2020 Wainberg Abstract

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LATE-BREAKING ABSTRACTS

LBA-1 First-line liposomal irinotecan + 5 fluorouracil/leucovorin + oxaliplatin in patients with pancreatic ductal adenocarcinoma: Long-term follow-up results from a phase 1/2 study

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Background: Liposomal irinotecan + 5-fluorouracil/leucovorin (5-FU/LV) is approved for adults with metastatic pancreatic ductal adenocarcinoma (PDAC) following progression with gemcitabine-based therapy. We report long-term follow-up results (data cut-off 26 Feb 2020) from an open-label phase 1/2 study (NCT02551991; EudraCT 2015-003086-28) of adults with previously untreated, unresectable, locally advanced/metastatic PDAC receiving liposomal irinotecan + 5-FU/LV + oxaliplatin (NALIRIFOX).

Methods: Following dose exploration (Part 1A), the dose selected for expansion (Part 1B), based on dose-limiting toxicities and cumulative safety data, was liposomal irinotecan 50 mg/m2 (free base), 5-FU 2400 mg/m2, LV 400 mg/m2, oxaliplatin 60 mg/m2 on days 1 and 15 of each 28-day cycle. The analyses included patients receiving the selected dose (pooled population 50/60): 7 patients from Part 1A and 25 from Part 1B. Patients were aged $\geq$ 18 years with ECOG performance status score $\leq$ 1 and adequate organ function. The primary endpoint was safety and tolerability; secondary efficacy endpoints were progression-free survival (PFS; primary efficacy endpoint), overall survival (OS), best overall response, overall response rate (ORR), disease control rate at 16 weeks (DCR16) and duration of response (DoR); exploratory endpoints included tumour subtype. Disease was assessed (RECIST v1.1) at screening, end of treatment and every 8 weeks. Archival tumour samples were subtyped (Moffitt schema) using the PurIST5M RNAseq assay (GeneCentric Therapeutics, Inc).

Results: The PP 50/60 comprised 32 patients (median age 58.0 years [range 39-76]; 14 [43.8%] men; 28 [87.5%] with metastatic disease at diagnosis; 18 [56.3%] with ECOG performance status score 1; 1 receiving study treatment at data cut-off). In total, 22 of these patients had grade $\geq$ 3 treatment-related treatment-emergent adverse events (TEAEs); the most common were neutropaenia (31.3%), febrile neutropaenia (12.5%), hypokalaemia (12.5%), diarrhoea (9.4%), nausea (9.4%) and decreased neutrophil count (9.4%); vomiting occurred in 6.3% of patients, while fatigue and peripheral neuropathy were not reported. Serious TEAEs (SAEs) were reported in 17 patients; 10 of these patients had SAEs considered related to treatment, most commonly nausea (9.4%) and febrile neutropaenia (9.4%). TEAEs leading to death occurred in 3 patients (malignant gastrointestinal obstruction, upper gastrointestinal haemorrhage, disease progression); none were considered related to treatment. TEAEs led to dose adjustment in 26 patients and discontinuation (of oxaliplatin or all four study drugs) in 8. Median PFS (95% CI) was 9.2 months (7.69, 11.96) and median OS was 12.6 months (8.74, 18.69). Complete response was observed in 1 patient (with locally-advanced disease), partial response in 10, and stable disease in 15. ORR (95% CI) was 34.4% (18.6, 53.2), DCR16 was 71.9% (53.3, 86.3) and median DoR was 9.4 months (3.52, NE). Tumour subtype and response data were available for 9 patients in the PP 50/60 (classical, n=8, PFS range 7.7-17.8 months; basal-like, n=1, PFS 9.6 months).

Conclusion: No new safety signals were observed with first-line NALIRIFOX in patients with locally advanced/metastatic PDAC, and anti-tumour activity was promising. The ongoing randomized phase 3 NAPOLI-3 study (NCT04083235; EudraCT 2018-003585-14) will compare NALIRIFOX with gemcitabine + nab-paclitaxel.

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LBA-2 A two arm randomized prospective superiority phase II multicentric clinical trial to evaluate the efficacy of capecitabine-irinotecan (CAPIRI) versus irinotecan in advanced gall bladder cancer progressing on first line chemotherapy

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Background: There is limited data with regard to second line chemotherapeutic options (CT2) in advanced gallbladder cancer (GBC) post progression on gemcitabine-based1st line chemotherapy (CT1). Using a combination or monotherapy as CT2 is an important question in this context.

Methods: Patients diagnosed with disease progression or recurrence post CT1 were randomized (1:1) to either capecitabine-Irinotecan (CAPIRI) or single agent Irinotecan (IRI). Patients with ECOG PS 0-1, and adequate end organ function were eligible. Primary endpoint was percentage overall survival (OS) at 6 months. Sample size was 98 patients with requirement of 68 events for analysis (80% power; 10% two-sided alpha), assuming median 6-month OS for IRI was 55% and 70% for CAPIRI, respectively.

Results: 98 patients (49 in each arm) were randomized (August 18 to Jan 20); median age 51 years (range: 29-70); gender: Women 60 (61%), Men 38 (39%). There were no significant differences in baseline characteristics between both groups. After sixty-nine OS events, the Hazard Ratio (HR) was 0.98 (95% CI: 0.61 — 1.57; p= 0.93: CAPIRI vs. IRI). Six months (mo.) OS (%), median OS and median progression free survival were 38.4%, 5.16 mo., and 2.27 mo. for CAPIRI arm and 54.2%, 6.28 mo. and 3.12 mo. for IRI arm, respectively. Thirteen patients (27%) required dose modifications in CAPIRI arm and 4 patients (9%) in IRI arm and this difference was statistically significant (p=0.03). No chemotherapy related deaths were seen.

Conclusion: Monotherapy with Irinotecan appears as efficacious as CAPIRI in terms of OS with lesser requirement for dose modifications in patients with GBC after progression on first line gemcitabine-based chemotherapy. Irinotecan mono therapy may be considered as a standard of care in this scenario.

