5], is currently used for first-line chemotherapy for locally advanced or metastatic disease.

Data for second-line chemotherapy in patients with advanced/metastatic pancreatic cancer are limited since the majority of progressing patients after first-line chemotherapy have poor performance status. Moreover, another reason that limits the therapeutic options for second-line treatment in these patients is the lack of active agents.

Nevertheless, there is some evidence from previous studies that some selected patients with adenocarcinoma of pancreas would benefit from more chemotherapy after failing single-agent gemcitabine or another first-line chemotherapy combination [6].

Capecitabine is an oral fluopyrimidine which offered a response rate of 24% when tested as first-line treatment [7, 8] for locally advanced or metastatic pancreatic cancer, suggesting a role in gemcitabine refractory disease. Capecitabine has also been combined with Oxaliplatin with encouraging results [9, 10]. Docetaxel is a semisynthetic taxane with a broad spectrum of antitumor activity. It has been previously investigated as single agent in phase II trials [11], with an objective response rate of 15% and stable disease rate of 38%.

The combination of docetaxel and capecitabine (DC regimen) was investigated in a phase I study in patients with various solid tumors [12]. The DC regimen has since been safely used in several disease settings, including gastric adenocarcinoma and breast cancer [13, 14]. Preliminary results of a phase II trial using the DC combination as second-line treatment for locally advanced and metastatic adenocarcinoma of pancreas were presented in the 2007 ASCO Annual Meeting [15]. The treatment was well tolerated and the response rate was 12.5%, while 70.8% of patients had stable disease for 2 or more cycles of treatment. The final results of this trial are pending.

The aim of the current phase II study, conducted by the Hellenic Oncology Research Group (HORG), was to evaluate the efficacy and tolerance of the DC regimen as second-line chemotherapy in patients with advanced/metastatic pancreatic cancer.

Patients and methods

Patient population

Eligible patients had to meet the following criteria: age >18 years, histologic confirmation of locally advanced or metastatic adenocarcinoma of the pancreas, one prior chemotherapeutic regimen with a gemcitabine-based combination, at least one bidimensionally measurable target lesion (i.e., lesions $\geq$2 cm other than the primary or $\geq$1.5 cm in case of lung metastasis, outside any previous eradicated area), WHO Performance Status (PS) of 0 to 2, recovery of the effects of previous chemotherapy, adequate hematologic function (defined as neutrophils >1,500/mm^3, platelets >100,000/mm^3, Hb > 10mgr/dl), adequate liver function (defined as bilirubin levels $\leq$1.5 times the institutional upper normal limit [ULN], after biliary drainage if previously abnormal, and as AST and alkaline phosphatase $\leq$2.5 times the UNL, or $\leq$5 times the UNL for patients with liver metastasis), normal renal function (defined as serum creatinine $\leq$1.5 times the UNL), absence of ascites. Patients with other primary tumors within the last 10 years were excluded from the study, except adequately treated in situ cervical carcinoma, and basal or squamous cell skin carcinoma.

Patients were also excluded from the study if they had symptomatic central nervous system metastasis or carcinomatous meningitis, a psychiatric disorder, active uncontrolled infection, a myocardial infarction within the last 12 months or congestive heart failure or cardiac arrhythmias not controlled on medication.

All patients have given their written informed consent before their enrollment to the study. The protocol has been approved by the Ethics and the Scientific Committees of the participating institutions.

Treatment plan

Docetaxel (Taxotere; Sanofi-Aventis, Bridgewater, NJ, USA) was given at a dose of 75 mg/m^2, on day 1 every 21 days, following pre-medication with dexamethasone 8 mg twice daily on days 0, 1, 2, for a total of 3 days. Capecitabine (Xeloda; Roche, Zurich, Switzerland) was given at a dose of 800 mg/m^2, orally, twice a day, from day 1 to day 14 of a 21-day cycle, starting the first dose at least 1 h after the first dose of Docetaxel. The chemotherapy regimen was continued for a total of 6 cycles, unless the patient suffered from an unacceptable chemotherapy adverse event or disease progression.

Patients with a PS $\geq$ 2 had the first cycle with a 20% dose reduction for both docetaxel and capecitabine; if the treatment was well tolerated, patients had to receive the subsequent chemotherapy cycles at the full protocol dose.

Response and toxicity evaluation

Response or progression were evaluated using the 2009, revised Response Evaluation Criteria in Solid Tumors (RECIST) [16]. Objective responses either complete (CR) or partial (PR) were to be confirmed at least 4 weeks later. Toxicities were graded according to the National Cancer Institute Common Toxicity Grading Criteria, version 2 [17] initially, and the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) after these were published (August, 2006).

Treatment was interrupted for $\geq$grade 2 toxicity (with the exception of alopecia, nausea or vomiting and anemia), and it was not restarted until improvement either complete or at least to a grade 1. Dose reduction for capecitabine or docetaxel was not necessary for the first occurence of a grade 2 toxicity. A second and a third occurence of a grade 2 event required a 20 and 40% dose reduction of both

drugs, respectively. The occurrence of ≥grade 3 toxicity required a 20% dose reduction of both drugs. In case of >grade 2 hand-foot syndrome, mucositis or diarrhea the dose of capecitabine had to be reduced by 25%. Patients who required more than two dose reductions as well as in the case of unresolved toxicity (>grade 1) 3 weeks after the last chemotherapy cycle had to be withdrawn from the study. Maximum delay for a chemotherapy cycle was up to 3 weeks. Granulocyte-Colony Stimulating Factor (G-CSF) could be administered for symptomatic neutropenia, but not prophylactically.

Pain assessment was made at baseline and every 6 weeks. Pain was assessed using the Memorial Pain Assessment Card. QoL was evaluated using the European Organisation for Research and Treatment of Cancer (EORTC) core QoL questionnaire (EORTC QLQ-C30) and European Study Group for Pancreatic cancer (ESPAC) QoL questionnaire pancreatic-specific module.

Statistics

This was a multicenter, single arm, open label, phase II study. The primary end-point of the study was the efficacy of the regimen in terms of objective response rate (CR, PR). Secondary end-points were the disease control rate, the progression-free survival, the overall survival and the toxicity profile of the regimen. Some investigators have used the cutoff of 5% response rate as significant [18]; others have used the 10% [19]. In any case, this assumption lacks any evidence and is based mainly on the RR that has already been achieved by other chemotherapy regimens in the past. We have decided that we would consider as significant any second-line regimen for metastatic pancreatic cancer associated with a ≥7% response rate, and any response rate equal or above that would be of further interest, but anything below would be unacceptable, as other regimens have been able to achieve better outcome. The study design employed a one-stage design with 31 eligible patients, with the assumption that if at least two of the 31 patients showed response, then the regimen would be considered to be of further interest for the patient population. Secondary end-points of this study included the duration of response, the progression-free survival, the overall survival, the toxicity profile and the quality of life of patients with locally advanced or metastatic adenocarcinoma of the pancreas previously treated with a gemcitabine-based chemotherapy combination.

Survival curves were estimated using the Kaplan–Meier method and Life tables. Safety analysis was carried out on the treated population using contingency tables and descriptive statistics. Statistical significance was set to be 0.05.

All clinical data were centrally collected and analyzed. Duration of tumor response is measured from the date the first objective response (complete or partial) was observed to the first date of tumor progression or death from any cause. The time to tumor progression (TTP) was measured from study entry until the day of the first evidence of disease progression whereas overall survival (OS) was measured from study entry to death or last contact. All patients who received at least 2 chemotherapy cycles were assessable for response, and all patients who received at least 1 cycle of chemotherapy were evaluated for toxicity.

Compliance with the EORTC QLQ-C30 was low, and QoL scores could not be calculated from all the patients, especially after the first two cycles of chemotherapy. We have decided that in the present study we could only present the percentage and number of patients experiencing disease-related symptoms that had an effect on the quality of their life, at baseline and after the first two cycles of chemotherapy without making specific statistical comparisons.

Results

Patient demographics

Between 08/05/2006 and 15/5/2009, 31 patients were enrolled in this study all over Greece. Baseline patient and disease characteristics are presented in Table 1. The patients' median age was 63 years and 19 (61.3%) were men. Most of the patients had a PS 0–1 (71.0%), all but one patients had stage IV disease and 26 (83.2%) had more than two organs involved. All patients had received first-line chemotherapy with gemcitabine either as a single agent or as combination treatment. Thirteen (41.9%) patients had previously received front-line treatment gemcitabine with erlotinib and 22 (71%) patients had previously been treated with a non-platinum-based regimen. The median interval from the previous treatment was 1.33 months (min–max: 0.23–8.87).

Compliance with treatment

The total number of chemotherapy cycles, median cumulative chemotherapy dose, dose intensity, reasons for treatment discontinuation are all summarized in Table 2. Overall, the DC regimen was found to be well tolerated, despite the fact that only 16.1% of patients managed to complete chemotherapy. There were two patients who discontinued treatment because of grade III neutropenia, grade I anemia, grade II diarrhea, and grade II mucositis ($n = 1$ patient) and consent withdrawn ($n = 1$ patient).

Table 1 Patient characteristics

	N (31)	%
Age		
Median (min–max)	63 (44–79)	
Sex		
Male	19	61.3
Female	12	38.7
Performance status		
0	7	22.6
1	22	71.0
2	2	6.5
Stage		
IIB	1	3.2
IV	30	96.8
Anatomic cancer site		
Head of pancreas	15	48.8
Body of pancreas	7	22.6
Tail of pancreas	2	6.5
Ampulla of Vater	3	9.7
Head and ampulla of vater	1	3.2
Body and tail	2	6.5
Degree of differentiation		
Well differentiated	4	12.9
Moderately differentiated	7	22.6
Poorly differentiated	5	16.1
Unknown	15	48.4
Response to previous treatment		
PR	3	9.7
SD	7	22.6
PD	20	64.5
NE	1	3.2
Organs involved		
Pancreas	23	74.2
Liver	20	64.5
Nodes	14	45.2
Lung	11	35.5
Peritoneum	3	9.7
Bones	1	3.2
Other	6	19.4

Table 2 Compliance with the treatment

	N	%
Total no of cycles	123	
Median no of cycles/ patient (range)	4 (1–9)	
Treatment completed as per protocol	5	16.1
Actual dose intensity (mg/m^2/week)		
Capecitabine		
Median (range)	6222.22 (1239.32–7467.00)	
Docetaxel		
Median (range)	22.22 (10.77–25.00)	
Relative dose intensity* (%)		
Capecitabine		
Median (range)	83.33 (16.60–100.00)	
Docetaxel		
Median (range)	88.88 (43.08–100.00)	
Reason for treatment discontinuation		
Disease progression	20	64.5
Adverse event (treatment related)	1	3.2
Denial	2	6.5
Death	2	6.5
Ongoing	1	2.7
No of patients with dose reductions and delays		
≥1 cycle with dose reduction	13	41.9
≥1 cycle with delay	13	41.9

* Actual dose intensity/planned dose intensity

Eleven (35.48%) patients received the treatment without dose reductions or delays, whereas six (19.35%) had dose reductions and treatment delays.

Response and survival

All patients were evaluated for response in the context of an intention-to-treat analysis. A partial response was achieved in three (9.7%; 95% CI: 0–20.09%) patients and stable disease (SD) in seven; 21 (67.7%) patients had disease progression (PD). Treatment was not evaluated in one patient for logistical reasons and the patient was characterized as progressor. The overall disease control rate (DCR) was 32.2% (95% CI: 15.80–48.71%). Among the 22 patients who had previously been treated with a non-platinum-based regimen, seven (31.8%) experienced disease control (PR + SD group); the same was observed in three (33.3%) out of nine patients who had previously been treated with a platinum-based regimen ($P = 0.935$). There was no difference in terms of response rate according to PS (0–1 vs. 2; $P = 0.558$).

After a median follow-up period of 14.5 months (range: 1.33–23.60), 30 (6.8%) patients experienced disease progression. The median time to progression was 2.37 months (range, 0.90–7.43; 95% CI: 1.60–3.13). No evidence of disease progression for >6 months was documented in two (6.5%) patients. The estimated 1-year progression-free survival (PFS) rate was 3.2% (Fig. 1). PFS was 5.1 months for patients who experienced disease control (PR + SD) and 2.07 months for patients with PD ($P < 0.001$).

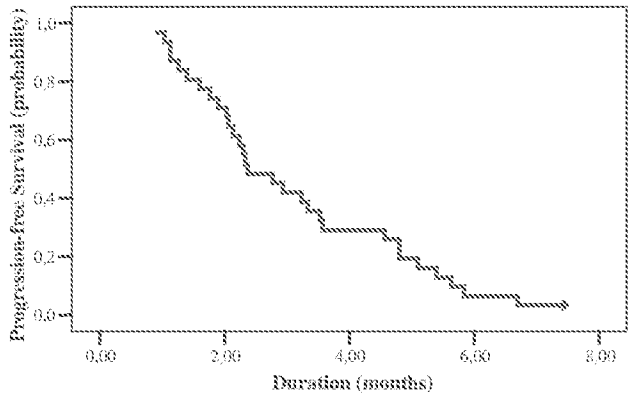

Fig. 1 Progression-free survival curve for patients treated with Docetaxel and Capecitabine

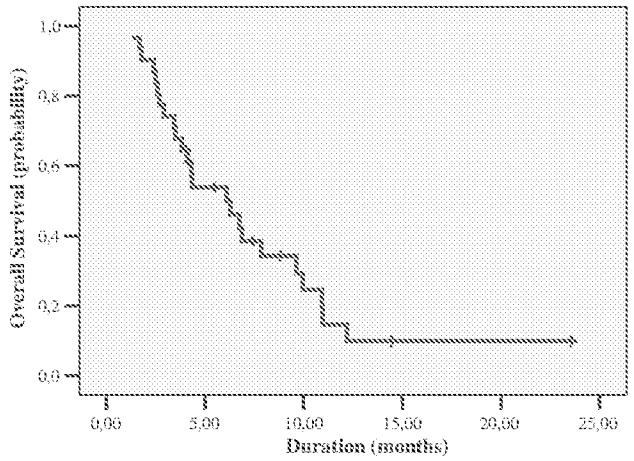

Fig. 2 Kaplan–Meier overall survival curve of patients treated with Docetaxel and Capecitabine

Twenty-four (77.4%) patients died due to disease progression during the follow-up period. The median overall survival (OS) was 6.3 months (range, 1.33–12.20; 95% CI: 3.38–9.23). Fourteen (45.2%) patients were alive for at least 6 months after enrollment. The estimated 1-year OS was 14.7% (Fig. 2).

Symptom control

All 31 patients completed QoL questionnaires at baseline and all but one, after 2 cycles of treatment. The number of patients available for QoL assessment decreased markedly after the second cycle of treatment, mainly because of symptom worsening and disease progression. The major benefit of chemotherapy was observed in patients after they had received 2 cycles of chemotherapy, and this effect was either maintained further (as observed in the very few patients that QoL was further assessed), or deteriorated toward the last period of treatment. Table 3 indicates the effect of treatment on the main disease-related symptoms. Pain was a major clinical problem in 58.1 and 38.7% of patients at enrollment and after 2 cycles of treatment, respectively. In addition, analgesia was used by 48.4 and 32.3% of patients at enrollment and after 2 chemotherapy cycles, respectively. Moreover, 32.3% of patients used opioids at baseline and this was reduced to 25.8%, after 2 cycles of treatment. In addition, 38.7% of the treated patients maintained their body weight.

Table 3 Incidence of disease-related symptoms at enrollment and after 2 cycles of chemotherapy

Disease-related symptoms	At baseline		After 2 cycles of treatment	
	N	%	*N*	%
Pain	18	58.1	10	32.3
Use of analgesics	15	48.4	10	32.3
Use of opiods	10	32.3	8	25.8
Fatigue	18	58.1	14	45.2
Weight loss	14	45.2	2	6.5

Table 4 Chemotherapy-induced adverse events

	GrI		*GrII*		*GrIII*		*GrIV*	
	N	%	*N*	%	*N*	%	*N*	%
Neutropenia	2	6.5	–	–	5	16.1	5	16.1
Febr./neutropenia	–	–	–	–	–	–	1	3.2
Anemia	14	45.2	11	35.5	–	–	1	3.2
Thrombocytopenia	8	25.8	–	–	–	–	1	3.2
Nausea	3	9.7	–	–	–	–	–	–
Vomiting	2	6.5	1	3.2	–	–	–	–
Constipation	2	6.5	1	3.2	–	–	–	–
Diarrhea	2	6.5	5	16.1	–	–	–	–
Stomatitis	1	3.2	2	6.5	1	3.2	–	–
Hand-Foot syndrome	2	6.5	–	–	–	–	–	–
Neurocensory	1	3.2	–	–	–	–	–	–
Neuromuscular	–	–	1	3.2	–	–	–	–
Allergy	–	–	1	3.2	–	–	–	–
Infection	–	–	–	–	–	–	–	–
Fatigue	5	16.1	7	22.6	2	6.5	–	–

Toxicity

The most common adverse event associated with the capecitabine/docetaxel combination chemotherapy was hematologic toxicity. Ten (32.3%) patients developed grade III–IV neutropenia but febrile neutropenia complicated treatment in only one patient (3.2%). All patients were treated with G-CSF support, and antibiotics were given prophylactically.

One patient developed grade IV thrombocytopenia without clinical evidence of bleeding; the patient had an uneventful recovery without necessitating hospitalization. There were no treatment-related deaths. Non-hematologic toxicity was mild (Table 4).

Discussion

Second-line chemotherapy for adenocarcinoma of the pancreas remains a major therapeutic challenge. Patients that have failed first-line chemotherapy, with a gemcitabine-based combination, are currently not able to be treated with an alternative chemotherapy that has proved as good as the first-line treatment. Standard of care needs to be established for this group of patients. There is evidence from previous studies that some of these patients may benefit from additional chemotherapy versus best supportive care (BSC) [6]. The NCCN Panel recommends that for patients with gemcitabine refractory disease, treatment should be delivered within a clinical trial [20].

The combination of capecitabine and docetaxel, which has been tested in the current study, was extremely well tolerated without major adverse events. However, only 16.1% of patients managed to complete the 6 chemotherapy cycles as per protocol. The main reason for treatment discontinuation was disease progression since only one patient, with febrile neutropenia, decided to stop treatment due to treatment-related toxicity. The main severe adverse event was grade III-IV neutropenia occurring in 32.3% of patients. Other severe toxicities were mild occurring in less than 5% of the treated patients. There were no documented treatment-related deaths.

Quality of life becomes extremely important when we deal with an aggressive and resistant to standard treatment disease, such as the adenocarcinoma of pancreas. This is even more important when we refer to second-line chemotherapy. In the present study, the DC regimen was associated with a clinical benefit, since almost half the patients that complained of some degree of pain at baseline had experienced good pain control (from 58.1% of patients initially to 32.3%) and 16.1% of patients, that used analgesia initially, stopped using it. An important proportion of patients (38.7%) maintained their body weight. Notably, this clinical benefit was observed without severe treatment-related adverse events. Unfortunately, we are not able to comment on QoL after the first two cycles of treatment (6 weeks), but we could assume that as disease control was gradually decreasing, symptom control was also deteriorating. With the DC regimen, patients have achieved a PFS of 2.4 months as described in detail above, and the fact is that most of them experienced good symptom control during this period.

The capecitabine/docetaxel combination resulted in a 9.7% objective response rate and a DCR of 32.2%. Moreover, 6.5% of patients did not have disease progression for at least 6 months whereas 53.9% of patients were alive for more than 6 months and 14.7% for more than 1 year. In addition, the data showed that patients achieving disease control have a significantly longer PFS compared to patients who failed to respond to treatment; for patients with a pancreatic cancer, it is important to achieve a delay to disease progression with a well-tolerated treatment that could at least partially explain the observed improvement of patients' quality of life. In any case, these results are in agreement with the reported preliminary data of a similar phase II trial of docetaxel/capecitabine as second-line chemotherapy for adenocarcinoma of the pancreas showing a PR rate of 12.5% [15]. Furthermore, the efficacy results of the DC regimen, reported in the current study, are practically similar to those reported in other studies, evaluating second-line treatment for pancreatic adenocarcinoma. However, most of these studies are small phase II trials with a limited number of patients [15, 21–23]. This is probably due to the patients' poor PS and, only few relapsing or progressing patients after first-line treatment preserve a PS good enough for second-line chemotherapy.

Several anticancer drugs used either as single agents or in combination regimens have been tested as second-line treatment for adenocarcinoma of the pancreas. Indeed, rubitecan has offered a 7% PR and 16% SD [24], whereas a 3.8% PR and 19.2% SD was achieved with pemetrexed [25]. In addition, paclitaxel was also found active with one patient from the 18 tested achieving CR and five patients SD [26]. Capecitabine was also found a safe and well-tolerated option with 39% of patients achieving SD [7] with a median survival of 7.6 months. More recently, S-1 resulted in a 15% PR and in a 43% SD as second-line chemotherapy in patients with a median survival of 4.5 months when tested in pre-treated patients with pancreatic cancer [27]. Combination chemotherapy based on oxaliplatin has also been tested, as second-line treatment for patients with advanced adenocarcinoma of the pancreas, that has failed single-agent gemcitabine. This agent has been combined with gemcitabine [28], capecitabine [10, 29], irinotecan [30], pemetrexed [31] or raltitrexed [32]. The results showed an overall response rate ranging from 3% for the oxaliplatin/capecitabine [10] to 24% for oxaliplatin/raltitrexed [32] and an OS ranging from 5.2 to 6 months, respectively. The CONKO-003 study has tested the Oxaliplatin, and 5FU/FA (OFF) combination versus the 5FU/FA as second-line treatment in patients with gemcitabine refractory pancreatic cancer. The authors conclude that treatment with OFF results in a significant improvement in PFS [13 weeks (95%CI 11.46–14.55) vs. 9 weeks (95% CI, 7.38–10.61),

$P = 0.012$] and OS [26 weeks (95% CI 19.56–32.41) vs. 13 weeks (95% CI 10.01–15.99) $P = 0.14$] [33].

Cis-platin-based chemotherapy has also been used in the second-line setting in patients with advanced adenocarcinoma of the pancreas. This agent when combined with gemcitabine [34] resulted to a PR rate of 8.3% and to SD rate of 58.3% of patients with a median OS of 4 months. Cisplatin was also used with gemcitabine, irinotecan and 5-FU/Leucovorin, in a very intense 2-day regimen [35]; the observed PR rate was 24% and the SD rate was 20.5% whereas the median OS was 10.3 months. More recently, the combination of cisplatin and S-1 resulted in a 29.4 and 11.8% of PR and SD, respectively, with a median OS of 10 months [33]. All these studies clearly indicate that despite the efficacy of the different regimens in terms of objective response rate the observed median OS is more or less similar and not more than 10 or 11 months.

A triple combination with docetaxel/gemcitabine/capecitabine resulted to an overall response rate of 29% with an OS of 11.2 months [36] whereas the combination of docetaxel/mitomycin-C/irinotecan was associated with a median OS of 6.1 months [34]. We can speculate that it is still unclear whether triple combinations in the second-line setting can offer substantial benefit to patients with pancreatic carcinoma.

In our study, previous treatments (both platinum-based or not) made no difference, to the final outcome. The same applies to PS. Obviously PS is essential, for patients to be able to have and complete any kind of treatment, but as long as patients have a PS ≤ 2, the combination of docetaxel and capecitabine is active and worth trying.

In conclusion, the results of the present study indicate that the combination of docetaxel and capecitabine is well tolerated and shows a degree of activity when used as second-line treatment for patients with advanced adenocarcinoma of the pancreas. Moreover, this regimen offers a benefit to the quality of life. Therefore, this combination merits to be used in the palliative setting in patients who progress under standard first-line chemotherapy. Further investigation is required to achieve a more satisfactory response for a second-line treatment in this disease setting.

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Conflict of interest statement None.

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1564P

Clinical pathway implications and real-world characteristics and outcomes for patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with first line category 1 National Comprehensive Cancer Network (NCCN) regimens

George Kim[1], Paul Cockrum[2], Stella Arndorfer[3], Andy Surinach[3]
[1]George Washington University, Division of Hematology & Oncology, Washington, DC; [2]Ipsen ,Cambridge, MA; [3]Genesis Research, Hoboken, NJ

BACKGROUND

- Pancreatic cancer is predicted to account for 47,050 deaths in the United States in 2020, making it the 4th deadliest cancer[1]
- The 5-year relative survival across all stages for patients with pancreatic cancer is 10%[2]
- Patients with pancreatic cancer often present at an advanced stage. 30% of newly diagnosed patients present with regional spread to lymph nodes and 52% present with metastases[2]
- Due to limited treatment options for patients with metastatic disease, the 5-year relative survival is only 2.9%[2]
- The National Comprehensive Cancer Network (NCCN) 2020 guidelines recommend treatment with FOLFIRINOX or gemcitabine + nab-paclitaxel (gem-nabP) for patients with mPDAC and good performance status (PS) and gemcitabine monotherapy (gem-mono) for patients with mPDAC and poor PS[3]
- FOLFIRINOX, gem-nabP, and gem-mono are all considered Category 1 (Cat 1) recommendations by NCCN and are included in select clinical pathways

OBJECTIVE

- To describe the clinical characteristics and real-world outcomes of patients with mPDAC treated with NCCN Cat 1 chemotherapy regimens in the first line (1L) setting

METHODS

Study Design and Data Source

A retrospective descriptive analysis was performed using the Flatiron Health® longitudinal database, a demographically and geographically diverse database derived from electronic health record (EHR) data which includes data from over 280 cancer clinics representing more than 2.4 million active US cancer patients

Patient Selection

- This analysis identified and evaluated adult patients diagnosed with mPDAC between January 1, 2015 and December 31, 2019
- Eligible patients were those who:
  - Had recorded activity within 90 days after their mPDAC diagnosis date
  - were at least 18 years old at diagnosis
  - were treated with systemic therapy
  - had at least one recorded activity after the start of treatment
  - were treated with FOLFIRINOX, gem-nabP, or gem-mono in the 1L setting

Measures and Statistical analyses

- Baseline patient demographics and clinical characteristics, real-world overall survival (OS), and duration of treatment (DOT) were determined
- DOT was defined as the number of weeks between the first and last administration of a therapy included in the treatment regimen
- Median OS was determined via Kaplan-Meier analysis
  - Patients without a death recorded in their follow-up were censored on the date of their last recorded activity
- Pearson's Chi-Square test was used to assess association between categorical variables, Kruskal-Wallis test was used to assess associations between continuous variables
- Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA)

Table 1. Patient characteristics at the start of therapy

Characteristic	FFX, N = 1420 (32%)	Gem-NabP, N = 2484 (56%)	Gem Mono N = 467 (10%)	p-value
Male, n (%)	861 (61%)	1331 (54%)	232 (50%)	<0.001
Age at Treatment Start, years, median (IQR)	64 (57 - 70)	70 (63 - 76)	75 (67 - 80)	<0.001
Stage at initial diagnosis, n (%)				<0.001
Other	328 (23%)	683 (27%)	157 (34%)	
Stage IV	1092 (77%)	1801 (73%)	310 (66%)	

Site of primary tumor, n (%)				<0.001
Body	285 (20%)	501 (20%)	72 (15%)	
Head	654 (46%)	1190 (48%)	254 (54%)	
Overlapping sites	150 (11%)	256 (10%)	46 (9.9%)	
Pancreas, NOS	22 (1.5%)	93 (3.7%)	21 (4.5%)	
Tail	309 (22%)	444 (18%)	74 (16%)	
ECOG PS, n (%)				<0.001
0	440 (44%)	528 (29%)	58 (17%)	
1	454 (45%)	946 (51%)	128 (38%)	
2+	106 (11%)	367 (20%)	147 (44%)	
Missing	420	643	134	

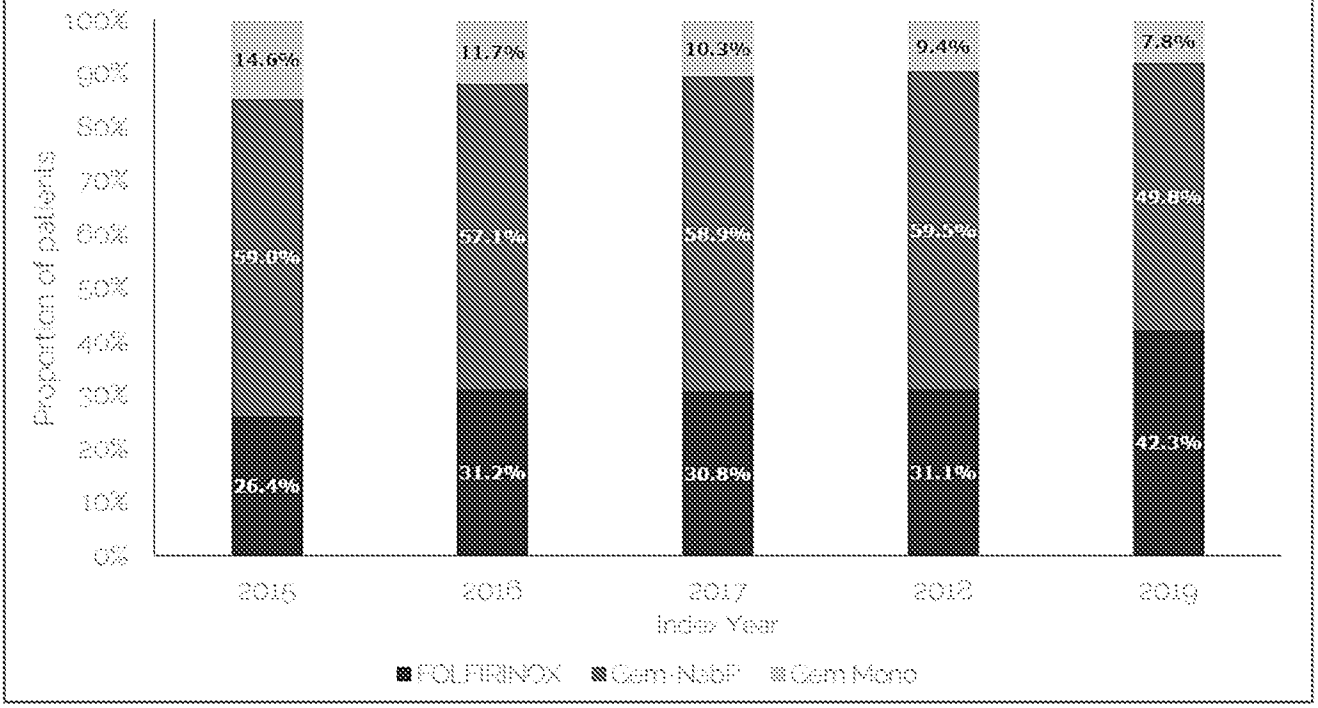
ECOG PS, Eastern Cooperative Oncology Group Performance Score
NOS, Not otherwise specified

RESULTS

Patient Characteristics

- 4,371 patients were included in the study, of whom 32.5% (n=1,420) received FFX, 56.8% (n=2,484) received gem-nabP, and 10.7% (n=467) received gem-mono in 1L
- The median age at treatment initiation was 64 years (IQR: 57 – 70), 70y (63 – 76), and 75y (67 – 80) for pts who received FFX, gem-nabP, and gem-mono, respectively ($p < 0.0001$) (Table 1)
- Gem-mono treated patients accounted for 14.6% of 1L patients treated with the 3 regimens in 2015 and for 7.8% of pts in 2019 (Figure 1)
- Among patients with non-missing ECOG PS, scores of 0-1 were reported for 89.4%, 80.1%, and 55.9% of patients who received FFX, gem-nabP, and gem-mono, respectively. ECOG PS of 2+ were reported for 10.6%, 19.9%, and 44.1% of patients treated with FFX, gem-nabP, and gem-mono, respectively ($p < 0.0001$)

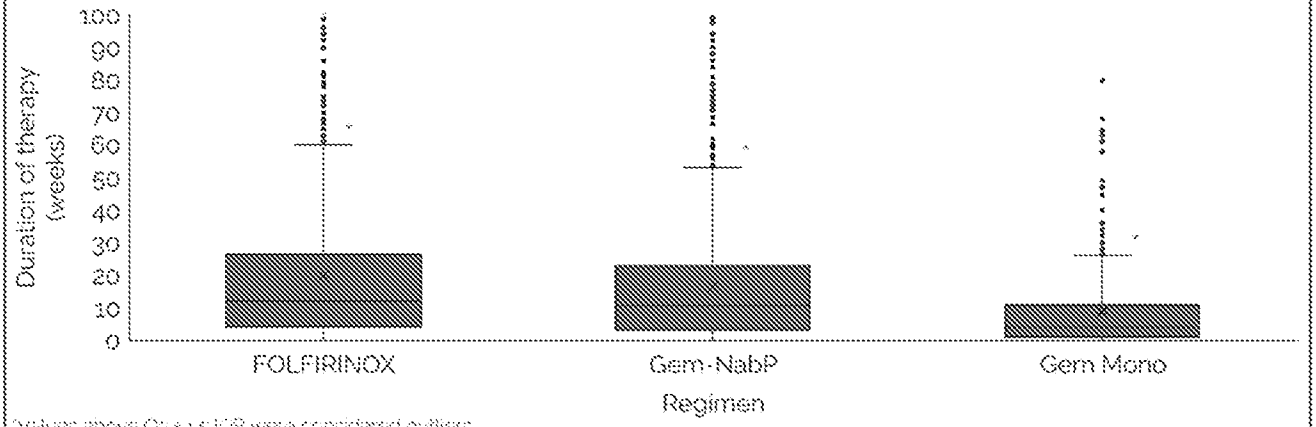
Figure 1. Regimens by year of index



Duration of Treatment

- Median DOT was 12.0 weeks (IQR: 4.1 – 26.5), 10.9 weeks (3.0 – 23.0), and 4.0 weeks (1.0 – 11.0) for patients who received FFX, gem-nabP, and gem mono, respectively ($p < 0.0001$) (Figure 2)

Figure 2. Duration of therapy by regimen

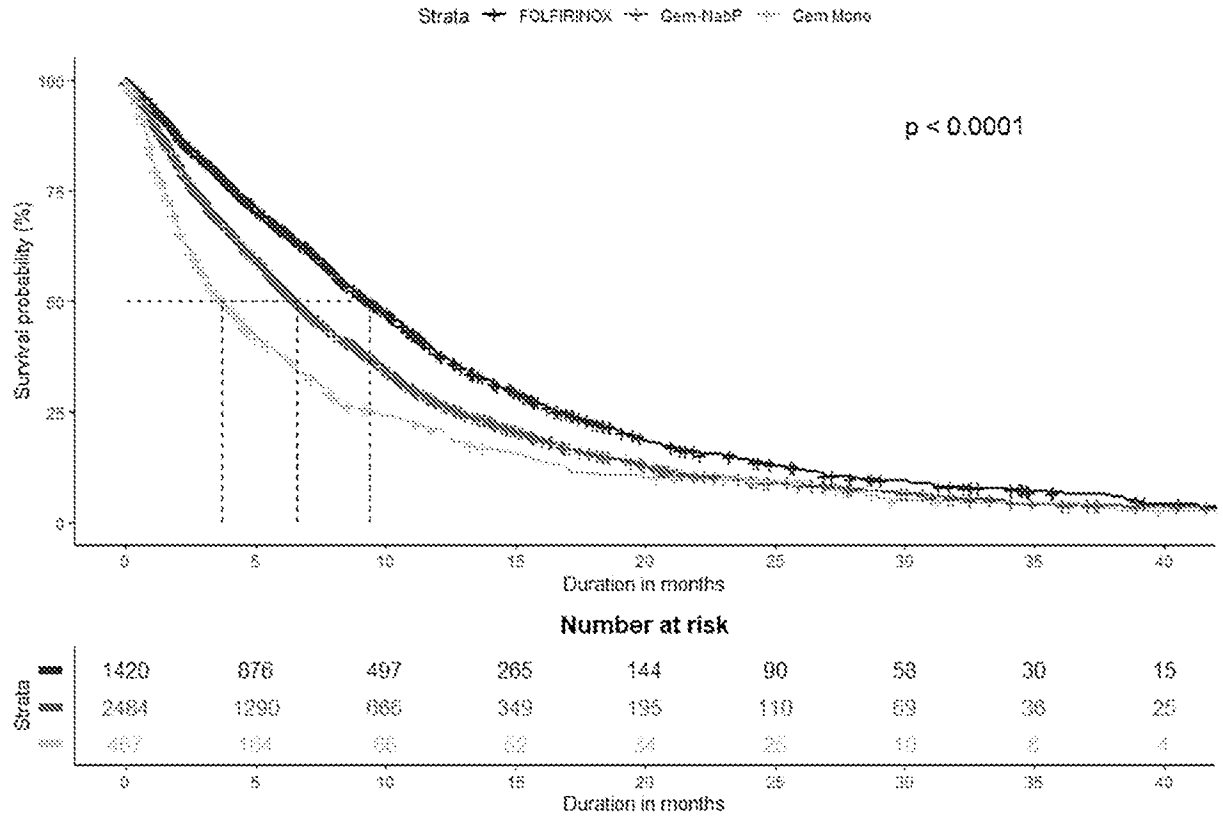


*Values above Q3 + 1.5 IQR were considered outliers

Overall Survival

- Median OS was 9.4 months (95% CI: 8.7 – 10.1), 6.6 months (95% CI: 6.2 – 7.0), and 3.7 months (95% CI: 3.2 – 4.5) for patients treated with FFX, gem-nabP, and gem mono, respectively ($p < 0.0001$) (Figure 3)

Figure 3. Overall Survival by Regimen



Conclusions

- Patients treated with gemcitabine monotherapy were older, had worse PS, and shorter DOT, and experience worse survival outcomes than patients treated with FOLFIRINOX or gem-nabP
- Further clinical pathway evaluation of gem monotherapy is suggested given the poorer outcomes observed in this study
- Larger patient cohort analyses will further elucidate real-world outcomes in patients treated with current NCCN Cat 1 regimens

Limitations

- EHR data are subject to possible entry errors and missing information which could have led to extreme or incorrect values
- Age was limited to 85 years and younger for de-identification reasons therefore the true age of the older patients of the population and true average age of the overall population is unknown
- There is no information available on physician or patient preference regarding 1L therapy choice and thus channeling bias may be present
- Survival estimates were not adjusted for prognostic factors

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Conflicts of Interest

GPV is on the speaker's bureau for Ipsen. PC is an employee of Ipsen. SA and AS are employees of Genesis Research, which receives funding from Ipsen.

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CT13

Impact of Treatment Sequence on Overall Survival in Metastatic Pancreatic Cancer Patients Treated with Liposomal Irinotecan in the Real-World Setting

George Kim[1], Andy Surinach[2], Frank A. Corvino[2], Paul Cockrum[3]
[1] George Washington University, Division of Hematology & Oncology, Washington, DC; [2] Genesis Research, Hoboken, NJ; [3] Ipsen, Cambridge, MA

BACKGROUND

- Pancreatic cancer was expected to account for 3.2% of all new cancer cases and 7.5% of all cancer deaths in the United States in 2019 making it the third deadliest cancer.[1]
- The expected 5-year survival of patients with metastatic pancreatic cancer is 2.9%.[1]
- There are limited treatment options for advanced and metastatic pancreatic adenocarcinoma (mPDAC)
- The NAPOLI-1 trial demonstrated improved survival outcomes for patients treated with liposomal irinotecan in combination with 5-fluorouracil and leucovorin and is approved for use in patients that have failed gemcitabine therapy[2]
- There is limited real-world evidence on the impact of treatment sequence on outcomes for patients with mPDAC treated with liposomal irinotecan

OBJECTIVE

- This study assessed clinical characteristics and overall survival in patients with mPDAC that received liposomal irinotecan in the third-line (3L) setting or beyond (3L+) following treatment with fluorouracil (5-FU) and gemcitabine-based treatment (Sequence 1), and patients who received liposomal irinotecan as second-line treatment following gemcitabine-based frontline treatment (Sequence 2).

METHODS

Study Design and Data Source

- An observational cohort analysis was performed using the Flatiron Health electronic health record-derived longitudinal database, a demographically and geographically diverse database derived from electronic health record (EHR) data. The database includes data from over 280 cancer clinics (~800 sites of care) representing more than 2.1 million US cancer patients available for analysis.[3]
- Patient-level data include structured and unstructured data, curated via technology-enabled abstraction.

- Data provided to third parties are de-identified and provisions are in place to prevent re-identification in order to protect patients' confidentiality

Selection Criteria

- This analysis identified adult (at least 18 years of age) patients with mPDAC treated with liposomal irinotecan between November 2015 and October 2018.
- Patients were included in the cohort if they were treated with liposomal irinotecan following a sequence gemcitabine and 5-FU based treatment, or vice versa, (Sequence 1) or liposomal irinotecan in the 2L setting following a gemcitabine-based treatment (Sequence 2). Lines of treatment were derived from structured medication administration and order data.
- Patients were excluded if their last activity date or date of death (imputed as the middle of the month) occurred before the start of liposomal irinotecan treatment

Measures and Statistical Analyses

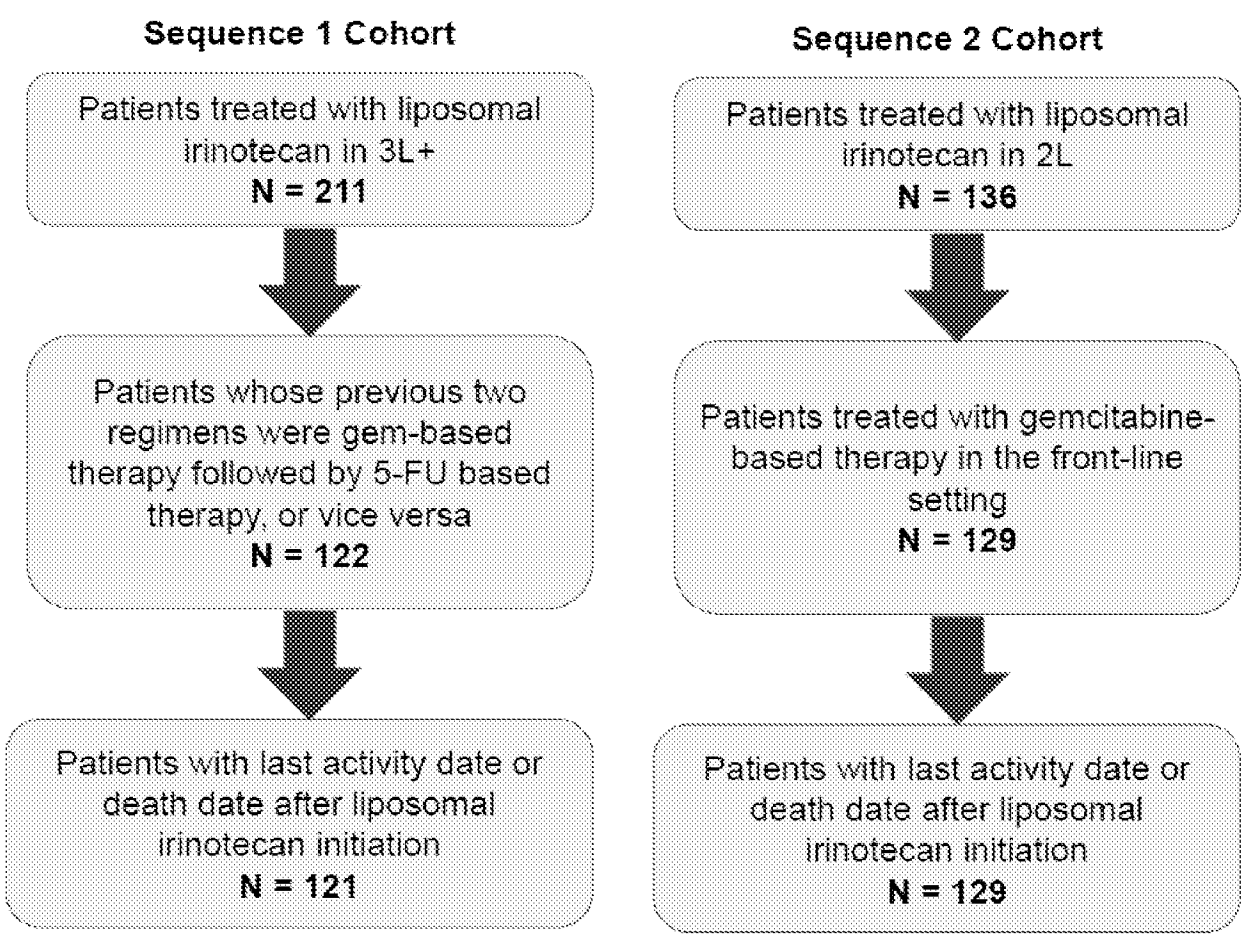
- Baseline demographic and clinical characteristics and overall survival (OS) from liposomal irinotecan initiation were determined.
- Kaplan-Meier methods were used to estimate OS (in months).
- Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Cohort attrition

- There were 121 patients treated with Sequence 1 (gemcitabine-based therapy ←→ 5-FU based therapy → liposomal irinotecan (3L+)) and 129 patients treated with Sequence 2 (gemcitabine-based treatment → liposomal irinotecan (2L)) that met the selection criteria **(Figure 1)**.

Figure 1: Cohort Attrition



Patient Characteristics

- Patients treated with Sequence 1 had a median age of 66y (IQR 60 – 73) at liposomal irinotecan initiation and patients treated with Sequence 2 were 72y (IQR 65 – 77) at initiation **(Table 1)**.
- 46.3% (N=56) of patients treated with Sequence 1 were male compared to 55.8% (N=72) of patients treated with Sequence 2.
- Most patients in both cohorts were White (>70%).

Table 1. Demographics and Clinical Characteristics

	Sequence 1	Sequence 2
Total Cohort	121 (100%)	129 (100%)
Age at Index		
65 and younger	57 (47.1%)	34 (26.4%)
66 and older	64 (52.9%)	95 (73.6%)
Age at index, median (IQR)	66 (60 - 73)	72 (65 - 77)
Male	56 (46.3%)	72 (55.8%)
BMI, median (IQR)	22.9 (20 - 25.9)	24.6 (21.6 - 27.6)
Stage at Initial Diagnosis		
Stage IV	67 (55.4%)	84 (65.1%)
Other	54 (44.6%)	45 (34.9%)
Race		
White	96 (79.3%)	95 (73.6%)
Other	25 (20.7%)	34 (26.4%)
Geographic Region		
Northeast	23 (19%)	19 (14.7%)
Midwest	15 (12.4%)	21 (16.3%)
South	52 (43%)	53 (41.1%)
West	18 (14.9%)	29 (22.5%)
Unknown	13 (10.7%)	7 (5.4%)
Tumor Location		
Head	67 (55.4%)	84 (65.1%)
Other	54 (44.6%)	45 (34.9%)
ECOG Score		
0	19 (15.7%)	20 (15.5%)
1	44 (36.4%)	48 (37.2%)
2+	19 (15.7%)	21 (16.3%)
Missing	39 (32.2%)	40 (31%)
Baseline Albumin		
<40 g/L	90 (74.4%)	95 (73.6%)
≥ 40g/L	23 (19%)	19 (14.7%)
Unknown	8 (6.6%)	15 (11.6%)
Prior Whipple procedure		
Yes	25 (20.7%)	19 (14.7%)
No	96 (79.3%)	110 (85.3%)

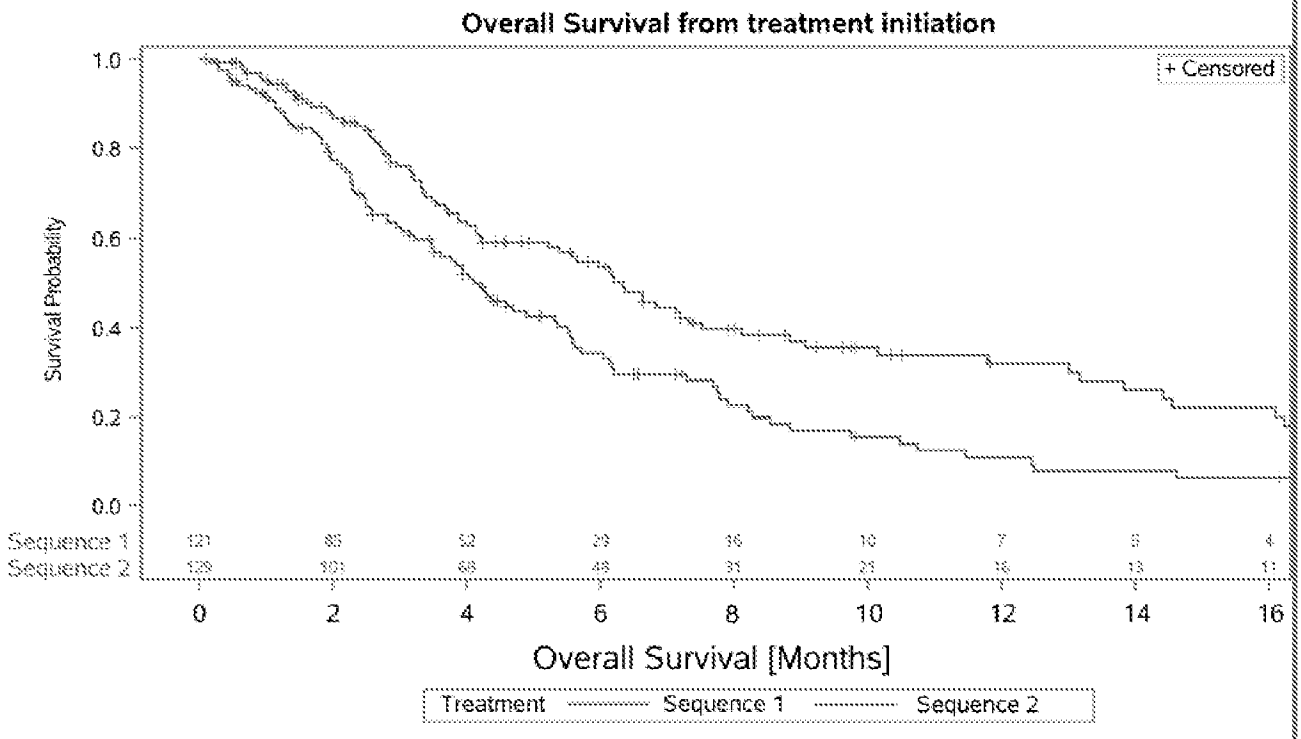
Clinical Characteristics

- 55.4% (N=67) of the patients treated with Sequence 1 were initially diagnosed with Stage IV pancreatic cancer compared to 65.1% (n=84) of patients treated with Sequence 2.
- ECOG scores were similar between the two cohorts; 52.1% (N=63) of patients treated with Sequence 1 had a score of 0-1 compared to 52.7% (N=68) of patients treated with Sequence 2
- Serum albumin prior to initiation liposomal irinotecan was similar for both cohorts with 74.4% of patients treated with Sequence 1 and 73.6% of patients treated with Sequence 2 with a serum albumin level <40g/L

Overall Survival

- Patients treated with Sequence 1 had a median OS of 4.1 months (95% CI 3.5 – 5.4) from liposomal irinotecan treatment initiation **(Figure 2)**.
- Patients treated with Sequence 2 had a median OS of 6.3 months (95% CI 4.2 – 7.5)
- Median OS for patients treated with Sequence 2 who subsequently received 3L treatment (N=30) was 13.2 months (95% CI 6.8 – 16.1) from liposomal irinotecan treatment initiation.

Figure 2: Overall Survival by Treatment Sequence



CONCLUSIONS

- This real-world analysis demonstrated similar results to a recent single center study conducted on liposomal irinotecan treated patients and the NAPOLI-1 trial.[2,4] As expected, patients treated with liposomal irinotecan in the 2L setting, post-gemcitabine, survived longer than those treated with liposomal irinotecan in 3L and after, post 5-FU and gem-based therapy. Further real-world studies are needed to understand the impact of liposomal irinotecan initiation timing among previously treated patients.

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Conflict of interest

GK received funding for consulting from Ipsen Biopharmaceuticals, Inc.
AS and FAC are employees of Genesis Research LLC.
PC is an employee of Ipsen Biopharmaceuticals, Inc., and holds stock or stock options.
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Presented at Hematology/Oncology Pharmacy Association (HOPA) Annual Conference| March 11-14, 2020 | Tampa, Florida

This study was sponsored by Ipsen

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CT13

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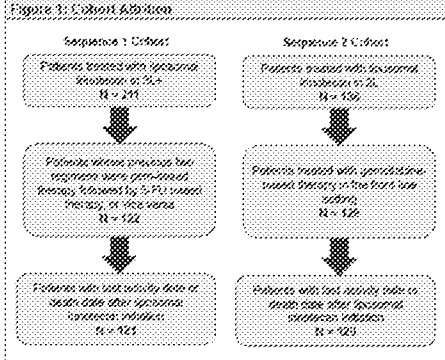

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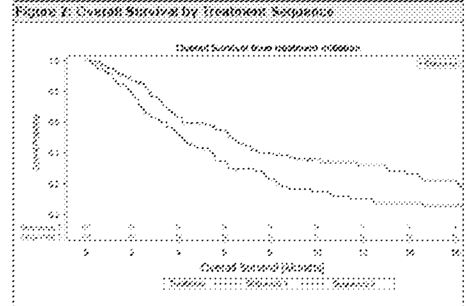

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References

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CLINICAL PATHWAY IMPLICATIONS AND REAL-WORLD CHARACTERISTICS AND OUTCOMES FOR PATIENTS WITH METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA (MPDAC) TREATED WITH FIRST LINE CATEGORY 1 NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) REGIMENS

Date
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Session
E-Poster Display

Presenters
George Kim

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More

Resources

Abstract 1564P

Background

FOLFIRINOX (FFX), gemcitabine plus nab-paclitaxel (gem-nabP), and gemcitabine monotherapy (gem mono) are included in select clinical pathways and listed as category 1 (cat 1) treatment recommendations by the NCCN guidelines for patients (pts) with mPDAC and good performance status (PS) in the first line (1L) setting. This study describes the patient characteristics and overall survival (OS) of 1L pts with mPDAC treated with NCCN cat 1 regimens in a real-world setting.

Methods

Data for pts diagnosed with mPDAC between 1-1-15 and 12-31-19, treated in 1L with FFX, gem-nabP, or gem mono were analyzed from the Flatiron Health EHR Database. Patient age and ECOG PS, and duration of treatment (DOT) were described. Median OS from treatment initiation was derived using Kaplan-Meier analysis.

Results

Of the 4,371 pts identified, 32.5% (n=1,420) received FFX, 56.8% (n=2,484) received gem-nabP, and 10.7% (n=467) received gem mono in 1L. The median age at treatment initiation was 64 years (IQR: 57 – 70), 70y (63 – 76), and 75y (67 – 80) for pts who received FFX, gem-nabP, and gem-mono, respectively (p < 0.0001). Gem mono treated pts accounted for 14.6% of 1L pts treated with the 3 regimens in 2015 and for 7.8% of pts in 2019. ECOG PS of 0-1 were reported for 63.0%, 59.3%, and 39.8% of pts who received FFX, gem-nabP, and gem mono, respectively; ECOG PS of 2+ were reported for 7.5%, 14.8%, and 31.5% of pts treated with FFX, gem-nabP, and gem mono, respectively (p < 0.0001). Median DOT was 12.0 weeks (IQR: 4.1 – 26.5), 10.9 wks (3.9 – 23.0), and 4.0 wks (1.0 – 11.0) for pts who received FFX, gem-nabP, and gem mono, respectively (p < 0.0001). Median OS was 9.4 months (95% CI: 8.7 – 10.1), 6.6 mos (95% CI: 6.2 – 7.0), and 3.7 mos (95% CI: 3.2 – 4.5) for pts treated with FFX, gem-nabP, and gem mono, respectively (p <0.0001).

Conclusions

regimens. Further clinical pathway evaluation of gem mono is suggested.

Clinical trial identification

Editorial acknowledgement

Legal entity responsible for the study

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Disclosure

G. Kim: Speaker Bureau/Expert testimony: Ipsen. P. Cockrum: Shareholder/Stockholder/Stock options, Full/Part-time employment: Ipsen. S. Arndorfer: Advisory/Consultancy, Work for Genesis Research which receives funding from Ipsen: Ipsen. A. Surinach: Advisory/Consultancy, Work for Genesis Research which receives funding from Ipsen: Ipsen.

GASTROINTESTINAL CANCER—GASTROESOPHAGEAL, PANCREATIC, AND HEPATOBILIARY

Real-world use of liposomal irinotecan-based regimens among patients (pts) with metastatic pancreatic adenocarcinoma (mPDAC) in the United States (U.S.).

George P. Kim, Paul Cockrum, Andy Surinach, Jim M. Koeller

Show More

Abstract Disclosures

Abstract

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Background: The goals of randomized control trials (RCTs) are to make causal inferences and precise treatment comparisons, not to describe large heterogeneous pt populations. RWE allows population-based healthcare decision makers to assess and manage therapeutic and economic options for their pts, including those who would and would not have met inclusion/exclusion criteria of a given RCT and are instead managed under usual care, irrespective of clinical trial protocols. In the pivotal phase 3 trial, NAPOLI-1, 117 pts were treated with liposomal irinotecan + 5-fluorouracil/folinic acid, median age 63 years; 66% were treated first- (1L) or second line (2L), and 91% had performance score ECOG 0 or 1. Pts in the trial had overall survival (OS) of 6.2 months (mos), time to treatment failure (TTF) 2.3 mos, and 27% experienced grades 3-4 neutropenia. The present study describes the patient characteristics and outcomes of pts with mPDAC treated with liposomal irinotecan in the US. **Methods:** This retrospective observational study used data from Flatiron Health EHR-derived de-identified database from over 280 cancer clinics. Patient characteristics, OS, TTF, and rates of neutropenia during treatment (tx) were assessed in adult pts diagnosed with mPDAC who received liposomal irinotecan based tx between November 1, 2015 and October 31, 2019. **Results:** 600 pts with mPDAC treated with a liposomal irinotecan based regimen were identified. Of these, 56% were initially diagnosed with stage IV disease, 53% were male, 21% had undergone a previous Whipple procedure, and 61% initiated liposomal irinotecan in the 1L or 2L metastatic setting. Median age at tx initiation was 68 (IQR: 62 – 75) years. 92% of pts were treated in the community setting. Among pts with available ECOG (n = 440), 77.5% were score 0-1. Grade 3/4 neutropenia was observed in 11% (n = 66)

Overall, median OS was 5.0 mos [95%CI: 4.2–5.6]. mOS among pts treated in 1L (n = 88), 2L (n = 280), and third line plus (3L+, n = 232) were 6.9 mos [5.3–9.2], 5.4 mos [4.6–6.4], and 4.0 mos [3.4–4.5], respectively. Overall, median TTF was 1.9 mos [1.6–2.1]. TTF by line was 3.5 mos [2.3–4.8] in 1L, 2.1 mos [1.7–2.8] in 2L, and 1.4 mos [1.2–1.6] in 3L. **Conclusions:** This real-world cohort of pts with mPDAC were older, had worse performance status, and had more prior lines compared to the pivotal trial for liposomal irinotecan. Median OS, TTF, and neutropenia were similar to those previously reported. As expected, pts receiving liposomal irinotecan in earlier lines had higher median OS and TTF.

Research Sponsor:

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Phase II study of palliative S-1 in combination with cisplatin as second-line chemotherapy for gemcitabine-refractory pancreatic cancer patients

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Abstract. In this study, we examined the efficacy and toxicity of S-1 with cisplatin as a second-line palliative chemotherapy for gemcitabine-refractory pancreatic cancer patients. Patients who had been previously treated with gemcitabine-based chemotherapy as palliative first-line chemotherapy received S-1/cisplatin [body surface area (BSA) <1.25 m^2, S-1 40 mg/day; BSA ≤1.25 to <1.5 m^2, 50 mg/day; BSA ≥1.5 m^2 60 mg/day, orally, bid, daily on days 1-14 followed by a 7-day washout and cisplatin 60 mg/m^2/day intravenously on day 1] every three weeks. The enrollment of 32 patients was planned, but the study was terminated early, prior to the first stage, following the enrollment of 11 patients. The median age of the patients was 56 (range, 42-74) years. Nine patients had a performance status (PS) of one. In total, there were 21 chemotherapy cycles and the median treatment duration was 21 (range, 7-96) days. Of the 11 patients, five could not be evaluated due to discontinuation prior to the response evaluation. One of the six evaluable patients achieved stable disease (9.1% in intention to treat analysis and 16.7% in per-protocol analysis), while five had progressive disease. Grade 3-4 hematological toxicities were anemia in one, neutropenia in one and thrombocytopenia in one cycle. Grade 3-4 nonhematological toxicities were fatigue in three, nausea in four, anorexia in two, diarrhea in one and peripheral neuropathy in two cycles. With a median follow-up period of 8.9 (range, 3.2-11.3) months, the median time to progression was 44 days [95% confidence interval (CI) 25.4-62.6] and the median overall survival was 81 days (95% CI 9.3-152.7). Combination chemotherapy with S-1 and cisplatin as applied in this study did not result in promising antitumor activity, a high degree of toxicity and poor compliance.

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Key words: pancreatic cancer, S-1, cisplatin, gemcitabine-refractory

Introduction

The prognosis of patients with advanced pancreatic carcinoma is extremely poor despite numerous trials with palliative chemotherapy or radiotherapy. Systemic chemotherapy with gemcitabine has been the standard chemotherapy for advanced pancreatic cancer since the mid-1990s (1). However, there is no standard second-line chemotherapeutic drug in cases refractory to or recurring following gemcitabine therapy. The median survival rate with best supportive care in patients who have failed gemcitabine therapy is approximately two months (2,3). Approximately half of patients with gemcitabine-pretreated disease may be candidates for further treatment. Data supporting the use of second-line therapy compared with best supportive care are lacking. Although there have been reports of clinical trials of second-line therapy in advanced pancreatic cancer, most of these have been published in abstract form with a small number of patients. Therefore, there is a continuing need for clinical trials with a new agent for advanced pancreatic cancer in cases of gemcitabine failure.

S-1 is a fourth-generation oral fluoropyrimidine that has been reported to be active with tolerable toxicity against gemcitabine-refractory pancreatic cancer (4-6) and chemotherapy-naïve pancreatic cancer (7,8), although most of the studies have been case reports or retrospective studies. The superior effect of combination therapy with cisplatin compared with 5-fluorouracil (5-FU) monotherapy has been

demonstrated in advanced pancreatic cancer (9,10). Thus, we conducted the present phase II study to investigate the feasibility and efficacy of S-1 in combination with cisplatin as palliative chemotherapy for gemcitabine-refractory advanced pancreatic cancer patients.

Patients and methods

Ethics. This was a prospective multicenter study. All patients provided written informed consent. In total, three centers participated. This study was approved by the Institutional Review Board (IRB) of each center and was conducted in accordance with the Declaration of Helsinki.

Patients. The inclusion criteria for this study were: i) histologically or cytologically proven pancreatic adenocarcinoma and unresectable locally advanced or metastatic disease; ii) at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) (11); iii) prior chemotherapy with gemcitabine-based palliative chemotherapy; iv) the ability to take oral medications; v) age, >18 years; vi) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2; vii) adequate bone marrow function (white blood cell count $\geq$4,000/mm^3, neutrophil count $\geq$2,000/mm^3 and platelet count $\geq$100,000/mm^3); viii) adequate renal function [serum creatinine level $\leq$1.5 mg/dl or creatinine clearance level (Ccr) $\geq$50 ml/min]; ix) adequate liver function [total bilirubin $\leq$3x UNL (if due to underlying liver metastasis, then total bilirubin may be $\leq$5x UNL); aspartate transaminase (AST) and/or alanine transaminase (ALT) $\leq$2.5x UNL (if liver function abnormalities were due to underlying liver metastasis, then AST and/or ALT may be $\leq$5x UNL)].

The exclusion criteria for this study were patients who: i) had received chemotherapy or radiotherapy within 3 weeks; ii) had previously received an oral fluoropyrimidine; iii) had central nervous system metastases; iv) had an active infection or uncontrolled concurrent medical illness; v) had a history of other malignancies; vi) were pregnant or lactating; vii) had severe neurological impairment, a mental disorder or any severe drug-induced allergy.

Treatment protocol. S-1 [body surface area (BSA) <1.25 m^2, 40 mg; BSA $\geq$1.25 to <1.5 m^2, 50 mg; BSA $\geq$1.5 m^2, 60 mg] was administered orally twice daily, following breakfast and dinner, for 14 consecutive days, followed by seven days of rest. Cisplatin (60 mg/m^2) was administered as a 60-min intravenous infusion on day 1 with adequate hydration. The treatment courses were repeated every three weeks. Antiemetic prophylaxis, including aprepitant, a 5-HT3 antagonist and dexamethasone, was used. Prophylactic myeloid growth factors were not administered prior to the first cycle.

Dose modification. Modifications to the S-1 or cisplatin dose were made in patients who had any of the following: a leukocyte count <1.0x10^3/μl, a neutrophil count <500/μl, a platelet count <2.5x10^4/μl, grade 3-4 febrile neutropenia or grade 3-4 non-hematological toxicity, based on the most severe grade of toxicity that had occurred during the previous cycle. Treatment was delayed for up to three weeks in patients with persistent symptomatic toxicity, absolute neutrophil counts <1,500/μl or platelet counts <100,000/μl. The dose of S-1 was decreased in a stepwise manner by up to two levels as follows: BSA <1.25 m^2, from 40 to 25 and 20 mg/dose; BSA $\geq$1.25 to <1.5 m^2, from 50 to 40 and 25 mg/dose; BSA $\geq$1.5 m^2, from 60 to 50 and 40 mg/dose. Additionally, the dose of cisplatin was decreased according to the serum Ccr as follows: Ccr $\geq$60 ml/min, no reduction; Ccr >40 ml/min to <60 ml/min, reduced to 30 mg/m^2; Ccr <40 ml/min, administration of cisplatin was stopped. Treatment was continued until signs of disease progression or unacceptable toxic effects developed or until a patient refused further treatment.

Pretreatment evaluation. Baseline laboratory analyses [blood cell count, serum creatinine, bilirubin, AST, ALT, alkaline phosphatase, lactic dehydrogenase and carbohydrate antigen (CA) 19-9] were performed within one week of starting the first cycle of therapy and tumor status was assessed using computed tomography (CT) within 4 weeks.

Assessment of efficacy and toxicity. Tumor assessments, using CT of the lesions, abdomen, pelvis and/or chest, were performed at baseline and repeated every 3 cycles using RECIST (11). The tumor marker CA 19-9 was checked every three cycles. A physical examination, including weight and toxicity assessments, ECOG performance status, complete blood count and blood chemistry, was performed prior to each cycle. Toxicity was graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 3.0. Treatment-related mortality (TRM) was defined as mortality that occurred within 30 days of treatment initiation.

Statistical analysis. The primary endpoint was response rate and the secondary endpoints were safety, time to progression (TTP), disease control rate and overall survival (OS). The sample size in this trial was calculated to reject a 5% response rate in favor of a target response rate of 20% with a significance level of 0.05 and a power of 80%, using Simon's optimal two-stage design. In the initial stage, in total, 10 evaluable patients were to be entered and evaluated for a response. If there was no response, accrual was to be terminated. If any response was observed in the first stage, then 19 additional patients were to be entered in the second stage, to achieve a target sample size of 29 evaluable patients. Further assessment of the regimen was thought to be necessary if more than three responses were observed in the 29 patients. Considering a withdrawal rate of 10%, the total target number was calculated to be 32 patients.

Assessment of the response rate was performed using the intention to treat (ITT) and per-protocol (PP) analyses. TTP and OS were calculated using the Kaplan-Meier method. Survival curves were compared using the log-rank test. Tests were two sided and $p<0.05$ was considered to indicate a statistically significant result. TTP was calculated from the date therapy was initiated to the date of disease progression, mortality or final follow-up. OS was calculated from the date therapy was initiated to the date of mortality or final follow-up.

Results

Patient characteristics. Between October 2009 and June 2010, in the stage I analysis, 11 patients were enrolled in this

Table I. Patient characteristics (n=11).

Characteristics	No.	%
Gender		
Male	7	63.6
Female	4	36.4
Age, years		
Median (range)	56 (42-74)	
Performance status (ECOG)		
0-1	9	81.8
2	2	18.2
CA 19-9 level		
Within normal range	5	45.5
>Normal	6	54.5
Location of primary tumor		
Head	6	54.5
Body	2	18.2
Tail	3	27.3
Disease status		
Locally advanced	2	18.2
Distant metastases	9	81.8
Sites of distant metastases		
Liver	7	-
Lymph node	3	-
Lung	5	-

ECOG, Eastern Cooperative Oncology Group; CA, carbohydrate antigen.

Table II. Response rate of S-1 and cisplatin for gemcitabine-refractory pancreatic cancer.

	No. of patients (n=11)	ITT analysis (%)	PP analysis (%)
Complete response	0	0	0
Partial response	0	0	0
Stable disease	1	9.1	16.7
Not evaluated	5	-	-
Response rate	0	0	0
Disease control rate	1	9.1	16.7

ITT, intention to treat; PP, per-protocol.

prospective study. The median age of the patients was 56 (range, 42-74) years. The male:female ratio was 7:4. Of the 11 patients, nine had a PS of one and two had a PS of two when enrolled. There were six (54.5%) cases of primary tumors in the head, two (18.2%) cases in the body and three (27.3%) in the tail portion of the pancreas. Of the 11 patients, nine (81.8%) had distant metastases, while the remaining two (18.2%) had locally advanced disease. Six (54.5%) patients had elevated CA 19-9 levels when enrolled (Table I).

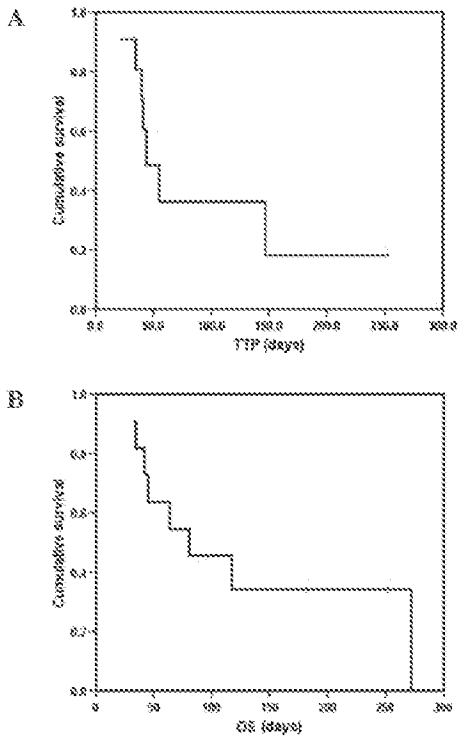

Figure 1. Kaplan-Meier curves for (A) the time to prognosis (TTP) and (B) overall survival (OS).

Delivery of drugs. In total, 21 cycles of therapy were administered, with a median of 1.5 (range, 1-5) cycles per patient and a median treatment duration of 21 (range, 7-96) days. The average relative dose intensities of S-1 and cisplatin were 0.98 and 0.91, respectively. Dose reduction for S-1 was required in one patient (two cycles) due to non-hematological toxicity, including diarrhea and fatigue. Dose reduction for cisplatin was required in two patients (three cycles) due to nausea and vomiting in one case (two cycles) and peripheral neuropathy in the other case (one cycle).

Tumor responses. Of the 11 patients enrolled in this study, six were evaluable in terms of treatment response. Five patients could not be evaluated for the following reasons: three withdrew consent due to therapy-related toxicities and worsening of their general condition and two died prior to the response evaluation. None of the six evaluable patients achieved a complete or partial response. Only one patient (9.1% by ITT analysis and 16.7% by PP analysis) achieved stable disease and five had progressive disease (Table II).

Survival (TTP and OS). The patients were evaluable for the survival analysis. With a median follow-up of 8.9 (range, 3.2-11.3) months, the median TTP was 44 days [95% confidence interval (CI) 25.4-62.6] and the median OS was 81 days (95% CI 9.3-152.7). Kaplan-Meier curves for TTP and OS are shown in Fig. 1.

Toxicities. Grade 3-4 hematological toxicities included anemia in one cycle, neutropenia in one cycle and thrombocytopenia in one cycle. Grade 3-4 non-hematological toxicities included

Table III. Adverse effects of S-1 and cisplatin for gemcitabine-refractory pancreatic cancer.

NCI-CTC Grade 3-4 toxicities	Per cycle no. (%) n=21	Per patient no. (%) n=21
Hematologic toxicity		
Neutropenia	1 (4.8)	1 (9.1)
Anemia	1 (4.8)	1 (9.1)
Thrombocytopenia	1 (4.8)	1 (9.1)
Non-hematologic toxicity		
Nausea	4 (19.0)	3 (27.3)
Vomiting	1 (4.8)	1 (9.1)
Diarrhea	1 (4.8)	1 (9.1)
Fatigue	3 (14.3)	3 (27.3)
Anorexia	2 (9.5)	2 (18.2)
Peripheral neuropathy	2 (9.5)	1 (9.1)

NCI-CTC, National Cancer Institute Common Toxicity Criteria.

fatigue in three cycles, nausea in four cycles, anorexia in two cycles, diarrhea in one cycle and peripheral neuropathy in two cycles (one patient). There were two TRMs. The cause of mortality in the first case was septic shock associated with grade 3 neutropenia following the first cycle; in the second case, the patient died suddenly without documented cause following the second cycle. These toxicities are shown in Table III. This study was terminated early, prior to the first stage, without reaching 10 response-evaluable patients due to severe toxicity, including TRM, and poor compliance, by agreement of the investigators and the IRB.

Discusssion

Pancreatic cancer is the fourth most common cause of cancer-related mortality in the US (12). In Korea, the incidence of this disease has increased. In 2009, the disease ranked 9th in incidence in Korea according to an annual report of cancer statistics; for cancer-related mortality, the disease ranked 5th (5.8% of the total). The prognosis of locally unresectable or metastatic pancreatic cancer remains extremely poor. Gemcitabine monotherapy or gemcitabine-based combination therapy, according to PS, has been the standard systemic therapy for advanced pancreatic cancer. FOLFIRINOX has been recommended as a first-line therapy with gemcitabine monotherapy or a gemcitabine-containing double regimen, based on a published phase III trial in which patients with metastatic pancreatic cancer showed marked improvements in median progression-free survival (PFS) (6.4 vs. 3.4 months; p<0.0001) and median OS (10.5 vs. 6.9 months; p<0.001) (13).

While first-line therapy has been established in advanced pancreatic cancer, there is no consensus with regards to a second-line therapy for advanced pancreatic cancer, particularly in gemcitabine-refractory cancer. It is difficult to conduct a clinical trial for second-line chemotherapy in advanced pancreatic cancer due to the rapidly progressive nature of the general condition and the lack of agents active in pancreatic cancer. However, it has been reported that 55-60% of patients had a relatively good PS following the failure of first-line therapy; thus, physicians should consider second-line therapy in such patients (14).

The results of previous studies concerning oxaliplatin (15), ralitrexed (16), paclitaxel (17) and pemetrexed (18) monotherapies in the second-line treatment of pancreatic cancer have revealed modest antitumor effects with no survival benefit. Studies have also reported combination chemotherapeutic regimens as second-line therapies for advanced pancreatic cancer. A representative study of second-line chemotherapy in pancreatic cancer is the CONKO-003 trial. In a preliminary report from the CONKO-003 trial, the use of second-line chemotherapy was compared with best supportive care (2). The study revealed the benefit of combination therapy with oxaliplatin, 5-FU and leucovorin as a second-line therapy compared with 5-FU and leucovorin (19). There have been other studies concerning combination chemotherapy for second-line therapy in pancreatic cancer with biological agents. However, the results are generally modest and preliminary (20,21).

S-1, an oral agent, consists of a mixture of tegafur, 5-chloro-2,4-dihydroxypyridine and potassium oxonate at a molar ratio of 1:0.4:1. The antitumor effect of S-1 in advanced pancreatic cancer as a first- or second-line therapy has been reported in Japan (8,22-24). Generally, the antitumor effect was promising and the toxicity was tolerable in these studies. In view of the favorable toxicity profile of S-1 monotherapy, its combination with other agents may improve therapeutic results.

The addition of cisplatin offers the possibility of a synergistic antitumor effect, beyond that observed with S-1 monotherapy. Cisplatin combined with 5-FU appears to be promising in metastatic pancreatic carcinoma, with a 26% response rate and a median survival rate of 7 months in a phase II trial (10). In a randomized trial comparing 5-FU with 5-FU plus cisplatin, FU-cisplatin was found to be superior to FU in terms of response and PFS, but not OS (9,10). The combination of S-1 and cisplatin has also been adopted in advanced gastric cancer, based on previous studies which revealed that combination therapy with S-1 and cisplatin had promising effects with tolerable toxicity (25,26).

Although this study was conducted based on published data similar to those above, the results were disappointing compared with those of previous studies concerning monotherapy in advanced pancreatic cancer as a second-line therapy. The cause of the poor response and poor compliance may have been the rapid worsening of the general condition of the patients. In contrast to our results, Togawa *et al* (27) revealed that S-1 with cisplatin had promising effects in patients who failed postoperative gemcitabine treatment for pancreatic cancer. In that study, the dose of cisplatin was 40 mg/m^2 and it was administered on day 8 every five weeks, to avoid the severe toxicity of cisplatin. Additionally, the group of patients had relapsed following postoperative gemcitabine treatment, unlike our patients who failed first-line palliative chemotherapy containing gemcitabine. These patients may have had a relatively good PS and maintained a good general condition relatively longer than those in our group. Additionally, in their group, there was no patient with previous exposure to cisplatin, unlike our group. These factors may explain the differences between our results and those of Togawa *et al* (27).

In this study, one patient achieved stable disease. However, this patient experienced severe adverse events, including anorexia and nausea, and ultimately did not undergo more than 5 cycles. In the present study, we observed several types of hematological and non-hematological severe adverse events, including anorexia, nausea, fatigue, peripheral neuropathy and cytopenia. These adverse events resulted in poor compliance. Two patients had moderate toxicities, including nausea and anorexia; however, even these patients were reluctant to undergo further chemotherapy. The general fragility of the patients may have contributed to their poor compliance.

We also observed TRM in two patients. One experienced sepsis with severe neutropenia following the first cycle. Another patient succumbed to the disease suddenly following the second cycle, complaining of abdominal pain. The cause of mortality was not certain, but a thromboembolic event may have been the cause. These adverse events resulted in the discontinuation of the second-line therapy in these vulnerable patients. This issue should be considered in designing future clinical studies of advanced pancreatic cancer patients.

In the present study, we observed that the advanced pancreatic cancer patients progressed rapidly and that the general condition of the patients often deteriorated rapidly to perform additional chemotherapy cycles. Thus, prospective studies of palliative second-line therapy in patients with pancreatic cancer using combinations of novel or biological agents should consider the expectation for the worsening of the PS of the patients. Additionally, patients with good prognostic factors, as suggested by Nakachi *et al* (3), including a good PS, lower serum C-reactive protein levels and no peritoneal dissemination, should be considered as initial candidates for second-line chemotherapy in advanced pancreatic cancer.

In conclusion, this prospective combination chemotherapy study of S-1 and cisplatin did not demonstrate promising antitumor activity. Additionally, moderate toxicity profiles, with two cases of TRM, and poor compliance were observed in patients with advanced pancreatic cancer. In future studies, dose and schedule modification, as well as patient selection, are necessary for the precise evaluation of the effects of S-1 plus cisplatin on pancreatic cancer.

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ORIGINAL ARTICLE

Phase II study of 5-fluorouracil and paclitaxel in patients with gemcitabine-refractory pancreatic cancer

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Abstract
Purpose There is no effective salvage regimen for failed gemcitabine-based chemotherapy. This study evaluated the efficacy and toxicity of 5-fluorouracil and paclitaxel in patients with gemcitabine-refractory pancreatic cancer.
Methods Between January 2004 and December 2007, 28 patients with pancreatic cancer previously treated with gemcitabine-based chemotherapy were enrolled. 5-Fluorouracil 1,000 mg/m^2 was infused (days 1, 2, and 3) and paclitaxel 175 mg/m^2 (day 1) was administered every 4 weeks. The primary endpoint of this study was efficacy and toxicity and the secondary endpoint was time to progression and overall survival.
Results A total of 75 cycles were given, for a mean of 2.68 cycles per patient. The response could be evaluated in 20 patients. Two patients (10%) obtained a partial response, and four patients (20%) had stable disease. The median time to progression and overall survival was 2.5 and 7.6 months, respectively.

Grade 3/4 hematological toxicity included neutropenia in six patients (21.4%), anemia in one (3.6%), and thrombocytopenia in one (3.6%). One (3.6%) patient experienced grade 4 neuropathy, and two (7.2%) patients experienced grade 3 diarrhea.

Conclusion The 5-fluorouracil and paclitaxel combination treatment seems to be effective in patients with advanced pancreatic cancer that did not respond to a gemcitabine-based regimen.

Keywords Pancreatic cancer · Paclitaxel · 5-Fluorouracil · Gemcitabine

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Introduction

Pancreatic cancer is the fourth most common cause of cancer-related death in Western countries [8] and the sixth most common cause in Korea [11]. Gemcitabine is the gold-standard chemotherapy agent for advanced pancreatic cancer, although it confers only a modest progression-free survival benefit. Almost all pancreatic cancer progresses with gemcitabine-based chemotherapy. Second-line chemotherapy after gemcitabine is needed for about half of the patients, who maintain a good performance status and can tolerate another chemotherapy treatment. However, only a few phase II trials have examined second-line chemotherapy for pancreatic cancer. The survival advantage of second-line chemotherapy in pancreatic cancer has not been proven, and an optimal second-line chemotherapeutic regimen after gemcitabine failure remains to be defined. We clearly need to find better agents or more appropriate drug combinations to improve treatment efficacy and survival in gemcitabine-refractory pancreatic cancer.

Before the gemcitabine era, 5-fluorouracil (5-FU)-based chemotherapeutic regimens were the standard first-line chemotherapy treatments in advanced pancreatic cancer [5, 13, 18]. Even now, 5-FU is used as a second-line chemotherapeutic regimen in gemcitabine-refractory pancreatic cancer, conferring a modest improvement in patient survival

[14, 22]. Paclitaxel is a semi-synthetic taxane with clinical activity in solid tumors. Paclitaxel has been used as a radiosensitizer in pancreatic cancer [19, 20]. In addition, paclitaxel was reported to be an effective second-line chemotherapy in pancreatic cancer [17]. Therefore, it is reasonable to predict that a regimen of 5-FU and paclitaxel may provide some benefit for patients with gemcitabine-refractory pancreatic cancer.

This study evaluated the efficacy and toxicity of a combined 5-FU and paclitaxel regimen in patients with gemcitabine-refractory pancreatic cancer.

Patients and methods

Eligibility criteria

Patients with histologically confirmed locally advanced or metastatic pancreatic cancer who failed to respond to a gemcitabine-based regimen were eligible for enrollment in this study. The other eligibility criteria included were 18 years of age or older, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, adequate bone marrow function (absolute granulocyte count $\geq$1,500/μL, platelet count $\geq$100,000/μL), and adequate renal and hepatic function (serum creatinine level <1.5 mg/dL, serum bilirubin level <1.5 mg/dL, transaminases < twice the upper limit of normal). Patients with any of the following were excluded: non-measurable lesion; history of other malignancy; concurrent insufficiently treated disease such as heart, hepatic, or renal failure; uncontrolled infection; presence of a psychological disorder; pre-existing chemotherapeutic drugs-related toxicities; and pregnancy. This study was approved by the Institutional Review Board of Severance Hospital. We fully informed all patients about the nature and purpose of the study and all patients gave written informed consent.

Treatment schedule

5-Fluorouracil was infused at a dose of 1,000 mg/m^2 as a 24-h continuous infusion (days 1, 2, and 3) and paclitaxel 175 mg/m^2 was administered (day 1). The chemotherapy was repeated every 28 days until disease progression or unacceptable toxicity occurred. The dose of the chemotherapeutic agents was reduced by 25% in cases of World Health Organization (WHO) grade 4 febrile neutropenia, thrombocytopenia, or any WHO grade 3 organ toxicity. The chemotherapy was delayed 2 weeks in patients who did not recover from the toxicity sooner. When WHO grade 4 toxicity or recurrent grade 3 toxicity occurred despite the dose adjustment or when more than 2 weeks were needed for the recovery from toxicity, the treatment was stopped.

Response and toxicity assessments

A medical history, physical examination, complete blood cell count, biochemical profile, CA19-9, chest X-ray, and computed tomography (CT) of the abdomen were obtained before the first chemotherapy session. During treatment, a complete blood cell count and biochemical profile were obtained before and 2 weeks after chemotherapy. Patients were assessed for responses using CT at every two cycles of chemotherapy. Complete remission (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) [21]. Survival time was defined as the time from the first day of treatment until the date of death. Time to progression was defined as the time from the first day of treatment until disease progression or death. Adverse events were graded according to the WHO criteria [15]. When multiple toxicities were observed, the dose was adjusted based on the most severe toxic event. All patients completing at least one cycle of chemotherapy were evaluated for toxicity.

Statistical methods

The overall survival, time to progression, and response duration were analyzed using the Kaplan–Meier product limit method and a linear interpolation for the point estimate of the median. The statistical analyses were performed using SPSS version 11 for Windows (SPSS, Chicago, IL, USA).

Results

Between January 2004 and December 2007, 28 patients (20 males and 8 females) were enrolled in this study. The patient characteristics are shown in Table 1. The mean patient age was 59.6 years. Gemcitabine plus cisplatin was the most common regimen before the study (Table 2). Three patients had been treated with more than one regimen. The median time from initial diagnosis to paclitaxel plus 5-FU chemotherapy was 7.54 months.

A total of 75 cycles of the 5-FU and paclitaxel regimen were given, with a mean of 2.68 cycles per patient. One patient completed eight cycles of chemotherapy, and three patients completed six cycles. Seven patients underwent only one cycle of chemotherapy. One patient required a 25% dose reduction of paclitaxel owing to general weakness. The dose intensities delivered to the patients are listed in Table 3. The causes of not being able to complete the scheduled chemotherapy were disease progression (13/27, 48.1%), chemotherapy-induced toxicity (2/27, 7.4%, one of grade 4 neutropenia combined with bacterial pneumonia

Table 1 Patient characteristics

Characteristic	No. of patients (%)
Gender	
Male	20 (71.4)
Female	8 (28.6)
Age (years, mean ± standard deviation)	59.6 ± 9.6
Performance status	
0–1	13 (46.4)
2	15 (53.6)
Primary tumor site	
Head	14 (50.0)
Body and tail	14 (50.0)
Differentiation	
Well	1 (3.6)
Moderate	11 (39.3)
Poor	6 (21.4)
Unknown	10 (35.7)
Distant metastases	
None	2 (7.1)
Liver	18 (64.3)
Lung	3 (10.7)
Lymph node	6 (21.4)
Other	2 (7.1)
Elevated Carbohydrate antigen 19–9 (>37.0 U/mL)	
Yes	24 (85.7)
No	4 (14.3)
Prior surgery	
None	22 (78.6)
Curative	5 (17.9)
Palliative	1 (3.6)
Prior radiotherapy	
Yes	15 (53.6)
No	13 (46.4)

Table 2 Initial chemotherapy regimen and response

	No. of patients (%)
Initial regimen	
Gemcitabine + cisplatin	19 (67.9)
Gemcitabine only	3 (10.7)
Gemcitabine + erlotinib	1 (3.6)
Gemcitabine + TS-1	1 (3.6)
Gemcitabine + cisplatin + UFT	1 (3.6)
Two or more regimens	3 (10.7)
Best response of prior chemotherapy	
Partial response	8 (28.6)
Stable disease	5 (17.9)
Progressive disease	10 (35.7)
Adjuvant chemotherapy	5 (17.9)
Time from initial diagnosis to 5-FU + paclitaxel chemotherapy, months, median (range)	7.54 (2–69.7)

Table 3 Drug delivery and dose intensity in patients with gemcitabine-refractory pancreatic cancer treated with paclitaxel and 5-fluorouracil ($N = 28$)

Agent	Dose intensity (mg/m^2 per week)	
	Planned	Delivered median (range)
5-FU	750	728.3 (600–750)
Paclitaxel	43.75	42.5 (33.5–43.75)

Table 4 Tumor response, time to progression ($N = 20$) and overall survival ($N = 28$) in patients with gemcitabine-refractory pancreatic cancer treated with paclitaxel and 5-fluorouracil

	No. of patients (%)
Response	
Partial response	2 (10%)
Stable disease	4 (20%)
Progressive disease	14 (70%)
Disease control rate	6 (30%)
Time to progression, median (range)[a]	2.5 (1.2–20.2)
Overall survival, median (range)[a]	7.6 (1.0–31.7)

[a] From the day of the initial second-line chemotherapy

and one of grade 4 neuropathy), disease-unrelated death (2/27, 7.4%), patient refusal (1/27, 3.7%), and deterioration of general condition (9/27, 33.3%).

The response could be evaluated in 20 of 28 patients. Of the eight patients in whom it was impossible to evaluate the response, one died (1/8, 12.8%) and the general condition had deteriorated in seven (7/8, 87.5%). As shown Table 4, two patients achieved PR (10%) and four (20%) achieved SD. The disease control rate (the sum of CR, PR, and SD) was 30% in the 20 patients who could be evaluated. The median duration of time to progression from the start of paclitaxel and 5-FU was 2.5 months, and the median overall survival was 7.6 months (Fig. 1).