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LBA-3 CheckMate 459: Long-term (minimum follow-up 33.6 months) survival outcomes with nivolumab versus sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma

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Background: Patients with advanced hepatocellular carcinoma (aHCC) not amenable to surgical resection or locoregional therapy may be treated with multitargeted kinase inhibitors or immuno-oncology—based combination therapy. Sorafenib is approved as first-line (1L) therapy but provides only a modest survival benefit. Despite approved 1L therapies for aHCC, there remains an unmet need to prolong survival while improving treatment tolerability. The phase 3 CheckMate 459 study compared 1L nivolumab versus sorafenib in patients with aHCC; initial efficacy and safety data were previously presented (Yau et al. ESMO 2019; NCT02576509). The protocol-defined statistical significance threshold for overall survival (OS) was not met. Although

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LBA-001

First-line liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin in patients with pancreatic ductal adenocarcinoma: long-term follow-up results from a phase 1/2 study

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BACKGROUND

- FOLFIRINOX (non-liposomal irinotecan + 5-fluorouracil [5-FU] + leucovorin [LV] + oxaliplatin)[1] is an established first-line treatment for patients with metastatic pancreatic ductal adenocarcinoma (PDAC).[2]
  - However, non-liposomal irinotecan has a complex and rapid metabolism,[3] and a short half-life,[4] and its toxicity is dose-limiting.[3]
- Liposomal irinotecan (ONIVYDE® pegylated liposomal) may provide additional benefits over the non-liposomal formulation.
  - During circulation, 95% of irinotecan remains contained within the liposome.[5]
  - The active metabolite persisted in tumours for longer following administration of liposomal irinotecan (168 h) than with non-liposomal irinotecan (< 48 h) in a preclinical setting.[6]
  - Preclinical data suggest that prolonged exposure may be more important than high concentrations for cytotoxic activity.[7]
- Liposomal irinotecan is indicated, in combination with 5-FU and LV, for the treatment of adults with metastatic PDAC after disease progression following gemcitabine-based therapy.[5]

OBJECTIVE

- To evaluate the safety, tolerability and efficacy of the NALIRIFOX regimen (liposomal irinotecan + 5-FU/LV + oxaliplatin) as a first-line treatment for patients with locally advanced or metastatic PDAC.

METHODS

Study design

- This open-label phase 1/2 study (EudraCT 2015-003086-28; NCT02551991) was conducted in two parts:
  - dose exploration using a traditional 3 + 3 design
  - dose expansion.

Study population

- Patients were adults (≥ 18 years old) with:
  - unresectable, locally advanced, or metastatic PDAC
  - diagnosis ≤ 6 weeks before screening and who were not treated previously in the metastatic setting
  - Eastern Cooperative Oncology Group Performance Status score of 0 or 1
  - Karnofsky Performance Status score ≥ 70 (dose-expansion part only)
  - adequate organ function.

Treatment regimen

- During dose exploration, patients in four cohorts were treated on days 1 and 15 of each 28-day cycle with 5-FU 2400 mg/m^2 and LV 400 mg/m^2 in combination with the following doses of liposomal irinotecan (free base) and oxaliplatin, respectively:
  - cohort A, 70 mg/m^2 and 60 mg/m^2
  - cohort B, 50 mg/m^2 and 60 mg/m^2
  - cohort C, 50 mg/m^2 and 85 mg/m^2
  - cohort D, 55 mg/m^2 and 70 mg/m^2.
- The dose selected for expansion was based on dose-limiting toxicities and cumulative safety data from dose exploration.

Endpoints and analyses

- Safety (primary objective): treatment-emergent adverse events (TEAEs); dose-limiting toxicities (dose exploration only).
- Efficacy (secondary objective): progression-free survival (PFS; primary efficacy endpoint), overall survival (OS), best overall response, overall response rate, disease control rate at week 16, and duration of response.
  - Disease was assessed using Response Evaluation Criteria in Solid Tumours v1.1 at screening, every 8 weeks thereafter, and at the end of study treatment.
  - Assessments continued until radiologically determined progressive disease; for the analyses, data could be censored before progression or death was recorded (e.g. on initiation of a new anticancer therapy).
- Exploratory objective: response data according to tumour subtype (classical or basal-like; Moffitt schema[8]) were assessed using genomic profiling of archival samples (PurIST^{SM} RNAseq assay,[9] GeneCentric Therapeutics, Inc.).
- The long-term follow-up results reported here focus on the patients who received the selected dose (pooled population receiving liposomal irinotecan 50 mg/m^2 and oxaliplatin 60 mg/m^2; pooled population 50/60); data cut-off 26 February 2020.

RESULTS

Patient disposition and baseline characteristics

- Overall, 31 patients were treated during dose exploration, and the pooled population 50/60 comprised 32 patients (seven from dose exploration cohort B and 25 from dose expansion) (Table 1).
  - One patient was still receiving treatment at data cut-off.
- In the pooled population 50/60, the median age was 58 years, 43.8% of patients were men, 87.5% had metastatic disease at baseline, and 56.3% had an Eastern Cooperative Oncology Group Performance Status score of 1 (Table 1).
- Mean (standard deviation) durations of treatment in the pooled population 50/60 were: liposomal irinotecan, 223.4 (202.49) days; oxaliplatin, 209.3 (197.96) days; 5-FU, 225.5 (202.59) days; and LV, 223.4 (202.49) days.

Dose selection

- The 50/60 dose received by cohort B was selected for expansion (Table 2).

Pooled population 50/60

Safety

- Treatment-related TEAEs of grade 3 or higher occurred in 22 patients (68.8%), and the most common were neutropaenia, febrile neutropaenia and hypokalaemia (Table 2).
  - No patients in the pooled population 50/60 experienced treatment-related grade ≥ 3 peripheral sensory neuropathy or fatigue.
  - Treatment-related grade ≥ 3 peripheral sensory neuropathy and fatigue were observed in cohort C (one patient) and cohort A (one patient), respectively.
- Three TEAEs led to death (malignant gastrointestinal obstruction, upper gastrointestinal haemorrhage and disease progression), but none were considered to be treatment related.
- Serious treatment-related TEAEs were reported for 10 patients (31.3%). The most common were febrile neutropaenia and nausea (three patients, 9.4%, in each case).

Efficacy

- Median PFS was 9.2 months (95% confidence internal [CI]: 7.69–11.96) and OS was 12.6 months (95% CI: 8.74–18.69) (Figure 1).
- The best overall responses were complete response in one patient (3.1%; the patient had locally advanced PDAC), stable disease in 15 patients (46.9%) and partial response in 10 patients (31.3%).
- Overall response rate was 34.4% (95% CI: 18.6–53.2%).
- Disease control rate at week 16 was 71.9% (95% CI: 53.3–86.3%).
- Median duration of response was 9.4 months (95% CI: 3.52–not estimable).

Genomic profiling

- Tumour subtype and tumour-response data were available for nine patients (eight had the classical subtype and one had the basal-like subtype) (Figure 2).
  - PFS values were 7.7–17.8 months and 9.6 months, respectively.

Table 1. Baseline demographic and clinical characteristics

	Dose-exploration cohorts				Dose-expansion cohort	Pooled population
	A (70/60[a]) (n = 7)	B (50/60[a]) (n = 7)	C (50/85[a]) (n = 10)	D (55/70[a]) (n = 7)	(50/60[a]) (n = 25)	(50/60[a,b]) (n = 32)
Age (years), median (range)	64.0 (58–78)	57.0 (44–74)	66.5 (57–73)	61.0 (54–73)	58.0 (39–76)	58.0 (39–76)
Age group, n (%) ≥ 65 years	4 (57.1)	4 (57.1)	3 (30.0)	4 (57.1)	19 (76.0)	23 (71.9)
Men, n (%)	1 (14.3)	3 (42.9)	8 (80.0)	5 (71.4)	11 (44.0)	14 (43.8)
Race, n (%) white	6 (85.7)	7 (100)	9 (90.0)	7 (100)	21 (84.0)	28 (87.5)
Tumour stage at diagnosis, n (%)						
IIA[c]	0	0	0	0	1 (4.0)	1 (3.1)
III	3 (42.9)	1 (14.3)	2 (20.0)	2 (28.6)	2 (8.0)	3 (9.4)
IV	4 (57.1)	6 (85.7)	8 (80.0)	5 (71.4)	22 (88.0)	28 (87.5)
ECOG Performance Status, n (%)						
Fully active (score = 0)	1 (14.3)	6 (85.7)	6 (60.0)	5 (71.4)	8 (32.0)	14 (43.8)
Restricted activity (score ≥ 1)	6 (85.7)	1 (14.3)	4 (40.0)	2 (28.6)	17 (68.0)	18 (56.3)

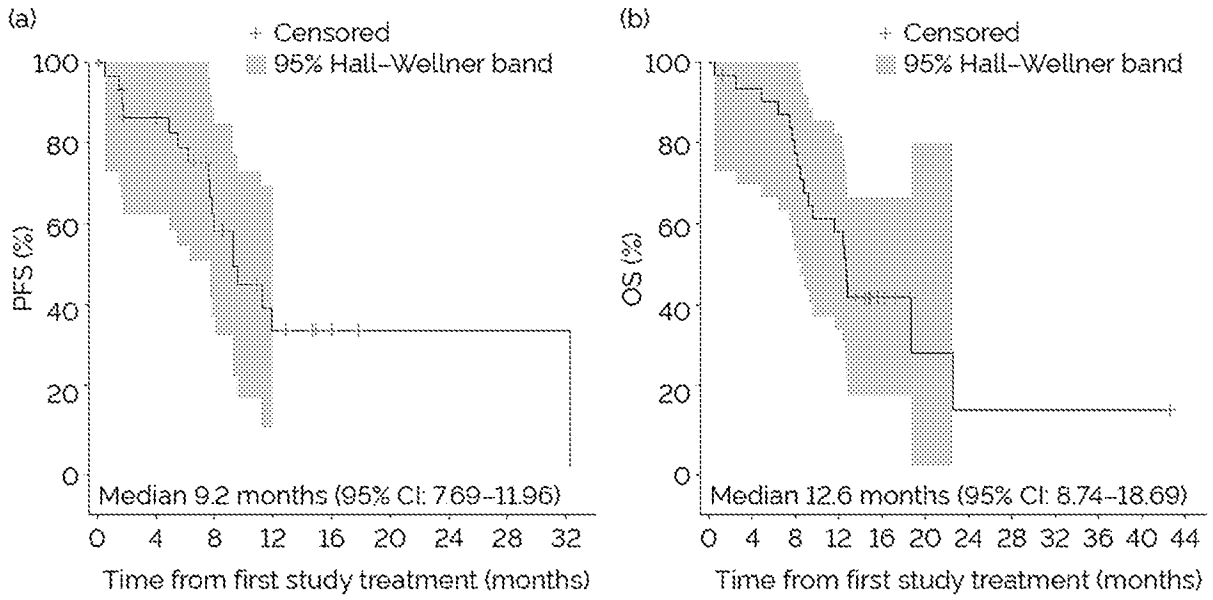
[a]Dose of liposomal irinotecan (free base)/dose of oxaliplatin expressed in mg/m² administered in combination with 5-fluorouracil 2400 mg/m² and leucovorin 400 mg/m² on days 1 and 15 of each 28-day cycle. [b]Comprises cohorts assigned to receive liposomal irinotecan 50 mg/m² and oxaliplatin 60 mg/m² during the dose-exploration or dose-expansion parts of the study. [c]One patient in the dose-expansion cohort had a diagnosis of stage IIA but entered the treatment phase with a diagnosis of stage IV.
ECOG, Eastern Cooperative Oncology Group

Table 2. Dose selection and treatment-emergent adverse events

	Dose-exploration cohorts				Dose-expansion cohort	Pooled population
	A (70/60[a]) (n = 7)	B (50/60[a]) (n = 7)	C (50/85[a]) (n = 10)	D (55/70[a]) (n = 7)	(50/60[a]) (n = 25)	(50/60[a,b]) (n = 32)
Tolerability assessment during dose exploration	Not tolerable	Tolerable	Not tolerable	Not tolerable		
Reason	DLT(s) in > 1 patient	DLT and assessment of cumulative safety data	DLT(s) in > 1 patient	Assessment of cumulative safety data, including TEAEs of grade ≤ 3 (not shown)		
DLTs (number of patients)	DLTs in 2 patients: neutropaenia infection (1), neutropaenic sepsis (1)	DLT in 1 patient: febrile neutropaenia (1)	DLTs in 2 patients: diarrhoea (2), vomiting (1), anal fissure (1), anal inflammation (1), proctalgia (1)	None		
Any TEAE	7 (100)	7 (100)	10 (100)	7 (100)	25 (100)	32 (100)
Leading to dose discontinuation[c]	5 (71.4)	1 (14.3)	3 (30.0)	3 (42.9)	7 (28.0)	8 (25.0)
Leading to dose adjustment[c]	2 (28.6)	4 (57.1)	7 (70.0)	4 (57.1)	22 (88.0)	26 (81.3)
Any serious TEAE	6 (85.7)	2 (28.6)	7 (70.0)	4 (57.1)	15 (60.0)	17 (53.1)
Leading to death	0	1 (14.3)	1 (10.0)	1 (14.3)	2 (8.0)	3 (9.4)
Treatment-related[d]	4 (57.1)	1 (14.3)	5 (50.0)	4 (57.1)	9 (36.0)	10 (31.3)
Any treatment-related TEAE	6 (85.7)	7 (100)	9 (90.0)	7 (100)	25 (100)	32 (100)
Grade ≥ 3	6 (85.7)	4 (57.1)	8 (80.0)	5 (71.4)	18 (72.0)	22 (68.8)
Treatment-related TEAEs[e] of grade ≥ 3 in ≥ 5% of the pooled population						
Neutropaenia	1 (14.3)	2 (28.6)	3 (30.0)	1 (14.3)	8 (32.0)	10 (31.3)
Febrile neutropaenia	0	1 (14.3)	0	0	3 (12.0)	4 (12.5)
Neutrophil count decreased	0	0	1 (10.0)	0	3 (12.0)	3 (9.4)
Anaemia	0	1 (14.3)	0	0	1 (4.0)	2 (6.3)
Diarrhoea	3 (42.9)	1 (14.3)	4 (40.0)	1 (14.3)	2 (8.0)	3 (9.4)
Nausea	0	0	2 (20.0)	0	3 (12.0)	3 (9.4)
Vomiting	1 (14.3)	0	3 (30.0)	0	2 (8.0)	2 (6.3)
Hypokalaemia	1 (14.3)	2 (28.6)	2 (20.0)	2 (25.6)	2 (8.0)	4 (12.5)
Hyponatraemia	0	0	0	0	2 (8.0)	2 (6.3)
Alanine aminotransferase increased	0	0	0	0	2 (8.0)	2 (6.3)
Gamma-glutamyltransferase increased	0	0	0	0	2 (8.0)	2 (6.3)
Lymphocyte count decreased	0	0	0	0	2 (8.0)	2 (6.3)
White blood cell count decreased	0	0	0	0	2 (8.0)	2 (6.3)