Toxicity could be evaluated in all 28 patients. Grade 3 anemia and grade 3/4 neutropenia were recorded in one (3.6%) and six (21.4%) cases, respectively. Grade 3/4 thrombocytopenia occurred in one (3.6%) patient (Table 5), but there was no thrombocytopenia-related bleeding. One patient required a dose reduction because of the deterioration of his general condition. In addition, this patient had to stop the chemotherapy due to pneumonia accompanied by grade 4 neutropenia. Another patient had to stop the chemotherapy because of grade 4 neuropathy. The most frequent non-hematological toxicity was gastrointestinal problems. Grade 3 nausea and vomiting occurred in two patients (7.2%), and another two (7.2%) patients experi-

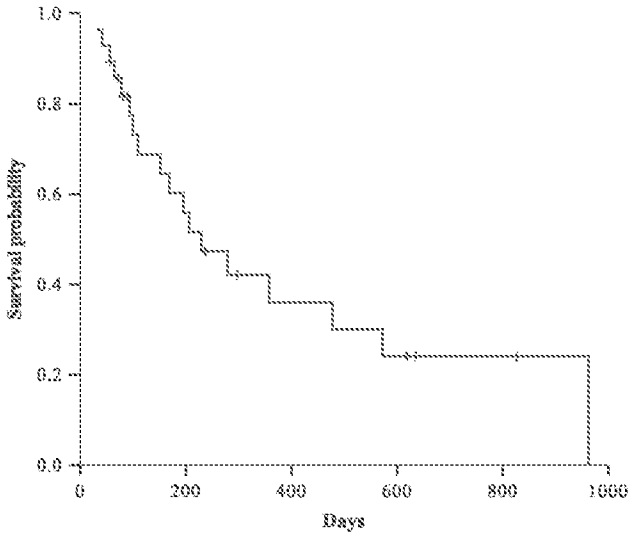

Fig. 1 Overall survival curve for the 28 pancreatic cancer patients, from the day of the initial second-line chemotherapy

Table 5 The numbers of patients who developed toxicities during chemotherapy ($N = 28$)

Toxicity parameter	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	7	3	1	0
Leukopenia	3	2	3	3
Thrombocytopenia	8	1	1	0
AST/ALT elevation	3	2	0	0
Bilirubin elevation	1	0	0	0
Nausea/vomiting	9	1	2	0
Diarrhea	3	1	2	0
Neuropathy	2	0	0	1

enced grade 3 diarrhea. There was grade 2 general asthenia in one patient.

Discussion

Gemcitabine was approved as the standard chemotherapeutic agent for advanced pancreatic cancer based on the clinical response and survival [3]. Nevertheless, the 5-year survival rate is still less than 5% because the response rate is low and chemoresistance occurs early [2]. Consequently, second-line chemotherapy is inevitable for pancreatic cancer patients. Unfortunately, no effective second-line chemotherapy has yet been established. It is difficult to prove the efficacy of new chemotherapeutic agents because pancreatic cancer progresses rapidly and the agents are very expensive. Therefore, we evaluated traditional chemotherapeutic agents as a salvage regimen for advanced pancreatic cancer in patients who were refractory to gemcitabine-based chemotherapy.

There are only a few reports on secondary chemotherapy for pancreatic cancer after failure of gemcitabine-based chemotherapy. Before the approval of gemcitabine, 5-FU was generally used as the first-line chemotherapeutic agent for pancreatic cancer patients. However, as first-line chemotherapy, 5-FU-based regimens only minimally prolong survival in advanced pancreatic cancer. [5, 13, 18]. There are only a few reports on the use of 5-FU as a second-line chemotherapeutic agent. In one report, the Folfox4 regimen was tried as second-line chemotherapy [4]. The disease control rate was 38%. In addition, Mitry et al. [16] reported that oxaliplatin chemotherapy combined with 5-FU was an effective second-line chemotherapy, with a disease control rate of 17%. Therefore, 5-FU may provide a benefit as a second-line chemotherapeutic agent in gemcitabine-refractory pancreatic cancer. The combination of gemcitabine and platinum has been reported to be effective and is frequently used as first-line chemotherapy [6]; thus, there is limited value to using 5-FU with oxaliplatin as a second-line therapy. In our study, 19 patients (67.9%) had received gemcitabine and cisplatin as the first-line regimen.

Paclitaxel interferes with spindle function to block cells at G2M, the most radiosensitive phase of the cell cycle [10]. Consequently, paclitaxel is often used as a radiosensitizer in pancreatic cancer. To our knowledge, only one phase II study has been reported for gemcitabine-refractory pancreatic cancer [17]. In that study, paclitaxel was used as a single second-line therapeutic agent, and the disease control rate was 33.3%, including one patient with CR.

Our study examined paclitaxel combined with 5-FU. This is the first report on this regime in pancreatic cancer. A chemotherapeutic regimen of 5-FU and paclitaxel, generally with the addition of folinic acid, has been studied in other gastrointestinal tract cancers, showing modest effectiveness and yielding response rates of 32–40.7% in advanced gastric cancer [1, 24]. One study reported an additive cytotoxic effect in vitro for paclitaxel followed by 5-FU, whereas sequential exposure to 5-FU followed by paclitaxel had subadditive effects [9]. Therefore, paclitaxel and 5-FU were infused sequentially every 4 weeks in our study.

In this second-line setting, a 30% disease control rate, median time to progression of 2.5 months, and overall survival of 7.6 months were achieved. In similar settings, the combination chemotherapy produced disease control rates of 25% with celecoxib plus 5-FU [14], 53.3% with oxaliplatin leucovorin plus 5-FU [22], and 37% with raltitrexed plus irinotecan [23], respectively. Epidermal growth inhibitors such as erlotinib have proven survival benefits but are not impressive as second-line treatment. The administration of capecitabine plus erlotinib and docetaxel with gefitinib in gemcitabine-refractory metastatic pancreatic cancer achieved disease control rates of 10 and 19.2% and respective median

overall survival times of 6.5 and 2.1 months [7, 12]. Our result was not inferior to those studies.

It is also important to consider the toxicity profile of the paclitaxel and 5-FU regimen. Although some patients experienced hematologic toxicity with the treatment regimen, the toxicity was generally manageable with supportive treatment. The median dose intensity exceeded 90%, and the incidence of grade 3–4 toxicity was similar to values reported for second-line chemotherapy.

In conclusion, we found that combination chemotherapy with 5-FU and paclitaxel is well tolerated and provides survival benefits in gemcitabine-refractory pancreatic cancer patients. Our result gives an additional therapeutic choice for patients with gemcitabine-refractory pancreatic cancer who maintain good performance status.

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Arsenic Trioxide in Patients With Adenocarcinoma of the Pancreas Refractory to Gemcitabine

A Phase II Trial of the University of Chicago Phase II Consortium

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Objectives: There is no effective therapy for patients with metastatic pancreatic cancer who fail initial therapy with gemcitabine. Arsenic trioxide has potent antiproliferative and proapoptotic effects in pancreatic cancer cell lines. We conducted a multicenter phase II trial in patients with advanced pancreatic cancer who experienced disease progression on or after a gemcitabine-containing regimen.

Methods: Arsenic trioxide 0.3 mg/kg was administered intravenously over 1 hour daily for 5 consecutive days every 28 days. Restaging computed tomography scans were obtained every 2 cycles.

Results: Thirteen patients were enrolled between December 2002 and November 2003. Twenty-four cycles were administered (median 2; range 1–2). There were no grade 3/4 hematologic toxicities; grade 1/2 anemia and leukopenia occurred in 50% and 25% of patients, respectively. Grade 3 toxicities included fatigue and thrombosis in 17% of patients. Only 1 patient developed a prolongation of the QTc interval. There were no objective responses. Median progression-free survival was 1.6 months (95% confidence interval, 1.2–1.9). Median survival was 3.8 months (95% confidence interval, 1.6–6.8).

Conclusions: Despite promising in vitro data, arsenic trioxide has no activity in pancreatic cancer patients who develop progressive disease after gemcitabine. Multicenter phase II trials are feasible in this patient population, and novel agents are clearly needed.

Key Words: arsenic trioxide, pancreatic cancer, phase II trial

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Pancreatic cancer is the fourth leading cause of cancer death in the United States, affecting an estimated 37,170 Americans in 2007.[1] Only 1%–4% of all patients with this disease survive 5 years, hence the incidence and mortality rates are nearly identical. In the pivotal randomized phase III study that compared gemcitabine to weekly bolus 5-fluorouracil (5-FU), gemcitabine produced an objective response rate of 5.4% (vs. 0% for 5-FU), a clinical benefit of 23.8% (vs. 4.8% for 5-FU), and a 1-year survival of 18% (vs. 2% for 5-FU). These modest results led to the FDA approval of gemcitabine for the front-line treatment of advanced pancreatic cancer.[2]

Once a patient with advanced pancreatic cancer develops progressive disease on a gemcitabine-containing regimen, performance status usually declines rapidly, and median survival is measured in weeks to a few months at best. There is no effective chemotherapy for these patients. New agents with novel mechanisms of action are clearly needed.

Arsenic has been used both as a medicine and as a poison for over 2 thousand years.[3] Arsenicals are an active ingredient in many Asian folk remedies. Observations from Chinese investigators that arsenic trioxide had activity in patients with acute promyelocytic leukemia (APL) led to clinical trials in the United States and Food and Drug Administration approval of arsenic trioxide for the treatment of relapsed or refractory acute promyelocytic leukemia.[4,5]

Although the precise mode of action of arsenic trioxide is unknown, several proposed mechanisms include induction of apoptosis, inhibition of angiogenesis, cytodifferentiation, and inhibition of proliferation.[3] Arsenic trioxide may affect other cellular processes, including histone deacetylase activity, cell cycle progression, DNA repair, ubiquitination, tubulin polymerization, and oncogene expression. Arsenic trioxide also down-regulates bcl-2 protein, enhancing apoptosis.[3,6]

Arsenic trioxide inhibits growth and promotes apoptosis in a variety of solid tumor cell lines, including pancreatic cancer.[7–9] In vitro, arsenic trioxide causes a dose-dependent inhibition of pancreatic cancer cell proliferation.[8] Arsenic trioxide also induces apoptosis in pancreatic cancer cell lines by activating the caspase cascade, by enhancing GADD expression, and by affecting progression through the cell cycle.[9]

Soignet and colleagues evaluated arsenic trioxide in a phase I trial in patients with advanced solid tumors using a daily times 5 schedule every 28 days. Pleural effusion was dose-limiting at 0.35 mg/kg/d. Other common toxicities were hyperglycemia, fatigue, and a prolonged QTc interval.[10]

Because the mechanism of action of arsenic trioxide is quite distinct from classic cytotoxic chemotherapy, and be-

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cause there appeared to be promising in vitro activity of this agent in pancreatic cancer cell lines, we evaluated arsenic trioxide in patients advanced pancreatic cancer that was refractory to gemcitabine.

PATIENTS AND METHODS

Eligibility

Eligibility required histologically or cytologically confirmed metastatic or locally advanced adenocarcinoma of the pancreas; disease progression on or after chemotherapy with a gemcitabine-containing regimen; no more than 1 prior chemotherapy regimen for metastatic disease; at least 4 weeks must have elapsed since the completion of chemotherapy or 6 weeks from nitrosoureas and mitomycin C; more than 4 weeks from any major surgical procedure; unidimensionally measurable disease; Eastern Cooperative Oncology Group performance status 0–1; age ≥18 years; no New York Heart Association functional class III or IV heart failure; baseline electrocardiogram with QTc <500 milliseconds; women of child-bearing age were required to be nonpregnant, nonlactating, and using adequate contraception; leukocytes ≥3,000/μL, granulocytes ≥1,500/μL, platelets ≥100,000/μL, aspartate aminotransferase/alanine aminotransferase ≤5.0 times the upper limit of normal, total bilirubin ≤1.5 mg/dL, serum creatinine ≤1.5 mg/dL or creatinine clearance ≥60 mL/min; no clinically significant brain metastases; no currently active second malignancy other than nonmelanoma skin cancer or carcinoma in situ of the cervix; no uncontrolled intercurrent illness; no history of severe allergic or anaphylactic reactions to compounds that contain arsenic; no concurrent treatment with medications known to prolong the QT interval; written informed consent. The protocol and consent form were approved by the Institutional Review Boards at all participating sites.

Study Design and Treatment

Arsenic trioxide 0.3 mg/kg per day, was administered intravenously over 1 hour daily for 5 consecutive days every 28 days. Patients received a minimum of 2 cycles unless unacceptable toxicity or rapid progression of disease occurred. Response was evaluated by the Response Evaluation Criteria in Solid Tumors after every 2 cycles of therapy.[11]

Toxicities were graded using the revised National Cancer Institute Common Toxicity Criteria (Version 2.0). Dose modifications depended on the nature of the individual toxicities and were based on the worst toxicity within a cycle. The starting dose level was 0.3 mg/kg, dose level-1 was 0.225 mg/kg, and dose level-2 was 0.15 mg/kg. The dose was decreased by one dose level for grade 3 or greater thrombocytopenia, grade 3 neutropenia lasting greater than 7 days, neutropenic fever, grade 3/4 nausea/vomiting, grade 1 creatinine elevation, grade 2 bilirubin elevation, or grade 2 neurologic/psychiatric toxicity. Treatment was held for grade 2 or greater elevation in bilirubin or creatinine, or grade 3 or greater neurologic/psychiatric toxicity. Patients who experienced a greater than 10% weight gain during treatment, or developed clinically significant pleural effusions, were removed from protocol therapy. The infusion time was extended to 4 hours in patients who developed acute vasomotor reactions. Patients whose toxicities did not resolve to grade 1 or less after 3 weeks after the last dose of arsenic trioxide were removed from protocol treatment.

Statistical Methods

The primary end point of this study was the objective response rate. The trial was conducted using a Simon, optimal two-stage design[12] to test the null hypothesis that the response rate was less than 5% versus the alternative that it was at least 20%. Twelve evaluable patients were to be enrolled in the first stage. If no responses (complete or partial) were observed, the trial was to be terminated for lack of efficacy. Otherwise an additional 25 patients were to be enrolled, and if 4 or more responses (≥10.8%) were observed among the 37 patients, the regimen would be considered worthy of further evaluation in this disease. This design has a 10% type I error rate and 90% power if the true response rate is 20%. The probability of early termination under the null hypothesis was 0.54. Time to progression and overall survival were calculated using the method of Kaplan and Meier.[13]

RESULTS

Patient Characteristics

Thirteen patients were enrolled between December 2002 and November 2003 at 5 centers. All patients were evaluable for toxicity and 12 were evaluable for efficacy. One patient, who received 1 cycle of arsenic trioxide and subsequently developed a small bowel obstruction, withdrew from the study and did not undergo restaging CT scans.

The patient characteristics are summarized in Table 1. Most (77%) of the patients were women, and the majority (62%) had a performance status of 1. The liver was the most common site of metastatic disease, in 85% of patients. A total

TABLE 1. Patient Characteristics

Characteristic	No. Patients (%)
Total	13
Age	
Median	61
Range	48–83
Sex	
Male	3 (23)
Female	10 (77)
Performance status	
0	3 (23)
1	8 (62)
2	2 (15)
Stage	
Stage IV	13 (100)
Site of disease	
Liver	11 (85)
Lung	1 (8)
Lymph node	5 (38)

TABLE 2. Toxicity (Worst of Any Course, n = 13)

	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Hematologic				
Neutropenia	1 (8)	0 (0)	0 (0)	0 (0)
Anemia	4 (33)	2 (17)	0 (0)	0 (0)
Thrombocytopenia	1 (8)	0 (0)	0 (0)	0 (0)
Nonhematologic				
Fatigue	4 (33)	1 (8)	2 (17)	0 (0)
Nausea/vomiting	5 (42)	1 (8)	1 (8)	0 (0)
Anorexia	3 (25)	0 (0)	0 (0)	0 (0)
Conjunctivitis	2 (17)	0 (0)	0 (0)	0 (0)
Rash	2 (17)	0 (0)	0 (0)	0 (0)
Edema	1 (8)	1 (8)	0 (0)	0 (0)
Fever	1 (8)	1 (8)	0 (0)	0 (0)
Neuropathy	1 (8)	1 (8)	0 (0)	0 (0)
QTc prolongation	1 (8)	0 (0)	0 (0)	0 (0)
Diarrhea	1 (8)	0 (0)	1 (8)	0 (0)
Constipation	0 (0)	0 (0)	1 (8)	0 (0)
Laboratory				
Alkaline phosphatase	3 (25)	2 (17)	0 (0)	0 (0)
Hyponatremia	4 (33)	0 (0)	0 (0)	0 (0)
Hypocalcemia	3 (25)	0 (0)	1 (8)	0 (0)
Increased transaminases	3 (25)	0 (0)	1 (8)	0 (0)
Hypomagnesemia	2 (17)	0 (0)	0 (0)	0 (0)
Hypokalemia	2 (17)	0 (0)	0 (0)	0 (0)

of 24 cycles of arsenic trioxide were administered. The median number of cycles was 2 (range, 1–2).

Toxicity

Arsenic trioxide was generally well-tolerated. The observed toxicities are summarized in Table 2. There were no grade 3 or 4 hematologic toxicities. Grade 1/2 anemia occurred in 50% of patients, and grade 1/2 leucopenia in 25%. Grade 4 small bowel obstructions developed in 2 patients, one was secondary to disease progression, another was attributed to postsurgical adhesions. Grade 3 fatigue developed in 17% of patients. Other grade 3 toxicities, including nausea/vomiting, diarrhea, constipation, hypocalcemia and increased hepatic transaminases each occurred in 8% of patients. Only 1 patient developed prolongation of the QTc interval, which was grade 1. Although, fluid retention was dose limiting in phase 1 trials, no patient experienced greater than grade 2 edema.

Response

There were no objective responses. No patient achieved disease stabilization. The median progression-free survival of the evaluable patients was 1.6 months (95% confidence interval, 1.2–1.9). The median overall survival was 3.8 months (95% confidence interval, 2.1–6.8). The Kaplan-Meier curve for overall survival is shown in Figure 1.

Accrual to the study was terminated early because of lack of efficacy, per the trial design.

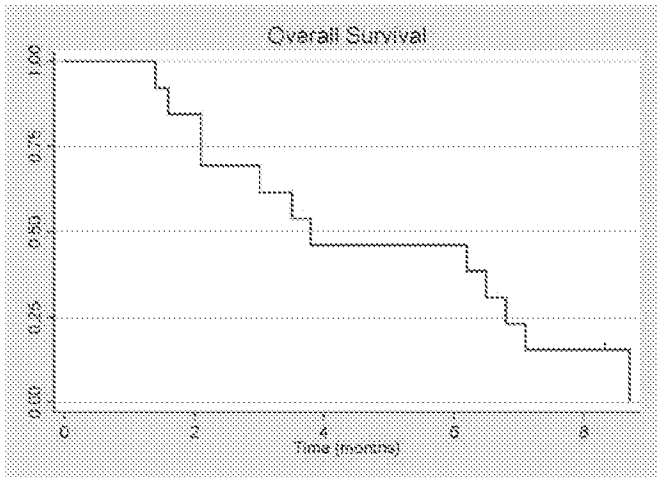

FIGURE 1. Overall survival for patients treated with arsenic trioxide (n = 13).

CONCLUSIONS

We evaluated a daily-times-5 regimen of arsenic trioxide in patients with gemcitabine-refractory advanced pancreatic cancer. The regimen was well tolerated in this patient population, producing minimal myelosuppression, fluid retention, or cardiac toxicity. Despite the encouraging preclinical activity of arsenic trioxide in pancreatic cancer cell lines, we observed no objective responses, and a brief median survival of 3.8 months.

Although our trial did not show any clinical activity for arsenic trioxide in refractory pancreatic cancer, it demonstrated that multi-institutional studies of novel agents are feasible and necessary in this patient population. Disease-related symptoms such as severe pain, anorexia/cachexia, thrombosis, fatigue, and declining performance status can make it difficult for previously treated pancreatic cancer patients to enroll in clinical trials and tolerate aggressive treatment regimens. Classic cytotoxic chemotherapy drugs such as irinotecan, paclitaxel, raltitrexed, and rubitecan have demonstrated very modest activity in gemcitabine-refractory disease.[14–17] Pancreatic cancer is clearly refractory to cytotoxic chemotherapy, and novel agents with unique mechanisms of action are needed. As we learn more about the biology of this disease, we need to continue to evaluate new agents targeted against specific molecular events involved in pancreatic carcinogenesis, invasion, and metastasis.

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ORIGINAL REPORT

Gemcitabine Plus Bevacizumab Compared With Gemcitabine Plus Placebo in Patients With Advanced Pancreatic Cancer: Phase III Trial of the Cancer and Leukemia Group B (CALGB 80303)

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See accompanying articles on pages 3605 and 3611

ABSTRACT

Purpose

The combination of gemcitabine plus bevacizumab produced a 21% response rate and a median survival of 8.8 months in a multicenter phase II trial in patients with metastatic pancreatic cancer. These encouraging data led Cancer and Leukemia Group B (CALGB) to conduct a double-blind, placebo-controlled, randomized phase III trial of gemcitabine/bevacizumab versus gemcitabine/placebo in advanced pancreatic cancer patients.

Patients and Methods

Eligible patients had no prior therapy for advanced disease, Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, no tumor invasion of adjacent organs, and no increased bleeding risk. The primary end point was overall survival. Patients were stratified by performance status, extent of disease, and prior radiotherapy. Patients received gemcitabine at 1,000 mg/m^2 over 30 minutes on days 1, 8, and 15 every 28 days and bevacizumab at 10 mg/kg or placebo on days 1 and 15 every 28 days.

Results

Between June 2004 and April 2006, 602 patients were enrolled onto the study and 535 were treated. Median overall survival was 5.8 months for gemcitabine/bevacizumab and 5.9 months for gemcitabine/placebo ($P = .95$). Median progression-free survival was 3.8 and 2.9 months, respectively ($P = .07$). Overall response rates were 13% and 10%, respectively. Patients with a performance status of 0, 1, and 2 survived a median of 7.9, 4.8, and 2.4 months, respectively. The only statistically significant differences in grades 3 and 4 toxicity occurred for hypertension (10% *v* 3%; $P < .001$) and proteinuria (5% *v* 1%; $P = .002$); venous thrombosis grade ≥ 3 was equivalent in both arms (14% and 15%, respectively).

Conclusion

The addition of bevacizumab to gemcitabine does not improve survival in advanced pancreatic cancer patients.

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Clinical Trials repository link available on JCO.org.

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INTRODUCTION

Pancreatic cancer has the lowest survival by stage of any solid tumor.[1] Gemcitabine, the cornerstone of chemotherapy, has a modest impact. In the landmark trial that compared gemcitabine to fluorouracil, gemcitabine produced a response rate of 5% and a median overall survival (OS) of 5.7 months.[2] Although many phase II studies have reported promising activity for various cytotoxic and targeted agents administered with gemcitabine, phase III trials of these combinations were uniformly negative,[3-10] until gemcitabine/erlotinib was shown to improve survival.[11] Although the results were statistically significant, with a hazard ratio (HR) of 0.82, the absolute improvement in median OS of 5.9 months with gemcitabine versus 6.2 months with the combination was modest.[11] Novel agents that have a greater impact are urgently needed.

Bevacizumab (Avastin, Genentech, South San Francisco, CA) is a recombinant humanized

monoclonal antibody against vascular endothelial growth factor A (VEGF-A).[12] In a phase II trial of gemcitabine/bevacizumab in metastatic pancreatic cancer patients, Kindler et al[13] reported a response rate of 21%, a median OS of 8.8 months, and a 1-year survival of 29%. Because these data appeared promising when compared with data for historical controls, the Cancer and Leukemia Group B (CALGB) evaluated this regimen in a randomized phase III trial. This article describes the results of that clinical trial; correlative studies of angiogenic biomarkers, pharmacogenomics, and clinical economics will be reported separately.

PATIENTS AND METHODS

Patients

Eligible patients had histologically or cytologically confirmed pancreatic adenocarcinoma not amenable to curative surgery. Measurable disease was not required. Prior chemotherapy for metastatic disease was not permitted. Adjuvant chemotherapy was allowed if it did not contain gemcitabine or bevacizumab, if it was given > 4 weeks before enrollment, and if the patient had subsequent disease progression. Prior radiation was allowed if it was completed > 4 weeks before enrollment and there was disease outside the radiation port. An Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 2 and adequate bone marrow (granulocytes ≥ 1,500/μL, platelets ≥ 100,000/μL), renal (creatinine ≤ 1.5 mg/dL or creatinine clearance ≥ 60 mL/min), and hepatic function (total bilirubin ≤ 1 × upper limit of normal, AST ≤ 2.5 × upper limit of normal) were required. An international normalized ratio (INR) ≤ 1.5 was required unless the patient was on warfarin; warfarin-treated patients needed to be on a stable dose with an INR between 2 and 3. A urine protein < 1+ or a 24-hour urine containing < 1 g/dL of protein was required. Eligible patients were at least 18 years of age and had a life expectancy of at least 12 weeks.

Patients could not have had a major surgery, open biopsy, or significant traumatic injury within 28 days before registration or a fine-needle aspirate within 7 days before registration. Patients who had significant bleeding within 6 months before registration, esophageal varices, computed tomography (CT) scan documentation of invasion of adjacent organs, clinically significant heart disease, or CNS disease were excluded. This protocol was reviewed by the institutional review board of each participating center. All patients provided written informed consent according to federal and institutional guidelines.

Treatment

Gemcitabine at 1,000 mg/m^2 was given intravenously over 30 minutes on days 1, 8, and 15 of a 28-day cycle. Bevacizumab at 10 mg/kg or placebo was administered intravenously after gemcitabine on days 1 and 15 of each cycle. The initial bevacizumab/placebo dose was given over 90 minutes. If no infusion reaction developed, the second dose was given over 60 minutes, and subsequent doses were given over 30 minutes. Treatment was discontinued for progressive disease, unacceptable adverse events, or patient withdrawal of consent.

Dose Adjustments

Dose modifications were based on toxicities within 1 day of treatment. Adverse effects were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 3.0. A cycle was not started until the absolute neutrophil count (ANC) was > 1.5 × 10^9/L and the platelet count was > 100 × 10^9/L. The following dose levels of gemcitabine were used: level 0 (1,000 mg/m^2), level −1 (750 mg/m^2), level −2 (550 mg/m^2), and level −3 (425 mg/m^2).

Within a cycle, if the ANC was between 0.5 and 0.999 × 10^9/L or the platelet count was between 50 and 75 × 10^9/L on the treatment day, the gemcitabine dose was reduced by one dose level. The dose was held for an ANC < 0.5 × 10^9/L or platelets < 50 × 10^9/L. Febrile neutropenia required a one-dose-level reduction of gemcitabine for subsequent cycles. Gemcitabine was reduced by one dose level for grade 3 and held for grade 4, hepatic toxicity, or edema.

There were no dose modifications of bevacizumab/placebo. If gemcitabine was held at the beginning of a new cycle, the bevacizumab/placebo dose was held until gemcitabine could be given. Bevacizumab/placebo was held on day 15 for platelets < 50 × 10^9/L. Bevacizumab/placebo was held for bilirubin or hepatic transaminase elevations grade ≥ 3 and was not resumed until these were grade ≤ 2. Bevacizumab/placebo was discontinued for grade ≥ 3 bleeding. For a grade 3 thrombosis or an asymptomatic grade 4 pulmonary embolus, bevacizumab/placebo was held and was resumed once the patient met the following criteria: an INR between 2 and 3 on a stable warfarin or a stable heparin dose, no pathologic conditions that carried a high risk of bleeding, and no bleeding grade ≥ 3 on study. Bevacizumab/placebo was discontinued for a symptomatic pulmonary embolus or recurrent or worsening thromboembolic events after it was resumed. Bevacizumab/placebo was held for persistent or symptomatic hypertension; it was discontinued if this delayed treatment for > 4 weeks, or if grade 4 hypertension developed. A 24-hour urine was required for proteinuria ≥ 2+ on a dipstick. If the urine protein was ≥ 2 g/24 hours, bevacizumab/placebo was held until it recovered to < 2 g/24 hours and was discontinued if it was held > 12 weeks. It was also discontinued for coagulopathy grade ≥ 3, grade 4 hypersensitivity reactions, and grade 4 adverse events attributable to bevacizumab, including GI perforation, intra-abdominal hemorrhage, abscess, fistula, or wound dehiscence.

Study Evaluations

Pretreatment evaluation included a complete medical history and physical examination, complete blood count and differential (CBC), chemistry panel, prothrombin time/INR, urinalysis, carbohydrate antigen 19-9 (CA 19-9), pregnancy test (in women of childbearing potential), CT scan or magnetic resonance imaging of the abdomen, and a chest x-ray or CT scan of the chest. Plasma, urine, serum, and whole blood were obtained for research studies.

A history and physical examination were performed every 14 days. A CBC was performed weekly. Serum chemistries were obtained every 14 days. A urinalysis was performed every 28 days. Prothrombin time/INR was obtained weekly only in patients receiving therapeutic warfarin. Imaging scans, CA 19-9, and plasma and urine for research studies were obtained every two cycles.

Response Criteria and Toxicity

Patients were evaluated for response according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria every two cycles.[14] Confirmatory scans were obtained at least 4 weeks following initial documentation of objective response.

Statistical Design and Analysis

The primary end point of this study was OS, measured from trial registration until death from any cause. Patients were randomly assigned with equal probability to gemcitabine plus bevacizumab or placebo, stratified by disease extent (locally advanced *v* metastatic), ECOG performance status (0/1 *v* 2), and prior radiation (no *v* yes). The study was powered to detect an HR of 1.35 with 90% confidence testing a two-sided log-rank hypothesis with $\alpha = .05$. The design assumed an accrual rate of 20 patients per month and an additional 12 months of follow-up. The sample size was inflated approximately 10% to compensate for patient cancellations and withdrawals for a target accrual of 590 patients. The primary efficacy analysis population was the intent-to-treat population, defined as all patients randomly assigned, irrespective of whether the assigned treatment was actually received. For efficacy analyses, patients were grouped according to the treatment assigned at randomization.

Secondary end points included objective response rate and duration, progression-free survival (PFS), and adverse events. Response was defined as complete response (CR) or partial response (PR) per RECIST criteria.[14] PFS was measured from trial entry until time of disease progression or death from any cause.

OS and adverse events were monitored with interim analyses during the trial with results reported to the CALGB Data and Safety Monitoring Board (DSMB) biannually. OS was monitored using the Lan-DeMets analog of the O'Brien-Fleming boundaries (two-sided $\alpha = .05$) truncating at 2.58[15] and began when 15% of information was available. At each interim analysis, the two-sided 99.5% CI was constructed for the observed HR, and if the targeted HR of 1.35 was not contained in this interval, consideration was given to

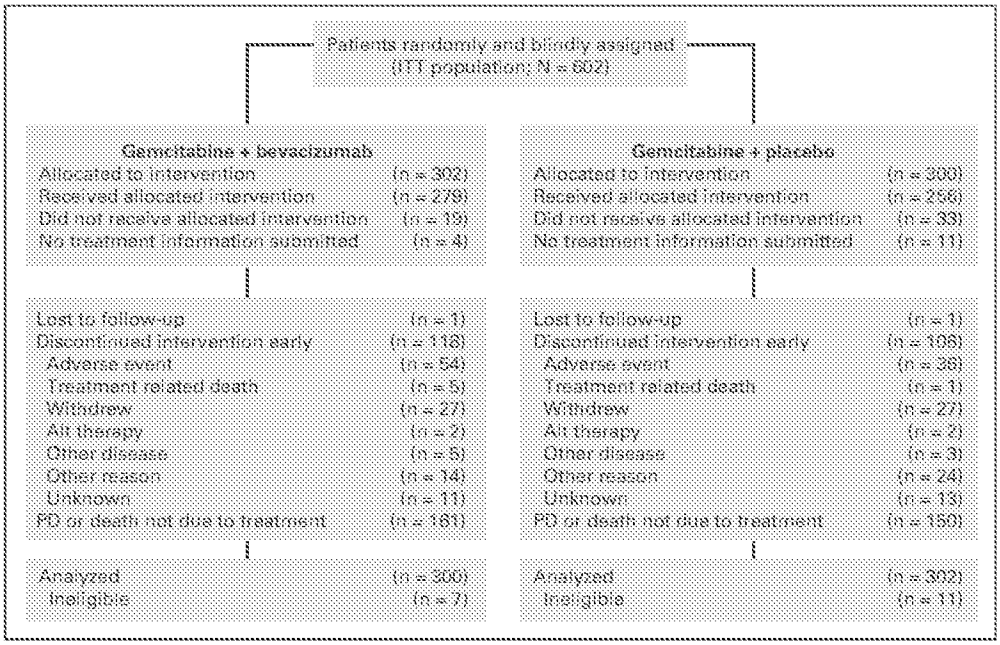

Fig 1. CONSORT diagram. ITT, intent to treat; Alt, alternative; PD, progressive disease.

accepting the hypothesis of no difference in median survival. Bevacizumab-specific adverse events were monitored for early stopping if the total rate difference for grade ≥ 3 bleeding, proteinuria, or thrombosis, or grade ≥ 4 hypertension was significantly greater on the bevacizumab arm. The Lan-DeMets analog of the Pocock boundaries[15] was used to determine significance at each test of the hypothesis. Conducting these interim analyses did not substantially impact the overall significance level of the test.[16]

A stratified Cox proportional hazards regression[17] was used to compare treatment arms controlling for the stratification factors at random assignment. Survival probability estimates were calculated using the Kaplan-Meier method.[17] Rates and proportions were compared using Fisher's exact test, where appropriate, or a χ^2 approximation. SAS 9.1 (SAS Institute, Cary, NC) was used for all statistical analyses. All analyses were based on the study database frozen on June 9, 2009.

Patient registration, data collection, and data analysis were performed by the CALGB Statistical Center. Data quality was ensured by careful review of data by CALGB Statistical Center staff and the study chairperson. Quarterly reports were submitted by the CALGB Statistical Center to the Clinical Trials Evaluation Program of the NCI using the Clinical Data Update System.

As part of the CALGB quality assurance program, members of the Audit Committee visit all participating institutions at least once every 3 years to review source documents. Auditors verify compliance with federal regulations and protocol requirements, including those pertaining to eligibility, treatment, adverse events, tumor response, and outcome in protocols at each institution. Such on-site medical record review was performed in 106 patients (18% of the 602 patients on this study).

RESULTS

Patient Characteristics

Between June 30, 2004, and April 14, 2006, 602 patients were randomly assigned (302 to gemcitabine/bevacizumab, 300 to gemcitabine/placebo); 279 and 256 patients, respectively, received study treatment. Of those who were randomly assigned but not treated, 52 patients withdrew consent, and no treatment information was submitted on 15 patients (Fig 1). Eighteen patients were ineligible. All randomly assigned patients were included in the intent-to-treat analysis.

Patient characteristics are listed in Table 1. There were no statistically significant differences between treatment arms with respect to age, sex, PS, extent of disease, or prior radiation. Approximately 85% of patients had metastatic disease, and 90% had a PS of 0 or 1. A slightly greater proportion of patients on the bevacizumab arm were male (58% *v* 51%); this difference was not statistically significant.

Interim Analysis

In June 2006, on the basis of a protocol-specified planned interim analysis with 64% of the information available on OS, the CALGB

Table 1. Patient Characteristics

Characteristic	Gemcitabine + Bevacizumab No.	Gemcitabine + Bevacizumab %	Gemcitabine + Placebo No.	Gemcitabine + Placebo %
No. of patients	302		300	
Age, years				
Median	63.7		65.0	
Range	26-88		35-86	
Male sex		58		51
ECOG performance status				
0		37		38
1		51		52
2		12		10
White race		88		88
Extent of disease				
Locally advanced		16		15
Metastatic		84		85
Prior radiation				
Yes		11		11
No		89		89
Median baseline CA 19-9	1,146		1,726	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; CA 19-9, carbohydrate antigen 19-9.

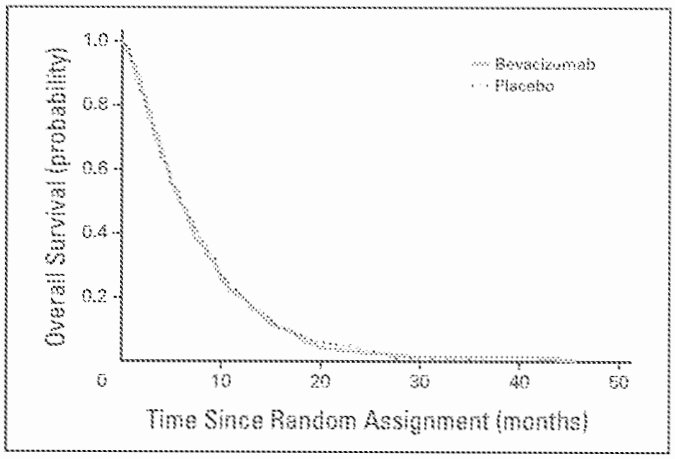

Fig 2. Overall survival by treatment arm.

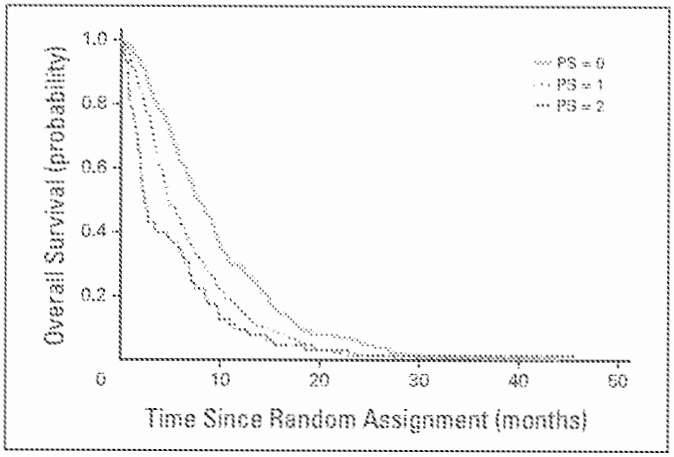

Fig 4. Overall survival by performance status (PS).

DSMB released study data. At that point, 300 deaths (159 on the bevacizumab arm, 141 on the placebo arm) had been reported. Median OS was 4.99 and 5.45 months for the bevacizumab and placebo arms, respectively. The HR estimate was 0.90 in favor of placebo with 99.5% CI of 0.65 to 1.23. This interval did not contain the targeted HR of 1.35. Thus, the futility boundary was met. Since it was considered unlikely that there would be significant differences in OS between treatment arms with further follow-up, all patients on treatment were unblinded and notified of these results. Patients thought to be benefiting from bevacizumab were allowed to continue it with informed consent. Adverse event monitoring was conducted for any grade ≥ 3 bleeding or proteinuria, or grade ≥ 4 hypertension. No protocol-specified boundaries were crossed during interim toxicity monitoring for these end points. Monitoring for grade ≥ 3 thrombosis was conducted separately and was not significantly different between arms at any interim analysis.

Treatment Administration

A mean of 4.4 cycles of gemcitabine/bevacizumab and 3.9 cycles of gemcitabine/placebo were administered ($P = .02$).

Survival and Response

There was no statistically significant difference in median OS between study arms. The resulting stratified HR was 1.044 for placebo versus bevacizumab (95% CI, 0.88 to 1.24). The Kaplan-Meier curves for OS by treatment arm are shown in Figure 2. The median OS was 5.8 months (95% CI, 4.9 to 6.6) for gemcitabine/bevacizumab and 5.9 months (95% CI, 5.1 to 6.9) for gemcitabine/placebo ($P = .95$).

There were statistically significant differences in survival by extent of disease and PS. Patients with metastatic disease survived a median of 5.7 months compared with 9.9 months for patients with locally advanced disease ($P = .009$; Fig 3). Patients with a PS of 0 survived a median of 7.9 months compared with 4.8 and 2.4 months for PS 1 and PS 2 patients, respectively ($P < .001$; Fig 4). These differences were consistent between treatment arms.

Figure 5 illustrates the Kaplan-Meier curves for PFS by treatment arm. The median PFS was 3.8 months (95% CI, 3.4 to 4.0 months) and 2.9 months (95% CI, 2.4 to 3.7 months) for the bevacizumab and placebo arms, respectively ($P = .075$).

Objective response rates were not significantly different: 13% for the bevacizumab arm (1% CR, 12% PR), and 10% for the placebo arm

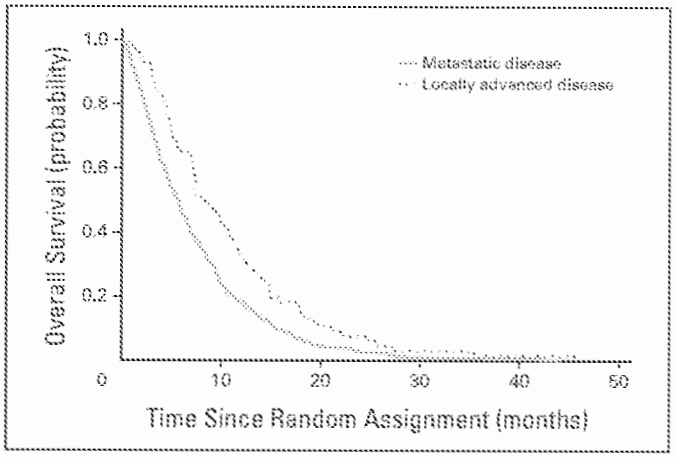

Fig 3. Overall survival by disease extent.

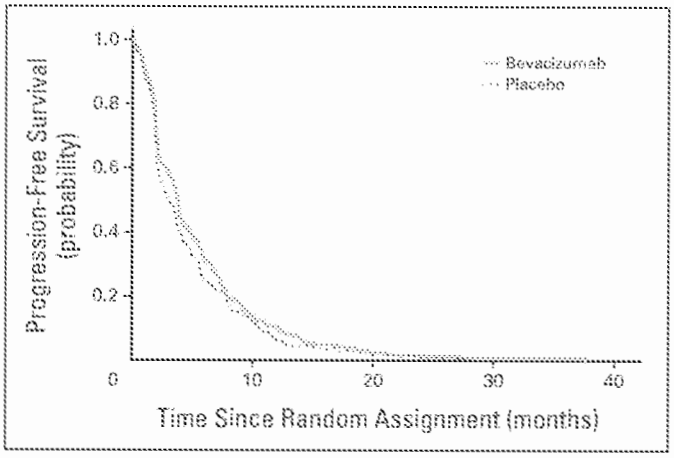

Fig 5. Progression-free survival by treatment arm.

Table 2. Grades 3 and 4 Toxicities per Patient by Common Toxicity Criteria Version 3.0

Toxicity	Gemcitabine + Bevacizumab (%) (n = 277)	Gemcitabine + Placebo (%) (n = 263)	P
Neutropenia	33	29	.35
Anemia	5	8	.22
Thrombocytopenia	12	12	1.0
Bleeding	5	4	.68
Cerebrovascular accident	2	2	1.0
Hypertension	10	3	< .001
Proteinuria	5	1	.002
Venous thrombosis	14	15	.72
Visceral perforation	0.4	0	1.0

(1% CR, 9% PR). Stable disease occurred in 41% and 34% of patients on the bevacizumab and placebo arms, respectively.

Adverse Events

Grade 3 and 4 adverse events are summarized in Table 2. There were 13 treatment-related deaths. Five of the 10 deaths on the experimental arm were potentially attributable to bevacizumab (one hemorrhage, two pulmonary embolism, and two perforations). There were no differences in 30- and 60-day all-cause mortality between treatment arms.

Hematologic adverse events were similar in both groups. Statistically significant differences in nonhematologic events occurred only for grade ≥ 3 hypertension (bevacizumab 10% *v* placebo 3%; $P < .001$) and proteinuria (5% *v* 1%; $P = .002$). Although high, rates of venous thrombosis grade ≥ 3 were nearly identical (14% and 15%) for the bevacizumab and placebo arms, respectively. There were 31 bleeding (grade ≥ 3), proteinuria (grade ≥ 3), or hypertension (grade ≥ 4) adverse events on the bevacizumab arm and 12 on the placebo arm ($P = .006$). This significant difference was principally due to the differences in proteinuria (15 *v* two events).

DISCUSSION

This randomized phase III study demonstrates that the addition of bevacizumab to gemcitabine does not improve survival in advanced pancreatic cancer patients. Not only does this trial fail to confirm the results of a prior phase II study of this regimen,[15] these data also differ from the results achieved by the addition of bevacizumab to chemotherapy in several other malignancies.[18-21] They are, however, similar to data from other randomized trials of the VEGF inhibitors bevacizumab, axitinib, and aflibercept in this disease.[22-24]

Patient selection is likely the most important factor in the disparate results of this phase III CALGB study and the phase II trial that provided the study rationale. The University of Chicago phase II trial[15] reported a PR rate of 21% and a median OS of 8.8 months. The CALGB considered these results sufficiently promising for evaluation in a phase III study.

In retrospect, it is clear that the Chicago trial accrued a more fit population. Although all of the patients had metastatic disease and 83% had liver metastases, both of which augur a poor prognosis, that trial also contained more patients with a PS of 0, excluded patients with prior thrombosis, and had more patients who had received adjuvant therapy.

The striking differences in OS by PS observed in CALGB 80303 highlight the critical importance of this metric in predicting prognosis in advanced pancreatic cancer patients.[25] Median survival was 7.9 months in PS 0 patients, 4.8 months in PS 1 patients, but only 2.4 months in PS 2 patients. It is likely that the 8.8-month median OS in the Chicago trial is partly attributable to the high proportion of PS 0 patients (60% *v* 38% in CALGB 80303) rather than to any bevacizumab effect. These data also suggest that future phase III trials evaluating new agents in advanced pancreatic cancer should be confined to patients with PS 0 and 1, since the limited survival of PS 2 patients is too brief to observe a potential drug effect.

Negative phase III results despite promising single-arm phase II data are, unfortunately, a common outcome in pancreatic cancer trials.[3-10] These collective data suggest that in this disease, a single-arm, phase II trial design may not be not optimal.[26] If the phase II study of gemcitabine/bevacizumab had employed a randomized phase II design, both arms would likely have contained similarly selected patients and shown little difference in outcome.

The addition of bevacizumab to chemotherapy increases OS and/or response rates and PFS in colorectal cancer, non–small-cell lung cancer, and breast cancer.[18-21] When CALGB 80303 was initiated, it was plausible that these results would be replicated in pancreatic cancer. There are several possible explanations why this did not occur.

By normalizing tumor vasculature, VEGF inhibitors may enhance drug delivery, thereby increasing chemotherapy activity.[27] Gemcitabine may be the most active agent for pancreatic cancer, but it is only modestly effective.[2] Better delivery of a marginal agent yields marginal activity.

The preclinical models that suggested that VEGF inhibitors would be effective in pancreatic cancer[28-33] may not replicate the human tumor microenvironment as well as newer genetically engineered models.[34] Similar to human tumors, the dysfunctional vasculature of genetically engineered pancreatic models have a markedly diminished vessel density embedded in dense stroma, limiting drug delivery.[34] Other potential mechanisms of resistance to VEGF inhibitors have been described.[35-37]

In conclusion, we have demonstrated that the addition of bevacizumab to gemcitabine does not improve survival in advanced pancreatic cancer. Our experience provides a rationale for favoring randomized phase II screening designs so that differences between the regimens rather than in the attributes of the study participants distinguish the differential impact of alternative treatment strategies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Liposomal irinotecan in gemcitabine-refractory metastatic pancreatic cancer: efficacy, safety and place in therapy

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Abstract: Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease. The majority of patients are diagnosed with locally advanced or metastatic disease with a prognosis of short months. Therapeutic options are limited and until recently, there was no standard second-line chemotherapy option. Liposomal constructs have been engineered to encapsulate chemotherapy thereby preventing premature metabolism, improving distribution and minimizing toxicity. Favourable preclinical data on liposomal irinotecan and early phase trials, led to a recently published phase III trial of liposomal irinotecan in combination with fluorouracil and folinic acid in patients with metastatic PDAC, who progressed after gemcitabine-based chemotherapy. As a direct result, the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) have approved the use of liposomal irinotecan in this setting. However, first-line treatment options for this disease now include the combination regimen, FOLFIRINOX, in patients with good performance status, and the role of second-line combination treatment with liposomal irinotecan in this setting is unclear. Recent advances have changed the therapeutic landscape, as clinicians are now able to choose a sequential approach to treatment tailored to the individual patient characteristics. This article reviews current treatment options for metastatic PDAC and focuses on the efficacy, safety and place in therapy of liposomal irinotecan.

Keywords: chemotherapy, liposomal irinotecan, metastatic pancreatic cancer, MM-398, nal-Iri, NAPOLI-1, pancreatic cancer, PDAC, PEP02, treatment

Introduction to pancreatic cancer

Despite decades of research, pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal malignancies. Although it is a relatively uncommon cancer, due to its high mortality rate it represents a significant global health burden. Worldwide in 2012 there were 338,000 new cases of pancreatic cancer and 331,000 associated deaths [Ferlay *et al.* 2015]. The striking similarity between incidence and deaths highlights the dismal prognosis of this disease. Further, by 2030 it has been predicted that pancreatic cancer will surpass breast, prostate and colorectal cancer to become the second leading cause of cancer related deaths in the United States [Rahib *et al.* 2014].

More than 95% of those diagnosed with pancreatic cancer will succumb to it and across Europe the 5-year overall survival (OS) ranges from 2–9% [Cancer Research UK]. This poor survival is multifactorial, attributed to the systemic and aggressive nature of PDAC, its complex mutational landscape [Waddell *et al.* 2015], desmoplastic stroma [Kleeff *et al.* 2007] and the current lack of effective therapies.

Surgery is the one curative treatment for PDAC but only a minority of patients present with potentially operable disease (10–20%) [Willett *et al.* 2005; Gandy *et al.* 2016]. Further, as the disease is characterized by early micrometastatic spread [Sohal *et al.* 2014] long-term survival following surgery is poor with 80% of patients experiencing a local or distant recurrence within 2 years [Geer *et al.* 1993].

The majority of patients present with locally advanced inoperable (40%) or metastatic disease

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(40–45%) where the outlook is even bleaker, with a median OS of 6–11 months and 2–6 months respectively [Willett *et al.* 2005; Sclafani *et al.* 2015; Cancer Research UK].

Current treatment for advanced disease

First-line treatment

Chemotherapy remains the cornerstone of treatment for advanced PDAC. Following the Burris and colleagues study in 1997, single-agent gemcitabine became the gold standard first-line treatment for patients with advanced disease [Burris *et al.* 1997]. This study demonstrated a modest improvement in survival of 1.24 months (5.65 *versus* 4.41 months, $p = 0.0025$) with gemcitabine *versus* 5-fluoropyrimidine (5-FU) but became a standard treatment due to the associated increment in clinical benefit rate from 4.2% with 5-FU to 23.8% with gemcitabine.

Despite a myriad of trials investigating the use of more intensive combination regimens, often with a gemcitabine backbone, no chemotherapy regimen was found to be superior to single-agent gemcitabine until more recently. In light of non-statistically significant trends in improved survival seen with gemcitabine combinations in a number of large phase III studies Sultana and colleagues conducted a meta-analysis of 51 trials, including almost 10,000 patients. This demonstrated a survival benefit with gemcitabine combination chemotherapy *versus* gemcitabine alone [hazard ratio (HR) = 0.91, 95% confidence interval (CI) 0.85–0.97] [Sultana *et al.* 2007]. The same group also assessed different gemcitabine combinations and found a trend favouring gemcitabine plus capecitabine or a platinum [Sultana *et al.* 2008]. Based on such analyses the National Comprehensive Cancer Network (NCCN) guidelines and recent American Society of Clinical Oncology (ASCO) guidelines include these gemcitabine combinations in their recommendations [Sohal *et al.* 2016].

With the elucidation of the molecular nature of pancreatic cancer, a wide variety of targeted agents have also been investigated, again often with a gemcitabine backbone. The targets studied have included EGFR, KRAS signalling, MEK, mTOR, HER2, VEGF and the Hedgehog pathway, all with disappointing clinical results, despite sometimes promising preclinical and early phase studies [Sclafani *et al.* 2015]. This is not entirely surprising considering the significant inter-tumoural heterogeneity seen in PDAC. In addition to common alterations in KRAS, TP53, SMAD4 and CDKN2A [Bryant *et al.* 2014], there are also a multitude of infrequently mutated genes in pancreatic cancer [Waddell *et al.* 2015] and the majority of the trials to date have been in unselected populations.

The one targeted agent to have demonstrated a survival benefit in a phase III study is erlotinib in combination with gemcitabine *versus* gemcitabine alone (HR 0.82, 95% CI 0.69–0.99, $p = 0.038$). However, in the results published in 2007 the numerical increase in median OS was only 12 days [Moore *et al.* 2007] with a higher incidence of adverse events, including rash, interstitial lung disease and diarrhoea. The group of patients who developed a rash of grade ⩾2 did have a more clinically meaningful benefit (median OS 10.5 months with grade ⩾2 rash *versus* 5.8 months with grade 1 rash *versus* 5.3 months for those who did not develop a rash) but this combination is rarely used in clinical practice despite being US FDA and EMA-approved.

The first combination chemotherapy regimen to demonstrate a statistically significant survival benefit *versus* gemcitabine in a phase III study was the ACCORD-11 study in 2011. This study demonstrated that the triplet FOLFIRINOX (5-FU, irinotecan and oxaliplatin) improved progression-free survival (PFS), OS and response rate (RR) when compared with single-agent gemcitabine (OS 11.1 *versus* 6.8 months, HR 0.57, $p < 0.001$, PFS 6.4 *versus* 3.3 months, HR 0.47, $p < 0.001$, RR 31.6% *versus* 9.4%, $p < 0.001$) [Conroy *et al.* 2011]. Unsurprisingly this increased efficacy came at the cost of increased toxicity and this is a regimen for patients with excellent performance status (PS). However, despite this increased toxicity the FOLFIRINOX patients had a significantly longer time to deterioration in quality of life than the gemcitabine patients [Gourgou-Bourgade *et al.* 2013]. Furthermore, since the adoption of this regimen into the clinic various institutional series have been published suggesting modifications to the regimen to increase its tolerability without reducing efficacy [Mahaseth *et al.* 2013; Mantripragada *et al.* 2016].

Following ACCORD-11 the MPACT study of the addition of nab-paclitaxel to gemcitabine reported a median OS of 8.5 months in the combination arm *versus* 6.7 months in the gemcitabine

alone arm (HR 0.72, $p < 0.0001$). Again PFS and RR were also improved (PFS 5.5 *versus* 3.7 months, HR 0.69, $p < 0.0001$, RR 23% *versus* 7%, $p < 0.001$) [von Hoff *et al.* 2013]. Again toxicity including sensory neuropathy was increased in the combination arm, although quality of life was not assessed, and this is a regimen for good PS patients.

The lack of direct comparisons of these regimens leaves some uncertainty as to the best first-line treatment for advanced PDAC and as yet there are no established biomarkers for selecting patients for a particular therapy. For patients with a PS of 2, single-agent gemcitabine remains a reasonable option. For those patients who are fitter, PS 0–1, either FOLFIRINOX or gemcitabine-nab-paclitaxel are preferred and the decision depends on a combination of factors including patient comorbidities, toxicity profile, consideration of central venous access and patient preference and reimbursement. Clinical trials in the first-line setting are also recommended and there are currently numerous ongoing trials globally of targeted drugs with a chemotherapy backbone and increasing studies of immune-directed approaches.

Second and subsequent line treatment

Historically there has been very little use of second-line chemotherapy for PDAC. However, with improvements in first-line therapy for advanced disease, this is now changing. Unfortunately, there is no good quality evidence to support a particular regimen following first-line treatment with FOLFIRINOX or gemcitabine and nab-paclitaxel as the few trials of second-line treatment conducted were following progression on gemcitabine monotherapy.

The randomized phase III CONKO-01 study sought to establish if the combination of oxaliplatin, folinic acid and 5-FU (OFF) was superior to best supportive care (BSC). Despite terminating early due to recruitment difficulties ($n = 46$ patients) this study demonstrated a survival benefit of 2.52 months with chemotherapy (mOS 4.82 OFF *versus* 2.30 BSC, HR 0.45, CI: 0.24–0.83, $p = 0.008$) [Pelzer *et al.* 2011]. CONKO-003, another phase III study, then evaluated whether oxaliplatin was required, randomizing 168 patients to OFF or 5-FU and folinic acid (FF). Both median OS and PFS favoured the addition of oxaliplatin (mOS 5.9 months OFF *versus* 3.3 months FF, HR 0.66, 95% CI 0.48–0.91, log-rank $p = 0.01$) with similar toxicity other than peripheral neuropathy which was, as would be expected, higher in the oxaliplatin arm (grade 1/2 neurotoxicity: 38.3% *versus* 7.1%, $p < 0.001$) [Oettle *et al.* 2014]. However, the results from the randomized phase III PANCREOX study were not aligned with CONO-003, with patients receiving FOLFOX having an inferior OS than those receiving FF (6.1 *versus* 9.9 months, HR 1.78, $p = 0.02$). It has been suggested that this disparity is due to a higher level of treatment discontinuation in the FOLFOX arm than the FF arm (20.4% *versus* 1.9% respectively) and an imbalance in the post-discontinuation treatments received in each arm (6.8% in the FOLFOX arm and 25% in the FF arm) [Gill *et al.* 2014].

The most recent phase III study is the NAPOLI-1 trial of nanoliposomal irinotecan, which is discussed in much greater detail below, and provides another second-line regimen for consideration [Wang-Gillam *et al.* 2016].

Additional regimens have been investigated in the second or subsequent line setting in a number of small phase II studies and case series, including capecitabine and oxaliplatin (CAPOX), taxanes, 5-FU and irinotecan (FOLFIRI) as well as FOLFIRINOX and gemcitabine plus nab-paclitaxel. These studies have reported mixed results and such regimens require further assessment in larger studies [Oettle *et al.* 2000; Xiong *et al.* 2008; Yoo *et al.* 2009; Hosein *et al.* 2013; Lee *et al.* 2013].

Extrapolating from the data available it is not unreasonable to consider that second-line chemotherapy may provide a clinical benefit. A systemic analysis of 34 second-line studies, including over 1500 patients who had progressed on gemcitabine, reported a median OS of 2.8 months for patients who received BSC and 6 months for patients who received second-line treatment [Rahma *et al.* 2013]. The choice of second-line regimen then depends upon the first-line regimen used, the patients' PS, residual toxicities and comorbidities and in this very palliative setting it must be remembered that toxicities and quality of life are of paramount importance. There are even less data to support third or subsequent line treatment and here clinical trial entry is strongly encouraged for fit patients.

Overall therefore, despite the small improvements in the treatment options for pancreatic cancer in

the last decade described above, prognosis remains poor and there is an urgent need to develop novel therapies, consider new combinations and appropriately select those patients who may benefit.

Introduction to irinotecan

Camptothecin is a naturally occurring cytotoxic alkaloid that targets topoisomerase I, a nuclear enzyme that reduces the torsional stress of supercoiled DNA during the replication, recombination, transcription, and repair of DNA [Garcia-Carbonero *et al.* 2002]. Irinotecan is a synthetic derivative of camptothecin, with functional groups to enhance solubility and was first approved by the US FDA in 1996 [Hsiang *et al.* 1985]. As a prodrug, it is converted in to the active metabolite SN38, predominantly in the liver, by carboxylesterases. SN-38 is subsequently conjugated, with significant pharmacogeneric variability, into inactive, nontoxic SN38-glucuronide (SN-38G). Both irinotecan and SN-38 have a labile α-hydroxy-δ-lactone ring that undergoes pH-dependent reversible hydrolysis [Swami *et al.* 2013]. In acidic conditions, the more active, potent lactone form predominates, while in more basic conditions, the inactive, less toxic carboxylate form is favoured. These properties contribute to the marked heterogeneity of the main dose-limiting toxicities observed in patients, that of neutropaenia and late onset diarrhoea. The direct effect of SN-38 on intestinal epithelium is thought to be responsible for irinotecan-induced diarrhoea [Hecht, 1998], which can be severe, resulting in dose reductions or omissions leading to ineffective treatment administration.

There is therefore a rationale for the development of formulations that can improve the distribution and protect the premature metabolism of irinotecan to achieve maximum efficacy while minimizing toxicity. Liposomal constructs have been engineered to improve the circulation time and intratumoural drug concentration of anthracyclines, for example, PEGylated liposomal doxorubicin [Gabizon, 2001], and nab-paclitaxel [Gradishar, 2006], but it has been difficult to replicate the technology in other classes of chemotherapy drugs.

Liposomal irinotecan (MM-398, PEP02, nal-iri)

In 2006, a novel liposomal construct containing irinotecan was developed [Drummond *et al.* 2006]. Unlike previous liposomal irinotecan preparations [Messerer *et al.* 2004], a reduced toxicity profile was reported, as well as increased tumour efficacy when compared with irinotecan in animal models [Drummond *et al.* 2006]. The nanoparticle consists of a lipid bilayer scaffold, which encapsulates the drug complex and facilitates *in vivo* drug retention. A transmembrane gradient of triethylammonium cations was used to drive the irinotecan into the liposome where upon sucrose octasulphate, a highly charged anion, trapped the irinotecan within the liposome (see Figure 1).

Pharmacokinetics, pharmacodynamics and pharmacogenetics

Preclinical *in vivo* pharmacokinetic studies have shown liposomal encapsulation of irinotecan was associated with significantly longer circulation times ($t_{½}$ = 10.7 h) compared with unencapsulated irinotecan ($t_{½}$ = 0.27 h) [Drummond *et al.* 2006]. At 24 h, 23.3% of injected liposomal irinotecan still remained, with no detectable conversion to SN-38 or the carboxylate form. Conversely, only 2% of the injected dose of unencapsulated irinotecan remained at 30 min, 35% of which had been converted to SN-38 and subsequently conjugated to the in the inactive carboxylate form. A similar pharmacokinetic profile was reported in patients by Chang and colleagues [Chang *et al.* 2015]. In this phase I trial, treatment with liposomal irinotecan at 120 mg/m^2 was characterized by slow clearance (mean = 0.0591 l/m^2/h), small volume of distribution (mean = 1.8 l/m^2 ≅ plasma volume) and prolonged terminal half-life of total irinotecan in circulation (mean = 29.5 h) when compared with published pharmacokinetic data for unencapsulated irinotecan [Chabot, 1997; Chang *et al.* 2015]. The plasma concentration profile of liposomal irinotecan matched that of the total irinotecan, suggesting the release of irinotecan from the liposome occurs slowly over time.

The mechanism of irinotecan release is not fully understood. Preclinical models have shown liposomal irinotecan increases tumoural drug retention, resulting in local release and conversion into irinotecan and SN-38 [Drummond *et al.* 2006]. However, the correlation between the C_{max} and $AUC_{0-\infty}$ of liposomal irinotecan and the active metabolite SN-38, reported by Chang and colleagues, was weak [Chang *et al.* 2015]. This variability may be attributable to the small sample

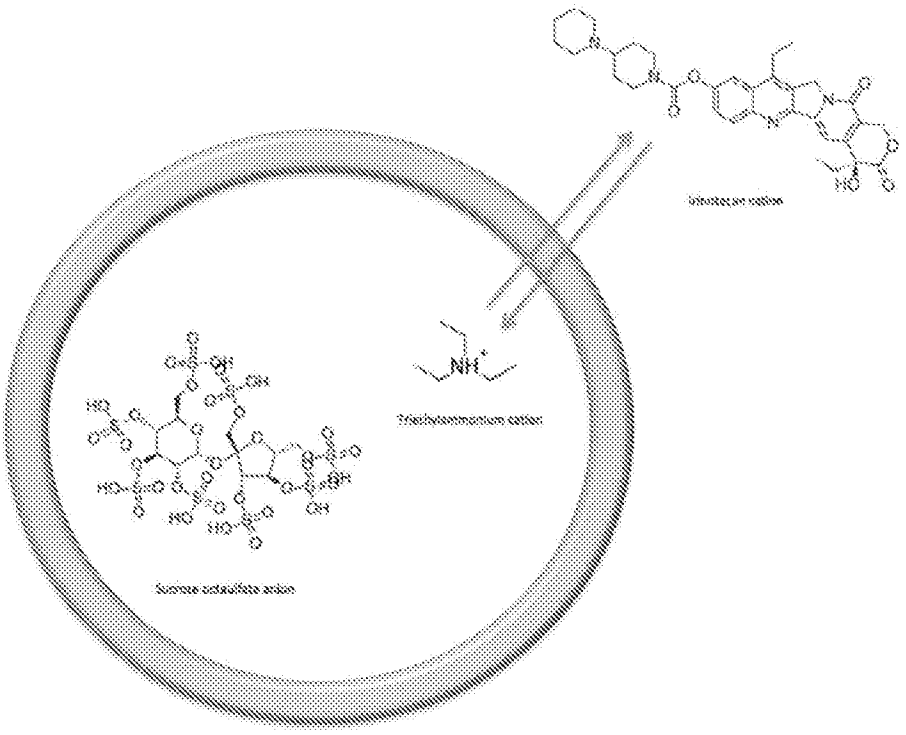

Figure 1. A schematic of encapsulation of irinotecan inside the liposome. Irinotecan is exchanged with triethylammonium cations across the bilipid layer.

size or the pharmacogenetic variability of irinotecan metabolism.

Patients with a genetic polymorphism in the gene encoding uridine diphosphate glucuronosyltransferase (UGT) 1A1, have a lower than normal capacity to metabolize SN-38, the active metabolite of irinotecan. UGT conjugates SN-38 into the inactive SN-38 glucuronide (SN-38G). The presence of the *UGT1A1*28* allele, present in approximately 17% of Whites [Lampe *et al.* 1999], has been shown to cause a 70% reduction in expression of UGT, leading to an increased exposure of patients to the cytotoxic metabolite, SN-38. Patients homozygous for the *UGT1A1*28* allele are 3.5 times more likely to suffer from grade 3/4 toxicities [Palomaki *et al.* 2009] and may benefit from a dose reduction of up to 40% [Innocenti *et al.* 2014].

In a phase I trial, a woman with heterozygosity of *UGT1A1*6/*28* died from grade 4 diarrhoea and was found to have C_{max} and $AUC_{0-\infty}$ of SN-38 that were 3-times higher than in other patients treated at the same dose [Chang *et al.* 2015]. Moreover, in a recent phase III study, the dose of liposomal irinotecan was reduced by 25% in 14 patients homozygous for the *UGT1A1*28* allele, 5 of whom were able to escalate to the standard dose, 2 of whom needed a further dose reduction and 1 discontinued secondary to grade 3 vomiting [Wang-Gillam *et al.* 2016].

Although early phase studies have demonstrated the different pharmacokinetic and toxicity profiles of patients homozygous and heterozygous for the *UGT1A1*28* allele, the available data are not conclusive for defining a precise genotype-based dosage [Toffoli *et al.* 2006; Biason *et al.* 2008; Palomaki *et al.* 2009]. There are therefore no current guidelines on how *UGT1A1* testing could be used to effect treatment with clinical practice.

Clinical Efficacy

Preclinical *in vivo* efficacy data have shown the enhanced anti-tumour effect of liposomal irinotecan compared with equivalent dose of free irinotecan in human pancreatic cancer cell line xenograft mouse models [Hann *et al.* 2007]. Chang and colleagues reported the results of a phase I dose-escalation study of liposomal irinotecan, in 11 patients with treatment refractory advanced solid tumours [Chang *et al.* 2015]. Liposomal irinotecan was delivered as a 90-min intravenous infusion every 21 days. Overall, two patients,

including one patient with pancreatic cancer who was treated with the higher dose of 180 mg/m^2, achieved a partial response to treatment. The disease control rate was 45% for the intention-to-treat population.

The favourable pharmacokinetics described in this study, led to a nonrandomized phase II trial that sought to establish the efficacy and toxicity of single-agent liposomal irinotecan, at 120 mg/m^2 3-weekly, in patients with metastatic pancreatic cancer after progression following first-line gemcitabine-based chemotherapy [Ko *et al.* 2013]. A total of 40 patients were enrolled, 60% of whom had a Karnofsky score of 90–100. The protocol was amended during the second stage of the study to permit a starting dose of 100 mg/m^2. However, 27 of the 40 patients remained on 120 mg/m^2 for the duration of their treatment. The mean and median number of cycles received was, 5.88 and 2.5, respectively. Half of the patients achieved disease control defined as objective response (7.5% of patients) or stable disease for more than two cycles (42.5% of patients). The median PFS and OS were, 2.4 and 5.2 months, respectively.

This phase II study provided evidence of antitumour activity and led to the pivotal NAPOLI-1 trial of liposomal irinotecan in advanced pancreatic cancer [Wang-Gillam *et al.* 2016]. Wang-Gillam and colleagues published the results from this global, randomized, open-label, phase III study in which 417 patients previously treated with gemcitabine-based chemotherapy, were assigned to receive either, liposomal irinotecan monotherapy (120 mg/m^2) every 3 weeks or folinic acid and fluorouracil (2000 mg/m^2 over 24 h every week for the first 4 weeks of every 6-week cycle, based on the CONKO-003 trial [Oettle *et al.* 2014]. A third arm, consisting of 2-weekly combination treatment of liposomal irinotecan (80 mg/m^2) with folinic acid and fluorouracil (2400 mg/m^2 infusion over 46 h) was added later in a protocol amendment. The rationale for protocol amendment was based on preliminary data from the PEPCOL study; a randomized phase II trial which showed liposomal irinotecan in combination with 5-fluorouracil/leucovorin (5-FU/LV) to have activity and an acceptable safety profile in patients with colorectal cancer [Chibaudel *et al.* 2016]. *In vitro* data suggest liposomal irinotecan may improve vascular function thereby increasing the delivery and accumulation of a second drug when used in combination [Baker *et al.* 2008].

In NAPOLI-1, OS was the primary endpoint and patients were stratified by baseline albumin level, PS and ethnicity. Although all patients had previously been treated with gemcitabine, 12% of patients had received this in the neoadjuvant, adjuvant or locally advanced setting. Interestingly, over half the patients enrolled had previously been treated with fluorouracil or irinotecan-based regimes; 56% and 15%, respectively.

Median OS was 6.1 months in the combination arm and 4.2 months in those assigned 5-FU/LV control (HR 0.67, 95% CI 0.49–0.92; p = 0.012). In patients who were allocated liposomal irinotecan monotherapy, median OS was 4.9 months, which was not significantly different to the control arm, (HR 0.99, 95% CI 0.77–1.28; p = 0.94) (see Table 1). Interestingly, quality of life scores and clinical benefit response did not differ significantly between treatment groups. The authors acknowledge that using a different 5-FU/LV regimen in the combination arm to the control arm is not standard design but argue it was unlikely to have created bias in favour of the investigational arm which delivered lower dose intensities of 5-FU.

In a pre-planned analysis of each subgroup, OS was increased in patients with poorer prognostic features who were treated in the combination arm compared with those treated with 5-FU/LV; lower PS (Karnofsky score 70–80), albumin <40 g/l, Ca19-9 ⩾40 U/ml, liver metastases, stage IV at diagnosis and patients whose time from diagnosis to enrolment was less than the median. However, it should be noted that patients with a Karnofsky score <70% or an albumin <30 g/l were not included in the study.

Safety

The dose-limiting toxicities for liposomal irinotecan are myelosuppression and diarrhoea. The two patients treated with 180 mg/m^2 of liposomal irinotecan suffered from grade 4 toxicities. One patient had grade 4 neutropaenia, while the second patient developed grade 4 febrile neutropaenia, grade 4 thrombocytopaenia with a bleeding event and grade 4 diarrhoea. The dose escalation was therefore stopped and 120 mg/m^2 was determined to be the maximum tolerated dose [Chang *et al.* 2015] (see Table 2). At a dose of 120 mg/m^2, the phase II trial found the majority of patients experienced at least one grade 3/4 event. The three deaths that occurred within 30 days of study

Table 1. Summary table of main efficacy results from the three arms of NAPOLI-1 trial [Wang-Gillam *et al.* 2016].

	Liposomal irinotecan + 5-FU/LV	Liposomal irinotecan	5-FU/LV
Median OS	6.1 months [CI 4.8–8.9]	4.9 months [CI 4.2–5.6]	4.2 months [CI 3.3–5.3]
Median PFS	3.1 months [CI 2.7–4.2]	2.2 months [CI 2.1–2.7]	1.5 months [1.4–1.8]
ORR	16% of patients	6% of patients	1% of patients
Reduction in Ca19-9 >50% from abnormal baseline	36% of patients	31% of patients	12% of patients

CI, 95% confidence interval; Ca19-9, carbohydrate antigen 19-9; 5-FU, 5-fluorouracil; LV, leucovorin; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Table 2. Summary table of trials investigating liposomal irinotecan in advanced pancreatic cancer.

	Phase I	Phase II	Phase III	
	Chang [Chang *et al.* 2015]	Ko [Ko *et al.* 2013]	Wang-Gillam [Wang-Gillam *et al.* 2016]	
	3-weekly 120 mg/m² liposomal irinotecan	3-weekly 120 mg/m² liposomal irinotecan	3-weekly 120 mg/m² liposomal irinotecan	2-weekly 80 mg/m² liposomal irinotecan +5-FU/LV
Patients (n)	6	40	151	149
	% All grades [% grade 3/4]			
Diarrhoea	100 [33.3]	75 [18]	70 [21]	59 [13]
Vomiting	83.3 [16.7]	57.5 [0]	54 [14]	52 [7]
Nausea	66.7 [33.7]	60 [10]	61 [5]	51 [8]
Fatigue	50 [16.7]	62.5 [20]	37 [6]	40 [14]
Anorexia	16.7 [0]	57.5 [10]	49 [12]	44 [4]
Neutropaenia	33.3 [16.7]	40 [30]	25 [15]	39 [27]
Anaemia	16.7 [0]	32.5 [18]	33 [11]	38 [9]
Hypernatraemia	NA	15 [15]	NA	NA
Hypokalaemia	NA	NA	22 [12]	12 [3]

5-FU, 5-fluorouracil; LV, leucovorin; NA, not applicable.

treatment were attributed to infection in the setting of neutropaenia [Ko *et al.* 2013]. Overall, one-third of patients treated with liposomal irinotecan, either as monotherapy (120 mg/m^2) or in combination (80 mg/m^2) with 5-FU/LV, were reported by Wang-Gillam and colleagues to suffer from adverse events necessitating a treatment dose reduction, compared with only 4% of patients treated with 5-FU/LV [Wang-Gillam *et al.* 2016]. In a predefined subgroup analysis recently reported, the safety profile of the combination arm was generally similar across patient subgroups, apart from an increased risk of grade ⩾3 neutropaenia and reduced neutrophil counts in Asian patients [Chen *et al.* 2016]. Single-agent liposomal irinotecan was associated with more diarrhoea (any grade) than the combination arm as well as more grade 4 treatment-related adverse events, 16% *versus* 10%, respectively. Moreover, 4 of the 5 treatment-associated toxicities which resulted in death, occurred in patients being treated with single-agent liposomal irinotecan.

Liposomal irinotecan, at the lower dose of (80 mg/m^2), in combination with 5-FU/LV appears to be associated with a more tolerable toxicity profile as well as improved efficacy compared with liposomal irinotecan monotherapy (120 mg/m^2). However, in the context of second-line treatment for metastatic pancreatic cancer, all toxicity grades need to be considered and it is worth highlighting that over half of patients who received liposomal irinotecan, as monotherapy or in combination, reported diarrhoea, vomiting or nausea.

Table 3. Trials of unencapsulated irinotecan as a single agent or in combination with 5-FU in pretreated patients with advanced pancreatic cancer.

Author	N	Treatment (cycle)	Treatment Regimen	Median PFS (months)	Median OS (months)
Yi [Yi *et al.*, 2009]	33	Irinotecan (2W)	150mg/m²	2	6.6
Takahara [Takahara *et al.*, 2013]	56	Irinotecan (4W)	100 mg/m² D1, 8, 15,	2.9	5.2
Yoo [Yoo *et al.*, 2009]	31	Irinotecan +5FU/LV (2W)	Irinotecan: 70mg /m² D1+3; LV: 400mg/m² D1, 5-FU: 2000 mg/m² D1+2	1.9	3.8
Zaniboni [Zaniboni *et al.*, 2012]	50	Irinotecan +5FU/LV (2W)	Irinotecan: 180mg /m² D1; LV: 200mg/m² D1 + D2, 5-FU: 400 mg/m² bolus D1+2 and 600 mg/m² CI D1 –2	3.2	5
Neuzillet [Neuzillet *et al.*, 2012]	63	Irinotecan +5FU/LV (2W)	FOLFIRI-1 regimen, 55 patients: Irinotecan: 180mg /m² D1; LV:400mg/ m² D1; 5-FU: 400 mg/m² bolus D1 and 2400 mg/m² CI D1+2 FOLFIRI-3 regimen: 8 patients Irinotecan: 100mg /m² D1+3; LV: 400mg/ m² D1; 5-FU: 2400 mg/m² CI D1 +2	3.0	6.6

N, number of patients; PFS, progression-free survival; OS, overall survival; D, Day; W, Week; LV, leucovorin; 5-FU, fluorouracil; CI, continuous infusion.

Place in therapy

Single-agent liposomal irinotecan does not have a role in the treatment of metastatic pancreatic cancer in patients who have progressed on gemcitabine-based treatment. Liposomal irinotecan monotherapy at 120 mg/m² performs similarly to single-agent 5-FU/LV, but has a less favourable toxicity profile. First-line treatment with gemcitabine-based chemotherapy has been standard of care for patients with metastatic pancreatic cancer for over 10 years and in October 2015 the results of NAPOLI-1 led to US FDA and EMA approval of liposomal irinotecan in combination with 5-FU/LV for the treatment of patients with metastatic pancreatic cancer following disease progression on gemcitabine-based therapy. This is the first treatment regime to be approved for use in the second-line setting for pancreatic cancer. However, as previously discussed, FOLFIRINOX has more recently emerged as an alternative to gemcitabine in the first-line setting, in patients with a good PS after demonstrating superior survival outcome. It is therefore unclear how combination liposomal irinotecan and 5-FU/LV will be used in clinical practice relative to first-line FOLFIRINOX.

Despite a clear preclinical rationale for liposomal preparations, the clinical efficacy and toxicity of liposomal irinotecan has not been directly compared with unencapsulated irinotecan in the treatment of patients with pancreatic cancer either as a single agent or in combination. The efficacy of unencapsulated irinotecan as a single agent, following failure of gemcitabine-based chemotherapy, was studied in a phase II of 33 patients treated with 150 mg/m² irinotecan every 2 weeks. They reported a PFS and OS of 2.0 months (95% CI, 0.7–3.3) and 6.6 months (95% CI, 5.8–7.4), respectively [Yi *et al.* 2009] (see Table 3). A similar PFS of 2.7 months (95% CI, 2.1–2.9) was found in patients treated with liposomal irinotecan in the NAPOLI-1 trial, although the OS was less, at 4.9 months (95% CI, 4.2–5.6). Toxicities following different irinotecan preparations were directly compared in a randomized phase II trial of patients with locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma. Grade 3/4 neutropaenia and diarrhoea was reported in 11.4% and 27.3% of patients treated with 120 mg/m² of liposomal irinotecan. While 15.9% and 18.2% of patients suffered from grade 3/4 neutropaenia and diarrhoea, respectively, following 300 mg/m² of unencapsulated irinotecan [Roy *et al.* 2013].

The combination of unencapsulated irinotecan with 5-FU/LV has also previously been explored. In a randomized phase II trial comparing modified FOLFOX (5-FU/LV and oxaliplatin) with FOLFIRI (5-FU/LV and irinotecan), the median OS of patients in the FOLFIRI arm was disappointing at 3.8 months [Yoo *et al.* 2009]. The two nonrandomized studies [Neuzillet *et al.*

2012; Zaniboni *et al.* 2012] with small sample sizes reported a more favourable median OS of 5 and 6.6 months, respectively, following treatment with encapsulated irinotecan in combination with 5-FU/LV using the schedules shown in Table 3. In one of these studies, Zaniboni and colleagues reported combination treatment resulted in grade 3/4 neutropaenia and diarrhoea in 20% and 12% of patients, respectively [Zaniboni *et al.* 2012]. Interestingly, a similar incidence of grade 3/4 neutropaenia and diarrhoea was reported in patients receiving combination liposomal irinotecan and 5-FU/LV within the NAPOLI-1 trial (Table 2).

Patients with metastatic pancreatic cancer, who are well for second-line treatment, may have a favourable biology and a longer survival independent of choice of therapy. Although combination treatment of liposomal irinotecan and 5FU/LV met criteria for a statistically significant increase in OS compared with the control, the overall clinical benefit to the individual patient must be considered. A 2-weekly regime, associated with grade 3/4 neutropaenia in 27% of patients and any grade diarrhoea, nausea and vomiting in over 50% of patients, is not insignificant in the palliative setting. Although, it must be noted that the quality of life of patients on combination treatment was not reported to be appreciably different from those allocated 5-FU/LV.

Despite preclinical studies suggesting otherwise, the toxicity profile of liposomal irinotecan does not seem to be significantly better than standard unencapsulated irinotecan *in vivo*. It would be interesting to compare the efficacy and toxicity profile of the two irinotecan preparations in FOLFIRINOX, which is likely to remain the treatment of choice in first-line metastatic pancreatic cancer for patients with a good PS.

Three trials involving liposomal irinotecan are currently recruiting patients with pancreatic cancer. A phase II comparative study to assess the safety, tolerability and efficacy of liposomal irinotecan and 5-FU/LV with and without oxaliplatin compared with nab-paclitaxel and gemcitabine, is currently recruiting patients with advanced pancreatic adenocarcinoma [ClinicalTrials.gov identifier: NCT02551991]. A randomized phase II trial is recruiting Japanese patients with metastatic pancreatic cancer to assess the safety, tolerability and the pharmacokinetics of liposomal irinotecan in combination with 5-FU/LV and to compare the efficacy of combination treatment with single-agent 5-FU/LV[ClinicalTrials.govidentifier:NCT02697058].

Patients are also currently being recruited to study the pharmacokinetic and pharmacodynamic profile of BBI608 (a first-in-class cancer stem cell inhibitor), when administered in combination with standard chemotherapies including combination liposomal irinotecan and 5-FU/LV in patients with metastatic pancreatic cancer [ClinicalTrials.gov identifier: NCT02231723].

There is a clear need for well-designed, randomized clinical trials in the second-line setting after FOLFIRNOX failure. The role of liposomal irinotecan and 5-FU/LV in this setting is unclear. A pre-planned subgroup analysis in NAPOLI-1, showed no survival benefit of combination therapy over control, in the 12 patients who had previously been treated with irinotecan; HR 1.25 (0.49–3.19). However, the results from NAPOLI-1 alter the therapeutic landscape for metastatic pancreatic cancer by enabling clinicians and patients to choose a sequential approach to treatment. For patients in whom first-line FOLFIRINOX is not the preferred option, gemcitabine-based chemotherapy followed by liposomal irinotecan and 5-FU/LV is a reasonable treatment paradigm for a subset of patients.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Irinotecan(Campto R): Efficacy as Third/Forth Line Therapy in Advanced Pancreatic Cancer

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Abstract. *Following the concept that the actual survival of pancreatic cancer patients can only be significantly improved by sequential poly-chemotherapy (EOSPC) in order to add one or two further progression free-survival times (PFST), in addition to the potential antitumoral effects of a first- or second-line therapy we studied the therapeutic efficacy of a third- or fourth-line chemotherapy with irinotecan alone, or in combination with oxaliplatin and high dose 5-FU/FA respectively, in a pilot study in 17 patients. Follow-up was performed on the basis of clinical investigations, imaging methods and the course of tumor markers, mainly CT and CA 19-9. The overall response rate in these cases of third/fourth- line therapies was 1PR, 4 MR, 6 SD in the imaging methods compared to 5 PR, 2 MR and 5 SD on the basis of the tumor marker courses in the serum. The median PFST amounted to 4 months. Side effects could be seen as reported in the literature. Only in 1 patient did treatment have to be stopped due to irinotecan-induced gastrointestinal symptoms. Our data might suggest that combinations are more effective than irinotecan alone. However, further studies have to demonstrate whether irinotecan alone or in combination with e.g. oxaliplatin and 5-FU /FA will be more effective. The results suggested that irinotecan alone or in combination might also be used as third- and fourth-line therapeutical trials in exocrine pancreatic cancer in order to improve the survival time of these patients based on efficacy orientated sequential poly-chemo-therapy (EOSPC).*

Irinotecan (Campto R) is well accepted as second/third-line therapy of colorectal cancer. Recently it has also been introduced as first-line therapy in combination with 5-fluorouracil. In addition, it is increasingly being discussed as an active regimen, alone or in combination in other tumor diseases like lung cancer, stomach or pancreatic cancer (1-3).

We here report on a pilot trial with irinotecan alone or in combination as third- or fourth-line therapy in patients suffering from exocrine pancreatic cancer. The treatment trials were started based on our first promising data (1) and following our concept (4) that significant prolongation of survival in pancreatic cancer patients by palliative chemotherapy might be realisable by efficacy orientated sequential poly-chemotherapy (EOSPC) in order to add one or two further progression free survival times (PFST) to the potential efficacy of a first- or second-line therapy.

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Key Words: Irinotecan, advanced pancreatic cancer.

Materials and Methods

17 patients with histologically proven exocrine pancreatic cancer were included in this trial (9 males, 8 females, age 47 - 74 years). Treatment with irinotecan was started as third-line (n=7) or fourth-line (n=10+1) therapy. In one patient third-line therapy was started as Irinotecan monotherapy, followed by a fourth-line therapy with Irinotecan in combination with 5-FU/FA.

Irinotecan monotherapy (n=12) was administered weekly (85 mg/m^2 for 90 minutes), irinotecan + oxaliplatin (n=3) in a two-weeks regimen (oxaliplatin 65 mg/m^2 day 1 over 3-4 hours and irinotecan 85 mg/m^2 day 8 and 15 over 90 minutes), and irinotecan + high dose 5-FU/FA (n=3) weekly (irinotecan 85 mg/m^2 over 90 minutes, followed by folinic acid 500 mg/m^2 over 2 hours and 5-FU 2,200 mg/m^2 over 20-24 hours).

Table 1. *Antitumor efficacy of third or forth line therapy of exocrine pancreatic cancer with Irinotecan alone or in combination with Oxaliplatin and 5-FU/FA resp.*

	Campto* Mono N=12		Campto+Oxaliplatin N=3		Campto+5-FU/FA N=3	
	TM	CT	TM	CT	TM	CT
CR						
PR	2		1		2	1
MR		3	1		1	1
SD	4	2	1	3		1
PD	6	7				

*Campto = Irinotecan

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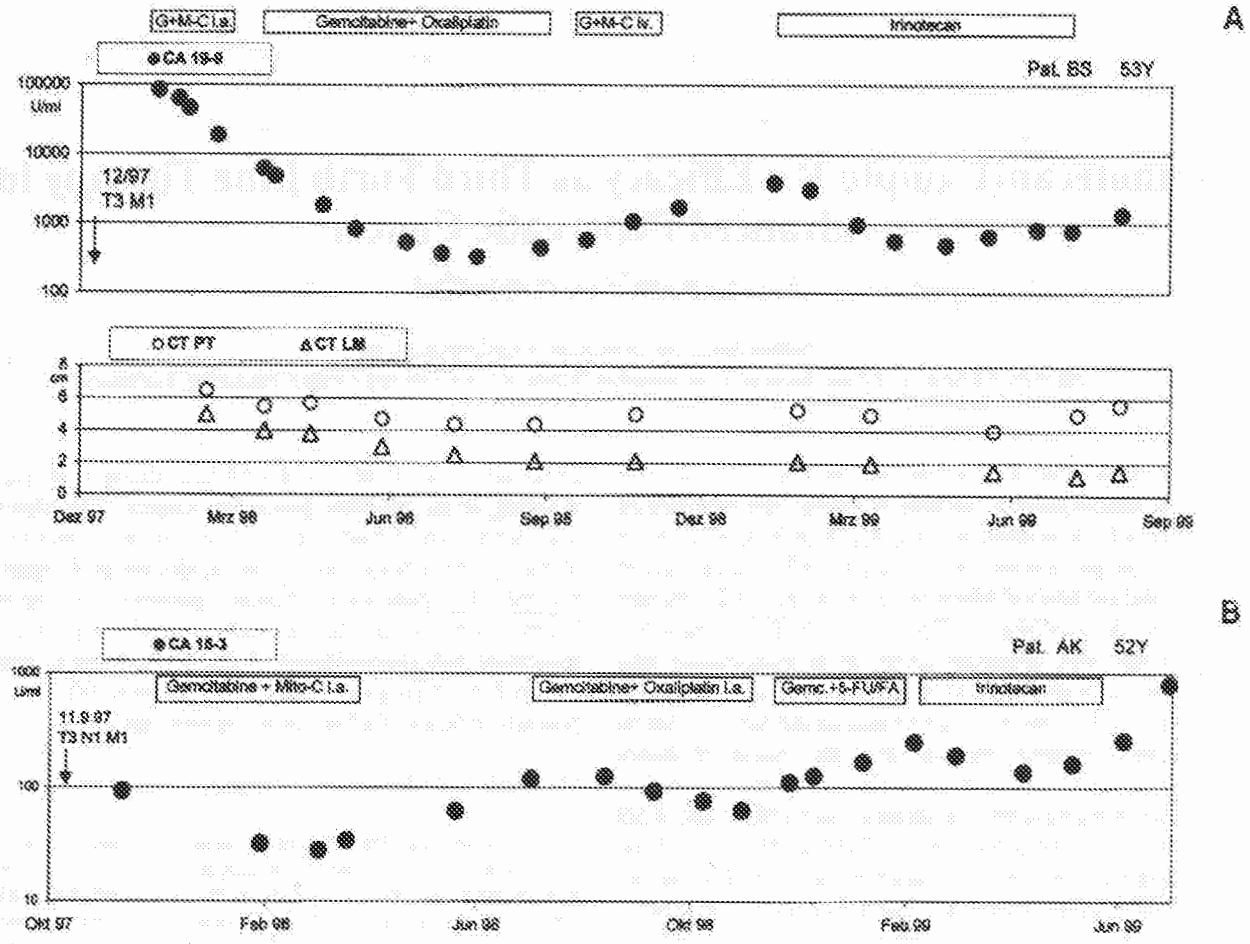

Figure 1 A and B. *Two examples for antitumoral efficacy of a forth line therapy of exocrine pancreatic cancer disease with irinotecan monotherapy. (CT = Computerized Tomography, PT = primary tumor, LM = liver metastases).*

First-, second- and third-line therapies before irinotecan treatment in these patients included locoregional therapy with a combination of gemcitabine + mitomycin-C (5) and intravenous treatment with gemcitabine + mitomycin-C (similar to the locoregional approach), gemcitabine monotherapy (1000 mg/m^2 weekly, 30 minutes i.v. infusion), high dose 5-FU/FA (6) or a combination of gemcitabine + oxaliplatin (Eloxantine R) (7).