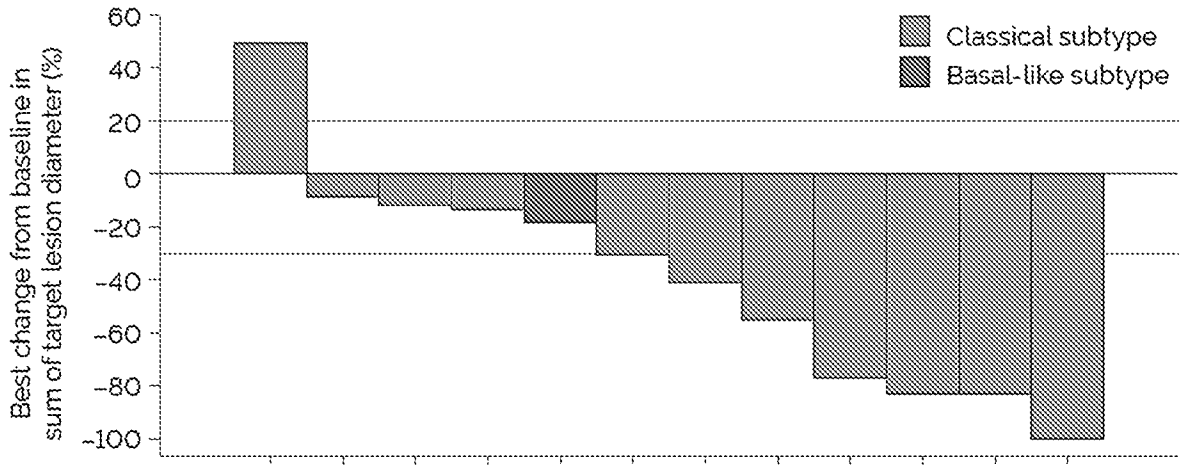
Data are number (%) of patients from the safety population unless stated otherwise. Events were coded according to the preferred terms in the Medical Dictionary for Regulatory Activities, v20.1, and toxicity was graded using National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.
[a]Dose of liposomal irinotecan (free base)/dose of oxaliplatin expressed in mg/m² administered in combination with 5-fluorouracil 2400 mg/m² and leucovorin 400 mg/m² on days 1 and 15 of each 28-day cycle. [b]Comprises cohorts assigned to receive liposomal irinotecan 50 mg/m² and oxaliplatin 60 mg/m² during the dose-exploration or dose-expansion parts of the study. [c]Refers to discontinuation or adjustment in dose for any of the four treatments administered. [d]Comprises TEAEs considered by the investigator to be related to any of the four treatments administered or for which the relationship was missing.
DLT, dose-limiting toxicity; TEAE, treatment-emergent adverse event

Figure 1. PFS (a) and OS (b) in the pooled population 50/60[a]



Data are from the safety population. Disease progression was assessed according to RECIST v1.1. PFS and OS were analysed using the Kaplan–Meier method. Median (95% CI) values were calculated using the Brookmeyer–Crowley method. One patient with minimal progressive disease as per RECIST v1.1 was approved for treatment continuation because the investigator believed there was a benefit from treatment. PFS time for this patient ended at the date of progressive disease. [a]Comprises cohorts assigned to receive liposomal irinotecan (free base) 50 mg/m² and oxaliplatin 60 mg/m², in combination with 5-fluorouracil 2400 mg/m² and leucovorin 400 mg/m², on days 1 and 15 of each 28-day cycle during either the dose-exploration or dose-expansion parts of the study.
CI, confidence interval; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours.

Figure 2. Tumour-response and PFS data



Cohort	A	Ex	B	D	Ex	A	Ex	Ex	Ex	Ex	Ex	Ex
Dose	70/60	**50/60**	**50/60**	55/70	**50/60**	70/60	**50/60**	**50/60**	**50/60**	**50/60**	**50/60**	**50/60**
PFS, months	3.0	7.8	17.8	10.9	9.6	0.6	9.2	14.9	7.7	9.2	14.7	10.9
Censored for PFS?			Yes			Yes		Yes			Yes	Yes

Patients in the pooled population (n = 9) are those for whom dose is given as 50/60 (liposomal irinotecan (free base) 50 mg/m² and oxaliplatin 60 mg/m², in combination with 5-fluorouracil 2400 mg/m² and leucovorin 400 mg/m², on days 1 and 15 of each 28-day cycle in the dose-exploration or dose-expansion parts of the study).
A–D, cohorts from the dose-exploration part of the study; Ex, dose-expansion cohort; PFS, progression-free survival.

Conclusions

- No new safety signals were observed with first-line NALIRIFOX in patients with locally advanced or metastatic PDAC, and anti-tumour activity was promising.
- The ongoing phase 3 NAPOLI-3 study (EudraCT 2018-003585-14, NCT04083235) will compare first-line NALIRIFOX with gemcitabine + nab-paclitaxel in adults with metastatic PDAC.

References

1. Conroy T *et al. N Engl J Med* 2011;364:1817–25.
2. Ducreux M *et al. Ann Oncol* 2015;26 Suppl. 5:v56–68.
3. de Man FM *et al. Clin Pharmacokinet* 2018;57:1229–54.
4. Pharmacia & Upjohn Company LLC. Prescribing information, CAMPTOSAR® (irinotecan) injection, for intravenous use. US Food and Drug Administration, January 2020. Available from: http://labeling.pfizer.com/ShowLabeling.aspx?id=533 (Accessed June 2020).
5. Les Laboratoires Servier. Summary of product characteristics, ONIVYDE pegylated liposomal 4.3 mg/mL concentrate for solution for infusion. European Medicines Agency, May 2020. Available from: https://www.ema.europa.eu/documents/product-information/onivyde-pegylated-liposomal-epar-product-information_en.pdf (Accessed June 2020).
6. Kalra AV *et al. Cancer Res* 2014;74:7003–13.
7. Gerrits CJ *et al. Br J Cancer* 1997;76:952–62.
8. Moffitt RA *et al. Nat Genet* 2015;47:1168–78.
9. Rashid NU *et al. Clin Cancer Res* 2020;26:82–92.

Author contributions

All authors have contributed to study conception/design, drafting the publication or revising it critically for scientific accuracy and important intellectual content, and final approval of the publication.

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First-line liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin in patients with pancreatic ductal adenocarcinoma: long-term follow-up results from a phase 1/2 study

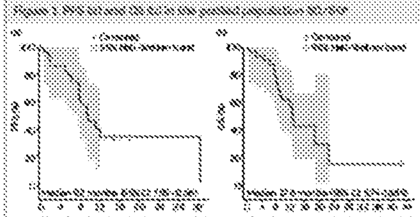
LBA-001

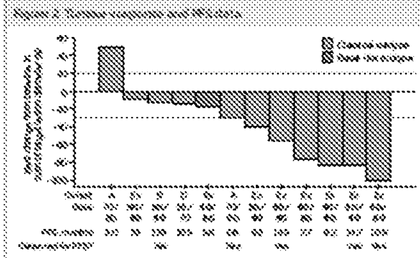
BACKGROUND

OBJECTIVES

METHODS

RESULTS





CONCLUSIONS

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2020 Wainberg Presentation

ESMO WORLD CONGRESS ON Gastrointestinal Cancer | 2020 VIRTUAL

First-line liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin in patients with pancreatic ductal adenocarcinoma: long-term follow-up results from a phase 1/2 study

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Abstract LBA-1

Disclosures

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Zev A. Wainberg	Research support (to institution): Five Prime Therapeutics, Ipsen, Novartis, Plexxikon; Consulting: AstraZeneca, Bayer, Daiichi Sankyo, Eli Lilly, Five Prime Therapeutics, Ipsen, Merck, QED Therapeutics
Tanios Bekaii-Saab	1Globe Health Institute, AbGenomics, Amgen, Array BioPharma, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Biomedical, Bristol-Myers Squibb, Celgene, Clovis Oncology, Eli Lilly, Exelixis, Genentech, Immuneering, Imugene, Incyte, Ipsen, Merck, Pancreatic Cancer Action Network (PanCAN), Seattle Genetics, Sobi, Sun BioPharma, Treos Bio
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Farshid Dayyani	Research support (to institution): Amgen, AstraZeneca, Bristol-Myers Squibb, Exelixis, Ipsen, Taiho Pharmaceutical; Consultant: Eisai, Exelixis, Foundation Medicine, Genentech, Ipsen, Natera, QED Therapeutics; Speakers' bureau: Amgen, Deciphera Pharmaceuticals, Eisai, Exelixis, Ipsen, Natera, Sirtex Medical; Spouse employee: Roche Diagnostics
Teresa Macarulla	Research support: AstraZeneca, Agios, Aslan Pharmaceuticals, Bayer, Biogen, Celgene, Eli Lilly, Genentech, Halozyme Therapeutics, Immonomedics, Merrimack Pharmaceuticals, Millennium Pharmaceuticals, Novartis, Novocure, OncoMed Pharmaceuticals, Pfizer, Pharmacyclics, Roche; Honoraria: Eli Lilly, Ipsen, Roche, Sanofi, Sanofi Genzyme, Shire, Tesaro; Consulting: Baxalta, Celgene, H3 Biomedicine, Incyte, QED Therapeutics, Sanofi Genzyme, Shire, Servier; Speakers' bureau: Celgene, Sanofi, Shire; Travel/accommodation/expenses: Bayer, H3 Biomedicine, Merck, Sanofi
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Bruce Belanger	Employment: Ipsen
Fiona Maxwell	Employment and stock/other ownership: Ipsen
Yan Moore	Employment, leadership and stock/other ownership: Ipsen
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Tiffany Wang	Employment and stock/other ownership: Ipsen
Bin Zhang	Employment, stock/other ownership and patents/royalties/other intellectual property: Ipsen
Andrew Dean	Non-paid consulting: Shire, Specialised Therapeutics; Travel/accommodation/expenses: Amgen

NCI, National Cancer Institute; NIH, National Institutes of Health

Liposomal irinotecan in patients with mPDAC

There is a need for therapies that prolong survival and are well tolerated for patients with PDAC,[1] who typically present with metastatic disease and have a poor prognosis[2]

- Established first-line treatment options for mPDAC include:
  - Gem/nab (gemcitabine + albumin-bound paclitaxel particles)[3]
  - FOLFIRINOX (non-liposomal irinotecan + 5-FU + LV + OX)[4]
- Non-liposomal irinotecan is an established component of the FOLFIRINOX combination but has a complex and rapid metabolism,[5] a short half-life,[6] and its toxicity is dose-limiting[5]
- Liposomal irinotecan (ONIVYDE® pegylated liposomal[a]) may provide additional benefits over the non-liposomal formulation
  - During circulation, 95% of irinotecan remains contained within the liposome[7]
  - The active metabolite persisted in tumours for longer following administration of liposomal irinotecan (168 h) than with non-liposomal irinotecan (< 48 h) in a preclinical setting[8]
  - Preclinical data suggest that prolonged exposure may be more important than high concentrations for cytotoxic activity[9]
- Liposomal irinotecan is indicated, in combination with 5-FU and LV, for the treatment of adults with mPDAC after disease progression following gemcitabine-based therapy[7]

[a]Historical names include nal-IRI, MM-398 and PEP02. 5-FU, 5-fluorouracil; LV, leucovorin; mPDAC, metastatic pancreatic ductal adenocarcinoma; OX, oxaliplatin; PI, prescribing information; SmPC, summary of product characteristics. 1. Hall BR *et al. Oncotarget* 2018;9:19396–405. 2. National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program. Cancer stat facts: pancreatic cancer. Available from: https://seer.cancer.gov/statfacts/html/pancreas.html (Accessed Jun 2020). 3. Von Hoff DD *et al. N Engl J Med* 2013;369:1691–703. 4. Conroy T *et al. N Engl J* Med 2011;364:1817–25; 5. de Man FM *et al. Clin Pharmacokinet* 2018;57:1229–54. 6. CAMPTOSAR US PI, Jan 2020. 7. ONIVYDE EU SmPC May 2020. 8. Kalra AV *et al. Cancer Res* 2014;74:7003–13. 9. Gerrits CJ *et al. Br J Cancer* 1997 76:952–62

Study objectives

This phase 1/2 study assessed liposomal irinotecan in combination with 5-FU/LV and OX ('NALIRIFOX') in treatment-naïve[a] patients with locally advanced or mPDAC

Primary objectives

- Evaluate the safety and tolerability of NALIRIFOX
- Characterize DLTs associated with NALIRIFOX and determine the recommended dose for future development

Secondary efficacy objectives

Antitumour activity

RECIST v1.1 assessment at screening (baseline), every 8 weeks until PD and at EoT

- PFS and OS
- Other clinical responses: best overall response, overall response rate, DCR at week 16, duration of response

Exploratory objectives included

Biomarkers – genomic profiling

When available, archival tumour samples were analysed for patients who had given additional consent