The efficacy of the treatment was evaluated by a combination of clinical investigation, imaging methods (mainly CT) and serial determinations of the relevant tumor markers. In most cases CA 19-9 (CEA= 2, CA 15-3 = 1) (ES 700 and Elecsys respectively, Roche, Germany). Aliquots of the serum samples were stored in a serum bank (-70°C)(ZeTDT GmbH) in order to re-evaluate the course of the tumor markers whenever necessary.

Imaging and tumor marker response was evaluated following WHO criteria for the evaluation of imaging methods: CR (complete response) = no tumor available and tumor markers within the normal range; PR (partial response) = decrease of tumor size or tumor markers < 50% of the initial values; MR (minor response) = decrease by 25-50%; SD (stable disease) = tumor size or tumor markers remain stable (+/- 25%) for more than two months; PD (progressive disease)= further increase > 25% of initial tumor size and > 25% of initial serum concentration of the relevant tumor markers within two months.

Results

The antitumor efficacies of the irinotecan regimens are presented in Table I.

Altogether we observed 1 PR, 4 MR, 6 SD and 7 PD in the imaging methods compared to 5 PR, 2 MR, 5 SD and 6 PD analysing the tumor marker courses. Median PFST in the responders (PR, MR, SD) amounted to 4 months. As already reported the relevant tumor marker, in the majority of patients CA 19-9, again represented the more sensitive and more rapid parameter compared to the imaging methods.

The irinotecan regimens in general were tolerated without severe complications. Side-effects could be registered as reported in the literature. Treatment with irinotecan alone or in combination in our 17 patients was interrupted because of PD or new progress, except from one patient with severe gastrointestinal symptoms.

Five, typical examples for tumor response (imaging methods and tumor markers respectively) during third/fourth-

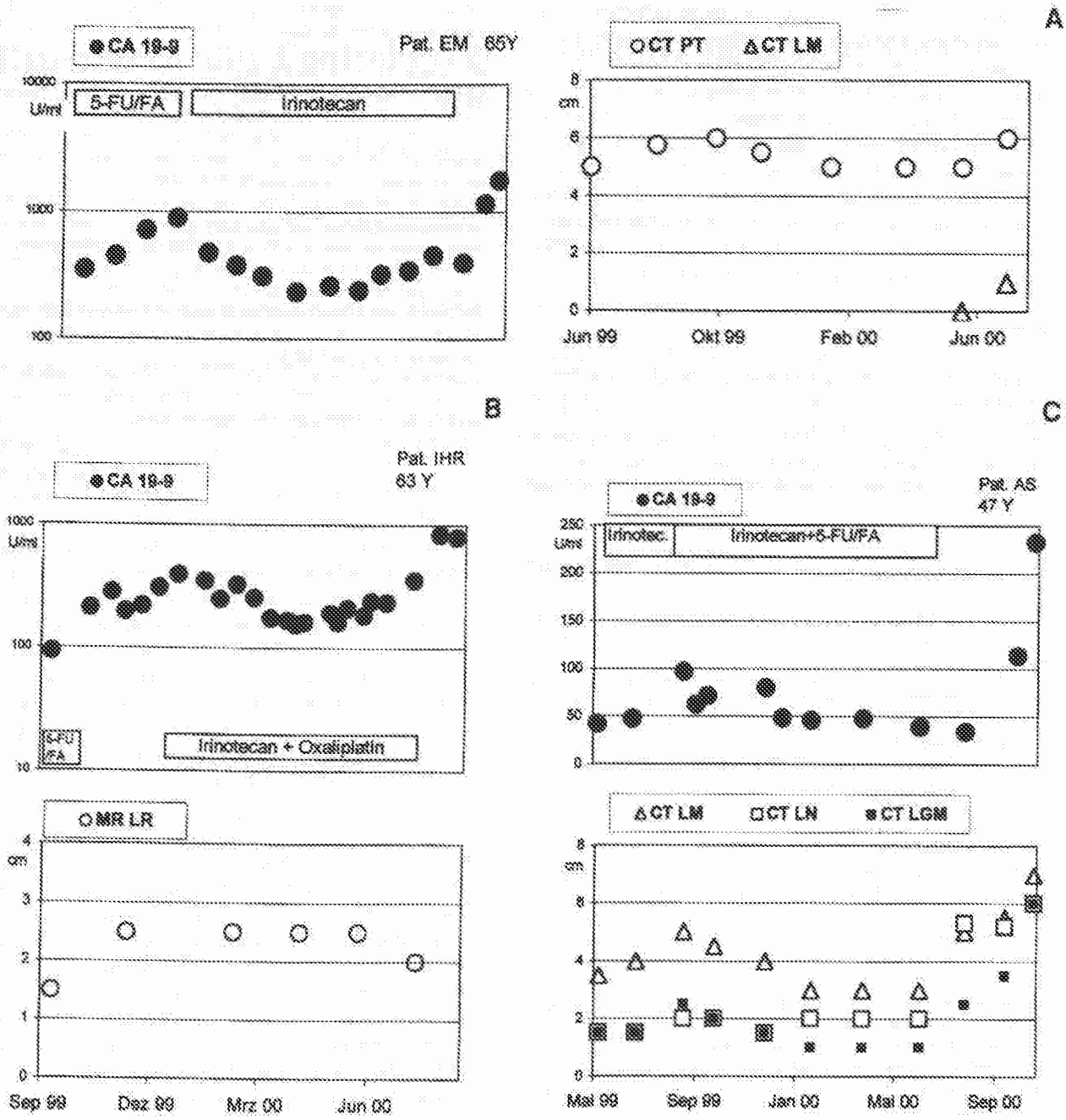

Figure 2A,B and C. *Three typical examples for antitumoral efficacy of irinotecan alone or in combination with oxaliplatin and 5-FU/FA, respectively as third- and fourth-line chemotherapy of exocrine pancreatic cancer. (CT = Computerized Tomography, MR = Magnetic Resonance Tomography, LR = local recurrence, PT = primary tumor, LM = liver metastasis, LN = lymph nodes, LG = lung metastasis)*

line irinotecan treatment are shown in Figures 1A,B and 2A,B and C.

Discussion

The results of this pilot study confirmed data recently reported that tumor markers, in the case of pancreatic cancer mainly CA 19-9, in general represent more sensitive parameters of tumor response to palliative therapy when compared to imaging methods. Furthermore, the data suggested that irinotecan alone or in combination may also be active in pancreatic cancer patients as a third/fourth-line trial with a median PFST of 4 months. On the basis of our data it might be speculated that irinotecan combinations with

oxaliplatin and 5-FU/FA will be more effective than irinotecan alone. However, prospective studies have to be undertaken to confirm this hypothesis.

In our opinion these data justify trying irinotecan alone or in combination as third/fourth-line treatment trials in exocrine pancreatic cancer patients in order to improve survival. This would follow the concept that significant prolongation of survival of these non-resectable patients seems to be realizable only by sequential palliative chemotherapy with the aim of adding a second or third PFST to the potential results of a first- or second-line therapy.

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Reflections on Treatment Strategies for Palliative Chemotherapy of Pancreatic Cancer

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Abstract. *Following our concept of efficacy-orientated sequential polychemotherapy, we report on the results of palliative chemotherapy in 69 patients suffering from exocrine pancreatic cancer, admitted to our unit in 2004. Evaluation of tumor response was mainly based on the serum courses of the tumor markers CA 19-9 and CEA; in addition, the modern imaging methods CT or MRT, including MRCP and MR-angiography, were performed bi-monthly. The median survival of the 69 patients (65% metastasized stages) was 16 months. The median survival increased with the number of effective treatment sequences, for the whole group from 5 to 10 and 23 months in relation to 0, 1 and >1 effective sequences respectively. The results support our concept of EOSPC in pancreatic cancer patients, compared to clinical studies following protocols with only 1 treatment sequence and median survival rates of no more than 6-9 months. Compared to the efficacy-orientated sequential polychemotherapy (EOSPC) concept, which does not exclude but also allows the inclusion of clinical trials for further evaluation of new drugs or drug combinations, the common practice looking for survival in studies following protocols with only 1 treatment sequence might represent a negative predictive factor with respect to overall survival, as can be demonstrated by a comparison of our data with relevant recent literature. Our results further indicate that the interest of the clinicians and companies should not be focused only on first-line therapies, but also on 2nd- and 3rd-line strategies, as in our patients a second- and third-line therapy could be started in 73% and 68% of the patients respectively.*

The majority of studies published during recent years still report on the results of a single treatment regimen in relation to survival of pancreatic cancer patients. In these presentations, no details are reported on second- or third-line therapies at all, or whether second-/third line therapies were given in an individual or prospectively planned sequence. The median survival in these studies following protocols with only 1 treatment sequence again amounted to no more than 6-9 months (1-13), in contrast to our data on efficacy-orientated sequential polychemotherapy (EOSPC) with overall median survival rates of 12 and more months, based on our clinical experience (14-16).

Therefore, the treatment and survival data of patients admitted to our unit in 2004, who were treated by us or in close cooperation with us, were analysed. The follow-up was mainly based on monthly determinations of the tumor markers CA 19-9 and CEA, complemented by bi-monthly performed CT / MR imaging methods in addition to the common laboratory and clinical investigations.

The aim of the study was not to evaluate the superiority of one single regimen, but to examine the possibility of improving survival of pancreatic cancer patients by a sequence of chemotherapeutic drugs or drug combinations.

Patients and Methods

Patients. Sixty-nine pancreatic cancer patients, 38 males, 31 females, aged 31-77 (median 60) and 39-73 (med 60) years, suffering from exocrine pancreatic cancer of the head (n=60), corpus (n=5) and cauda (n=4) respectively, admitted in 2004 with start of treatment before or within 2004 were studied.

The patients suffered from proven non-resectable pancreatic exocrine cancer (n=43) without (n=16) or with liver metastases (n=27), or tumor recurrence (n=26) without (n=8) or with distant metastasis (n=18). G1 /G2 and G3 tumors were found in 3%, 66% and 31% of patient respectively.

Treatment regimens. Gemcitabine was applied as monotherapy (1000 mg/m^2 weekly as commonly used) or in combinations. Gemcitabine + mitomycin-C (3-week regimen; day 1: 7 mg/m^2 mitomycin-C over 30 min followed by 450 mg/m^2 gemcitabine over 60 min; day 8 and 15: 450 mg/m^2 gemcitabine over a period of 90 min. Day 21 was the first day of the second cycle. In the locoregional approach, mitomycin-C + gemcitabine were given at day 1 *via* a catheter inserted in the celiac trunk or into the hepatic artery, gemcitabine at day 8 and 15 intravenously) (14, 17, 18).

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Key Words: Pancreatic cancer, chemotherapy, treatment strategies.

5-Fluorouracil/folinic (5FU/FA) acid was applied *via* the central venous system according to Ardalan *et al.* (19). Irinotecan was applied weekly either as monotherapy (85 mg/m^2 over 90 min) or in combination with 5FU/FA, based on previous studies (20).

Gemcitabine in combination with oxaliplatin was given as described elsewhere (21).

Oxaliplatin was given in combination with 5FU/FA. Day 1: oxaliplatin (80 mg/m^2 over 2 h) + 5FU/FA; day 8: 5FU/FA. Day 14 was the first day of the second cycle.

In single patients, other drug/drug combinations were tried: gemcitabine in combination with pemetrexed (international first-line study), capecitabine alone or in combination with gemcitabine or oxaliplatin, and taxotere as monotherapy.

Follow-up. Follow-up was mainly based on clinical signs as well as on tumor marker determinations (CA 19-9 and CEA) every 4 weeks and on the results of bi-monthly performed CT or/and MR including MRCP and MR angiography. Ultrasound (US) was used mainly to look for ascites and in the case of clinical signs needing acute differential diagnosis of diseases of the biliary tract system and the pancreas.

In 52 patients, CA 19-9 represented the most relevant tumor marker, in 5 patients CEA. Twelve patients did not show elevated levels of either tumor markers at time of commencing chemotherapy. In these patients, the follow-up was mainly based on the results of the imaging methods CT/MR using the conventionally accepted response criteria.

Based on our previously published results indicating a more rapid and sensitive response of CA 19-9 to tumor treatment compared to the imaging methods, the tumor response in this study was mainly based on the results of the tumor marker determinations except from the 12 patients not expressing tumor markers at the beginning of the treatment.

The imaging methods were mainly used for pretherapeutical staging, in order to avoid potential misinterpretations of tumor marker serum curves in the case of concomitant biliary infections, to diagnose local or distant complications, and for future analyses needing a comparison of our data with those of other groups mainly using imaging methods for follow-up.

Tumor response criteria. Tumor marker response was analysed in relation to the generally accepted morphological criteria: CR (complete response): decrease into the normal range, PR (partial response): decrease below 50% of the initial values, MR (minor response): decrease to values between 25-50% of the initial values SD (stable disease): +/- 25% of the initial values over a time period of more than 2 months, PD (progressive disease): increase to more than 25% of the initial values in 2 or more determinations.

A progress of the tumor disease was also diagnosed in the case of a significant increase of the tumor marker levels (>25%) even in the case of an only slight increase of the tumor lesions in the imaging methods (>10%).

Efficacy-orientated sequential polychemotherapy (EOSPC). First-line therapy mainly consisted of gemcitabine monotherapy (n=53), a combination of gemcitabine+mitomycin C (14), given intravenously (n=8) or locoregionally (n=6), as well as gemcitabine + pemetrexed (n=2).

Second-line treatment was performed in 50 patients with 24 h infusion with 5FU/FA (n=30), gemcitabine+mitomycin-C (n=12, intravenously n=6, intraarterially n=6) and gemcitabine +5FU/FA (n=1), gemcitabine mono (n=2), Fu/FA (n=1), capecitabine (n=1), 5FU+irinotecan (n=1) and taxotere (n=2), respectively.

Third-line therapy in 47 patients comprised 5FU/FA (n=14), 5FU/FA+irinotecan (n=6), 5FU/oxaliplatin (n=7), capecitabine+oxaliplatin (n=1), 5FU+oxaliplatin (n=7), irinotecan (n=3), gemcitabine mono (n=3) and gemcitabine+mitomycin-C (n=6; intravenously n=4, intraarterially n=2).

A fourth-line therapy was started in 15 patients with 5FU/FA alone (n=1) or in combinations with oxaliplatin (n=3), irinotecan (n=2) or gemcitabine (n=1), with irinotecan (n=2) or with gemcitabine (n=2), gemcitabine+mitomycin-C (n=3 intravenously) or in a single case with cetuximab+gemcitabine.

Tumor marker determinations. The tumor markers CA 19-9 and CEA were determined following international quality control recommendations (22, 23). Aliquots of serum samples were additionally stored at -70˚C in order to improve the results by redetermination if desired. CA 19-9 was determined using a Kryptor system (BRAHMS, Henningsdorf, Berlin, Germany), CEA using the ELECSYS system (Roche).

Supportive care. In addition to palliative chemotherapy in all patients, we also stressed the actual possibilities of supportive therapy, pain therapy, nutrition including supplements and parenteral home nutrition *via* port systems, as well as antiemetics, palliative surgical endoscopy (biliary stents/PTCD/ intestinal, and in one case also repeated colonic stents).

Results

Our results in patients admitted to our unit in 2004 confirm our previous data in so far that the overall survival for pancreatic cancer patients increases with the number of effective treatments up to median survivals of 18.5 (M1 stages) and 27.5 months (M0 stages) for patients with >1 effective treatment on the basis of the tumor marker analyses, *i.e.* for 62% of the M0 tumors and 49 % of the M1 tumors (Figure 1).

The overall survival of all 69 patients treated within this period was 16 months. The overall survival for the M0 tumors (n=31) was 18 months and for the M1 tumors (n=38) 13 months.

These survival data are comparable to those reported during recent years (14-16).

In addition, we analysed our data for the relation between the number of effective treatments and the survival. Even these data support the concept that survival increases in relation to the number of effective treatments. In relation to 0 effective and 1 or >1 effective treatments, we found a median survival for all 69 patients of 5 (n=9), 10 (n=22) and 23 (n=38) months respectively (Figure 1).

The individual data are shown in Figure 2. The grey bars represent patients still alive at the time of evaluation.

The combination of gemcitabine + mitomycin again proved a rather effective treatment regimen. In the 15 first-line

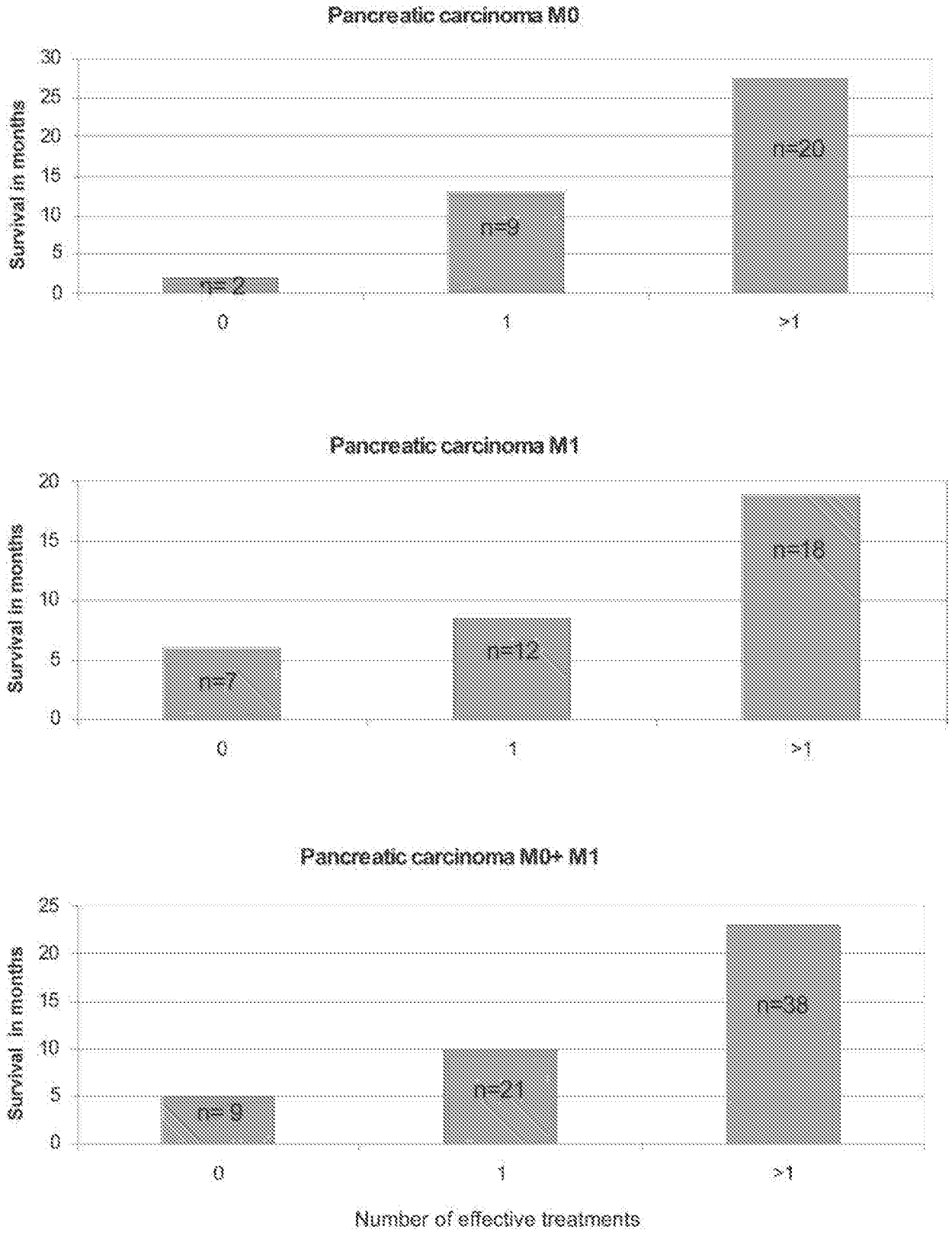

Figure 1. *Median survival (months) of pancreatic cancer patients in relation to the number of effective treatment sequences, demonstrated for advanced disease without distant metastasis (M0), metastasized stages (M1) and the whole group of patients (M0+M1).*

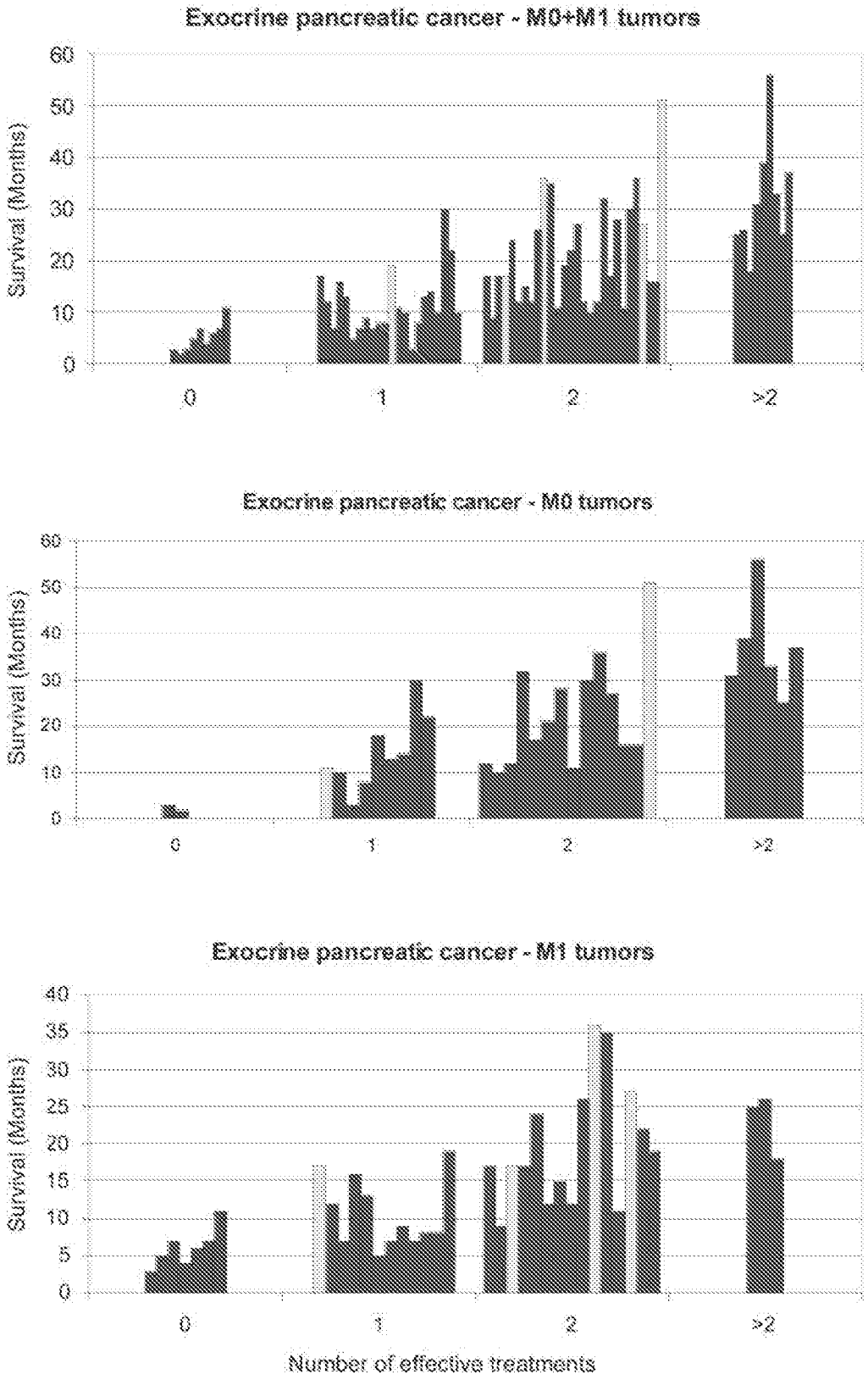

Figure 2. *Survival (months) of 69 patients admitted with pancreatic cancer in relation to the number of effective therapies, demonstrated for advanced disease without distant metastasis (M0), metastasized stages (M1) and the whole group of patients (M0+M1).*

treatments we diagnosed CR, PR, MR and SD in 1/14, 5/14, 5/14 and 3/14 patients respectively, based on CT/MR imaging methods and 3/14, 6/14, 1/1 and 2/14 patients based on the course of the relevant tumor markers. Second-line therapy with gemcitabine+mitomycin-C was performed in 12 patients with the following results: PR in 9 patients on the basis of the tumor marker determinations, as well as MR in 2 and 3, and SD in 1 and 7 patients on the basis of serum tumor markers curves and the imaging methods respectively.

Analysing the number of different treatment regimens tried in our 69 patients in 2004, we found that 50/69 patients (73%) presented the opportunity for a second-line treatment, 47/69 (68%) for a third-line treatment in the case of follow-up by serial tumor marker determinations (monthly), as well as bi-monthly cimaging methods.

Discussion

The presented data further support the concept that an efficacy-orientated sequential polychemotherapy seems to improve the survival of pancreatic cancer patients, in locally advanced, as well as metastasized stages, in relation to the number of effective treatment lines.

In contrast to our data, clinical studies looking for median survival following protocols with only one treatment sequence report survival data of no more than 6-8 to 9 months, *e.g.* for gemcitabine alone (1, 2), gemcitabine in combination with oxaliplatin (5, 11) or irinotecan (4, 10) or mitomycin-C (9) or other cytostatics (13), for capecitabine (3), or combinations of gemcitabine with newer drugs like erlotinib (8, 12), bevacizumab (7) or pemetrexed (6).

However, in 2005, two further studies supported our concept that further treatments after a first-line treatment can improve survival. Oettle *et al.* demonstrated that a second-line therapy with 5FU/FA+oxaliplatin after first-line treatment with gemcitabine improved overall median survival by 6 weeks compared to a best supportive care arm (24). Moreover, in a study of 30 patients, Cantore *et al.* found that a second-line treatment with a combination of irinotecan+oxaliplatin improved median overall survival of patients with metastasized stages from diagnosis up to 16 months – after a first-line treatment with gemcitabine (n=17), 5FU (n=7) and a first-line therapy with gemcitabine followed by a therapy with intraarterial application of FLEC (n=6) (25).

Clearly, our clinical practice with EOSPC is not able to determine the superiority of one or the other treatment regimen in comparison to the others. However, our concept with a first-line therapy with gemcitabine alone or in combination, followed by second-line regimens with 5FU/FA alone or in combination and a third-line treatment with further gemcitabine combinations or 5FU/FA or irinotecan combinations seems to offer a good chance for pancreatic cancer patients to live longer than supposed by all the prospective randomized studies on survival after a single treatment.

The concept of EOSPC for pancreatic cancer patients also seems to be supported by results of a sequential chemotherapy study in patients suffering from colorectal cancer, published in 2004. Tournigand and coworkers demonstrated that a sequential therapy with FOLFIRI (first-line) followed by FOLFOX 6 (second-line), or FOLFOX 6 (first-line) followed by FOLFIRI (second-line) improves survival of colorectal cancer patients compared to survival after first-line therapy with FOLFOX 6 and FOLFIRI respectively, without second-line or further regimes (26).

Three further conclusions might be drawn from the data of our publications in 2000, 2003 and 2005 and the presented data here, supported by the publications of Oettle *et al.* (24) and Cantore *et al.* (25): 1) Individualized sequential treatment strategies seem to improve survival of pancreatic cancer patients compared to that suggested by clinical studies on survival after treatment with only one sequence. This sequential concept does not exclude the performance of clinical studies. Clinical studies are essential for evaluation of the efficacy of new drugs and/or drug combinations. However, in order to evaluate a new drug or new drug combination, clinical studies should include a sequential strategy with at least 2 or 3 treatment sequences described within the protocol in detail. 2) Companies and institutions should not only look for the activity of new drugs or drug combinations in first-line treatment studies, but also for their potential activity as second- or third-line therapies, as modern follow-up in our studies allowed a second-line therapy in 73% of our patients admitted in 2004, and a third-line therapy in 68%. 3) Prospective randomized studies as mainly published during recent years, only looking for the effects of first-line therapies on survival and therefore neclecting the possibility of second- or third-line therapies, might have a negative influence on survival of pancreatic cancer patients.

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GASTROINTESTINAL (NONCOLORECTAL) CANCER

DNA damage with liposomal irinotecan (nal-IRI) in pancreatic cancer xenografts: Multimodal analysis of deposition characteristics.

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Ipsen Bioscience, Inc., Cambridge, MA; Merrimack Pharmaceuticals, Inc., Cambridge, MA; Merrimack Pharmaceuticals, Cambridge, MA

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Abstract Disclosures

Abstract

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Background: nal-IRI facilitates intratumoral drug deposition through enhanced permeability and retention, with pharmacokinetic and pharmacodynamic (PK/PD) analyses demonstrating an extended circulation of the liposome and its encapsulated payload. Here we investigate nal-IRI and non-liposomal irinotecan (IRI-HCl) in pancreatic tumor models. **Methods:**AsPC-1, BxPC-3 and CFPAC-1 tumors were grown in NOD-SCID mice, with animals dosed q7d with IRI-HCl (25–50 mg/kg) or nal-IRI (5–10 mg/kg) to evaluate efficacy under equivalent exposure. To assess PK/PD, samples were collected at multiple timepoints up to 72 h (IRI-HCl) and 168 h (nal-IRI) and evaluated for liposome localization, macrophage, tumor and vessel markers, DNA damage and apoptosis. **Results:** At equal dose levels, nal-IRI resulted in prolonged circulation and tumor exposure of IRI and active metabolite SN-38. Nal-IRI increased the duration of active metabolite above a hypothetical threshold compared with IRI-HCl, with an improved control of growth rates in pancreatic tumor models even at 5x lower doses. DNA damage in BxPC-3 tumors with IRI-HCl and nal-IRI was comparable, but maximal at 6 h after IRI-HCl (50 mg/kg) and 72 h after nal-IRI (10 mg/kg). Liposomes deposited in tumors heterogeneously around functional vessels. Accumulation peaked after 6–24 h, with similar deposition patterns in cell– or patient–derived xenografts. Liposomes were taken up by macrophages and to lesser extent by tumor or other stromal cells. Similar patterns were observed in a pancreatic PDX models. DNA damage was

observed 24–72 h after treatment, mostly in tumor cells even without internalized liposomes. DNA damage and apoptosis were minimally seen in non-tumor cells. Induction of apoptosis was more prevalent in tumor cells even at lower liposomal uptake levels, while most non-tumor cells showing liposome uptake did not undergo apoptosis. **Conclusions:** Nal-IRI improved tumoral payload deposition in pancreatic models, with heterogeneous deposition restricted to perivascular areas. DNA damage patterns suggests sufficient intratumoral bioavailability of SN-38 outside of deposition areas. Effects of repeated dosing should be explored.

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REVIEW

Nanomedicine developments in the treatment of metastatic pancreatic cancer: focus on nanoliposomal irinotecan

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Abstract: Nanoliposomal irinotecan (nal-IRI) was originally developed using an efficient and high-loading capacity system to encapsulate irinotecan within a liposomal carrier, producing a therapeutic agent with improved biodistribution and pharmacokinetic characteristics compared to free drug. Specifically, administration of nal-IRI results in prolonged exposure of SN-38, the active metabolite of irinotecan, within tumors, while at the same time offering the advantage of less systemic toxicity than traditional irinotecan. These favorable properties of nal-IRI, confirmed in a variety of tumor xenograft models, led to its clinical evaluation in a number of disease indications for which camptothecins have proven activity, including in colorectal, gastric, and pancreatic cancers. The culmination of these clinical trials was the NAPOLI-1 (Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy) trial, an international Phase III study evaluating nal-IRI both alone and in combination with 5-fluorouracil and leucovorin in patients with metastatic pancreatic adenocarcinoma following progression on gemcitabine-based chemotherapy. Positive results from NAPOLI-1 led to approval of nal-IRI (with 5-fluorouracil/leucovorin) in October 2015 by the US Food and Drug Administration specifically for the treatment of metastatic pancreatic cancer in the second-line setting and beyond, a clinical context in which there had previously been no accepted standard of care. As such, nal-IRI represents an important landmark in cancer drug development, and potentially ushers in a new era where a greater number of patients with advanced pancreatic cancer can be sequenced through multiple lines of therapy translating into meaningful improvements in survival.

Keywords: pancreatic cancer, irinotecan, nanoliposomal, clinical trial, NAPOLI-1

Introduction

Pancreatic cancer currently represents the fourth leading cause of cancer-related mortality in the United States among both males and females, with an estimated 48,960 new cases and 40,560 deaths attributed to this malignancy in 2015.[1] Moreover, the number of pancreatic cancer-related deaths continues to increase, with current projections indicating it will likely rise to the second-leading cause of cancer-related mortality in the United States sometime during the next decade, trailing only lung cancer.[2] Globally, pancreatic cancer ranks as the seventh most common cause of cancer death, responsible for more than 330,000 deaths worldwide as of 2012 (4% of the total).[3]

These statistical findings reflect the sobering realities of this disease: the vast majority of patients present at advanced stages of disease beyond which a potentially curative operation is feasible; and therapeutic gains in this disease have been more modest rather than transformative over the past several decades. Moreover, while our understanding of the fundamental pathogenic and molecular bases of pancreatic

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cancer continues to grow, an ability to translate these findings into "actionable" results has been limited,[4] and we still lack useful predictive biomarkers that can aid in decision-making and bring our treatment paradigms into the modern realm of precision medicine.

On a more positive note, over the past several years we have seen positive results from multiple Phase III clinical trials that have expanded our therapeutic options for patients with advanced pancreatic cancer. The most recent of these developments has led to the approval by the US Food and Drug Administration (FDA) of nanoliposomal irinotecan (herein referred to as nal-IRI) in October 2015. This represents a significant milestone as this drug represents the first agent specifically approved for use in the second-line treatment of metastatic pancreatic cancer.

This paper will start by reviewing briefly the current treatment landscape for pancreatic cancer, with special attention on the proven therapeutic options (or, more accurately, lack thereof) that exist beyond frontline chemotherapy, as this is the specific indication for which nanoliposomal irinotecan has been approved. This will be followed by a discussion of the preclinical development of nal-IRI and its pharmacologic properties; and finally clinical evaluation of nal-IRI from early dose-finding studies to disease-specific clinical trials, with a particular focus on the development and approval of this novel agent in pancreatic cancer.

The current treatment landscape for metastatic pancreatic cancer

Chemotherapy remains the mainstay of treatment for patients diagnosed with metastatic pancreatic cancer. Single-agent gemcitabine became the standard of care back in the mid-1990s following results of a Phase III study that demonstrated improvements in overall survival (OS), response rate, as well as a quality of life measure termed clinical benefit response (a composite measure of analgesic requirements, performance status, and change in weight) when compared with 5-fluorouracil (5-FU).[5] Over the subsequent decade plus, a number of Phase III trials were designed to assess whether any survival benefit could be derived from adding additional cytotoxic or targeted agents to gemcitabine. With the exception of the PA.3 trial, which evaluated erlotinib, an oral tyrosine kinase inhibitor that binds to the epidermal growth factor receptor (EGFR),[6] none of these studies demonstrated a statistically significant survival advantage of combination therapy when compared to gemcitabine alone. Moreover, despite approval of erlotinib by the FDA in 2005, its use has not been very widespread, based on a fairly modest incremental survival benefit when added to gemcitabine (hazard ratio (HR) of 0.81 for overall survival) and substantial toxicities.

After this relatively fallow period through the early 2000s, positive data from a couple of randomized Phase III trials over the past several years have led to the acceptance of two new standards of care for the first-line treatment of metastatic pancreatic cancer. PRODIGE 4/ACCORD 11 was a 342-patient French trial in which FOLFIRINOX, a multidrug combination consisting of bolus plus infusional 5-FU, leucovorin (LV), irinotecan, and oxaliplatin administered on a biweekly dosing schedule, was compared to single-agent gemcitabine in patients with previously untreated metastatic pancreatic cancer and intact functional status (Eastern Cooperative Oncology Group performance status of 0–1).[7] This study unequivocally demonstrated the superiority of FOLFIRINOX in terms of all clinically relevant parameters, including prolongation of overall survival (median OS: 11.1 vs 6.8 months, HR of 0.57; $P<0.001$) and progression-free survival, higher objective response rate, and longer preservation of quality of life.[8] As a result, FOLFIRINOX has become the preferred first-line choice for select patients who are robust enough to tolerate this somewhat more aggressive chemotherapy regimen.

A second chemotherapy platform now in widespread use for metastatic pancreatic cancer consists of the combination of gemcitabine plus nab-paclitaxel (Celgene, Summit, NJ, USA), a 130-nm albumin-bound formulation of paclitaxel particles. Nab-paclitaxel, originally FDA-approved for advanced breast cancer back in 2005, was developed in part to eliminate the allergic reactions that could occur from polyoxyethylated castor oil (Cremphor EL; BASF, Ludwigshafen, Germany), a vehicle needed for parenteral administration of free paclitaxel. Its subsequent evaluation in pancreatic cancer was based in part on molecular profiling of pancreatic tumor samples, in which overexpression of the SPARC protein (secreted protein acidic and rich in cysteine), an albumin-binding protein, was observed.[9] Following promising results from a Phase I/II trial of gemcitabine plus nab-paclitaxel,[10] an international Phase III study (the MPACT trial) was conducted in which 861 patients with metastatic pancreatic cancer were randomized to receive gemcitabine either alone or in combination with nab-paclitaxel.[11] Patients receiving the doublet had superior outcomes, including a significant prolongation of survival (median OS: 8.5 vs 6.7 months, HR =0.72; $P<0.001$), thus leading to FDA approval of nab-paclitaxel for this indication in 2014.

What options do we currently have beyond frontline chemotherapy?

Data from contemporary pancreatic cancer trials suggest that fewer than half of patients receiving first-line chemotherapy go on to receive any additional therapy; for example, in the aforementioned MPACT trial, only 40% of patients received second-line treatment.[11] This reflects both the often rapid clinical deterioration of patients at this stage of their disease trajectory as well as the lack of available therapeutic options in the salvage setting. The emergence of two frontline standards for metastatic pancreatic cancer may now afford greater opportunity to sequence patients across multiple lines of therapy. It is important, however, to recognize that randomized clinical trial data supporting a sequential approach of FOLFIRINOX followed by gemcitabine/nab-paclitaxel (or the reverse) are still lacking, with only small series (primarily retrospective) and case reports suggesting modest efficacy of each of these regimens in the second-line setting.[12–16]

A variety of other therapies, including not only classical cytotoxic drugs (alone and in combination) but also molecularly targeted agents and, more recently, immunotherapies, have been investigated in this salvage setting. One systematic review published in 2013 evaluating 34 clinical trials of different second-line regimens following gemcitabine-based therapy concluded that continuing with some form of therapy after progression on first-line treatment did confer a survival advantage when compared to best supportive care,[17] thus supporting this strategy as a general principle. However, the challenges of interpreting this mix of studies include small sample sizes, nonrandomized trial design for the majority with resultant selection bias, and sometimes conflicting results. For example, the de facto standard of care for many years when treating patients with gemcitabine-resistant pancreatic cancer was to move next to a combination of a platinum analog plus a fluoropyrimidine. This approach was informed in large part by results from one of the largest randomized studies (a German trial called CONKO-003) in this disease setting demonstrating a survival advantage of OFF (oxaliplatin, folinic acid, and fluorouracil) compared to FF alone (median OS: 5.9 vs 3.3 months, HR =0.66; log-rank P=0.010).[18] Conversely, a later trial conducted in Canada called PANCREOX showed almost the precise opposite results in a similar patient population, with patients treated with FOLFOX (chemotherapy regimen of folinic acid, 5-FU, and oxaliplatin) faring no better – and possibly worse – than those receiving 5-FU/LV alone.[19]

In addition to nal-IRI, several other novel agents have shown promising results in the second-line (and beyond) setting for metastatic pancreatic cancer and are moving ahead in clinical development. In the randomized Phase II RECAP trial,[20] the JAK 1/2 inhibitor ruxolitinib (Jakafi, Incyte Pharmaceuticals, New York, NY, USA) was evaluated in combination with capecitabine in patients who had failed gemcitabine-based chemotherapy. In a preplanned analysis of the subgroup of patients with elevated levels of C-reactive protein (CRP) (an indicator of high levels of systemic inflammation that contributes to cancer-related cachexia), median survival was significantly longer in those patients who received the ruxolitinib/capecitabine combination compared to capecitabine alone (83 vs 55 days, HR =0.47; P=0.01). These results have led to two Phase III trials (JANUS 1 and JANUS 2) that are currently underway to evaluate ruxolitinib specifically in gemcitabine-refractory pancreatic cancer patients with high CRP levels. A second, immune-based approach being tested in this setting is CRS-207 (Aduro Biosciences, Berkeley, CA, USA), a live-attenuated *Listeria monocytogenes* vaccine vector genetically engineered to express the tumor-associated antigen, mesothelin. Immunotherapeutic strategies have not produced as dramatic results in pancreatic cancer when compared with other solid malignancies, perhaps due to pancreatic cancer being generally considered a more immune-privileged tumor.[21] Nevertheless, in a randomized Phase II trial in patients with chemorefractory metastatic pancreatic cancer, CRS-207, when combined with the cellular vaccine GVAX, significantly improved survival when compared to GVAX alone (median OS: 6.0 vs 3.4 months, HR =0.4477; P=0.0057), including in some patients with very prolonged disease stabilizations.[22] These results have led to successor trials comparing this vaccine-based strategy to chemotherapy, as well as evaluating it in combination with immune checkpoint blockade, in the second- and third-line settings.

Introduction to nal-IRI: initial drug development

Liposomes are spherical drug carrier vehicles with a bilayer lipid membrane, typically ranging in size anywhere from approximately 40 nm to several microns.[23] The theoretical benefits of developing liposomal formulations of anticancer drugs, including both traditional chemotherapy agents as well as molecularly targeted therapies (such as small molecule inhibitors), are well-established; these include the possibility of encapsulating poorly soluble drugs, protecting therapeutic agents from premature clearance and metabolism, and improving biodistribution and pharmacokinetics via slow release of the parent agent (reviewed in Bertrand

et al[24]), resulting in simultaneously greater potency and decreased side effects. Ideally, liposomes should retain encapsulated drug in circulation and then release the drug in a time-controlled fashion after arrival at the target tissue. This release rate is an important factor in drug potency that can be controlled, to some extent, by various physiochemical properties of the liposome, including both lipid and interior buffer composition.[25]

It is believed that nanoliposomes accumulate preferentially in the tumor through a phenomenon known as the enhanced permeability and retention (EPR) effect.[26] This EPR effect describes the combination of irregular, permeable tumor blood vessels with large fenestrations that enable extravasation of macromolecules (such as liposomes), together with impaired lymphatic drainage. These findings in concert lead to increased cumulative trapping of liposomal drug in the tumor microenvironment, relative to other tissues, in what could be characterized as a form of passive targeting. Once deposited in the tumor, the liposomal agent can then be taken up by tumor-resident macrophages, which release the bound drug resulting in high intratumoral levels of active drug.[27] The final result is improved pharmacological potency of the liposomal formulation compared to the same drug administered in free form.

At the same time, some technical challenges persist in liposomal technology, including the efficient loading of cancer drugs at high drug-to-lipid ratios, and preventing phagocytosis of liposome–plasma protein complexes by the reticuloendothelial system. Newer stealth technologies, such as the incorporation of polyethylene glycol (PEG) to the liposome surface, are being applied to prevent binding of liposomes by circulating plasma proteins with the goal of decreasing elimination from the circulation.

The therapeutic efficacy of liposomal agents in oncology has been established in routine clinical practice, with agents such as liposome-encapsulated doxorubicin currently being used for a variety of malignant indications (Kaposi sarcoma, multiple myeloma, ovarian cancer), offering the advantage of decreased cardiac toxicity of the cytotoxic drug. However, specific to pancreatic cancer, only a small number of liposomally formulated agents have been tested in the clinical setting, with none gaining significant traction. A PEGylated liposomal formulation of cisplatin (lipoplatin) was evaluated in a small Phase I/II trial in combination with gemcitabine for patients with previously treated advanced pancreatic cancer; efficacy was modest, with two of 24 subjects (8.3%) achieving an objective response, and an additional 14 patients (58.3%) demonstrating stable disease for a median duration of 3 months.[28] A larger randomized Phase II trial evaluating a novel cationic liposomal formulation of paclitaxel (EndoTAG-1) in combination with gemcitabine as first-line treatment for patients with advanced pancreatic cancer showed somewhat greater promise.[29] The investigators reported (in abstract form only) a survival benefit with the addition of EndoTAG-1 to gemcitabine, with an HR for overall survival of 0.67 when the highest dose level of this agent was administered together with gemcitabine compared to gemcitabine alone. Nevertheless, neither of these liposomal agents went on to further clinical development in pancreatic cancer.

nal-IRI (originally referred to as PEP-02 when licensing rights were owned by PharmaEngine [Taipei, Taiwan]; subsequently relicensed as MM-398 [Merrimack Pharmaceuticals, Cambridge, MA, USA]), represents a novel nanoliposomal formulation of irinotecan hydrochloride, a semisynthetic analog of the natural alkaloid camptothecin currently used in the treatment of a wide variety of malignancies, including colorectal, gastroesophageal, small cell lung, and breast cancer. Irinotecan, by stabilizing the complex between topoisomerase I (TOP1) and bound DNA, induces stalling of replication forks, ultimately leading to DNA strand breaks and inhibition of replication. Time of drug exposure is an important driver for its cytotoxic effects,[30] suggesting that irinotecan and other TOP1-targeting agents, in liposomal form, would be able to take particular advantage of the EPR effect with preferential intratumoral accumulation and exposure.

The dose-limiting toxicities (DLTs) of irinotecan are well-described, most notably diarrhea (which can be severe) and cytopenias. nal-IRI was designed in part to reduce the incidence and severity of these toxicities while maintaining or increasing the antitumor activity of the parent drug, offering an improved therapeutic window. Specifically, the liposomal carrier system offers a way to protect irinotecan from premature conversion by nonspecific carboxylesterases into its active metabolite, SN-38, which is about 100- to 1,000-fold more potent.[31] This produces lower maximum plasma concentration (C_{max}) and consequently reduced drug toxicity, even while lower drug elimination prolongs systemic circulation of the liposomal construct. Despite these theoretical advantages, prior liposomal formulations of irinotecan, as well as of other camptothecins (lurtotecan and SN-38, among others), have not necessarily shown improved pharmacokinetic characteristics or toxicity profiles compared to their free drug counterparts when evaluated in the preclinical setting.[32–34]

The development of nal-IRI was originally described in 2006 by Drummond et al,[35] who used a novel intraliposomal drug stabilization technique to load irinotecan into a nanoparticle/liposome construct in efficient manner. Specifically, a polyalkylammonium salt of a nonpolymeric (sucrose octasulfate) highly charged multivalent anion was employed as an intraliposomal trapping agent, resulting in formation of intraliposomal drug–polyanion complexes. (A polymeric agent, polyphosphate, was also tested for synthesis of this drug; but the superior results of sucrose octasulfate led to this being the choice for subsequent clinical development). The triethylammonium component of the salt ensures the charge neutrality of the liposome interior by simultaneous efflux of cations accompanying the influx of the drug, and possibly even formation of a self-perpetuating pH gradient to drive progressive drug accumulation. This may help explain the remarkably high loading capacity of triethylammonium sucrose octasulfate liposomes, with 800 g of irinotecan per mole of phospholipid (corresponding to 109,000 drug molecules per particle).

Preclinical evaluation of nal-IRI

Pharmacokinetic testing of nal-IRI in normal female rats demonstrated high in vivo stability of the liposomal construct, with significantly longer circulation times when compared to administration of free drug (half-life [$t_{1/2}$] =10.7 hours compared to 0.27 hours, respectively).[35] Almost one-quarter (23.2%) of the injected dose of nal-IRI was detectable in circulation at 24 hours, compared to free CPT-11 (irinotecan), of which 98% is cleared within 30 minutes. Moreover, with the nal-IRI formulation there was less premature conversion to SN-38, due in part to slow release of irinotecan from liposomes ($t_{1/2}$ for irinotecan release =56.8 hours). When tested in mice, nal-IRI showed dramatic regressions in a breast (BT474) tumor xenograft model with a 100% cure rate, without significant corresponding treatment-related toxicities aside from transient weight loss. Antitumor activity in a colon cancer (HT29) xenograft model was also observed, albeit not quite to as striking a degree.

Hann et al[36] were the first to evaluate nal-IRI in pancreatic cancer, in the context of a bioluminescent-based orthotopic xenograft model (COLO357/L3.6pl). Compared to the equivalent dose of free drug, nal-IRI (as well as a separate, novel EGFR-targeted immunoliposomal form of irinotecan) showed superior antitumor activity, including a number of durable tumor regressions, without any significant systemic toxicity.

In a more recently published study, Kalra et al[37] measured irinotecan and SN-38 levels in both plasma and tumor in mice harboring a variety of cell-line and patient-derived tumor xenografts (colorectal, ovarian, lung, and pancreatic) following administration of either nal-IRI or free irinotecan. Consistent with prior findings, plasma levels of both irinotecan and SN-38 persisted much longer in circulation (>50 hours) following administration of nal-IRI compared to free irinotecan. Similarly, prolonged exposure within tumors of both irinotecan and SN-38 was observed following nal-IRI administration; levels of both were still detectable at 168 hours, far longer than free irinotecan, where tumoral clearance of drug and active metabolite was noted by 24–48 hours. Ultimately, using model sensitivity analyses, these investigators determined that tumor SN-38 duration – reflecting both drug deposition and local activation of irinotecan by carboxylesterases to its active metabolite – represents the key driver of in vivo sensitivity to irinotecan-based treatment. Hence, the superior antitumor activity of nal-IRI could be attributed to its superior pharmacokinetic properties, with the ability of this liposomal construct to prolong drug exposure within tumors, compared to free irinotecan.

Clinical development of nal-IRI

The first-in-human clinical trial of nal-IRI, conducted in Taiwan by Chang et al,[38] consisted of a Phase I dose-escalation study in patients with advanced refractory solid tumors, including cervical, breast, neuroendocrine, pancreatic, non-small-cell lung, and thymic cancers. In total, eleven patients were enrolled across three dose levels, with the maximal tolerated dose (MTD) established at 120 mg/m^2 on an every-3-week schedule. DLTs at the next higher dose level (180 mg/m^2) included grade 4 neutropenia in one patient and grade 4 febrile neutropenia, grade 4 thrombocytopenia with bleeding, and grade 4 diarrhea in a second patient resulting in death from septicemia and disseminated intravascular coagulation. Pharmacokinetic analyses demonstrated slow clearance, small volume of distribution, and prolonged terminal half-life of nal-IRI – all findings consistent with preclinical PK studies of nal-IRI in mice and rats – with a plasma concentration-time profile approximately matching that of total irinotecan, reflecting the slow release of free-form irinotecan from the nanoliposomal carrier over time. The area under the curve of SN-38 at MTD of nal-IRI was comparable to historic data for conventional irinotecan dosed at 300–350 mg/m^2. Of the six patients enrolled at MTD, gastrointestinal toxicities were frequently observed, including grade 3/4 diarrhea in two patients

(33.3%) and grade 3/4 vomiting in four patients (66.7%). Two of ten (20%) response-evaluable patients demonstrated a partial response by RECIST (Response Evaluation Criteria in Solid Tumors); notably, this included the one patient with pancreatic cancer treated at 180 mg/m^2 who had failed several prior lines of chemotherapy.

A number of Phase I, II, and III clinical trials of nal-IRI have since been conducted across a variety of solid tumors, with a particular focus on those disease indications in which irinotecan has demonstrable clinical activity. A summary of these studies is listed in Table 1. Chen et al[39] were the first to report (in abstract form) the feasibility of combining nal-IRI with a second chemotherapeutic agent, 5-FU, in a dose-finding Phase I trial in patients with heavily pretreated solid tumors. The MTD using an every-3-week dosing schedule consisted of nal-IRI 80 mg/m^2 (day 1) plus 24-hour infusional 5-FU 2,000 mg/m^2 and LV 200 mg/m^2 (days 1 and 8). DLTs at higher doses of nal-IRI included diarrhea and cytopenias. The best response of 15 evaluable patients was partial response in two patients (gastric cancer and breast cancer) and stable disease in an additional nine.

Given the proven efficacy of irinotecan in colorectal cancer, there has naturally been considerable interest in studying nal-IRI for this indication to see if it compares favorably to the free-form drug. The first trial of nal-IRI specific for advanced colorectal cancer evaluated a biweekly schedule of the drug administered as monotherapy in patients who had failed first-line oxaliplatin-based therapy, with a dose of 100 mg/m^2 established as the MTD.[40] Four of 17 evaluable patients (23.5%) achieved a partial response while an additional eight showed stable disease, for an overall disease control rate of 70.6%. These promising results prompted a subsequent randomized Phase II study, the PEPCOL trial, in a similar patient population conducted by the Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR) in France.[41] In this trial, 55 patients with advanced colorectal cancer were randomized in a 1:1 fashion to receive either nal-IRI plus 5-FU/LV administered at a biweekly dose schedule (referred to in this study as FUPEP) or 5-FU/LV plus irinotecan (FOLFIRI). While objective response rate was similar between the two arms (16.7% for FUPEP, 11.5% for FOLFIRI), the toxicity profile favored FUPEP, with lower rates of grade 3–4 diarrhea (21% vs 33%) and neutropenia (11% vs 30%). Importantly, on the basis of these results, most notably the attractive safety profile, the decision was made to add this combination (herein referred to as 5-FU/LV/nal-IRI) as a third arm to the NAPOLI-1 Phase III trial in metastatic pancreatic cancer, as will be discussed.

One other study of nal-IRI in gastric and gastroesophageal junction (GEJ) cancer[42] warrants mention here as it represents the largest published clinical trial of this agent at the time of this writing. This Phase II trial enrolled patients with locally advanced or metastatic gastric/GEJ adenocarcinomas who had progressed on frontline therapy, a clinical context in

Table 1 Completed and ongoing clinical studies of nal-IRI

Indication	Regimen	Phase	Source
Advanced solid tumors	nal-IRI q3 weeks	I	Chang et al[38]
Advanced solid tumors	nal-IRI (day 1) plus infusional 5-FU/LV (days 1 and 8) q3 weeks	I	Chen et al[39]
Recurrent high-grade glioma	nal-IRI q3 weeks	I	Clarke et al[49]
Pediatric solid tumors	nal-IRI plus cyclophosphamide (dosing schedule not specified)	I	NCT02013336[a]
Metastatic colorectal cancer, following first-line oxaliplatin-based chemotherapy	nal-IRI q2 weeks	II	Chen et al[40]
Metastatic pancreatic cancer, gemcitabine-refractory	nal-IRI q3 weeks	II	Ko et al[45]
Metastatic gastric cancer, following first-line chemotherapy	nal-IRI q3 weeks (comparator arms: irinotecan, docetaxel)	II (3-arm randomization)	Roy et al[42]
Metastatic colorectal cancer, following first-line oxaliplatin-based chemotherapy	nal-IRI plus 5-FU/LV q2 weeks (comparator arm: FOLFIRI)	II (2-arm randomization)	Chibaudel et al[41]
Metastatic pancreatic cancer, untreated	nal-IRI plus oxaliplatin and infusional 5-FU/LV q2 weeks (comparator arms: FOLFOX, gemcitabine/nab-paclitaxel)	II (3-arm randomization)	NCT02551991[a]
Metastatic pancreatic cancer, gemcitabine-refractory	nal-IRI q3 weeks nal-IRI plus 5-FU/LV q2 weeks (comparator arm: 5-FU/LV)	III	von Hoff et al[46], Chen et al[47]

Note: [a]Trial ongoing.

Abbreviations: q3, every 3 weeks; q2, every 2 weeks; nal-IRI, nanoliposomal irinotecan; 5-FU, 5-fluorouracil; LV, leucovorin; FOLFIRI, 5-FU/LV plus irinotecan; FOLFOX, 5-FU/LV plus oxaliplatin.

Table 2 Comparison of pharmacokinetic properties of nal-IRI vs free irinotecan

Parameter	Free irinotecan	Nanoliposomal irinotecan
C_{max} (ng/mL)	4,265	60,842
T_{max} (hours)	1.6	2.1
AUC_{0-t} (hr·ng/mL)	24,155	1,651,508
$AUC_{0-\infty}$ (hr·ng/mL)	26,159	1,812,221
CL (mL/h/m^2)	12,886	191
$t_{1/2}$ (hours)	7.7	21.2

Note: Adapted from Roy AC, Park SR, Cunningham D, et al. A randomized phase II study of PEP02 (MM-398), irinotecan or docetaxel as a second-line therapy in patients with locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma. *Ann Oncol.* 2013;24(6):1567–1573.[42] By permission of Oxford University Press on behalf the European Society for Medical Oncology.

Abbreviations: nal-IRI, nanoliposomal irinotecan; C_{max}, peak plasma concentration; T_{max}, time to reach C_{max}; AUC, area under the curve; CL, clearance; $t_{1/2}$, elimination half-life.

which single-agent irinotecan represents one of the standards of care. Patients were randomized in 1:1:1 fashion to receive nal-IRI, irinotecan, or docetaxel (n=44 in each arm). Objective response rate, which represented the primary study endpoint, was similar for nal-IRI (13.6%) and docetaxel (15.9%), both of which were higher than for irinotecan (6.8%). Median progression-free and overall survival rates were similar across all three arms. This study was also informative in allowing the opportunity to directly compare the toxicity profile of nal-IRI (dosed at 120 mg/m^2 in this trial) with that of standard irinotecan (300 mg/m^2). Rates of grade 3–4 adverse events were similar between these two treatment arms (38.6% vs 34.1%), as was diarrhea of any grade (72.7% vs 68.2%). Additionally, similar to prior preclinical and clinical studies, nal-IRI also demonstrated favorable pharmacokinetic properties, including a larger area under the curve, lower clearance, and smaller volume of distribution for total irinotecan when compared to free irinotecan. A summary comparing the major pharmacokinetic properties of nal-IRI and free irinotecan is provided in Table 2.

nal-IRI in pancreatic cancer

The track record of irinotecan in pancreatic cancer clinical trials has a somewhat checkered past. As noted earlier, irinotecan comprises a key component of the FOLFIRINOX regimen that now represents a gold standard in the frontline setting. Conversely, in two randomized Phase III trials for metastatic pancreatic cancer, the addition of irinotecan to gemcitabine did not confer any survival benefit.[43,44] Other smaller Phase II trials evaluating irinotecan alone and in combination with other agents, in particular fluoropyrimidines, have demonstrated modest activity in pancreatic cancer, most commonly in the postgemcitabine setting (Table 3).

Ko et al[45] conducted the first pancreas-specific trial of nal-IRI, consisting of a multinational Phase II study in patients with metastatic pancreatic cancer who had progressed on frontline gemcitabine-based chemotherapy. For this single-arm trial, conducted in the United States and Taiwan, forty patients received single-agent nal-IRI on an every 3-week schedule. Starting doses were 120 mg/m^2, with the option of dose-escalating to 150 mg/m^2 if the first cycle was well-tolerated. Overall, 26 patients (65%) experienced at least one treatment-emergent adverse event categorized as grade 3 or higher by National Cancer Institute Common Toxicity Criteria (NCI-CTC) criteria. Most frequent grade 3–5 toxicities included neutropenia (30%), fatigue/asthenia (20%), diarrhea (15%), nausea (10%), and anorexia (10%). Also of particular note was three patients (7.5%) who died related to complications of treatment, including aspiration pneumonia, sepsis, and respiratory failure, all developed in the setting of neutropenia. In terms of efficacy, three patients achieved a partial response as evaluated by RECIST criteria, with an additional 17 (42.5%) demonstrating stable disease for a minimum of two cycles. Ten patients (31.3%) experienced a CA19-9 response, defined as a decline in this tumor marker by 50% or greater for those with baseline levels greater than two times

Table 3 Select studies of irinotecan, alone or in combination with a fluoropyrimidine, in advanced pancreatic cancer

Regimen	Sample size	RR (%)	PFS/TTP (months)	Median survival (months)	Source
Irinotecan	33	9	2.0	6.6	Yi et al[50]
Irinotecan	56	3.6	2.9	5.3	Takahara et al[51]
FOLFIRI[a]	40	37.5	5.6	12.1	Taieb et al[52]
FOLFIRI	31	0	1.9	3.9	Yoo et al[53]
FOLFIRI	40	15	3.7	6.0	Gebbia et al[54]
FOLFIRI or XELIRI	34	0	2.0	4.2	Cereda et al[55]
FOLFIRI	50	8.0	3.2	5.0	Zaniboni et al[56]
FOLFIRI	63	7.9	3.0	6.6	Neuzillet et al[57]
Irinotecan plus S-1	60	18	3.6	6.9	Mizuno et al[58]

Notes: [a]Evaluated in first-line setting; all other studies were conducted in previously treated patients.

Abbreviations: RR, relative risk; PFS, progression-free survival; TTP, time to progression; FOLFIRI, 5-FU/LV plus irinotecan; nal-IRI, nanoliposomal irinotecan; 5-FU, 5-fluorouracil; LV, leucovorin.

the upper limits of normal. Median progression-free and overall survival for the entire cohort was 2.4 and 5.2 months, respectively, with a 6-month survival rate of 42.5%.

Based on this signal of activity, a global Phase III, randomized, open-label trial called NAPOLI-1 (von Hoff et al;[46] updated in Chen et al[47]) was designed to formally evaluate the efficacy of nal-IRI for patients with metastatic pancreatic cancer previously treated with a gemcitabine-based regimen (one or more prior lines of therapy allowed). The study was originally intended to provide a direct head-to-head comparison between two arms: nal-IRI at the same dose schedule used in the Phase II trial (120 mg/m^2 every 3 weeks), and a control arm of 5-FU (administered as a 24-hour infusion at 2,000 mg/m^2) plus LV (200 mg/m^2), administered weekly for 4 out of 6 weeks. However, shortly after the study began enrollment, results of the PEPCOL colorectal trial[41] became available suggesting a favorable safety profile of biweekly nal-IRI plus infusional 5-FU and LV; on this basis, the trial design was modified to include a third arm consisting of the combination of nal-IRI (80 mg/m^2), 46-hour infusion of 5-fluorouracil (2,400 mg/m^2), and LV (400 mg/m^2), administered in 2-week cycles. In total, 417 patients were enrolled across the three treatment arms.

The main safety and efficacy findings of NAPOLI-1 are summarized in Table 4. Gastrointestinal-related toxicities, including nausea, vomiting, and diarrhea, were the most common adverse events reported, and occurred more frequently in the two nal-IRI-containing arms compared to the 5-FU/LV alone arm (with the highest incidence observed in the nal-IRI monotherapy arm). The majority of these were grades 1 and 2, although grade 3 or 4 diarrhea was reported in 21% of patients receiving nal-IRI alone and 13% in those receiving nal-IRI plus 5-FU/LV. Complications of neutropenia (neutropenic sepsis, febrile neutropenia) occurred in less than 5% of patients on either nal-IRI-containing arm, vs no reported cases on the 5-FU/LV alone arm. In total, five deaths attributed to study treatment were reported, four in the nal-IRI arm (gastrointestinal toxicity, infectious enterocolitis, septic shock, and disseminated intravascular coagulation with pulmonary embolism) and one in the nal-IRI plus 5-FU/LV arm (septic shock).

In the entire (intention-to-treat) cohort, patients on the nal-IRI plus 5-FU/LV arm demonstrated statistically significant improvements compared with those on the 5-FU/LV alone arm in terms of all clinical relevant parameters, as shown in Table 3. Hazard ratios for median OS, PFS, and time to treatment failure were 0.67, 0.56, and 0.6, respectively, all statistically significant. Significantly higher rates of objective radiographic response and CA19-9 decline ≥50% were also observed. Meanwhile, while nal-IRI alone also produced significantly higher rates of radiographic and biomarker response compared to 5-FU/LV, overall and progression-free survival rates were not significantly higher (HR for OS and PFS =0.99 and 0.81, respectively). Forest plot analyses showed that survival benefit for the MM-398-containing combination was maintained across all subgroups, including those with lower Karnofsky performance status (KPS 70–80), age greater than 65 years old, and receiving two or more prior lines of systemic therapy.

On the basis of these positive results, the FDA in October 2015 approved nal-IRI in combination with 5-FU/LV for the treatment of patients with metastatic pancreatic cancer following disease progression on gemcitabine-based therapy. This represented a landmark of sorts, as it became

Table 4 Safety and efficacy results of the Phase III NAPOLI-1 trial

Adverse event (%)	nal-IRI +5-FU/LV (n=117)		5-FU/LV (n=149)		nal-IRI (n=151)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Safety						
Diarrhea	59	13	26	5	70	21
Vomiting	52	11	26	3	54	14
Nausea	51	8	34	3	61	5
Decreased appetite	44	4	32	2	49	19
Fatigue	40	14	28	4	37	6
Neutropenia	39	27	5	2	25	15
Efficacy						
Median overall survival (months)	6.1		4.2		4.9	
Median progression-free survival (months)	3.1		1.5		2.7	
Median time to treatment failure (months)	2.3		1.4		1.7	
Objective response rate (%)	16		1		6	
CA19-9 reduction ≥50% (%)	29		10		24	

Notes: Data from von Hoff D, Dhindsa N, Bayever E, et al.[46], Chen L, Von Hoff D, Li C, et al.[47]
Abbreviations: nal-IRI, nanoliposomal irinotecan; 5-FU, 5-fluorouracil; LV, leucovorin; CA19-9, carbohydrate antigen 19-9.

the first therapeutic agent to receive approval in this disease specifically for use in the second-line setting and beyond.

Future directions

The approval of nal-IRI raises a number of practical issues as well as considerations that may inform future clinical trial design. First of all, selection of the individuals most likely to benefit from, and tolerate, nal-IRI requires further clarification and refinement. The FDA-approved indication specifies this drug should be limited to those patients who have received prior gemcitabine-based treatment; at present, this would most commonly consist of the combination of gemcitabine and nab-paclitaxel, or less commonly another gemcitabine-based doublet or monotherapy. On the other hand, whether nal-IRI plus 5-FU/LV has any activity following first-line treatment with FOLFIRINOX, the other first-line standard for metastatic pancreatic cancer, is unknown; to date, we have no knowledge regarding whether the superior biodistribution and pharmacokinetic properties of nal-IRI can overcome resistance to a standard irinotecan-containing regimen. This highlights a related question: how does nal-IRI compare to standard irinotecan in pancreatic cancer? It seems unlikely that a randomized clinical trial directly comparing FOLFIRI to nal-IRI plus 5-FU/LV will ever be performed, and so we are left using historic FOLFIRI data from relatively small patient cohorts to make (admittedly inexact) cross-study comparisons regarding their respective efficacies in this disease setting.

Furthermore, does the nal-IRI-based combination now supplant the prior de facto second-line standard of care, FOLFOX, for the treatment of metastatic pancreatic cancer? Again, a head-to-head comparison of these two regimens has not been formally performed. One might conceivably develop a biomarker- or pharmacogenetically-driven approach to guide selection of therapy (eg, to choose between an irinotecan- vs platinum-based regimen). It is well-known, for instance, that genetic variants in isoforms of the enzyme UDP-glucuronosyltransferase, in particular UGT1A1, contribute to variability in the metabolism and excretion of irinotecan, producing significant interpatient differences in drug-related toxicity. The most common example of this is UGT1A1*28; individuals who are homozygous for this allele (also known as 7/7, based on the number of repeats of the two-base insertion TA in the promoter region of the gene), which is associated with severely reduced enzymatic activity, are more than threefold likely to develop severe neutropenia following irinotecan-based therapy compared to those with wild genotype (reviewed in Palomaki et al[48]). While relatively scant pharmacogenetic data are available from prior nal-IRI studies to provide guidance, it would be reasonable to use UGT1A1 genotyping to help in this decision-making process. For example, those individuals harboring genetic polymorphisms known to confer greater toxicity might proceed with nal-IRI at reduced starting doses, or even steer away from this agent, if they are particularly fragile and the risk of major toxicity is too high.

Certainly the other area ripe for consideration in future studies centers on the feasibility of combining nal-IRI with other drugs; this could entail either combinations with other cytotoxic agents, or using nal-IRI (±5-FU/LV) as a chemotherapy backbone upon which to add molecularly targeted agents or immunotherapies. Of particular interest is evaluation of nal-IRI in the frontline setting, most notably as part of an FOLFIRINOX regimen where nal-IRI is substituted for standard irinotecan. An ongoing clinical trial that recently opened in September 2015 is looking at this particular combination in newly diagnosed patients with metastatic disease (NCT02551991). Following a safety run-in to confirm the proper dosing and tolerability of nal-IRI in combination with oxaliplatin and 5-FU/LV, the study will then randomize patients to one of three arms: this triple-drug combination regimen, nal-IRI plus 5-FU/LV, or the combination of gemcitabine plus nab-paclitaxel.

Conclusion

In summary, nal-IRI is an important advance in the treatment landscape for metastatic pancreatic cancer. Not only does it represent the first drug specifically approved for use in the second-line setting and beyond in this disease, but nal-IRI also serves as an important proof of principle as the first liposomal formulation of an anticancer agent to gain an indication for any gastrointestinal malignancy. Taking advantage of its ability to deliver an increased drug payload to sites of disease, without concomitant increased systemic toxicity, nal-IRI offers several pharmacologic advantages over free irinotecan. Whether this success ushers in a new era of exploration of liposomal anticancer drugs, or other efficient delivery vehicles, remains to be seen. Successor studies will be critical not only to further define the appropriate use of nal-IRI in pancreatic and other camptothecin-sensitive malignancies, but also to explore predictive biomarkers of drug sensitivity as well as the pharmacodynamics effects of nal-IRI on the tumor and its microenvironment (which could be readily evaluated, for example, in the neoadjuvant setting). For now, from a practical perspective, nal-IRI represents a valuable step in allowing more patients with

metastatic pancreatic cancer to be sequenced through two, or even more, lines of systemic therapy with the promise of clinically meaningful improvements in longevity.

Disclosure

The author has previously participated in several advisory board meetings for Merrimack. PharmaEngine provided financial support to his institution for conduct of the Phase II trial of nal-IRI in pancreatic cancer. The author reports no other conflicts of interest in this work.

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ORIGINAL ARTICLE

A phase II study of bevacizumab plus erlotinib for gemcitabine-refractory metastatic pancreatic cancer

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Abstract
Purpose No standard of care exists for patients with metastatic pancreatic cancer following progression on first-line chemotherapy. Based on potential for additive or synergistic activity by concurrent inhibition of VEGF and EGFR, we conducted a phase II study evaluating the combination of bevacizumab plus erlotinib in this patient population.
Methods Patients with metastatic pancreatic adenocarcinoma, ECOG performance status 0–1, and previous exposure to 1–3 systemic therapies (at least one gemcitabine-based) were eligible. Treatment consisted of bevacizumab 15 mg/kg every 21 days plus erlotinib 150 mg daily.
Results Thirty-six patients were enrolled, including eight who had previously received VEGF-targeted therapy and nine prior erlotinib. Median number of treatment cycles was 2 (range, 1–7). Common toxicities included rash (72%), diarrhea (25%), venous thromboembolic events (15%), and hypertension (11%). One patient demonstrated partial response and seven others stable disease for >2 cycles. CA19-9 decline ≥25% was observed in 4/26 patients with baseline levels >2*x* ULN. Estimated median time to progression was 40 days (95% CI, 35–41 days) and median survival 102 days (95% CI, 74–117 days), with a 6-month survival rate of 22%. Baseline concentration of circulating endothelial cells ($CD45^-/CD34^+/CD31^+$) was inversely associated with overall survival.
Conclusions The combination of bevacizumab and erlotinib is safe but relatively ineffective in patients with gemcitabine-refractory metastatic pancreatic cancer. Future studies should focus on refining subsets of patients in this challenging population likely to benefit from treatment beyond first-line.

Keywords Bevacizumab · Circulating endothelial cells · Erlotinib · Pancreatic cancer · Phase II · Refractory

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Introduction

Pancreatic cancer was responsible for an estimated 35,240 deaths in the United States in 2009 and, stage for stage, is associated with the lowest survival rate of any cancer site [1]. Over the past decade, gemcitabine-based regimens have been the mainstay of treatment for patients diagnosed with advanced stages of disease. A few gemcitabine-containing combinations have demonstrated modest improvements compared to gemcitabine alone, particularly in patients with good performance status [2]; nevertheless, median survival rates even with these regimens remain in the range of only 6–9 months [3–6]. At the time of disease progression on front-line therapy, only approximately half of patients are suitable for further treatment [7], reflecting the inanition and rapid clinical deterioration that so often characterizes these individuals. There are few effective alternative therapeutic options in this salvage setting, with no established standard of care.

Bevacizumab and erlotinib, both independently and concurrently, have been added to gemcitabine in clinical trials for patients with previously untreated advanced pancreatic cancer [8, 9]. Erlotinib, an orally bioavailable small molecule inhibitor targeting the epidermal growth factor receptor

(EGFR), gained FDA approval for this indication based on a statistically significant but modest improvement in survival when added to gemcitabine [5]. Dual inhibition of the EGFR and vascular endothelial growth factor (VEGF) pathways may confer additive or even synergistic benefit [10, 11], and the combination of bevacizumab and erlotinib has shown evidence of clinical activity in a variety of other solid tumors [12–15]. On these bases, we conducted a non-randomized, single-arm phase II study evaluating the combination of these two agents for patients with gemcitabine-refractory, metastatic pancreatic cancer.

Methods

Patient eligibility

Patients were eligible for this study if they were 18 years of age or older, had an ECOG performance status of 0 or 1, and had a confirmed diagnosis of pancreatic adenocarcinoma with radiographic or biopsy-proven evidence of extrapancreatic metastases (stage IVb). Those with locally advanced unresectable disease only were not eligible. Extrapancreatic metastases did not have to be measurable by formal RECIST criteria. Patients must have received at least one, but no more than three, prior systemic therapies for advanced disease (locally advanced or metastatic), at least one of which was gemcitabine-based. Chemotherapy given in the adjuvant setting either alone or concurrently with radiation did not count as prior therapy as long as progressive disease occurred >6 months following completion of treatment. Patients were allowed to have received either an anti-VEGF or an anti-EGFR agent as part of their prior therapy, but not both.

Adequate hematologic, renal, and hepatic function was required as defined by the following: absolute neutrophil count $\geq$ 1,500/μl, platelet count $\geq$ 100,000/μl, hemoglobin $\geq$ 9 g/dl, an international normalized ratio $\leq$ 1.5 (except for participants receiving full-dose warfarin at the time of study entry), creatinine level $\leq$ 2.0 mg/dl, bilirubin level $\leq$ 2.0 mg/dl, and transaminases $\leq$ 2.5*x* ULN ($\leq$5*x* ULN in patients with liver metastases). Any major surgical procedure had to be completed more than 28 days from the time of study entry. Female patients of childbearing potential must have had a negative urine pregnancy test before study entry.

Patients were excluded if they had central nervous system metastases, another active malignancy, or any history of other malignancy within the past 5 years except for non-melanoma skin cancer and carcinoma in situ of the cervix. A history of myocardial infarction or stroke within the last 6 months, uncontrolled hypertension (blood pressure of >150/100 mmHg on medication), unstable angina, New York Heart Association Grade II or greater congestive heart failure, unstable symptomatic arrhythmia requiring medication, grade II or greater peripheral vascular disease, non-healing wounds, ulcers, or bone fractures, or evidence of bleeding diathesis or coagulopathy, all represented additional exclusion criteria. Moreover, patients with any concurrent medical condition that, in the opinion of the treating physician, would constitute a hazard for participation in this study, were also excluded. Patients on therapeutic doses of warfarin or low-molecular weight heparin were eligible as long as they had been on a stable dose for at least 28 days with no further clotting or bleeding complications.

Study design and treatment

This was a phase II, single center, open-label, single-arm study. The trial was approved by, and conducted in accordance with the ethical standards of, the University of California San Francisco Committee on Human Research. All patients signed informed consent prior to study participation. Patients received bevacizumab 15 mg/kg as a 60–90 min infusion every 21 days (representing one treatment cycle) and erlotinib 150 mg by mouth daily, noting that this erlotinib dose is higher than that approved by the FDA for pancreatic cancer when administered concurrently with gemcitabine.

Dose adjustments in erlotinib were made depending on the toxicity observed with each treatment cycle. The erlotinib dose was reduced to 100 mg daily and then 50 mg daily based on the development grade 3 diarrhea, intolerable rash, or other grade 3/4 adverse events. No dose re-escalation was permissible. Erlotinib was discontinued for grade 4 diarrhea or evidence of interstitial lung disease. There was no reduction in the bevacizumab dose allowed. Bevacizumab was discontinued for grade 4 hypertension, uncontrolled grade 3 hypertension despite maximal medical therapy, grade 4 or repeated grade 3 bleeding episodes, symptomatic grade 4 pulmonary embolism, any arterial thromboembolic event, grade 4 proteinuria, gastrointestinal perforation, or wound dehiscence requiring surgical or medical intervention. Bevacizumab was held in patients who developed a grade 3 or asymptomatic grade 4 deep venous thrombosis, but could be resumed once patients were on a stable dose of anticoagulant without any evidence of bleeding for >1 week.

Patients who could not resume study treatment for 3 weeks from the time of last treatment because of unresolved toxicities were removed from the study. Additionally, patients were removed from study if any of the following occurred: progressive disease based upon radiographic and/or clinical criteria, patient withdrawal of consent, or non-compliance.

Evaluation

The primary efficacy measure was overall survival rate at 6 months, measured from the first date of study treatment to the date of death. In the absence of confirmation of death, survival was censored at the last date of follow-up. Secondary efficacy measures included time to tumor progression (TTP), objective response rate by RECIST criteria in patients with measurable disease at baseline, and CA19-9 biomarker response. TTP was defined as the time from initial therapy to the first objective documentation of tumor progression (for patients with measurable disease) or to the date of death, if death was ascribed to progression of disease. Patients initially without measurable disease were included in the TTP analysis based either on the appearance of new measurable lesions or on strongly suggestive radiographic evidence of progression of non-measurable disease (e.g. peritoneal carcinomatosis). TTP was censored for patients who did not have objective evidence of tumor progression at the time of study discontinuation or who died of causes unrelated to pancreatic cancer. CA19-9 biomarker response was defined as a reduction in CA 19-9 values by ≥50% from baseline in those patients with a twofold or greater elevation at baseline. Changes in CA 19-9 alone were not the sole basis for making decisions regarding whether to continue or stop treatment.

Safety was evaluated in terms of adverse events and clinical laboratory abnormalities, graded according to the National Cancer Institute common toxicity criteria (version 2.0). Adverse event assessments were performed on day 1 of each treatment cycle and at the end of treatment. Hematologic, renal, and hepatic function tests were performed at baseline, on day 1 of each treatment cycle and at the end of treatment.

Statistical methods

The primary endpoint in this study was 6-month survival rate. The sample size was based on the presumption that a survival rate of 30% at 6 months would be indicative of significant biological activity of this regimen and warrant further investigation. With 40 patients, if a 6-month survival of 30% (12/40) was observed, the 95% confidence interval for that proportion would be 17–47%, and for any value the CI would be no wider than the observed ±16% points. Early stopping rules were in place for both safety (i.e., if >3 of the first 10, or 6 of the first 20, patients experienced serious adverse events leading to removal from study) and efficacy (if fewer than 4 of the first 18 patients were alive at 6 months).

Time to event endpoints was derived by Kaplan–Meier methods. Radiographic response, treatment administration, adverse events, and laboratory abnormalities were summarized descriptively.

Correlative studies

Isolation and enumeration of circulating endothelial cells (CECs) were performed by flow cytometric analysis both at baseline and, when feasible, following two treatment cycles. Fluorescence-activated cell sorting was performed using a FACS Calibur (Becton–Dickinson) with four-color option to identify tumor cells based on surface marker phenotype. CECs were classified based on two separate phenotypes: $CD45^-/CD34^+/CD31^+/thioflavin^+$ and $CD45^-/CD34^+/CD146^+/thioflavin^+$.

In a subset of patients, CECs were also measured using the CellSearch System (Veridex, LLC, Warren, NJ, USA). This involved an initial immunomagnetic enrichment step in which cells were captured using ferrofluids coated with CD146 antibodies. The CD146-enriched, fluorescently labeled cells were identified as CECs using the CellSpotter Analyzer, a semiautomated fluorescence-based microscopy system, when the cells exhibited the $DAPI^+/CD105^+/CD45^-$ phenotype.

Results

Patient characteristics

Thirty-six patients were enrolled on study between March 2006 and December 2008. Accrual slowed dramatically after June 2008, following results from two large randomized trials (CALGB 80303 and AVITA) that demonstrated no significant survival benefit of bevacizumab when added to gemcitabine-based regimens in advanced pancreatic cancer. The decision was made to stop study enrollment in December 2008, with 36 of the planned 40 patients accrued.

Baseline characteristics are listed in Table 1. There was an approximately even distribution of patients with ECOG performance status zero versus one. Most patients had received exactly one prior line of systemic therapy, including nine and eight patients who had received either erlotinib or anti-VEGF therapy, respectively. The majority of patients had an elevated serum CA19-9 level greater than twofold the upper limits of normal. One patient remains alive at the time of the writing of this manuscript.

Treatment administration and safety

Table 2 provides a summary of study treatment. The maximum number of treatment cycles delivered on this trial was 7, with the majority of patients receiving two cycles (at which time point the first formal response evaluation was undertaken) or fewer. Greater than 80% of patients were discontinued from study treatment because of progressive disease.

Table 1 Patient baseline characteristics

Characteristic	Patients, no., % ($N = 36$)
Median age, years (range)	60 (36–82)
Sex	
Male	20 (56)
Female	16 (44)
Ethnicity	
Caucasian (non-Hispanic)	28 (78)
Hispanic	3 (8)
African-American	3 (8)
Asian-American/Pacific Islander	3 (8)
ECOG performance status	
0	16 (44)
1	20 (56)
Number of prior lines of systemic therapy	
1	24 (67)
2	9 (25)
3	3 (8)
Prior VEGF/VEGFR therapy	8 (22)
Prior EGFR therapy	9 (25)
Prior Whipple resection	8 (22)
Prior radiation	10 (28)
Elevated baseline CA19-9 (>2x ULN)	26 (72)

Table 2 Summary of study treatment

Median no. of treatment cycles (range)	2 (1–7)
Patients receiving two or fewer cycles	28/36 (78%)
Patients requiring dose reduction in erlotinib	5 (14%)
Reasons for study discontinuation, no. (%)	
Progressive disease	29 (81%)
Self-withdrawal due to poor tolerance	2 (6%)[a]
Adverse event	4 (10%)[b]
Prolonged treatment interruption for palliative XRT	1 (3%)

[a] One patient secondary to asthenia and grade 3 rash; one patient secondary to asthenia

[b] One patient with grade 3 upper GI bleed; one patient with unexplained severe abdominal pain not related to disease progression; one patient with pulmonary embolism and increasingly symptomatic pleural effusion; one patient with bilateral DVTs (accompanied by asthenia)

Cutaneous toxicity and diarrhea were the most common adverse events observed, although in only one patient each were these classified as grade 3. Erlotinib dose was reduced in five patients, primarily secondary to cutaneous toxicity; prophylactic use of topical emollients, steroids, and antibiotics was not mandated by study protocol. Other bevacizumab-associated adverse events observed on the study included hypertension, venous thromboembolic events, and gastrointestinal bleeding. There were no bowel perforations, arterial thromboembolic events, or cases of interstitial pneumonitis. No patient deaths were ascribed to be a direct result of study treatment. Table 3 provides a summary of major toxicities.

Table 3 Treatment-associated toxicity

Toxicity	No. (%)
Rash	26 (72)
Grade 1	6 (17)
Grade 2	19 (53)
Grade 3	1 (3)
Diarrhea	9 (25)
Grades 1–2	8 (22)
Grade 3	1 (3)
Hypertension (grade 3)	4 (11)
Gastrointestinal bleeding	2 (6)
Grade 1	1 (3)[a]
Grade 2	0
Grade 3	1 (3)[b]
Venous thromboembolic events	5 (14)
Grade 2	2 (6)[c]
Grade 3	1 (3)
Grade 4 (pulmonary embolism)	2 (6)
Dyspnea	2 (6)[d]
Pancreatogastric fistula	1 (3)
Suspected hemorrhage into intrapulmonic metastases	1 (3)

[a] Rectal bleeding likely 2o to hemorrhoids

[b] Upper GI bleed 2o to duodenal ulcers. Patient had been on low-molecular weight heparin at the time

[c] One had a Mediport-associated deep vein thrombosis, and one had an asymptomatic SMV thrombosis

[d] Etiology was uncertain in these two cases. There was no evidence of interstitial pneumonitis

Efficacy

Eight of 36 patients (22.2%) demonstrated disease control for >2 cycles on study treatment, including a single patient showing a partial response in measurable hepatic metastases and two others with a reduction in non-measurable disease sites (Table 4). Kaplan–Meier curves for time to progression and overall survival are shown in Fig. 1a and b, respectively. In terms of the primary efficacy measure (overall survival rate at 6 months), 8 of 36 patients (22.2%) achieved this threshold.

Correlative studies

Peripheral blood samples were collected from 31 patients at baseline for CEC measurements by flow cytometry. In general,

Table 4 Efficacy results

Efficacy measure	Number
Objective response by RECIST	1 PR
Stable disease >2 cycles	7 (19%)[a]
CA19-9 biomarker decline of ≥25% (patients with >2x ULN as baseline, $N = 26$)	4 (15%)
Estimated median TTP, days (95% CI)	40 (35–41)
Estimated median overall survival, days (95% CI)	102 (74–117)
6-Month survival rate, %	8/36 (22%)

[a] Includes one patient with a decrease in size of peritoneal metastases, and one with decreased ascites

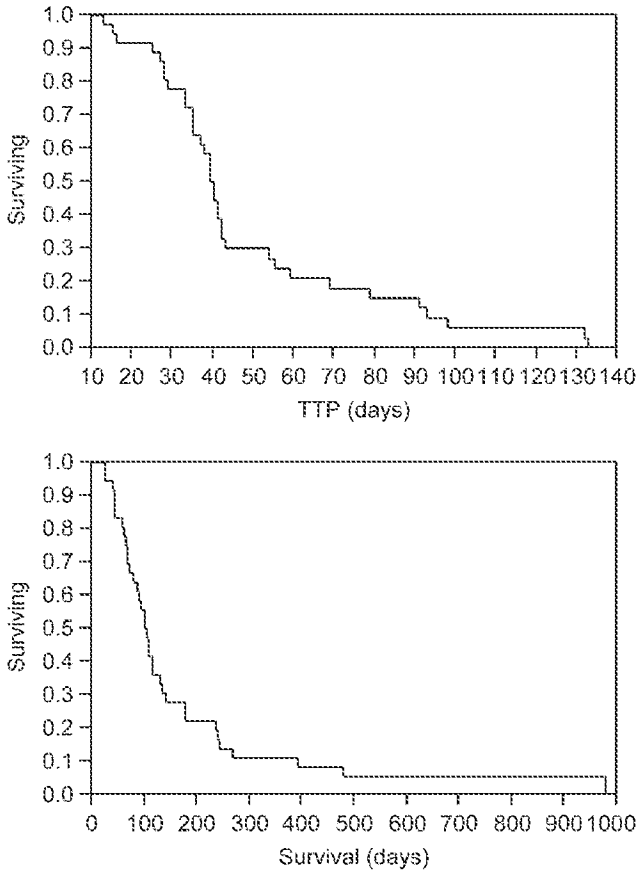

Fig. 1 Kaplan–Meier curves demonstrating time to tumor progression (**a**) and overall survival (**b**)

a higher CEC concentration was found by $CD34^+/CD31^+$ immunophenotyping than by $CD34^+/CD146^+$ immunophenotyping (median concentration, 11.9 $CD34^+/CD31^+$ cells/μl (range, 0.5–54.2) vs. 2.0 $CD34^+/CD146^+$ cells/μl (range, 0.2–14.9)). In 27 patients, the CellSearch automated system was also used, with a median of 10.0 CECs/μl detected (range, 3.0–66.3). There was no correlation observed between these methods. Using Cox proportional hazard regression, only baseline concentration of $CD34^+/CD31^+$ cells was inversely associated with overall survival ($P = 0.0217$). Because the majority of patients showed disease progression within the first two treatment cycles, we were able to perform protocol-specified follow-up CEC collection on only 11 patients, a sample size too small to correlate with any clinical outcome measures.

Discussion

There is a relative paucity of published studies evaluating the safety and effectiveness of chemotherapy regimens in patients with advanced pancreatic cancer who have progressed following first-line therapy. Several selected studies are shown in Table 5, which highlights the low response rates and exceedingly poor survival that is characteristic for these patients. Recently, results from one of the largest studies conducted to date for the second-line treatment of advanced pancreatic cancer (CONKO-003) suggested that a weekly regimen called OFF (oxaliplatin, 5-FU given as a 24 h infusion, and folinic acid) may improve patient outcomes [16]. In this randomized study of 165 patients, OFF demonstrated superiority to 5-FU/folinic acid alone in terms of both progression-free survival (13 vs. 9 weeks, $P = 0.012$) and overall survival (26 vs. 13 weeks, $P = 0.014$).

However, given the marginal performance status and inanition so often manifest in these patients, a therapeutic strategy using exclusively non-cytotoxic targeted agents represents an attractive alternative. Our selection of erlotinib and bevacizumab for this study was based upon preclinical and clinical evidence that these two agents, both separately and in combination, could be well-tolerated and potentially effective in this disease context. EGFR and VEGF share common downstream signaling pathways. VEGF is down-regulated by EGFR inhibition, and blockade of VEGF may also inhibit EGFR autocrine signaling [17–19]. Several preclinical studies have reported at least additive, if not synergistic, effects of anti-EGFR and anti-VEGF agents when used in combination [10, 11]. In the clinical arena, phase II trials of bevacizumab/erlotinib have been conducted in breast [14], renal cell [12], head and neck [13], and non-small cell lung cancers [15]. In NSCLC, the regimen appears to be at least as effective as chemotherapy plus bevacizumab and superior to chemotherapy alone [15].