- Subtyped as classical or basal-like (Moffitt schema,[1] as used in COMPASS trial[2]) using PurIST[SM] RNAseq assay[3]
- PFS and best change from baseline in sum of target-lesion diameter

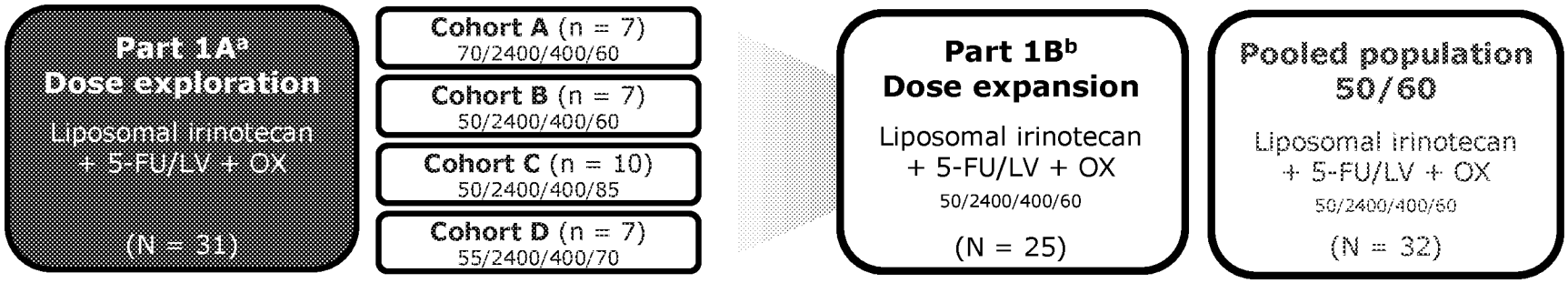
[a]Not previously treated in the metastatic setting.

5-FU, 5-fluorouracil; DCR, disease control rate; DLT, dose-limiting toxicity; EoT, end of treatment; LV, leucovorin; mPDAC, metastatic pancreatic ductal adenocarcinoma; OS, overall survival; OX, oxaliplatin; PD, progressive disease; PFS, progression-free survival; PurIST, Purity Independent Subtyping of Tumors; RECIST, Response Evaluation Criteria in Solid Tumors; RNA, ribonucleic acid.

1. Moffitt RA *et al. Nat Genet* 2015;47:1168–78. 2. Aung KL *et al. Clin Cancer Res* 2018;24:1344–54. 3. GeneCentric Therapeutics, Inc; Rashid NU *et al. Clin Cancer Res* 2020;26:82–92

Study methods

Open-label, two-part phase 1/2 trial enrolled patients at 15 sites
Australia (1 site), Spain (4 sites) and the USA (10 sites)



- **Dose-exploration**: safety run-in (traditional 3 + 3 design) performed to confirm an appropriate dose for NALIRIFOX in the **dose-expansion** part
- **Pooled population 50/60**: all patients who received liposomal irinotecan, 50 mg/m^2 (free base), 5-FU 2400 mg/m^2, LV 400 mg/m^2 and OX 60 mg/m^2
- **Long-term follow-up results**: data cut-off 26 Feb 2020

Study drugs were administered on days 1 and 15 of each 28-day cycle
[a]Enrolled between 26 Oct 2015 and 28 Mar 2018. [b]Enrolled between 11 Jun 2018 and 29 Oct 2018.
5-FU, 5-fluorouracil; LV, leucovorin; NALIRIFOX, liposomal irinotecan+ 5-FU/LV + OX; OX, oxaliplatin

Study population

Inclusion criteria

- ≥ 18 years of age
- Histologically/cytologically confirmed PDAC
- Unresectable, locally advanced or metastatic disease
- Diagnosed ≤ 6 weeks before screening
- ≥ 1 measurable lesion using CT or MRI, defined by RECIST v1.1
- Adequate haematologic parameters and liver function
- ECOG Performance Status score 0 or 1
- KPS ≥ 70 (dose-expansion only)

Exclusion criteria

- Prior treatment of locally advanced or mPDAC (palliative radiotherapy or biliary-stent placement permitted)
- Any second malignancy in the prior 3 years
- Use of strong CYP3A4 inhibitors/inducers
- Known contraindications/hypersensitivity to any study drug
- Clinically significant GI disorder, active infection or unexplained fever > 38.5°C at screening/first dose
- Concurrent illnesses/other conditions deemed likely to interfere with the study

CT, computed tomography; CYP, cytochrome P450; ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; KPS, Karnofsky Performance Score; mPDAC, metastatic pancreatic ductal adenocarcinoma; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria in Solid Tumors

Demographics, characteristics and disposition

	Dose-exploration cohorts				Dose-expansion cohort N = 25	Pooled population (50/60[a,b]) N = 32
	A (70/60[a]) (n = 7)	B (50/60[a]) (n = 7)	C (50/85[a]) (n = 10)	D (55/70[a]) (n = 7)		
Age (years)						
Median (range)	64 (58–78)	57 (44–74)	66.5 (57–73)	61 (54–73)	58 (39–76)	58 (39–76)
Age group, n (%)						
< 65 Years	4 (57.1)	4 (57.1)	3 (30.0)	4 (57.1)	19 (76.0)	23 (71.9)
Sex, n (%)						
Men	1 (14.3)	3 (42.9)	8 (80.0)	5 (71.4)	11 (44.0)	14 (43.8)
Race, n (%)						
White	6 (85.7)	7 (100)	9 (90.0)	7 (100)	21 (84.0)	28 (87.5)
Tumour stage at diagnosis						
IIA[c]	0	0	0	0	1 (4.0)	1 (3.1)
III	3 (42.9)	1 (14.3)	2 (20.0)	2 (28.6)	2 (8.0)	3 (9.4)
IV	4 (57.1)	6 (85.7)	8 (80.0)	5 (71.4)	22 (88.0)	28 (87.5)
Baseline ECOG Performance Status score						
Fully active (ECOG 0)	1 (14.3)	6 (85.7)	6 (60.0)	5 (71.4)	8 (32.0)	14 (43.8)
Restricted activity (ECOG 1)	6 (85.7)	1 (14.3)	4 (40.0)	2 (28.6)	17 (68.0)	18 (56.3)
Disposition						
Discontinued treatment,[d] n (%)	7 (100)	7 (100)	10 (100)	7 (100)	24 (96.0)	31 (96.9)

[a]Dose of liposomal irinotecan (free base)/dose of OX expressed in mg/m^2 to be administered in combination with 5-FU 2400 mg/m^2 and LV 400 mg/m^2 every 2 weeks.
[b]Comprises cohorts assigned to receive liposomal irinotecan 50 mg/m^2 and OX 60 mg/m^2 during the dose-exploration or dose-expansion parts of the study.
[c]One patient in dose-expansion cohort was diagnosed as stage IIA, but entered the treatment phase as stage IV. [d]At time of data cut-off (26 Feb 2020).
5-FU, 5-fluorouracil; ECOG, Eastern Cooperative Oncology Group; LV, leucovorin; OX, oxaliplatin