Specific to pancreatic cancer, erlotinib has demonstrated a significant survival benefit when added to gemcitabine in a placebo-controlled phase III trial in patients with advanced, unreated disease, although the absolute magnitude of benefit was quite modest (an improvement in median survival of 0.4 months) [5]. Moreover, at the time of conception of our study, bevacizumab was garnering a

Table 5 Previous studies in gemcitabine-refractory advanced pancreatic cancer

Regimen	# pts	RR (%)	Median survival (mos)	References
Paclitaxel	18	5.6	4.0	[24]
Raltitrexed	19	0	4.3	[25]
Raltitrexed/irinotecan	19	16	6.5	[25]
5FU/LV/oxaliplatin	30	23.3	5.8	[26]
	76	N/A	5.9	[16]
5-FU/LV	84	N/A	3.0	[16]
9-Nitrocamptothecin	58	7	3.0	[27]
Pemetrexed	52	3.8	4.6	[28]
Capecitabine/erlotinib	30	11	6.7	[29]
Docetaxel/irinotecan	14	0	4.4	[30]

great deal of interest in pancreatic cancer based upon the putative role of VEGF signaling in this disease and promising results from a phase II trial. In that study, bevacizumab was evaluated in the front-line setting in combination with gemcitabine, with a progression-free survival of 5.4 months and median survival of 8.8 months [20]. This led to two separate phase III trials, one conducted in the United States (CALGB 80303) and the other in Europe (AVITA), in which bevacizumab was added to gemcitabine and gemcitabine/erlotinib, respectively. Disappointingly, neither of these trials showed a significant survival benefit for the bevacizumab-containing arms, although the AVITA trial did demonstrate an improvement in PFS with the addition of bevacizumab (4.6 vs. 3.6 months; $P = 0.0002$) [8, 9]. Once those results became publicly available, enrollment to our study declined, ultimately leading to its closure slightly before reaching its intended accrual goal.

While the combination of bevacizumab and erlotinib did benefit a small number of patients in our trial, the primary endpoint was not met, with only 22% of patients remaining alive 6 months from the time of study entry. Moreover, the vast majority of patients discontinued therapy within 6 weeks due to disease progression, typically accompanied by a rapid clinical decline. Our results parallel those recently reported in a CALGB trial (80603), which also evaluated a non-cytotoxic regimen in gemcitabine-refractory pancreatic cancer [21]. In that trial, which investigated the oral VEGFR inhibitor sunitinib ($N = 77$), median PFS was 1.4 months, and OS was 3.2 months, outcomes strikingly similar to ours.

We did also evaluate the prognostic value of circulating endothelial cells (CECs) in our study population using several different methods. CECs have been shown to correlate significantly with patient outcomes in other solid malignancies in which bevacizumab has been evaluated, including rectal and breast cancer [22, 23]. While we did detect a statistically significant inverse association between baseline CEC concentration (as defined by cells with a $CD45^-/CD34^+/CD31^+$ immunophenotype) and overall survival, the utility of this test both as a prognostic marker and as a tool to assess the effectiveness of ongoing anti-angiogenic treatment in pancreatic cancer requires further validation.

In summary, these data demonstrate that a "targeted-only" approach to pancreatic cancer, while conceptually appealing, should be considered a work in progress and cannot yet be recommended, with results that are currently inferior to those reported with cytotoxic regimens. Particularly in the second-line setting and beyond, the challenge remains to find safe and effective therapies for this fragile patient population in whom judicious selection of therapeutic agents is especially critical.

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GASTROINTESTINAL CANCER—GASTROESOPHAGEAL, PANCREATIC, AND HEPATOBILIARY

Trends in real-world clinical outcomes among patients (pts) with metastatic pancreatic adenocarcinoma (mPDAC) treated with liposomal irinotecan based regimens in the United States (US).

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Show Less

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Abstract Disclosures

Abstract

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Background: The NAPOLI-1 study, a randomized phase 3 study in pts with mPDAC previously treated with gemcitabine-based therapy, demonstrated an improvement in overall survival (OS) with liposomal irinotecan + 5-fluorouracil/ leucovorin (5-FU/LV) vs. 5-FU/LV. In this analysis we describe the trends in pt characteristics, real-world OS (rwOS), and real-world time to-treatment failure (rwTTF) among pts with mPDAC treated with liposomal irinotecan based regimens overall and stratified by tx initiation prior to 2018 (pre-2018) or after 2018 (post-2018). **Methods:**This retrospective observational study used de-identified data from Flatiron Health EHR database from over 280 cancer clinics in the US. Pt characteristics, rwOS, and rwTTF were assessed in adult pts diagnosed with mPDAC who received liposomal irinotecan treatment (tx) between January 1, 2016 and October 31, 2019. **Results:** Of the 590 pts treated with liposomal irinotecan based regimens, 53% were male, 56% were initially diagnosed with Stage IV disease, 92% were treated in the community setting, and median age at tx initiation was 69 (IQR: 62 – 75) years. Among pts with available ECOG scores (N = 435), 77% had a score of 0 or 1. 43% (n = 254) initiated tx pre-2018 and 57% (n = 336) post-2018. Pre-2018, 106 (42%) pts initiated liposomal irinotecan in the third line metastatic setting or later (3rd line+), 125 (49%) had ECOG score of 0-1, and median age was 68 (62–74) years. Post-2018, 36% of pts initiated tx in 3rd line+, 211 (63%) had ECOG

score of 0-1, and median age was 70 (63 – 75) years. Median rwOS was 4.4 months [95% CI: 4.3–6.2] pre-2018 and 5.2 mos [4.3–6.2] post-2018. rwTTF was 1.6 mos [1.4–1.9] pre-2018 and 2.1 mos [1.6–2.5] among pts post-2018. Among pts treated in first- or second-line, pre-2018 rwOS was 5.3 mos [3.9–6.4] and post-2018 rwOS was 6.3 mos [5.0– 7.6]. **Conclusions:** In this descriptive real-world study of pts with mPDAC receiving liposomal irinotecan based regimens, pts initiating treatment post-2018 appear to be less pre-treated, older, and have better performance status than pts pre-2018. Pts treated post-2018 experienced numerically longer rwTTF and rwOS than pts treated pre-2018.

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ORIGINAL REPORT

Capecitabine Plus Erlotinib in Gemcitabine-Refractory Advanced Pancreatic Cancer

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ABSTRACT

Purpose
The addition of either capecitabine or erlotinib to gemcitabine in the first-line treatment of advanced pancreatic cancer is associated with modest improvements in overall survival. We evaluated an oral regimen of capecitabine and erlotinib in patients with advanced pancreatic cancer who had experienced treatment failure with standard first-line therapy with gemcitabine.

Patients and Methods
Thirty patients with gemcitabine-refractory metastatic pancreatic cancer were treated with capecitabine, administered at a dose of 1,000 mg/m^2 twice daily for 2 weeks, followed by a 1-week break. All patients also received erlotinib 150 mg daily. Patients were observed for evidence of response, toxicity, and survival. *EGFR* mutational status was assessed in available tumor blocks.

Results
Treatment with capecitabine and erlotinib in gemcitabine-refractory patients was associated with an overall objective radiologic response rate of 10% and a median survival duration of 6.5 months. In addition, 17% of the treated patients experienced decreases in tumor marker (CA 19-9) levels of more than 50% from baseline. Common toxicities included diarrhea, skin rash, fatigue, and hand-foot syndrome. *EGFR* mutations were detected in two of five available tumors; no association between treatment response and *EGFR* mutational status was evident.

Conclusion
The combination of capecitabine and erlotinib is active in patients with gemcitabine-refractory pancreatic cancer. This regimen may represent an acceptable treatment option in patients who experience treatment failure with standard first-line therapy with gemcitabine or for whom gemcitabine may not be an appropriate first-line treatment option.

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INTRODUCTION

Pancreatic cancer remains a leading cause of cancer-related death in North America and Europe.[1] Although the systemic administration of gemcitabine has been associated with both clinical benefit and prolongation of survival in patients with advanced disease, objective tumor responses occur in fewer than 10% of patients, and survival times are generally less than 6 months.[2] Gemcitabine-based combination chemotherapy regimens have been associated with promising activity in phase II studies.[3-6] When subsequently compared with single-agent gemcitabine in randomized trials, however, treatment with many of these regimens has failed to translate into significant improvements in overall survival. Survival times associated with combinations of gemcitabine/fluorouracil, gemcitabine/irinotecan, gemcitabine/cisplatin, and gemcitabine/oxaliplatin appear to be either equivalent or only marginally superior to those associated with single-agent gemcitabine.[7-10]

Treatment with the oral fluoropyrimidine capecitabine was associated with an overall objective response rate of 7.3% in a 42-patient phase II study of treatment-naive patients with advanced pancreatic cancer.[11] Phase II studies of capecitabine administered in combination with gemcitabine demonstrated reasonable tolerance and evidence of activity, leading to the development of large phase III randomized trials.[12,13] An initial randomized study, involving 319 patients, compared gemcitabine alone with a combination of gemcitabine and capecitabine and failed to demonstrate significant survival differences between the two arms.[14] However, in a second, larger study involving 533 patients, the

gemcitabine/capecitabine combination was associated with both an enhanced overall response rate (14.2% *v* 7.1%) and a modest improvement in median survival time (7.4 *v* 6 months) when compared with gemcitabine alone.[15] The toxicities associated with the combination arm were also greater, and included an increased incidence of grade 3 or 4 neutropenia, thrombocytopenia, diarrhea, and hand-foot syndrome.

Erlotinib is a small-molecule tyrosine kinase inhibitor that inhibits phosphorylation of the epidermal growth factor receptor (EGFR).[16] Phase II studies of erlotinib administered alone have demonstrated activity in several epithelioid malignancies, including non–small-cell lung cancer, squamous cell carcinoma of the head and neck, and gastroesophageal adenocarcinoma.[17-20] Notably, in non–small-cell lung cancer, response to oral tyrosine kinase inhibitors of EGFR appears greatest in tumors with selected somatic mutations in the *EGFR* gene.[21,22] In a large, randomized phase III study, patients with advanced pancreatic cancer receiving a combination of gemcitabine/erlotinib experienced a significant, though modest, improvement in survival compared with those treated with gemcitabine alone (1-year survival: 23% *v* 17%, respectively).[23] Patients in the erlotinib-containing arm experienced an increased incidence of rash, diarrhea, and hematologic toxicity.

The relatively modest survival benefits, taken together with the increased potential for toxicity associated with the gemcitabine/erlotinib and gemcitabine/capecitabine combination regimens has tempered enthusiasm for their use in the first-line setting. Given the activity of both capecitabine and erlotinib in pancreatic cancer, we performed a phase II multicenter study evaluating the safety and efficacy of a combination of these two drugs in patients with advanced pancreatic cancer who had experienced treatment failure with first-line therapy with a gemcitabine-containing regimen. Patients were treated with capecitabine 1,000 mg/m^2 twice daily, together with erlotinib 150 mg, using a regimen similar to that in a published study of colorectal cancer.[24] Patients were observed for evidence of toxicity, radiologic response, and survival, and available tumor blocks were evaluated for mutations in *EGFR*.

PATIENTS AND METHODS

Patient Population

The study population consisted of patients with histologically confirmed metastatic pancreatic carcinoma who had experienced treatment failure with one prior gemcitabine-based chemotherapy regimen for metastatic disease. Patients may have also received prior fluorouracil-based adjuvant therapy. Patients who had received prior therapy with capecitabine or EGFR inhibitors, or who had received more than one prior chemotherapy treatment regimen for the treatment of metastatic disease, were excluded.

Patients were further required to have measurable disease (by Response Evaluation Criteria in Solid Tumors [RECIST]), Eastern Cooperative Oncology Group (ECOG) performance status of 1 or better; life expectancy of at least 12 weeks; adequate renal function (creatinine clearance ≥ 50 mL/min), adequate hepatic function (total bilirubin ≤ 1.5× upper limit of normal [ULN]; AST ≤ 2.5× ULN, or ≤ 5× ULN if there was evidence of liver metastases; alkaline phosphatase ≤ 2.5× ULN, or ≤ 5× ULN if there was evidence of liver metastases); and adequate bone marrow function (absolute neutrophil count ≥ 1,500 μL, platelets ≥ 100,000 μL, hemoglobin ≥ 9.0 g/dL).

Patients were excluded if they had clinically apparent CNS metastases or carcinomatous meningitis, clinically significant cardiac disease (eg, congestive heart failure, symptomatic coronary artery disease and cardiac arrhythmias not well controlled with medication, or myocardial infarction within the last 12 months), major surgery within 4 weeks of the start of study treatment, without complete recovery, or uncontrolled serious medical or psychiatric illness. Patients who were pregnant or lactating were excluded from study entry. All patients provided a signed, informed consent as required by the institutional review boards of their respective institutions.

Treatment Program

The starting dose of capecitabine was 1,000 mg/m^2 bid (total 2,000 mg/m^2/d, rounded to the nearest 150 mg tablet. Treatment with capecitabine was given for 14 days followed by a 7-day rest period without treatment, constituting a 21-day treatment cycle. Erlotinib was administered at a dose of 150 mg once daily. Erlotinib was held for grade 2 or worse diarrhea or skin rash, and capecitabine was held for grade 2 or worse hand-foot syndrome, stomatitis, or diarrhea. In the event of other toxicities grade 3 or higher, both drugs were held. Treatment was resumed with dose reduction (erlotinib 100 mg and capecitabine 750 mg/m^2 bid) if toxicities resolved within 14 days; if toxicities did not resolve, patients were removed from study treatment. Patients with evidence of response (complete response or partial response) or stable disease continued receiving treatment until there was evidence of disease progression, unacceptable toxicity, or withdrawal of patient consent.

On-study evaluation included toxicity assessments and measurement of hematologic, renal, and hepatic function weekly for the first 3 weeks of treatment and every 3 weeks thereafter. Patients were evaluated with computed tomography at 6 weeks, 12 weeks and subsequently every 9 weeks after treatment initiation. Response and progression were evaluated using RECIST.[25]

Statistical Methods

The study was designed with a primary end point of response. We anticipated that any second-line regimen for metastatic pancreatic cancer associated with a 10% response rate or greater would be of further interest. Our study design employed a one-stage design with 32 eligible patients, with the assumption that if at least two of the 32 eligible patients showed response, then this regimen would be considered to be of further interest in this patient population. The secondary objectives of the study were to assess toxicity, overall survival (OS), and progression-free survival (PFS). OS was defined as the time from study entry until death from any cause. PFS was defined as the time from first dose to the date of documented progression or death from any cause. OS and PFS were calculated using the Kaplan-Meier method.

RESULTS

Patient Characteristics

A total of 32 eligible patients were enrolled onto the study. Two patients withdrew from the study before receiving treatment. The remaining 30 received treatment and were included in subsequent analysis. Baseline characteristics of the treated patient population are shown in Table 1. Patients were recruited from two sites: Dana-Farber Cancer Institute and Massachusetts General Hospital (both Boston, MA). The median age of the patient population was 60 years; 43% were male and 57% female. As anticipated in a second-line study, nearly all patients were symptomatic from their disease. Only 23% had an ECOG performance status of 0, and 77% had a performance status of 1. Eight patients (27%) had undergone surgery and received prior adjuvant therapy; all 30 patients had received prior therapy with a gemcitabine-containing regimen for metastatic disease.

The treatment-related toxicities are summarized in Table 2. The most common toxicity was diarrhea, which developed in 77% of the patients. In five cases (17%), diarrhea was severe (grade 3). Rash developed in 67%; in four (13%), rash was graded as severe (grade 3). Other common toxicities included fatigue, hand-foot syndrome, and stomatitis. Hand-foot syndrome and stomatitis were severe (grade 3) in four (13%) and three (10%) cases, respectively. Hematologic toxicity was uncommon and generally mild, with only two (7%) cases of

Table 1. Patient Characteristics (N = 30)

Characteristic	No.	%
Age, years		
Median	60	
Range	42-80	
Sex		
Male	13	43
Female	17	57
ECOG PS		
0	7	23
1	23	77
Liver metastases	21	70
Prior adjuvant therapy	8	27
Prior metastatic treatment regimens		
Gemcitabine	20	67
Gemcitabine/cisplatin	6	20
Gemcitabine/oxaliplatin	4	13
CA 19-9, U/mL		
Median	1,960	
Range	3-368,996	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status.

grade 3 neutropenia observed; thrombocytopenia was not observed as a treatment-related adverse event.

Twenty-one patients required dose modifications or delays of capecitabine. The most common reasons for dose modification were hand-foot syndrome, stomatitis, or diarrhea classified as grade 2 or greater. Twenty patients required dose modifications or delays for erlotinib-related toxicity. The most common reasons for modifying the erlotinib dose were diarrhea or skin rash classified as grade 2 or greater.

Patients received a median of 2.5 3-week cycles of therapy, remaining on study for a median of 7.4 weeks. However, 25% of the treated patients remained on study for 4 or more months, and one patient remained on study for 21 months. The majority of patients (73%) treated on this study discontinued treatment for progressive disease, 10% of patients discontinued therapy for unacceptable toxicity, and the remaining patients discontinued therapy after withdrawing consent.

The primary end point of the study was objective response rate, as measured by RECIST. Three patients (10%) experienced a partial response to therapy. In addition, five patients experienced biochemical responses, as defined by decreases in serum tumor marker CA 19-9 of more than 50%. Of the three patients who experienced partial radiologic responses, two also experienced biochemical responses. The median progression-free survival time was 3.4 months, and the median overall survival time was 6.5 months. One-year overall survival was 26% (Fig 1). We found no correlation between the development of skin rash and either response or survival.

EGFR and *Ras* mutation analysis was performed on archival tumor tissue from five patients enrolled onto the study, as previously described and reported.[26] These patients had undergone prior pancreaticoduodenectomy at one of the participating institutions, and therefore had adequate tissue for analysis. Mutation analysis was not attempted in patients who had undergone only diagnostic needle biopsy or whose tumor blocks were not available. *EGFR* mutations were identified in two of the five available tumor specimens; both mutations occurred in exon 19 (Del 2235-2249), previously identified in patients with non–small-cell lung cancer (Table 3).[21,22] Mutations

Table 2. Treatment-Related Toxicities Experienced by > 10% of Patients

	Maximum Grade							
	1		2		3		4	
Toxicity	No.	%	No.	%	No.	%	No.	%
Hematologic								
Hemoglobin	5	17	4	13	—		—	
Neutrophils/granulocytes	1	3	1	3	2	7	—	
Leukocytes (total WBC)	2	7	1	3	—		—	
Nonhematologic								
Bilirubin	—		2	7	1	3	—	
Alkaline phosphatase	1	3	—		1	3	—	
AST	1	3	1	3	—		—	
Creatinine	1	3	—		—		—	
Other								
Diarrhea	7	23	11	37	5	17	—	
Rash/desquamation	11	37	5	17	4	13	—	
Fatigue	3	10	11	37	1	3	—	
Hand-foot skin reaction	5	17	5	17	4	13	—	
Stomatitis/pharyngitis	3	10	6	20	3	10	—	
Anorexia	7	23	5	17	—		—	
Nausea	5	17	4	13	2	—	—	
Taste disturbance (dysgeusia)	4	13	2	7	—		—	
Vomiting	2	7	3	10	1	—	—	
Constipation	4	13	1	3	—		—	
Pruritis	2	7	2	7	—		—	
Edema	2	7	1	3	—		—	

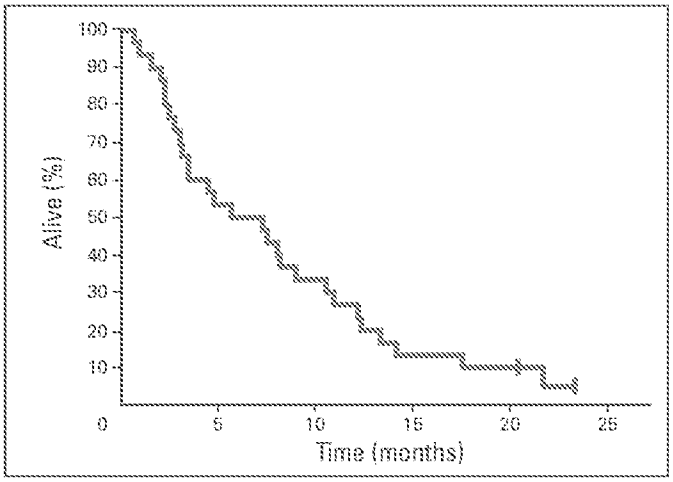

Fig 1. Overall survival

in *Ras* codon 12 were detected in three of the five specimens. Among the two patients with an *EGFR* mutation, one individual experienced a partial response to treatment; whereas among the three participants without a mutation in *EGFR*, one patient also experienced a partial response to treatment. Both tumors with *EGFR* mutations also contained *Ras* mutations. Within this small data set, *EGFR* mutational status did not appear to materially influence treatment response or overall survival. Survival times were 9.2 and 11 months in patients whose tumors contained *EGFR* mutations, and 4.1, 8.3, and 11.5 months in patients whose tumors had no mutations.

DISCUSSION

This phase II study demonstrated antitumor activity associated with the combination of capecitabine and erlotinib in patients with gemcitabine-refractory metastatic pancreatic cancer. The objective tumor response rate associated with this regimen was 10%, and OS 6 months. The toxicities observed were similar to toxicities previously known to be associated with the two agents when administered independently.

Relatively few other studies have evaluated second-line treatments for patients with pancreatic cancer, and capecitabine alone has not been evaluated in this setting (Table 4). Direct comparisons between our results and those of the other studies listed are necessarily limited by the relatively small size of our patient cohort and our selected population. The tumor response rates associated with the regimens used in these second-line studies range, from 3.8% to 24%, and the median survival times range from 3.4 to 10.3 months. These broad ranges likely reflect not only variation in efficacy but also differences in patient selection.

The toxicity associated with our regimen reflects the known toxicities associated with both capecitabine and erlotinib. Diarrhea has been associated with both agents, and was the most common toxicity experienced by patients in this study; other common toxicities included rash, stomatitis, and hand-foot syndrome. The dose of erlotinib used in our study was 150 mg/m^2, identical to the dose currently used in non–small-cell lung cancer, but higher than the 100 mg/m^2 dose used in the majority of patients in the randomized trial of gemcitabine versus gemcitabine/erlotinib in pancreatic cancer.[23] Among a small cohort of 23 patients in the randomized trial who were treated with 150 mg, 11 required dose reductions, suggesting that the higher dose level may be associated with more toxicity. The use of the 150- rather than the 100-mg dose of erlotinib in may well have contributed to the observed incidence of diarrhea and other adverse events in our study.

Although the survival benefit associated with the addition of erlotinib to gemcitabine in the first-line setting clearly supports a role for EGFR inhibition in pancreatic cancer, the precise mechanisms by which EGFR inhibitors exert their clinical activity in this disease remain uncertain. In lung cancer patients, tumors with activating *EGFR* mutations have been shown to be particularly susceptible to therapy with EGFR tyrosine kinase inhibitors.[21,22] Mutations in *EGFR* appear to be rare in pancreatic cancer. In one study evaluating 43 individual tumors, no mutations in *EGFR* were identified.[27] In a second study, performed by Kwak et al,[26] two tumors with *EGFR* mutations were identified among 55 pancreatic adenocarcinomas (3.6%). The study by Kwak et al included five available tumors from patients enrolled onto the current trial of capecitabine and erlotinib; both tumors with mutations were among these five specimens. The mutations identified in our patients were identical, and consisted of an in-frame deletion delE746-A750, previously described in non–small-cell lung cancer.[21,22]

The small number of tumors available for *EGFR* mutational analysis precluded a formal analysis correlating *EGFR* mutational status with clinical outcome in this study. The lack of available tumor specimens reflects the propensity for pancreatic cancer to be diagnosed by fine-needle biopsy at a late stage, and the consequent lack of

Table 3. Tumor *EGFR* and *Ras* Mutation Status

Patient No.	Age (years)	Sex	Months on Study	Best Response to Treatment	Survival Duration (from study entry)	Mutation Status	
						EGFR	*Ras*[a]
3	56	M		PR	11	Del 2235-2248 (exon 19)	GAT
4	53	M	4.8	SD	9.2	Del 2235-2249 (exon 19)	GAT
5	60	F	5.3	PR	11.5	No mutation	No mutation
6	77	M	5.5	SD	8.3	No mutation	No mutation
13	87	F	3.3	SD	4.1	No mutation	GAT

Abbreviations: PR, partial response; SD, stable disease.
[a]Listed as the mutated Ras codon 12. Wild-type codon 12 is GGT.

Table 4. Clinical Trials in Chemotherapy-Refractory Patients With Advanced Pancreatic Cancer

Regimen	No. of Patients	Objective Tumor Response Rate (%)	Median Survival Time (months)	Reference
Capecitabine/erlotinib	30	10	6.5	Current study
Pemetrexed	52	3.8	4.6	Boeck et al, 2007[31]
Gemcitabine/oxaliplatin	31	23	6	Demols et al, 2006[32]
Raltitrexed/oxaliplatin	41	24	5.2	Reni et al, 2006[33]
Oxaliplatin/leucovorin/fluorouracil	30	23	5.7	Tsavaris et al, 2005[34]
Rubitecan	198*	11	3.5	Jacobs et al, 2004[35]
Irinotecan/oxaliplatin	30	10	5.9	Centone et al, 2004[36]
Celecoxib/infusional fluorouracil	17	12	3.4	Milella et al, 2004[37]
Raltitrexed/irinotecan	19	16	6.5	Ulrich-Pur, 2003[38]
Gemcitabine, fluorouracil, leucovorin, cisplatin	34	24	10.3	Kozuch et al, 2001[39]
Paclitaxel	18	5	4	Ostrle, 2000[40]

*Treatment arm of randomized trial (v best supportive care).

resected tumor specimens with sufficient tissue to extract DNA. Among the patients with available tissue, one patient with an *EGFR* mutation experienced a radiologic partial response, and one experienced stable disease. Of the three assessable patients without *EGFR* mutations, one responded and two experienced stable disease. Survival times did not appear significantly different between patients with and without mutations. Although the limited number of assessable cases precludes drawing definitive conclusions, these results suggest that *EGFR* mutational status may not be a major predictor of response to capecitabine and erlotinib in patients with advanced pancreatic cancer.

KRAS mutations are common in pancreatic cancer, and, in our study, were present in both patients with mutations in *EGFR*. KRAS functions downstream of EGFR, and, in non–small-cell lung cancer, the presence of *KRAS* mutations appears to diminish responsiveness to EGFR inhibition.[28] The antitumor activity of cetuximab, a monoclonal antibody targeting the extracellular domain of EGFR, seems to be independent of *EGFR* mutation status.[29] In a preliminary report, the addition of cetuximab to gemcitabine failed to improve the survival of patients with advanced pancreatic cancer, compared with gemcitabine alone.[30]

In conclusion, both the gemcitabine/erlotinib and gemcitabine/capecitabine combination regimens have been associated with improvements in overall survival when used as first-line therapy for patients with advanced pancreatic cancer. Our study demonstrates that a regimen containing two of these agents, capecitabine and erlotinib, can be safely administered and has activity in the second-line setting. The combination of capecitabine and erlotinib may represent a reasonable second-line treatment option for patients with advanced pancreatic cancer who experience treatment failure with single-agent gemcitabine, and may also be considered as a first-line option for patients in whom first-line gemcitabine is not appropriate.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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ORIGINAL REPORT

Randomized Phase II Study of Gemcitabine Administered at a Fixed Dose Rate or in Combination With Cisplatin, Docetaxel, or Irinotecan in Patients With Metastatic Pancreatic Cancer: CALGB 89904

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See accompanying editorial on page 5487 and articles on pages 5499, 5513, and 5660

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose

The relative value of gemcitabine-based combination chemotherapy therapy and prolonged infusions of gemcitabine in patients with advanced pancreatic cancer remains controversial. We explored the efficacy and toxicity of gemcitabine administered at a fixed dose rate or in combination with cisplatin, docetaxel, or irinotecan in a multi-institutional, randomized, phase II study.

Patients and Methods

Patients with metastatic pancreatic cancer were randomly assigned to one of the following four regimens: gemcitabine 1,000 mg/m^2 on days 1, 8, and 15 with cisplatin 50 mg/m^2 on days 1 and 15 (arm A); gemcitabine 1,500 mg/m^2 at a rate of 10 mg/m^2/min on days 1, 8, and 15 (arm B); gemcitabine 1,000 mg/m^2 with docetaxel 40 mg/m^2 on days 1 and 8 (arm C); or gemcitabine 1,000 mg/m^2 with irinotecan 100 mg/m^2 on days 1 and 8 (arm D). Patients were observed for response, toxicity, and survival.

Results

Two hundred fifty-nine patients were enrolled onto the study, of whom 245 were eligible and received treatment. Anticipated rates of myelosuppression, fatigue, and expected regimen-specific toxicities were observed. The overall tumor response rates were 12% to 14%, and the median overall survival times were 6.4 to 7.1 months among the four regimens.

Conclusion

Gemcitabine/cisplatin, fixed dose rate gemcitabine, gemcitabine/docetaxel, and gemcitabine/irinotecan have similar antitumor activity in metastatic pancreatic cancer. In light of recent negative randomized studies directly comparing several of these regimens with standard gemcitabine, none of these approaches can be recommended for routine use in patients with this disease.

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INTRODUCTION

Pancreatic adenocarcinoma is resistant to many systemic therapies and continues to be a leading cause of cancer-related death.[1] The administration of single-agent gemcitabine has been a mainstay of pancreatic cancer treatment based on evidence of clinical benefit and prolongation of survival when compared with fluorouracil in patients with advanced disease.[2] However, objective tumor responses after treatment with gemcitabine occur in less than 10% of patients, and median survival times are usually less than 6 months.

Combining gemcitabine with a second systemic agent has seemed to be a logical way to potentially enhance response rates and survival times for patients with advanced pancreatic cancer. This approach has unfortunately met with only limited success. A combination of gemcitabine and erlotinib was associated with a modest improvement in survival (hazard ratio for death = 0.82; $P = .038$) when compared with gemcitabine alone. However, the addition of the erlotinib was also associated with a higher incidence of rash, diarrhea, and hematologic toxicity.[3] In the preliminary report of a randomized study comparing gemcitabine and capecitabine with gemcitabine alone in 533 patients, the gemcitabine/capecitabine combination was associated with an enhanced overall response rate (14.2% *v* 7.1%, respectively) and a modest improvement in median survival time (7.4 *v* 6 months, respectively).[4] The

final report of a similar study, however, failed to demonstrate a significant survival advantage in the capecitabine-containing arm.[5]

Both irinotecan and docetaxel have been reported to have modest single-agent activity in pancreatic cancer.[6-8] Single-arm studies combining either of these agents with gemcitabine demonstrated their safety and showed preliminary evidence of promising activity.[9,10] Similarly, the combination of gemcitabine and cisplatin was associated with encouraging antitumor activity, with a reported overall response rate of 11% in a phase II study comprising 41 pancreatic cancer patients.[11] A fourth approach, modulating gemcitabine by administration at a fixed dose rate, was developed as an alternative technique to potentially increase the efficacy of gemcitabine.[12] After intravenous administration, gemcitabine undergoes intracellular phosphorylation to its active triphosphate metabolite, 2′,2′-difluoro 2′-deoxycytidine triphosphate.[13] The rate of formation of this metabolite is dose rate dependent and can be increased through the use of prolonged infusions, thereby enhancing its cytotoxic effect.

To further evaluate the efficacy and toxicity of gemcitabine-based chemotherapy regimens in pancreatic cancer, we performed a randomized phase II study of three different gemcitabine-based combinations or fixed dose rate infusion gemcitabine in patients with advanced pancreatic cancer, with the goal of identifying a promising regimen to take forward into a formal phase III study. Two hundred fifty-nine patients were randomly assigned to receive either gemcitabine/cisplatin, fixed dose rate gemcitabine, gemcitabine/docetaxel, or gemcitabine/irinotecan. Patients were observed for the primary end point of overall survival (OS) at 6 months. Secondary end points included toxicity, radiologic response, biochemical (CA 19-9) response, and time to tumor progression (TTP).

PATIENTS AND METHODS

Patient Characteristics

Eligible patients for this study were required to have biopsy-documented pancreatic adenocarcinoma, with evidence of distant metastatic disease. Patients with locally advanced disease without metastases were not eligible. Prior adjuvant therapy with fluorouracil and/or radiation therapy was allowed if such treatment had been completed at least 2 weeks before registration. All patients were age ≥ 18 years and had Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, adequate hematologic function, creatinine ≤ 1.5 mg/dL, total bilirubin ≤ 1.5 mg/dL, AST ≤ 2.5× upper limit of normal (ULN), and alkaline phosphatase ≤ 2.5× ULN if AST was more than 1.5× ULN (alkaline phosphatase of any value was accepted if AST ≤ 1.5× ULN). This protocol was reviewed by the institutional review board of each participating center, and all patients provided written informed consent before participation in the study.

Trial Structure and Organization

Patient registration and data collection were managed by the Cancer and Leukemia Group B (CALGB) Statistical Center. Data quality was ensured by careful review of data by CALGB Statistical Center staff and by the study chair. All analyses were performed by CALGB statisticians based on the study database frozen on March 11, 2008.

Treatment Plan

Patients were randomly assigned to receive one of the following four regimens: gemcitabine/cisplatin (arm A), fixed dose rate gemcitabine (arm B), gemcitabine/docetaxel (arm C), or gemcitabine/irinotecan (arm D). Initial dosing regimens were as follows. In arm A, gemcitabine was administered as a 30-minute infusion at a dose of 1,000 mg/m^2 on days 1, 8, and 15, every 28 days. Cisplatin was administered over 30 minutes at a dose of 50 mg/m^2 on days 1 and 15, every 28 days. In arm B, gemcitabine was administered at a dose of 1,500 mg/m^2 at a rate of 10 mg/m^2/min on days 1, 8, and 15, every 28 days.

Table 1. Patient Characteristics

Characteristic	Gemcitabine/ Cisplatin (arm A)		FDR Gemcitabine (arm B)		Gemcitabine/ Docetaxel (arm C)		Gemcitabine/ Irinotecan (arm D)		All Patients	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Patients enrolled	66		64		65		64		259	
Patients treated	62		58		65		60		245	
Age, years										
Median	58.9		58.9		62.9		60.5		60.5	
Range	36-84		31-81		41-79		32-77		31-84	
Sex										
Male	35	56	38	66	40	62	41	68	154	63
Female	27	44	20	34	25	38	19	32	91	37
Performance status										
0	15	24	14	24	22	34	23	39	74	30
1	40	65	36	62	36	55	31	53	143	58
2	7	11	8	14	7	11	6	8	27	11
Prior treatment with FU										
No	58	94	49	84	58	89	51	86	216	89
Yes	4	6	9	16	7	11	8	14	28	11
Prior treatment with radiation therapy										
No	56	90	47	81	57	88	51	86	211	86
Yes	6	10	11	19	8	12	8	14	33	14
Median weeks on study treatment	9.6		6.1		8.4		12.1		9.0	
Required dose modifications or delays	58	94	45	78	46	71	49	83	198	81
Received second-line treatment after study	21	34	15	26	21	32	15	25	72	30

Abbreviations: FDR, fixed dose rate; FU, fluorouracil.

In arm C, gemcitabine was administered as a 30-minute infusion at a dose of 1,000 mg/m^2 on days 1 and 8, every 21 days. Docetaxel was administered immediately after gemcitabine at a dose of 40 mg/m^2 on days 1 and 8. Premedication with dexamethasone was recommended. In arm D, gemcitabine was administered as a 30-minute infusion at a dose of 1,000 mg/m^2 on days 1 and 8, every 21 days. Irinotecan was administered immediately after gemcitabine at a dose of 100 mg/m^2 on days 1 and 8.

A physical examination and an assessment of hematologic, hepatic, and renal function were carried out at baseline and on the first day of each subsequent cycle in all treatment arms. All patients had hematologic function measured again on day 1; patients in arm A (gemcitabine/cisplatin) or arm B (fixed dose rate gemcitabine) had hematologic function also measured on day 15. Renal function was repeated on day 15 for patients receiving gemcitabine/cisplatin. Dose reductions were instituted for febrile neutropenia, hematologic toxicity, pulmonary toxicity, neurotoxicity, or hepatic toxicity in all arms of the study. Drug-specific dose modifications were also instituted for renal toxicity (cisplatin), hypersensitivity reactions (docetaxel), or diarrhea (irinotecan). For other nonhematologic toxicities, treatment was held until resolution and then resumed at 75% of the previous dose of all drugs in the event of grade 2 or 3 toxicity or at 50% of the previous dose in the event of grade 4 toxicity.

Disease response was documented by computed tomography, which was performed at baseline and every two cycles for patients in arms A and B or every three cycles for patients in arms C and D. Tumor response was measured according to Response Evaluation Criteria in Solid Tumors (RECIST); however, given the extensive fibrosis common in primary pancreatic tumors, only metastatic tumor sites were considered measurable for response evaluation. Patients evaluable for CA 19-9 response included those whose baseline CA 19-9 was elevated ≥ 75% from normal. A CA 19-9 response was defined as a decrease of ≥ 75% sustained over two measurements at least 4 weeks apart. Patients continued treatment until documented disease progression, unacceptable toxicity, withdrawal of consent, or the investigator thought change in therapy was in the best interest of the patient.

Statistical Plan

OS at 6 months was the primary efficacy end point of the study and was measured from time of protocol registration to time of death from any cause. Assuming a median OS of 6 months, with 60 patients in each arm, the proportion of patients surviving 6 months could be estimated within, at most, ± 0.11 month with 90% confidence in each arm. Estimation of the biomarker CA 19-9 response was a secondary objective. Patients were additionally observed for radiologic tumor response, time to disease progression, and toxicity. Treatment arms were compared descriptively for efficacy and toxicity end points. OS and TTP were estimated using the Kaplan-Meier method. TTP was defined as the time from study entry until documented progression or death from pancreatic cancer. OS was measured from study entry until death from any cause.

RESULTS

Patient Characteristics

A total of 259 patients were enrolled onto the study between January 15, 2001 and December 12, 2003; the patient characteristics are listed in Table 1. Of the patients enrolled, 245 were eligible and received treatment. Patients were evenly distributed among the four treatment arms with regard to age and performance status. The majority of patients in all four arms (56% to 68%) were male. Less than 20% of patients in each arm had received prior adjuvant chemotherapy with fluorouracil or external-beam radiation. Thirty percent of patients subsequently received second-line chemotherapy after treatment on the study; the frequency of second-line therapy was similar in the four arms.

Table 2. Selected Grade 3 or 4 Adverse Events, According to Treatment Arm

	Maximum Toxicity Grade (% of patients)							
	Arm A: Gemcitabine/ Cisplatin (n = 62)		Arm B: FDR Gemcitabine (n = 58)		Arm C: Gemcitabine/ Docetaxel (n = 65)		Arm D: Gemcitabine/ Irinotecan (n = 60)	
Adverse Event	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Hematologic toxicity								
Neutrophils	27	19	26	22	18	14	18	7
Leukocytes	32	6	21	16	18	8	13	7
Platelets	47	2	22	3	9	0	12	2
Hemoglobin	13	3	12	0	14	2	5	0
Nonhematologic toxicity								
Fatigue	11	5	12	2	18	3	17	2
Hyperglycemia	6	3	7	2	32	2	8	2
Nausea	23	0	12	0	9	0	15	0
Vomiting	18	0	12	2	8	0	10	0
Dehydration	5	0	5	0	8	0	10	0
Diarrhea	0	0	2	0	6	2	18	0
Infection	6	0	4	2	13	0	3	0
Alkaline phosphatase	6	0	3	0	8	0	8	0
Anorexia	3	2	5	0	8	0	0	0
Dyspnea	0	0	2	0	9	0	3	2
Thrombosis	0	3	0	0	5	5	3	0
Bilirubin	2	0	2	2	2	0	3	0
Febrile neutropenia	2	0	3	0	5	0	2	0
Edema	3	0	2	0	2	0	3	2
GI bleeding	0	0	0	0	3	2	0	0

NOTE. Grade 3 or 4 adverse events experienced by two or more patients in any arm are listed. Grade 5 (fatal) toxicities included: arm A, renal failure (n = 2); arm B, infection (n = 1) and seizure (n = 1); and arm D, infection (n = 1).
Abbreviation: FDR, fixed dose rate.

Table 3. Reason for Treatment Discontinuation

Reason for Ending Treatment	Arm A: Gemcitabine/ Cisplatin (n = 62)		Arm B: FDR Gemcitabine (n = 58)		Arm C: Gemcitabine/ Docetaxel (n = 65)		Arm D: Gemcitabine/ Irinotecan (n = 60)		All Patients (N = 245)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Progressive disease	38	61	32	55	39	60	33	55	142	58
Adverse event	13	21	9	16	12	18	12	20	46	19
Death	3	5	6	10	7	11	5	8	21	9
Withdrew from study	7	11	9	16	7	11	6	10	29	12
Other	1	2	2	4	0		4	7	7	3

Abbreviation: FDR, fixed dose rate.

Study Treatment

The median length of time that patients remained on study treatment varied from 6.1 weeks (fixed dose rate gemcitabine) to 12.1 weeks (gemcitabine/irinotecan). Dose modifications or delays for toxicity were common and occurred in nearly all of the patients (94%) receiving gemcitabine/cisplatin, 83% of patients receiving gemcitabine/irinotecan, 78% of patients receiving fixed dose rate gemcitabine, and 71% of patients receiving gemcitabine/docetaxel.

Neutropenia was the most common significant hematologic toxicity, and fatigue was the most common nonhematologic toxicity; both occurred at a similar incidence in all four treatment arms (Table 2). Other toxicities seemed to be more treatment arm dependent and reflected known adverse effects of the regimens used. Thrombocytopenia, nausea, and vomiting were most pronounced in patients receiving gemcitabine/cisplatin, whereas diarrhea occurred almost exclusively in patients receiving gemcitabine/irinotecan. Grade 3 or 4 hyperglycemia developed in 34% of patients receiving gemcitabine and docetaxel and was likely related to pretreatment with corticosteroids.

Overall, 19% of the patients withdrew from the study as a result of adverse events; the rate of withdrawal as a result of adverse events was similar in the four treatment arms (Table 3). A total of 21 patients died while receiving study treatment. Of these, five patients were classified as having experienced grade 5 (fatal) toxicities. Two patients receiving gemcitabine/cisplatin died of treatment-induced renal failure. Two patients died of treatment-related infections (one receiving fixed dose rate gemcitabine and one receiving gemcitabine/irinotecan), and one patient receiving fixed dose rate gemcitabine experienced a fatal seizure.

Efficacy

Six-month survival, the primary end point, was similar in all four treatment arms and ranged from 53% (gemcitabine/cisplatin) to 57% (fixed dose rate gemcitabine and gemcitabine/irinotecan; Table 4). OS was also similar in all four treatment arms (Table 4; Fig 1A). The median OS ranged from 6.4 months (fixed dose rate gemcitabine) to 7.1 months (gemcitabine/irinotecan). The median TTP ranged from

Table 4. Efficacy Results According to Treatment Arm

Efficacy	Arm A: Gemcitabine/ Cisplatin (n = 56)		Arm B: FDR Gemcitabine (n = 43)		Arm C: Gemcitabine/ Docetaxel (n = 57)		Arm D: Gemcitabine/ Irinotecan (n = 51)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Radiologic response (RECIST)								
Complete response*	1	2	0		0		1	2
Partial response*	6	11	6	14	7	12	6	12
Stable disease	30	54	25	58	30	53	28	55
Progressive disease	19	34	12	28	20	35	16	31
CA 19-9 response	15/46†	33	16/38	42	19/48	42	16/48	33
Time to tumor progression, months								
Median	4.5		3.3		4.1		4.0	
95% CI	2.6 to 5.5		2.7 to 4.6		2.4 to 4.9		2.5 to 5.2	
Patients alive at 6 months	33	53	33	57	35	54	34	57
Overall survival, months								
Median	6.7		6.4		6.4		7.1	
95% CI	5.0 to 7.8		4.4 to 8.9		5.1 to 7.9		5.4 to 8.8	

Abbreviations: FDR, fixed dose rate; RECIST, Response Evaluation Criteria in Solid Tumors.
*Confirmed.
†No. of patients/total No. of patients.

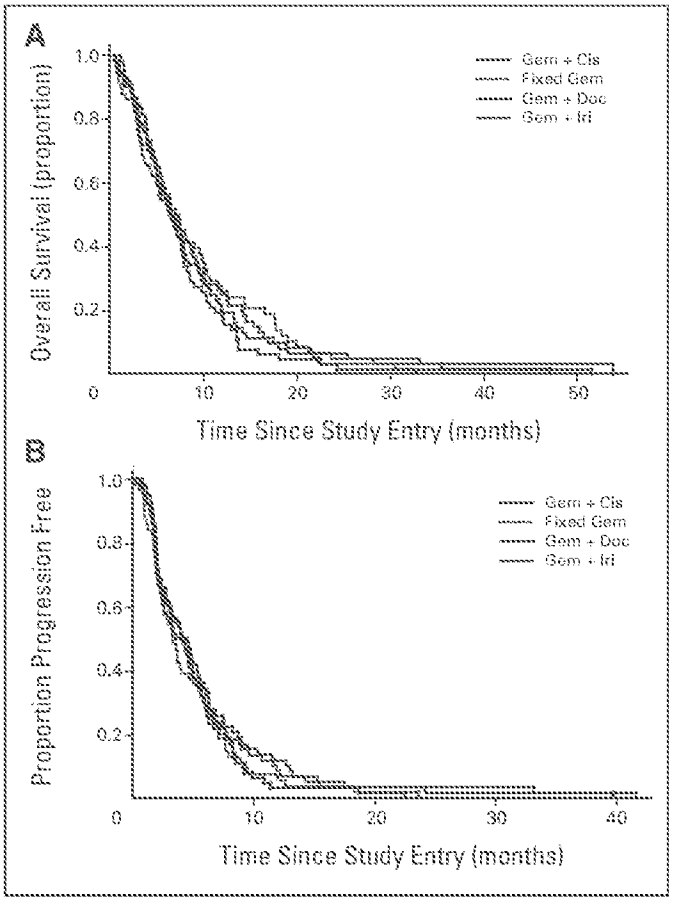

Fig 1. (A) Overall survival and (B) time to progression according to treatment arm. Gem, gemcitabine; Cis, cisplatin; Doc, docetaxel; Iri, irinotecan.

3.3 months (fixed dose rate gemcitabine) to 4.5 months (gemcitabine/cisplatin; Table 4; Fig 1B).

Radiologic and biochemical (CA 19-9) responses were secondary end points of our study. The number of patients evaluable for these end points was less than the number evaluable for survival as a result of the definitions of response used for the study (Table 4). One of the clinical characteristics of pancreatic cancer is extensive desmoplasia around the primary tumor, making it difficult to assess response or progression of disease at this site using standard imaging criteria. For the purposes of this study, therefore, we elected to consider only metastatic sites measurable for response. Confirmed radiologic response rates were indistinguishable among treatment arms and ranged from 12% (gemcitabine/docetaxel) to 14% (fixed dose rate gemcitabine and gemcitabine/irinotecan). CA 19-9 response rates were also similar between treatment arms and ranged from 33% (gemcitabine/cisplatin and gemcitabine/irinotecan) to 42% (fixed dose rate gemcitabine).

DISCUSSION

This multi-institutional, randomized, phase II study showed that four gemcitabine-based regimens (gemcitabine/cisplatin, fixed dose rate gemcitabine, gemcitabine/docetaxel, and gemcitabine/irinotecan) result in similar response and survival times in patients with advanced pancreatic cancer. Objective tumor response rates associated with the four regimens were within the narrow range of 12% to 14%. Median OS times were also similar and ranged from 6.4 to 7.1 months. Toxicities, although not prohibitive, were apparent in all four arms and were consistent with the anticipated effects of the four regimens. Consequently, we concluded that none of these regimens merited further assessment in a phase III study.

After the completion of this study, three of the four regimens we evaluated were directly compared with standard gemcitabine in randomized phase III trials performed by other groups. The combination of gemcitabine and cisplatin was evaluated in a German multicenter randomized trial comprising 195 patients, of whom 20% had locally advanced disease and 80% had metastatic disease.[14] The treatment regimen used in that study (cisplatin 50 mg/m^2 on days 1 and 15 and gemcitabine 1,000 mg/m^2 on days 1, 8, and 15 of a 28-day cycle) was identical to that used in our study. As in our study, nausea and vomiting, presumably secondary to the incorporation of cisplatin, were common. Tumor response rates were similar in the cisplatin/gemcitabine and gemcitabine alone arms (10.2% *v* 8.2%, respectively). Although both the reported progression-free and median survival times associated with the combination arm were longer than those associated with standard gemcitabine, the median survival difference did not reach statistical significance.

Fixed dose rate gemcitabine, which comprised the second arm of our study, was first compared with gemcitabine administered as a standard infusion in a randomized phase II study and, subsequently, with standard gemcitabine or fixed dose rate gemcitabine/oxaliplatin in an 833-patient, three-arm, randomized phase III study performed by the ECOG (ECOG 6201).[12,15] The randomized phase II study compared gemcitabine 1,500 mg/m^2 administered at a fixed dose rate of 10 mg/m^2/min (the regimen used in our study) with a standard 30-minute infusion of high-dose gemcitabine (2,200 mg/m^2).[12] The median survival time was 8 months in the fixed dose rate arm compared with only 5 months in the standard infusion arm ($P = .013$). In the subsequent phase III study (ECOG 6201), a small improvement in survival was observed with fixed dose rate gemcitabine, although this did not meet the threshold set for statistical significance.[15]

Two randomized trials have compared gemcitabine and irinotecan with standard gemcitabine. In the first study, which used the same gemcitabine/irinotecan regimen that was part of our study, the combination arm, compared with standard gemcitabine, was associated with a higher tumor response rate (16.1% *v* 4.4%, respectively) but no difference in OS (6.3 *v* 6.6 months, respectively).[16] The incidence of grade 3 or 4 diarrhea in patients receiving irinotecan in this study was 18.5%, which is identical to the 18% incidence observed in arm D of our study. A second randomized study comprising 145 patients used a different combination regimen, in which standard gemcitabine was compared with gemcitabine administered at a dose of 900 mg/m^2 weekly for 3 out of 4 weeks combined with irinotecan 300 mg/m^2 on day 8.[17] Combination therapy was again associated with a higher response rate compared with standard gemcitabine (15% *v* 10%, respectively), but there were no significant differences in TTP or median survival.

Survival durations associated with other combinations have also been either equivalent or only marginally superior to those associated with single-agent gemcitabine in randomized studies. The median survival time associated with gemcitabine/pemetrexed was 6.2 months, compared with 6.3 months with single-agent gemcitabine, in a randomized study comprising 565 patients.[18] A study performed by

the Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR) and Italian Group for the Study of Gastrointestinal Tract Cancer (GISCAD) compared standard gemcitabine with a regimen of fixed dose rate gemcitabine administered in combination with oxaliplatin.[19] This study reported an improvement in progression-free survival associated with the combination regimen but failed to demonstrate a significant OS difference.

One potential difficulty in comparing results across studies of novel regimens in pancreatic cancer has been the variable inclusion of patients with locally advanced and metastatic disease. To minimize patient heterogeneity in our study, we included only patients with metastatic disease. The median survival times associated with combination chemotherapy in our study, which ranged from 6.4 to 7.1 months, match closely with the median survival time reported for patients with metastatic disease receiving single-agent gemcitabine (6.7 months) in the GERCOR/GISCAD trial. This finding is consistent with our interpretation that none of the four regimens evaluated in our study is likely to offer a significant improvement over treatment with gemcitabine alone.

To date, only two gemcitabine-based regimens—gemcitabine/erlotinib and, in a preliminary report, gemcitabine/capecitabine—have been associated with statistically significant improvements in OS when compared directly with gemcitabine alone in the randomized setting.[3,4] In both of these two studies, the survival benefit was relatively small and was achieved at a cost of increased toxicity. Both the gemcitabine/capecitabine and gemcitabine/erlotinib randomized studies included more than 500 patients and were thus powered to detect small survival differences. Several meta-analyses have, in fact, suggested a benefit associated with combination chemotherapy.[20,21] The largest of these studies evaluated 9,970 patients from 51 randomized trials and reported a statistically significant survival advantage associated with gemcitabine combination therapy compared with gemcitabine alone (hazard ratio = 0.91; 95% CI, 0.85 to 0.97).[22] Whether this difference is clinically meaningful remains unclear, particularly in light of the enhanced toxicity associated with many combination regimens.

In conclusion, we observed similar efficacy associated with four gemcitabine-based regimens in patients with metastatic pancreatic adenocarcinoma. These findings do not support the further study of any of these regimens in this setting. Our study demonstrates the feasibility of evaluating four potentially promising regimens in a randomized fashion in this disease. The observed results are consistent with subsequent phase III studies in advanced pancreatic cancer and suggest that adopting a similar approach to evaluate future agents in pancreatic cancer may be an efficient way to rapidly assess which regimens to bring forward in phase III randomized studies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Prognostic value of baseline biliary stents on outcomes in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) in the NAPOLI-1 trial

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INTRODUCTION

- Liposomal irinotecan (nal-IRI) is a topoisomerase I inhibitor that has been found to exhibit extended circulation and enhanced intratumoural drug deposition vs. non-liposomal irinotecan. The exposure to the more active irinotecan metabolite SN-38 is thereby increased and prolonged.[1–3]
- The NAPOLI-1 study previously reported that nal-IRI+5-fluorouracil/leucovorin (5-FU/LV) significantly improved median overall survival (OS) by 45% (6.1 vs. 4.2 months; unstratified hazard ratio [HR] = 0.67; $P = 0.0122$) vs. 5-FU/LV control. Additionally, median progression-free survival was doubled (PFS; 3.1 vs. 1.5 months; unstratified HR = 0.56; $P = 0.0001$) vs. 5-FU/LV control in patients with mPDAC that progressed following gemcitabine-based therapy.[4]
- nal-IRI has since been approved in combination with 5-FU/LV for the treatment of patients with mPDAC after disease progression following gemcitabine-based therapy in various countries, and has also influenced pancreatic cancer treatment guidelines in Europe and the US.[5,6]
- Patients with pancreatic cancer affecting the head of the pancreas are commonly affected by obstructive jaundice and pruritus.[7]
- Biliary stenting is used as a palliative measure to treat malignant obstructive jaundice and associated complications in the last months of life. Stenting allows bile efflux resulting in normalised bilirubin levels.[7]
- Patients with a biliary stent were allowed to enter the NAPOLI-1 study if plasma bilirubin was normal.

METHODS

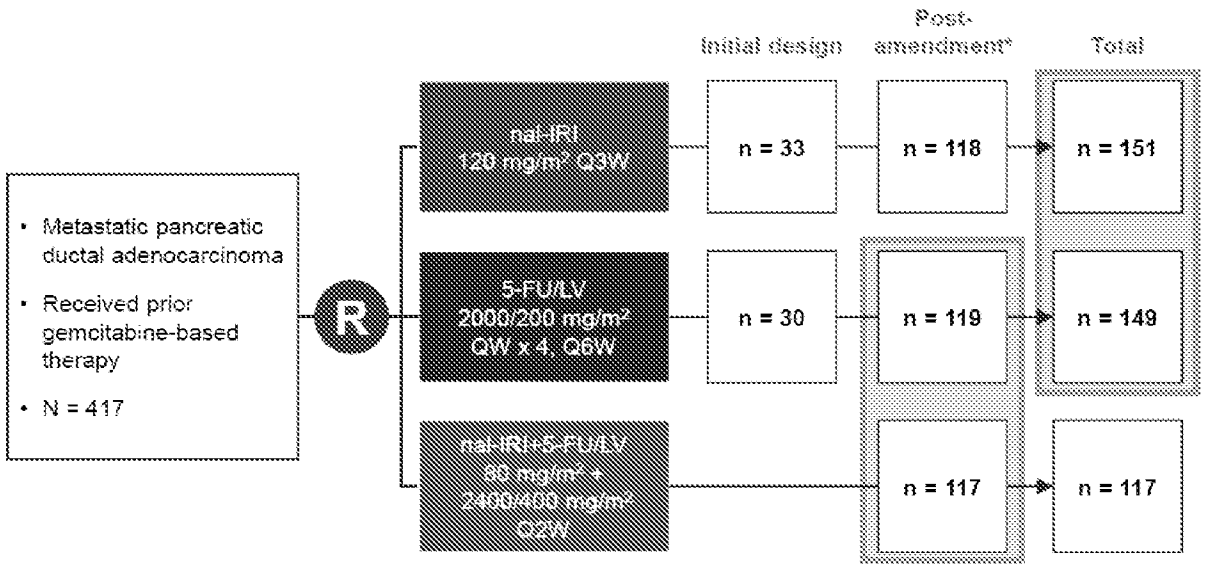
Objectives and subgroup analysis

- This *post-hoc* analysis explored outcomes in patients in the NAPOLI-1 study population with or without a biliary stent at baseline.

STUDY DESIGN

- NAPOLI-1 was an international, open-label, randomised, phase 3 trial (Figure 1).

Figure 1. Study design[4]



*The study was amended to add the nal-IRI+5-FU/LV arm once safety data on the combination became available. Only those patients enrolled in the 5-FU/LV arm after the amendment (n = 119) were used as the control for the combination arm. nal-IRI 80 mg/m² expressed as irinotecan hydrochloride trihydrate salt, equivalent to 70 mg/m² irinotecan free base. (Trial registered at ClinicalTrials.gov, number NCT01494506).

Key inclusion criteria

- Adults ≥18 years of age.
- Histologically or cytologically confirmed PDAC.
- Documented metastatic disease; disease status permitted to be measurable or non-measurable as per RECIST v. 1.1 guidelines.
- Disease progression after prior gemcitabine or gemcitabine-containing therapy in a neoadjuvant, adjuvant (only if distant metastases occurred within 6 months of completing adjuvant therapy), locally advanced, or metastatic setting.
- Karnofsky performance status (KPS) score ≥70.
- Adequate hematologic (including absolute neutrophil count >1.5×10^9 cells/L), hepatic (including normal serum total bilirubin and albumin levels ≥30 g/L), and renal function.

Key exclusion criteria

- Clinically significant gastrointestinal disorders.

RESULTS

Patient Characteristics

- Prior to study entry, 37/417 (9%) patients had a biliary stent.
- A higher proportion of patients with a stent at baseline had a primary tumour located in the head of the pancreas at diagnosis vs patients without a stent at the start of the study (89% vs. 59%) (Table 1).

Table 1. Patient demographics and baseline characteristics in subgroups per treatment arm (overall ITT, nal-IRI+5-FU/LV and 5-FU/LV)

	Baseline stent: with			Baseline stent: without		
	Overall ITT n = 37	nal-IRI+ 5-FU/LV n = 15	5-FU/LV n = 8	Overall ITT n = 380	nal-IRI+ 5-FU/LV n = 102	5-FU/LV n = 111
Gender, n (%)						
Female	15 (41)	5 (33)	3 (38)	165 (43)	43 (42)	49 (44)
Male	22 (59)	10 (67)	5 (63)	215 (57)	59 (58)	62 (56)
Age (yrs)						
Median Min, Max	61 52, 83	61 52, 77	61 54, 67	64 31, 87	64 41, 81	62 34, 80
Race, n (%)						
White	14 (38)	8 (53)	4 (50)	239 (63)	64 (63)	72 (65)
Black or African American	0	0	0	10 (3)	4 (4)	3 (3)
American Indian or Alaska Native	1 (3)	0	0	0	0	0
Asian	16 (43)	5 (33)	3 (38)	120 (32)	29 (28)	33 (30)
Other	6 (16)	2 (13)	1 (13)	11 (3)	5 (5)	3 (3)
Baseline KPS, n (%)						
90–100	20 (54)	9 (60)	5 (63)	211 (56)	60 (59)	52 (47)
70–80	17 (46)	6 (40)	3 (38)	165 (43)	39 (38)	58 (52)
50–60	0	0	0	3 (1)	3 (3)	0
Measurable metastatic lesions at baseline, n (%)						
1	3 (8)	0	1 (13)	78 (21)	19 (19)	21 (19)
2	20 (54)	9 (60)	2 (25)	164 (43)	40 (39)	56 (50)
3	4 (11)	2 (13)	2 (25)	61 (16)	20 (20)	13 (12)
>3	3 (8)	0	2 (25)	21 (6)	7 (7)	6 (5)
Primary tumour location, n (%)						
Head only	29 (78)	11 (73)	7 (88)	210 (55)	59 (58)	58 (52)
Body only	1 (3)	0	1 (13)	53 (14)	12 (12)	18 (16)
Tail only	1 (3)	0	0	61 (16)	14 (14)	19 (17)
Multi-locations including head	4 (11)	3 (20)	0	13 (3)	3 (3)	4 (4)
Multi-locations excluding head	0	0	0	30 (8)	9 (9)	10 (9)
Unknown	2 (5)	1 (7)	0	13 (3)	5 (5)	2 (2)
Anatomical location of lesions at baseline,* n (%)						
Liver	26 (70)	10 (67)	7 (88)	258 (68)	65 (64)	75 (68)
Median CA-19-9 (U/mL)	1929	2236	5878	1539	1192	1292
Median albumin (g/dL)	3.8	3.9	4.0	4.0	4.1	4.0

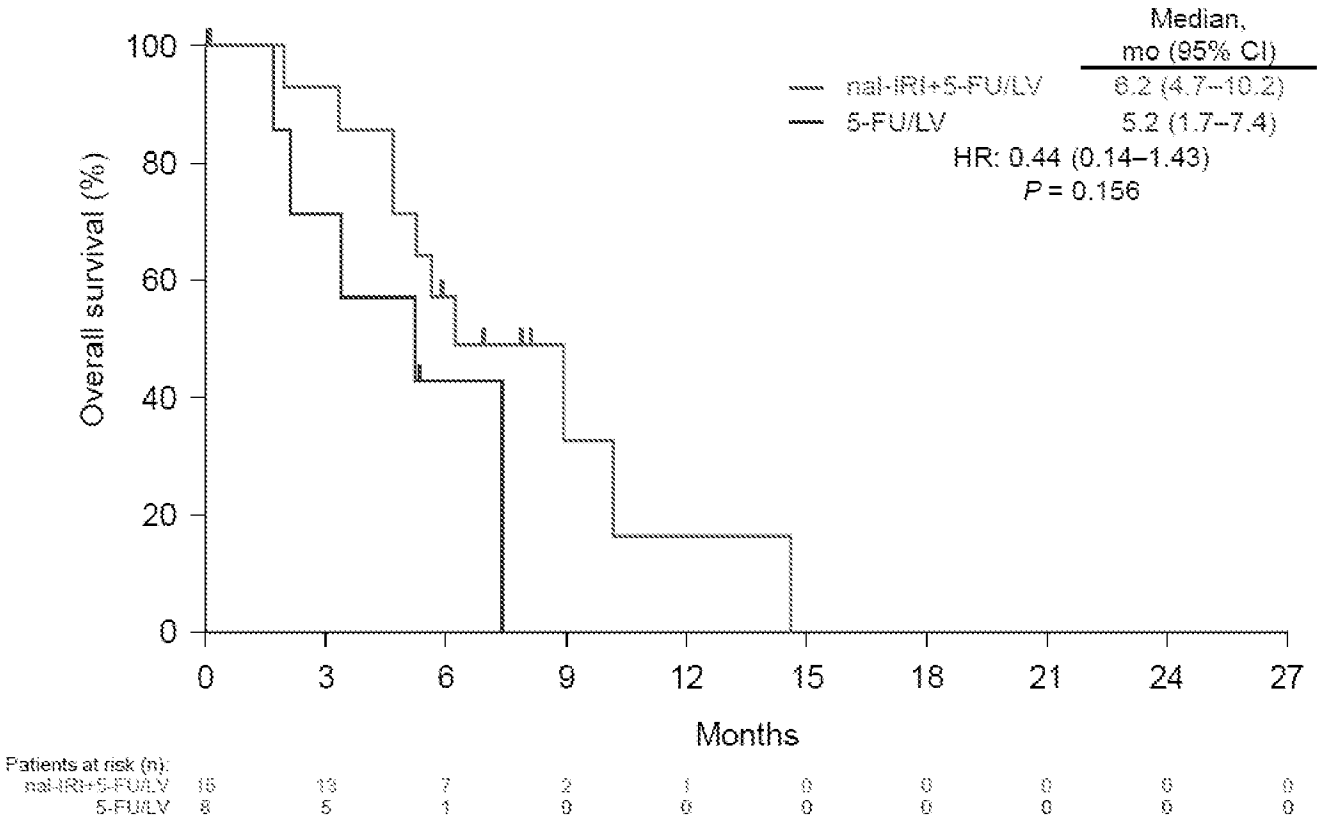
*Based on lesion locations followed for RECIST v1.1. Includes all measurable and non-measurable lesions; includes all metastatic and non-metastatic lesions. Patients may be included in more than one category.
5-FU/LV, 5-fluorouracil and leucovorin; ITT, intent-to-treat; KPS, Karnofsky performance status; nal-IRI, liposomal irinotecan.

Overall survival

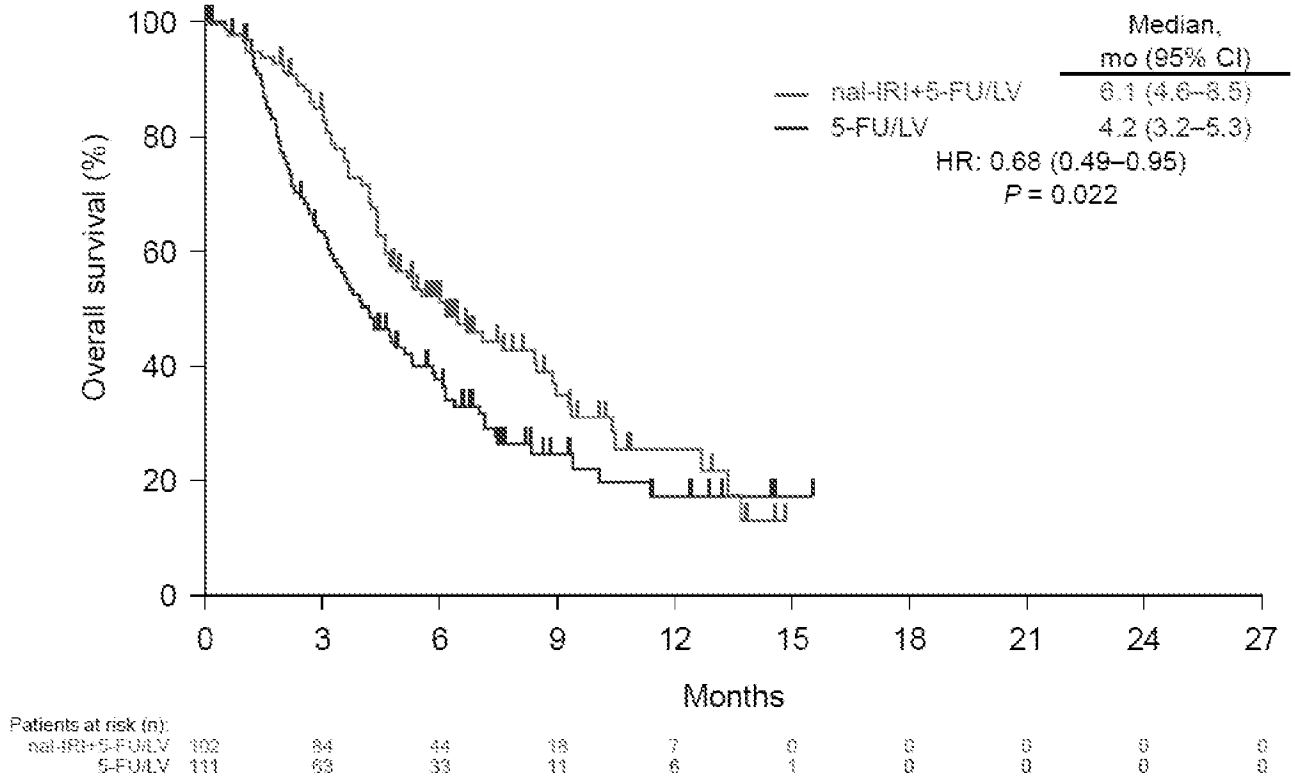
- In the overall intent-to-treat (ITT) population, mOS was similar for patients with or without a stent at baseline (mOS: 5.3 vs. 4.8 months, HR = 0.97, *P* = 0.895) (Table 2).
- mOS was similar among patients in the nal-IRI+5-FU/LV arm with vs. without a stent at baseline (6.2 vs. 6.1 months, HR = 0.91, *P* = 0.785) (Table 2).
- Patients **with** a stent at baseline receiving nal-IRI+5-FU/LV exhibited a trend towards increased mOS (6.2 vs. 5.2 months, HR = 0.44, *P* = 0.156) (Table 2 and Figure 2A).
- Patients **without** a stent at baseline receiving nal-IRI+5-FU/LV had improved mOS (6.1 vs. 4.2 months, HR = 0.68, *P* = 0.022) (Table 2 and Figure 2B).

Figure 2. Overall survival of patients with and without a stent at baseline receiving nal-IRI+5-FU/LV or 5-FU/LV (ITT population)

(A) With a stent at baseline



(B) Without a stent at baseline



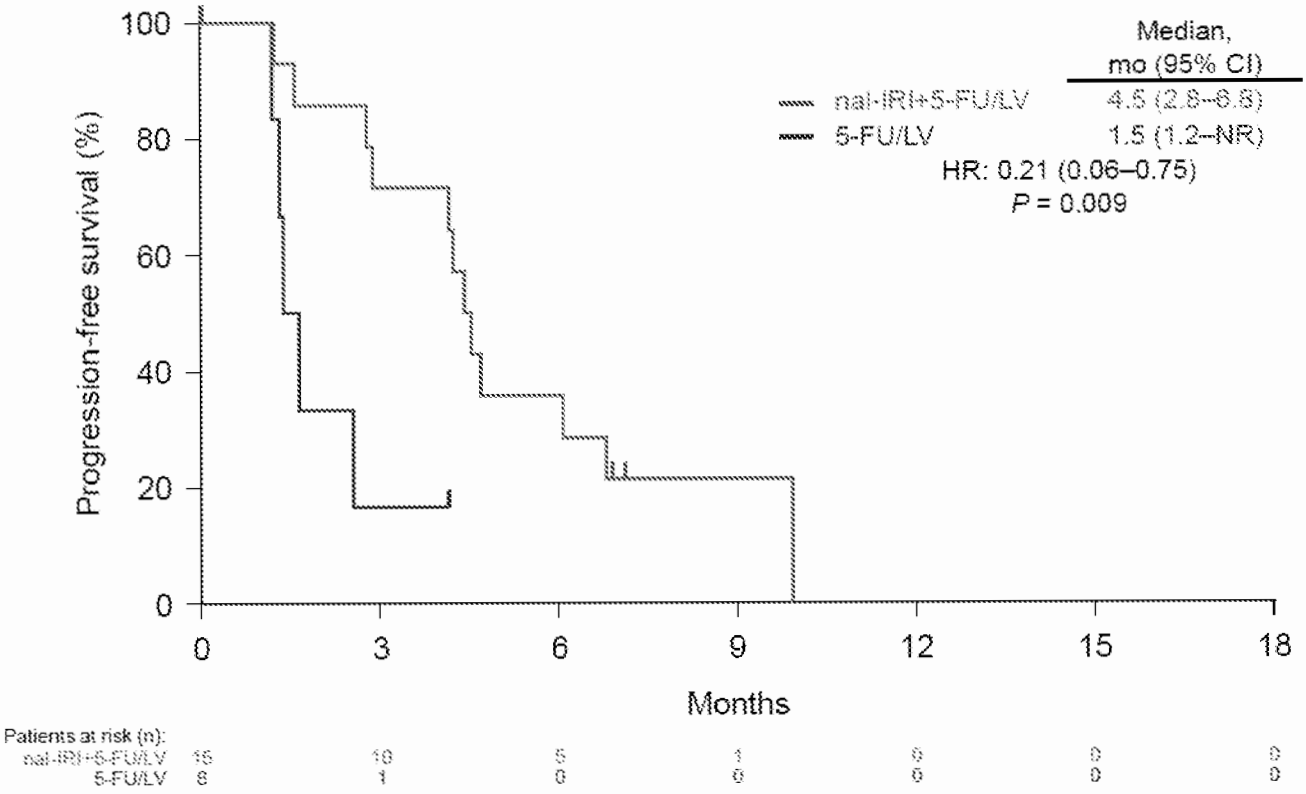
5-FU/LV, 5-fluorouracil and leucovorin; CI, confidence interval; HR, hazard ratio; mo, months; nal-IRI, liposomal irinotecan.

Progression-free survival

- In the overall ITT population, mPFS was similar for patients with or without a stent at baseline (3.5 vs. 2.4 months, HR = 0.82, *P* = 0.319) (Table 2).
- In the nal-IRI+5-FU/LV arm, mPFS was similar in patients with vs. without a stent at baseline (4.5 vs. 3.0 months, HR = 0.79, *P* = 0.471) (Table 2).
- Patients **with** a stent at baseline receiving nal-IRI+5-FU/LV had improved mPFS vs. 5-FU/LV (4.5 vs. 1.5 months, HR = 0.21, *P* = 0.009) (Table 2 and Figure 3A).
- Patients **without** a stent at baseline receiving nal-IRI+5-FU/LV had improved mPFS vs. 5-FU/LV (3.0 vs. 1.5 months, HR = 0.59, *P* < 0.001) (Table 2 and Figure 3B).

Figure 3. Progression-free survival of patients with and without a stent at baseline receiving nal-IRI+5-FU/LV or 5-FU/LV (ITT population)

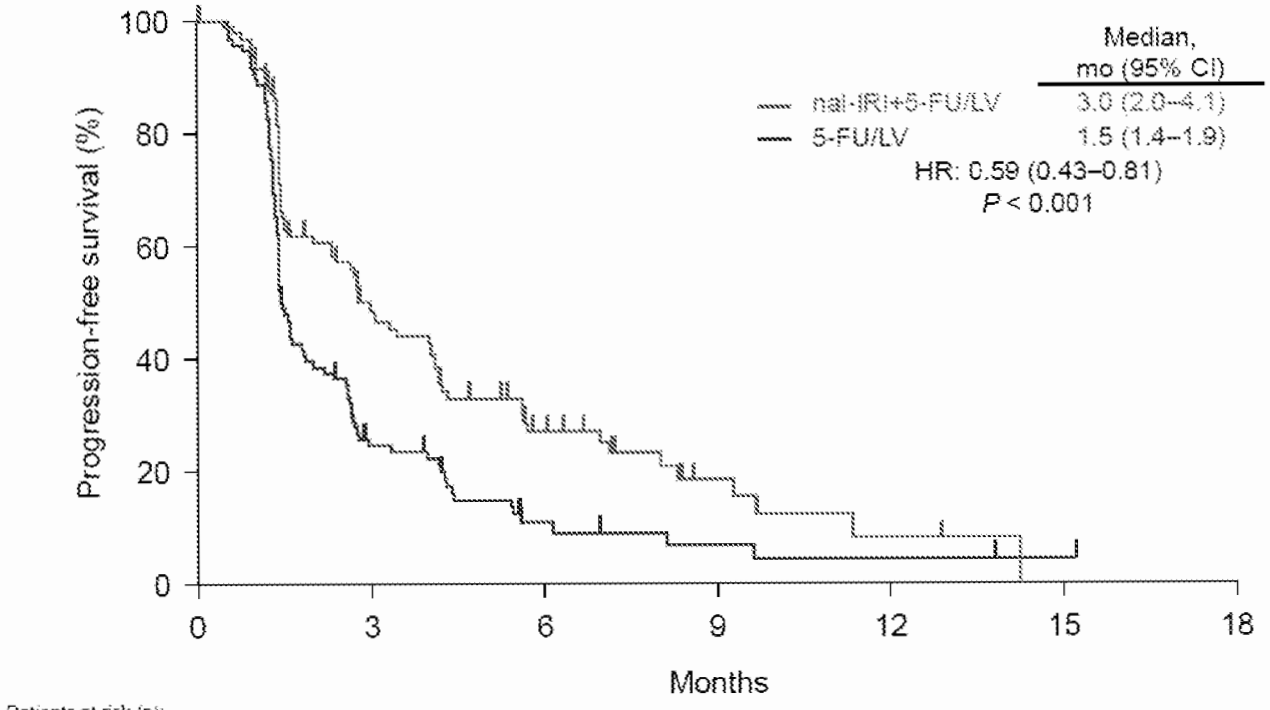
(A) With a stent at baseline



Patients at risk (n):

nal-IRI+5-FU/LV	16	10	5	1	0	0	0
5-FU/LV	6	1	0	0	0	0	0

(B) Without a stent at baseline



Patients at risk (n):

nal-IRI+5-FU/LV	102	40	17	6	2	0	0
5-FU/LV	111	22	6	3	2	1	0

5-FU/LV, 5-fluorouracil and leucovorin; CI, confidence interval; HR, hazard ratio; mo, months; nal-IRI, liposomal irinotecan; NR, not reached.

Tumour response

- In the overall ITT population, patients with a stent at baseline demonstrated a higher objective response rate (ORR) (16% vs. 6%; $P = 0.033$) and a greater proportion of CA19-9 responses (37% vs. 20%; $P = 0.048$) than those without (Table 2).
- In the nal-IRI+5-FU/LV arm, ORR (27% vs. 15%, $P = 0.263$) and CA19-9 responses (42% vs. 27%, $P = 0.312$) were numerically higher in patients with a stent at baseline (Table 2).
- Patients **with** a stent at baseline receiving nal-IRI+5-FU/LV exhibited trends towards increased ORR (27% vs. 0%, $P = 0.257$) and similar CA19-9 responses (42% vs. 40%, $P = 1.000$) vs. patients receiving 5-FU/LV (Table 2).
- Patients **without** a stent at baseline receiving nal-IRI+5-FU/LV had improved ORR (15% vs. 1%, $P < 0.001$) and CA19-9 responses (27% vs. 8%, $P = 0.002$) vs. patients receiving 5-FU/LV (Table 2).

Table 2. Summary of efficacy for all patients separated by treatment group and presence of baseline stent (ITT population)

	Comparison by baseline stent (with vs. without)				Comparison by treatment group			
	All patients		nal-IRI+5-FU/LV		Baseline stent: with		Baseline stent: without	
	Baseline stent: With n = 37	Baseline stent: Without n = 380	Baseline stent: With n = 15	Baseline stent: Without n = 102	nal-IRI+ 5-FU/LV n = 15	5-FU/LV n = 8	nal-IRI+ 5-FU/LV n = 102	5-FU/LV n = 111
Overall survival (OS)								
Median OS time (months)	5.3	4.6	6.2	6.1	6.2	5.2	6.1	4.2
95% CI	4.1–7.4	4.4–5.4	4.7–10.2	4.6–8.5	4.7–10.2	1.7–7.4	4.6–8.5	3.2–5.3
HR	0.97		0.91		0.44		0.68	
95% CI	0.65–1.46		0.47–1.78		0.14–1.43		0.49–0.95	
P value*	*P* = 0.895		*P* = 0.785		*P* = 0.156		*P* = 0.022	
Progression-free survival (PFS)								
Median PFS time (months)	3.5	2.4	4.5	3.0	4.5	1.5	3.0	1.5
95% CI	1.6–4.4	1.7–2.7	2.8–6.8	2.0–4.1	2.8–6.8	1.2–NR	2.0–4.1	1.4–1.9
HR	0.82		0.79		0.21		0.59	
95% CI	0.56–1.20		0.43–1.47		0.06–0.75		0.43–0.81	
P value*	*P* = 0.319		*P* = 0.471		*P* = 0.009		*P* < 0.001	
Best overall response, n (%)								
ORR	6 (16)	23 (6)	4 (27)	15 (15)	4 (27)	0	15 (15)	1 (1)
P value†	*P* = 0.033		*P* = 0.263		*P* = 0.257		*P* < 0.001	
PR	6 (16)	23 (6)	4 (27)	15 (15)	4 (27)	0	15 (15)	1 (1)
SD	14 (38)	114 (30)	8 (53)	31 (30)	8 (53)	0	31 (30)	26 (23)
Non-CR/non-PD	1 (3)	7 (2)	0	3 (3)	0	1 (13)	3 (3)	1 (1)
PD	10 (27)	146 (38)	2 (13)	32 (31)	2 (13)	4 (50)	32 (31)	52 (47)
NE	6 (16)	90 (24)	1 (7)	21 (21)	1 (7)	3 (38)	21 (21)	31 (28)
CBR	20 (54)	137 (36)	12 (80)	46 (45)	12 (80)	0	46 (45)	27 (24)
Tumour marker (CA 19-9) response								
CA19-9 response rate,‡ n/N (%)	10/27 (37)	59/298 (20)	5/12 (42)	22/83 (27)	5/12 (42)	2/5 (40)	22/83 (27)	6/77 (8)
P value†	*P* = 0.048		*P* = 0.312		*P* = 1.000		*P* = 0.002	

‡Response defined as 50% reduction in baseline CA19-9 levels, in patients with baseline levels >30 U/ml, and at least one post baseline CA19-9 measurement. *Two-sided *P* value from log-rank test; †Two-sided *P* value from pairwise Fisher's exact test.
5-FU/LV, 5-fluorouracil and leucovorin; CBR, clinical benefit rate; CI, confidence interval; HR, hazard ratio; nal-IRI, liposomal irinotecan; NE, not evaluable; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Safety, dose modifications and treatment exposure

- Treatment-related grade 3–4 adverse events were similar for patients with or without a stent at baseline, including infectious complications such as febrile neutropenia (overall safety population 3% vs. 2%; nal-IRI+5-FU/LV arm 7% vs. 1%), diarrhoea (overall safety population 12% vs. 13%; nal-IRI+5-FU/LV arm 14% vs. 13%) and decreased neutrophil count (overall safety population 21% vs. 12%; nal-IRI+5-FU/LV 14% vs. 21%) (Table 3).

Table 3. Adverse events in patients with and without biliary stents (overall safety population, nal-IRI+5-FU/LV and 5-FU/LV), including infectious complications

	Baseline stent: with			Baseline stent: without		
	All safety patients n = 34	nal-IRI+ 5-FU/LV n = 14	5-FU/LV n = 6	All safety patients n = 364	nal-IRI+ 5-FU/LV n = 103	5-FU/LV n = 99
Alopecia (grade 1/2), n (%)	5 (15)	3 (21)	0	49 (13)	13 (13)	5 (5)
Febrile neutropenia (grade 3/4)	1 (3)	1 (7)	0	7 (2)	1 (1)	0
Grade 3/4 non-haematologic AEs in >5% of the overall safety population, n (%)						
Diarrhoea, late onset*	4 (12)	2 (14)	1 (17)	48 (13)	13 (13)	5 (5)
Vomiting	0	0	0	37 (10)	13 (13)	3 (3)
Nausea	1 (3)	1 (7)	0	20 (5)	8 (8)	2 (2)
Fatigue	2 (6)	1 (7)	0	28 (8)	15 (15)	4 (4)
Asthenia	3 (9)	3 (21)	0	25 (7)	6 (6)	6 (6)
Abdominal pain	5 (15)	3 (21)	0	23 (6)	5 (5)	6 (6)
Grade 3/4 haematologic AEs based on laboratory values,† n (%)						
Neutrophil count decreased	7 (21)	2 (14)	1 (17)	43 (12)	21 (21)	2 (2)
Haemoglobin decreased	7 (21)	3 (21)	0	16 (4)	4 (4)	4 (4)
Platelet count decreased	2 (6)	1 (7)	0	1 (0)	1 (1)	0
Drug-related AE of CTCAE Grade ≥3, n (%)	20 (59)	8 (57)	3 (50)	143 (39)	55 (53)	14 (14)

Safety was assessed by grading adverse events according to the National Cancer Institute CTCAE, version 4.0.
*>24 h after starting nal-IRI. †Includes only patients who had at least one post-baseline assessment.
5-FU/LV, 5-fluorouracil and leucovorin; AE, adverse events; CTCAE, *Common Terminology Criteria for Adverse Events*; nal-IRI, liposomal irinotecan

- Incidence of dose modifications with nal-IRI+5-FU/LV was broadly similar to the overall NAPOLI-1 population for patients with or without a stent at baseline (Table 4).

Table 4. Dose modification and treatment exposure by sub-group and treatment (safety population)

	Baseline stent: with			Baseline stent: without		
	All safety patients n = 34	nal-IRI+ 5-FU/LV n = 14	5-FU/LV n = 6	All safety patients n = 364	nal-IRI+ 5-FU/LV n = 103	5-FU/LV n = 99
Patients with TEAE leading to any dose modification, n (%)	22 (65)	11 (79)	2 (33)	190 (52)	72 (70)	35 (35)
Patients with TEAEs resulting in dose delayed,* n (%)	19 (56)	11 (79)	2 (33)	145 (40)	61 (59)	31 (31)
Patients with TEAE resulting in dose reduction,† n (%)	12 (35)	5 (36)	1 (17)	78 (21)	34 (33)	3 (3)
Patients with TEAE leading to dose discontinuation, n (%)	2 (6)	1 (7)	0	38 (10)	12 (12)	7 (7)

TEAEs are events that occurred or worsened on or after the day of first dose of the study drug and within 30 days after last administration of study drug.
*TEAEs with action taken as: dose not given or infusion interrupted. †TEAEs with action taken as: dose decreased or slowing infusion rate
5-FU/LV, 5-fluorouracil and leucovorin; nal-IRI, liposomal irinotecan; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- No clear prognostic effect of biliary stent at baseline on efficacy outcomes was observed in patients with mPDAC that progressed on gemcitabine-based therapy, both in the NAPOLI-1 ITT population and the nal-IRI+5-FU/LV treatment arm.
- Both patients with and without a stent at baseline benefitted from treatment with nal-IRI+5-FU/LV compared with 5-FU/LV alone.
- These findings indicate that irrespective of the presence of a biliary stent before treatment initiation, nal-IRI+5-FU/LV is well-tolerated and can benefit patients with mPDAC that progressed on gemcitabine-based treatment.

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- Jie Chen (Shire) was responsible for statistical analyses of this *post-hoc* study.
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Prognostic value of baseline biliary stents on outcomes in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) in the NAPOLI-1 trial

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INTRODUCTION

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Presented at the European Society for Medical Oncology 20th World Congress on Gastrointestinal Cancer, Barcelona, Spain, 25 — 28 June 2025

P – 151 **Prognostic value of baseline biliary stents on outcomes in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) in the NAPOLI-1 trial**

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Introduction: In the NAPOLI-1 phase 3 study of patients with mPDAC who progressed following gemcitabine-based therapy (NCT01494506), nal-IRI+5-FU/LV significantly increased median overall survival (mOS) vs 5-FU/LV control (6.1 vs 4.2 months; unstratified hazard ratio [HR]=0.67 [0.49–0.92]; P = 0.012). Biliary stenting is used to treat malignant obstructive jaundice and associated complications, allowing bile efflux resulting in normalised bilirubin levels. Patients with a biliary stent were allowed to enter the NAPOLI-1 study if plasma bilirubin was normal.

Methods: This post-hoc analysis explored outcomes in patients in the NAPOLI-1 study population with or without biliary stent at baseline (BL).

Results: Prior to study entry, 37/417 (9%) patients had a biliary stent. A higher proportion of patients with a BL stent had a primary tumour located in the head of the pancreas at diagnosis vs patients without a BL stent (89% vs 58%). In the overall intent-to-treat (ITT) population, mOS and median progression-free survival (mPFS) were similar for patients with or without a BL stent (mOS: 5.3 vs 4.8 months, HR = 0.97, P = 0.90; mPFS: 3.5 vs 2.4 months, HR = 0.82, P = 0.32). Patients with a BL stent demonstrated a higher objective response rate (ORR) (16% vs 6%; P = 0.03) and a greater proportion of cancer antigen 19-9 (CA19-9) responses (37% vs 20%; P < 0.05) than those without. mOS was similar among patients in the nal IRI+5 FU/LV arm with (n = 15) vs without (n = 102) a BL stent (6.2 vs 6.1 months, HR = 0.91, P = 0.78); mPFS (4.5 vs 3.0 months, HR = 0.79, P = 0.47), ORR (27% vs 15%, P = 0.26) and CA19 9 responses (42% vs 27%, P = 0.31) were numerically lower. Patients with a BL stent receiving nal-IRI+5-FU/LV (n = 15) exhibited trends towards increased mOS (6.2 vs 5.2 months, HR = 0.44, P = 0.16) and ORR (27% vs 0, P = 0.26), improved mPFS (4.5 vs 1.5 months, HR = 0.21, P < 0.01), and similar CA19-9 responses (42% vs 40%, P = 1.00) vs patients receiving 5-FU/LV (n = 8). Patients without a BL stent receiving nal IRI+5 FU/LV (n = 102) had improved mOS (6.1 vs 4.2 months, HR = 0.68, P = 0.02), mPFS (3.0 vs 1.5 months, HR = 0.59, P < 0.01), ORR (15% vs 1%, P < 0.01) and CA19 9 responses (27% vs 8%, P < 0.01) vs patients receiving 5 FU/LV (n = 111). Treatment-related grade 3–4 adverse events were similar for patients with or without a BL stent, including infectious complications such as febrile neutropenia (overall safety population n = 1/34 vs n = 7/364; nal IRI+5 FU/LV arm n = 1/14 vs n = 1/103), diarrhoea (overall safety population n = 4/34 vs n = 48/364; nal-IRI+5-FU/LV arm n = 2/14 vs n = 13/103) and decreased neutrophil count (overall safety population n = 7/34 vs n = 43/364; nal IRI+5 FU/LV n = 2/14 vs n = 21/103). Incidence of dose modifications with nal IRI+5 FU/LV was broadly similar to the overall NAPOLI 1 population for patients with or without a BL stent.

Conclusion: No clear prognostic effect of biliary stent at BL on efficacy outcomes was observed in patients with mPDAC who progressed on gemcitabine-based therapy, both in the NAPOLI-1 ITT population and the nal-IRI+5-FU/LV treatment arm. Both patients with and without a BL stent benefitted from treatment with nal-IRI+5-FU/LV compared with 5-FU/LV alone. These findings indicate that irrespective of the presence of a biliary stent before treatment initiation, nal-IRI+5-FU/LV is well-tolerated and can benefit patients with mPDAC who progressed on gemcitabine-based treatment.

(4% with bleeding; 18% without bleeding). Before initiating LOT1 systemic therapy, 27% received TAE/TACE or TARE (59% had 1 procedure, 34% had 2-3 procedures, 7% had 4+ procedures). The median durations of LOT1 sorafenib, bevacizumab, and ICI therapy were 56, 43, and 61 days, respectively. Only 10% received a second LOT (of whom 39% got IO therapy). The mean (standard deviation [SD]) total all-cause PPPM healthcare costs were $20,217 ($19,165). About 80% of these costs were HCC-related. Patient OOP costs were $422 (all-cause) and $300 (HCC-related) PPPM.

CONCLUSIONS: Patients with HCC in the U.S. had significant comorbidities, especially related to cardiovascular conditions. For every 4 patients receiving systemic therapy, three patients had no prior embolization, suggesting that a relatively high proportion of patients were first diagnosed at advanced stages. The direct healthcare economic burden of HCC patients treated with systemic therapy is substantial.

SPONSORSHIP: AstraZeneca Pharmaceuticals.

C5 Utilization of hospital inpatient services among patients with metastatic pancreatic cancer with commercial and Medicare insurance treated with FDA-approved/NCCN category 1 regimens

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BACKGROUND: There is currently limited real-world evidence on hospital inpatient resource utilization for patients with metastatic pancreatic cancer (m-PANC).

OBJECTIVE: To analyze rates of hospital inpatient utilization among patients (pts) with m-PANC with commercial insurance and Medicare fee-for-service (FFS), by FDA-Approved/NCCN Category 1 therapeutic regimen.

METHODS: We identified pts with m-PANC using ICD-9/10 diagnosis codes in the 2014-18 MarketScan and 2014-17 Medicare 100% Research Identifiable Files (RIF). Pts in our study had at least 2 claims with a pancreatic cancer (PANC) diagnosis more than 30 days apart and at least 1 claim with a secondary malignancy (metastasis) diagnosis on or after the first PANC diagnosis date. We defined index date as the earliest metastasis diagnosis date. Pts in our study had pre- and post-index insurance coverage (3 and 1 months for commercial pts, 6 and 3 months for Medicare FFS pts). We measured rates of hospital admissions (admits/pt), readmissions, intensive care unit (ICU) use, surgery, and average length of stay (ALOS) for 28,063 Medicare and 3,904 commercially insured m-PANC pts. Pts in our study were treated with NCCN Cat 1 regimens in any line of therapy: gemcitabine monotherapy (gem mono), gemcitabine/nab-paclitaxel (gem-nabP), FOLFIRINOX (FFX), and liposomal irinotecan (nal-IRI).

RESULTS: Across all regimens, admits/pt among pts with Medicare (0.62-0.91) were higher than among pts with commercial insurance (0.54-0.72). Gem-nabP pts had the highest admits/pt in both cohorts (Medicare: 0.91, commercial: 0.72). Nal-IRI had the lowest admits/pt among Medicare pts (0.62); Gem mono (0.54) and nal-IRI (0.56) had the lowest admits/pt among commercial pts. Nal-IRI pts had the lowest readmission (Medicare: 16%, commercial: 14%) and surgery rates (Medicare: 7%, commercial: 6%) among both Medicare and commercial patients. In both cohorts, gem mono pts had the highest ICU admit rate (Medicare: 26%, commercial: 26%).

CONCLUSIONS: Nal-IRI had the lowest admits/pts in the Medicare cohort, as well as the lowest readmission rates and surgery rates in both cohorts. Gem mono and nal-IRI had the lowest admits/pt among commercial pts. As providers adopt value-based care payment models, balancing hospital resource utilization with therapy cost will become increasingly important for the population budget planning and management of m-PANC.

SPONSORSHIP: Ipsen Biopharmaceuticals.

C6 An evaluation of the efficacy and safety of second-line (2L) treatments in metastatic colorectal cancer (mCRC)

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BACKGROUND: mCRC is associated with a poor prognosis and overall survival (OS). Treatment options typically include cytotoxic chemotherapy (FOLFOX or FOLFIRI) and targeted therapies (TT), combined and sequenced through several lines of treatment. Among treated patients, up to 60% will receive first line (1L) FOLFOX until disease progression. In patients who received FOLFOX, guidelines recommend 2L treatment with FOLFIRI alone or in combination with TT.

OBJECTIVE: A systematic literature review (SLR) was conducted to evaluate efficacy and safety outcomes of FOLFIRI-based 2L regimens in mCRC.

METHODS: Using PRISMA guidelines and pre-defined search terms, EMBASE, MEDLINE, and Cochrane were searched to identify studies from 2009 to the search date (01/21/2020) reporting efficacy and safety outcomes in patients receiving any systemic 2L treatment for mCRC. Relevant congresses (2017 to 2019) and clinicaltrials.gov were also searched. Outcome measures of interest included OS, progression-free survival (PFS), objective response rate (ORR), and safety.

RESULTS: 36 randomized controlled trials (RCTs) met inclusion criteria: 16 were FOLFIRI-based, 9 FOLFOX-based, 5 FOLFIRI- or FOLFOX-based, and 6 evaluated other therapies. Of the 16 FOLFIRI-based RCTs, five were Phase 3 RCTs with a total 3953 patients (128 to 614 per arm). Among patients in 5 RCTs, 57-63% were male, mean 61-62 years old, 94-100% with ECOG 0-1. 3 RCTs compared FOLFIRI alone to FOLFIRI+TT (2 RCTs of VEGF inhibitors, 1 RCT of an EGFR inhibitor), 1 RCT compared FOLFIRI to mXELIRI, and 1 to irinotecan+S-1. Median OS for FOLFIRI+TT ranged from 11.7 to 17.8 months, with -0.4 to 2 months incremental improvement vs. FOLFIRI alone. Median PFS ranged from 4.5 to 8.4 months, with -3.1 to 5.4 months incremental PFS vs. FOLFIRI alone. Response rates of 13.4% to 36% were reported with FOLFIRI+TT, vs. 9.8% to 18.8% with FOLFIRI alone. Treatment regimens were associated with severe toxicity, with 54% to 84% of patients reporting grade 3+ adverse events. Skin toxicities were commonly reported with EGFR inhibitors; thromboembolic events were common with VEGF inhibitors.

CONCLUSIONS: Few of the current FOLFIRI-based regimens in 2L mCRC offer meaningful improvements in PFS and OS, demonstrating only modest incremental gains in survival compared to chemotherapy alone. A significant unmet need exists for treatments that provide a robust and more lasting survival benefit with meaningful response, while offering an acceptable and manageable toxicity profile.

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Conceptual Framework for Cutting the Pancreatic Cancer Fuel Supply

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Abstract

Pancreatic ductal adenocarcinoma (a.k.a. pancreatic cancer) remains one of the most feared and clinically challenging diseases to treat despite continual improvements in therapies. The genetic landscape of pancreatic cancer shows near ubiquitous activating mutations of *KRAS*, and recurrent inactivating mutations of *CDKN2A*, *SMAD4*, and *TP53*. To date, attempts to develop agents to target KRAS to specifically kill cancer cells have been disappointing. In this regard, an understanding of cellular metabolic derangements in pancreatic cancer could lead to novel therapeutic approaches. Like other cancers, pancreatic cancer cells rely on fuel sources for homeostasis and proliferation; as such, interrupting the use of two major nutrients, glucose and glutamine, may provide new therapeutic avenues. In addition, *KRAS*-mutant pancreatic cancers have been documented to depend on autophagy, and the inhibition of autophagy in the preclinical setting has shown promise. Herein, the conceptual framework for blocking the pancreatic fuel supply is reviewed. *Clin Cancer Res; 18(16); 4285–90. ©2012 AACR.*

Introduction

Although inherited and acquired mutations are believed to cause pancreatic cancer (see review by Iacobuzio-Donahue and colleagues in this issue; ref. 1), common mutations in canonical oncogenes, such as AKT, MYC, PI3K, and RAS, and tumor suppressors, including TP53 and PTEN, also alter cancer metabolism to enable cancer cells to survive and proliferate in the hypoxic and nutrient-deprived tumor microenvironment (see review by Feig and colleagues in this issue; ref. 2). Oncogenes and tumor suppressors alter metabolism through transcriptional and posttranscriptional mechanisms. Mutations in genes encoding metabolic enzymes, such as succinate dehydrogenase (SDH), fumarate hydratase (FH), and isocitrate dehydrogenase (IDH) have also been linked to tumorigenesis, underscoring the intimate connections between metabolism and cancer (11, 12). Loss-of-function SDH or FH mutations result in accumulation of precursors such as succinate or fumarate. Mutated IDH1 or IDH2, on the contrary, are neomorphic enzymes that reverse the chemical reaction to produce 2-hydroxyglutarate (2-HG) from α-ketoglutarate (α-KG; ref. 13). These accumulated metabolic intermediates all have the ability to inhibit α-KG–dependent dioxgenases, which are involved in histone or DNA demethylation and in prolyl hydroxylases that modulate the hypoxia-inducible factors (HIF; refs. 14–16). In this regard, mutations in enzymes cause epigenetic deregulation that contributes to tumorigenesis.

To survive and proliferate in an adverse tumor microenvironment with limited nutrients and oxygen, cancer cells must rely on their ability to reprogram canonical biochemical pathways to provide the necessary bioenergetics and precursors of proteins, nucleic acids, and membrane lipids (17–19; Fig. 1). In addition to rewiring metabolism, tumor cells can also activate autophagy, a process that permits recycling of cellular constituents as internal fuel sources when external nutrient supplies are limited (20–22). Although nutrient-rich conditions inhibit autophagy through activation of mTOR, nutrient-deprived conditions decrease ATP production, resulting in activated AMPK that stimulates autophagy (23, 24; Fig. 1). As such, cancer cells have multiple mechanisms for metabolic adaptation to the tumor microenvironment.

Proliferating cancer cells transport glucose and glutamine into the cell as major nutrient sources for the production of ATP and building blocks for macromolecular synthesis (3, 4, 6; Fig. 1). The mitochondrion serves not only as the cellular powerhouse, producing ATP efficiently from glucose and glutamine, but it is also a hub for the production of key intermediates involved in nucleic acid, fatty acid, and heme synthesis. The proliferating cancer cells, hence, also produce toxic by-products that must be eliminated or extruded for cell survival. Reactive oxygen species (ROS) from the mitochondrion are neutralized; superoxide is converted by SOD to hydrogen peroxide, which is neutralized by catalase via its conversion to water and oxygen (25–27). Lactate and carbon dioxide, produced from glucose and glutamine catabolism, are exported through monocarboxylate transporters or neutralized and extruded by

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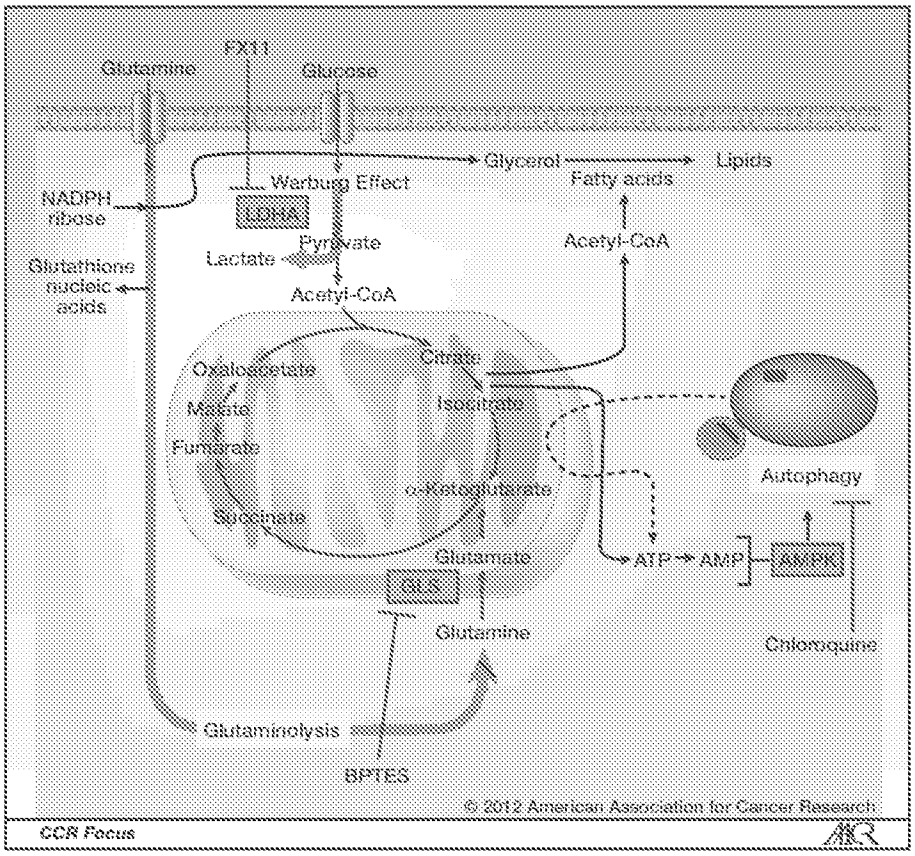

Figure 1. Diagram depicting the metabolism of glucose and glutamine via glycolysis and the TCA cycle. Both substrates contribute to the production of ATP, which when depleted would activate AMPK that in turn triggers autophagy. Autophagy increases lysosomal recycling of cellular constituents to recover ATP. GLS, glutaminase.

carbonic anhydrase (28). Although this article focuses on blocking cancer fuel supply as a promising new approach to pancreatic cancer therapy, therapeutic opportunities may also exist in blocking the exhaust pipes that eliminate metabolic toxic by-products from cancer cells.

Characteristic Features of Metabolism in Cancers

Aberrant metabolism is now considered one of the hallmarks of cancer (29). As a result of genetic alterations and tumor hypoxia, cancer cells reprogram metabolism to meet increased energy demand for enhanced anabolism, cell proliferation, and protection from oxidative damage and cell death signals. The molecular underpinnings for the reprogrammed metabolism of cancer cells have been linked to the activation of oncogenes or loss of tumor suppressors, which can function independently of, or through constitutive stabilization of the HIF, HIF-1α. Activated Ras and AKT oncogenes can increase glycolysis, enhancing the conversion of glucose to lactate (3). The *MYC* oncogene, which encodes the transcription factor Myc, increases the expression of glycolytic genes, thereby enhancing glycolysis and production of lactate (35).

Glycolysis is a multienzymatic pathway that catabolizes glucose to pyruvate via more than a dozen different enzymes with several apparent rate-limiting steps. Phosphofructose kinase provides the first rate-limiting step where fructose-1-phosphate, derived from glucose, is converted to fructose-1,6-bisphosphate. The other rate-limiting step is the conversion of phosphoenolpyruvate to pyruvate by pyruvate kinase (muscle form) PKM. Recent studies have raised an intense interest in the embryonic M2 isoform of pyruvate kinase (PKM2), which is highly expressed in human tumors. A study by Gao and colleagues (30) showed that dimeric, not tetrameric PKM2 that localizes the cellular nucleus, activates transcription of MEK5 by phosphorylating stat3 at Y705 using PEP as a phosphate donor. This protein kinase activity of PKM2 plays a role in promoting cell proliferation, revealing an important link between metabolism alteration and gene expression during tumor transformation and progression. The xenografted adenocarcinoma cells, which carry a mutant form of PKM2 that preferentially forms dimers, grow more rapidly and seem more aggressive than cells carrying wild-type (WT) PKM2. Although the dynamics of PKM2 oligomeric states and their roles in cancer remain confusing, these studies suggest that perturbation of glycolysis via manipulation of PKM2 could have a significant therapeutic effect.

Alteration of glucose metabolism in cancer is known as aerobic glycolysis or the Warburg Effect (3, 5, 31), which describes the ability of cancer cells to avidly metabolize

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glucose to lactate, even in the presence of oxygen. A manifestation of the Warburg Effect is the increased 2[^{18}F]fluoro-2-deoxy-D-glucose import by pancreatic cancers as determined by positron emission tomographic (PET) scans. However, only about 50% of pancreatic cancers have positive clinical PET, suggesting additional complexities and the possibility that pancreatic cancers could use other fuels or resort to other metabolic survival modes (32, 33).

In addition to glucose, proliferating cancer cells also rely on glutamine as a major source of energy and building blocks. In fact, MYC, which is frequently amplified or overexpressed in pancreatic cancer (34), has been mechanistically linked to the regulation of glutamine metabolism (35). In this regard, it is reasonable to surmise that PET negative pancreatic cancers may use glutamine as a major nutrient source. The Myc transcription factor emerges as a master regulator of a plethora of genes involved in cell growth including those regulating ribosome and mitochondrial biogenesis and intermediary metabolism. The normal MYC gene is under the scrutiny of many internal as well as extracellular cues such as nutrient and oxygen availability, such that deprivation of these supplies results in the downregulation of MYC expression. By contrast, many oncogenic pathways activate MYC or alterations of MYC itself resulting in a constitutive program of ribosome biogenesis and biomass accumulation that renders cancer cells addicted to nutrients. Indeed withdrawal of either glucose or glutamine triggers death of cells with MYC overexpression (35). In this regard, targeting enzymes involved in glucose or glutamine has also provided proof-of-concept that metabolic inhibition could provide a beneficial therapeutic effect (36).

Applying metabolomics technologies, with the use of nuclear magnetic resonance and mass spectrometer–based stable isotope resolved metabolomics with ^{13}C-labeled glucose and glutamine, a study by Le and colleagues (36) documents that cancer cells use either glucose or glutamine, depending on the availability of the nutrients. This flexibility of cancer metabolism enables cancer cells to proliferate and survive even under the hypoxic and nutrient-deprived conditions, which are often encountered in the tumor microenvironment. Moreover, in hypoxia, they observed the enhanced conversion of glutamine to glutathione, an important reducing agent for control of the accumulation of mitochondrial ROS. Most importantly, this study uncovered a previously unsuspected glucose-independent glutamine-driven tricarboxylic acid (TCA) cycle. Cancer cells subjected to glucose deficiency and/or hypoxia would benefit from such glucose-independent TCA cycle activity in the tumor microenvironment. Cell growth and survival can be sustained by glutamine metabolism alone. In addition to the links between oncogenes and tumor suppressors to altered cancer cell metabolism, mutations in specific TCA cycle enzymes contribute to tumorigenesis of familial or spontaneously acquired cancers. The study by Mullen and colleagues (37) uncovered other metabolic reprogrammed pathways in cancer cells, which have mutations in complex I or complex III of the electron transport chain (ETC). These are often found in patient-derived renal carcinoma cells with mutations in FH, and also in pharmacologically ETC-inhibited cells with normal mitochondria. These cancer cells use glutamine-dependent reductive carboxylation generating acetyl-CoA for lipid synthesis. These processes use mitochondrial and cytosolic isoforms of $NADP^+$/NADPH-dependent IDH. The ETC-deficient cancer cells, like FH mutations, cannot grow without glutamine. Hence, depending on the genetic make-up, a cancer cell could be distinctively addicted to glucose or glutamine.

Given that pancreatic cancers uniquely display increased levels of fibrotic stroma, the pancreatic cancer cell environment could be highly nutrient deficient (38, 39). In this nutrient-deprived state, increased AMPK activity could trigger autophagy (21). The process of self-eating or autophagy provides starved cells a means to survive by recycling cellular components as bioenergetic substrates for energy production and building blocks. As such, certain metabolic hubs should be exploitable for therapy, particularly if a specific cancer type is "addicted" to that pathway. Metabolic enzymes are readily pharmacologically targetable; in fact, many historical clinically effective chemotherapeutic drugs were termed "antimetabolites." Seeking drugs that directly inhibit these new metabolic targets involved in cancer cell energy metabolism while sparing normal cells is among the most desirable goal to improve cancer therapy, especially for the treatment of pancreatic cancer.

Blocking pancreatic cancer fuel supply

Addiction to glucose could be exploited through targeted inhibition of enzymes involved in glycolysis. One such target is the glycolytic pathway, in which the most consistent abnormality is its ultimate step of conversion of pyruvate to lactic acid by lactate dehydrogenase A (LDHA) to regenerate NAD^+ that is required for the further glycolytic conversion of glucose to pyruvate to generate ATP. Recent studies (40, 41) have targeted this phenotype of altered metabolism for therapy. The first drug-like small molecule (called FX11) that inhibits LDHA was used as proof of concept for targeting aerobic glycolysis in cancer. This compound, 7-benzyl-2,3-dihydroxy-6-methyl-4-*n*-propyl-1-napthoic acid, has shown an antitumorigenic effect in mouse models of human lymphoma and pancreatic cancer through the increased production of ROS and cell death (40). By blocking LDHA, FX11 diminishes the ability of malignant cells to metabolize pyruvate to lactate, and halts the regeneration of NAD^+ for glycolysis processing. This study also showed a strong synergy effect *in vitro* and *in vivo* with the use of FX11 in combination with FK866, an inhibitor of NAD^+ biosynthesis, which accentuates NAD^+ depletion.

Besides the Warburg Effect, cancer cells also maintain mitochondrial oxidation of glutamine by glutaminase that converts glutamine to glutamate, which enters the TCA cycle as 2-oxoglutarate. Two recent studies targeted glutaminolysis in cancer by a specific glutaminase inhibitor, bis-2-[5-(phenylacetamido)-1,3,4-thiadiazol-2-yl]ethyl sulfide (BPTES;

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ref. 42). The first study by Seltzer and colleagues (43) reported a preferable inhibition of mutant IDH1 cell growth by BPTES as compared with the WT enzyme. Mutation at the R132 residue of IDH1 creates a novel enzyme function that produces 2-HG from α-KG, which is from glutamate, a product of glutamine via glutaminase. Cancer cells with mutant IDH1 become addicted to glutamine and heavily depend on glutaminase. The addition of exogenous α-KG rescued growth suppression of mutant IDH1 cells by BPTES, which lowered glutamate and α-KG levels, inhibited glutaminase activity, and increased glycolytic intermediates. However, 2-HG levels were unaffected by BPTES. This presents a potential therapeutic opportunity. The study by Wang and colleagues (44) provided another aspect of targeting mitochondrial glutaminase activity inhibiting oncogenic transformation. They showed that glutaminase activity, which is dependent on Rho GTPases and NF-κB activity, increased in transformed fibroblasts and breast cancer cells. Targeting glutaminase activity by BPTES to inhibit oncogenic transformation had thus been shown, through a connection between Rho GTPase activation and cellular metabolism, to be a promising way forward. The importance of hypoxic glutamine metabolism in the study by Le and colleagues was also underscored by the antiproliferative therapeutic effect of BPTES on neoplastic cells *in vitro* and in a tumor xenograft model *in vivo* (36).

In addition to the proof-of-concept studies suggesting the feasibility of targeting glucose or glutamine metabolism in pancreatic cancer, it has been noted that pancreatic cancers display significant autophagic activities for survival (45–49). In fact, Ras-transformed cells depend on autophagy for survival (50). Hence, inhibition of autophagy with the antimalarial agent chloroquine has resulted in significant preclinical responses of pancreatic cancer xenografts and allografts in treated mice as compared with control (49, 51). Chloroquine also diminishes pancreatic tumorigenesis in a transgenic model (49). These studies suggest that 2 related and widely used agents with extremely favorable safety profiles, chloroquine or hydroxychloroquine, could have profound clinical effects. Indeed, there are now clinical trials testing this concept in pancreatic cancer. As for targeting glycolysis or glutaminolysis, the field is awaiting pharmaceutical companies to develop clinically safe, highly potent drugs to be tested in the clinic. Notwithstanding the inherent challenges for drug development, the concept of blocking the pancreatic cancer fuel supply provides a reasonable framework for the development of what is hoped to be a new class of anticancer agents.

Future directions

Although cancer cells can exhibit unique metabolic pathways, they also use the classic metabolic pathways of normal cells. This presents a great challenge to directly target metabolic pathways, especially metabolic enzymes as drug targets. The success of small molecular agents depends on how much cancer cells are "addicted" to the fuel nutrition versus normal cells, as shown in the studies mentioned above. The combination of multiomics technologies will give a functional perspective of cancer progression, beyond genes and protein expression profiles. The extensive data obtained from metabolic flux will be mined to identify specific pathways active in the tumor compared with untransformed cells. These data are essential for understanding the metabolic activity in tumor tissue, especially how cancer cells can respond to different environmental conditions and how they respond to therapy to detect likely responders and nonresponders to a particular chemotherapeutic agent. This is highly desirable because it is important to avoid the use of cytotoxic drugs that have no benefit. The ultimate goal is to characterize and enable targeted selection of patients based on predicted metabolic responses. The metabolic signatures that correlate with sensitivity of pancreatic cancers to metabolic inhibitors will also be used in the future to help us combine existing drugs to target multiple metabolic pathways and attack specific attributes of each patient's cancer. In fact, metformin, which inhibits NADH dehydrogenase and mitochondrial respiration, has preclinical activity against pancreatic cancer xenografts (Kumar and colleagues, unpublished data) and is used in clinical trials. However, parameters that predict resistance or response remain poorly understood. Hence, defining the metabolic pathways of pancreatic cancer through metabolomics will pave the way for prediction of response and the identification of new enzyme targets for pancreatic cancer therapies. A major technical challenge in this arena is the heterogeneity of the pancreatic tumor tissue, which is laced with an extensive fibrotic stroma comprising of host immune cells.

The potential for cancer cells to reprogram their metabolism to bypass the targeted enzymatic step may occur and hence poses a challenge to metabolic therapy. This issue is especially significant given the interconnectivity of the cellular metabolic network. In combination with appropriate computational tools (e.g., flux balance analysis), metabolomics offers a powerful way to identify possible "metabolic escape routes." With the insight of this guide, we will eliminate these escape routes through rational combination therapies, for example, in combination with current antimetabolites. This will allow for more cost-effective and personalized cancer treatment.

Further complicating attempts at developing pancreatic cancer therapies, there is emerging evidence of pancreatic cancer stem cells in pancreatic cancers and these cells are responsible for drug resistance to standard chemotherapy, resulting in relapse and metastasis of pancreatic adenocarcinoma (see review by Penchev and colleagues in this issue; ref. 52). Therefore, recognizing the heterogeneity of multisubpopulation of pancreatic tumors and understanding the distinguished metabolic modes of each are critical important for targeting of these subpopulations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interests were disclosed.

Authors' Contributions

Conception and design: A. Maitra

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.V. Dang

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P – 153 **Decreased appetite (DA) at baseline impacts prognosis in the NAPOLI-1 phase 3 study in metastatic pancreatic ductal adenocarcinoma (mPDAC)**

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Introduction: In NAPOLI-1 (NCT01494506), treatment with liposomal irinotecan + 5-fluorouracil/leucovorin (nal-IRI+5-FU/LV) significantly increased median overall survival (mOS) vs. 5-FU/LV (6.1 vs. 4.2 months; unstratified hazard ratio [HR]=0.67,

95% confidence interval [CI] 0.49–0.92; P = 0.012) in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) who had progressed following gemcitabine-based therapy. We investigated the effect of metabolism and nutrition disorders (MNDs) on survival in NAPOLI-1 patients.

Methods: This post-hoc analysis explored outcomes in patients with vs. without MNDs (based on MedDRA v14.1), including diabetes mellitus (DM), decreased appetite (DA; which included anorexia, poor appetite, lack of appetite, loss of appetite), hypercholesterolemia (HC), and dyslipidemia.

Results: At baseline, 267/417 intent-to-treat (ITT) patients had any MND. Differences in baseline characteristics were observed in some MND subgroups vs. the ITT population: e.g. Karnofsky performance status (DA), gender and race (HC), albumin (DA, HC). Both mOS (3.6 vs. 5.3 months; HR = 1.65, 95% CI 1.25–2.18; P < 0.001) and median progression-free survival (mPFS) (1.6 vs. 2.6 months; HR = 1.42, 95% CI 1.09–1.85; P = 0.010) were significantly lower in patients with (n = 77) vs. those without DA (n = 340). A trend for lower OS was also noted in patients with HC but this did not reach statistical significance. mOS was 4.4 vs. 5.1 months in patients with (n = 47) vs. without HC (n = 370) (HR = 1.37, 95% CI 0.98–1.91; P = 0.063) while mPFS in these populations was 2.3 vs. 2.6 months, respectively (HR = 1.15, 95% CI 0.83–1.60; P = 0.398). No significant difference was observed in survival between patients with (n = 159) vs. without DM (n = 258) or those with (n = 87) vs. without dyslipidemia (n = 330). mOS was 5.6 vs. 4.8 months for patients with vs. without DM (HR = 0.88, 95% CI 0.70–1.11, P = 0.279) while mPFS was 2.8 vs. 2.3 months (HR = 0.86, 95% CI 0.69–1.08; P = 0.191). mOS was 4.7 vs. 5.1 months for patients with vs. without dyslipidemia (HR = 1.13, 95% CI 0.86–1.48; P = 0.375) while mPFS was 2.2 vs. 2.6 months (HR = 1.19, 95% CI 0.91–1.54; P = 0.196). For patients with vs. without any MND, mOS was 4.8 vs. 5.3 months (HR = 1.10, 95% CI 0.87–1.39; P = 0.412) while mPFS was 2.5 vs. 2.6 months (HR = 1.11, 95% CI 0.88–1.39; P = 0.358). In patients treated with nal-IRI+5-FU/LV, mOS (4.6–6.7 vs. 2.7–6.1 months; HR = 0.46–1.05) and mPFS (2.8–4.1 vs. 1.4–1.6 months; HR = 0.24–0.60) were generally improved vs. 5-FU/LV in all subgroups. Safety data, drug-related AEs and dose modifications/discontinuations were broadly similar to the overall NAPOLI-1 study arms.

Conclusion: DA at baseline appears to have a prognostic impact on OS (P < 0.001) in mPDAC patients who progressed after gemcitabine-based therapy. The presence of HC may also impact OS. It is important to consider and appropriately manage patients with DA. Treatment with nal-IRI+5-FU/LV provides a benefit regardless of the presence/absence of MNDs. The effect of DM treatment should be explored further.

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Decreased appetite at baseline impacts prognosis in the NAPOLI-1 phase 3 study in metastatic pancreatic ductal adenocarcinoma (mPDAC)

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INTRODUCTION

- Liposomal irinotecan (nal-IRI) is a liposomally encapsulated topoisomerase I inhibitor. This formulation has been shown to extend circulation and enhance intratumoural drug deposition vs. non-liposomal irinotecan, prolonging and increasing exposure to the more active irinotecan metabolite SN-38.[1–3]
- It was previously reported that in NAPOLI-1, a pivotal phase 3 study, nal-IRI plus 5-fluorouracil/leucovorin (5-FU/LV) significantly improved median overall survival (OS) by 45% (6.1 vs. 4.2 months; unstratified hazard ratio [HR] = 0.67; p = 0.0122) and median progression-free survival (PFS; 3.1 vs. 1.5 months; unstratified HR = 0.56; *P* = 0.0001) compared with 5-FU/LV alone in patients with mPDAC that progressed following gemcitabine-based therapy.[4]
- Based on the NAPOLI-1 results, nal-IRI has been approved in combination with 5-FU and LV for the treatment of patients with mPDAC after disease progression following gemcitabine-based therapy in numerous countries, and has been included in international treatment guidelines.[5,6]
- The pancreas has both endocrine and exocrine functions. Through its endocrine functions, the pancreas regulates blood sugar levels by releasing insulin and glucagon; the exocrine portion produces enzymes that are essential for digestion.[7]
- Patients suffering from pancreatic cancer are commonly affected by metabolic and nutrition disorders such as malnutrition due to reduced production of pancreatic digestive enzymes, and diabetes mellitus due to disrupted glucose homeostasis.[7]
- Metabolism and nutrition disorders, including diabetes, were commonly observed in patients from the NAPOLI-1 study.

METHODS

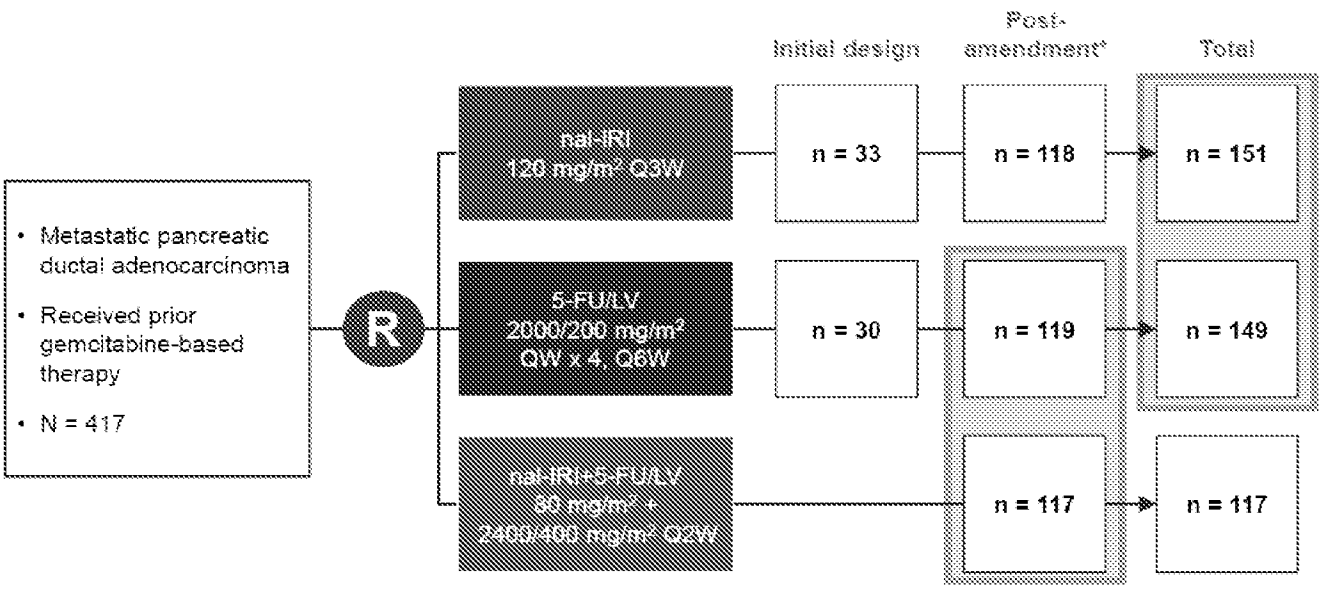
Objectives and subgroup analysis

- This *post-hoc* analysis explored outcomes in patients with vs. without metabolism and nutrition disorders (based on MedDRA v14.1), including diabetes mellitus, decreased appetite (which included anorexia, poor appetite, lack of appetite, loss of appetite), hypercholesterolaemia, and dyslipidaemia.

Study Design

- NAPOLI-1 was an international, open-label, randomised, phase 3 trial (Figure 1).

Figure 1. Study design[a]



*The study was amended to add the nal-IRI+5-FU/LV arm once safety data on the combination became available. Only those patients enrolled in the 5-FU/LV arm after the amendment (n = 119) were used as the control for the combination arm. nal-IRI 80 mg/m² expressed as irinotecan hydrochloride trihydrate salt, equivalent to 70 mg/m² irinotecan free base. (Trial registered at ClinicalTrials.gov, number NCT01494506).

Key inclusion criteria

- Adults ≥18 years of age.
- Histologically or cytologically confirmed PDAC.
- Documented metastatic disease; disease status permitted to be measurable or non-measurable as per RECIST v. 1.1 guidelines.
- Disease progression after prior gemcitabine or gemcitabine-containing therapy in a neoadjuvant, adjuvant (only if distant metastases occurred within 6 months of completing adjuvant therapy), locally advanced, or metastatic setting.
- Karnofsky performance status (KPS) score ≥70.
- Adequate hematologic (including absolute neutrophil count >1.5×10^9 cells/L), hepatic (including normal serum total bilirubin and albumin levels ≥30 g/L), and renal function.

Key exclusion criteria

- Clinically significant gastrointestinal disorders.

RESULTS

Patient characteristics

- At baseline, 267/417 intent-to-treat (ITT) patients had any metabolism and nutrition disorder. Differences in baseline characteristics were observed in some metabolism and nutrition disorder subgroups vs. the ITT population: e.g. Karnofsky performance status (decreased appetite), gender and race (hypercholesterolaemia), albumin (decreased appetite, hypercholesterolaemia) (Table 1).

Table 1. Demographic and baseline characteristics comparison by sub-group measurements (ITT Population)

	All ITT N = 417	Metabolism and nutrition disorders		Diabetes mellitus and/or type 2 diabetes mellitus		Decreased appetite		Hyper-cholesterolaemia		Hyper-cholesterolaemia and/or hyperlipidaemia and/or dysilpidaemia	
		With n = 267	Without n = 150	With n = 159	Without n = 258	With n = 77	Without n = 340	With n = 47	Without n = 370	With n = 87	Without n = 330
Gender, n (%)											
Female	180 (43)	104 (39)	76 (51)	61 (38)	119 (46)	32 (42)	148 (44)	15 (32)	165 (45)	36 (41)	144 (44)
Male	237 (57)	163 (61)	74 (49)	98 (62)	139 (54)	45 (58)	192 (56)	32 (68)	205 (55)	51 (59)	186 (56)
Age (yrs)											
Median Min, Max	63 31, 87	65 40, 87	61 31, 79	66 41, 87	62 31, 83	65 40, 80	63 31, 87	59 45, 80	63 31, 87	66 45, 83	63 31, 87
Race, n (%)											
White	253 (61)	159 (60)	94 (63)	88 (55)	165 (64)	48 (62)	205 (60)	37 (79)	216 (58)	61 (70)	192 (58)
Black or African American	10 (2)	7 (3)	3 (2)	5 (3)	5 (2)	2 (3)	8 (2)	1 (2)	9 (2)	4 (5)	6 (2)
American Indian or Alaska Native	1 (0)	0 (0)	1 (1)	0 (0)	1 (0)	0 (0)	1 (0)	0 (0)	1 (0)	0 (0)	1 (0)
Asian	136 (33)	89 (33)	47 (31)	58 (36)	78 (30)	25 (32)	111 (33)	1 (2)	135 (36)	14 (16)	122 (37)
Other	17 (4)	12 (4)	5 (3)	8 (5)	9 (3)	2 (3)	15 (4)	8 (17)	9 (2)	8 (9)	9 (3)
Baseline KPS, n (%)											
90–100	231 (55)	138 (52)	93 (62)	88 (55)	143 (55)	26 (34)	205 (60)	26 (55)	205 (55)	51 (59)	180 (55)
70–80	182 (44)	125 (47)	57 (38)	70 (44)	112 (43)	48 (62)	134 (39)	20 (43)	162 (44)	34 (39)	148 (45)
50–60	3 (1)	3 (1)	0 (0)	1 (1)	2 (1)	2 (3)	1 (0)	1 (2)	2 (1)	2 (2)	1 (0)
Measurable metastatic lesions at baseline, n (%)											
1	81 (19)	58 (22)	23 (15)	38 (24)	43 (17)	20 (26)	61 (18)	8 (17)	73 (20)	19 (22)	62 (19)
2	184 (44)	115 (43)	69 (46)	66 (42)	118 (46)	35 (45)	149 (44)	19 (40)	165 (45)	31 (36)	153 (46)
3	65 (16)	35 (13)	30 (20)	22 (14)	43 (17)	9 (12)	56 (16)	9 (19)	56 (15)	13 (15)	52 (16)
>3	24 (6)	17 (6)	7 (5)	10 (6)	14 (5)	7 (9)	17 (5)	4 (9)	20 (5)	5 (6)	19 (6)
Anatomical location of lesions at baseline*, n (%)											
Liver	284 (68)	182 (68)	102 (68)	105 (66)	179 (69)	57 (74)	227 (67)	33 (70)	251 (68)	61 (70)	223 (68)
Median CA-19-9 (U/mL)	1542	2040	1137	2108	1252	3260	1462	2411	1507	930	1865
Median albumin (g/dL)	4	4	4	4	4	4	4	4	4	4	4

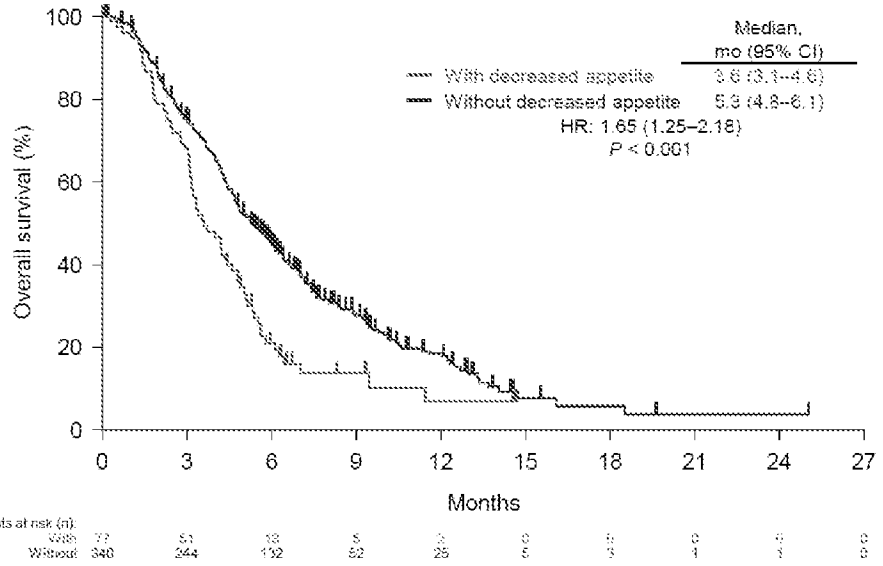
Disorders are defined by MedDRA v14.1.
*Based on lesion locations followed for RECIST v1.1, includes all measurable and non-measurable lesions; includes all metastatic and non-metastatic lesions. Patients may be included in more than one category
ITT, intent-to-treat; KPS, Karnofsky performance status.

Overall survival

- For patients with vs. without any metabolism and nutrition disorder at baseline, mOS was 4.8 vs. 5.3 months (HR = 1.10; *P* = 0.412) (Table 2).

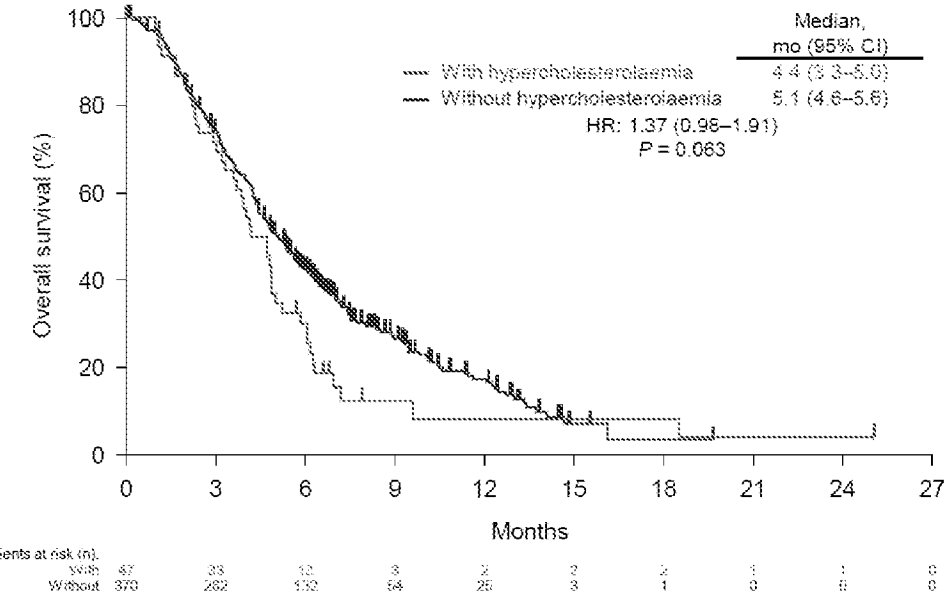
- mOS was significantly lower in patients with vs. those without decreased appetite at baseline (3.6 vs. 5.3 months; HR = 1.65; $P < 0.001$) (Table 2 and Figure 2).
- A trend for lower OS was also noted in patients with hypercholesterolaemia at baseline, but this did not reach statistical significance. mOS was 4.4 vs. 5.1 months in patients with vs. without hypercholesterolaemia (HR = 1.37; $P = 0.063$) (Table 2 and Figure 3).
- No significant difference was observed in survival between patients with vs. without diabetes mellitus or those with vs. without dyslipidaemia (Table 2).
  - mOS was 5.6 vs. 4.8 months for patients with vs. without diabetes mellitus at baseline (HR = 0.88; $P = 0.279$).
  - mOS was 4.7 vs. 5.1 months for patients with vs. without dyslipidaemia at baseline (HR = 1.13; $P = 0.375$)

Figure 2. Overall survival in patients with or without decreased appetite at baseline (ITT population)



CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months.

Figure 3. Overall survival in patients with or without hypercholesterolaemia at baseline (ITT population)

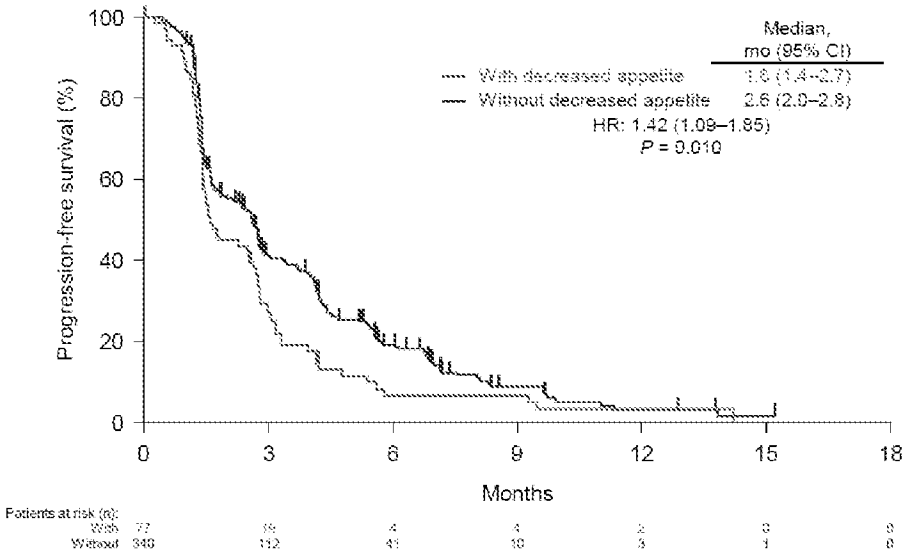


CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months.

Progression-free survival

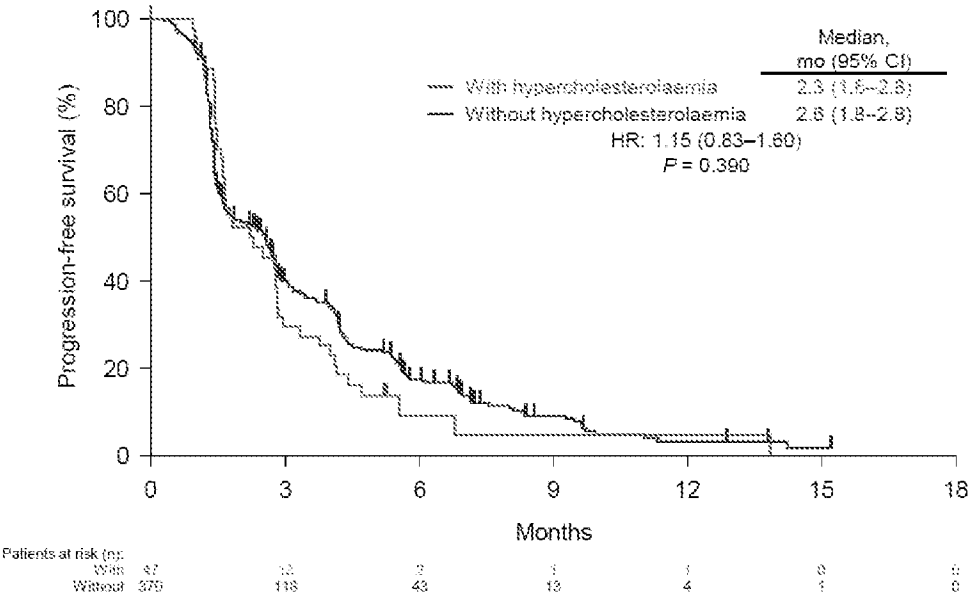
- For patients with vs. without any metabolism and nutrition disorder at baseline, mPFS was 2.5 vs. 2.6 months (HR = 1.11; *P* = 0.358) (Table 2).
- mPFS was significantly lower in patients with vs. those without decreased appetite at baseline (1.6 vs. 2.6 months; HR = 1.42; *P* = 0.010) (Table 2 and Figure 4).
- mPFS was 2.3 vs. 2.6 months for patients with or without hypercholesterolaemia at baseline (HR = 1.15; *P* = 0.390) (Table 2 and Figure 5).
- No significant difference was observed in survival between patients with vs. without diabetes mellitus or those with vs. without dyslipidaemia (Table 2).
  - mPFS for patients with vs. without diabetes mellitus at baseline was 2.8 vs. 2.3 months (HR = 0.86; *P* = 0.191).
  - mPFS for patients with vs. without dyslipidaemia at baseline was 2.2 vs. 2.6 months (HR = 1.19; *P* = 0.196).

Figure 4. Progression-free survival in patients with or without decreased appetite at baseline (ITT population)



CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months.

Figure 5. Progression-free survival in patients with or without hypercholesterolaemia at baseline (ITT population)



CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months.

Table 2. Efficacy comparison by subgroup survival measurements (ITT population)

	Metabolism and nutrition disorders		Diabetes mellitus and/or type 2 diabetes mellitus		Decreased appetite		Hyper-cholesterolaemia		Hyper-cholesterolaemia and/or hyperlipidaemia and/or dyslipidaemia	
	With n = 267	Without n = 150	With n = 159	Without n = 258	With n = 77	Without n = 340	With n = 47	Without n = 370	With n = 87	Without n = 330
Overall survival (OS)										
Median OS (months)	4.8	5.3	5.6	4.6	3.6	5.3	4.4	5.1	4.7	5.1
95% CI	4.2–5.4	4.4–6.1	4.5–6.3	4.3–5.3	3.1–4.6	4.8–6.1	3.3–5.0	4.6–5.6	3.7–5.8	4.5–5.6
HR	1.10		0.88		1.65		1.37		1.13	
95% CI	0.87–1.39		0.70–1.11		1.25–2.18		0.98–1.91		0.86–1.48	
P value*	*P* = 0.412		*P* = 0.279		*P* < 0.001		*P* = 0.063		*P* = 0.375	
Progression-free survival (PFS)										
Median PFS (months)	2.6	2.6	2.8	2.3	1.6	2.6	2.3	2.6	2.2	2.8
95% CI	1.7–2.8	1.6–3.1	2.0–3.1	1.6–2.7	1.4–2.7	2.0–2.8	1.6–2.8	1.8–2.8	1.6–2.8	1.8–2.8
HR	1.11		0.86		1.42		1.15		1.19	
95% CI	0.88–1.39		0.69–1.08		1.09–1.85		0.83–1.60		0.91–1.54	
P value*	*P* = 0.358		*P* = 0.191		*P* = 0.010		*P* = 0.390		*P* = 0.196	

Disorders are defined by MedDRA v14.1.
*Two-sided *P* value from log-rank test.
CI, confidence intervals; HR, hazard ratio; ITT, intent-to-treat.

Overall survival and progression-free survival in patients treated with nal-IRI+5-FU/LV vs. 5-FU/LV across all subgroups

- In patients treated with nal-IRI+5-FU/LV, mOS (4.6–6.7 vs. 2.7–6.1 months; HRs = 0.46–1.05) and mPFS (2.8–4.1 vs. 1.4–1.6 months; HRs = 0.24–0.69) were generally improved vs. 5-FU/LV in all baseline nutrition disorder subgroups (Table 3).

Table 3. Efficacy of combination treatment vs. control treatment (nal-IRI+5-FU/LV vs. 5-FU/LV) within each sub-population (ITT population)

	Metabolism and nutrition disorders		Diabetes mellitus and/or type 2 diabetes mellitus		Decreased appetite		Hyper-cholesterolaemia		Hyper-cholesterolaemia and/or hyperlipidaemia and/or dyslipidaemia	
	With	Without	With	Without	With	Without	With	Without	With	Without
	Comb/Ctrl n = 71/77	Comb/Ctrl n = 46/42	Comb/Ctrl n = 42/49	Comb/Ctrl n = 75/70	Comb/Ctrl n = 21/23	Comb/Ctrl n = 96/96	Comb/Ctrl n = 13/9	Comb/Ctrl n = 104/110	Comb/Ctrl n = 22/21	Comb/Ctrl n = 95/96
Overall survival (OS)										
HR	0.53	1.05	0.69	0.67	0.46	0.74	0.51	0.67	0.58	0.67
95% CI	0.36–0.78	0.61–1.82	0.42–1.12	0.44–1.01	0.23–0.95	0.52–1.05	0.20–1.32	0.48–0.94	0.29–1.15	0.47–0.96
P value*	*P* = 0.001	*P* = 0.853	*P* = 0.133	*P* = 0.052	*P* = 0.032	*P* = 0.089	*P* = 0.151	*P* = 0.019	*P* = 0.112	*P* = 0.029
Progression-free survival (PFS)										
HR	0.47	0.69	0.53	0.57	0.24	0.59	0.43	0.56	0.34	0.59
95% CI	0.32–0.68	0.41–1.15	0.33–0.87	0.39–0.83	0.11–0.54	0.42–0.83	0.16–1.19	0.40–0.77	0.16–0.72	0.42–0.82
P value*	*P* < 0.001	*P* = 0.157	*P* = 0.011	*P* = 0.003	*P* < 0.001	*P* = 0.002	*P* = 0.090	*P* < 0.001	*P* = 0.003	*P* = 0.002

Disorders are defined by MedDRA v14.1.
*Two-sided *P* value from log-rank test.
CI, confidence intervals; Comb, combination treatment (nal-IRI+5-FU/LV); Ctrl, control treatment (5-FU/LV); HR, hazard ratio; ITT, intent-to-treat.

Safety, dose modifications and treatment exposure

- Safety data, drug-related adverse events and dose modifications/discontinuations for nal-IRI+5-FU/LV were broadly similar to the overall NAPOLI-1 study arms (Tables 4 and 5).

Table 4: Treatment-emergent adverse events, comparison by sub-group measurements (safety population): nal-IRI+5-FU/LV treatment arm

	Metabolism and nutrition disorders		Diabetes mellitus and/or Type 2 diabetes mellitus		Decreased appetite		Hyper-cholesterolaemia		Hyper-cholesterolaemia and/or hyperlipidaemia and/or dyslipidaemia	
	With n = 69	Without n = 48	With n = 41	Without n = 76	With n = 21	Without n = 96	With n = 13	Without n = 104	With n = 21	Without n = 96
Alopecia (grade 1/2), n (%)	11 (16)	5 (10)	6 (15)	10 (13)	2 (10)	14 (15)	1 (8)	15 (14)	3 (14)	13 (14)
Febrile neutropenia (grade 3/4)	1 (1)	1 (2)	1 (2)	1 (1)	0	2 (2)	1 (8)	1 (1)	1 (5)	1 (1)
Grade 3/4 non-haematologic AEs in >5% of the overall safety population, n (%)										
Diarrhoea, late onset*	10 (14)	5 (10)	5 (12)	10 (13)	4 (19)	11 (11)	0	15 (14)	0	15 (16)
Vomiting	8 (12)	5 (10)	3 (7)	10 (13)	2 (10)	11 (11)	1 (8)	12 (12)	1 (5)	12 (13)
Nausea	7 (10)	2 (4)	3 (7)	6 (8)	3 (14)	6 (6)	0	9 (9)	1 (5)	8 (8)
Fatigue	13 (19)	3 (6)	7 (17)	9 (12)	5 (24)	11 (11)	2 (15)	14 (13)	2 (10)	14 (15)
Asthenia	5 (7)	4 (8)	5 (12)	4 (5)	1 (5)	8 (8)	1 (8)	8 (8)	2 (10)	7 (7)
Abdominal pain	2 (3)	6 (13)	2 (5)	6 (8)	0 (0)	8 (8)	1 (8)	7 (7)	1 (5)	7 (7)
Grade 3/4 haematologic AEs based on laboratory values,† n (%)										
Neutrophil count decreased	14 (21)	9 (19)	7 (18)	16 (21)	5 (24)	18 (19)	0	23 (23)	4 (19)	19 (20)
Haemoglobin decreased	3 (4)	4 (9)	1 (3)	6 (8)	1 (5)	6 (6)	0	7 (7)	0	7 (7)
Platelet count decreased	1 (1)	1 (2)	1 (3)	1 (1)	0	2 (2)	0	2 (2)	1 (5)	1 (1)
Drug-related AE of CTCAE Grade ≥3, n (%)	38 (55)	25 (52)	20 (49)	43 (57)	11 (52)	52 (54)	5 (38)	58 (56)	11 (52)	52 (54)

Disorders are defined by MedDRA v14.1. Safety was assessed by grading adverse events according to the National Cancer Institute CTCAE v4.0.
*>24 h after starting nal-IRI. †Includes only patients who had at least one post-baseline assessment.
AE, adverse events; CTCAE, *Common Terminology Criteria for Adverse Events*.

Table 5: Dose modification and treatment exposure, comparison by sub-group measurements (safety population): nal-IRI+5-FU/LV treatment arm

	Metabolism and nutrition disorders		Diabetes mellitus and/or type 2 diabetes mellitus		Decreased appetite		Hyper-cholesterolaemia		Hyper-cholesterolaemia and/or hyperlipidaemia and/or dyslipidaemia	
	With n = 69	Without n = 48	With n = 41	Without n = 76	With n = 21	Without n = 96	With n = 13	Without n = 104	With n = 21	Without n = 96
Patients with TEAE leading to any dose modification, n (%)	51 (74)	32 (67)	32 (78)	51 (67)	13 (62)	70 (73)	9 (69)	74 (71)	17 (81)	66 (69)
Patients with TEAEs resulting in dose delayed,* n (%)	44 (64)	28 (58)	28 (68)	44 (58)	10 (48)	62 (65)	7 (54)	65 (63)	15 (71)	57 (59)
Patients with TEAE resulting in dose reduction,† n (%)	22 (32)	17 (35)	10 (24)	29 (38)	7 (33)	32 (33)	4 (31)	35 (34)	8 (38)	31 (32)
Patients with TEAE leading to dose discontinuation, n (%)	7 (10)	6 (13)	6 (15)	7 (9)	3 (14)	10 (10)	2 (15)	11 (11)	2 (10)	11 (11)

Disorders are defined by MedDRA v14.1. TEAEs are events that occurred or worsened on or after the day of first dose of the study drug and within 30 days after last administration of study drug.
*TEAEs with action taken as: dose not given or infusion interrupted. †TEAEs with action taken as: dose decreased or slowing infusion rate.
TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Decreased appetite at baseline appears to have a prognostic impact on OS ($P < 0.001$) in mPDAC patients that progressed after gemcitabine-based therapy.
  - It is therefore important to consider and appropriately manage these patients.
- The presence of hypercholesterolaemia at baseline may also impact OS.
- Treatment with nal-IRI+5-FU/LV provides a benefit regardless of the presence/absence of metabolism and nutrition disorders at baseline.

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- Jie Chen (Shire) was responsible for statistical analyses of this *post-hoc* study.
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P-153

Decreased appetite at baseline impacts prognosis in the NAPOLI-1 phase 3 study in metastatic pancreatic ductal adenocarcinoma (mPDAC)

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Background: Many cancer patients lose appetite, which can impact prognosis. The aim of this post hoc analysis was to evaluate the prognostic impact of decreased appetite at baseline in patients with mPDAC treated with nal-IRI + 5-FU/LV vs 5-FU/LV alone in the NAPOLI-1 phase 3 study.

Methods

- Decreased appetite was defined as a score of 1 or 2 on the appetite item of the EORTC QLQ-C30 questionnaire at baseline.
- Kaplan-Meier estimates of median overall survival (OS) and progression-free survival (PFS) were calculated for patients with decreased appetite and those without decreased appetite.
- Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for OS and PFS.
- Multivariate Cox models were used to evaluate the prognostic impact of decreased appetite at baseline after adjusting for other prognostic factors.

Results

- Of 417 patients in the nal-IRI + 5-FU/LV arm and 412 patients in the 5-FU/LV arm, 169 and 164, respectively, had decreased appetite at baseline.
- Patients with decreased appetite had worse OS and PFS than those without decreased appetite in both treatment arms.
- In the nal-IRI + 5-FU/LV arm, median OS was 4.9 months (95% CI, 4.1–5.7) for patients with decreased appetite and 6.9 months (95% CI, 6.1–8.1) for those without decreased appetite (HR, 1.57; 95% CI, 1.25–1.98; $P < 0.0001$).
- In the 5-FU/LV arm, median OS was 3.7 months (95% CI, 3.1–4.3) for patients with decreased appetite and 5.2 months (95% CI, 4.5–6.0) for those without decreased appetite (HR, 1.49; 95% CI, 1.17–1.89; $P = 0.0009$).
- Median PFS was 3.1 months (95% CI, 2.8–3.4) for patients with decreased appetite and 4.2 months (95% CI, 3.7–4.9) for those without decreased appetite in the nal-IRI + 5-FU/LV arm (HR, 1.61; 95% CI, 1.29–2.01; $P < 0.0001$).
- In the 5-FU/LV arm, median PFS was 2.3 months (95% CI, 1.9–2.6) for patients with decreased appetite and 3.2 months (95% CI, 2.8–3.7) for those without decreased appetite (HR, 1.49; 95% CI, 1.17–1.89; $P = 0.0009$).
- Multivariate analysis confirmed decreased appetite as an independent prognostic factor for OS and PFS.

Conclusions

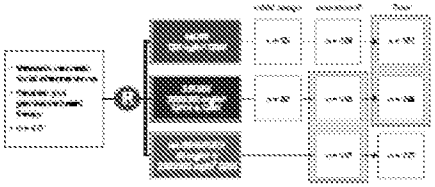
- Decreased appetite at baseline is a strong prognostic factor for worse OS and PFS in patients with mPDAC treated with nal-IRI + 5-FU/LV or 5-FU/LV alone.
- Assessing appetite at baseline may help identify patients who are more likely to have poor outcomes and may benefit from additional supportive care.

Introduction

- Cancer-related anorexia is common and can lead to malnutrition, cachexia, and poor prognosis.
- Decreased appetite is a symptom that can be easily assessed in clinical practice.
- The impact of decreased appetite on prognosis in patients with mPDAC has not been well studied.
- The NAPOLI-1 phase 3 study demonstrated that nal-IRI + 5-FU/LV improved OS and PFS compared with 5-FU/LV alone in patients with mPDAC previously treated with gemcitabine-based therapy.
- This post hoc analysis aimed to evaluate the prognostic impact of decreased appetite at baseline in patients treated with nal-IRI + 5-FU/LV or 5-FU/LV alone.

Study design and methods

Figure 1. Study design



- NAPOLI-1 was an international, open-label, randomized, phase 3 study.
- Patients were randomized 1:1 to receive nal-IRI + 5-FU/LV or 5-FU/LV alone.
- Key inclusion criteria:
  - Histologically confirmed mPDAC
  - Disease progression during or after gemcitabine-based therapy
  - Measurable disease per RECIST 1.1
  - Karnofsky performance status ≥70
  - Adequate hematologic, hepatic, and renal function
- Key exclusion criteria:
  - Previously received irinotecan
- Decreased appetite was defined as a score of 1 or 2 on the appetite item of the EORTC QLQ-C30 questionnaire.
- Kaplan-Meier estimates of median OS and PFS were calculated for patients with decreased appetite and those without decreased appetite.
- Cox proportional hazards models were used to estimate HRs and 95% CIs for OS and PFS.
- Multivariate Cox models were used to evaluate the prognostic impact of decreased appetite at baseline after adjusting for other prognostic factors.

Results

Table 1. Patient demographics and baseline characteristics

	Overall	Nal-IRI + 5-FU/LV		5-FU/LV		Nal-IRI + 5-FU/LV vs 5-FU/LV
		Decreased appetite	No decreased appetite	Decreased appetite	No decreased appetite	Decreased appetite
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total						
Median age (range), years						
<65						
≥65						
Sex						
Male						
Female						
Race						
White						
Asian						
Black or African American						
American Indian or Alaska Native						
Native Hawaiian or other Pacific Islander						
Other						
Unknown						
ECOG PS						
0						
1						
2						
Metastatic disease sites						
Liver						
Lung						
Peritoneum						
Other						
Prior surgery						
Yes						
No						
Prior radiotherapy						
Yes						
No						

Figure 2. Overall survival in patients with or without decreased appetite at baseline

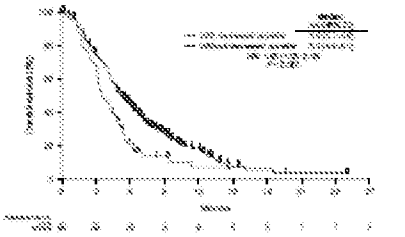
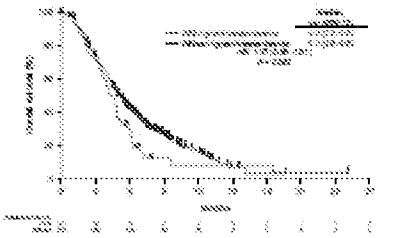


Figure 3. Overall survival in patients with or without decreased appetite at baseline by treatment arm



- Patients with decreased appetite had worse OS and PFS than those without decreased appetite in both treatment arms.
- In the nal-IRI + 5-FU/LV arm, median OS was 4.9 months (95% CI, 4.1–5.7) for patients with decreased appetite and 6.9 months (95% CI, 6.1–8.1) for those without decreased appetite (HR, 1.57; 95% CI, 1.25–1.98; $P < 0.0001$).
- In the 5-FU/LV arm, median OS was 3.7 months (95% CI, 3.1–4.3) for patients with decreased appetite and 5.2 months (95% CI, 4.5–6.0) for those without decreased appetite (HR, 1.49; 95% CI, 1.17–1.89; $P = 0.0009$).
- Median PFS was 3.1 months (95% CI, 2.8–3.4) for patients with decreased appetite and 4.2 months (95% CI, 3.7–4.9) for those without decreased appetite in the nal-IRI + 5-FU/LV arm (HR, 1.61; 95% CI, 1.29–2.01; $P < 0.0001$).
- In the 5-FU/LV arm, median PFS was 2.3 months (95% CI, 1.9–2.6) for patients with decreased appetite and 3.2 months (95% CI, 2.8–3.7) for those without decreased appetite (HR, 1.49; 95% CI, 1.17–1.89; $P = 0.0009$).

Figure 4. Progression-free survival in patients with or without decreased appetite at baseline

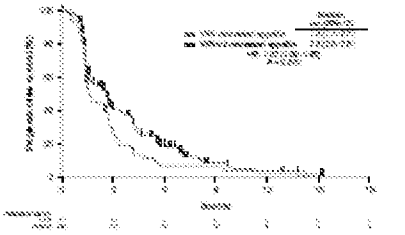


Figure 5. Progression-free survival in patients with or without decreased appetite at baseline by treatment arm

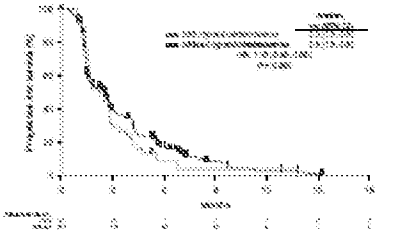


Table 2. Univariate and multivariate analysis of overall survival

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Decreased appetite				
Nal-IRI + 5-FU/LV				
5-FU/LV				
Nal-IRI + 5-FU/LV vs 5-FU/LV				
Decreased appetite				
No decreased appetite				

Table 3. Univariate and multivariate analysis of progression-free survival

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Decreased appetite				
Nal-IRI + 5-FU/LV				
5-FU/LV				
Nal-IRI + 5-FU/LV vs 5-FU/LV				
Decreased appetite				
No decreased appetite				

Table 4. Univariate and multivariate analysis of overall survival

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Decreased appetite				
Nal-IRI + 5-FU/LV				
5-FU/LV				
Nal-IRI + 5-FU/LV vs 5-FU/LV				
Decreased appetite				
No decreased appetite				

Table 5. Univariate and multivariate analysis of progression-free survival

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Decreased appetite				
Nal-IRI + 5-FU/LV				
5-FU/LV				
Nal-IRI + 5-FU/LV vs 5-FU/LV				
Decreased appetite				
No decreased appetite				

Conclusions

- Decreased appetite at baseline is a strong prognostic factor for worse OS and PFS in patients with mPDAC treated with nal-IRI + 5-FU/LV or 5-FU/LV alone.
- Assessing appetite at baseline may help identify patients who are more likely to have poor outcomes and may benefit from additional supportive care.

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Deposition characteristics and resulting DNA damage patterns of liposomal irinotecan (nal-IRI) in pancreatic cancer xenografts

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Background

- Liposomal irinotecan (nal-IRI, MM-398) is a liposomal formulation of irinotecan, a topoisomerase-1 inhibitor, for intravenous use.[1] (Figure 1a)
- Nal-IRI facilitates intratumoral drug deposition through an enhanced permeability and retention effect,[2] with pharmacokinetic analyses demonstrating an extended circulation of the liposome and its encapsulated payload.[3,4]
- The uptake of nal-IRI by phagocytic and tumor cells results in release of payload and conversion to SN-38, the active metabolite. Topoisomerase-1 inhibition in tumor cells leads to exposure time–dependent double-strand DNA damage and cell death. (Figure 1b).[5]
- In mice bearing human tumor xenografts, nal-IRI administered at irinotecan HCl-equivalent doses 5-fold lower than irinotecan HCl achieved similar intratumoral exposure of SN-38.[2]

Figure 1a. Liposomal Irinotecan (nal-IRI; MM-398)

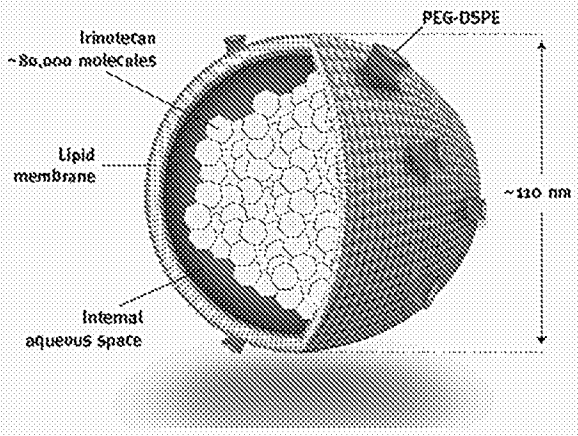
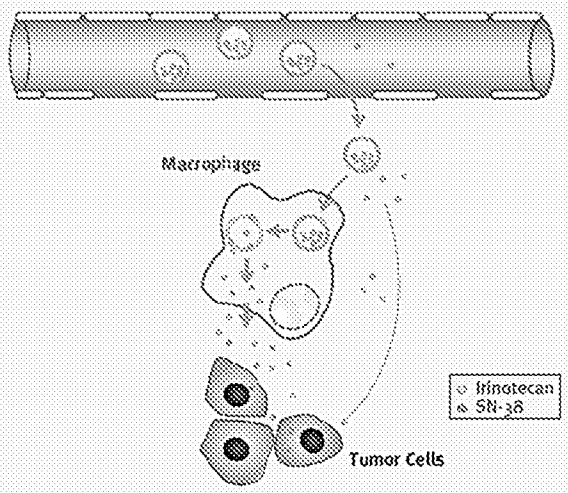


Figure 1b. Schematic of Proposed Mechanism of Action



nal-IRI comprises irinotecan free base encapsulated in liposomal particles.

- The half-life of total irinotecan and total SN-38 following administration of nal-IRI, 70 mg/m^2 of irinotecan expressed as irinotecan free base (equivalent to 80 mg/m^2 of irinotecan expressed as the hydrochloride trihydrate), was 25.8 and 67.8 hours, respectively.[6] (Figure 2a)
- Preliminary data from a clinical pilot study across different cancer types showed a 5-fold higher level of SN-38 (the active metabolite of irinotecan) in tumor biopsies compared with plasma at 72 hours, suggesting local metabolic activation of irinotecan, released from liposomal nanoparticles, to SN-38.[5] (Figure 2b)

Figure 2a. Plasma Levels of Irinotecan After nal-IRI and Irinotecan Treatment[2]

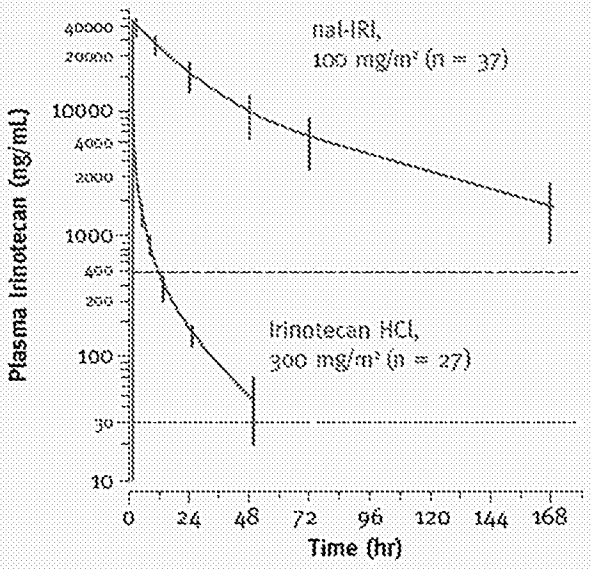
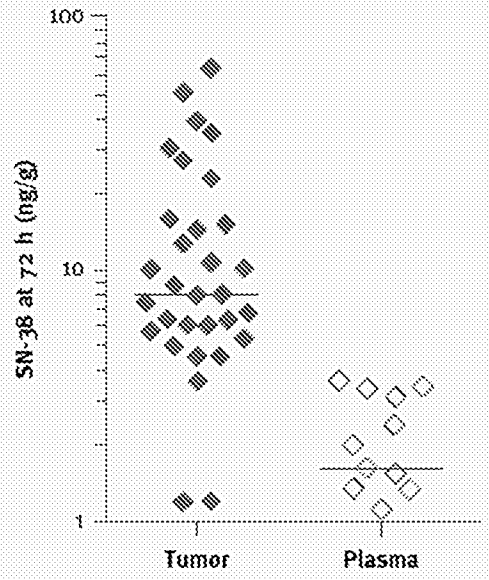


Figure 2b. Levels of SN-38 in Patient Tumor and Plasma 72 Hours Post-administration of nal-IRI



- Liposomal irinotecan (nal-IRI, ONIVYDE®) is approved in the US, EU, and other countries in combination with 5-fluorouracil/leucovorin for treatment of adult patients with metastatic pancreatic cancer after disease progression following gemcitabine-based therapy.

Objective

- The objective of this analysis is to evaluate the pharmacokinetic and extended pharmacodynamic effects of nal-IRI in pancreatic tumor models compared to non-liposomal irinotecan HCl.

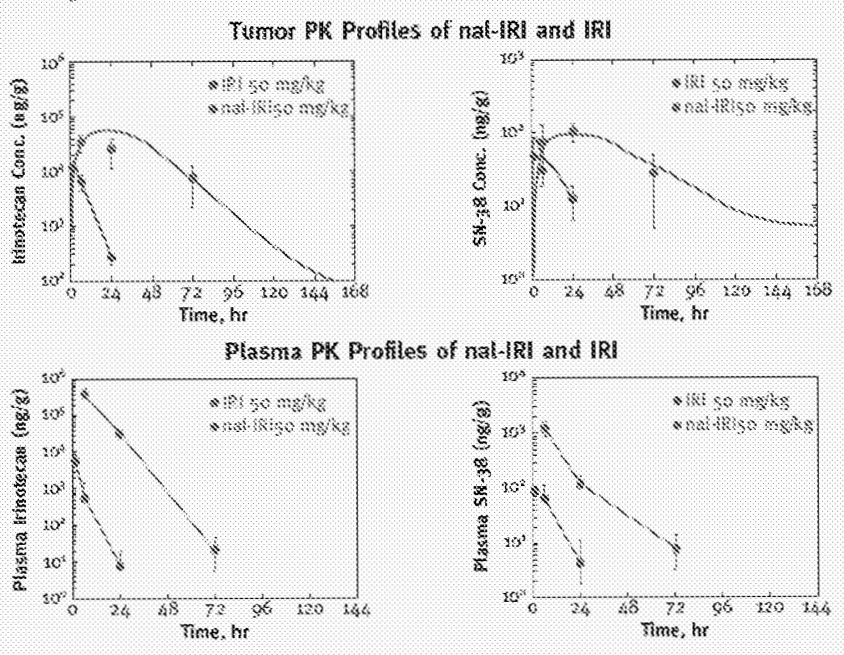
Methods

- AsPC-1, BxPC-3, and CFPAC-1 tumors were grown in NOD-SCID mice. The patient-derived tumor model CTG-288 (pancreatic) was established by Champions Oncology using their Champions TumorGraft® (CTG) technology.
- To evaluate efficacy under conditions of equivalent SN-38 exposure[2], animals were dosed every 7 days with either 25–50 mg/kg non-liposomal irinotecan HCl (IRI) or 5–10 mg/kg nal-IRI.
- To evaluate pharmacokinetics and pharmacodynamics, animals were dosed with 10–50 mg/kg of fluorescently labeled nal-IRI or for comparative purposes with 50 mg/kg IRI.
- Samples were collected at multiple timepoints up to 72 hours for irinotecan HCl (IRI) and up to 168 hours for nal-IRI.
- Tumor samples were evaluated for liposome localization, macrophage and tumor markers, vessels, DNA damage, and apoptosis.
- Images of fluorescently stained tumor sections were acquired with an Aperio Scanscope FL slide scanner (Leica Biosystems). Quantitative image analysis was performed with HALO™ software (Indica Labs).

Results

- Treatment with nal-IRI yields a sustained circulation and delivery of its payload to tumors compared with irinotecan HCl. (Figure 3)
  - At same irinotecan dose levels, nal-IRI results in a prolonged circulation and tumor exposure of irinotecan and SN-38.
  - nal-IRI also increases duration of active metabolites present above a hypothetical threshold compared with non-liposomal irinotecan.

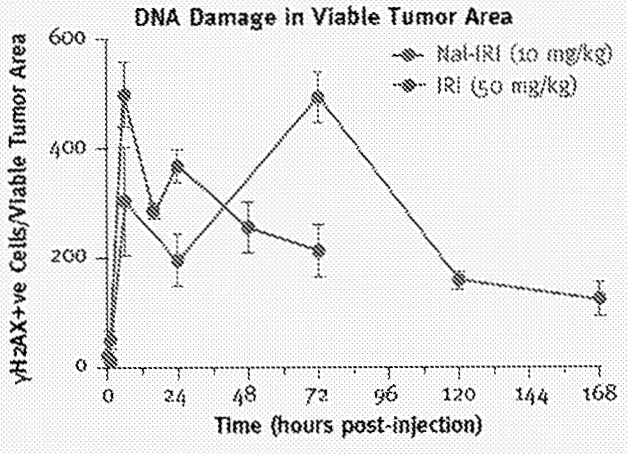
Figure 3. Tumor and Plasma Pharmacokinetic Profile of nal-IRI and Non-liposomal Irinotecan in NOD-SCID Mice Bearing BxPC-3 Tumors



Tumor-bearing mice received a single intravenous administration of nal-IRI or IRI at a dose of 50 mg/kg each. Plasma and tumor samples were collected, and extracted metabolites were measured by HPLC and fluorescent detection of irinotecan and SN-38. Median and interquartile ranges are shown. For tumor PK values a PKPD model simulation[3] is overlaid.

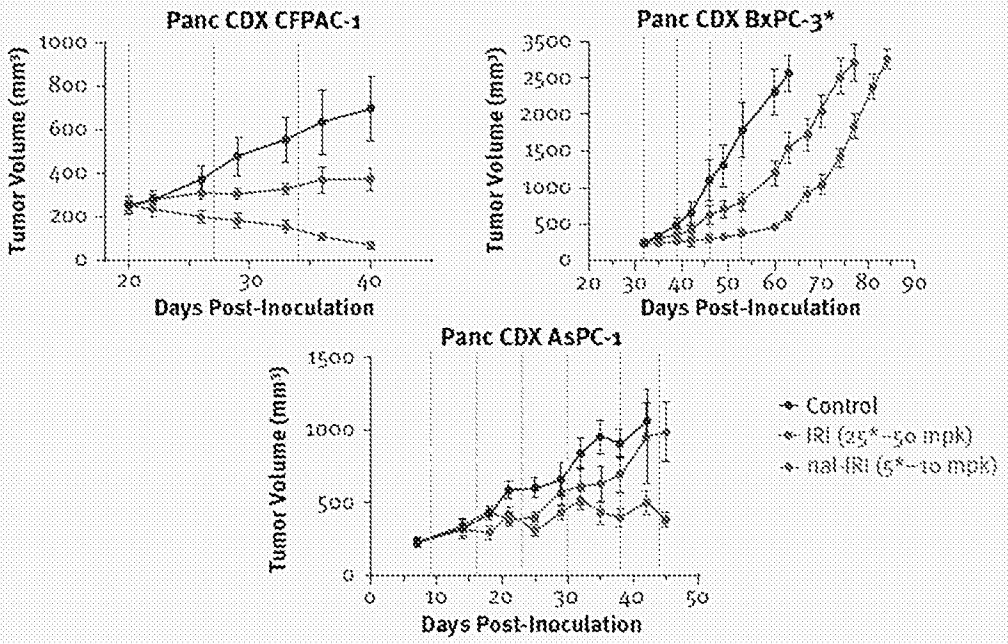
- Efficacy benefit with nal-IRI was identified from extended circulation and sustained delivery.
  - At 5-fold lower dose, treatment with nal-IRI results in similar magnitude of DNA damage in BxPC-3 tumors compared to irinotecan. (Figure 4)
  - DNA damage in IRI-treated tumors (50 mg/kg) peaked around 6 hours, while nal-IRI–treated tumors (10 mg/kg) peaked at 72 hours.
  - The rate of growth (as measured by tumor volume) was reduced with nal-IRI (10 mg/kg) compared to irinotecan (50 mg/kg) in CFPAC-1, BxPC-3, and AsPC-1 models, with only nal-IRI treatment resulting in tumor shrinkage in CFPAC-1. (Figure 5)

Figure 4. DNA Damage in BxPC-3 Tumors After Single-Dose Administration of nal-IRI and Irinotecan (IRI)



Mice bearing subcutaneous BxPC-3 tumors (n=5 per group and time-point) received a single administration of nal-IRI (10 mg/kg) or IRI (50 mg/kg). Tumor tissue was harvested at 1, 6, 16, 24, 48 and 72 hr for IRI and at 1, 6, 24, 72, 120 and 168 h for nal-IRI. γH2AX staining was quantified across assembled tissue microarrays using HALO image analysis software.

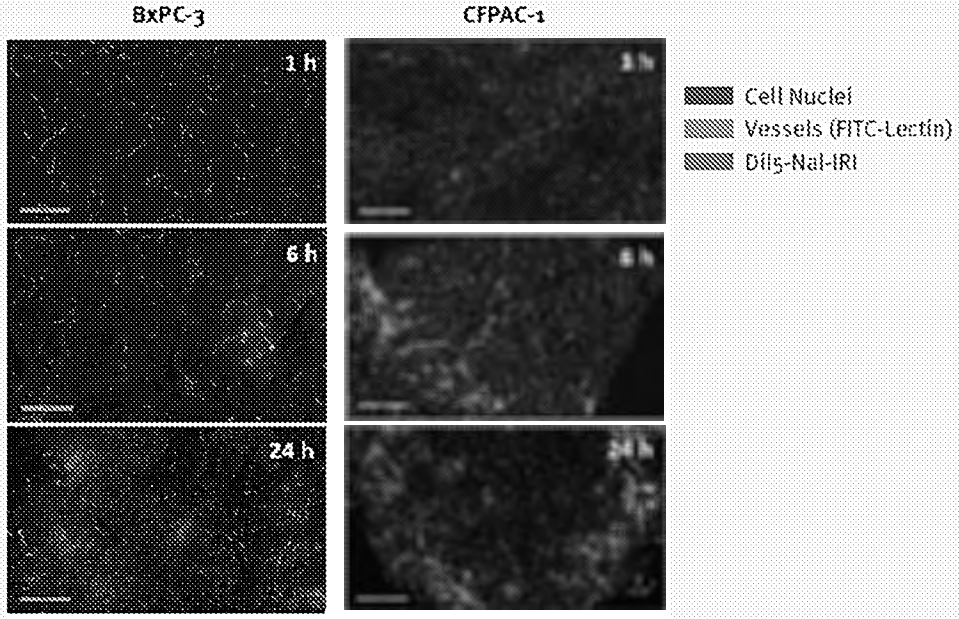
Figure 5. Changes in Tumor Volumes After Weekly Administration of 5x Lower Doses of nal-IRI Compared to Irinotecan (IRI)



NOD-SCID mice (n=5-7/group) bearing subcutaneous cell-line derived xenograft (CDX) tumors were treated with nal-IRI (5-10 mg/kg) or irinotecan (25-50 mg/kg). Vertical lines indicate the weekly dosing schedules. Error bars indicate standard error of the mean.

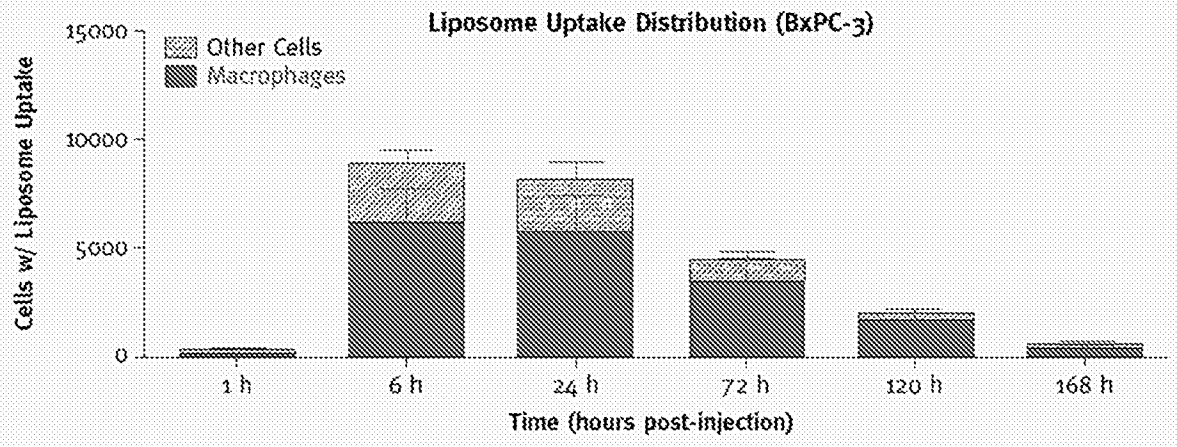
- nal-IRI deposits in tumors through FITC-lectin positive vessels, with peak liposome accumulation between 6–24 hours. (Figure 6a/b)
  - Deposition was heterogeneous in the tumors around functional vessels.
  - Similar deposition patterns were observed in cell-derived xenografts (Figure 7).

Figure 6a. Deposition Patterns for nal-IRI around functional vessels in BxPC-3 and CFPAC-1 Tumors



Subcutaneously grown BxPC-3 and CFPAC-1 tumors were collected at various time points after intravenous administration of DiI5-labeled nal-IRI (10 mg/kg). Functional tumor vasculature was marked by injection of FITC-labeled lectin prior to perfusion and tumor tissue collection. DAPI stain of cell nuclei (blue), FITC-lectin signal (green) and DiI5 signal (purple) are shown for representative images of tumor core sections for timepoints at 1, 6 and 24 h after liposome administration.

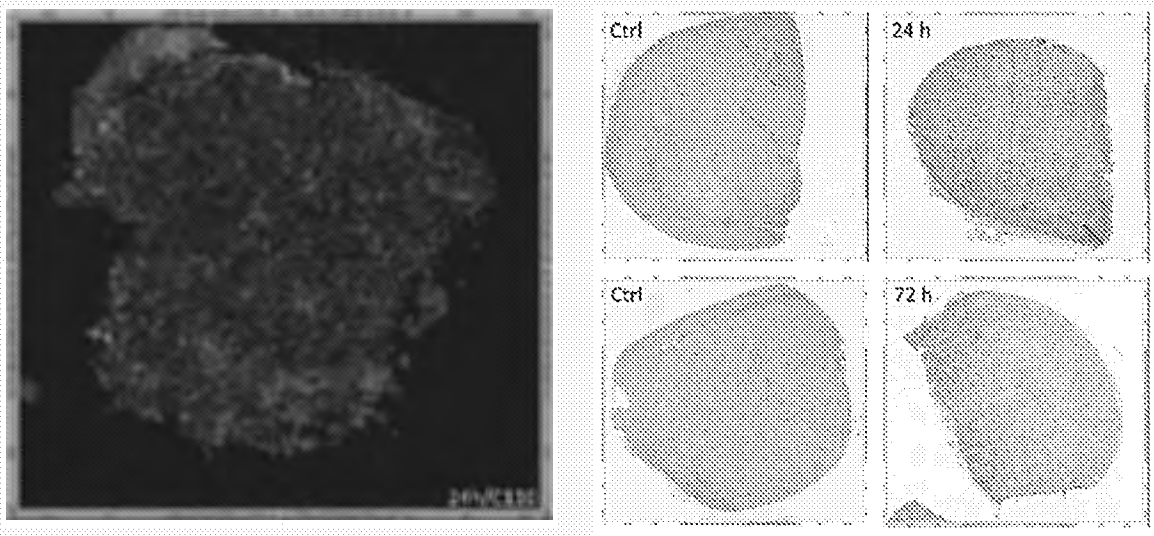
Figure 6b. Kinetics and Distribution of Liposome Uptake



Quantitative image analysis of co-localization of Dil5 signals with $F_4/80$-positive (blue) and $F_4/80$-negative (diagonal stripes) cells in frozen tumor core sections harvested at the indicated timepoints after administration of nal-IRI to mice bearing subcutaneous BxPC-3 tumors.