Safety – overview of DLTs and TEAEs

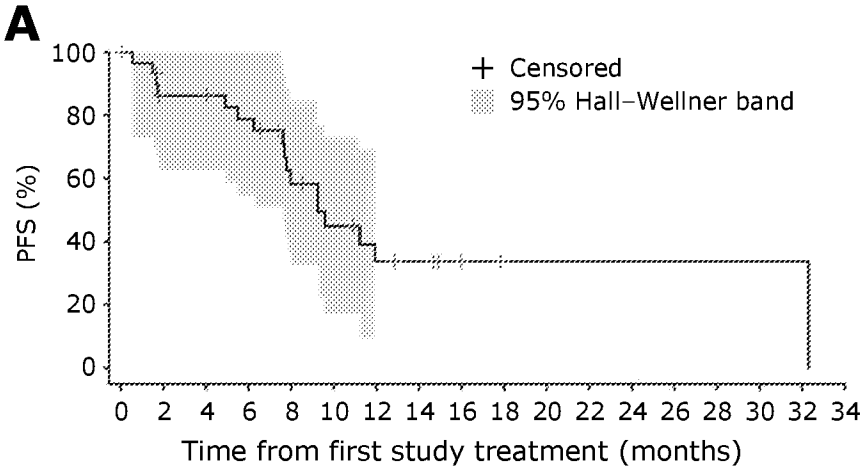
	Dose-exploration cohorts				Dose-expansion cohort (50/60) (N = 25)	Pooled population (50/60) (N = 32)
	A (70/60) (n = 7)	B (50/60) (n = 7)	C (50/85) (n = 10)	D (55/70) (n = 7)		
Dose-safety assessment during dose escalation (rationale) and details of DLTs	Not tolerable (DLTs) DLTs in 2 patients: neutropaenia infection (1 patient), neutropaenic sepsis (1)	Tolerable (DLTs and cumulative safety data) DLT in 1 patient: febrile neutropaenia (1 patient)	Not tolerable (DLTs) DLTs in 2 patients: diarrhoea (2 patients), vomiting (1), anal fissure (1), anal inflammation (1), proctalgia (1)	Not tolerable (cumulative safety data: TEAEs of grade ≥ 3) No DLTs; cumulative safety data are not shown here	NA	NA
Any TEAE	7 (100)	7 (100)	10 (100)	7 (100)	25 (100)	32 (100)
Leading to dose discontinuation[a]	5 (71.4)	1 (14.3)	3 (30.0)	3 (42.9)	7 (28.0)	8 (25.0)
Leading to dose adjustment[a]	2 (28.6)	4 (57.1)	7 (70.0)	4 (57.1)	22 (88.0)	26 (81.3)
Any serious TEAE	6 (85.7)	2 (28.6)	7 (70.0)	4 (57.1)	15 (60.0)	17 (53.1)
Leading to death	0	1 (14.3)	1 (10.0)	1 (14.3)	2 (8.0)	3 (9.4)[b]
Treatment-related[c]	4 (57.1)	1 (14.3)	5 (50.0)	4 (57.1)	9 (36.0)	10 (31.3)[d]
Treatment-related TEAE	6 (85.7)	7 (100)	9 (90.0)	7 (100)	25 (100)	32 (100)
Treatment-related of grade ≥ 3	6 (85.7)	4 (57.1)	8 (80.0)	5 (71.4)	18 (72.0)	22 (68.8)
Treatment-related TEAE of grade ≥ 3 in at least 5% of the pooled population						
Neutropaenia	1 (14.3)	2 (28.6)	3 (30.0)	1 (14.3)	8 (32.0)	10 (31.3)
Febrile neutropaenia	0	1 (14.3)	0	0	3 (12.0)	4 (12.5)
Neutrophil count decreased	0	0	1 (10.0)	0	3 (12.0)	3 (9.4)
Anaemia	0	1 (14.3)	0	0	1 (4.0)	2 (6.3)
Diarrhoea	3 (42.9)	1 (14.3)	4 (40.0)	1 (14.3)	2 (8.0)	3 (9.4)
Nausea	0	0	2 (20.0)	0	3 (12.0)	3 (9.4)
Vomiting	1 (14.3)	0	3 (30.0)	0	2 (8.0)	2 (6.3)
Hypokalaemia	1 (14.3)	2 (28.6)	2 (20.0)	2 (28.6)	2 (8.0)	4 (12.5)
Hyponatraemia	0	0	0	0	2 (8.0)	2 (6.3)
Alanine aminotransferase increased	0	0	0	0	2 (8.0)	2 (6.3)
GGT increased	0	0	0	0	2 (8.0)	2 (6.3)
Lymphocyte count decreased	0	0	0	0	2 (8.0)	2 (6.3)
White blood cell count decreased	0	0	0	0	2 (8.0)	2 (6.3)

Treatment-related grade ≥ 3 peripheral sensory neuropathy present only in cohort C (1 patient); fatigue present only in cohort A (1 patient)

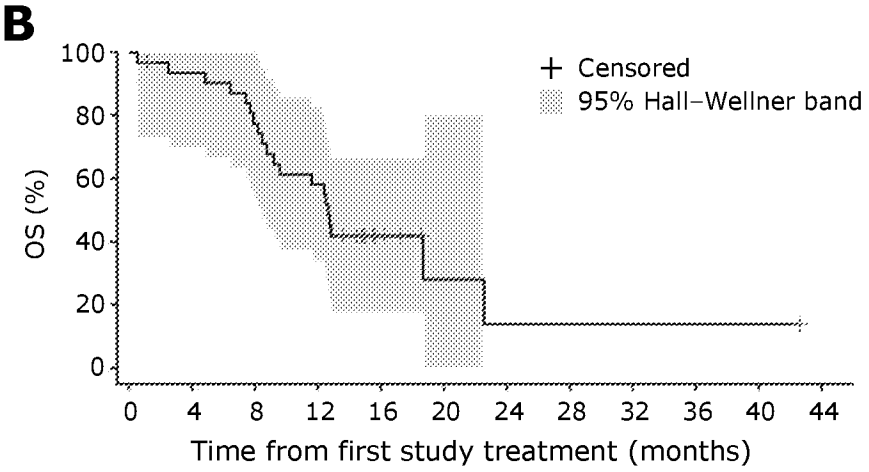
Data are number (%) of patients from the safety population unless otherwise stated. Events were coded according to the preferred terms in the Medical Dictionary for Regulatory Activities, version 20.1, and toxicity was graded using National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. [a]Refers to discontinuation or adjustment in dose for any of the four treatments administered. [b]Malignant gastrointestinal obstruction, upper gastrointestinal haemorrhage and disease progression, none were considered related to treatment. [c]Comprises TEAEs considered by the investigator to be related to any of the four treatments administered or for which the relationship was missing. [d]Most common were febrile neutropenia and nausea, each reported in 3 patients (9.4%). DLT, dose-limiting toxicity; GGT, gamma-glutamyltransferase; grd, grade; NA, not applicable; TEAE, treatment-emergent adverse event; TR, treatment related