- Similar patterns of nal-IRI deposition were observed in a CTG-288 pancreatic PDX model; DNA damage is extensively observed at 24 ~ 72 h after treatment. (Figure 7)

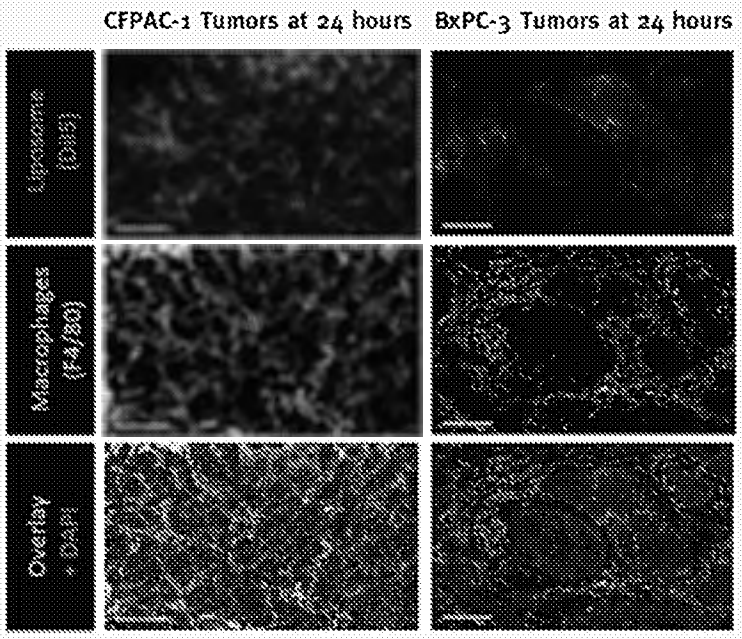
Figure 7. Deposition Patterns of nal-IRI in a Pancreatic PDX Model (CTG-288)



CTG-288 pancreatic PDX model treated with 10mg/kg Dil5-labeled MM-398 or Dil5-empty liposome. (Left) TMA section prepared from frozen tumor sample imaged for Dil5 (purple) and CD31 (green). A tumor core harvested 24 h after administration of Dil5-empty liposome is shown. (Right) FFPE tumor samples were stained with anti-γH2AX to show DNA damage. Whole core sections are shown.

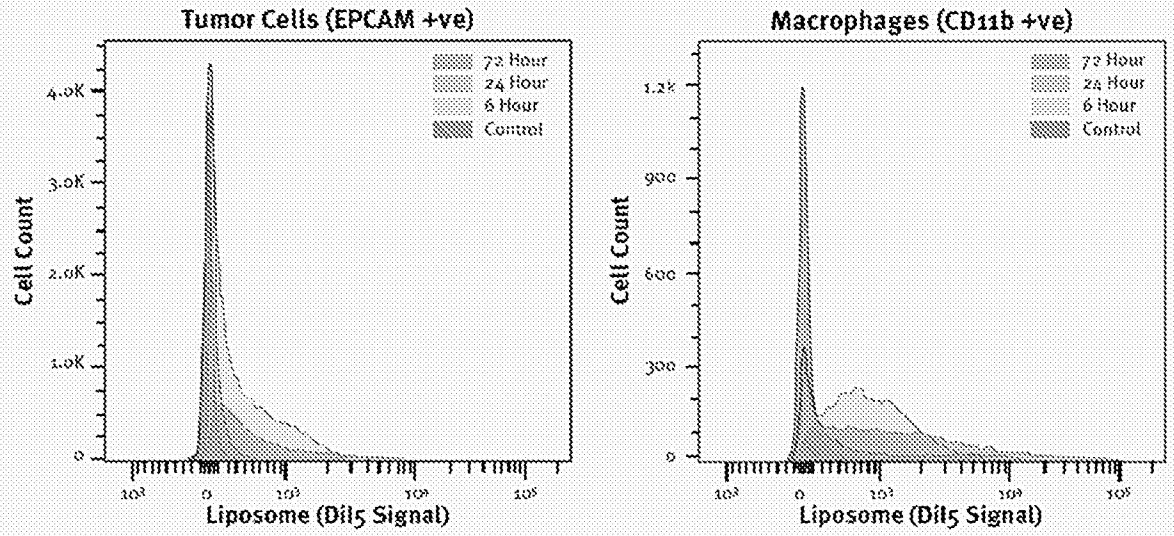
- Liposomes are predominantly taken up by macrophages and to a lesser extent by some tumor and stromal cells (Figure 8a)
- Macrophages take up more liposomes and uptake is faster than in tumor cells (Figure 8b)

Figure 8a. Distribution Patterns of nal-IRI Uptake in CFPAC-1 and BxPC-3 Tumors



Subcutaneously grown BxPC-3 and CFPAC-1 tumors were collected at various time points after intravenous administration of Dil5-labeled nal-IRI (10 mg/kg). Dil5 signal (red), F4/80 signal (yellow) and DAPI stain of cell nuclei (blue) are shown for representative images of tumor core sections collected at 24 h after liposome administration.

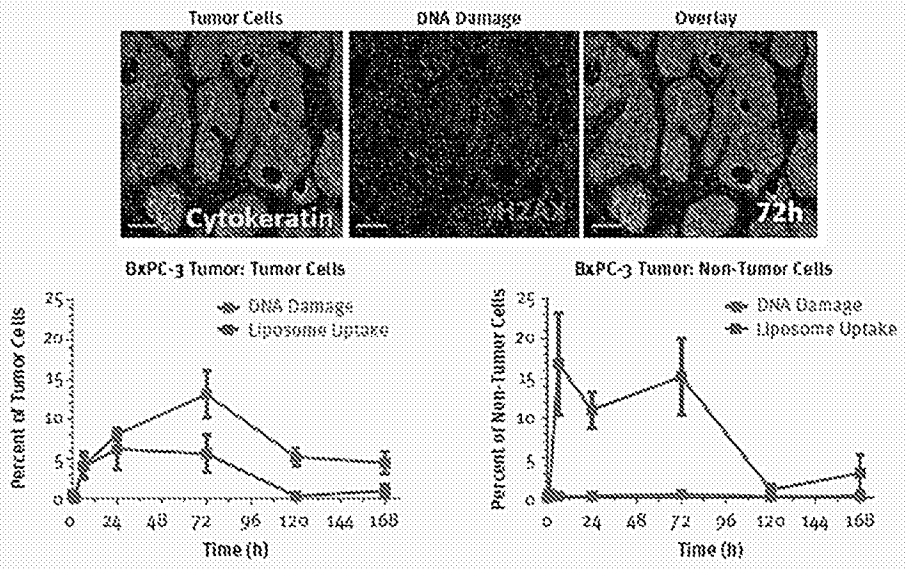
Figure 8b. Magnitude and Kinetics of nal-IRI Uptake in Tumor Cells and Macrophages



Flow cytometry analysis of dissociated BxPC-3 tumor 6 h, 24 h and 72 h after administration of a single dose of Dil5-labeled MM-398 (50 mg/kg). Histograms for Dil5 signals in EpCAM-positive tumor cells and CD11b-positive myeloid-lineage cells are shown.

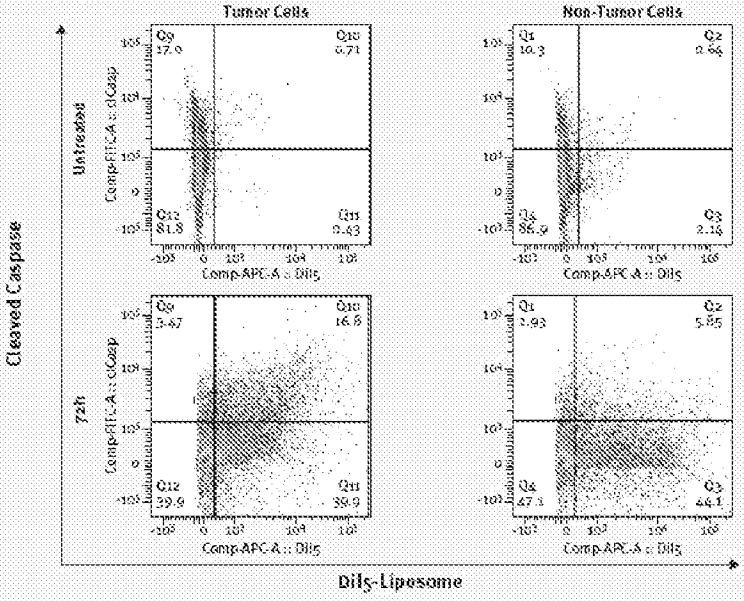
- DNA damage by γH2AX staining after nal-IRI treatment is mostly confined to tumor cells, the majority of which have not internalized liposomes, while DNA damage is very limited in non-tumor cells. (Figure 9a)
- Induction of apoptosis by cleaved caspase staining is more prevalent in tumor cells even at lower liposomal uptake levels, while most non-tumor cells showing liposome uptake do not undergo apoptosis (Figure 9b)

Figure 9a. DNA Damage in Tumor Cells and Non-Tumor Cells



(Top) Representative images and overlay for staining of BxPC-3 tumor at 72 h after administration of nal-IRI with cytokeratin and γH2AX. (Bottom) Quantitative image analysis of co-localization of Dil5 or γH2AX signals with cytokeratin-positive (left) and cytokeratin-negative (right) cells.

Figure 9b. Induction of Apoptosis in Tumor Cells and Non-Tumor Cells



Flow cytometry analysis of dissociated BxPC-3 tumor 72 h after administration of a single dose of Dil5-labeled MM-398 (10 mg/kg). Dotplots for Dil5 and Cleaved Caspase 3 signals are shown. Tumor cells are EpCAM-positive.

Conclusions

- Treatment with nal-IRI improves tumoral deposition of its payload in pancreatic tumor models.
- Liposomal deposition into tumors is heterogeneous, restricted to perivascular areas and is mainly observed in stromal macrophages/non-tumor cells.
- DNA damage with nal-IRI treatment occurs predominantly in tumor cells outside of the liposomal deposition area.
- Our results therefore suggest sufficient intratumoral bioavailability of the active metabolite, SN-38, possibly after payload release by stromal macrophages and concomitant conversion.
- nal-IRI demonstrates a greater reduction in tumor growth in a variety of pancreatic tumor models at a 5-fold lesser dose that irinotecan.
- The effects of repeated dosing cycles should be explored.

Acknowledgements

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This presentation was sponsored by Ipsen

Deposition characteristics and resulting DNA damage patterns of liposomal irinotecan (nal-IRI) in pancreatic cancer xenografts
Background
Methods
Results
Conclusions
Objectives

CANCERS OF THE PANCREAS, SMALL BOWEL, AND HEPATOBILIARY TRACT

Deposition characteristics and resulting DNA damage patterns of liposomal irinotecan (nal-IRI) in pancreatic cancer xenografts.

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Merrimack Pharmaceuticals, Inc., Cambridge, MA; Ipsen Bioscience, Inc., Cambridge, MA;

Show Less

Abstract Disclosures

Abstract

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Background: Liposomal irinotecan (nal-IRI, ONIVYDE) is approved in the US, EU and other countries in combination with 5-fluorouracil/leucovorin for treatment of patients with metastatic pancreatic cancer after disease progression following gemcitabine-based therapy. We report pharmacokinetic and extended pharmacodynamic effects of nal-IRI in pancreatic tumor models compared to non-liposomal irinotecan HCl. **Methods:** AsPC-1, BxPC-3 and CFPAC-1 tumors were grown in NOD-SCID mice. For efficacy animals were dosed q7d with 25-50 mg/kg irinotecan HCl or at 5x lower doses of nal-IRI. For PK-PD studies doses of 10-50 mg/kg of fluorescently-labeled nal-IRI were used; samples were collected up to 72 hr for irinotecan HCl and up to 168 hr for nal-IRI. Tumor samples were evaluated for liposome localization, macrophage and tumor markers, vessels, DNA damage and apoptosis. **Results:** nal-IRI yields sustained circulation and delivery of its payload to tumors compared to irinotecan HCl. This results in improved control of growth rates across a range of pancreatic tumor models even at 5x lower doses. DNA damage in BxPC-3 tumors has a comparable extent with both formulations, but is maximal at 6 hr after irinotecan HCl (50 mg/kg) and at 72 hr after nal-IRI (10 mg/kg). Liposomes deposit in tumors heterogeneously around functional vessels. Accumulation peaks at 6 - 24 hr with similar deposition patterns in cell- or patient-derived xenografts. Liposomes are predominantly taken up by macrophages and to a lesser extent by tumor or other stromal cells. DNA damage is mostly confined to tumor cells, a majority of which have not internalized liposomes. DNA cleavage and

apoptosis are seen only minimally in non-tumor cells even when displaying high liposome uptake. **Conclusions:** nal-IRI improves tumoral deposition of its payload in pancreatic tumor models. Deposition is heterogeneous and restricted to perivascular areas. DNA damage predominantly in tumor cells outside of the liposomal deposition area suggests sufficient intratumoral levels of the SN-38 active metabolite, possibly after payload release by stromal macrophages and concomitant conversion. Effects of repeated dosing cycles should be explored.

HIGHLIGHT ARTICLE

Any Progress in the Management of Advanced Pancreatic Cancer?

Highlights from the "45th ASCO Annual Meeting". Orlando, FL, USA. *May 29 - June 2, 2009*

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Summary

Majority of the patients with pancreatic cancer present with advanced disease that is lethal and notoriously difficult to treat. Survival has not improved dramatically despite routine use of chemotherapy and radiotherapy; this situation signifies an urgent need for novel therapeutic approaches. The treatment of advanced disease with gemcitabine has only a modest activity on survival with a favorable impact on quality of life. So far, the current targeted agents that have been used in combination with gemcitabine have failed to improve clinical outcomes. This failure may stem from the heterogeneous molecular pathogenesis of pancreatic cancers, which involves several oncogenic pathways and defined genetic mutations. However, recent data support the evidence that the combination of gemcitabine with erlotinib, capecitabine or platinum compounds could be more active than gemcitabine alone in advanced pancreatic cancer. New therapeutic strategies, particularly using molecular target agents, are under evaluation. A number of molecular mechanisms responsible of transformation and progression of pancreatic cancer have been identified, opening the possibility to identify also possible pharmacological targets. Pancreatic cancer remains the 4th leading cause of cancer death in the U.S.A.. How to treat a non-resectable pancreatic cancer has been a challenging topic for all medical oncologists. Historical 5-fluorouracil has been replaced by single agent gemcitabine since 1997. Numerous combinations using gemcitabine as a backbone have been tested in clinical trials; unfortunately, none of the combinations including the ones with biological agents was proved to be significantly superior to gemcitabine alone. This year, more combinations were investigated and the results were presented on the meeting. In first-line setting, two large phase III trials (Abstracts #4504 and #4601) failed to prove any additional benefit of a second cytotoxic agent or a vaccine. Folinic acid plus 5-FU plus oxaliplatin (FOLFOX) and 5-fluorouracil plus leucovorin plus irinotecan (FOLFIRI) could be considered in the second-line setting after failure of gemcitabine therapy (Abstract #4618). Novel agents (Abstracts #4501, #4625, #4626, #4617) provide some hope; however, in general, all combinations are still significantly relying on the backbone of gemcitabine. Thinking beyond the gemcitabine box and exploring novel agents are very crucial now.

Introduction

American Cancer Society has estimated in 2009, there will be 21,050 new pancreatic cancer cases in men and 21,420 in women, while 35,240 (about 83%) will die of pancreatic cancer in 2009 [1]. Pancreatic cancer remains the 4th cause of death by cancer after lung, prostate (breast in women), colorectal cancer since 1970s in the USA, although it represents only 2-3% of all cancers. Endless effort has been put on this aggressive disease; however, surgical resection remains the only curative option. Locally advanced or metastatic diseases are considered non-curable, palliative chemotherapies are often administered for alleviating symptoms. Fluorouracil (5-FU) had been the only active drug in pancreatic cancer for over decades until the emerging of gemcitabine in 1997 [2]. A significantly higher clinical benefit response associated with gemcitabine treatment was observed (23.8% *vs.* 4% in 5-FU arm) although the overall objective response rate remained modest [2]. Based on these results, FDA approved gemcitabine as the first line therapy for advanced pancreatic cancer in 1997. Since then, various combinations using gemcitabine as a backbone were designed and tested in clinical trials. Unfortunately, none of the combinations is proved to be superior to gemcitabine monotherapy.

With the advances in molecular biology, newer biologic agents such as erlotinib, cetuximab and bevacizumab are adding some benefit to the conventional cytotoxic agents. Unfortunately, these agents all failed to show any significant superiority over gemcitabine except the combination of erlotinib plus gemcitabine [3]; however, the clinical impact of this combination remains very controversial until now. The disappointing results did not discourage investigators but stimulated them to look for more

Key words Clinical Trials as Topic; Disease-Free Survival; erlotinib; gemcitabine; Pancreatic Neoplasms; Survival

Abbreviations CONKO: Charité Onkologie; LMWH: low molecular weight heparin

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pharmaceutical agents or combinations. We have gladly seen over 80 abstracts presented in the 2009 annual meeting of the American Society of Clinical Oncology (ASCO) in the field of pancreatic cancer. In this highlight article, we will focus on the management of advanced (locally advanced and metastatic) pancreatic cancer.

Since the approval of gemcitabine, true progress in the management of pancreatic cancer has been very minimal. There has been persistent effort in the field of medical oncology regards to explore novel agents based on better understanding of the diseases.

1. First-Line Therapies

Current standard first-line therapies for advanced pancreatic cancer are gemcitabine or gemcitabine plus erlotinib. A number of abstracts are exploring further first-line options. Interestingly, gemcitabine remains the core of the combinations.

1.1 Phase III Trials

Three large trials were presented (Table 1) [4, 5, 6]; unfortunately, two large trials (Abstracts #4504 and #4601) failed to prove any additional benefit of a second cytotoxic agent or a vaccine. The third trial (Abstract #4604) comparing erlotinib plus capecitabine with erlotinib plus gemcitabine only presented interim toxicity data from 127 patients, efficacy data are pending. To think beyond the gemcitabine box and search for novel agents have become crucially urgent in order to conquer this very aggressive disease.

1.1.1 Gemcitabine vs. Gemcitabine plus Cisplatin

The *"Gruppo Oncologico dell'Italia Meridionale"* conducted a phase III trial to compare gemcitabine with or without oxaliplatin, the benefit was only observed in progression-free survival but not overall survival, however later pooled- and meta-analysis proved that the addition of platinum to gemcitabine did offer survival benefit in selected patients [7, 8, 9]. The *"Gruppo Italiano Pancreas"* (GIP) conducted another superiority study to compare gemcitabine monotherapy with gemcitabine plus cisplatin in advanced pancreatic cancer patients [4]. The data were presented in this annual meeting. A total of 400 patients were enrolled from 46 Italian institutions. One-hundred and ninety-nine patients received gemcitabine single agent (1,000 mg/m^2 weekly x 7, then weekly x 3 every 4 weeks), whereas the other 201 patients received combination therapy of gemcitabine plus cisplatin (in addition to gemcitabine administered as above, cisplatin was given at 25 mg/m^2 weekly). Surprisingly, this large trial did not demonstrate any survival benefit by adding cisplatin to gemcitabine. The results not only confirmed a previously published negative phase III trial, but also warned all clinicians to carefully interpret pooled or meta-analyses.

1.1.2 Gemcitabine vs. GV1001 plus Gemcitabine

GV1001 is a telomerase peptide vaccine which showed a median overall survival of 8.6 months in non-resectable pancreatic cancer [10]. In order to compare the efficacy of a combination therapy of GV1001 and gemcitabine with gemcitabine monotherapy, a phase III trial was designed [5]. A total of 520 patients were planned. Patients were randomly assigned to either gemcitabine monotherapy (1,000 mg/m^2 over 30 min weekly x 7, then weekly x 3 every 4 weeks) or a sequential combination of GV1001 and gemcitabine (GV1001 0.56 mg subcutaneous plus granulocyte-macrophage colony-stimulating factor as immune adjuvant on days 1, 3, 5, 8, 15, 22, 36, then every 4 weeks, gemcitabine was added when disease progressed on GV1001). Unfortunately, after 365 patients were enrolled, a preliminary analysis indicated no survival benefit by giving GV1001. Thus this trial was prematurely terminated.

1.1.3 Erlotinib plus Capecitabine vs. Erlotinib plus Gemcitabine

Erlotinib has been proved to have effect in combination with gemcitabine for advanced pancreatic cancer. Whether erlotinib can be combined with other cytotoxic agents such as capecitabine in treating advanced pancreatic cancer was investigated in a phase III trial conducted by the *"Arbeitsgemeinschaft Internistische Onkologie"* (AIO) group [6]. Two-hundred and eighty-one patients randomly received either capecitabine (200 mg/m^2/day, days 1-14 every 3 weeks) plus erlotinib (150 mg/day) or gemcitabine (1,000 mg/m^2 over 30 min weekly x 7, then weekly x 3 every 4 weeks) plus erlotinib. The first interim analysis was reported on the meeting. Sixty patients received capecitabine plus erlotinib, 67 patients received gemcitabine plus erlotinib. Toxicity data indicated that erlotinib can be safely combined with capecitabine; however, the efficacy data are not completed yet. Whether this combination could achieve similar efficacy in terms of progression free survival and/or overall survival as the combination of erlotinib with gemcitabine, we will have to wait for the final results.

Table 1. Randomized phase III trials of gemcitabine-based first-line therapies.

Abstract	Study design	PFS (months)	OS (months)	Comments
#4504 [4]	Arm A: gemcitabine, Arm B: gemcitabine + cisplatin	3.9 *vs.* 3.8 (P=0.8)	8.3 *vs.* 7.2 (P=0.38)	Combination therapy did not provide any benefit in PFS, OS or clinical benefit, but increased toxicities
#4601 [5]	Arm A: gemcitabine, Arm B: GV1001 + gemcitabine	3.7 *vs.* 1.9	7.3 *vs.* 5.9	GV1001 has no benefit in treating pancreatic cancer benfit when administered in sequential combination with gemcitabine
#4604 [6]	Arm A: capecitabine plus erlotinib, Arm B: gemcitabine plus erlotinib	Not presented	Not presented	The first interim analysis only presented toxicity data from the first 127 patients. The combination of erlotinib and capecitabine seems to be tolerable, however, the efficacy data are not finalized yet

OS: overall survival; PFS: progression-free survival

Table 2. Phase I/II trials of gemcitabine-based first-line therapies

Abstract	Study design	Phase level	Efficacy	PFS (months)	OS (months)	Severe toxicities	Comments
#4607 [11]	Triple combination of gemcitabine + erlotinib + capecitabine (n=43)	II	PR: 32.6% SD: 51.2%	6.5	12.0	Cytopenia, GI toxicity, and rash	EGFR expression is poor prognostic factor
#4614 [12]	Arm A: PDXG regimen (n=46) Arm B: PEXG regimen (n=46)	II	PR: 61% vs. 37%	6-month PFS: 58% vs. 54%	1-year OS: 41% vs. 41%	Cytopenia, fatigue	Capecitabine is equivalent to 5-FU, docetaxel seems to be slightly superior to epirubicin in terms of response rate
#4623 [13]	GTX regimen (n=41)	II	PR: 21.9% SD: 41.5%	6.9	14.5	Cytopenia, infections, and mucositis	Large trial is warranted to validate this promising regimen

GTX: gemcitabine, docetaxel and capecitabine; OS: overall survival; PDXG: cisplatin, docetaxel, 5-FU, gemcitabine; PEXG: epirubicin replacing docetaxel; PFS: progression-free survival; PR: partial response; SD: stable disease

1.2 Phase I/II Trials

Several phase I/II trials studied more combinations, including four novel agents which will be discussed in more details in next section (Tables 2 and 3).

2. Second-Line Therapies

Lack of attention to second line treatment strategy in advanced pancreatic cancer is due to the fact that we still do not have first line option that renders true survival benefit; therefore, development of novel therapeutic agents should be an obvious area of our focus in the future. However, there is growing evidence supporting benefit of chemotherapy after gemcitabine failure in selected patients with good performance status [14].

Few clinical trials investigating second-line options in patients with advanced pancreatic cancer after failure of gemcitabine were presented at the meeting. One study aimed at exploring folinic acid plus 5-FU plus oxaliplatin (FOLFOX) and 5-fluorouracil plus leucovorin plus irinotecan (FOLFIRI.3), two commonly used regimens in colorectal cancer in this setting (Aabstract #4618) [15]. Sixty patients were randomly assigned to either FOLFOX (oxaliplatin 85 mg/m^2 over 120 min on day 1, leucovorin 400 mg/m^2 on day 1, 5-FU 2,000 mg/m^2 over 46 hours every two weeks) or FOLFIRI.3 (irinotecan 70 mg/m^2 over 60 min on day 1, leucovorin 400 mg/m^2 over 2 hours on day 1, 5-FU 2,000 mg/m^2 over 46 hours from day 1, then irinotecan 70 mg/m^2 over 60 min at the end of the 5-FU infusion every two weeks). Six-month overall survival rate in both arms were 25% and 20%, respectively. Based on patients' overall performance status, and prior chemotherapy toxicities, these two regimens can certainly be considered as second-line option; however, the clinical benefit needs to be validated in larger trials.

Table 3. Novel agents in the treatment of advanced pancreatic cancer.

Novel agents; Abstract#	Rationale	Administration/schedule	Clinical trials	Results	Future directions
AMG655 **#4501 [18]**	AMG655 is an agonist monoclonal antibody against human death receptor 5 (DR5), activates caspases, and subsequently induces apoptosis in sensitive tumor cells. Preclinical studies showed synergistic effect of AMG655 and gemcitabine.	AMG655 at 3 mg/kg or 10 mg/kg on day 1 and 15 plus gemcitabine at 1,000 mg/m^2 on days 1, 8 and 15 every 28 days	Phase I, first-line therapy	13 patients. PR: 31%. PFS: 5.3 months. 6-month survival rate: 76.2%. Severe toxicities: 9 (69%); especially cytopenia.	Same group is conducting a phase II trial to compare gemcitabine with or without AMG655.
Nab-paclitaxel **#4525 [19]**	Pancreatic cancer cells and surrounding stroma overexpress SPARC. A new formulated paclitaxel, nab-P, an albumin-bound nanoparticle form of paclitaxel increased tumor accumulation of paclitaxel through binding of albumin to SPARC	Nab-paclitaxel at 100-150 mg/m^2 plus gemcitabine at 1,000 mg/m^2 were given on days 1, 8, and 15 every 28 days	Phase I/II, first-line therapy	63 patients. CR: 2%, PR: 12%, SD: 41%. PFS: 4.8 months for SPARC-. PFS: 6.2 months for SPARC+. mOS: 9 months. Severe toxicities 12 patients; especially cytopenia.	Nab-paclitaxel is very promising. SPARC could be a predictive factor. A phase III trial in larger populations is warranted.
EndoTAG-1 **#4526 [20]**	EndoTAG-1 is a novel cationic liposomal formulation of paclitaxel which targets negatively charged endothelial cells of tumor blood vessels	Weekly gemcitabine at 1,000 mg/m^2, with or without twice weekly endoTAG-1 at 3 dose levels: 11, 22 and 44 mg/m^2	Phase II, first-line therapy	200 patients. Response rate and PFS were not presented. mOS: 11.5 months for gemcitabine plus high dose endoTAG-1. More infusion-reaction is associated with endoTAG-1 treatment groups.	Needs large trial to confirm the data.
Masitinib **#4617 [21]**	Masitinib is a tyrosine kinase inhibitor targeting c-Kit, PDGFR, FGFR3 and affecting the FAK pathway. Masitinib was found to enhance the antiproliferative effects of gemcitabine in preclinical studies.	Masitinib at 9 mg/kg/day plus weekly gemcitabine at 1,000 mg/m^2	Phase II, first-line therapy	22 patients. Clinical benefit: 16%. mPFS: 6.4 months. mOS: 7.1 months. 18-month survival rate: 23%. Severe toxicities were: cytopenia, diarrhea and rash.	The same group is conducting a phase III trial to compare gemcitabine with or without masitinib.

CR: complete response; FAK: focal adhesion kinase; FGFR3: fibroblast growth factor receptor 3; mOS: median overall survival; mPFS: median progression-free survival; PDGFR: platelet-derived growth factor receptor; PFS: progression-free survival; PR: partial response; SD: stable disease; SPARC: secreted protein acid rich in cysteine

Table 4. Results of CONKO-004 trial after a median follow-up of 30.4 weeks.

Primary/secondary end-points	Chemotherapy arm (n=152)	Chemotherapy plus enoxaparin arm (n=160)	Comments
Venous thromboembolic events	22 (14.5%)	8 (5.0%)	P<0.05
Bleeding	15 (9.9%)	10 (6.3%)	P=0.6
Median overall survival	29 weeks	31 weeks	Preliminary results, not statistically calculated yet

Current standard dose of erlotinib is 100 mg/day in combination with gemcitabine [3]. Skin acne-like rash has been proposed to be a "surrogate" marker for response to biologic agents such as erlotinib and cetuximab. In the 2007 ASCO Gastrointestinal Cancers Symposium (Orlando, FL, U.S.A.; January 20th, 2007), Van Cutsem *et al.* presented a dose-escalation study of cetuximab in colorectal cancer (EVEREST). The higher grade of skin rash correlating with increased response rate was observed [17]. Whether this "surrogate" marker can be used to maximize the benefit from erlotinib was studied by Tang *et al.* in a phase II trial [16]. Fifty patients with gemcitabine-refractory pancreatic cancer were orally administered erlotinib starting at 150 mg/day, dose-escalating by 50 mg every two weeks until rash more than grade 1 or maximum dose of 300 mg/day (Figure 1). Twenty-five percent of eligible patients achieved stable disease for more than 8 weeks which met the primary end-point of this trial. This trial certainly revolutionized our understanding of erlotinib. It is worthwhile to perform a large trial to validate these results and re-compare gemcitabine with or without erlotinib in which the dose of erlotinib should be based on skin rash.

3. Novel Agents

Development of novel therapeutic agents is an obvious area of focus of research in pancreatic cancer. Several novel agents either new biologic target agents (AMG655 and masitinib) or newly formulated conventional cytotoxic agents (endoTAG-1 and nab-paclitaxel) are tested and results are promising (Table 3).

4. Supportive Therapy

Palliative care represents an important aspect of care in patient with pancreatic malignancy. Identifying and treating disease related symptomatology are priorities [22].

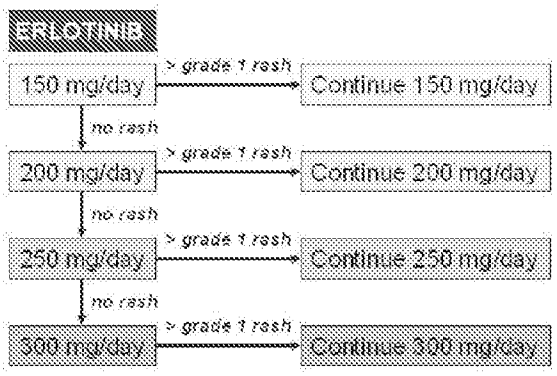

Figure 1. Schema of phase II erlotinib single agent as second-line therapy.

The incidence of venous thromboembolism in pancreatic cancer patients ranges from 17% to 57%. Clinical data also suggest that the occurrence of venous thromboembolism may be associated with poorer prognosis in such patients. Recent data suggest that anticoagulant treatments may improve cancer patient survival by decreasing thromboembolic complications as well as by anticancer effects [23]. Riess *et al.* conducted the "*Charité Onkologie*" (CONKO-004) trial to investigate whether the addition of enoxaparin, a low molecular weight heparin (LMWH) improves overall survival (Abstract #LBA4506) [24]. Safety and feasibility of adding enoxaparin to chemotherapy have been completed in their previously published pilot study "Prospective, Randomized trial Of Simultaneous Pancreatic cancer treatment with Enoxaparin" (PROSPEC-CONKO-004) [25]. The primary endpoint was to decrease the incidence of symptomatic venous thromboembolic events. Three-hundred and twelve patients were enrolled, 160 patients were treated with chemotherapy plus enoxaparin. The occurrence of venous thromboembolic events were 8/160 (5.0%) compared with 14.5% in the non-LMWH arm (Table 4). Clearly, enoxaparin is effective and safe for prevention of symptomatic venous thromboembolic events; however, whether the low incidence of venous thromboembolic events is associated with some survival benefit is still unclear. CONKO-004 preliminary data showed no difference in median overall survival with or without enoxaparin. We are looking forward to their final results.

Future Directions

Options for pancreatic cancer in advanced/metastatic setting are still very limited. Gemcitabine remains the standard of care despite so many combinations were examined. The two large phase III trials failed to show any benefit beyond gemcitabine monotherapy by adding a second cytotoxic agent such as cisplatin or a vaccine GV1001. These combinations were promising in early phase trials or pooled/meta-analysis. Again, we should be careful when interpreting results from early phase trials. Many promising results from phase II trials were unable to be translated into phase III trials. Over the last 12 years, we have extensively and intensively explored all possible agents to combine with gemcitabine, it is the time to think out of the gemcitabine box and put more effort on novel agents.

Nab-paclitaxel, "an old drug in a new bottle", seems to be very promising when combined with gemcitabine.

We are looking forward to the phase III results. New biologic target agent such as AMG655, a monoclonal antibody against human death receptor-5, also achieved encouraging results. However, the current designs of clinical trials in advanced pancreatic cancer still rely on gemcitabine, even for the aforementioned novel agents. Nevertheless, gemcitabine is the only cytotoxic agent providing significant clinical benefit for pancreatic cancer. We encourage more novel agents should be tested in second-line setting.

Conflict of interest The authors have no potential conflicts of interest

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HIGHLIGHT ARTICLE

Any Second-Line Therapy for Advanced Pancreatic Cancer?

Highlights from the "2010 ASCO Gastrointestinal Cancers Symposium", Orlando, FL, USA. January 22-24, 2010

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Summary

Majority of pancreatic cancers are unresectable upon diagnosis. Palliative chemotherapy is usually administered in an attempt of prolonging survival potentially and providing quality of life. Gemcitabine has been the solo player in the field of pancreatic cancer treatment after replacing 5-FU since 1997. How to treat a patient with advanced pancreatic cancer failing to respond or progressing after gemcitabine is a true challenge. No established second-line treatment exists yet. Chinese herbal medicine PHY906 provides cytoprotective effects without dampening the anti-tumor activity of chemotherapeutic agents. Several combinations such as S-1/gemcitabine, GTX, FOLFIRINOX showed promising results in retrospective studies. Among single agents, erlotinib and Src inhibitor failed to show seemingly benefit, while abraxane and pemetrexed deserve further investigation.

Introduction

Pancreatic cancer remains the 4th cause of cancer death after lung, prostate (breast in women), and colorectal cancer since 1970s in the USA [1]. Small localized tumors can be possibly cured by surgical resection, however, majority of the tumors are either locally advanced or metastatic upon diagnosis. Among all studied chemotherapeutic agents, gemcitabine was the only one demonstrating a significantly higher clinical benefit response compared to historical 5-fluorouracil (5-FU) infusion [2]. Since 1997, gemcitabine established its unshakable status as first-line therapy for advanced pancreatic cancer. Various combinations using gemcitabine as a backbone were subsequently investigated in large randomized clinical trials; none of the combinations is proved to be superior to gemcitabine monotherapy except erlotinib plus gemcitabine [3].

What if patients are not responding to first-line gemcitabine-based regimen? Is there a standard second-line therapy? Unfortunately, the answer is still no, though there is growing evidence supporting some benefit of chemotherapy after gemcitabine in selected patients. Several encouraging abstracts presented on the 2010 ASCO Gastrointestinal Cancers Symposium in the field of pancreatic cancer deserve a discussion here (Table 1).

Keywords: erlotinib; gemcitabine; Pancreatic Neoplasms; S-1 (combination)

Abbreviations GTX: gemcitabine, docetaxel and capecitabine; S-1: tegafur, 5-chloro-2,4-dihydroxyuridine and potassium oxonate, SPARC: secreted protein acidic and rich in cysteine; Src: v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (avian)

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Combination Therapies

Capecitabine plus Chinese Herbal Medicine PHY906

PHY906 has not only synergistic antitumor activity with several chemotherapeutic agents including irinotecan, capecitabine and gemcitabine, but also cytoprotective effect. Our institute, Yale Cancer Center, has opened several early phase trials investigating the use of PHY906 in different types of cancers such as colorectal, pancreatic cancer and hepatocellular carcinoma. In our phase II trial, PHY906 is administered with capecitabine for patients refractory to first-line gemcitabine therapy [4]. The anti-diarrhea and anti-hand-foot syndrome effects were very promising. In patients who received more than 2 cycles, median overall survival was 6.8 months.

S-1 Followed by Gemcitabine

Among all combination trials, tegafur, 5-chloro-2,4-dihydroxyuridine and potassium oxonate (S-1) followed by gemcitabine sequential use is probably the most exciting one. Its anti-tumor activity has been explored beyond gastric cancer in Japan. S-1 and gemcitabine were administrated sequentially in 29 patients with gemcitabine refractory pancreatic cancer

Table 1. Summary of trials investigating second-line treatment.

Abstract	Study design	Testing drug	Enrolled patients	Overall survival	Median survivals (months)	
					Overall	Progression-free
#246 [4]	Phase II	Capecitabine plus PHY906	25	22% (9 months)	5.13	1.63
#241 [5]	Retrospective	S-1 followed by gemcitabine	29	NR	12.3	3.5
#269 [6]	Retrospective	FOLFIRINOX	13	62% (1 year)	10.0	NR
#221 [7]	Retrospective	GTX	59	NR	5.1	2.3
#165 [8]	Phase II	Src inhibitor: saracatinib	19	11% (6 months)	2.5	1.5
#214 [9]	Phase II	Abraxane	20	63% (6 months)	7.3	1.7
#276 [10]	Phase II	Pemetrexed	17	NR	NR	2.0
#258 [11]	Phase II	Erlotinib	18	NR	3.1	1.38

FOLFIRINOX: 5-fluorouracil, leucovorin, irinotecan and oxaliplatin; GTX: gemcitabine, docetaxel and capecitabine; NR: not reported; S-1: tegafur, 5-chloro-2,4-dihydroxyuridine and potassium oxonat; Src: v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (avian)

[5]. One patient (3.4%) achieved complete response and 5 patients (17.2%) achieved partial response. Median overall and progression free survivals were 12.3 and 3.5 months, respectively.

5-Fluorouracil, Leucovorin, Irinotecan and Oxaliplatin (FOLFIRINOX)

Both oxaliplatin and irinotecan are known to have survival benefit in combination with 5-fluorouracil and leucovorin (5-FU/LV) in metastatic colorectal cancer. Breysacher *et al*. reported a retrospective study investigating the role of FOLFIRINOX as second-line therapy [6]. No response was seen in 13 patients and 1-year survival rate was 62%. GI toxicity was frequent but mild and manageable.

Gemcitabine, Docetaxel, and Capecitabine (GTX) Regimen

GTX regimen has shown activity in both neoadjuvant and metastatic settings. No data exists on the use of GTX in second-line. In a retrospective study of 59 patients received GTX after initial standard therapies, a drop greater than 75% in CA 19-9 after treatment predicted longer overall survival [7].

Single Agents

Abraxane

Pancreatic cancer cells and surrounding stroma overexpress SPARC (secreted protein acidic and rich in cysteine). Abraxane increased tumor accumulation of paclitaxel through binding of albumin to SPARC. Abraxane plus gemcitabine did demonstrate clinical benefit in early phase trials [12]. Abraxane alone appears to be promising as well. One of 19 patients (5.3%) achieved partial response [8]. Whether SPARC expression is a predicative biomarker needs further investigation.

Pemetrexed

In a phase II trial, pemetrexed rendered median progression free survival of 2 months to patients who failed gemcitabine [8]. No concerning adverse events were found except grade 3 neutropenia in two patients (10.5%).

Molecular Target Therapy

Erlotinib with gemcitabine combination gained FDA approval for a small overall survival benefit. However, when erlotinib used as single agent, it lost this modest benefit completely [9]. Src family tyrosine kinases are overexpressed in pancreatic cancers. The anti-tumor activity of Src inhibitor saracatinib was demonstrated in a mouse model [13]. Unfortunately, saracatinib failed to improve 6-month survival in a phase II trial [10]. Only 2 of 18 patients survived beyond 6 months (11.1%).

Discussion

Options for pancreatic cancer in advanced or metastatic setting remain limited. Gemcitabine as the only FDA-approved chemotherapeutic agent has been intensively and extensively investigated in combination with other drugs; unfortunately, no additional benefit was seen. Unlike the first-line setting, there is no standard of care after gemcitabine failure. Drugs in this setting should consider clinical benefit more importantly than anti-tumor activity. Several abstracts report either single agents or combinations with or without gemcitabine did demonstrate some potential clinical benefit. Chinese herbal medicine PHY906 provides convincing cytoprotective effect when used in combination with chemotherapeutic agents. More clinical trials of PHY906 are being conducted at Yale Cancer Center. FOLFIRINOX is also an interesting and promising combination. Surprisingly, the toxicity profile was not alarming. Other two combinations continued to use gemcitabine even after failure in the initial therapy. Sequential S-1 and gemcitabine should be tested in clinical trial setting. Among single agents, abraxane and pemetrexed warrant further investigation.

Conflict of interest The authors have no potential conflicts of interest

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Cationic liposomal paclitaxel plus gemcitabine or gemcitabine alone in patients with advanced pancreatic cancer: a randomized controlled phase II trial

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Background: Paclitaxel embedded in cationic liposomes (EndoTAG™-1; ET) is an innovative agent targeting tumor endothelial cells. This randomized controlled phase II trial evaluated the safety and efficacy of ET in combination with gemcitabine (GEM) in advanced pancreatic cancer (PDAC).

Patients and methods: Chemotherapy-naive patients with locally advanced or metastatic disease were randomly assigned to receive weekly GEM 1000 mg/m^2 or GEM plus twice-weekly ET 11, 22 or 44 mg/m^2 for 7 weeks. After a safety run-in of 100 patients, a second cohort continued treatment. End points included overall survival (OS), progression-free survival (PFS), tumor response and safety.

Results: Two hundred and twelve patients were randomly allocated to the study and 200 were treated (80% metastatic, 20% locally advanced). Adverse events were manageable and reversible. Transient thrombocytopenia and infusion reactions with chills and pyrexia mostly grade 1 or 2 occurred in the ET groups. Disease control rate after the first treatment cycle was 43% with GEM and 60%, 65% and 62% in the GEM + ET cohorts. Median PFS reached 2.7 compared with 4.1, 4.6 and 4.4 months, respectively. Median OS was 6.8 compared with 8.1, 8.7 and 9.3 months, respectively.

Conclusions: Treatment of advanced PDAC with GEM + ET was generally well tolerated. GEM + ET showed beneficial survival and efficacy. A randomized phase III trial should confirm this positive trend.

Key words: cationic liposomes, EndoTAG™-1, liposomal paclitaxel, pancreatic cancer, vascular targeting

introduction

Pancreatic cancer (PDAC) is the fourth most common cause of cancer-related death in the Western world, with an estimated 36 800 deaths in the United States in 2010 [1]. Less than 20% of PDAC patients are diagnosed with resectable and potentially curable disease; usually patients have advanced disease at the time of diagnosis [2, 3].

Gemcitabine (GEM) has been the standard systemic therapy for palliative treatment of advanced PDAC during the last decade, with a median survival of ~6 months and 1-year survival rates of ~18% [4, 5]. Numerous phase III trials failed to demonstrate superiority of combinations of GEM with other agents [6, 7]. Only the combination with erlotinib achieved a modest but statistically significant improvement of survival and was approved in this indication [4, 5]. Due to the poor prognosis and limited treatment options, there is a high medical need for the development of new therapies.

Treatment with taxanes was examined in several studies with good tolerability. Docetaxel was judged to be active in untreated patients in a phase II trial [8], also after pretreatment [9]. Paclitaxel has been proven to be safe but was considered moderately effective, even in recent studies [10, 11].

Angiogenesis is essential for growth and metastasis of most solid malignancies. While not grossly vascular, pancreatic adenocarcinoma exhibits foci of micro-angiogenesis and overexpresses multiple pro-angiogenic factors [12, 13].

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EndoTAG™-1 (ET) is a novel formulation of charged liposomes, carrying paclitaxel embedded in the cationic liposome membrane. Tumor endothelia lack the glycocalix usually covering endothelia under normal conditions, thus exposing the negatively charged cell surface. Through this mechanism, positively charged liposomes can selectively bind to tumor endothelial cells and internalize after i.v. administration [14–17] (Figure 1). Paclitaxel is thereby selectively delivered to the activated intratumoral endothelial cells [18]. These targeting properties and antitumor effects of ET have been demonstrated in animal models including orthotopic pancreatic carcinoma [18–20].

Several phase I studies demonstrate an acceptable safety profile and antitumor activity of ET in patients with different solid tumors (MediGene on file). The present trial was conducted to evaluate the safety and efficacy of ET at three different dose levels in combination with GEM in patients with locally advanced or metastatic adenocarcinoma of the pancreas, with GEM monotherapy used to define the patient cohort.

patients and methods

study design and treatment

This trial was an open-label, randomized, controlled, multicenter phase II study. Patients were randomly assigned to one of the four treatment groups: gemcitabine monotherapy or gemcitabine in combination with 11 mg/m^2 liposomal paclitaxel (ET; GEM + Endo11), 22 mg/m^2 (GEM + Endo22) or 44 mg/m^2 (GEM + Endo44). Patients were centrally randomized. Due to the characteristic application schedule of ET, a blinded study design was not appropriate.

Treatment consisted of 7 weekly infusions of GEM (1000 mg/m^2/30 min) on days 4, 11, etc. and, if applicable, 14 twice-weekly infusions of ET on days 1, 4, etc. (10 min at 0.5 ml/min, 10 min at 1.0 ml/min and thereafter 1.5 ml/min). Treatment was administered for one complete cycle unless there was documented disease progression, unacceptable toxicity or patient refusal. Premedication was optional. In the event of toxic effects, treatment with study medication was delayed or GEM was administered at a reduced dose (80%) depending on the severity of the toxicity. Dose reductions for ET were not permitted.

After enrollment of 100 patients, the protocol was amended to allow continued treatment with ET in the GEM + Endo groups. Further antitumor therapy after discontinuation of study medication was at the discretion of the investigator.

patient characteristics

Eligibility criteria were age ≥18 years; histologically or cytologically confirmed unresectable locally advanced or metastatic ductal adenocarcinoma of the exocrine pancreas suitable for chemotherapy; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of two or less; adequate renal, hepatic and cardiac function; adequate bone marrow reserve (white blood cells > 3×10^3/mm^3, absolute neutrophil count > 1.5×10^3/mm^3, platelets > 100 000/mm^3, hemoglobin > 9.0 g/dl); bilirubin two times or less the upper limit of normal. Patients were

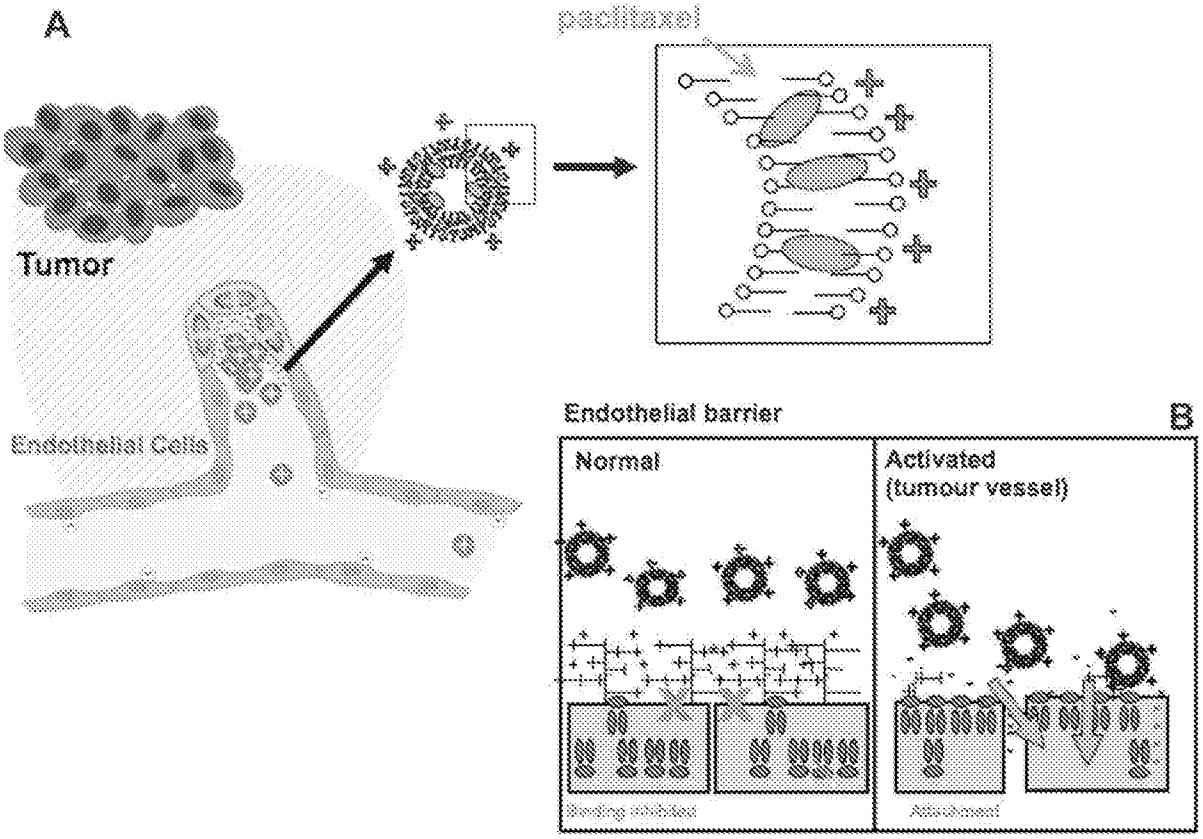

Figure 1. Mode of action of EndoTAG-1. In a simplified model of tumor cell angiogenesis (A), liposomal-embedded paclitaxel targets the vascular endothelial cells. The mechanism of selective targeting is delinated in (B). Tumor endothelial cells become negatively charged through the loss of surface glycocalix, which allows selective attachment and internalization of EndoTAG-1 impossible.

excluded if they had a history of other malignancies within 5 years of enrollment (except for skin cancer treated locally), prior chemotherapy or radiotherapy for PDAC (except for treatment of bone metastases), major surgery within 4 weeks of enrollment or other diseases likely to interfere with study treatment or assessments.

Informed consent was obtained from all patients. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was registered with ClinicalTrials.gov, number NCT00377936. The protocol was approved by the review boards of the participating institutions and was endorsed by the 'Arbeitsgemeinschaft Internistische Onkologie' in Germany (AIO PK0104).

assessments

Patients underwent medical examination at baseline. The first treatment cycle consisted of a screening visit and a treatment phase comprising 7 weekly visits for patients in the GEM group and 14 twice-weekly visits for patients in the GEM + Endo groups. Tumor assessment was conducted according to RECIST 1.0 guidelines [21] at baseline and at the end of each treatment cycle. After termination of study treatment, patients were invited for follow-up evaluations every 8 weeks until documented disease progression. Thereafter, patient follow-up was conducted by phone until patient death. Adverse events (AEs), if applicable, were recorded at each visit and classified according to Common Terminology Criteria for Adverse Events v3.0. Quality of life and pain were self-reported by patients using the European Organisation for Research and Treatment of Cancer QLQ-C30 and QLQ-PAN26 questionnaires and the visual analog scale (VAS; 100 mm), respectively.

statistical analysis

This trial was exploratory and was not powered for formal superiority analysis in any end point. Sample sizes were extrapolated from comparable phase II trials in PDAC due to previous data on ET. The cut-off date for the analysis was 48 weeks after the last patient completed the first treatment cycle. All patients who were randomly assigned to the trial [intent to treat (ITT)] or received study medication [modified intent to treat (mITT)] were included in the efficacy and safety population. No individual parameter of the study was defined as primary end point. End points included overall survival (OS), progression-free survival (PFS), tumor response, quality of life, pain and the frequency and severity of AEs.

OS was defined as the time from randomization to death. Patients with no documented event (death) were censored at the date of last documented contact. Twelve-month survival rates were calculated as the number of patients still alive after 12 months from the start of treatment, of all patients with known vital status.

PFS was defined as the time from randomization to disease progression or death, whichever occurred first. Patients who discontinued prematurely for reasons other than progressive disease (PD) were censored at the date of discontinuation.

Investigator-assessed tumor response after the first treatment cycle was classified as complete response (CR), partial response (PR), stable disease (SD), or PD according to RECIST 1.0 guidelines [21]. In addition, the number of patients with disease control (CR, PR or SD) was assessed.

Other end points comprised mean changes in quality of life and pain assessment during the first treatment cycle and toxic effects. For quality of life and pain, patients were only included in the analysis if they had a baseline assessment and if at least 50% of the respective assessments during treatment were available.

Time-to-event variables were estimated using the Kaplan–Meier method. Medians and their respective 95% confidence intervals (CIs) were calculated. Cox proportional hazards models were applied to estimate the effect of the treatment group (three combination treatment groups versus GEM monotherapy) on OS and PFS stratified for ECOG PS at baseline, extent of disease (locally advanced, metastatic disease), country (Germany, Czech Republic, Hungary or Ukraine) and whether patients were enrolled according to the amended protocol allowing for continuation of treatment with study medication until disease progression. Clopper–Pearson method was used to calculate the 95% CIs for 12-month survival rates. Mean changes in quality of life and pain assessment were calculated exerting all available quality of life or pain assessments after first infusion of study medication up to the date of last infusion in the first treatment cycle and estimated together with the corresponding 95% CIs.

All tabulations of summary statistics, graphical presentations and statistical analyses were carried out by using SAS software (version 8.2) and StatXact (version 7).

results

patient characteristics

From September 2005 to June 2007, 212 chemonaive patients with advanced unresectable PDAC were randomly allocated to the trial at 32 centers in 4 countries. Twelve patients did not start treatment because of AEs in five (2.4%), withdrawal of consent in three (1.4%) and other reasons in four (1.9%) patients (Figure 2). Two hundred patients were treated with at least one dose of study medication (50 patients in each treatment group). All 212 randomized patients were included in the ITT efficacy population and all treated patients in the mITT efficacy and safety population. Baseline characteristics of the study population (Table 1) were well balanced across treatment groups, except for the ECOG PS. The number of patients with grade 2 ECOG PS was higher in the GEM + Endo treatment groups, especially for the GEM + Endo22 and GEM + Endo44 study arms. The proportion of patients with metastatic disease at baseline ranged from 76% to 84%.

treatment

Of the 200 patients treated, 158 (79%) completed the first treatment cycle (90% in GEM, 84% in GEM + Endo11, 68% in GEM + Endo22 and 74% in GEM + Endo44 group; Figure 1). The most common reasons for discontinuation during the first cycle were investigator decision in 20 (10%) patients [15 (8%) patients due to AEs] and withdrawal of consent in 14 patients (7%). Median relative dose intensity of ET was 83% in the GEM + Endo11, 87% in the GEM + Endo22 and 78% in the GEM + Endo44 arm. Correspondingly, the proportion of patients with dose delay or reduction of GEM dose tended to increase with increasing ET dose (data not shown).

An amendment allowed 80 patients of the GEM + Endo groups with clinical benefit to continue on study medication beyond the first cycle, but only 28 patients received further therapy with ET: 13 in the GEM + Endo11, 8 in the GEM + Endo22 and 7 patients in the GEM + Endo44 group. The longest treatment was achieved by one patient in the GEM + Endo22 group (five cycles completed).

efficacy

At the cut-off point for analysis, i.e. 48 weeks after the last patient completed the first treatment cycle, 161 patients had died, 39 were still alive and one patient was still receiving study medication. Median OS was 8.1 months in the GEM + Endo11, 8.7 months in the

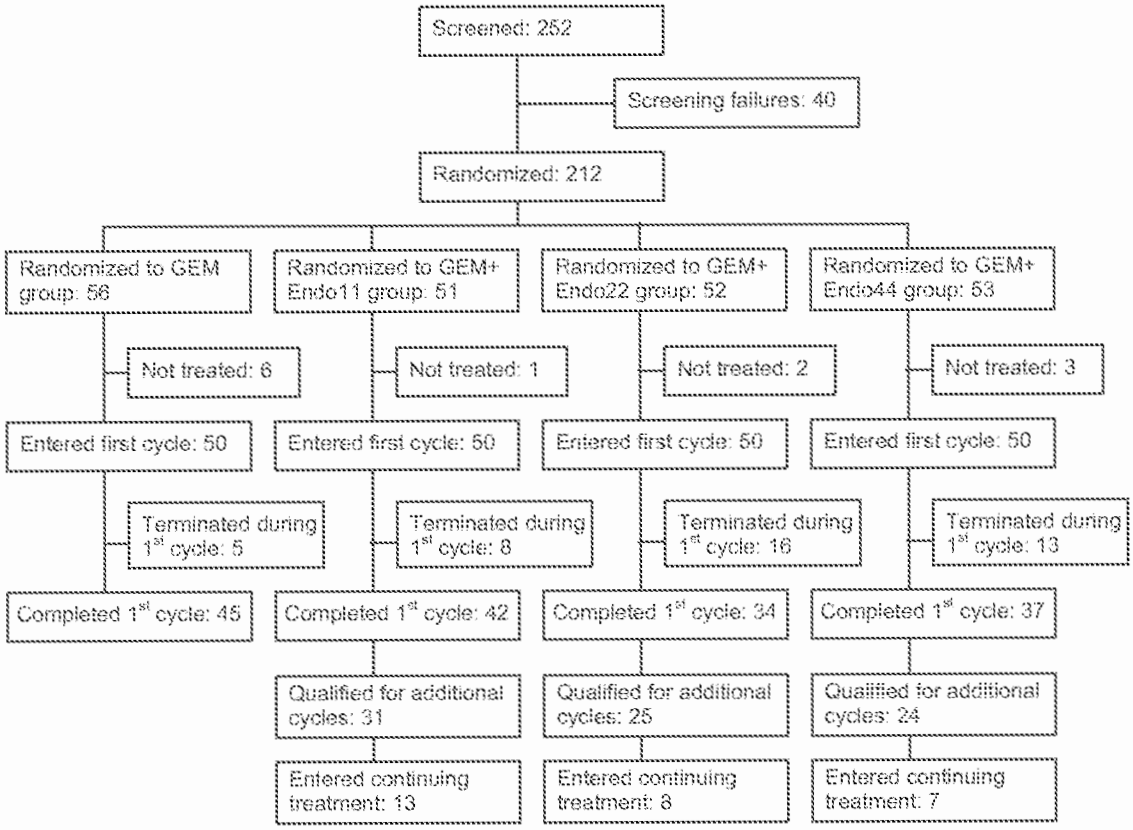

Figure 2. Study population (CONSORT diagram). CONSORT, Consolidated Standards of Reporting Trials; GEM, gemcitabine; GEM + Endo11, gemcitabine in combination with 11 mg/m^2 liposomal paclitaxel; GEM + Endo22, gemcitabine in combination with 22 mg/m^2 liposomal paclitaxel; GEM + Endo44, gemcitabine in combination with 44 mg/m^2 liposomal paclitaxel.

Table 1. Baseline characteristics of the study population

Baseline characteristic	Treatment group (mITT population)			
	GEM (*N* = 50)	GEM + Endo11 (*N* = 50)	GEM + Endo22 (*N* = 50)	GEM + Endo44 (*N* = 50)
Sex, *n* (%)				
Male	32 (64)	34 (68)	32 (64)	33 (66)
Female	18 (36)	16 (32)	18 (36)	17 (34)
Age, years				
Median	59.5	63.0	61.0	62.5
Range	34–80	32–75	44–72	33–81
Extent of disease, *n* (%)				
Locally advanced	12 (24)	8 (16)	11 (22)	12 (24)
Metastatic	38 (76)	42 (84)	39 (78)	38 (76)
ECOG performance status, *n* (%)				
Grade 0	20 (40)	22 (44)	20 (40)	18 (36)
Grade 1	26 (52)	22 (44)	20 (40)	23 (46)
Grade 2	4 (8)	6 (12)	10 (20)	9 (18)

mITT, modified intent to treat; GEM, gemcitabine; GEM + Endo11, gemcitabine in combination with 11 mg/m^2 liposomal paclitaxel; GEM + Endo22, gemcitabine in combination with 22 mg/m^2 liposomal paclitaxel; GEM + Endo44, gemcitabine in combination with 44 mg/m^2 liposomal paclitaxel; ECOG, Eastern Cooperative Oncology Group.

GEM + Endo44 arm compared with 6.8 months in the GEM group (Figure 3A). Hazard ratios (HRs) for OS relative to GEM monotherapy were 0.93 for the GEM + Endo11, 0.69 for the GEM + Endo22 and 0.66 for the GEM + Endo44 group (Table 2). Accordingly, 12-month survival rates were 21% for the GEM + Endo11, 35% for the GEM + Endo22 and 30% for the GEM + Endo44 group compared with 15% for the GEM cohort (Table 2).

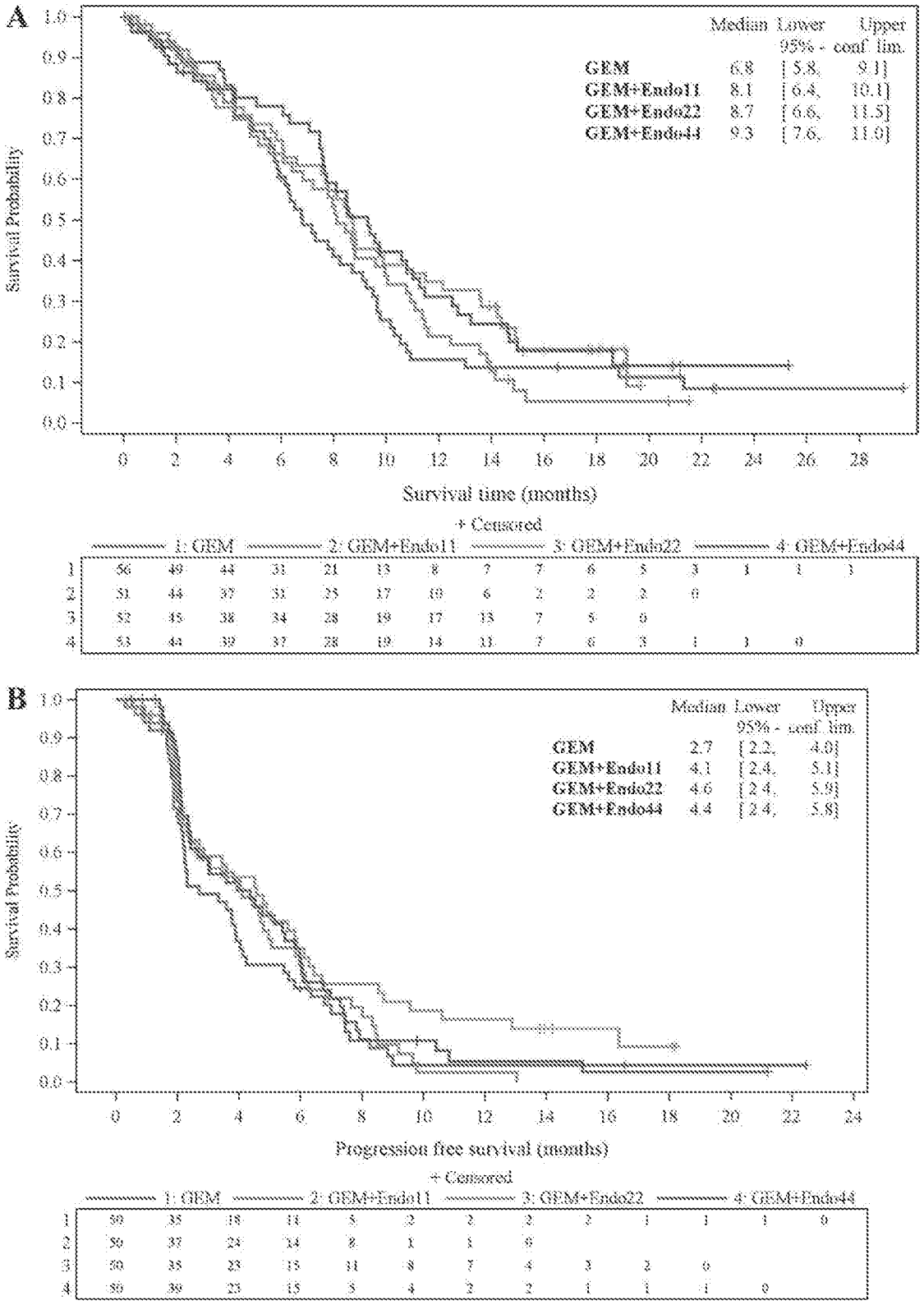

Figure 3. Kaplan–Meier curves for overall survival (A; ITT population) and progression-free survival (B; mITT population). ITT, intent to treat; mITT, modified intent to treat; GEM, gemcitabine; GEM + Endo11, gemcitabine in combination with 11 mg/m^2 liposomal pachitaxel; GEM + Endo22, gemcitabine in combination with 22 mg/m^2 liposomal pachitaxel; GEM + Endo44, gemcitabine in combination with 44 mg/m^2 liposomal pachitaxel.

Median PFS times were longer in the GEM + Endo arms (4.1, 4.6 and 4.4 months for GEM + Endo11, GEM + Endo22 and GEM + Endo44, respectively) compared with the GEM group (2.7 months) (Figure 3B). The corresponding adjusted HRs for

PFS were, respectively, 0.84, 0.58 and 0.74 for the GEM + Endo groups (Table 2). The 95% CIs for all survival results are listed in Table 2.

After the first cycle, tumor response according to RECIST 1.0 criteria has been measured (Table 3). PRs were similar in all study arms. However, compared with 43% of patients in the GEM group, disease control was achieved by 60%, 65% and 52% of patients in the GEM + Endo11, GEM + Endo22 and GEM + Endo44 groups, respectively.

Quality of life and pain score were evaluable in 86% and 72% of patients, respectively. Noteworthy differences in average change from baseline for QLQ-C30, QLQ-PAN26 and VAS were not observed.

Of the 200 patients treated, 56%, 42%, 50% and 54% in the GEM, GEM + Endo11, GEM + Endo22 and GEM + Endo44 groups, respectively, received second-line therapy after discontinuation of study participation at the discretion of the investigator. The most frequently used agents were GEM (38%), 5-fluorouracil (5-FU; 18%), oxaliplatin (11%), calcium folinate (9%) and capecitabine (6%); antitumor therapy agents appeared to be equally distributed across treatment groups.

safety

No unexpected toxic effects have been observed. During the first treatment cycle, severe hematological toxic effects (National Cancer Institute—Common Toxicity Criteria grade 3/4) occurred in 22%, 32% and 40% of patients in the different GEM + Endo groups (11, 22 and 44 mg/m^2, respectively) compared with 24% of the controls (Table 4). Combination of ET and GEM resulted in dose-dependent increase in grade 3/4 thrombocytopenia reaching up to 16% and 14% at the two higher dose levels, albeit without clinical symptoms or bleeding complications. At the highest ET dose level (44 mg/m^2 twice

Table 2. Survival results

	Treatment groups (ITT/mITT population)			
	GEM (*N* = 50/50)	GEM + Endo11 (*N* = 51/50)	GEM + Endo22 (*N* = 52/50)	GEM + Endo44 (*N* = 52/50)
OS (ITT)				
Median (months)	6.8	8.1	8.7	9.3
OS 95% CI	5.8–9.1	6.4–10.1	6.6–11.5	7.6–11.0
HR[a]		0.93	0.69	0.66
HR 95% CI		0.60–1.43	0.44–1.07	0.43–1.03
12-month survival (ITT)				
Survival rate (%)	15	21	35	30
95% CI	6.9–28.1	10.7–35.7	21.7–49.6	17.3–44.9
PFS (mITT)				
Median (months)	2.7	4.1	4.6	4.4
PFS 95% CI	2.2–4.0	2.4–5.1	2.4–5.9	2.4–5.8
HR[a]		0.84	0.58	0.74
HR 95% CI		0.55–1.28	0.38–0.90	0.49–1.13

[a]Relative to GEM monotherapy.

ITT, intent to treat; mITT, modified intent to treat; GEM, gemcitabine; GEM + Endo11, gemcitabine in combination with 11 mg/m^2 liposomal paclitaxel; GEM + Endo22, gemcitabine in combination with 22 mg/m^2 liposomal paclitaxel; GEM + Endo44, gemcitabine in combination with 44 mg/m^2 liposomal paclitaxel; OS, overall survival; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Table 3. Tumor response according to RECIST 1.0

Evaluable for response[a]	Treatment groups (mITT population)			
	GEM (*N* = 50, *n* (%))	GEM + Endo11 (*N* = 50, *n* (%))	GEM + Endo22 (*N* = 52, *n* (%))	GEM + Endo44 (*N* = 50, *n* (%))
Response				
CR	0 (–)	0 (–)	0 (–)	0 (–)
PR	5 (14)	5 (14)	5 (14)	5 (16)
SD	11 (30)	17 (46)	19 (51)	11 (35)
Progressive disease	21 (57)	15 (41)	13 (35)	15 (48)
Disease control (CR + PR + SD)	16 (43)	22 (60)	24 (65)	16 (52)

[a]Reasons for nonevaluability were mainly premature termination and noncompliance with RECIST 1.0 guidelines (change of imaging method, lack of evaluable image).

mITT, modified intent to treat; GEM, gemcitabine; GEM + Endo11, gemcitabine in combination with 11 mg/m^2 liposomal paclitaxel; GEM + Endo22, gemcitabine in combination with 22 mg/m^2 liposomal paclitaxel; GEM + Endo44, gemcitabine in combination with 44 mg/m^2 liposomal paclitaxel; CR, complete response; PR, partial response; SD, stable disease.

Table 4. Adverse events related to any study medication occurring in ≥10 patients (20%) in any individual treatment group during the first treatment cycle

Adverse event	Treatment group (n) / % (numbers)							
	GEM (n = 50)		GEM + Endo11 (n = 50)		GEM + Endo22 (n = 50)		GEM + Endo44 (n = 50)	
	% of patients		% of patients		% of patients		% of patients	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Hematological disorders	48	24	40	22	50	32	66	40
Neutropenia	32	18	24	12	24	16	44	22
Anemia	20	4	8	–	14	4	32	8
Thrombocytopenia	14	2	16	8	28	16	42	14
Leukopenia	18	4	16	10	18	12	24	10
General + administration site disorders	16	4	52	4	56	12	80	40
Chills	4	–	22	–	36	–	52	16
Pyrexia	4	2	16	–	30	6	38	8
Gastrointestinal disorders	30	2	40	4	32	–	56	10
Nausea	22	–	20	–	24	–	28	6
Vomiting	12	2	16	2	10	–	30	4

mITT, modified intent to treat; GEM, gemcitabine; GEM + Endo11, gemcitabine in combination with 11 mg/m^2 liposomal paclitaxel; GEM + Endo22, gemcitabine in combination with 22 mg/m^2 liposomal paclitaxel; GEM + Endo44, gemcitabine in combination with 44 mg/m^2 liposomal paclitaxel.

weekly), increased rates of grade 3/4 neutropenia (22%) and anemia (12%) were observed.

During the first cycle, a total of seven cases of febrile neutropenia were reported in the two higher GEM + Endo dose levels, including four cases of grade 3/4. During additional cycles with GEM + Endo therapy, none was observed.

Infusion-related reactions, predominantly pyrexia and chills, were found to a higher extent in the GEM + Endo groups. The addition of ET to GEM did not increase the known liver toxicity of GEM. In the GEM+ Endo44 arm, one case of peripheral neuropathy was reported in a patient with diabetes but was considered unrelated to study medication.

AEs resulting in discontinuation of study medication were reported in four patients (8%) in the GEM + Endo11 and seven patients (14%) in each of the GEM + Endo22 and GEM + Endo44 groups. During the first cycle, two patients (4%) in each of the GEM + Endo11 and GEM + Endo22 groups and one patient (2%) in the GEM + Endo44 group died, but deaths were considered not related to study medication. During additional cycles, another two patients of the GEM + Endo11 group had severe adverse events with fatal outcome. Both events staphylococcal sepsis and death from unknown cause were considered unlikely to be related to study medication.

discussion

This phase II study examines the safety and efficacy of liposomal paclitaxel in combination with GEM in patients with advanced PDAC. The study was designed as a randomized controlled trial to select the regimen with the best risk-to-benefit ratio, most likely to succeed in phase III. Approximately 20% of patients had locally advanced PDAC and 80% had metastases, with an ECOG PS grade 0–1 in the vast majority and grade 2 in up to 20%, similar to the patient populations in other advanced PDAC trials [5, 22].

For patients with advanced PDAC, chemotherapy with GEM has been the standard therapy with an average survival of ~6 months. To improve survival, several GEM-based combination regimens, including taxanes, have been tested in the past. Only one regimen, GEM–erlotinib [5], achieved a statistically significant but modest survival benefit compared with GEM monotherapy. Meta-analyses indicate, however, that patients may benefit from GEM-based combination chemotherapies [23–25]. Recently, a combination regimen of 5-FU, folinic acid, irinotecan and oxaliplatin (FOLFIRINOX) demonstrated a significant clinically relevant benefit in younger patients with good PS and metastatic disease [26]. In this selected patient group, median survival time increased from 6.8 to 11.1 months, with the 1-year survival rate of 48%.

At 7 weeks of treatment, our results in the GEM + Endo groups show consistent rates of disease control ranging from 52% to 65%, with median PFS between 4.1 and 4.6 months and median OS from 8.1 to 9.3 months. Even though a formal comparative analysis was not foreseen, these numbers compare well with those in the GEM arm, where the disease control rate was 43%, median PFS was 2.7 months and OS was 6.8 months, indicating a reference population with an outcome well within the range of comparable trials [5, 27]. In contrast to the trial with FOLFIRINOX, we also included patients with ECOG PS of two and locally advanced disease. Even though sample sizes are too small to allow formal subgroup analyses, we could not observe differences related to the PS but noticed that patients with locally advanced tumors may benefit most.

A similar formulation of paclitaxel, paclitaxel-loaded polymeric micelles, achieved disease control in 27 of 45 patients (60%), PFS of 2.8 months and OS of 6.5 months when given as monotherapy [11]. The formulation of paclitaxel in nanoparticles with albumin (NP) resulted in disease control in 33 of 49 patients (67%) and an OS of 9 months (preliminary results) when given in combination with GEM [8]. Both studies were conducted as single-arm trials without a control group.

Nevertheless, the results, together with historical data from other trials [28, 29], seem to indicate an effect for the combination of taxanes with standard chemotherapy, which may be further enhanced by novel targeted therapies with a potentially better risk-to-benefit ratio.

The safety and tolerability of GEM in combination with paclitaxel is well known, with grade 3/4 hematologic toxic effects, especially neutropenia, and sensory neuropathies as major dose-limiting side-effects in 34% of the patients with non-small-cell lung cancer [30] and 70% of patients with metastatic breast cancer [31]. Combination of GEM with docetaxel resulted in grade 3/4 neutropenia in 32% of patients with advanced PDAC [28]. In the present trial, severe neutropenia occurred in 12%, 16% and 22% of patients in the different GEM + Endo groups (11, 22 and 44 mg/m^2, respectively). Grade 3/4 febrile neutropenia, which is usually of concern in combination therapies with taxanes, was observed in only four patients. No treatment-related neuropathy has been reported. This compares favorable with the trials with FOLFIRINOX or the trials investigating GPM and NP, agents with a similar chemotherapeutic backbone, where grade 3/4 neutropenia and neuropathies were frequent (FOLFIRINOX: 46% and 9%, respectively; GPM: 40% and 13.3%, respectively; NP: >20% neutropenia, no numbers for neuropathies, respectively) [8, 11], probably due to the different treatment regimens using less frequent applications at higher paclitaxel doses. The primary toxic effects of ET were infusion-related reactions associated with pyrexia or chills, mostly of mild or moderate severity, usually managed by postponement of therapy or symptomatic treatment.

There is still limited understanding of the complex modifications contributing to the aggressiveness of PDAC. Pancreatic tumors are characterized by an abundant fibrous reaction and multiple genetic alterations and epigenetic changes [32]. Attempts to develop targeted therapies, such as inhibition of metalloproteases [33] or inhibition of membrane binding of K-Ras by farnesyltransferase inhibitors [34], have largely been to no avail. Conflicting data indicate that the epidermal growth factor receptor mAb cetuximab [35] is not effective but that inhibition of its tyrosine kinase activity with erlotinib shows a moderate benefit [5]. This effect may be further increased by combination with the vascular endothelial growth factor (VEGF) inhibitor bevacizumab, which led to a nonsignificant increase in median OS from 6.0 to 7.1 months in a large phase III trial with a significant 1-month benefit in PFS (4.6 versus 3.6 months) [36]. Again, other VEGF pathway-directed agents like the oral VEGF inhibitor axitinib [37] did not meet their primary end points, indicating a complex and not well-understood role for the VEGF/vascular endothelial growth factor receptor pathway and its role for tumor microenvironment. Indeed, the abundant fibrous desmoplasia in pancreatic tumors is hypothesized to be one of the major therapeutic challenges in their treatment [38, 39]. In addition to its role as a barrier in terms of drug delivery to the tumor cells, desmoplasia may play a crucial role for tumor growth and invasion [40].

The mechanism of action of ET (Figure 1) likely involves selective targeting of the drug to tumor endothelial cells [23–25]. Since combination of GEM with ET resulted in improved survival time, it might overcome these challenges by altering vessel leakiness and thereby achieving enhanced drug delivery compared with conventional therapies [19, 20, 41, 42].

conclusions

This study indicates that ET in combination with GEM is well tolerated and may prolong survival, with dose level of 22 mg/m^2 ET achieving the best risk-to-benefit ratio. The 12-month OS rate of 35% in the whole population would be a clinically meaningful improvement if these results could be confirmed in the planned phase III trial. Because of its low toxicity, ET–GEM would be well suited as backbone for additional agents in patients who do not qualify for FOLFIRINOX.

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disclosure

JML and MPL have advisory relationships with MediGene AG. In addition, JML has received honoraria from MediGene AG. All remaining authors have declared no conflicts of interest.

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2365 POSTER

Nanoliposomal irinotecan (MM-398, nal-IRI) population pharmacokinetics (PK) and its association with efficacy and safety in patients with solid tumors based on the phase 3 study NAPOLI-1 and five phase 1 and 2 studies

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Background: NAPOLI-1, a global, phase 3 randomized trial in 417 patients with metastatic pancreatic cancer previously treated with gemcitabine evaluating a nanoliposomal formulation of irinotecan (nal-IRI) with or without 5-fluorouracil and leucovorin (5FU/LV). Nal-IRI+5FU/LV vs 5FU/LV significantly improved OS (median 6.1m vs 4.2m; HR = 0.67; P = 0.0008). The most frequent grade 3+ AEs were neutropenia, fatigue, diarrhea, and vomiting. Mouse xenograft models have shown that unlike free irinotecan, nal-IRI prolonged circulation and increased intratumoral concentration of irinotecan (IRI) and SN-38 (active metabolite of irinotecan) corresponding with antitumor activity. We report population PK of total irinotecan (IRI) and SN-38 and their associations with safety in patients from 6 studies and with efficacy in patients from NAPOLI-1.

Methods: PK analysis was performed for IRI and SN-38 in 353 patients from 6 studies of nal-IRI 60–80 mg/m^2 and also administered alone (120 mg/m^2 q3 weeks) or nal-IRI (80 mg/m^2 q2 weeks) + 5FU/LV in NAPOLI-1. Covariates included body surface area (BSA), UGT1A1*28 7/7, bilirubin, liver metastasis, AST, ALT, albumin, CrCl, gender, ethnicity, age, and external factors (co-treatment with 5FU/LV, manufacturing site). Relationships of PK-efficacy (OS, PFS, ORR) were evaluated for each treatment arm in NAPOLI-1 and PK-safety (neutropenia, diarrhea, and anemia) were evaluated from all 6 studies.

Results: In NAPOLI-1, compared to patients treated with 120 mg/m^2 q3 weeks, nal-IRI 80 mg/m^2 q2 weeks had similar C_{avg}, but 1.5-fold lower C_{max} for both IRI and SN-38. In patients treated with nal-IRI+5FU/LV, higher SN-38 C_{avg} was associated with improved OS, PFS, and ORR. In a pooled analysis of 353 patients from 6 studies, SN-38 C_{max} was associated with grade 3+ neutropenia and IRI C_{max} was associated with grade 3+ diarrhea. Based on PK analysis of 353 patients, significant covariates to IRI were ethnicity and BSA and covariates to SN-38 were baseline bilirubin and BSA. No other covariates, including UGT1A1*28, were significant. When nal-IRI exposures and incidence rates of AEs were predicted from a dose of 80 mg/m^2, Asians (43%) had a 0.5 x lower IRI C_{max} than Caucasians (5% lower predicted grade 3+ diarrhea), but a 1.5 x higher SN-38 C_{max} than Caucasians (7% higher predicted grade 3+ neutropenia). Patients with bilirubin 1.0–2.0 mg/dL (n = 20) had a 1.4 x higher SN-38 C_{max} vs patients with bilirubin <1.0 mg/dL.

Conclusions: Lower-dose nal-IRI given more frequently was predicted to have similar C_{avg} and lower C_{max}. IRI C_{max} was associated with diarrhea and SN-38 C_{max} with neutropenia. Asians had lower IRI, but higher SN-38. Increasing baseline bilirubin was associated with higher SN-38 levels. Association between SN-38 and efficacy endpoints is consistent with the preclinical observation that nal-IRI increased prolonged intratumoral delivery.

Conflict of interest: *Ownership: Merrimack employees (JK, BE, EB, BA). Advisory Board: JC (Eli Lilly). BM (Eli Lilly, Roche). Corporate-sponsored Research: WWM (Merrimack). JOP (GSK, Sanofi).*

2366 POSTER

Metronomic capecitabine and bevacizumab is an active combination in patients with relapsed peritoneal pseudomyxoma

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Background: The standard treatment of peritoneal pseudomyxoma (PMP) is based on cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC). The establishment of newer systemic treatments is an unmet clinical need for unresectable or relapsed PMP, which is traditionally considerered chemoresistant due to low proliferation index and malignant potential. We previously published data on promising activity and efficacy of FOLFOX-4 regimen in these orphan disease, highlighting that modern chemotherapy may improve outcomes. The aim of the present study was to assess the efficacy and safety of chemotherapy with metronomic capecitabine and bevacizumab in relapsed PMP.

Material and Methods: Patients were included in an open-label, monoinstitutional study and treated with metronomic capecitabine at the daily oral dose of 625 mg/mq b.i.d. and intravenous bevacizumab at the dose of 7,5 mg/Kg every 3 weeks, until progressive disease or unacceptable toxicity. All patients were relapsed after CRS and HIPEC; six (43%) patients received one prior treatment line with FOLFOX-4 regimen.
Ion Torrent® next generation sequencing technology ("Hot-spot Cancer Panel") was used to used to obtain most of the molecular data. MGMT and MET status were determined respectively by methylation-specific PCR and in situ hybridization (ISH) respectively.

Results: Fourteen patients were included from February 2014 up today. Three patients are too early for response assessment. Partial response was observed in 2 (18%) patients, progressive disease in 2 (18%), while radiological stable disease in all remaining 7 (64%). Treatment was associated with a significant decrease of sierological markers (CEA, Ca19.9, and/or Ca125) in all the evaluable patients except for the two patients who had progressive disease. Median PFS was 7.3 months, while overall survival data are not mature. Safety data for this combination were consistent with the literature, only one severe adverse event was observed (hand-foot syndrome G3).
Next generation sequencing was successfully performed in 14 samples. KRAS mutations were found in 13 (92%) cases; GNAS mutations in 7 (50%), always coupled with KRAS mutation; also rare mutations were discovered: HNF1A in one case, FGF3 and LKB1 mutations in another case; TP53 mutation in two cases. MGMT promoter methylation was found in 3 patients (23%). MET amplifications were never observed.

Conclusions: Metronomic capecitabine and bevacizumab combination is tolerable and active in patients with PMP when disease is relapsed after CRS and HIPEC. The identification of predictive biomarkers is a priority for the development of evidence-based treatment strategies for this orphan disease.

No conflict of interest.

2367 POSTER

Second line treatments (slts) in metastatic, pre-treated gastric cancer. Pooled analysis of randomized clinical trials

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Background: To assess the role of SLTs in the treatment of metastatic, pre-treated gastric cancer we have recently concluded a systematic review of literature with meta-analysis of randomized clinical trials.

Material and Methods: A systematic review of literature in the MEDLINE and EMBASE data bases from 1966 to 2014 was independently performed by two authors (DT and ET). All the randomized phase III trials comparing any SLTs with Best Supportive Care (BSC) in the treatment of metastatic, pre-treated gastric cancer were considered eligible and included into the pooled analysis. Overall Survival was the primary end point of the analysis; overall survival in the groups of patients treated with chemotherapy or biological agents as SLTs were the secondary ones. Primary and secondary end points were assessed as Hazard Ratio (HR) and 95% Confidence Interval (95CI). Heterogeneity between the trials was assessed

733P

NAPOLI-1 phase 3 trial outcomes by prior surgery, and disease stage, in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC)

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INTRODUCTION

- The topoisomerase I inhibitor, liposomal irinotecan (nal-IRI), is approved in many countries in combination with 5-fluorouracil (5-FU) and leucovorin (LV) for treatment of patients with metastatic pancreatic adenocarcinoma that had progressed after gemcitabine-based therapy.[1,2]
- The innovative liposomal formulation of irinotecan exhibits extended circulation and enhanced intratumoural drug deposition vs. non-liposomal irinotecan.[2] This allows for increased and prolonged exposure of the tumour to the active metabolite of irinotecan, SN-38, following local activation.[2]
- In the global, phase 3 NAPOLI-1 trial, nal-IRI+5-FU/LV significantly improved survival in patients with mPDAC that had progressed after gemcitabine-based therapy.[3]
  - nal-IRI+5-FU/LV is recommended as an option in the second-line setting for patients with mPDAC with disease progression after treatment with gemcitabine-based (category 1) or fluoropyrimidine-based (category 2A) therapy.[4]
  - nal-IRI monotherapy was given at 120 mg/m^2 (irinotecan hydrochloride trihydrate salt, equivalent to 100 mg/m^2 irinotecan free base) every three weeks, the combination arm comprised nal-IRI 80 mg/m^2 (irinotecan hydrochloride trihydrate salt, equivalent to 70 mg/m^2 irinotecan free base), 5-FU 2,400 mg/m^2, and LV 400 mg/m^2 every two weeks, and the control included 5-FU 2,000 mg/m^2 and LV 200 mg/m^2 once weekly for the first four weeks of a six-week cycle.[3]
  - ESMO clinical practice guidelines state that nal-IRI+5-FU/LV may be a suitable second-line treatment in patients with disease that progressed on gemcitabine-based therapy and who are fit, taking into account the risk/benefit ratio.[5,6]
  - A recent ASCO clinical practise guideline update includes nal-IRI+5-FU/LV as preferred second-line treatment option for patients who received gemcitabine+nab-paclitaxel in the first line, are fit and have a favourable comorbidity profile.[7]
- Surgical tumour resection is known to improve survival outcomes in patients with metastatic pancreatic cancer, and adjuvant therapy following resection can enhance this.[8]
- There is a clear association from patients with pancreatic cancer between disease stage at diagnosis and survival rates from diagnosis.[9]

METHODS

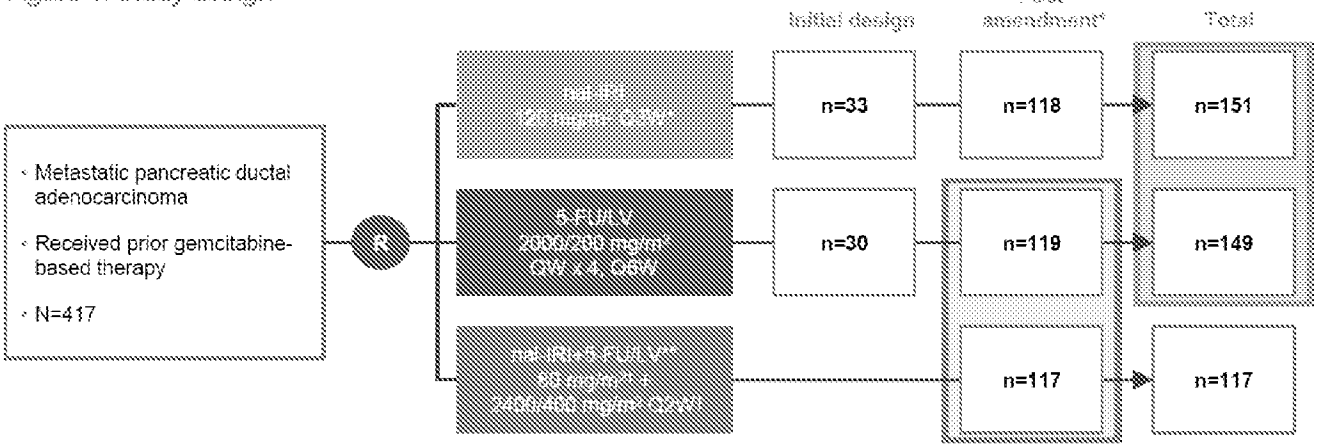
Objectives and subgroup analysis

- These *post-hoc* subgroup analyses of the NAPOLI-1 trial investigated study outcomes according to whether patients had undergone tumour resection prior to study entry, and also according to disease stage at diagnosis (stage IIA, IIB, III and IV).
- The effect of these parameters was assessed in both the overall intent-to-treat (ITT) population and in patients who had received treatment with either nal-IRI+5-FU/LV or 5-FU/LV only.
- Safety of the study drug treatments was also evaluated in these subgroups.

STUDY DESIGN

- NAPOLI-1 was an international, open-label, randomized, phase 3 trial (Figure 1).

Figure 1. Study design[a]



[a]nal-IRI 120 mg/m² irinotecan hydrochloride trihydrate salt, equivalent to 100 mg/m² irinotecan free base. [b]nal-IRI 80 mg/m² irinotecan hydrochloride trihydrate salt, equivalent to 70 mg/m² irinotecan free base. [c]The study was amended to add the nal-IRI+5-FU/LV arm once safety data on the combination became available. Only those patients enrolled in the 5-FU/LV arm after the amendment (n=119) were used as the control for the combination arm.
(Trial registered at ClinicalTrials.gov, NCT01494506).

Q2W, every two weeks; Q3W, every three weeks; Q6W, every six weeks.

Key inclusion criteria

- Adults ≥18 years of age.
- Histologically or cytologically confirmed PDAC.
- Documented measurable or non-measurable distant metastatic disease.
- Disease progression after prior gemcitabine or gemcitabine-containing therapy in a neoadjuvant, adjuvant (only if distant metastases occurred within 6 months of completing adjuvant therapy), locally advanced, or metastatic setting.
- Karnofsky performance status (KPS) score ≥70.
- Adequate hematologic (including absolute neutrophil count >1.5×10^9 cells/L), hepatic (including normal serum total bilirubin and albumin levels ≥30 g/L), and renal function.

Key exclusion criterion

- Clinically significant gastrointestinal disorders.

RESULTS

- In the ITT population (N=417), 142 patients had undergone prior tumour resection and 275 had not.
  - Of the patients who had undergone resection, 40 were treated with nal-IRI+5-FU/LV and 43 with 5-FU/LV (Table 1).
- A greater number of patients in the ITT population had stage IV disease at diagnosis (n=213) than stages IIA (n=36), IIB (n=77) and III (n=75) (Table 1).
- There was some variation in ethnicity, KPS score, primary tumour location and baseline CA19-9 levels between patients who had and had not undergone tumour resection.
  - Similar variations were observed between patients when categorised by disease stage at diagnosis, which, together with low patient numbers in the included subgroups, should be taken into account when interpreting the results of these analyses.

Table 1. Patient demographics and baseline characteristics (ITT population)

	Overall treatment groups		Prior tumour resection				Disease stage at diagnosis							
			Yes		No		IIA		IIB		III		IV	
	Comb (n=117)	Ctrl (n=119)	Comb (n=40)	Ctrl (n=43)	Comb (n=77)	Ctrl (n=76)	Comb (n=6)	Ctrl (n=9)	Comb (n=26)	Ctrl (n=22)	Comb (n=21)	Ctrl (n=19)	Comb (n=61)	Ctrl (n=62)
Gender														
Female, %	41	44	40	47	42	42	17	33	50	50	48	63	38	39
Male, %	59	56	60	53	58	58	83	67	50	50	52	37	62	61
Median age, years Min–Max	63.0 41–81	62.0 34–80	58.5 43–81	61.0 42–80	66.0 41–80	62.0 34–80	56.0 47–66	64.0 44–74	59.0 43–78	60.0 42–77	64.0 46–81	64.0 53–80	64.0 41–80	61.0 34–80
Ethnicity, %														
Caucasian	52	64	43	67	71	62	67	56	50	64	67	74	64	60
Black or African American	3	3	3	5	4	1	0	0	0	0	5	11	5	2
Asian	29	30	50	26	18	33	33	33	42	32	29	5	23	37
Other	6	3	5	2	6	4	0	11	8	5	0	0	6	2

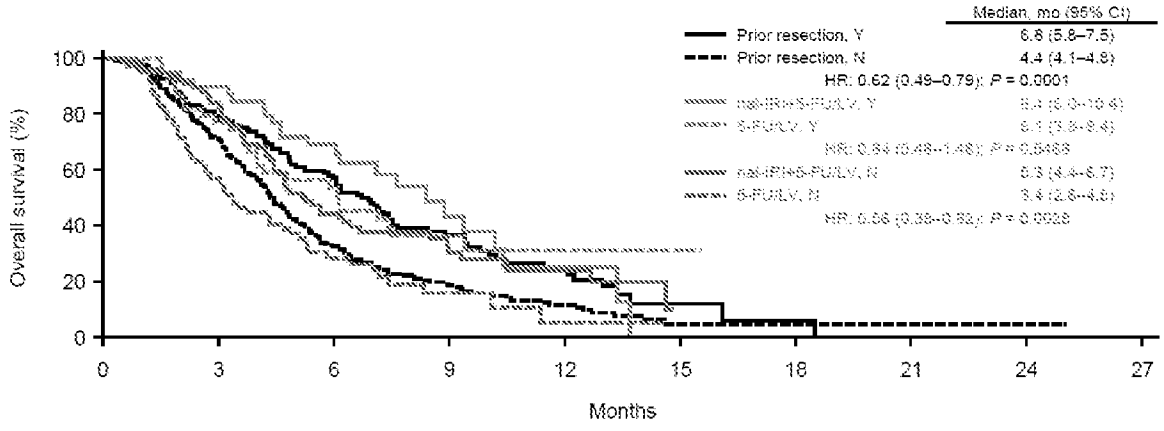
KPS Score, %														
90–100	59	46	53	58	57	42	33	56	65	59	67	53	52	48
70–80	38	51	35	42	40	57	17	44	35	41	29	47	44	50
50–60	3	0	3	0	3	0	0	0	0	0	5	0	3	0
Measurable metastatic lesions at baseline, %														
1	15	19	20	23	14	16	17	44	23	9	19	32	11	16
2	42	49	40	44	43	51	50	44	54	59	33	37	41	48
3	19	13	18	19	19	9	0	0	15	14	5	5	23	15
>3	6	7	8	5	5	8	0	11	0	5	0	5	8	10
Primary tumour location, %														
Head only	60	55	73	77	53	42	50	67	69	77	61	53	48	44
Body only	10	16	8	9	12	20	0	22	12	18	14	16	10	16
Tail only	12	16	10	9	13	20	0	11	19	0	0	5	15	27
Locations incl. head	5	3	3	0	6	5	17	0	0	0	0	11	8	3
Locations excl. head	8	8	5	5	9	11	17	0	0	5	5	11	11	8
Liver lesions at baseline,*, %	64	70	55	74	69	67	67	67	58	82	48	53	74	69
Median baseline CA19-9, U/mL	1278.0	1292.0	1881.0	480.0	631.0	2227.0	1278.0	315.0	3297.0	874.0	238.0	496.5	1092.0	2561.0
Median baseline albumin, g/dL	n=114 4.1	n=114 4.0	n=38 4.1	n=41 4.2	n=76 4.1	n=75 3.9	n=6 4.1	n=9 4.1	n=25 4.1	n=13 4.2	n=20 4.0	n=19 4.0	n=60 4.0	n=62 3.9

*Lesion locations based on RECIST v1.1 guidelines. Includes all measurable and non-measurable lesions; includes all metastatic and non-metastatic lesions. Patients may be included in more than one category. Comb, nal-IRI+5-FU/LV combination therapy; Ctrl, 5-FU/LV control for combination arm; ITT, intent-to-treat; KPS, Karnofsky Performance Status; Max, maximum age; Min, minimum age.

Impact of prior tumour resection on overall survival after trial inclusion in the NAPOLI-1 ITT population and nal-IRI+5-FU/LV arm

- Median overall survival (OS) after trial inclusion was increased in patients in the ITT population who had undergone tumour resection prior to the study compared with those who had not (6.8 vs. 4.4 months, hazard ratio [HR]=0.62, *P*=0.0001; Table 2, Figure 2).
- Patients treated with nal-IRI+5-FU/LV had increased OS compared with patients treated with 5-FU/LV only, regardless of whether they had undergone prior tumour resection, although the increase was only significant in patients who had not undergone prior tumour resection (Table 2).

Figure 2: Overall survival after trial inclusion of patients with and without prior tumour resection in the NAPOLI-1 ITT population and nal-IRI+5-FU/LV arm



Patients at risk (n):

Prior resection, Y	142	108	69	28	13	3	1	0	0	0
Prior resection, N	275	157	76	29	14	2	2	1	1	0
nal-IRI+5-FU/LV, Y	43	33	22	8	3	0	0	0	0	0
5-FU/LV, Y	43	30	28	8	6	1	0	0	0	0
nal-IRI+5-FU/LV, N	77	52	28	12	6	0	0	0	0	0
5-FU/LV, N	78	38	14	3	1	0	0	0	0	0

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months; N, no prior tumour resection; Y, prior tumour resection.

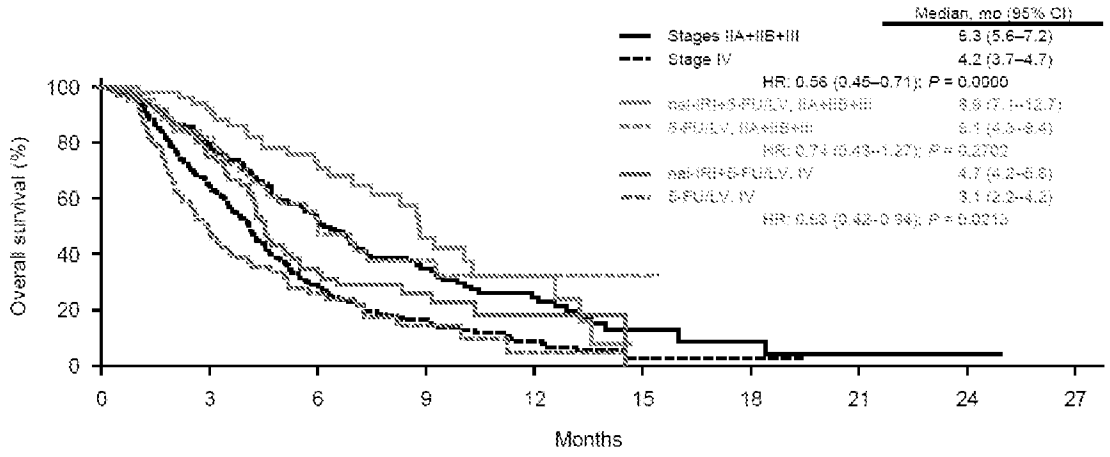
Impact of prior tumour resection on progression-free survival after trial inclusion in the NAPOLI-1 ITT population and nal-IRI+5-FU/LV arm

- An increase in progression-free survival (PFS) after trial inclusion was observed in patients who had undergone tumour resection vs. those who had not in the overall ITT population, however this increase was not significant (2.7 vs. 2.2 months, HR=0.84, *P*=0.1294; Table 2).
- A significant difference in PFS was observed in patients who had not undergone prior tumour resection between nal-IRI+5-FU/LV and 5-FU/LV arms (3.3 vs 1.4 months, HR=0.47, *P*=0.0001).
  - A non-significant difference was observed between the two arms in patients who had undergone prior tumour resection (2.8 vs 2.6 months, HR=0.72).

Impact of disease stage at diagnosis on overall survival after trial inclusion in the NAPOLI-1 ITT population and nal-IRI+5-FU/LV arm

- In the ITT population, OS was significantly increased in patients with disease stage IIA (6.4 months, HR=0.59, *P*=0.013), IIB (6.1 months, HR=0.54, *P*<0.001), and III (6.3 months, HR=0.57, *P*<0.001) vs. stage IV (4.2 months) at diagnosis.
- Similar increases were observed across patient subgroups in the nal-IRI+5-FU/LV treatment arm: stage IIA (8.6 months, HR=0.63, *P*=0.390), IIB (10.2 months, HR=0.50, *P*=0.024) and III (9.0 months, HR=0.43, *P*=0.021) vs. stage IV (4.7 months).

Figure 3: Overall survival after trial inclusion in the NAPOLI-1 ITT population and nal-IRI+5-FU/LV arm by disease stage at diagnosis



Patients at risk (n):

Stages IIA+IIB+III	156	144	85	37	18	4	2	1	1	0
Stage IV	213	142	56	19	9	1	1	0	0	0
nal-IRI+5-FU/LV, IIA+IIB+III	83	47	31	12	4	0	0	0	0	0
5-FU/LV, IIA+IIB+III	80	55	20	6	3	1	0	0	0	0
nal-IRI+5-FU/LV, IV	81	48	19	8	4	0	0	0	0	0
5-FU/LV, IV	69	31	13	3	1	0	0	0	0	0

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months.

Table 2: Efficacy of combination therapy vs. control in prior tumour resection and disease stage at diagnosis subgroups (ITT population)

Prior tumour resection	Overall ITT		Yes*		No*	
	Yes (n=142)	No (n=275)	Comb (n=40)	Ctrl (n=43)	Comb (n=77)	Ctrl (n=76)
Median OS, months 95% CI	6.8 5.8–7.5	4.4 4.1–4.8	8.4 6.0–10.4	6.1 3.6–9.4	5.3 4.4–6.7	3.4 2.6–4.8
HR 95% CI *P* value	0.62 0.49, 0.79 0.0001		0.84 0.48, 1.48 0.5468		0.55 0.38, 0.82 0.0028	
Median PFS, months 95% CI	2.7 2.0–3.4	2.2 1.6–2.8	2.8 1.4–7.0	2.6 1.4–4.0	3.3 2.8–4.2	1.4 1.3–1.5
HR 95% CI *P* value	0.84 0.66, 3.42 0.1294		0.72 0.43, 1.23 0.2171		0.47 0.32, 0.68 0.0001	

Disease stage at diagnosis	Stage IIA			Stage IIB		
	All ITT (n=36)	Comb (n=6)	Ctrl (n=9)	All ITT (n=77)	Comb (n=26)	Ctrl (n=22)
Median OS, months 95% CI	6.4 4.8–8.9	8.6 6.4–9.4	6.1 1.7–NR	6.1 4.6–7.5	10.2 6.0–13.7	5.6 3.5–NR
HR† 95% CI *P* value	0.59 0.39–0.90 0.013	0.63 0.23–1.77 0.390	0.42 0.17–1.06 0.070	0.54 0.39–0.75 <0.001	0.50 0.27–0.91 0.024	0.43 0.22–0.83 0.012

Disease stage at diagnosis	Stage III			Stage IV		
	All ITT (n=75)	Comb (n=21)	Ctrl (n=19)	All ITT (n=213)	Comb (n=61)	Ctrl (n=62)
Median OS, months (95% CI)	6.3 5.0–4.3	9.0 4.2–NR	7.5 3.4–9.4	4.2 3.7–4.7	4.7 4.2–5.6	3.1 2.2–4.2
HR† (95% CI) *P* value	0.57 0.43–0.78 <0.001	0.43 0.21–0.88 0.021	0.49 0.25–0.96 0.039	–	–	–

*Comparison of treatments: †vs Stage IV
CI, confidence interval; Comb, nal-IRI+5-FU/LV combination therapy; Ctrl, 5-FU/LV control for combination arm; HR, hazard ratio; ITT, intent-to-treat; NR, not reached; OS, overall survival; PFS, progression-free survival.

Safety and Dose Modifications (overall safety population)

- The safety profiles of the prior tumour resection subgroups (yes/no) were generally similar to the overall safety population (Table 3).
  - Small differences in the occurrence of alopecia and decreased neutrophil count were observed in patients who had previously undergone tumour resection vs the overall safety population.
- The frequency of adverse events did not differ significantly from the overall safety population within the disease stage at diagnosis subgroups.

Table 3. Selected adverse events (by prior tumour resection and disease stage at diagnosis subgroups; safety population)

	All safety patients (n=398)	Prior tumour resection		Disease stage at diagnosis			
		Yes (n=136)	No (n=262)	IIA (n=35)	IIB (n=74)	III (n=71)	IV (n=205)
Alopecia, %	14	20	10	26	16	15	8
Febrile neutropenia, %	2	3	2	3	3	1	1
Grade 3/4 non-hematologic AEs in >5% of the overall safety population, %							
Diarrhoea, late onset*	13	16	11	14	12	18	11
Vomiting	9	12	8	3	14	13	8
Nausea	5	5	5	0	4	7	6
Fatigue	8	6	8	6	5	8	9
Asthenia	7	4	8	3	4	11	8
Abdominal pain	7	4	8	3	1	4	10
Grade 3/4 hematologic AEs based on laboratory values, % evaluable patients							
Neutrophil count decreased	13	22	8	17	20	17	8
Haemoglobin decreased	5	5	6	14	3	4	5
Platelet count decreased	1	0	1	0	0	0	1
Drug-related AEs of CTCAE grade 23, %	41	50	36	46	49	52	34

Safety was assessed by grading adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. *>24 h after starting nal-IRI. AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events.

- The number of patients in the overall safety population requiring a dose modification due to a treatment-emergent adverse event (TEAE) during the study was similar regardless of prior tumour resection and disease stage at diagnosis (Table 4).
- Although dose modifications were more frequent in the nal-IRI+5-FU/LV treatment arm than in the overall safety population, the number of patients with TEAEs leading to discontinuation were generally similar between the nal-IRI+5-FU/LV treatment arm and the overall safety population (data not shown).

Table 4. Dose modifications due to prior treatment, duration and disease stage at diagnosis subgroups (safety population)

	All safety patients (n=398)	Prior tumour resection		Disease stage at diagnosis			
		Yes (n=136)	No (n=262)	IIA (n=35)	IIB (n=74)	III (n=71)	IV (n=205)
Patients with TEAE leading to any dose modification, %	53	57	51	51	62	63	47
Patients with TEAE resulting in dose delayed,* %	41	46	39	37	47	51	38
Patients with TEAE resulting in dose reduction,† (%)	23	29	19	23	28	31	17
Patients with TEAEs leading to treatment discontinuation, %	10	7	11	11	16	10	8

TEAEs are events that occurred or worsened on or after the day of first dose of the study drug and within 30 days after last administration of study drug. *TEAEs with action taken as: dose not given or infusion interrupted. †TEAEs resulting in dose decreased or slowing infusion rate. TEAE, treatment-emergent adverse event.

CONCLUSIONS

- In the NAPOLI-1 trial, OS and PFS after trial inclusion were higher in patients who had undergone tumour resection prior to the trial compared with patients who had not
  - Consistent increases in OS and PFS were observed regardless of prior tumour resection in patients treated with nal-IRI+5-FU/LV compared with 5-FU/LV only.
- Patients in the ITT population with disease stages IIA, IIB and III at diagnosis had significantly improved OS after trial inclusion vs. those with stage IV disease.
  - Treatment with nal-IRI+5-FU/LV showed a consistent survival benefit across disease stages IIA, IIB and III vs. stage IV.
- A limitation of this study was that patient numbers in the subgroups analysed were low compared to the entire ITT population in the trial.
  - Additionally, there were some variations in patient demographics and baseline characteristics between the subgroups analysed.
- Despite the differences in patient characteristics amongst subgroups, the results of these analyses suggest that tumour resection prior to study entry increases survival after trial inclusion, and that this effect is increased by treatment with nal-IRI+5-FU/LV.
- Our results also suggest that patients with disease stage IIA, IIB and III at diagnosis are likely to survive for longer after trial inclusion than patients with stage IV disease.
  - This effect also appears to be enhanced by nal-IRI+5-FU/LV treatment in these patients.

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Footer

P-150

Prognostic effect of primary tumour location in the NAPOLI-1 phase 3 study in metastatic pancreatic ductal adenocarcinoma (mPDAC)

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INTRODUCTION

- Liposome encapsulation of irinotecan (nal-IRI) allows for extended circulation and boosts intratumoural deposition, prolonging and increasing exposure to its active metabolite, SN-38.[1–3]
- The combination of nal-IRI and 5-fluorouracil/leucovorin (5-FU/LV) is now approved by numerous international regulatory bodies, and has been recommended by international treatment guidelines for patients with mPDAC that progressed after gemcitabine-based therapy.[4,5]
- The phase 3 NAPOLI-1 study previously showed that nal-IRI+5-FU/LV, compared with 5-FU/LV alone
  - extended median overall survival (OS)
    (6.1 vs. 4.2 months; unstratified hazard ratio [HR] = 0.67; $P = 0.0122$).
  - improved median progression-free survival
    (PFS; 3.1 vs. 1.5 months; unstratified HR = 0.56; $P = 0.0001$).[6]
- An analysis of SEER-data (*Surveillance, Epidemiology and End Results Program* by the National Cancer Institute [NCI], USA) revealed a small but significant difference in the 3-year survival rates in patients with the primary tumour location in the body and tail of the pancreas (3.9%) vs. primary tumour location in the head (6.2%).[7]
- It has been suggested that poorer outcomes may be a result of advanced disease, when surgery is no longer beneficial: primary diagnosis of stage IV pancreatic cancer is associated more frequently with the pancreatic body/tail (56–73%) vs. the head (26–39%).[7,8]
- A 5-year survival-rate of 32% (tail) vs. 11% (head) for stage I disease, 12% (tail) vs. 6% (head) for stage II, and 11% (tail) vs. 7% for stage III disease has been reported,8 but these findings were not supported by observational research[9] and other larger studies.[10–14]
- We sought to assess the potential prognostic impact of primary tumour location on outcomes in patients of the NAPOLI-1 study.

METHODS

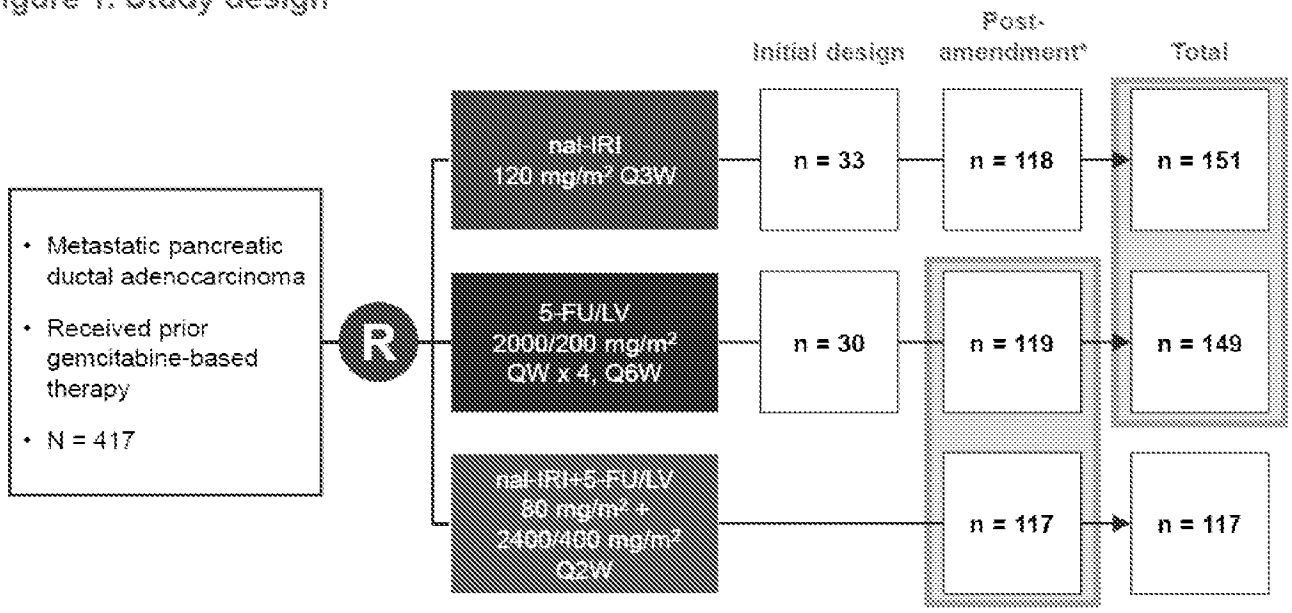
Objectives and subgroup analysis

- This *post-hoc* analysis assesses the overall survival rate of patients in the overall NAPOLI-1 intent-to-treat (ITT) population (n = 417) and those receiving nal-IRI+5-FU/LV Q2W (n = 117) vs. 5-FU/LV 4Q6W (n = 119), within subgroups of patients depending upon the primary tumour location.

STUDY DESIGN

- NAPOLI-1 was an international, open-label, randomized, phase 3 trial (Figure 1).

Figure 1. Study design[1]



*The study was amended to add the nal-IRI+5-FU/LV arm once safety data on the combination became available. Only those patients enrolled in the 5-FU/LV arm after the amendment (n = 119) were used as the control for the combination arm. nal-IRI 80 mg/m² expressed as irinotecan hydrochloride trihydrate salt, equivalent to 70 mg/m² irinotecan free base. (Trial registered at ClinicalTrials.gov, number NCT01494506).

Key inclusion criteria

- Adults ≥18 years of age.
- Histologically or cytologically confirmed PDAC.
- Documented metastatic disease; disease status permitted to be measurable or non-measurable as per RECIST v. 1.1 guidelines.
- Disease progression after prior gemcitabine or gemcitabine-containing therapy in a neoadjuvant, adjuvant (only if distant metastases occurred within 6 months of completing adjuvant therapy), locally advanced, or metastatic setting.
- Karnofsky performance status (KPS) score ≥70.
- Adequate hematologic (including absolute neutrophil count >1.5×10^9 cells/L), hepatic (including normal serum total bilirubin and albumin levels ≥30 g/L), and renal function.

Key exclusion criteria

- Clinically significant gastrointestinal disorders.

RESULTS

Patient characteristics

- Of 417 patients within the ITT population, the primary tumour location was determined to be the pancreatic head only in 239 patients (57%), body only in 54 patients (13%), tail only in 62 patients (15%), multiple locations including head in 17 patients (4%), in multiple locations not including head in 30 patients (7%) and unknown in 15 patients (4%).
- Patient demographics and baseline characteristics were generally similar between treatment arms and within location subgroups (Table 1; patients with unknown primary tumour location excluded).

Table 1. Patient demographics and baseline characteristics (ITT population)

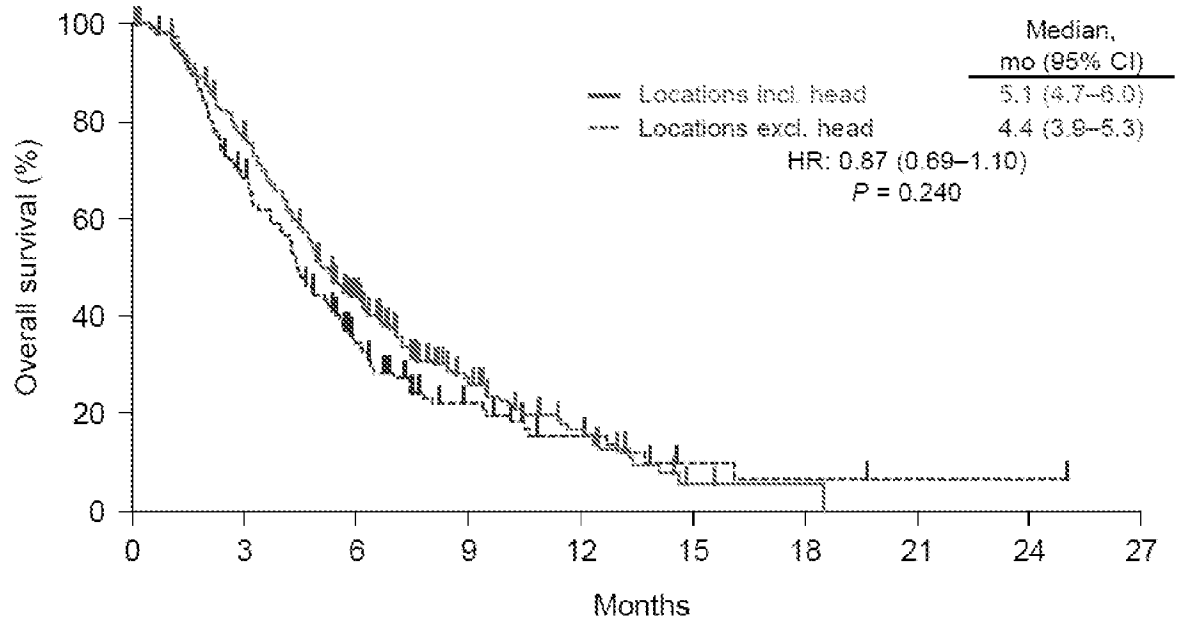
	ITT		Head only		Body only		Tail only		Locations incl. head		Locations excl. head	
	nal-IRI+ 5-FU/LV (n = 117)	5-FU/LV (n = 119)	nal-IRI+ 5-FU/LV (n = 70)	5-FU/LV (n = 65)	nal-IRI+ 5-FU/LV (n = 12)	5-FU/LV (n = 19)	nal-IRI+ 5-FU/LV (n = 14)	5-FU/LV (n = 19)	nal-IRI+ 5-FU/LV (n = 76)	5-FU/LV (n = 69)	nal-IRI+ 5-FU/LV (n = 35)	5-FU/LV (n = 48)
Gender, n (%)												
Female	48 (41)	52 (44)	31 (44)	26 (40)	8 (67)	9 (47)	5 (36)	8 (42)	34 (45)	29 (42)	14 (40)	22 (46)
Male	69 (59)	67 (56)	39 (56)	39 (60)	4 (33)	10 (53)	9 (64)	11 (58)	42 (55)	40 (58)	21 (60)	26 (54)
Age (yrs)												
Median	63.0	62.0	64.0	62.0	66.0	62.0	64.5	62.0	63.5	63.0	63.0	61.5
IQR	57, 70	55, 69	57, 70	54, 69	56, 75	55, 66	54, 66	58, 64	57, 70	55, 69	54, 68	55, 66
Min, Max	41, 81	34, 80	41, 81	39, 80	43, 79	44, 73	49, 80	34, 80	41, 81	39, 80	43, 80	34, 80
Race, n (%)												
White	72 (62)	76 (64)	42 (60)	41 (63)	6 (50)	10 (53)	9 (64)	13 (68)	46 (61)	45 (65)	20 (57)	29 (60)
Black or African American	4 (3)	3 (3)	1 (1)	3 (5)	1 (8)	0	0	0	2 (3)	3 (4)	2 (6)	0
Asian	34 (29)	36 (30)	23 (33)	19 (29)	3 (25)	8 (42)	4 (29)	6 (32)	24 (32)	19 (28)	10 (29)	17 (35)
Other	7 (6)	4 (3)	4 (6)	2 (3)	2 (17)	1 (5)	1 (7)	0	4 (5)	2 (3)	3 (9)	2 (4)
Baseline KPS, n (%)												
90–100	69 (59)	57 (48)	42 (60)	34 (52)	8 (67)	10 (53)	6 (43)	6 (32)	46 (61)	35 (51)	19 (54)	21 (44)
70–80	45 (38)	61 (51)	25 (36)	30 (46)	4 (33)	9 (47)	8 (57)	13 (68)	27 (36)	33 (48)	16 (46)	27 (56)
50–60	3 (3)	0	3 (4)	0	0	0	0	0	3 (4)	0	0	0
Measurable metastatic lesions at baseline, n (%)												
1	19 (16)	22 (18)	10 (14)	10 (15)	3 (25)	3 (16)	4 (29)	7 (37)	10 (13)	10 (14)	8 (23)	11 (23)
2	49 (42)	58 (49)	32 (46)	33 (51)	4 (33)	12 (63)	7 (50)	6 (32)	33 (43)	35 (51)	15 (43)	22 (46)
3	22 (19)	15 (13)	12 (17)	8 (12)	3 (25)	1 (5)	2 (14)	2 (11)	13 (17)	9 (13)	6 (17)	6 (13)
>3	7 (6)	8 (7)	5 (7)	4 (6)	0	0	0	3 (16)	5 (8)	4 (6)	1 (3)	4 (8)
Anatomical location of lesions at baseline, n (%)												
Liver	75 (64)	83 (70)	44 (63)	49 (75)	10 (83)	11 (58)	8 (57)	11 (58)	46 (61)	52 (75)	24 (69)	30 (63)
Baseline CA19-9 (U/mL)												
Median	1278	1292	1137	766	7126	2743	908	1545	783	857	2381	2227
Baseline albumin (g/dL)												
Median	4.1	4.0	4.0	4.0	4.2	4.2	4.2	4.1	4.0	4.0	4.2	4.1

ITT, intent-to-treat; nal-IRI, liposomal irinotecan; 5-FU/LV, 5-fluorouracil and leucovorin; IQR, interquartile range; KPS, Karnofsky performance status.

Overall survival and progression-free survival

- In the overall ITT population, across primary tumour location subgroups, mOS and mPFS, were similar and no clear prognostic signal was detected.
  - Within the different subgroups, OS and PFS were 5.0 and 2.7 months (head only), 5.4 and 2.8 months (body only), 4.3 and 1.7 months (tail only), 5.1 and 2.7 months (locations including the head), and 4.4 and 1.7 months (locations excluding the head).
  - Patients with primary tumour locations including the head had increased OS and PFS vs. patients with primary tumours in locations excluding the head (Figure 2, Figure 3).

Figure 2. Overall survival in patients with primary tumour locations including the pancreatic head vs. excluding the head (ITT population)

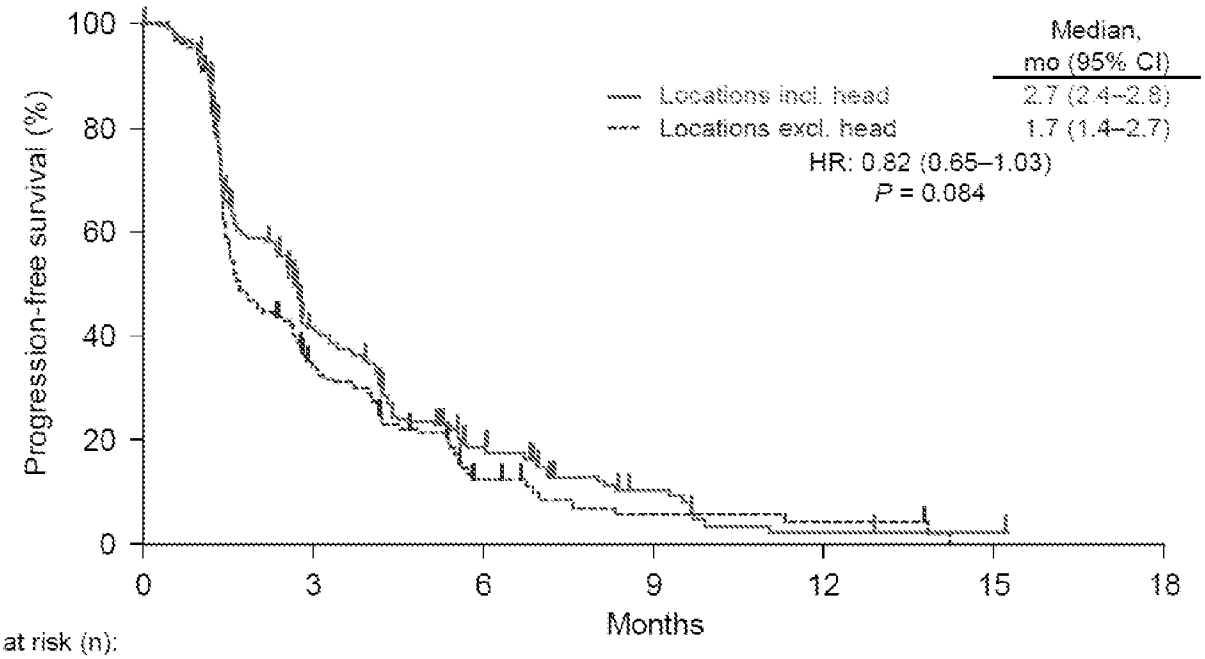


Patients at risk (n):

Locations incl. head 258	189	98	36	17	2	1	0	0	0
Locations excl. head 146	95	40	19	10	3	2	1	1	0

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months.

Figure 3. Progression-free survival in patients with primary tumour locations including the pancreatic head vs. excluding the head (ITT population)



Patients at risk (n):

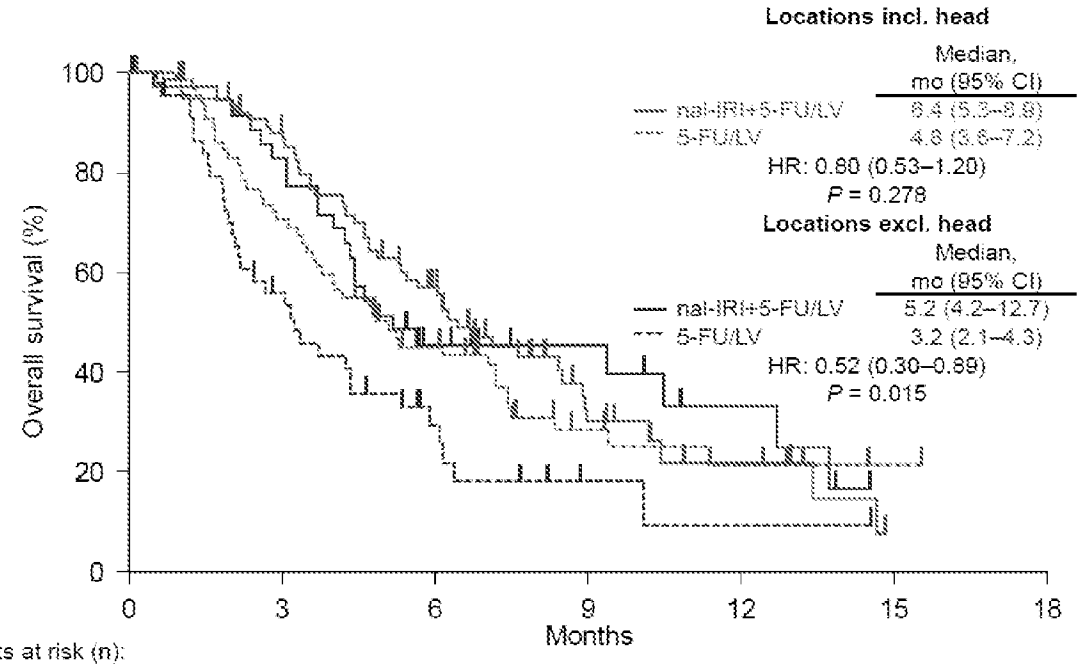
Locations incl. head 258	88	33	10	2	1	0
Locations excl. head 146	40	11	4	3	0	0

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months.

Effect of treatment with nal-IRI+5-FU/LV on survival outcomes in primary tumour location subgroups (ITT population)

- Patients treated with nal-IRI+5-FU/LV were at a reduced risk of mortality compared with patients receiving 5-FU/LV alone (Figure 4, Figure 5, Table 2).
- Across all primary tumour location subgroups, patients treated with nal-IRI+5 FU/LV had increased OS and PFS compared with patients treated with 5-FU/LV (Table 2).
  - HRs for OS were 0.39–0.88, and HRs for PFS were 0.28–0.65 (two groups with n<10 per arm were discounted).

Figure 4. Effect of nal-IRI+5-FU/LV vs. 5-FU/LV on OS in patients with primary tumour locations including the pancreatic head vs. excluding the head (ITT population)

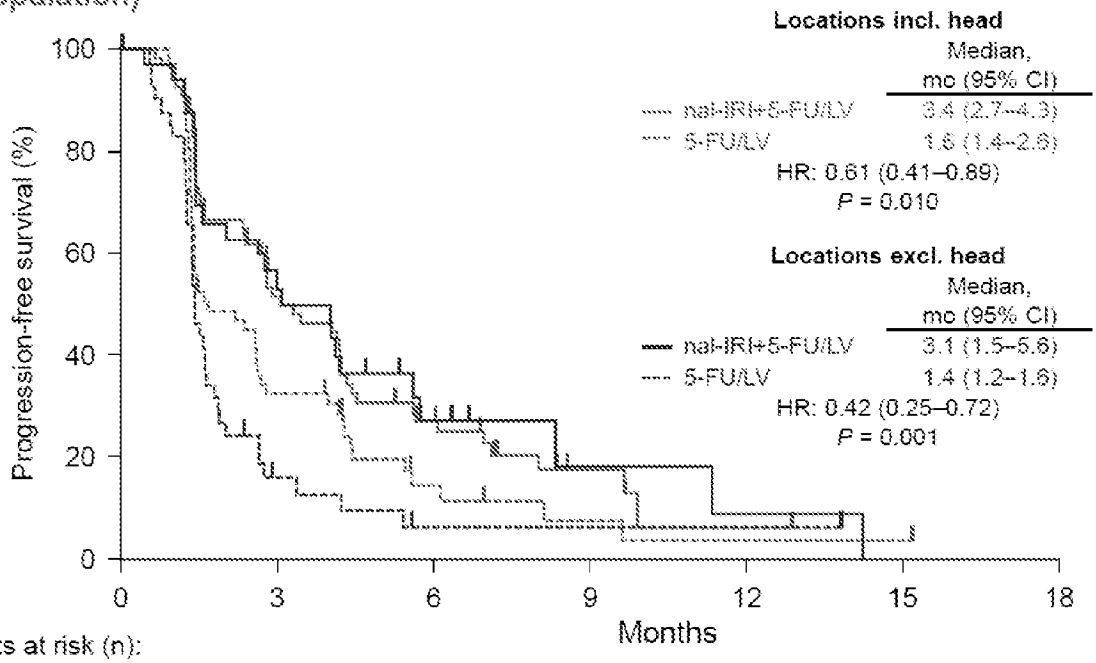


Patients at risk (n):

nal-IRI+5-FU/LV	78	63	36	11	4	0	0
5-FU/LV	69	45	26	9	5	1	0
nal-IRI+5-FU/LV	35	29	12	8	4	0	0
5-FU/LV	48	22	6	2	1	0	0

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months.

Figure 5. Effect of nal-IRI+5-FU/LV vs. 5-FU/LV on PFS in patients with primary tumour locations including the pancreatic head vs. excluding the head (ITT population)



Patients at risk (n):

nal-IRI+5-FU/LV	76	33	17	5	1	0	0
5-FU/LV	69	18	5	2	1	1	0
nal-IRI+5-FU/LV	35	16	5	2	1	0	0
5-FU/LV	48	5	1	1	1	0	0

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months.

Overall response rates and CA19-9 tumour marker response

- Objective response rates (ORRs) were higher in patients treated with nal-IRI+5-FU/LV (16%) compared with 5-FU/LV alone (1%), $P < 0.001$ (Table 2).
  - Higher ORRs were documented for patients treated with nal-IRI+5-FU/LV in each primary tumour location subgroup. Small group sizes and low ORR, however, limit meaningful statistical comparisons beyond the two subgroups that include the head, where $P < 0.001$.
- In the overall ITT population (n = 417), ORRs between primary tumour location subgroups were similar:
  - Head only, 8% (n = 20/239), compared with tail only, 3% (n = 2/62), $P = 0.271$.
  - Head only, 8%, compared with locations excluding the head, 5% (n = 7/146), $P = 0.220$.
- CA19-9 tumour marker responses were found to be higher in patients with the primary tumour location only in the pancreatic body (38%) compared with only in the head (18%; $P = 0.010$ for comparison of head only vs. body only).
  - CA19-9 responses were similar between patients with the primary tumour in the pancreatic head only vs. tail only (18% vs. 17%, $P = 1.000$).
- CA19-9 responses were generally increased in patients receiving nal-IRI+5-FU/LV compared with those receiving 5-FU/LV across primary tumour location subgroups (Table 2) (two groups with n<10 per arm were discounted).

Table 2. Summary of efficacy of nal-IRI+5-FU/LV vs. 5-FU/LV in primary tumour location subgroups (ITT population)

	ITT		Head only		Body only		Tail only		Locations incl. head		Locations excl. head	
	nal-IRI+ 5-FU/LV (n = 117)	5-FU/LV (n = 119)	nal-IRI+ 5-FU/LV (n = 70)	5-FU/LV (n = 65)	nal-IRI+ 5-FU/LV (n = 12)	5-FU/LV (n = 19)	nal-IRI+ 5-FU/LV (n = 14)	5-FU/LV (n = 19)	nal-IRI+ 5-FU/LV (n = 76)	5-FU/LV (n = 69)	nal-IRI+ 5-FU/LV (n = 35)	5-FU/LV (n = 48)
Median OS, mo (95% CI)	6.1 (4.8–8.9)	4.2 (3.3–5.3)	6.2 (4.9–8.5)	5.1 (3.6–7.4)	10.5 (3.1– NR)	4.2 (1.9–10.1)	5.6 (4.0– NR)	3.1 (1.8–5.9)	6.4 (5.3–8.9)	4.8 (3.6–7.2)	5.2 (4.2–12.7)	3.2 (2.1–4.3)
HR (95% CI) *P* value*	0.67 (0.49–0.92) *P* = 0.012		0.88 (0.58–1.34) *P* = 0.552		0.47 (0.16–1.40) *P* = 0.160		0.39 (0.16–0.95) *P* = 0.030		0.80 (0.53–1.20) *P* = 0.276		0.52 (0.30–0.89) *P* = 0.015	
Median PFS, mo (95% CI)	3.1 (2.7–4.2)	1.5 (1.4–1.9)	3.3 (2.4–4.2)	1.7 (1.4–2.6)	4.2 (1.4–8.3)	1.6 (1.2–2.7)	4.1 (1.5–14.2)	1.5 (1.3–1.8)	3.4 (2.7–4.3)	1.6 (1.4–2.6)	3.1 (1.5–5.6)	1.4 (1.2–1.6)
HR (95% CI) *P* value*	0.56 (0.41–0.75) *P* < 0.001		0.65 (0.44–0.97) *P* = 0.033		0.36 (0.14–0.97) *P* = 0.033		0.28 (0.11–0.70) *P* = 0.004		0.61 (0.41–0.89) *P* = 0.010		0.42 (0.25–0.72) *P* = 0.001	
Best overall response												
ORR, n (%)	19 (16)	1 (1)	14 (20)	1 (2)	3 (25)	0	1 (7)	0	15 (20)	1 (1)	4 (11)	0
P value†	*P* < 0.001		*P* < 0.001		*P* = 0.049		*P* = 0.424		*P* < 0.001		*P* = 0.029	
PR, n (%)	19 (16)	1 (1)	14 (20)	1 (2)	3 (25)	0	1 (7)	0	15 (20)	1 (1)	4 (11)	0
SD, n (%)	39 (33)	26 (22)	24 (34)	18 (28)	3 (25)	5 (26)	7 (50)	2 (11)	26 (34)	19 (28)	12 (34)	7 (15)
Non-CR/ non-PD, n (%)	3 (3)	2 (2)	0	2 (3)	1 (8)	0	1 (7)	0	0	2 (3)	2 (6)	0
PD, n (%)	34 (29)	56 (47)	19 (27)	30 (46)	3 (25)	7 (37)	3 (21)	10 (53)	20 (26)	32 (46)	11 (31)	23 (48)
NE, n (%)	22 (19)	34 (29)	13 (19)	14 (22)	2 (17)	7 (37)	2 (14)	7 (37)	15 (20)	15 (22)	6 (17)	18 (38)
CBR, n (%)	58 (50)	27 (23)	38 (54)	19 (29)	6 (50)	5 (26)	8 (57)	2 (11)	41 (54)	20 (29)	16 (46)	7 (15)
CA19-9 response rate, n (%)	27/95 (28)	8/82 (10)	14/53 (26)	4/45 (9)	7/12 (58)	3/11 (27)	2/13 (15)	0/15 (0)	15/57 (26)	5/47 (11)	11/32 (34)	3/33 (9)
P value†	*P* = 0.002		*P* = 0.036		*P* = 0.214		*P* = 0.206		*P* = 0.049		*P* = 0.017	

*Two-sided *P* value from log-rank test. †Two-sided *P* value from pairwise Fisher's exact test. ‡Response defined as 50% reduction in baseline CA19-9 levels, in patients with baseline levels >30 U/ml, and at least one post-baseline CA19-9 measurement.

CBR, clinical benefit rate (CR+PR+SD); CI, confidence interval; CR, complete response; HR, hazard ratio; ITT, intent-to-treat; mo, months; NE, not evaluable; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Safety, dose modifications and treatment exposure

- Safety, drug-related adverse events (AEs) and dose modifications/discontinuations were similar between primary tumour location subgroups, and consistent with the overall NAPOLI 1 study arms.
  - 54% of all patients treated with nal-IRI+5-FU/LV experienced a drug-related AE grade 3 or higher, compared with 16% of patients treated with 5-FU/LV (Table 3).
- The most common grade 3/4 AEs reported in patients receiving nal-IRI+5-FU/LV (Table 3) were decrease in neutrophil count (20% of patients), fatigue (14%), late-onset diarrhoea (13%) and vomiting (11%).

Table 3. Adverse events in patients in primary tumour location subgroups (safety population*)

	Overall safety population		Head only		Body only		Tail only		Locations incl. head		Locations excl. head	
	nal-IRI+ 5-FU/LV (n = 117)	5-FU/LV (n = 105)	nal-IRI+ 5-FU/LV (n = 70)	5-FU/LV (n = 60)	nal-IRI+ 5-FU/LV (n = 13)	5-FU/LV (n = 13)	nal-IRI+ 5-FU/LV (n = 14)	5-FU/LV (n = 18)	nal-IRI+ 5-FU/LV (n = 75)	5-FU/LV (n = 63)	nal-IRI+ 5-FU/LV (n = 36)	5-FU/LV (n = 40)
Alopecia (grade 1/2), n (%)	16 (14)	5 (5)	8 (11)	4 (7)	3 (23)	1 (8)	3 (21)	0	9 (12)	4 (6)	7 (19)	1 (3)
Febrile neutropenia	2 (2)	0	2 (3)	0	0	0	0	0	2 (3)	0	0	0
Grade 3/4 non-haematologic AEs in >5% of the overall safety population, n (%)												
Diarrhoea, late-onset†	15 (13)	6 (6)	8 (11)	4 (7)	3 (23)	1 (8)	1 (7)	0	9 (12)	4 (6)	6 (17)	2 (5)
Vomiting	13 (11)	3 (3)	7 (10)	3 (5)	1 (8)	0	2 (14)	0	7 (9)	3 (5)	5 (14)	0
Nausea	9 (8)	2 (2)	3 (4)	1 (2)	0	0	5 (36)	1 (6)	3 (4)	1 (2)	5 (14)	1 (3)
Fatigue	16 (14)	4 (4)	5 (7)	4 (7)	3 (23)	0	4 (29)	0	6 (8)	4 (6)	9 (25)	0
Asthenia	9 (8)	6 (6)	5 (7)	3 (5)	0	0	2 (14)	1 (6)	5 (7)	3 (5)	3 (8)	3 (8)
Abdominal pain	8 (7)	6 (6)	2 (3)	3 (5)	1 (8)	1 (8)	1 (7)	1 (6)	3 (4)	3 (5)	4 (11)	3 (8)
Grade 3/4 haematologic AEs based on laboratory values,‡ n (%)												
Neutrophil count decreased	23 (20)	3 (3)	15 (22)	2 (3)	3 (23)	1 (8)	3 (23)	0	15 (20)	2 (3)	8 (24)	1 (3)
Haemoglobin decreased	7 (6)	4 (4)	5 (7)	3 (5)	0	0	2 (14)	0	5 (7)	4 (6)	2 (6)	0
Platelet count decreased	2 (2)	0	0	0	0	0	0	0	1 (1)	0	1 (3)	0
Drug-related AE of CTCAE Grade ≥3, %, n (%)	63 (54)	17 (16)	35 (50)	13 (22)	9 (69)	1 (8)	10 (71)	1 (6)	36 (48)	14 (22)	24 (67)	3 (8)

*>24 h after starting nal-IRI. No grade 3/4 early-onset diarrhoea was reported (≤24 h after starting nal-IRI). ‡Includes only patients who had at least one post-baseline assessment.

AE, adverse events; CTCAE, *Common Terminology Criteria for Adverse Events*.

- 71% of patients (83/117) treated with nal-IRI+5-FU/LV required at least some form of dose modification, compared with 35% of patients (37/105) treated with 5-FU/LV (Table 4).
- 11% of patients (13/117) treated with nal-IRI+5-FU/LV required treatment discontinuation, compared with 7% of patients (7/105) treated with 5-FU/LV (Table 4).

Table 4. Dose modifications and treatment exposure in primary tumour location subgroups (safety population)

	Overall safety population		Head only		Body only		Tail only		Locations incl. head		Locations excl. head	
TEAE leading to	nal-IRI+ 5-FU/LV (n = 117)	5-FU/LV (n = 105)	nal-IRI+ 5-FU/LV (n = 70)	5-FU/LV (n = 60)	nal-IRI+ 5-FU/LV (n = 13)	5-FU/LV (n = 13)	nal-IRI+ 5-FU/LV (n = 14)	5-FU/LV (n = 18)	nal-IRI+ 5-FU/LV (n = 75)	5-FU/LV (n = 63)	nal-IRI+ 5-FU/LV (n = 36)	5-FU/LV (n = 40)
Any dose modification, n (%)	83 (71)	37 (35)	49 (70)	22 (37)	11 (85)	4 (31)	10 (71)	6 (33)	53 (71)	23 (37)	27 (75)	13 (33)
Dose delayed,* n (%)	72 (62)	33 (31)	43 (61)	20 (33)	9 (69)	3 (23)	8 (57)	6 (33)	46 (61)	20 (32)	23 (64)	12 (30)
Dose reduction,† n (%)	39 (33)	4 (4)	22 (31)	2 (3)	7 (54)	1 (8)	6 (43)	0	23 (31)	3 (5)	15 (42)	1 (3)
Dose discontinuation, n (%)	13 (11)	7 (7)	8 (11)	4 (7)	1 (8)	2 (15)	1 (7)	0	9 (12)	4 (6)	4 (11)	2 (5)

*Dose not given or infusion interrupted. †Dose decreased or slowing of infusion rate.

Treatment-emergent adverse events (TEAEs) are events that occurred or worsened on or after the day of first dose of the study drug and within 30 days after last administration of study drug.

CONCLUSIONS

- Treatment with nal-IRI in combination with 5-FU/LV in the NAPOLI-1 study has demonstrated clinical benefit and predictable and manageable toxicity in patients with mPDAC previously treated with gemcitabine-based therapy.[5]
- This analysis did not detect a clear prognostic effect of primary tumour location on survival after trial inclusion in patients with mPDAC progressing after gemcitabine-based treatment.
  - 61% of patients had a primary tumour location including the pancreatic head.
  - Patients with primary tumours in the pancreatic head only or locations including the pancreatic head had similar OS and PFS compared with other patients.
- A consistent treatment benefit was shown with nal-IRI+5-FU/LV vs. 5 FU/LV regardless of primary tumour location.

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- Jie Chen (Shire) was responsible for statistical analyses of this *post-hoc* study.
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Presented at the European Society for Medical Oncology 19th World Congress on Gastrointestinal Cancer, Barcelona, Spain, 20–23 June 2018

Prognostic effect of primary tumour location in the NAPOLI-1 phase 3 study in metastatic pancreatic ductal adenocarcinoma (mPDAC)

[redacted]

Presented at the European Society for Medical Oncology (ESMO) Congress on Gastrointestinal Cancer, Barcelona, Spain, 29–31 January 2018

Selected subgroup analyses of liposomal irinotecan in patients with metastatic pancreatic ductal adenocarcinoma in the global NAPOLI-1 phase III trial

[redacted]

Presented at the European Society for Medical Oncology 20th World Congress on Gastrointestinal Cancer, Barcelona, Spain, 20 – 23 June 2018

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- Floris A de Jong:
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- Other authors have nothing to disclose

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- Jie Chen (Shire) was responsible for statistical analyses of these *post-hoc* studies.
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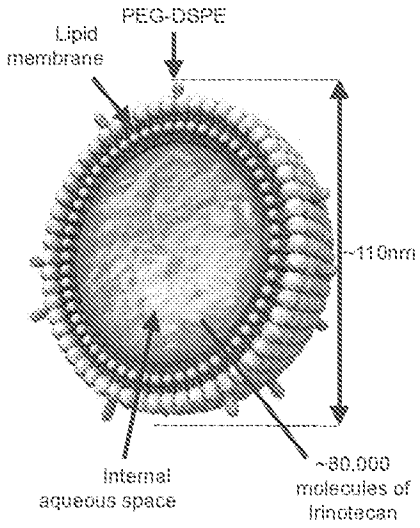
Introduction

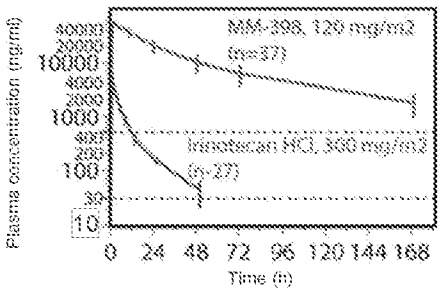
- nal-IRI is an innovative liposomal formulation of irinotecan for intravenous use[1–3]
- The liposomal formulation protects the irinotecan payload from premature metabolism and exhibits enhanced intratumoural drug deposition vs. non-liposomal irinotecan[1–3]



1. Roy AC, et al. Ann Oncol. 2013;24:1567;
2. Kalra AV, et al. Cancer Res. 2014;72:7003;
3.Ramanathan RK, et al. Annual Meeting AACR; April 5-9, 2014; San Diego, CA. abstract CT224 (and poster)

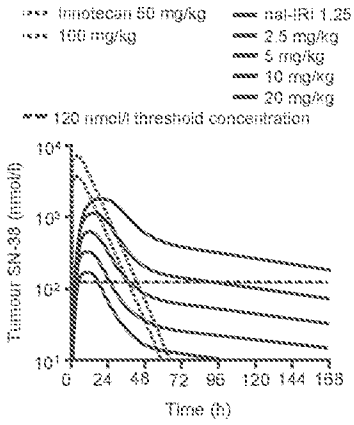
nal-IRI pharmacokinetics and preclinical activity vs. non-liposomal irinotecan

Total irinotecan[1]



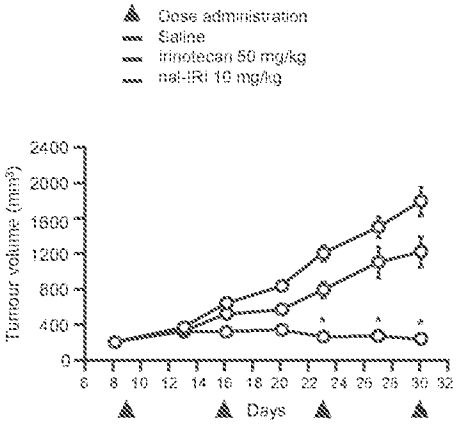
- Higher plasma exposure with nal-IRI vs. non-liposomal irinotecan in patients with gastric cancer
- $AUC_{0-\infty}$ 46-fold increased
- C_{max} 13.4-fold increased
- 42% of encapsulated payload remained encapsulated

Tumour exposure to SN-38[2]



- Preclinical studies demonstrated that nal-IRI increases and prolongs tumour exposure to the active metabolite SN-38 vs. non-liposomal irinotecan

HT-29 mouse xenograft model[3]



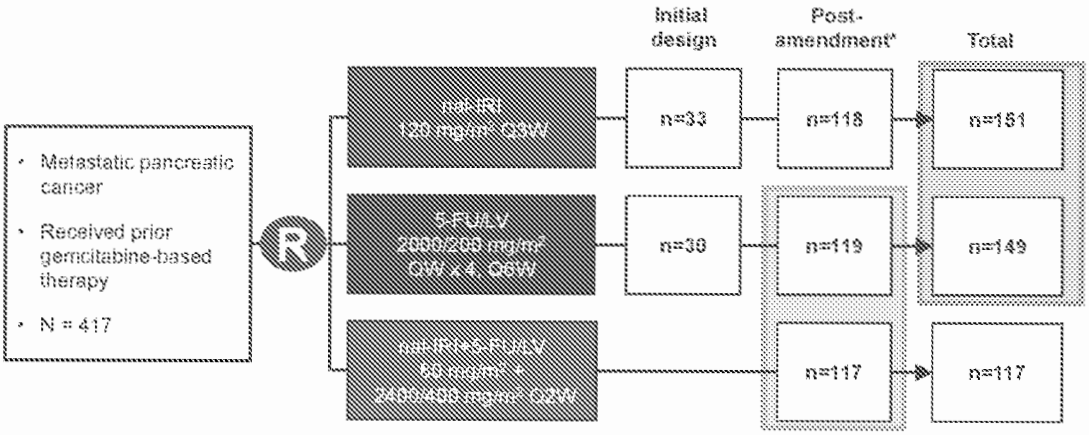
- nal-IRI significantly and substantially retarded tumour growth in an HT-29 mouse xenograft model

*P <0.05 vs. saline and IRI

1. Total irinotecan: Supplementary Figure S2, Adiwijaya BS, et al. Clin Pharmacol Ther 2017;102:997. https://doi.org/10.1002/cpt.720. Used under Creative Commons License BY-NC-ND 4.0. Excerpt from original
2. Tumour exposure to SN-38: Figure 2B, Kalra AV, et al. Cancer Res 2014;74:7003
3. HT-29 mouse xenograft model: Figure 2D, Kalra AV, et al. Cancer Res 2014;74:7003

The NAPOLI-1 study

NAPOLI-1 study design – overall ITT population



*The study was amended to add the nal-IRI+5-FU/LV arm once safety data on the combination became available. Only those patients enrolled in the 5-FU/LV arm after the amendment (n = 119) were used as the control for the combination arm. (Trial registered at ClinicalTrials.gov, number NCT01494506).
QW, every week; Q2W, every two weeks; Q3W, every three weeks; Q8W, every 8 weeks.

Wang-Gillam A, et al. Lancet 2016;387:545

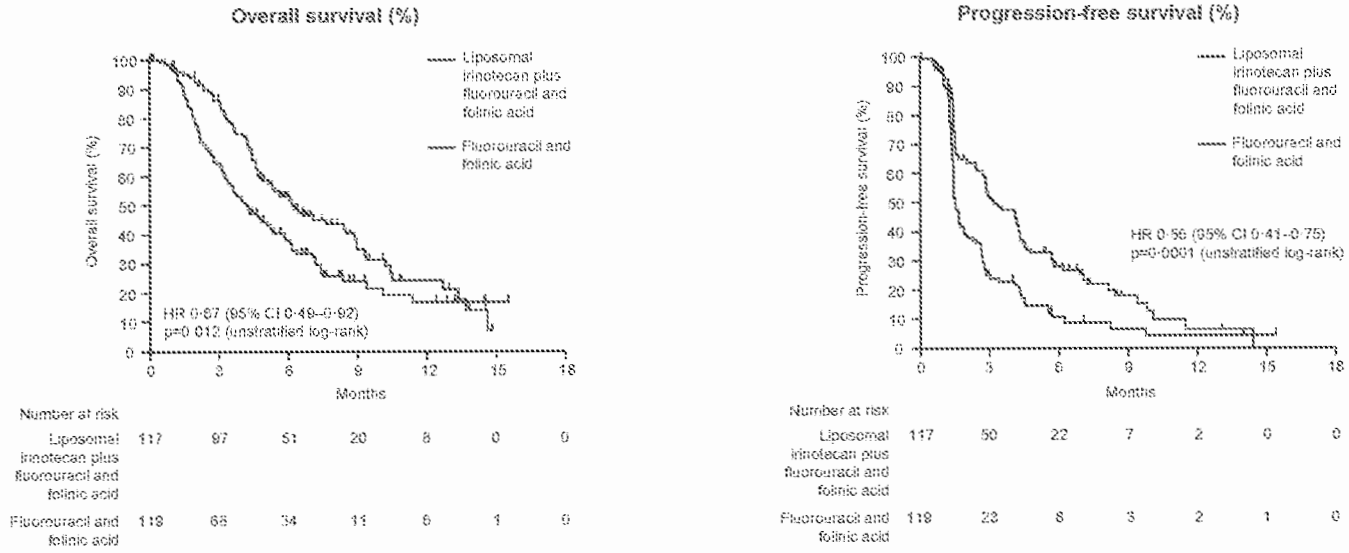
NAPOLI-1 ITT patient demographics and baseline characteristics

	Overall population	
	nal-IRI + 5-FU/LV (n = 117)	5-FU/LV (n = 116)
Sex, n (%)		
Female	48 (41)	52 (44)
Male	69 (59)	67 (56)
Median age, years (IQR) (Full range)	**63 (57–70) (41–81)**	**62 (55–69) (34–88)**
Previous lines of metastatic therapy, n (%)		
0	15 (13)	15 (13)
1	62 (53)	67 (56)
≥2	40 (34)	37 (31)
KPS score, n (%)		
90–100	**69 (59)**	**57 (48)**
70–80	**45 (38)**	**61 (51)**
50–60	**3 (3)**	**0**
Missing	**0**	**1 (1)**

	Overall population	
	nal-IRI + 5-FU/LV (n = 117)	5-FU/LV (n = 116)
Pancreatic tumour location, n (%)		
Head	**76 (65)**	**69 (59)**
Other	**41 (35)**	**58 (42)**
Measurable metastatic lesions at baseline, n (%)		
1	19 (16)	22 (19)
2	49 (42)	58 (49)
3	22 (19)	15 (13)
>3	7 (6)	8 (7)
Liver metastases, n (%)	75 (64)	83 (70)
Median CA19-9, U/mL (IQR)	1278 (120, 9001)	1292 (99, 16381)
Median albumin (g/dL)	**4.1**	**4.0**

IQR, interquartile range; ITT, intent-to-treat; KPS, Karnofsky Performance Status

NAPOLI-1: a 45% increase in median OS was observed with nal-IRI+5-FU/LV vs. 5-FU/LV alone



- **mOS:** 6.1 vs. 4.2 months; unstratified HR = 0.67; $P = 0.012$
- **mPFS:** 3.1 vs. 1.5 months; unstratified HR = 0.56; $P = 0.0001$

Overall survival with liposomal irinotecan plus fluorouracil and folinic acid versus fluorouracil and folinic acid. Survival analysis after 313 deaths on 14 February 2014; Vertical bars indicate censoring points
CI, confidence interval; mo, month

Figure 2A and 2C, Wang-Gillam A, et al. Lancet 2016;387:545
https://doi.org/10.1016/S0140-6736(15)00986-1

Adverse events in the NAPOLI-1 safety population

	Overall safety population	
	nal-IRI+ 5-FU/LV (n = 117)	5-FU/LV (n = 134)
Grade 3/4 non-haematologic AEs in >5% of the overall safety population, n (%)		
Diarrhoea, late onset*	15 (13)	6 (5)
Vomiting	13 (11)	4 (3)
Nausea	9 (8)	4 (3)
Fatigue	16 (14)	5 (4)
Febrile neutropenia	2 (2)	0
Asthenia	9 (8)	9 (7)
Abdominal pain	8 (7)	8 (6)
Grade 3/4 haematologic AEs based on laboratory values, n (%)†		
Neutrophil count decreased	23 (20)	3 (2)
Haemoglobin decreased	7 (6)	6 (5)
Platelet count decreased	2 (2)	0
Drug-related AE of CTCAE Grade ≥3, n (%)	63 (54)	24 (18)
Alopecia, n (%)	16 (14)	6 (5)

*>24 h after starting nal-IRI. No grade 3/4 early onset diarrhoea reported (≤24 h after starting nal-IRI);
†includes only patients who had at least one post-baseline assessment.
AE, adverse events; CTCAE, Common Terminology Criteria for Adverse Events.

Selected NAPOLI-1 subgroup analyses

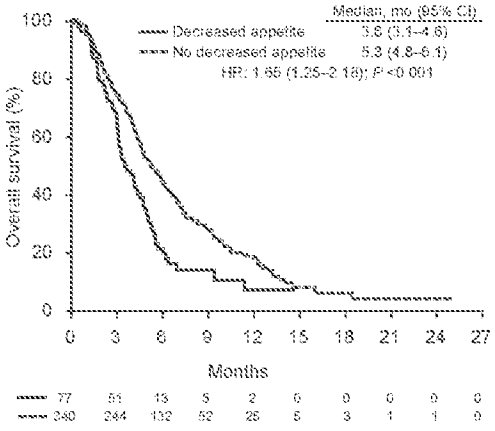
NAPOLI-1 subgroup analyses

Subanalyses of the NAPOLI-1 study population were performed based on the following subgroups:

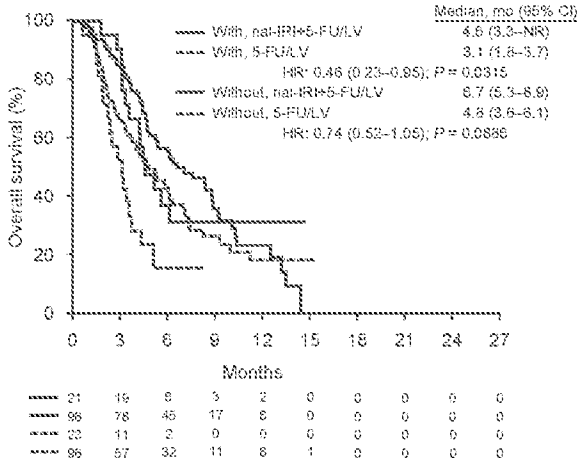
- Metabolism and nutrition disorders at baseline
  - Including decreased appetite, diabetes mellitus, hypercholesterolaemia and dyslipidaemia
- Best response to prior anticancer therapy
- Presence or absence of biliary stent at baseline
- Primary tumour location

Decreased appetite has a prognostic effect on overall survival in the overall NAPOLI-1 ITT population

Overall survival (ITT population)



Overall survival (decreased appetite subgroups)

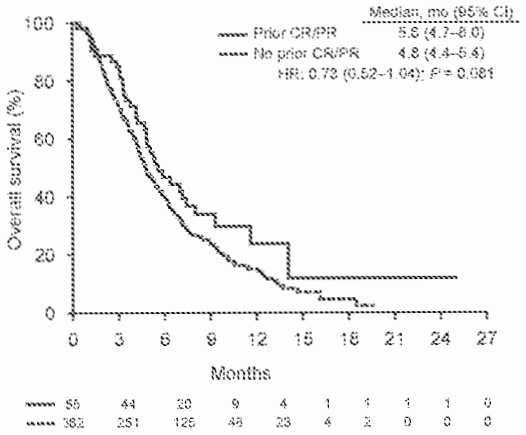


- Following trial inclusion, mOS and mPFS were significantly lower in ITT patients with vs. without decreased appetite at baseline
- In patients treated with nal-IRI+5-FU/LV, mOS and mPFS were generally improved vs. 5-FU/LV in all nutrition disorder subgroups, including decreased appetite

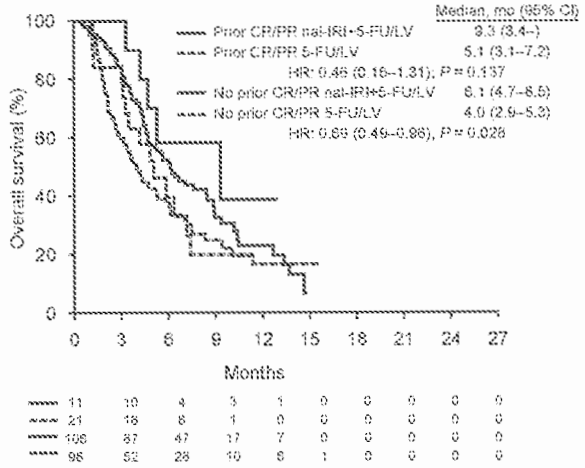
For full details, please see poster P-153
(Thursday 21st June)

Response to prior therapy may have a prognostic effect on survival outcomes in the overall NAPOLI-1 ITT population

Overall survival (ITT population)



Overall survival (prior response subgroups)

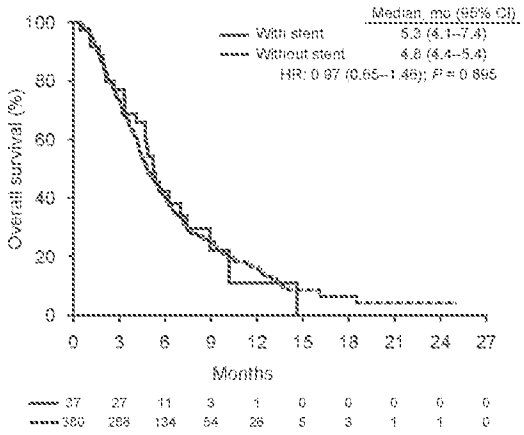


- In ITT patients with prior CR/PR, mOS and mPFS after trial inclusion tended to be improved vs. those with no prior CR/PR, suggesting a prognostic value of prior CR/PR in this population
- Patients in all prior therapy response groups showed consistent mOS and mPFS benefits from treatment with nal-IRI+5-FU/LV vs. 5-FU/LV

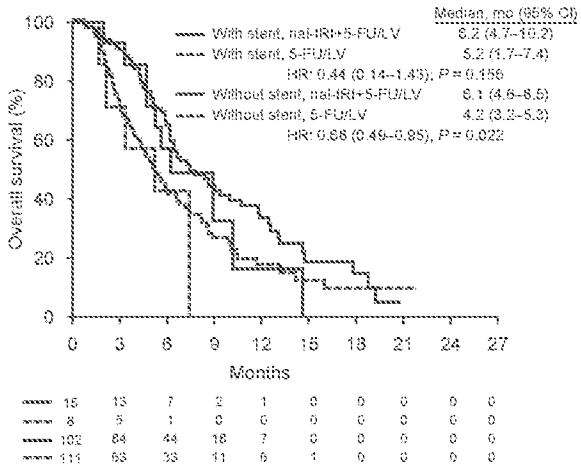
For full details, please see poster P–152
(Thursday 21st June)

No prognostic effect of biliary stent at baseline on survival outcomes in the overall NAPOLI-1 ITT population

Overall survival (ITT population)



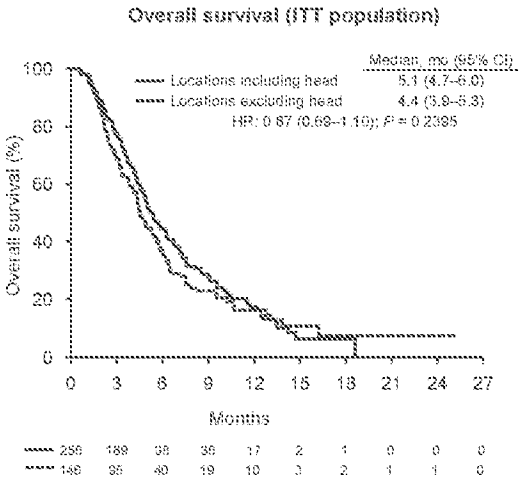
Overall survival (biliary stent subgroups)

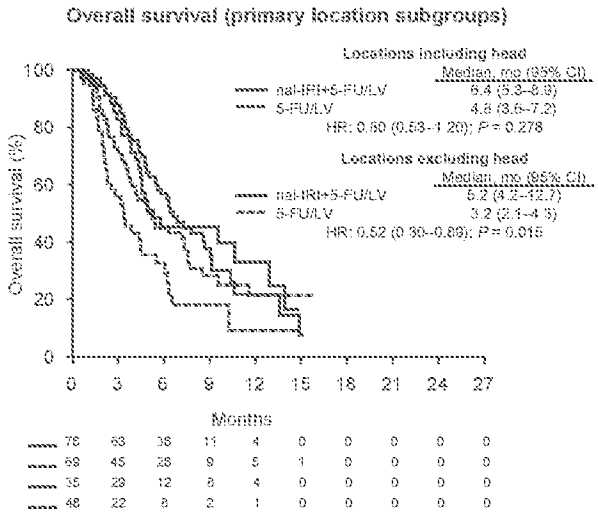


- No prognostic effect of biliary stent at baseline on mOS and mPFS outcomes after trial inclusion was observed in ITT patients and those receiving nal-IRI+5-FU/LV
- Both patients with and without a stent at baseline benefitted from treatment with nal-IRI+5-FU/LV vs. 5-FU/LV alone

For full details, please see poster P–151
(Thursday 21st June)

Primary tumour location does not have a prognostic effect on survival outcomes in the overall NAPOLI-1 ITT population





- There was no clear prognostic effect of primary tumour location on mOS and mPFS after trial inclusion in this patient population
- Across all primary tumour location subgroups, mOS and mPFS were increased with nal-IRI+5-FU/LV vs. 5-FU/LV

For full details, please see poster P-150
(Thursday 21st June)

Conclusions from selected NAPOLI-1 subgroup analyses

- nal-IRI+5-FU/LV increased survival vs. 5-FU/LV in adult patients with mPDAC previously treated with gemcitabine-based therapy[1]
- Decreased appetite at baseline was prognostic for survival in this patient population
- No significant prognostic effect of primary tumour location, biliary stent, or best response to prior therapy was found
- nal-IRI+5-FU/LV had a similar safety profile across all subgroups
- nal-IRI+5-FU/LV can benefit patients irrespective of the presence of metabolism and nutrition disorders such as decreased appetite, the presence of a biliary stent, primary tumour location, or patient response to prior therapies
  - Limited patient numbers in smaller subgroups should be taken into consideration

For further details, please see posters O-004, P-150, P-151, P-152, and P-153, displayed on Thursday, 21st June

1. Wang-Gillam A, et al. Lancet 2016;387:545

Subgroup analysis by baseline pain intensity (BPI) and baseline analgesic use (BAU) in NAPOLI-1, a phase 3 study of liposomal irinotecan (nal-IRI)±5-fluorouracil/leucovorin (5-FU/LV) in patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy

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INTRODUCTION

- Liposomal irinotecan (nal-IRI) is an innovative liposomal formulation of irinotecan, a topoisomerase 1 inhibitor, for intravenous use, which exhibits extended circulation and enhanced intratumoral drug deposition vs. conventional irinotecan.[1–3]
- NAPOLI-1, a global, phase 3 study, demonstrated that nal-IRI (80 mg/m^2 expressed as irinotecan hydrochloride trihydrate salt, equivalent to 70 mg/m^2 irinotecan free base; Q2W) in combination with 5-fluorouracil and leucovorin (5-FU/LV) significantly improved median overall survival (OS) by 45% (6.1 vs. 4.2 months; unstratified hazard ratio [HR] 0.67; *P*=0.0122) and doubled median progression-free survival (PFS; 3.1 vs. 1.5 months; unstratified HR 0.56; *P*=0.0001) compared with 5-FU/LV alone in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) who progressed following gemcitabine-based therapy.[4]
- Currently, nal-IRI is approved in combination with 5-FU/LV for the treatment of adult patients with mPDAC after disease progression following gemcitabine-based therapy.
  - NCCN guidelines recommend nal-IRI+5-FU/LV as a category 1 option for mPDAC patients previously treated with gemcitabine-based therapy, or a category 2 option for fluoropyrimidine-based therapy if no prior irinotecan.[5]
  - A 2017 update of the ESMO 2015 Clinical Practice Guidelines states that second-line therapy of pancreatic cancer has to be considered in terms of risk benefit for the patient. For fit patients, nal-IRI+5-FU/LV may constitute an active and tolerable second-line treatment option.[6]
- Here, we present results from a post-hoc subgroup analysis by baseline pain intensity (BPI) and analgesic use (BAU) from the NAPOLI-1 study.

METHODS

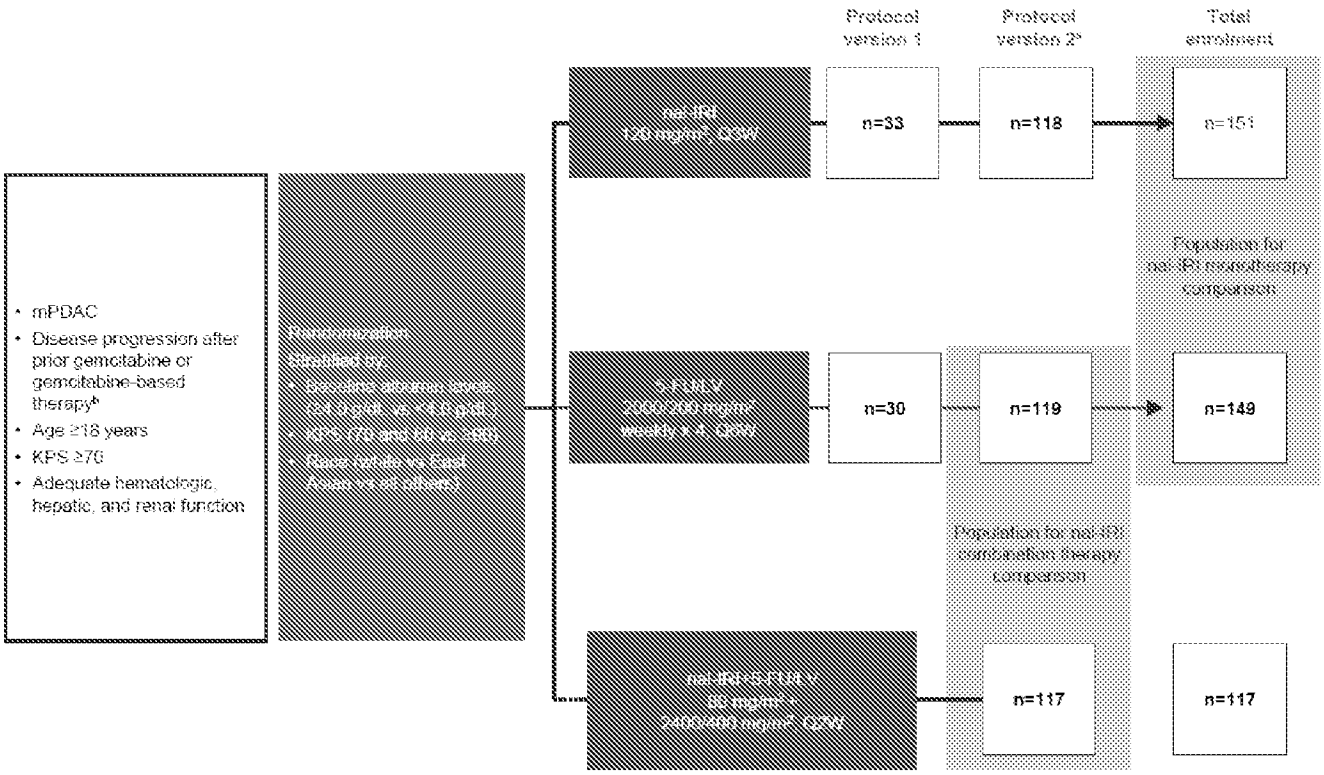
Objectives and subgroup analysis

- This post-hoc subgroup analysis of the NAPOLI-1 study aimed to assess the association of BPI or BAU on outcomes and efficacy within subgroups of patients defined by BPI and BAU, including the the overall intent-to-treat (ITT) population, and the nal-IRI+5-FU/LV (Q2W, n=117) and 5-FU/LV (4Q6W, n=119) treatment arms.
- *P* values in this post-hoc analysis are descriptive.

STUDY DESIGN

- NAPOLI-1 was an international, open-label, randomized, phase 3 trial (Figure 1).

Figure 1. Study design[a]



[a]Patients were initially randomized to nal-IRI monotherapy or 5-FU/LV. The protocol was amended to add a third arm (nal-IRI+5-FU/LV) after safety data on the combination became available from a concurrent study; 53 patients were enrolled under protocol version 1 before all sites switched to version 2. Only those patients enrolled in the 5-FU/LV arm after the amendment (n=119) were used as the control for the combination arm. [b]In a neoadjuvant, adjuvant (only if distant metastases occurred within 6 months of completing adjuvant therapy), locally advanced, or metastatic setting.

- BPI and BAU were based on the average value over the seven-day period prior to the first dose of study drug. A minimum of 3 days of data were required.
  - Pain was evaluated daily and patients were requested to record pain intensity on the visual analog scale (100 mm). Higher measurements were indicative of greater pain, each daily score reflecting pain experienced during the previous 24 hours.
  - Patients were also required to keep a detailed daily analgesic medication diary to record actual analgesic consumption. For patients unable to complete the analgesic diary, analgesic consumption was tracked based on prescriptions and recorded in the patient medical records. Patients' analgesic needs were evaluated and converted to morphine equivalent (mg/day) for standardization.

RESULTS

Patient characteristics

- Numerical differences in patient demographics and baseline characteristics emerged between BPI and BAU subgroups (Table 1).
- Gender, ethnicity and KPS score distribution varied across BPI and BAU subgroups compared with the corresponding overall ITT populations. There was also a large variation in subgroup populations. Any differences should be taken into account when considering results (Table 1).
- Of 417 ITT patients, 295 had BPI and 299 had BAU data. Median BPI was 25.0, and median BAU was 8.1 mg/day (Table 1).

Table 1. Patient demographics and baseline characteristics (ITT population)

	BPI											BAU (mg/day)										
	ITT			=0		>0		≤25.0		>25.0		ITT			=0		>0		≤8.1		>8.1	
	Total (n=299)	Comb (n=88)	Ctrl (n=78)	Comb (n=18)	Ctrl (n=12)	Comb (n=70)	Ctrl (n=54)	Comb (n=43)	Ctrl (n=35)	Comb (n=43)	Ctrl (n=41)	Total (n=299)	Comb (n=85)	Ctrl (n=77)	Comb (n=35)	Ctrl (n=33)	Comb (n=51)	Ctrl (n=44)	Comb (n=48)	Ctrl (n=37)	Comb (n=43)	Ctrl (n=40)
Female, %	45	40	43	28	58	43	41	33	49	47	42	43	37	42	26	46	45	39	29	49	47	35
Male, %	55	60	57	72	42	57	59	67	54	54	59	58	63	58	74	55	55	61	72	51	53	65
Median age, years Min–Max	63 39–87	65 43–81	62 39–80	61 49–75	65 42–74	66 43–81	61 39–80	66 45–81	61 42–79	63 47–78	62 39–80	63 39–87	63 43–81	61 39–80	65 47–81	59 42–79	63 43–78	61 39–80	63 45–81	62 42–79	64 47–48	61 39–80
Race, %																						
White	65	69	61	50	42	61	64	67	63	63	59	67	60	62	63	73	57	55	61	70	58	65
Black or African American	2	3	1	6	9	3	2	2	0	5	2	2	3	1	3	0	4	2	4	0	2	3
Asian	39	33	37	44	58	30	33	40	37	26	37	38	34	35	32	27	35	41	33	30	35	40
Other	3	5	1	0	0	6	2	2	0	7	2	3	3	1	3	0	4	2	2	0	5	3
KPS score, %																						
90–100	53	56	43	78	83	50	35	54	63	47	27	53	56	42	76	55	41	32	79	51	42	33
70–80	46	42	57	22	17	47	64	36	37	49	73	47	43	58	24	45	57	68	33	49	58	68
Median baseline CA19-9, U/mL	1539	1364	925	253	158	1753	1292	682	305	1482	2746	1521	1278	901	531	199	2007	3573	1364	267	682	3077
Liver metastases, %	66	64	57	67	58	63	69	58	69	61	56	67	63	69	61	76	65	58	65	73	61	65
Median baseline albumin, g/dL	4.0	4.0	4.0	4.6	4.1	4.0	4.0	4.1	4.1	3.9	3.9	4.0	4.0	4.1	4.1	4.1	4.0	4.0	4.1	4.1	4.0	4.0

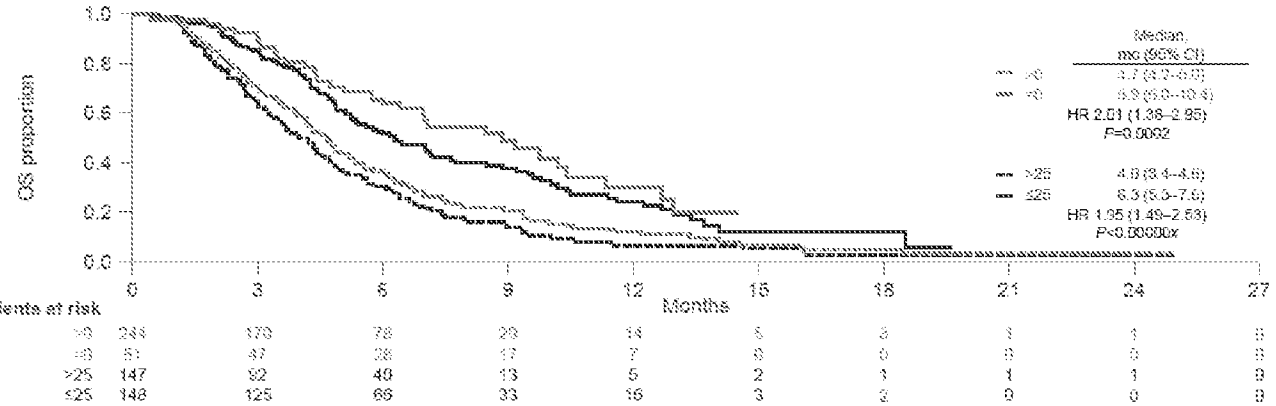
Comb, nal-IRI+5-FU/LV combination therapy; Ctrl, 5-FU/LV control for combination arm; ITT, intent-to-treat; KPS, Karnofsky Performance Status; Max, maximum age; Min, minimum age.

- As expected, there was variability in patient Karnofsky Performance Status (KPS) across BPI and BAU subgroups compared with the corresponding overall ITT populations (patients with BPI =0/≤25 and BAU =0/≤8.1 had a better KPS than patients with BPI >0/>25 and BAU >0/>8.1) (Table 1).

Impact of BPI and BAU on overall survival in the NAPOLI-1 study population

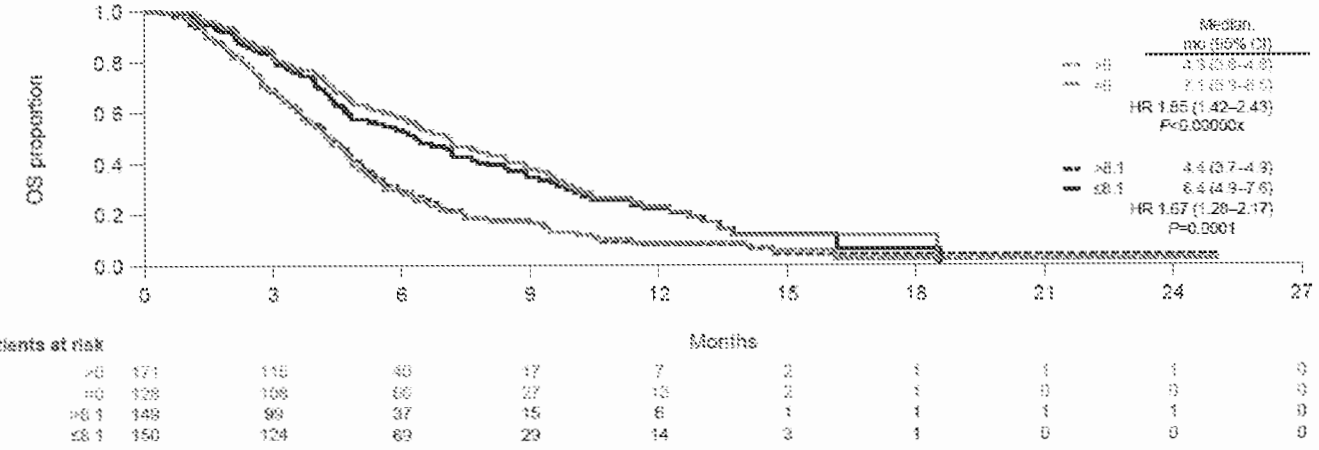
- Patients in the overall ITT population subgroups with higher BPI and BAU were generally at greater risk for mortality than patients with lower BPI and BAU (BPI: >0 vs. =0, HR 2.01; >25 vs. ≤25, HR 1.95; BAU: >0 vs. =0, HR 1.65; >8.1 vs. ≤8.1, HR 1.67) (Figures 2–3).
- Median OS was consistently lower in subgroups with higher BPI or BAU (BPI: >0 vs. =0, 4.7 vs. 8.9 months; >25 vs. ≤25, 4.0 vs. 6.3 months; BAU: >0 vs. =0, 4.3 vs. 7.1 months; >8.1 vs. ≤8.1, 4.4 vs. 6.4 months) (Figures 2–3).

Figure 2. Increased mortality risk in patients with higher baseline pain intensity (BPI ITT population*)



*Patients with BPI data available (includes all treatment arms). CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months.

Figure 3. Increased mortality risk in patients with higher baseline analgesic use (BAU ITT population*)

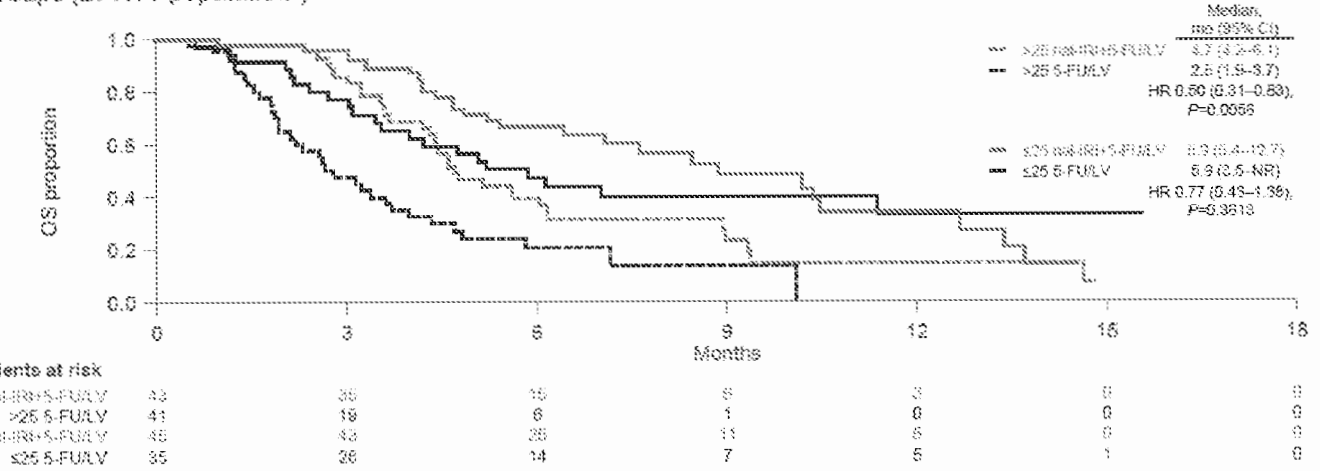


*Patients with BAU data available (includes all treatment arms). CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months.

Overall survival (nal-IRI+5-FU/LV vs. 5-FU/LV alone)

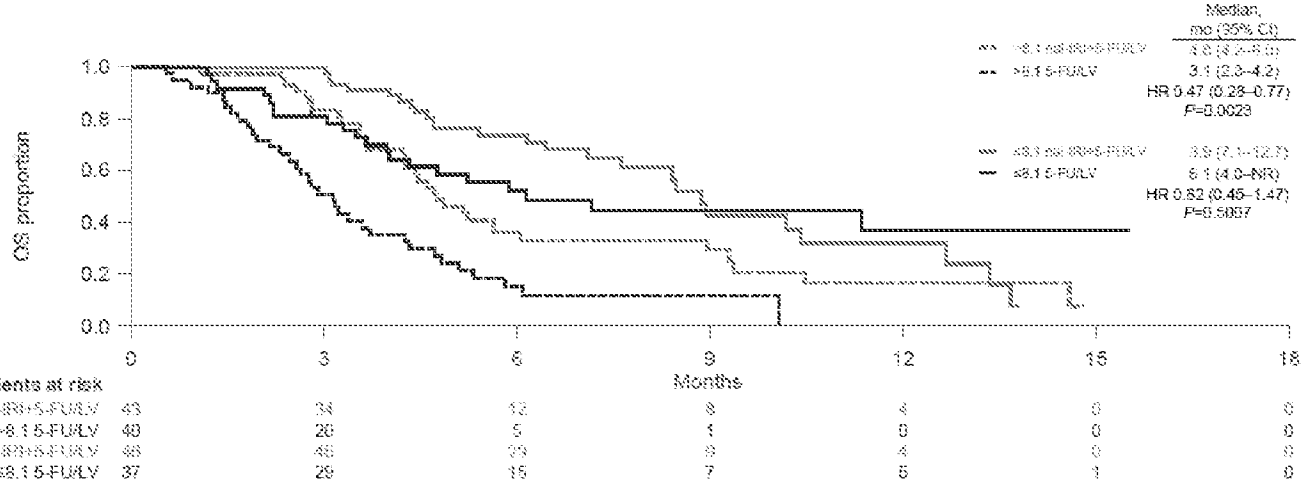
- Patients treated with nal-IRI+5-FU/LV had a reduced risk of mortality compared with patients receiving 5-FU/LV alone across all but one BPI and BAU subgroup (BPI: >0, HR 0.54; =0, HR 1.48; >25.0, HR 0.50; ≤25, HR 0.77; BAU: >0, HR 0.48; =0, HR 0.77; >8.1, HR 0.47; ≤8.1, HR 0.82) (Figures 4–5; Table 2).
  - Median OS in the control arm of the very small subgroup with BPI =0 (n=12) was higher than in the overall population control arm and low patient numbers may have impacted on this result (Table 2).
- This increase in median OS was statistically significant in the BPI >0 and >25.0, and BAU >8.1 subgroups (Figures 4–5; Table 2).

Figure 4. Reduced mortality risk in patients receiving nal-IRI+5-FU/LV vs. 5-FU/LV alone across baseline pain intensity subgroups (BPI ITT population*)



*Patients with BPI data available (includes nal-IRI+5-FU/LV combination therapy and 5-FU/LV combination control arms). CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months; NR, not reported.

Figure 5. Reduced mortality risk in patients receiving nal-IRI+5-FU/LV vs. 5-FU/LV alone across baseline analgesic use subgroups (BAU ITT population*)



*Patients with BAU data available (includes nal-IRI+5-FU/LV combination therapy and 5-FU/LV combination control arms). CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months; NR, not reported.

Progression-free survival (nal-IRI+5-FU/LV vs. 5-FU/LV alone)

- There was a reduced risk of disease progression across BPI and BAU subgroups in patients receiving nal-IRI+5-FU/LV compared with patients receiving 5-FU/LV alone (Table 2).
- This reduction was statistically significant in BPI subgroups >0 and >25.0, and BAU subgroups >0 and >8.1 (Table 2).

Table 2. Efficacy of nal-IRI+5-FU/LV vs. 5-FU/LV alone in BPI and BAU subgroups (ITT population)

	BPI										BAU (mg/day)									
	Overall			=0		>0		≤25.0		>25.0										
	Total (n=295)	Comb (n=88)	Ctrl (n=78)	Comb (n=16)	Ctrl (n=12)	Comb (n=70)	Ctrl (n=64)	Comb (n=45)	Ctrl (n=35)	Comb (n=43)	Ctrl (n=41)	Overall			=0		>0		≤8.1		>8.1	
												Total (n=295)	Comb (n=89)	Ctrl (n=77)	Comb (n=38)	Ctrl (n=33)	Comb (n=51)	Ctrl (n=44)	Comb (n=46)	Ctrl (n=37)	Comb (n=43)	Ctrl (n=40)
Median OS, months 95% CI	4.9 4.5,5.6	6.1 4.6,8.9	3.7 2.8,5.1	8.9 6.4,12.7	11.4 4.8,NR	5.4 4.6,6.9	3.2 2.4,4.0	8.9 6.4,12.7	5.9 3.5,NR	4.7 4.2,6.1	2.8 1.9,3.7	4.9 4.6,5.6	7.6 5.2,9.0	4.6 3.2,5.2	8.9 6.4,12.7	7.2 4.0,NR	4.7 4.3,6.0	3.2 2.6,4.2	8.9 7.1,12.7	5.1 4.0,NR	4.6 4.2,6.0	3.1 2.3,4.2
HR 95% CI *P* value†	–	0.63 0.43,0.91 *P*=0.013		1.46 0.51,4.24 *P*=0.477		0.54 0.36,0.80 *P*=0.002		0.77 0.49,1.38 *P*=0.381		0.50 0.31,0.83 *P*=0.006		–	0.61 0.42,0.89 *P*=0.009		0.77 0.46,1.47 *P*=0.424		0.48 0.30,0.75 *P*=0.002		0.82 0.45,1.47 *P*=0.501		0.47 0.28,0.77 *P*=0.002	
Median PFS, months 95% CI	2.6 1.8,2.8	4.0 2.7,4.2	1.4 1.3,1.8	4.3 1.5,14.2	4.2 1.3,9.6	3.6 2.4,4.2	1.4 1.3,1.8	4.2 2.8,6.1	1.6 1.3,2.8	2.7 1.4,4.2	1.4 1.3,1.6	2.6 1.8,2.8	4.0 2.6,4.3	1.4 1.3,1.8	4.5 2.8,7.1	2.2 1.3,4.4	2.9 1.5,4.2	1.4 1.3,1.8	4.3 2.8,6.8	2.2 1.3,4.2	3.6 1.5,4.2	1.4 1.3,1.5
HR (95% CI) *P* value†	–	0.55 0.39,0.79 *P*<0.001		0.68 0.27,1.68 *P*=0.399		0.50 0.33,0.73 *P*<0.001		0.66 0.40,1.09 *P*=0.105		0.45 0.27,0.76 *P*=0.002		–	0.54 0.38,0.77 *P*<0.001		0.64 0.36,1.11 *P*=0.112		0.39 0.24,0.63 *P*<0.001		0.67 0.40,1.11 *P*=0.119		0.37 0.22,0.64 *P*<0.001	
Best overall response																						
ORR, %	8	18	1	17	0	10	2	24	0	12	2	8	19	1	24	3	16	0	22	3	16	0
P value†	–	*P*<0.001		*P*=0.255		*P*=0.001		*P*=0.002		*P*=0.202		–	*P*<0.001		*P*=0.516		*P*=0.007		*P*=0.018		*P*=0.012	
PR, %	8	18	1	17	0	10	2	24	0	12	2	8	19	1	24	3	16	0	22	3	16	0
SD, %	32	35	24	50	50	31	19	44	34	26	15	31	36	25	48	39	28	14	46	38	26	13
PD, %	49	31	53	28	42	31	55	27	49	35	56	41	29	55	26	46	31	61	28	49	30	60
NE, %	19	14	21	6	8	16	25	4	14	23	27	18	14	18	3	9	22	25	4	8	23	28
CBR, %	40	53	25	67	50	50	20	69	34	37	17	40	55	26	71	42	43	14	67	41	42	13
CA19-9 response rate,‡ n/N (%)	50/248 (20)	23/76 (30)	5/61 (8)	6/11 (55)	3/9 (33)	17/65 (26)	2/52 (4)	13/35 (37)	4/26 (15)	10/41 (24)	1/35 (3)	50/253 (20)	24/75 (32)	6/61 (10)	11/28 (39)	5/24 (21)	13/47 (28)	1/37 (3)	12/36 (33)	5/28 (18)	12/39 (31)	1/33 (3)
P value†	–	*P*=0.001		*P*=0.486		*P*<0.001		*P*=0.085		*P*=0.008		–	*P*=0.002		*P*=0.229		*P*=0.002		*P*=0.254		*P*=0.002	

*Response defined as ≥50% reduction in baseline CA19-9 levels, in patients with baseline levels >30 U/ml, and at least one post baseline CA19-9 measurement; †Unstratified HR and log-rank *P* value. ‡Two-sided *P* values from pairwise Fisher's exact test. CBR, clinical benefit rate (CR[=0] + PR + SD); CI, confidence intervals; Comb, nal-IRI+5-FU/LV combination therapy; CR, complete response; Ctrl, 5-FU/LV control for combination arm; HR, hazard ratio NE, not evaluable; NR, not reported; ORR, objective response rate; PD, progressive disease; PR, partial response SD, stable disease.

Tumor and CA19-9 responses by treatment arm

- Patients receiving nal-IRI+5-FU/LV had a higher objective response rate (ORR) and CA19-9 response rate compared with patients receiving 5-FU/LV alone across all BPI and BAU subgroups (Table 2).
- The increase in ORR was statistically significant in BPI subgroups >0 and >25.0, and BAU subgroups >0 and >8.1 (Table 2).

Safety, dose modifications and treatment exposure

- The safety profile in the overall BPI and BAU safety populations was similar across subgroups and did not reveal any unexpected findings (Table 3). Similar observations were made for the nal-IRI+5-FU/LV and 5-FU/LV alone treatment arms (data not shown).
- No differences of note were observed between 0 and >0, ≤median and >median subgroups, except for abdominal pain in both populations (Table 3).

Table 3. Selected adverse events in BPI and BAU subgroups (overall safety population)

	BPI					BAU (mg/day)				
	Overall (n=295)	0 (n=51)	>0 (n=244)	≤25.0 (n=148)	>25.0 (n=147)	Overall (n=299)	0 (n=128)	>0 (n=171)	≤8.1 (n=150)	>8.1 (n=149)
Alopecia, %	15	16	14	18	12	15	16	13	17	12
Febrile neutropenia, %	2	4	1	1	2	2	2	2	1	3
Grade 3/4 non-hematologic AEs in >5% of the overall safety population, %										
Diarrhea, late onset*	12	14	11	14	10	12	12	12	11	13
Vomiting	8	6	9	5	12	8	5	9	8	7
Nausea	5	8	5	4	7	6	3	8	5	6
Fatigue	7	8	7	5	9	6	5	8	5	7
Asthenia	7	6	7	8	6	7	7	8	8	7
Abdominal pain	7	0	9	4	11	8	3	11	3	12
Grade 3/4 hematologic AEs based on laboratory values, % evaluable patients										
Neutrophil count decreased	15	18	14	17	12	15	15	14	14	15
Hemoglobin decreased	7	14	6	8	6	7	7	7	7	7
Platelet count decreased	1	0	1	0	2	1	0	2	1	1
Drug-related AE of CTCAE Grade ≥3	38	39	37	39	37	39	38	39	39	38

Safety was assessed by grading adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. *>24 h after starting nal-IRI. No grade 3/4 early onset diarrhea reported (≤24 h after starting nal-IRI). AE, adverse events; CTCAE, Common Terminology Criteria for Adverse Events.

- Dose modifications based on treatment-emergent adverse events (TEAEs) were similar across BPI and BAU subgroups (Table 4).
- Patients in subgroups with higher BPI or BAU had a higher incidence of TEAEs leading to treatment discontinuation compared with patients in subgroups with lower BPI or BAU (Table 4).

Table 4. Dose modifications in BPI and BAU subgroups (overall safety population)

	BPI					BAU (mg/day)				
	Overall (n=295)	=0 (n=51)	>0 (n=244)	≤25.0 (n=148)	>25.0 (n=147)	Overall (n=299)	=0 (n=128)	>0 (n=171)	≤8.1 (n=150)	>8.1 (n=149)
Patients with TEAE leading to any dose modification, %	52	53	52	49	55	52	50	54	49	56
Patients with TEAEs leading to treatment discontinuation, %	10	6	11	7	13	9	5	13	5	13

TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Treatment with nal-IRI in combination with 5-FU/LV in the NAPOLI-1 study has demonstrated clinical benefit (46% median OS increase) and predictable and manageable toxicity in patients with mPDAC previously treated with gemcitabine-based therapy.[4]
- The results of this post-hoc subgroup analysis suggest that:
  - Higher baseline pain intensity and analgesic use may be useful prognostic parameters for patients with metastatic pancreatic cancer previously treated with gemcitabine-based therapy.
  - Treatment benefit was maintained in patients with high and low BPI and BAU across most subgroups who received nal-IRI+5-FU/LV compared with patients who received 5-FU/LV alone.
    - However, the differences did not reach statistical significance in all groups, and firm conclusions are precluded by small patient numbers in many subgroups.
  - The safety profile for nal-IRI+5-FU/LV within BPI and BAU subgroups was consistent with the overall NAPOLI-1 population.
    - There were no notable differences between high and low BPI and BAU subgroups, except for a higher incidence of abdominal pain in the BPI and BAU <0 and =median subgroups.
    - Drug discontinuations due to TEAEs were numerically higher in higher pain and analgesic use subgroups.
- Overall, this post-hoc analysis supports the use of nal-IRI+5-FU/LV in patients with mPDAC previously treated with gemcitabine-based therapy who have either high or low BPI and BAU.

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Subgroup analysis by baseline weight-associated parameters: a phase 3 study of liposomal irinotecan (nal-IRI)±5-fluorouracil/leucovorin (5-FU/LV) in patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy

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INTRODUCTION

- Liposomal irinotecan (nal-IRI) is an innovative liposomal formulation of irinotecan, a topoisomerase I inhibitor, for intravenous use, which exhibits extended circulation and enhanced intratumoral drug deposition vs. conventional irinotecan.[1–3]
- NAPOLI-1, a global, phase 3 study, demonstrated that nal-IRI (80 mg/m^2 expressed as irinotecan hydrochloride trihydrate salt, equivalent to 70 mg/m^2 irinotecan free base; Q2W) in combination with 5-fluorouracil and leucovorin (5-FU/LV) significantly improved median overall survival (OS) by 45% (6.1 vs. 4.2 months; unstratified hazard ratio [HR] 0.67; *P*=0.0122) and doubled median progression-free survival (PFS; 3.1 vs. 1.5 months; unstratified HR=0.56; *P*=0.0001) compared with 5-FU/LV alone in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) who progressed following gemcitabine-based therapy.[4]
- Currently, nal-IRI is approved in combination with 5-FU and LV for the treatment of adult patients with mPDAC after disease progression following gemcitabine-based therapy.
  - NCCN guidelines recommend nal-IRI+5-FU/LV as a category 1 option for patients with locally advanced and mPDAC previously treated with gemcitabine-based therapy, or fluoropyrimidine-based therapy (if no prior irinotecan; category 2A).[5]
  - A 2017 update of the ESMO 2015 Clinical Practice Guidelines states that second-line therapy of pancreatic cancer has to be considered in terms of risk benefit for the patient. For fit patients, nal-IRI+5-FU/LV may constitute an active and tolerable second-line treatment option.[5]
- Here, we present results from a post-hoc subgroup analysis by baseline body surface area (BSA), body mass index (BMI) and weight (BL weight).

METHODS

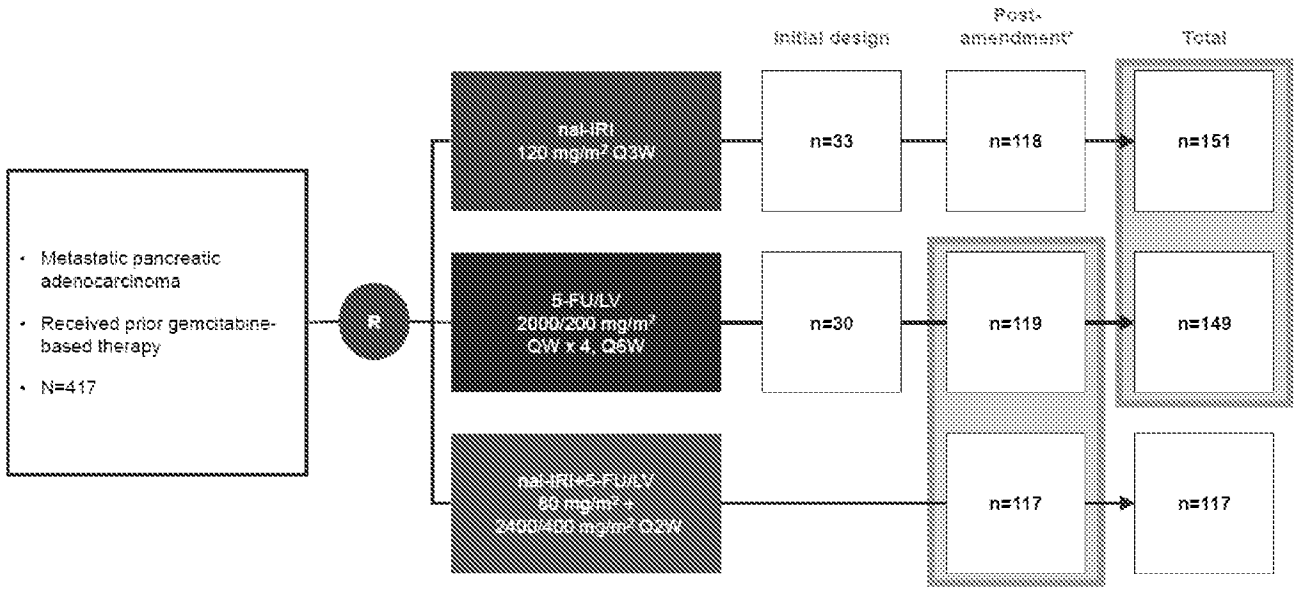
Objectives and subgroup analysis

- This post-hoc subgroup analysis of the NAPOLI-1 trial aimed to assess the impact of baseline BSA, BMI and weight parameters on outcomes in the whole population (N=417) and the efficacy and safety of nal-IRI+5-FU/LV Q2W (n=117) vs. 5-FU/LV 4Q6W (n=119), within subgroups of patients defined by median baseline BSA, BMI and weight.
- *P* values in this post-hoc analysis are descriptive.

STUDY DESIGN

- NAPOLI-1 was an international, open-label, randomized, phase 3 trial (Figure 1).

Figure 1. Study design*



*The study was amended to add the nal-IRI+5-FU/LV arm once safety data on the combination became available. Only those patients enrolled in the 5-FU/LV arm after the amendment (n=119) were used as the control for the combination arm. (Trial registered at ClinicalTrials.gov, NCT01494506)

Q2W, every two weeks; Q3W, every three weeks; Q6W, every six weeks

Key inclusion criteria

- Adults ≥18 years of age.
- Histologically or cytologically confirmed PDAC.
- Documented measurable or non-measurable distant metastatic disease.
- Disease progression after prior gemcitabine or gemcitabine-containing therapy in a neoadjuvant, adjuvant (only if distant metastases occurred within 6 months of completing adjuvant therapy), locally advanced, or metastatic setting.
- Karnofsky performance status (KPS) score ≥70.
- Adequate hematologic (including absolute neutrophil count >1.5 × 10^9 cells per L), hepatic (including normal serum total bilirubin and albumin levels ≥30 g/L), and renal function.

Key exclusion criteria

- Active central nervous system metastasis.
- Clinically significant gastrointestinal disorders.
- Severe arterial thromboembolic events <6 months before inclusion.

RESULTS

- Baseline weight parameters were available for all patients in the ITT population (N=417); median baseline BSA, BMI and weight were 1.71 m^2, 22.9 kg/m^2 and 63.6 kg, respectively.
- There was some variation across weight parameter subgroups in the proportion of patients of different races and genders, and KPS status also differed from the overall population in some of the subgroups above the baseline median value. Any differences should be considered when interpreting results.

Table 1: Patient demographics and baseline characteristics (ITT population)

	ITT		BSA				BMI				BL weight			
			<1.71 m²		≥1.71 m²		<22.9 kg/m²		≥22.9 kg/m²		<63.6 kg		≥63.6 kg	
	Comb (n=117)	Ctrl (n=119)	Comb (n=55)	Ctrl (n=57)	Comb (n=62)	Ctrl (n=62)	Comb (n=59)	Ctrl (n=61)	Comb (n=58)	Ctrl (n=58)	Comb (n=58)	Ctrl (n=61)	Comb (n=59)	Ctrl (n=58)
Female, %	41	44	68	67	19	23	46	48	36	40	62	57	26	29
Male, %	59	56	35	33	81	77	54	53	64	60	38	43	80	71
Median age, years Min–Max	63 41–81	62 34–80	68 43–81	61 34–80	63 41–81	63 41–79	63 43–81	61 34–80	63 41–81	63 41–79	65 43–81	61 34–80	63 41–81	63 41–79
Race, %														
White	62	64	42	56	79	71	58	56	66	72	41	59	81	69
Black or African American	3	3	2	0	5	5	2	0	5	5	2	0	5	5
Asian	29	30	51	44	10	18	36	41	22	19	50	41	9	19
Other	6	3	6	0	7	7	5	3	7	3	7	0	5	7
KPS Score, %														
90–100	59	48	51	47	66	48	54	38	64	59	50	43	68	53
70–80	38	51	47	51	31	52	44	61	33	41	47	56	31	47
Median baseline CA19-9, U/mL	1278	1292	1498	2435	1192	905	580	1545	1482	951	933	2695	1370	305
Liver metastases, %	64	70	53	70	74	69	58	64	72	76	55	69	73	71
Median baseline albumin, g/dL	4.1	4.0	4.0	4.0	4.1	4.0	4.0	4.1	4.1	4.0	4.0	4.0	4.1	4.0

BMI, body mass index; BL, baseline; BSA, body surface area; Comb, nal-IRI+5-FU/LV combination therapy; Ctrl, 5-FU/LV control for combination arm; ITT, intent-to-treat; KPS, Karnofsky Performance Status; Max, maximum age; Min, minimum age

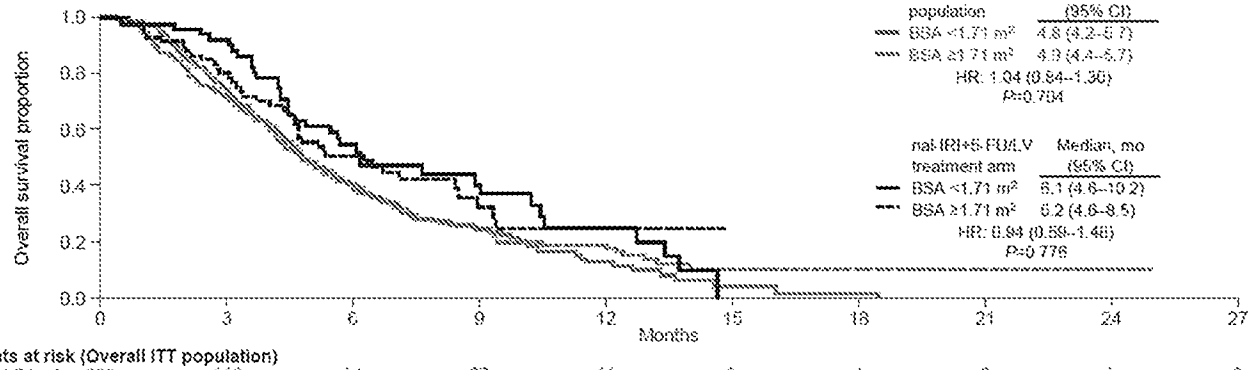
Impact of baseline weight parameters on overall survival in the NAPOLI-1 ITT population

- Risk of mortality was not significantly different between patients with baseline weight characteristics less than vs. greater than or equal to median values (BSA <1.71 m² vs. ≥1.71 m², HR 1.04; BMI <22.9 kg/m² vs. ≥22.9 kg/m², HR 1.17; BL weight <63.6 kg vs. ≥63.6 kg, HR 1.13) (Figures 2–4).

Impact of baseline weight parameters on overall survival in patients treated with nal-IRI+5-FU/LV

- Similarly, the risk of mortality was not significantly different between patients with baseline weight characteristics less than vs. greater than or equal to median values who were treated with nal-IRI+5-FU/LV (BSA <1.71 m² vs. ≥1.71 m², HR 0.94; BMI <22.9 kg/m² vs. ≥22.9 kg/m², HR 1.05; BL weight <63.6 kg vs. ≥63.6 kg, HR 1.07) (Figures 2–4).

Figure 2: Overall survival in the NAPOLI-1 ITT population* and nal-IRI+5-FU/LV arm by baseline BSA



Patients at risk (Overall ITT population)

BSA <1.71 m²	202	146	64	27	11	2	1	0	0	0
BSA ≥1.71 m²	215	149	81	30	16	3	2	1	1	0

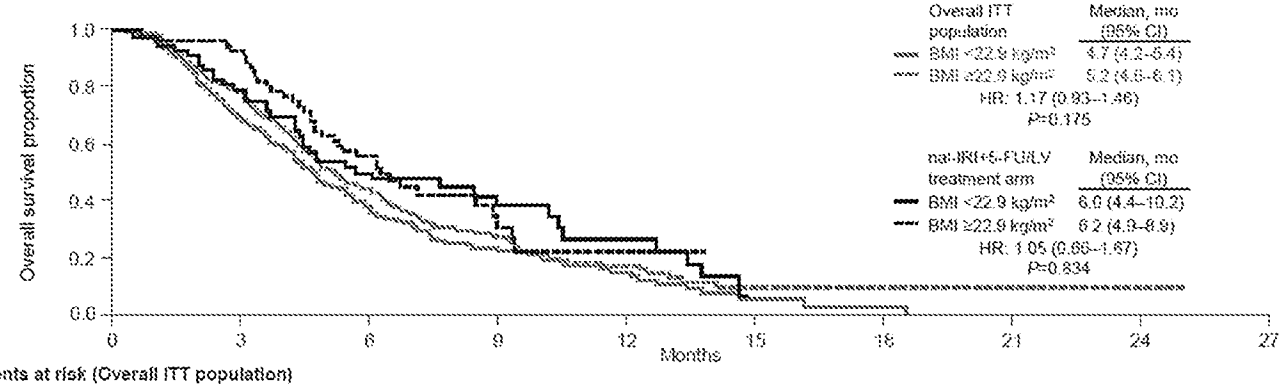
Patients at risk (nal-IRI+5-FU/LV arm)

BSA <1.71 m²	55	48	22	11	5	0	0	0	0	0
BSA ≥1.71 m²	62	49	29	9	3	0	0	0	0	0

*Includes all treatment arms

BSA, body surface area; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months.

Figure 3: Overall survival in the NAPOLI-1 ITT population* and nal-IRI+5-FU/LV arm by baseline BMI



Patients at risk (Overall ITT population)

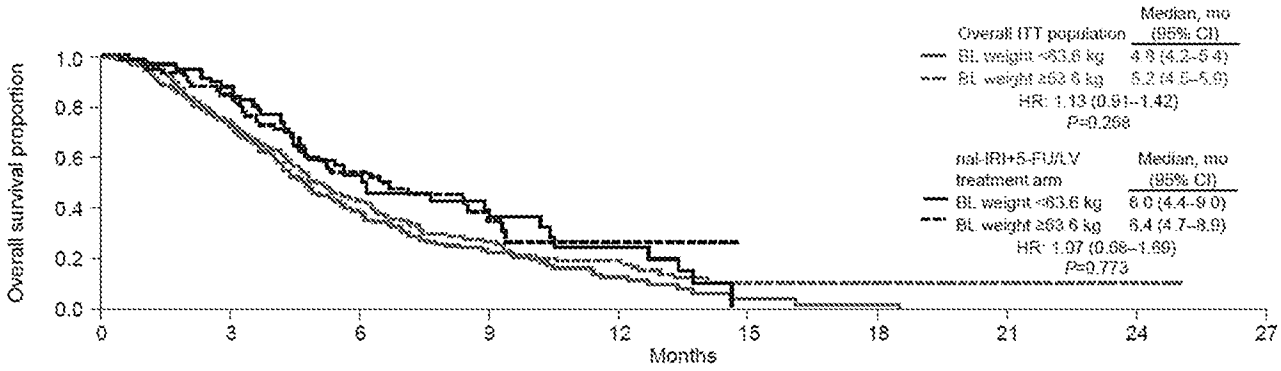
BMI <22.9 kg/m²	208	138	69	22	12	2	1	0	0	0
BMI ≥22.9 kg/m²	269	159	85	35	15	3	2	1	1	0

Patients at risk (nal-IRI+5-FU/LV arm)

BMI <22.9 kg/m²	59	44	22	12	6	0	0	0	0	0
BMI ≥22.9 kg/m²	58	53	29	8	2	0	0	0	0	0

*Includes all treatment arms
BMI, body mass index; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months.

Figure 4: Overall survival in the NAPOLI-1 ITT population* and nal-IRI+5-FU/LV arm by baseline weight



Patients at risk (Overall ITT population)

BL weight <63.6 kg	207	144	83	25	11	2	1	0	0	0
BL weight ≥63.6 kg	210	151	82	32	16	3	2	1	1	0

Patients at risk (nal-IRI+5-FU/LV arm)

BL weight <63.6 kg	58	46	22	11	5	0	0	0	0	0
BL weight ≥63.6 kg	59	49	29	9	3	0	0	0	0	0

*Includes all treatment arms
BL, baseline; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months.

Impact of baseline weight parameters on progression-free survival in the NAPOLI-1 ITT population

- Risk of disease progression was not significantly different between patients with baseline weight characteristics less than vs. greater than or equal to median values (BSA <1.71 m^2 vs. ≥1.71 m^2, HR 1.09; BMI <22.9 kg/m^2 vs. ≥22.9 kg/m^2, HR 1.07; BL weight <63.6 kg vs. ≥63.6 kg, HR 1.12).

Impact of treatment on overall survival (nal-IRI+5-FU/LV vs. 5-FU/LV)

- Patients treated with nal-IRI+5-FU/LV were at a reduced risk of mortality compared with patients receiving 5-FU/LV alone. This was true in patients in both lower and higher baseline weight parameter subgroups (Table 2).
  - The decreased mortality risk was statistically significant in the lower baseline weight parameter subgroups ($P<0.05$) (Table 2).

Impact of treatment on progression-free survival (nal-IRI+5-FU/LV vs. 5-FU/LV)

- Patients treated with nal-IRI+5-FU/LV were at a reduced risk of disease progression compared with patients receiving 5-FU/LV alone.
  - This decreased risk was statistically significant in patients in both lower and higher baseline weight parameter subgroups ($P<0.05$) (Table 2).

Impact of treatment on tumor and CA19-9 responses (nal-IRI+5-FU/LV vs. 5-FU/LV)

- Patients treated with nal-IRI+5-FU/LV had better objective response rates (ORR) and CA19-9 response rates compared with patients receiving 5-FU/LV in all patient subgroups (Table 2).
  - The increase in ORR was statistically significant in all subgroups, and the improved CA19-9 response was statistically significant in the BSA ≥1.71 m^2, BMI ≤22.9 kg/m^2 and BL weight <63.6 kg subgroups ($P<0.05$).

Table 2. Efficacy of combination vs. control in baseline weight subgroups (ITT population)

	ITT		BSA				BMI				BL weight			
			<1.71 m²		≥1.71 m²		<22.9 kg/m²		≥22.9 kg/m²		<63.6 kg		≥63.6 kg	
	Comb (n=117)	Ctrl (n=119)	Comb (n=55)	Ctrl (n=57)	Comb (n=62)	Ctrl (n=62)	Comb (n=59)	Ctrl (n=61)	Comb (n=58)	Ctrl (n=58)	Comb (n=58)	Ctrl (n=61)	Comb (n=59)	Ctrl (n=58)
Median OS, months (95% CI)	6.1 (4.8,8.9)	4.2 (3.3,5.3)	6.1 (4.6,10.2)	4.0 (3.1,5.9)	6.2 (4.6,8.5)	4.2 (2.6,6.1)	6.0 (4.4,10.2)	4.2 (2.8,6.1)	6.2 (4.9,8.9)	4.2 (3.2,6.4)	6.0 (4.4,9.0)	4.0 (2.8,5.3)	6.4 (4.7,8.9)	4.3 (3.2,7.2)
HR (95% CI) *P* value‡	0.67 (0.49,0.92) *P*=0.012		0.57 (0.35,0.90) *P*=0.015		0.71 (0.45,1.10) *P*=0.123		0.60 (0.38,0.95) *P*=0.028		0.68 (0.43,1.07) *P*=0.091		0.55 (0.36,0.87) *P*=0.009		0.75 (0.47,1.19) *P*=0.219	
Median PFS, months (95% CI)	3.1 (2.7,4.2)	1.5 (1.4,1.8)	4.6 (2.4,4.2)	1.5 (1.4,2.4)	3.1 (1.5,4.3)	1.4 (1.3,2.3)	4.0 (1.5,5.6)	1.5 (1.4,2.6)	3.1 (2.4,4.2)	1.5 (1.3,1.8)	3.1 (2.3,4.2)	1.4 (1.4,1.9)	3.3 (2.0,4.6)	1.6 (1.3,2.6)
HR (95% CI) *P* value‡	0.56 (0.41,0.75) *P*<0.001		0.49 (0.31,0.76) *P*=0.001		0.59 (0.39,0.90) *P*=0.013		0.47 (0.30,0.75) *P*=0.001		0.58 (0.38,0.88) *P*=0.010		0.52 (0.34,0.80) *P*=0.002		0.67 (0.37,0.87) *P*=0.008	
Best overall response, n (%)														
ORR, %	16	1	13	0	19	2	14	2	19	0	12	2	20	0
P value†	*P*<0.001		*P*=0.006		*P*=0.002		*P*=0.016		*P*<0.001		*P*=0.030		*P*<0.001	
PR, %	16	1	13	0	19	2	14	2	19	0	12	2	20	0
SD, %	33	22	36	21	31	23	32	23	35	21	35	20	32	24
PD, %	29	47	29	56	29	39	27	49	31	45	31	54	27	40
Not evaluable, %	19	29	18	21	19	36	24	26	14	31	19	25	19	33
CBR, %	50	23	49	21	50	24	46	25	53	21	47	21	53	24
CA19-9 response rate,* n/N (%)	28/97 (29)	7/81 (9)	12/46 (26)	4/45 (9)	16/51 (31)	3/36 (8)	15/49 (31)	1/46 (2)	13/48 (27)	6/35 (17)	12/48 (25)	2/47 (4)	16/49 (33)	5/34 (15)
P value†	*P*<0.001		*P*=0.052		*P*=0.016		*P*<0.001		*P*=0.428		*P*=0.007		*P*=0.077	

*Response defined as ≥50% reduction in baseline CA19-9 levels, in patients with baseline levels >30 U/ml, and at least one post baseline CA19-9 measurement.
†Two-sided p values from pairwise Fisher's exact test. ‡Unstratified HR and log-rank P value.
BL, baseline; BMI, body mass index; BSA, body surface area; CBR, clinical benefit rate (CR + PR + SD); CI, confidence interval; Comb, nal-IRI+5-FU/LV combination therapy; CR, complete response; Ctrl, 5-FU/LV control for combination arm; HR, hazard ratio; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Safety and Dose Modifications (overall safety population)

- The safety profile was similar across higher and lower baseline weight subgroups and did not reveal any unexpected findings (Table 3).
  - Numerical differences were noted for asthenia, abdominal pain and decreased neutrophil count between some higher and lower parameter subgroups.
- Drug-related grade ≥3 AEs were generally higher in lower weight parameter subgroups (Table 3), and were more frequent in the nal-IRI+5-FU-LV arm vs. the overall safety population (54% vs. 41%).

Table 3. Selected adverse events in baseline weight parameter subgroups (safety population)

	All safety (n=396)	BSA		BMI		BL weight	
		<1.71 m² (n=196)	≥1.71 m² (n=202)	<22.9 kg/m² (n=197)	≥22.9 kg/m² (n=201)	<63.6 kg (n=199)	≥63.6 kg (n=199)
Alopecia, %	14	16	11	12	15	15	13
Febrile neutropenia, %	2	2	2	2	2	3	2
Grade 3/4 non-hematologic AEs in >5% of the overall safety population, %							
Diarrhea, late onset†	13	12	14	14	13	12	14
Vomiting	9	7	12	9	10	7	12
Nausea	5	5	5	6	4	6	5
Fatigue	8	7	8	8	7	8	8
Asthenia	7	9	5	10	4	9	5
Abdominal pain	7	7	7	10	4	9	5
Grade 3/4 hematologic AEs based on laboratory values, % evaluable patients							
Neutrophil count decreased, %	13	16	10	14	12	15	10
Hemoglobin decreased, %	6	8	4	7	5	8	4
Platelet count decreased, %	1	1	1	1	1	1	1
Drug-related AEs of CTCAE grade ≥3, %	41	49	33	46	36	48	34

Safety was assessed by grading adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. †>24 h after starting nal-IRI. No grade 3/4 early onset diarrhea reported (≤24 h after starting nal-IRI).
AE, adverse event; BMI, body mass index; BL, baseline; BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events.

- Patients in lower baseline weight parameter subgroups had similar numbers of dose modifications and treatment discontinuations (Table 4).
- Dose modifications were more frequent in the nal-IRI+5-FU/LV treatment arm than in the overall safety population (71% vs. 53%), and there was a somewhat higher incidence of dose discontinuations in higher weight parameter subgroups in this arm (13–14%).

Table 4. Dose modifications in baseline weight parameter subgroups (safety population)

	All safety (n=398)	BSA		BMI		BL weight	
		<1.71 m² (n=196)	≥1.71 m² (n=202)	<22.9 kg/m² (n=197)	≥22.9 kg/m² (n=201)	<63.6 kg (n=199)	≥63.6 kg (n=199)
Patients with TEAE leading to any dose modification, %	53	56	51	53	53	54	53
Patients with TEAEs leading to treatment discontinuation, %	10	10	10	9	11	9	12

BL, baseline; BMI, body mass index; BSA, body surface area; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Treatment with nal-IRI in combination with 5-FU/LV has demonstrated clinical benefit (46% median OS increase) and predictable and manageable toxicity in patients with mPDAC previously treated with gemcitabine-based therapy.[4]
- This post-hoc subgroup analysis from the NAPOLI-1 study suggests that:
  - Baseline patient weight parameters (BSA, BMI and weight) are not prognostic of patient mortality or disease progression in this population of patients with mPDAC previously treated with gemcitabine-based therapy.
    - This was also observed in the nal-IRI+5-FU/LV treatment arm.
  - Patients in both high and low baseline weight parameter subgroups showed a general improvement in OS when treated with nal-IRI+5-FU/LV compared with 5-FU/LV alone.
  - nal-IRI+5-FU/LV exhibited a safety profile in all baseline weight parameter subgroups that was consistent with the overall nal-IRI+5-FU/LV arm population.
    - Drug-related grade ≥3 AEs were higher in lower weight parameter subgroups, apart from BMI, and were more frequent in patients treated with nal-IRI+5-FU/LV.
    - Dose discontinuations occurred in similar numbers of patients in all baseline weight subgroups.
- This post-hoc analysis supports the treatment of patients with mPDAC previously treated with gemcitabine-based therapy and the use of nal-IRI+5-FU/LV in all patients, irrespective of baseline weight parameter values.

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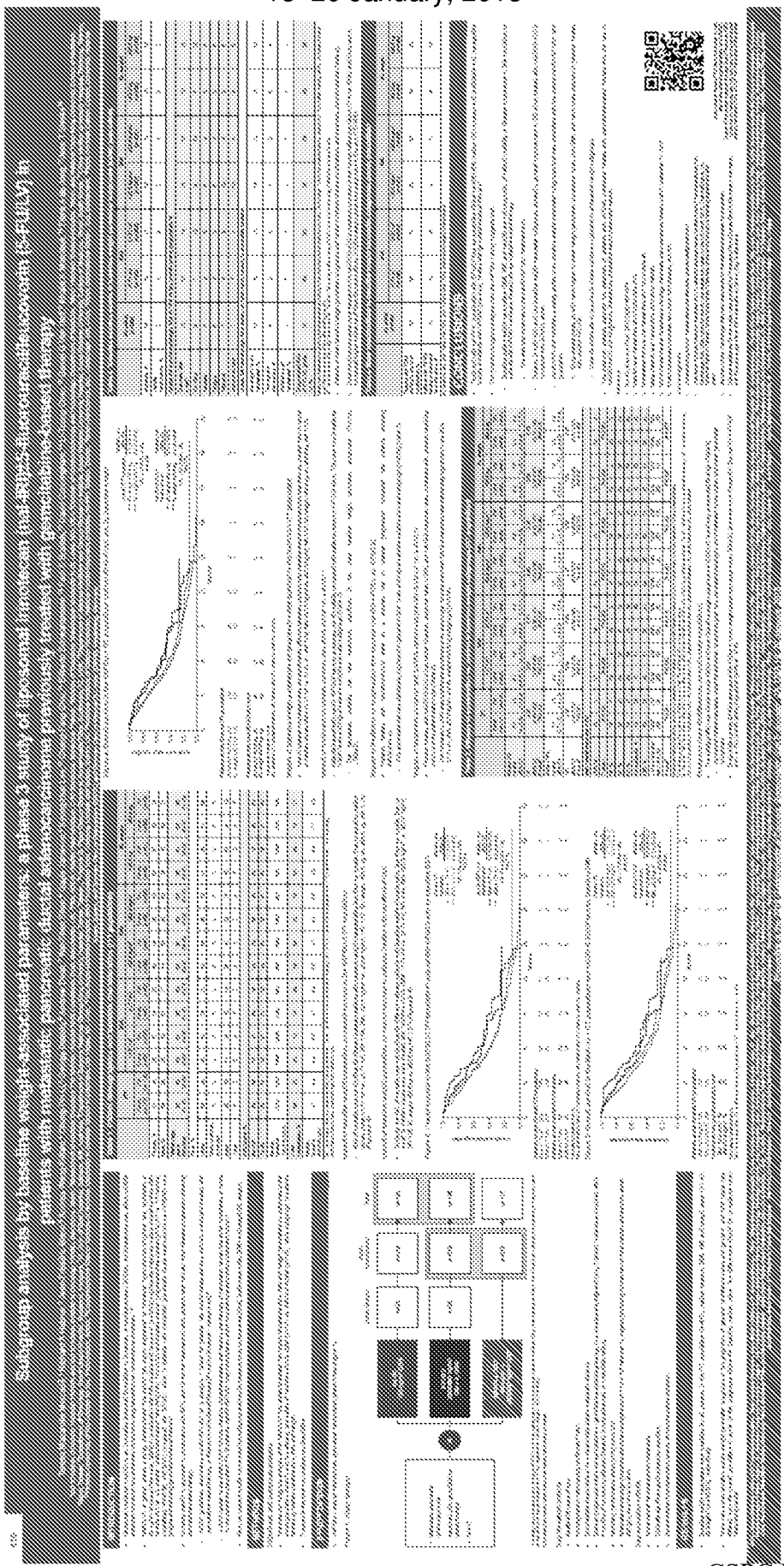

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The effect of best response to prior anticancer therapy on efficacy outcomes in the NAPOLI-1 trial of patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) previously treated with gemcitabine-based therapy

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INTRODUCTION

- In the pivotal NAPOLI-1 phase 3 study, the combination of liposomal irinotecan (nal-IRI) with 5-fluorouracil/leucovorin (5-FU/LV) significantly increased median overall survival (mOS) (6.1 vs. 4.2 months; unstratified hazard ratio [HR] = 0.67; P = 0.0122) and median progression-free survival (PFS; 3.1 vs. 1.5 months; unstratified HR = 0.56; P = 0.0001) vs. 5-FU/LV control in patients with mPDAC that progressed after gemcitabine-based therapy.[1]
- nal-IRI comprises liposomes with an irinotecan payload, an antineoplastic inhibitor of topoisomerase I.[2-4]
  - Liposomal encapsulation increases circulation time in plasma and increases intratumoural drug deposition vs. non-liposomal irinotecan, increasing and extending exposure to SN-38, the more active irinotecan metabolite.[2-4]
- Based on these findings, the nal-IRI+5-FU/LV regimen is now approved for the treatment of patients with mPDAC that progressed following gemcitabine-based therapy in numerous territories and has been incorporated into international treatment guidelines:
  - NCCN guidelines recommend nal-IRI+5-FU/LV as an option for mPDAC patients previously treated with gemcitabine-based therapy (cat. 1) or fluoropyrimidine (if no prior irinotecan; cat. 2A).[5]
  - As indicated in the 2017 update for the ESMO 2015 Clinical Practice Guidelines, second-line therapy of pancreatic cancer has to be considered in terms of risk benefit for the patient. Treatment with nal-IRI+5-FU/LV may constitute an active and tolerable second-line option for fit patients.[6]
- Tumour responses to previous anticancer therapies may be indicative of response to subsequent lines of therapy, and thus may influence efficacy of treatment with nal-IRI+5-FU/LV after progression on gemcitabine-based therapy.
- We therefore sought to assess the potential impact of best response to prior therapy on survival outcomes in NAPOLI-1 patients.

METHODS

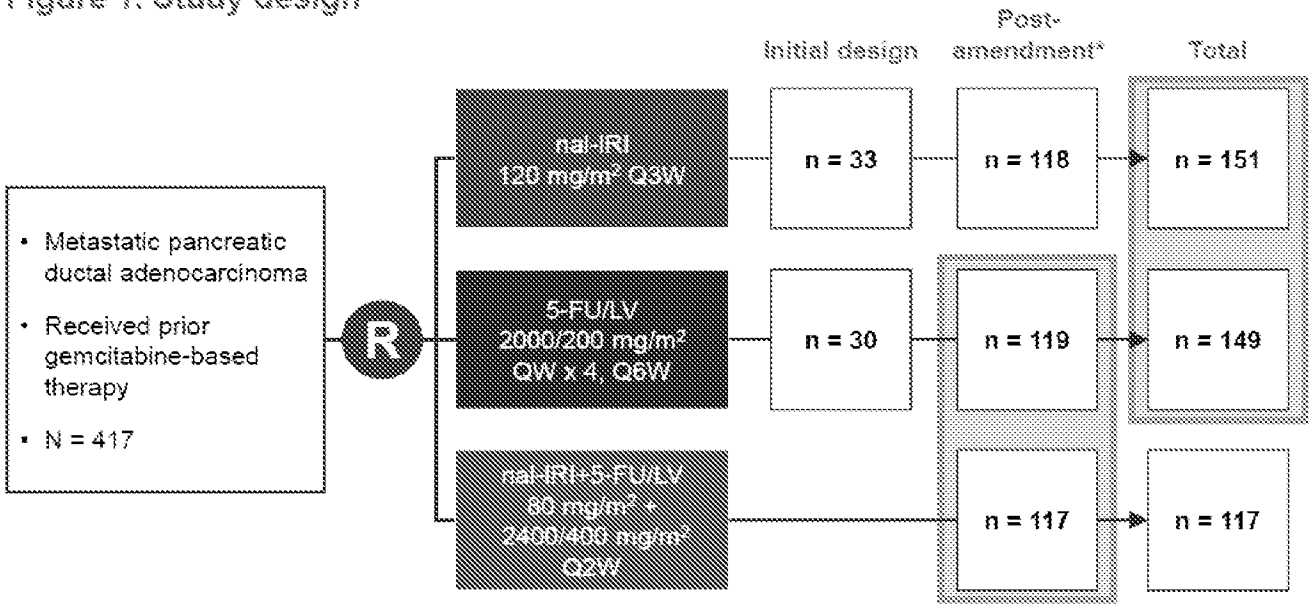
Objectives and analyses

- This *post-hoc* subgroup analysis aimed to assess the efficacy and safety of therapy in NAPOLI-1 patients, within subgroups of patients with prior complete or partial response (CR/PR) vs. no prior CR/PR, and also prior complete response, partial response or stable disease (CR/PR/SD) vs. no prior CR/PR/SD.

STUDY DESIGN

- NAPOLI-1 was an international, open-label, randomized, phase 3 trial (Figure 1).

Figure 1. Study design[4]



*The study was amended to add the nal-IRI+5-FU/LV arm once safety data on the combination became available. Only those patients enrolled in the 5-FU/LV arm after the amendment (n = 119) were used as the control for the combination arm. nal-IRI 80 mg/m² expressed as irinotecan hydrochloride trihydrate salt, equivalent to 70 mg/m² irinotecan free base. (Trial registered at ClinicalTrials.gov, number NCT01494506).

Key inclusion criteria

- Adults ≥18 years of age.
- Histologically or cytologically confirmed PDAC.
- Documented metastatic disease; disease status permitted to be measurable or non-measurable as per RECIST v. 1.1 guidelines.
- Disease progression after prior gemcitabine or gemcitabine-containing therapy in a neoadjuvant, adjuvant (only if distant metastases occurred within 6 months of completing adjuvant therapy), locally advanced, or metastatic setting.
- Karnofsky performance status (KPS) score ≥70.
- Adequate haematologic (including absolute neutrophil count >1.5×10^9 cells/L), hepatic (including normal serum total bilirubin and albumin levels ≥30 g/L), and renal function.

Key exclusion criteria

- Clinically significant gastrointestinal disorders.

RESULTS

Patient Characteristics

- Before to study entry, 55/417 (13%) of patients in the ITT population had prior CR/PR on a previous anticancer therapy, and 211/417 (51%) had prior CR/PR/SD.
- Patient characteristics were generally similar between treatment arms and within prior response groupings (Table 1).

Table 1. Patient demographics and baseline characteristics (ITT population)

	Overall population		Prior CR/PR		No prior CR/PR		Prior CR/PR/SD		No prior CR/PR/SD	
	nal-IRI+ 5-FU/LV (n = 117)	5-FU/LV (n = 119)	nal-IRI+ 5-FU/LV (n = 11)	5-FU/LV (n = 21)	nal-IRI+ 5-FU/LV (n = 105)	5-FU/LV (n = 98)	nal-IRI+ 5-FU/LV (n = 58)	5-FU/LV (n = 61)	nal-IRI+ 5-FU/LV (n = 59)	5-FU/LV (n = 58)
Sex, n (%)										
Female	48 (41)	52 (44)	4 (36)	11 (52)	44 (42)	41 (42)	24 (41)	27 (44)	24 (41)	25 (43)
Male	69 (59)	67 (56)	7 (64)	10 (48)	62 (58)	57 (58)	34 (59)	34 (56)	35 (59)	33 (57)
Median age, years	63	62	66	59	63	62	64	63	63	61
(IQR)	(57–70)	(55–69)	(58–68)	(53–65)	(57–70)	(55–69)	(57–70)	(55–69)	(55–70)	(54–67)
(Full range)	(41–81)	(34–80)	(48–73)	(41–77)	(41–81)	(34–80)	(46–81)	(41–80)	(41–81)	(34–79)
Race, n (%)										
White	72 (62)	76 (64)	8 (73)	9 (43)	64 (60)	67 (68)	32 (55)	32 (52)	40 (68)	44 (76)
Black or African American	4 (3)	3 (3)	0	0	4 (4)	3 (3)	1 (2)	2 (3)	3 (5)	1 (2)
Asian	34 (29)	36 (30)	1 (9)	9 (43)	33 (31)	27 (28)	21 (36)	23 (38)	13 (22)	13 (22)
Other	7 (6)	4 (3)	2 (18)	3 (14)	5 (5)	1 (1)	4 (7)	4 (7)	3 (5)	0
KPS score, n (%)										
90–100	69 (59)	57 (48)	6 (55)	12 (57)	63 (59)	45 (46)	33 (57)	31 (51)	36 (61)	26 (45)
70–80	45 (38)	61 (51)	5 (45)	9 (43)	40 (38)	52 (53)	23 (40)	30 (49)	22 (37)	31 (53)
50–60	3 (3)	0	0	0	3 (3)	0	2 (3)	0	1 (2)	0
Missing	0	1 (1)	0	0	0	0	0	0	0	0
Measurable metastatic lesions at baseline, n (%)										
1	19 (16)	22 (19)	1 (9)	4 (19)	18 (17)	18 (18)	10 (17)	11 (18)	9 (15)	11 (19)
2	49 (42)	58 (49)	5 (45)	8 (38)	44 (42)	50 (51)	21 (36)	27 (44)	28 (47)	31 (53)
3	22 (19)	15 (13)	3 (27)	2 (10)	19 (18)	13 (13)	10 (17)	6 (10)	12 (20)	9 (16)
>3	7 (6)	8 (7)	0	0	7 (7)	8 (8)	4 (7)	5 (8)	3 (5)	3 (5)
Primary tumour location, n (%)										
Head	76 (65)	69 (58)	8 (73)	13 (62)	68 (64)	56 (57)	39 (67)	35 (57)	37 (63)	34 (59)
Other	41 (35)	50 (42)	3 (27)	8 (38)	38 (36)	42 (43)	19 (33)	26 (43)	22 (37)	24 (41)
Liver metastases, n (%)	75 (64)	83 (70)	8 (73)	11 (52)	67 (63)	72 (73)	36 (62)	38 (62)	39 (66)	45 (78)
Median CA19-9, U/mL	1278	1292	302	1176	1364	1408	933	929	1437	1678
IQR	120, 9001	99, 16381	18, 69606	199, 5754	149, 8388	43, 26736	42, 8695	199, 6829	174, 18377	21, 38331
Median albumin (g/dL)	4.1	4.0	4.2	4.2	4.0	4.0	4.0	4.0	4.1	4.0

IQR, interquartile range; ITT, intent-to-treat; KPS, Karnofsky Performance Status

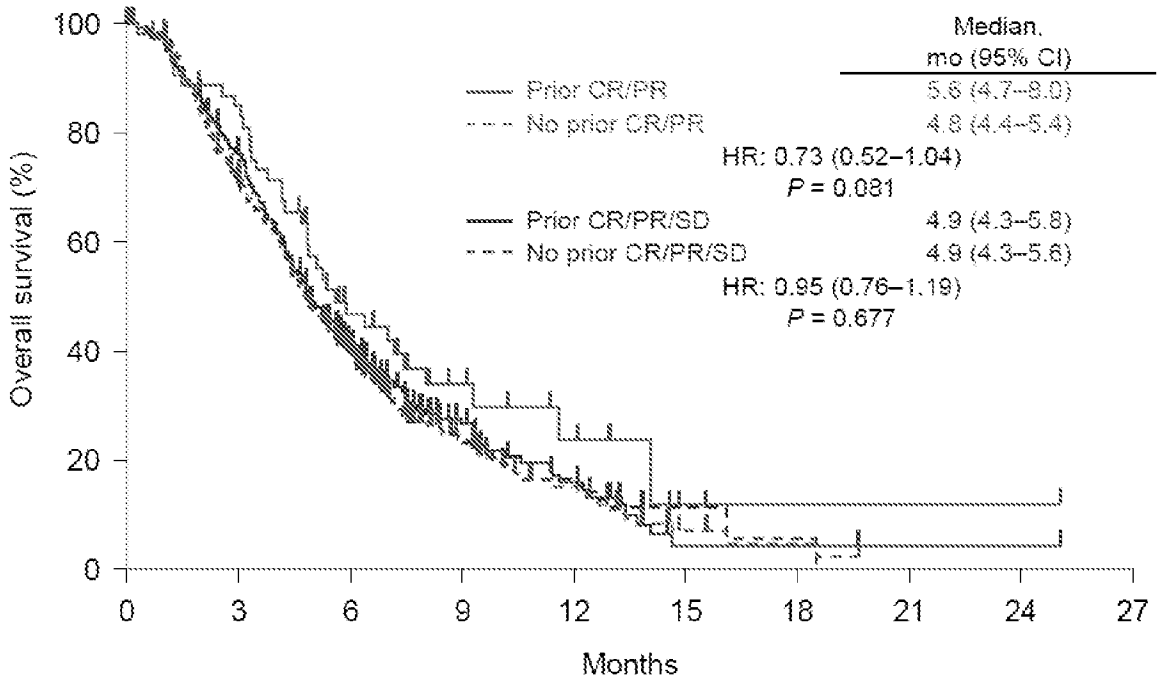
Impact of response to prior therapy on overall survival in the NAPOLI-1 ITT population

- A trend towards improved outcomes was observed in patients with prior CR/PR (n = 55) vs. no prior CR/PR (n = 362) (mOS 5.6 vs. 4.8 months, HR = 0.73, *P* = 0.081) (Figure 2).
- mOS was similar for patients with prior CR/PR/SD (n = 211) vs. no prior CR/PR/SD (n = 206) as best response (mOS 4.9 vs. 4.9 months, HR = 0.95, *P* = 0.677) (Figure 3).

Impact of response to prior therapy on progression-free survival and tumour response in the NAPOLI-1 ITT population

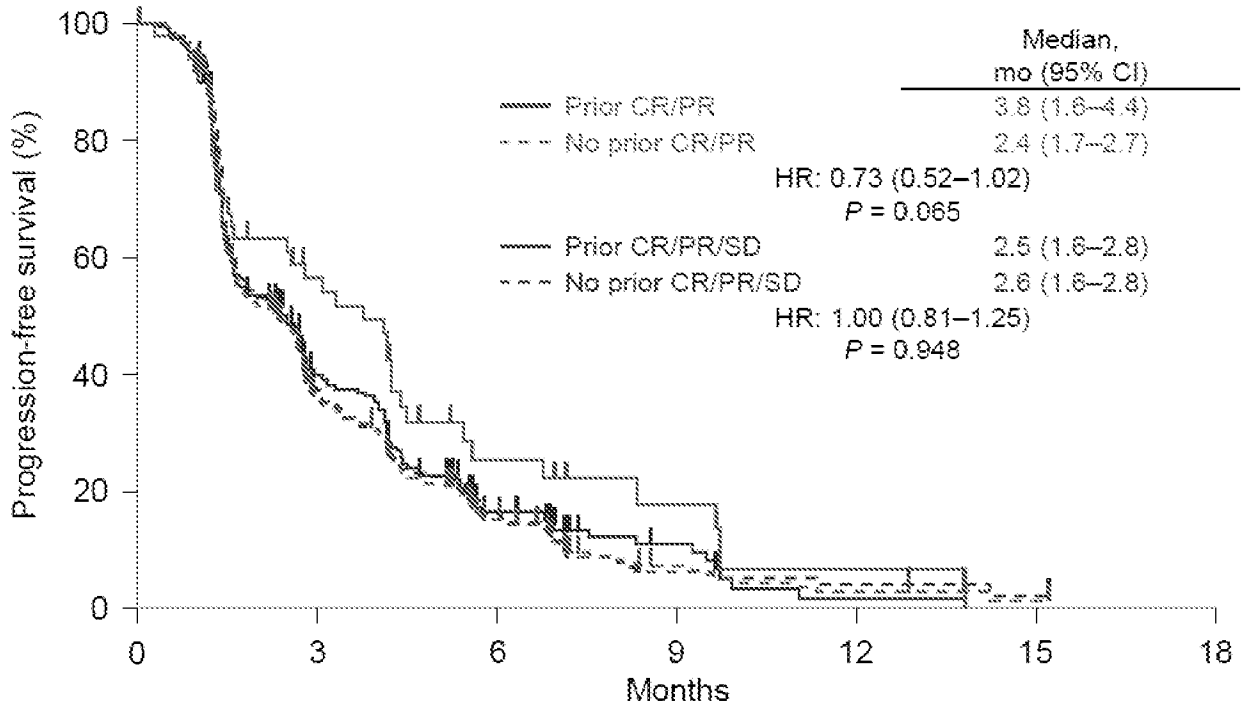
- A trend towards improved PFS outcomes was observed in patients with prior CR/PR vs. no prior CR/PR (3.8 vs. 2.4 months, HR = 0.73, *P* = 0.065). mPFS was similar in patients with prior CR/PR/SD vs. no prior CR/PR/SD (2.5 vs. 2.6 months, HR = 1.00, *P* = 0.948) (Figure 3).
- A trend towards improved objective response rate (ORR) was observed in patients with prior CR/PR vs. no prior CR/PR (13% vs. 6%, *P* = 0.085). No difference was found in ORR for patients with prior CR/PR/SD vs. no prior CR/PR/SD (7% vs. 7%, *P* = 1.00).
- There was no prognostic effect of prior therapy response on CA19-9 responses (prior CR/PR vs. no prior CR/PR: 29% vs. 20%, *P* = 0.219; prior CR/PR/SD vs. no prior CR/PR/SD: 23% vs. 19%, *P* = 0.416).

Figure 2. Effect of best response to prior anticancer therapy on overall survival (ITT population)



CI, confidence interval; CR, complete response; HR, hazard ratio; mo, months; PR, partial response; SD, stable disease.

Figure 3. Effect of best response to prior anticancer therapy on progression-free survival (ITT population)



Patients at risk (n):							
Prior CR/PR	55	24	8	4	1	0	0
No prior CR/PR	382	167	37	10	4	1	0
Prior CR/PR/SD	211	69	23	8	1	0	0
No prior CR/PR/SD	206	82	22	6	4	1	0

CI, confidence interval; CR, complete response; HR, hazard ratio; mo, months; PR, partial response; SD, stable disease.

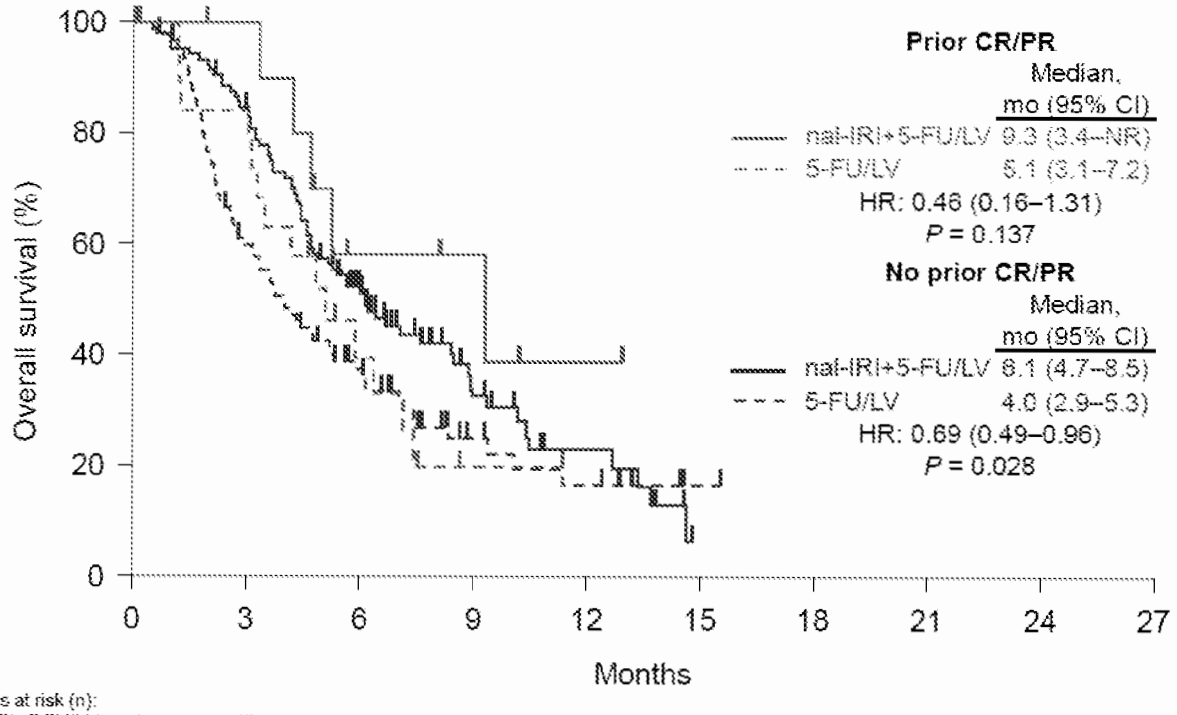
Impact of response to prior therapy on survival outcomes and tumour response with nal-IRI+5-FU/LV

- A trend towards improved mOS was observed in patients with prior CR/PR (n = 11) vs. no prior CR/PR (n = 106) (9.3 vs. 6.1 months, HR = 0.64, *P* = 0.335), but not in patients with prior CR/PR/SD (n = 58) vs. no prior CR/PR/SD (n = 59) (6.2 vs. 6.1 months, HR = 1.04, *P* = 0.881).
- A trend towards improved mPFS was observed in patients with prior CR/PR (n = 11) vs. no prior CR/PR (n = 106) treated with nal-IRI+5-FU/LV (mPFS 4.2 vs 3.0 months, HR = 0.53, *P* = 0.125), but not in patients with prior CR/PR/SD vs. no prior CR/PR/SD (4.0 vs. 3.3 months, HR = 1.18, *P* = 0.447).
- A trend towards improved ORR was observed in patients with prior CR/PR vs. no prior CR/PR (27% vs. 15%, *P* = 0.383), but not in patients with prior CR/PR/SD vs. no prior CR/PR/SD (14% vs. 19%, *P* = 0.617).
- CA19-9 responses were numerically higher in patients with prior CR/PR vs. no prior CR/PR (43% vs. 27%, *P* = 0.401), however the low number of patients with prior CR/PR limits interpretation.
  - CA19-9 responses were similar in patients with prior CR/PR/SD vs. no prior CR/PR/SD (30% vs. 27%, *P* = 0.824).

Impact of treatment with nal-IRI+5-FU/LV vs. 5-FU/LV alone on overall survival

- There was a consistent treatment benefit with nal-IRI+5-FU/LV in patients in all prior therapy response classification groups vs. 5-FU/LV (HRs = 0.46–0.69) (Figure 4 and 5, Table 2).

Figure 4. Effect of treatment with nal-IRI+5-FU/LV vs. 5-FU/LV on overall survival in patients with or without prior CR/PR

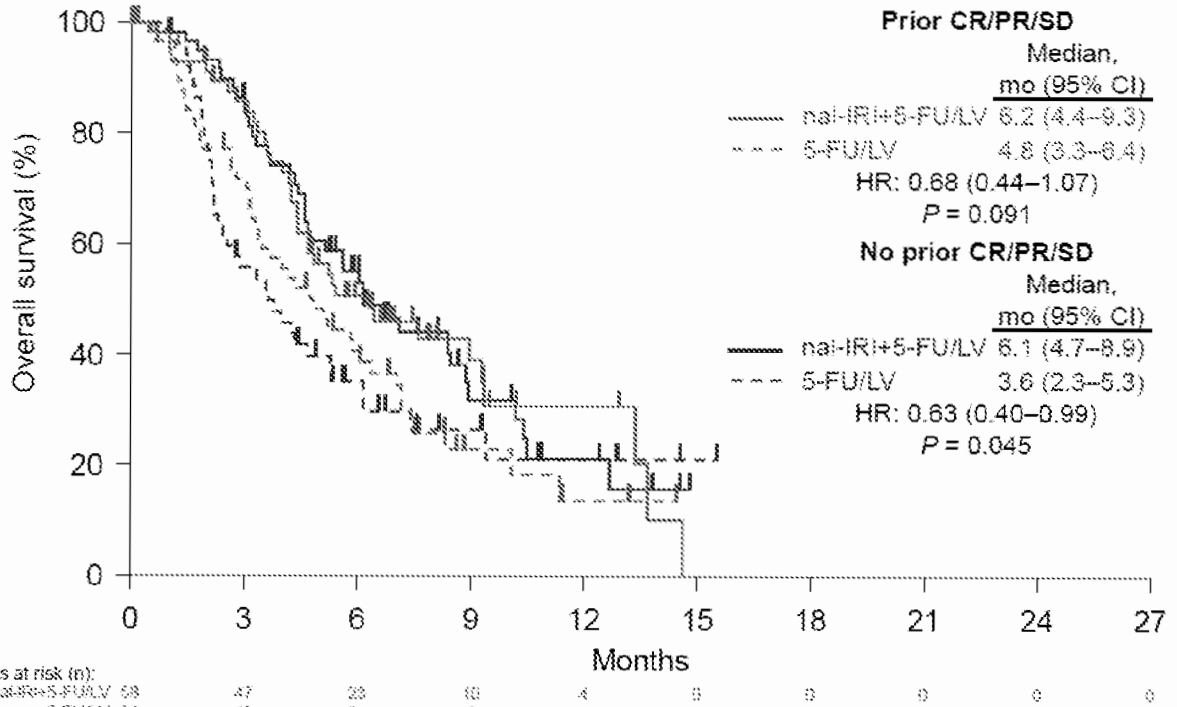


Patients at risk (n):

nal-IRI+5-FU/LV	11	10	4	3	1	0	0	0	0	0
5-FU/LV	21	15	6	1	0	0	0	0	0	0
nal-IRI+5-FU/LV	106	87	47	17	7	0	0	0	0	0
5-FU/LV	98	52	28	10	6	1	0	0	0	0

CI, confidence interval; CR, complete response; HR, hazard ratio; mo, months; NR, not reached; PR, partial response.

Figure 5. Effect of treatment with nal-IRI+5-FU/LV vs. 5-FU/LV on overall survival in patients with or without prior CR/PR/SD



Patients at risk (n):

nal-IRI+5-FU/LV	58	47	23	10	4	0	0	0	0	0
5-FU/LV	61	40	21	5	2	0	0	0	0	0
nal-IRI+5-FU/LV	59	50	28	10	4	0	0	0	0	0
5-FU/LV	58	28	13	6	4	1	0	0	0	0

CI, confidence interval; CR, complete response; HR, hazard ratio; mo, months; PR, partial response; SD, stable disease.

Impact of treatment with nal-IRI+5-FU/LV vs. 5-FU/LV alone on progression-free survival and tumour responses

- Progression-free survival was improved in patients treated with nal-IRI+5-FU/LV vs. 5-FU/LV for all prior therapy response classification groups (HRs = 0.33–0.58) (Table 2).
- Improved tumour responses, including ORR and CA19-9 responses, were observed in all prior response classification groups when treated with nal-IRI+5-FU/LV vs. 5-FU/LV alone (Table 2).
  - All ORR responses were statistically significant, however results in the small prior CR/PR group (n = 11 vs. n = 21) should be interpreted with caution.
  - CA19-9 responses were statistically significant in patients with no prior CR/PR and prior CR/PR/SD.

Table 2. Summary of efficacy in patient subgroups based on best response to prior anticancer therapy (ITT population)

	Overall population		Prior CR/PR		No prior CR/PR		Prior CR/PR/SD		No prior CR/PR/SD	
	nal-IRI+ 5-FU/LV (n = 117)	5-FU/LV (n = 119)	nal-IRI+ 5-FU/LV (n = 11)	5-FU/LV (n = 21)	nal-IRI+ 5-FU/LV (n = 106)	5-FU/LV (n = 98)	nal-IRI+ 5-FU/LV (n = 58)	5-FU/LV (n = 61)	nal-IRI+ 5-FU/LV (n = 59)	5-FU/LV (n = 58)
Median OS, months	6.1	4.2	9.3	5.1	6.1	4.0	6.2	4.6	6.1	3.6
HR (95% CI) *P*-value	0.67 (0.49–0.92) *P* = 0.012		0.46 (0.16–1.31) *P* = 0.137		0.69 (0.49–0.96) *P* = 0.028		0.68 (0.44–1.07) *P* = 0.091		0.63 (0.40–0.99) *P* = 0.045	
Median PFS, months	3.1	1.5	4.2	1.4	3.0	1.5	4.0	1.4	3.3	1.6
HR (95% CI) *P*-value	0.56 (0.41–0.75) *P* < 0.001		0.33 (0.12–0.93) *P* = 0.026		0.58 (0.42–0.80) *P* < 0.001		0.53 (0.35–0.83) *P* = 0.004		0.58 (0.37–0.88) *P* = 0.008	
Best overall response, n (%)										
ORR, n (%)	19 (16)	1 (1)	3 (27)	0 (0)	16 (15)	1 (1)	8 (14)	1 (2)	11 (19)	0 (0)
***P*-value**	*P* < 0.001		*P* = 0.033		*P* < 0.001		*P* = 0.015		*P* < 0.001	
PR, n (%)	19 (16)	1 (1)	3 (27)	0 (0)	16 (15)	1 (1)	8 (14)	1 (2)	11 (19)	0 (0)
SD, n (%)	39 (33)	26 (22)	3 (27)	4 (19)	36 (34)	22 (22)	17 (29)	11 (18)	22 (37)	15 (26)
Non-CR/ non-PD, n (%)	3 (3)	2 (2)	2 (18)	2 (10)	1 (1)	0 (0)	2 (3)	2 (3)	1 (2)	0 (0)
PD, n (%)	34 (29)	56 (47)	2 (18)	7 (33)	32 (30)	49 (50)	22 (38)	28 (46)	12 (20)	28 (48)
Not evaluable, n (%)	22 (19)	34 (29)	1 (9)	8 (38)	21 (20)	26 (27)	9 (16)	19 (31)	13 (22)	15 (26)
CBR, n (%)	58 (50)	27 (23)	6 (55)	4 (19)	52 (49)	23 (23)	25 (43)	12 (20)	33 (56)	15 (26)
CA19-9 response rate,* n/N (%)	28/97 (29)	7/81 (9)	3/7 (43)	2/14 (14)	24/88 (27)	6/68 (9)	13/44 (30)	4/47 (9)	14/51 (27)	4/35 (11)
***P*-value**	*P* < 0.001		*P* = 0.280		*P* = 0.004		*P* = 0.015		*P* = 0.105	

*Response defined as ≥50% reduction in baseline CA19-9 levels, in patients with baseline levels >39 U/ml, and at least one post baseline CA19-9 measurement; †Two-sided *P*-values from pairwise Fisher's exact test. CI, confidence interval; CBR, clinical benefit rate (CR + PR + SD); CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Safety, Dose Modifications and Treatment Exposure

- The occurrence of adverse events was generally similar between prior therapy response groups, however decreased neutrophil count was more frequently reported in patients with prior CR/PR/SD treated with nal-IRI+5-FU/LV than in other nal-IRI+5-FU/LV treatment groups (Table 3).

Table 3. Adverse events in prior therapy response classification groups (safety population)

	Prior CR/PR		No prior CR/PR		Prior CR/PR/SD		No prior CR/PR/SD	
	nal-IRI+ 5-FU/LV (n = 11)	5-FU/LV (n = 16)	nal-IRI+ 5-FU/LV (n = 106)	5-FU/LV (n = 89)	nal-IRI+ 5-FU/LV (n = 56)	5-FU/LV (n = 54)	nal-IRI+ 5-FU/LV (n = 61)	5-FU/LV (n = 51)
Alopecia (grade 1/2),* n (%)	3 (27)	0 (0)	13 (12)	5 (6)	9 (16)	1 (2)	7 (11)	4 (8)
Grade 3/4 non-haematologic AEs in >5% of the overall safety population, n (%)								
Diarrhoea, late onset*	1 (9)	1 (6)	14 (13)	5 (6)	6 (11)	4 (7)	9 (15)	2 (4)
Vomiting	1 (9)	0 (0)	12 (11)	3 (3)	5 (9)	1 (2)	8 (13)	2 (4)
Nausea	1 (9)	0 (0)	8 (8)	2 (2)	3 (5)	1 (2)	6 (10)	1 (2)
Fatigue	1 (9)	1 (6)	15 (14)	3 (3)	7 (13)	2 (4)	9 (15)	2 (4)
Febrile neutropenia	0	0	2 (2)	0	2 (4)	0	0	0
Asthenia	1 (9)	1 (6)	8 (8)	5 (6)	6 (11)	2 (4)	3 (5)	4 (8)
Abdominal pain	1 (9)	0	7 (7)	6 (7)	5 (9)	2 (4)	3 (5)	4 (8)
Grade 3/4 haematologic AEs based on laboratory values, n (%)†								
Neutrophil count decreased	1 (9)	0 (0)	22 (21)	3 (3)	15 (27)	1 (2)	8 (14)	2 (4)
Haemoglobin decreased	1 (9)	0 (0)	6 (6)	4 (4)	4 (7)	2 (4)	3 (5)	2 (4)
Platelet count decreased	0 (0)	0 (0)	2 (2)	0 (0)	0	0	2 (3)	0
Drug-related AE of CTCAE Grade ≥3, n (%)	5 (45)	2 (13)	58 (55)	15 (17)	30 (54)	8 (15)	33 (54)	9 (18)

*>24 h after starting nal-IRI. No grade 3/4 early onset diarrhea reported (≤24 h after starting nal-IRI); †includes only patients who had at least one post-baseline assessment.
AE, adverse events; CTCAE, *Common Terminology Criteria for Adverse Events*.

- The proportion of dose modifications was lower in patients with prior CR/PR treated with nal-IRI+5-FU/LV than in patients with no prior CR/PR, however very few patients were in the prior CR/PR group (n = 11) (Table 4).
- Other dose reductions and modifications were generally similar between nal-IRI+5-FU/LV treatment groups (Table 4).

Table 4. Dose modifications in prior therapy response classification groups (safety population)

	Prior CR/PR		No prior CR/PR		Prior CR/PR/SD		No prior CR/PR/SD	
	nal-IRI+ 5-FU/LV (n = 11)	5-FU/LV (n = 16)	nal-IRI+ 5-FU/LV (n = 106)	5-FU/LV (n = 89)	nal-IRI+ 5-FU/LV (n = 56)	5-FU/LV (n = 54)	nal-IRI+ 5-FU/LV (n = 61)	5-FU/LV (n = 51)
TEAE leading to any dose modification, n (%)	6 (55)	9 (56)	77 (73)	28 (31)	39 (70)	19 (35)	44 (72)	18 (35)
Dose reduction, n (%)	3 (27)	1 (6)	36 (34)	3 (3)	17 (30)	3 (6)	22 (36)	1 (2)
Dose delays, n (%)	6 (55)	9 (56)	66 (62)	24 (27)	36 (64)	18 (33)	36 (59)	15 (29)
Treatment discontinuation, n (%)	0	1 (6)	13 (12)	6 (7)	3 (5)	2 (4)	10 (16)	5 (10)

*Duration of exposure is the time from the date of the last administration of study drug + projected days to next dose of study drug administration - date of first study drug administration.
TEAE, treatment-emergent adverse event.

CONCLUSIONS

- This *post-hoc* subgroup analysis showed that patients with prior CR/PR had generally improved OS and PFS following trial inclusion vs. those with no prior CR/PR in the NAPOLI-1 ITT population, suggesting that prior CR/PR is prognostic of improved survival outcomes in the post-gemcitabine setting.
- Patients in all prior therapy response classification groups consistently benefitted from treatment with nal-IRI+5-FU/LV vs 5-FU/LV, in terms of both survival and disease progression.
- Patients with no prior CR/PR and no prior CR/PR/SD had a statistically significant OS benefit from treatment with nal-IRI+5-FU/LV, with statistical significant PFS benefit in all prior response classification groups.
  - Limited patient numbers in smaller prior therapy response groups should be taken into consideration when interpreting these findings.
- nal-IRI+5-FU/LV demonstrated a similar safety profile in all prior therapy response groups, apart from numerical differences for decreased neutrophil count in the small prior CR/PR group.
- These data support the notion that nal-IRI+5-FU/LV can benefit patients with mPDAC that progressed following gemcitabine-based therapy irrespective of their response to prior therapies.

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- Jie Chen (Shire) was responsible for statistical analyses of this *post-hoc* study.
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The effect of best response to prior anticancer therapy on efficacy outcomes in the NAPOLI-1 trial of patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) previously treated with gemcitabine-based therapy

[redacted]

Introduction

Methods

Results

Conclusions

References

Presented at the European Society for Medical Oncology 20th World Congress on Gastrointestinal Cancer, Barcelona, Spain, 25 – 28 June, 2025

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Application Number:	15809815
International Application Number:	
Confirmation Number:	5137
Title of Invention:	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin
First Named Inventor/Applicant Name:	Eliel Bayever
Customer Number:	153749
Filer:	Mary Rucker Henninger/Richard King
Filer Authorized By:	Mary Rucker Henninger
Attorney Docket Number:	263266-421428
Receipt Date:	25-FEB-2021
Filing Date:	10-NOV-2017
Time Stamp:	20:28:04
Application Type:	Utility under 35 USC 111(a)

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33	Non Patent Literature	Kulke_2009.pdf	106430 43936b91a6d88938520496e8cf20d288cbb7d37e	no	7
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34	Non Patent Literature	Lakatos_ESMO_GI_2018_poster.pdf	1188590 b9b1d1e9632bc7db156a4b608386c060c66c0412	no	10
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35	Non Patent Literature	Lakatos_ESMO_GI_2018_abstract.pdf	45714 f8041ee79d9c3adc33893427f3e74bd041cc277c	no	1
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36	Non Patent Literature	Latimer_AMCP_Nexus_2020_abstract.pdf	297193 33d9b651568a8c6d23b4e5e8239a1e02899328ca	no	2
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40	Non Patent Literature	Leonard_ASCO_GI_2018_poster.pdf	6144356 83f0f7d73d6e7384f1471f12c5ef270e50dffb5b	no	9
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41	Non Patent Literature	Leonard_ASCO_GI_2018_abstract.pdf	67452 1c7e840e6d1d9f257fbd0571c5cd6d5e7cb8b68a	no	2
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42	Non Patent Literature	Li_2009.pdf	218777 13a3c6a46b7a6b1f130d53cc96c2af6a13d68f7c	no	5
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44	Non Patent Literature	Lohr_2012.pdf	300510 8eeac7676797c6d15ff03de1a9da1ab2bf662abf	no	9
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45	Non Patent Literature	Ma_ESMO_2015_abstract.pdf	42720 416de6c831302cea6d8a34e981604b663b49ec51	no	1
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46	Non Patent Literature	Macarulla_ESMO_2018_poster.pdf	2427334 be9a2ef8b44c625307520fe16a3c365df98e82e4	no	7
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47	Non Patent Literature	Macarulla_ESMO_GI_2018_2_Poster.pdf	1927799 2140662a1c53dd6839cb3471645979a15d574970	no	10
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48	Non Patent Literature	Macarulla_ESMO_GI_2018_1_presentation.pdf	220233 d233b073a41cb05dc00269fca2b9a29e8a4688e6	no	16
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49	Non Patent Literature	Macarulla_ASCO_GI_2018_2_poster.pdf	2239408 3f96e2401660f62ec2a0f2bb05a56f05954b8217	no	8
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50	Non Patent Literature	Macarulla_ASCO_GI_2018_1_poster.pdf	3280011 b2829db3d6b06a777e7a1f380eb95dfc33347b7e	no	7
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51	Non Patent Literature	Macarulla_ESMO_GI_2018_poster.pdf	1227032 d781dc87a0f8e96038766e4aae50ad202caafdcb	no	10
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15809815
Filing Date	2017-11-10
First Named Inventor	Eliel Bayever
Art Unit	1612
Examiner Name	Celeste A. RONEY
Attorney Docket Number	01208-0007-01US

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	1	WANG-GILLAM A, et al., Abstract 459. "Nomogram for Predicting Overall Survival (OS) in Patients (pts) Treated With Liposomal Irinotecan (nal-IRI) ± 5-Fluorouracil/Leucovorin (5-FU/LV) in Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Previously Treated With Gemcitabine-Based Therapy in NAPOLI-1," J Clin Oncol. 36(4_Suppl):459 DOI: 10.1200/JCO.2018.36.4_suppl.459 (2018), 2 printed pages.
	2	WANG-GILLAM A, et al., Abstract e15795. "The Prognostic Value of Baseline Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) for Predicting Clinical Outcome in Patients with Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Treated With Liposomal Irinotecan (nalIRI; MM398) + 5-Fluorouracil and Leucovorin (5-FU/LV) vs 5-FU/LV," J Clin Oncol. 35(15_Suppl):e15795 DOI: 10.1200/JCO.2017.35.15_suppl.e15795 (2017), 3 printed pages.
	3	WANG-GILLAM A, et al., Abstract e16204. "A Survival Prediction Nomogram for Liposomal Irinotecan (nal-IRI)+5-Fluorouracil/Leucovorin (5-FU/LV) in Patients (pts) With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Previously Treated With Gemcitabine-Based Therapy," J Clin Oncol. 36(15_Suppl):e16204 DOI: 10.1200/JCO.2018.36.15_suppl.e16204 (2018), 2 printed pages.
	4	WANG-GILLAM A, et. al., letter to editor, "Nanoliposomal Irinotecan in the Clinical Practice Guideline for Metastatic Pancreatic Cancer: Applicability to Clinical Situations," J Clin Oncol. 35(6):689-90 (2017). Epub 2016.
	5	XIONG H, et. al., "Phase 2 Trial of Oxaliplatin Plus Capecitabine (XELOX) as Second-line Therapy for Patients With Advanced Pancreatic Cancer," Cancer. 113(8):2046-52 (2008).
	6	YU K, et al., "Hospitalizations and Real-World Clinical Outcomes of Liposomal Irinotecan in a NAPOLI1-Based Regimen Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC): A Multi-Center Chart Review," Poster presented at the Academy of Managed Care Pharmacy, Nexus (AMCP, Nexus): virtual meeting, week of October 19, 2020, 9 pages.
	7	YU K, et al., Abstract C3. "Hospitalizations and Real-World Clinical Outcomes of Liposomal Irinotecan in a NAPOLI1-Based Regimen Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC): A Multi-Center Chart Review," J Manag Care Spec Pharm. 26(10-a):S19 (2020).
	8	YU K, et al., "A US Multicenter Chart Review Study of Patients With Metastatic Pancreatic Ductal Adenocarcinoma Receiving Liposomal Irinotecan after Gemcitabine-Based Therapy." Poster presented at the International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE) All Access, September 16-17, 2020, 8 pages.
	9	YU K, et al., "Real-World Treatment Patterns and Effectiveness of Liposomal Irinotecan in a NAPOLI1-Based Regimen Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC): A Multi-Academic Center Chart Review." Poster presented at the European Society for Medical Oncology (ESMO) Virtual Congress 2020, September 19-21, 2020, 9 pages.
	10	YU K, et al., Abstract 1555P. "Real-World Treatment Patterns and Effectiveness of Liposomal Irinotecan in a NAPOLI1-Based Regimen Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC): A Multi-Academic Center Chart Review," Ann Oncol. 31(Suppl_4):S950-S951 doi.org/10.1016/j.annonc.2020.08.2038 (2020), 2 printed pages.
	11	YU K, et al., Abstract e16733. "A Multicenter Chart Review Study of Patients with Metastatic Pancreatic Ductal Adenocarcinoma Receiving Liposomal Irinotecan after Gemcitabine-Based Therapy," J Clin Oncol. 38(15_Suppl): e16733 DOI: 10.1200/JCO.2020.38.15_suppl.e16733 (2020), 4 printed pages.

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	12	YU K, et al., Abstract PO-3727. "A US Multicenter Chart Review Study of Patients With Metastatic Pancreatic Ductal Adenocarcinoma Receiving Liposomal Irinotecan after Gemcitabine-Based Therapy," International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE), September 14, 2020, available at eventscribe.com/2020/ICPEAllAccess/PosterTitles.asp?pfp=PosterTitles, 1 page.
	13	YU X, et. al., "Targeted Drug Delivery in Pancreatic Cancer," Biochim Biophys Acta. 21805(1):97-104 (2010). Epub 2009, author manuscript version, 16 pages.

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	Examiner Name	Celeste A. RONEY
	Attorney Docket Number	01208-0007-01US

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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Mary R. Henninger/	Date (YYYY-MM-DD)	2021-02-25
Name/Print	Mary R. Henninger	Registration Number	56992

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