Clinical response (I)

Kaplan–Meier curves for PFS (A) and OS (B): pooled population 50/60 (N = 32)



Median PFS: 9.2 months
[95% CI: 7.69–11.96]



Median OS: 12.6 months
[95% CI: 8.74–18.69]

Data are from the safety population. PFS and OS were analysed using the Kaplan–Meier method. Median [95% CI] values were calculated using the Brookmeyer–Crowley method. One patient with minimal progressive disease per RECIST v1.1 was approved for treatment continuation as the investigator believed there was a benefit from treatment. Data from this patient were censored at PD date.
CI, confidence interval; OS, overall survival; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors

Clinical response (II)

	Dose-exploration cohorts				Dose-expansion cohort (50/60) (N = 25)	Pooled population (50/60) (N = 32)
	A (70/60) (n = 7)	B (50/60) (n = 7)	C (50/85) (n = 10)	D (55/70) (n = 7)		
Best overall response[a]						
CR	0	0	0	0	1 (4.0)	1 (3.1)[b]
PR	0	3 (42.9)	3 (30.0)	1 (14.3)	7 (28.0)	10 (31.3)
SD	2 (28.6)	3 (42.9)	1 (10.0)	3 (42.9)	12 (48.0)	15 (46.9)
PD	1 (14.3)	0	2 (20.0)	1 (14.3)	3 (12.0)	3 (9.4)
Non-PD/non-CR[c]	1 (14.3)[c]	0	0	0	0	0
NE	3 (42.9)	1 (14.3)	4 (40.0)	2 (28.6)	2 (8.0)	3 (9.4)
Overall response rate						
(CR + PR), rate [95% CI][d]	0 [0 –41.0]	42.9 [9.9–81.6]	30.0 [6.7–65.2]	14.3 [0.4–57.9]	32.0 [14.9–53.5]	34.4 [18.6–53.2]
Disease control rate at 16 weeks						
(CR + PR + SD), rate [95% CI][e]	42.9 [9.9–81.6]	71.4 [29.0–96.3]	40.0 [12.2–73.8]	28.6 [3.7–71.0]	72.0 [50.6–87.9]	71.9 [53.3–86.3]
Duration of response[f]	(n = 0)	(n = 3)	(n = 3)	(n = 1)	(n = 8)	(n = 11)
Median, months [95% CI]	NE [NE–NE]	28.4 [3.52–NE]	NE [NE–16.39]	NE [NE–NE]	9.4 [2.20–NE]	9.4 [3.52–NE]
Rate, % [95% CI], at:						
6 months	NE [NE–NE]	66.7 [9.4–99.2]	100 [29.2–100]	0 [0–97.5]	62.5 [24.5–91.5]	63.6 [30.8–89.1]
12 months	NE [NE–NE]	33.3 [0.8–90.6]	100 [29.2–100]	0 [0–97.5]	25.0 [3.2–65.1]	27.3 [6.0–61.0]
24 months	NE [NE–NE]	33.3 [0.8–90.6]	0 [0–70.8]	0 [0–97.5]	0 [0–36.9]	9.1 [0.2–41.3]

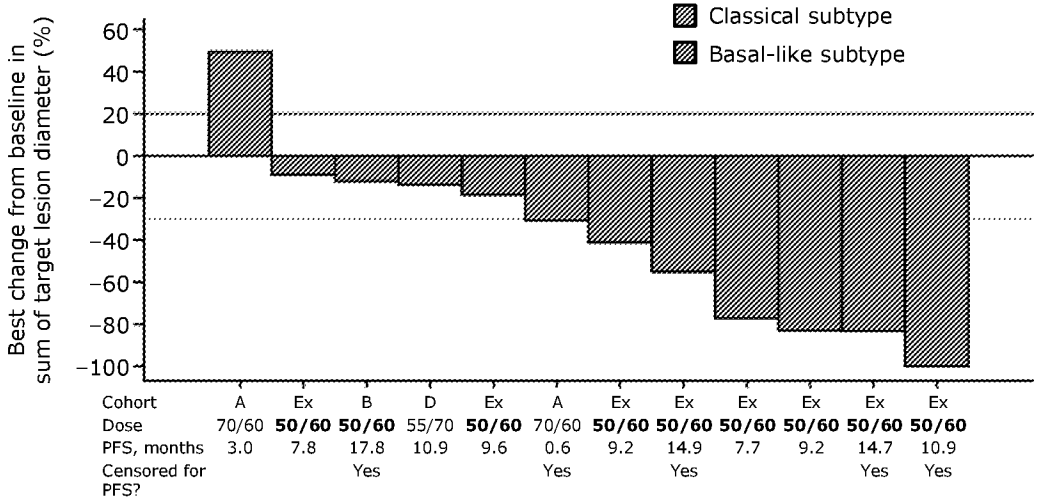
Data are from the safety population and with responses determined using RECIST v1.1 [a]Best response recorded from start of study treatment until disease progression or start of new anticancer therapy. [b]Patient received a diagnosis of locally advanced stage III disease. [c]As per the protocol at the time of their screening (version 1.0), one patient had a measurable lymph node lesion at screening that was too small to be considered a target lesion per RECIST 1.1 criteria. Consequently, this patient was only followed for NT lesions (hence non PD/non CR) but is considered in the summary of overall response. The protocol was later amended to require the presence of target lesion(s). [d]Proportion of patients with a CR or PR as the best overall response; 95% CIs were calculated using the Clopper–Pearson method. [e]Proportion of patients with CR, PR or SD at the week-16 assessment; patients who died, whose tumours were no longer assessed or who started new anticancer treatment before the week-16 assessment were not considered to have achieved disease control at week 16. [f]Time from the first date of response (CR or PR) to date of first documented radiologically determined PD per RECIST v1.1; duration of response was not calculated for patients who started a new anticancer treatment before the first response. CI, confidence interval; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease

Biomarkers – genomic profiling

Tumour samples were analysed for 16 patients

- Pooled population 50/60, n = 11
  - 10 in dose expansion, one in cohort B
- Cohort A (70/60), n = 3
- Cohort D (55/70), n = 1
- Plus one patient who gave consent for archived sample analysis but did not pass screening for the main study

Tumour response data were available for 12 patients



Cohort	A	Ex	B	D	Ex	A	Ex	Ex	Ex	Ex	Ex	Ex
Dose	70/60	**50/60**	**50/60**	55/70	**50/60**	70/60	**50/60**	**50/60**	**50/60**	**50/60**	**50/60**	**50/60**
PFS, months	3.0	7.8	17.8	10.9	9.6	0.6	9.2	14.9	7.7	9.2	14.7	10.9
Censored for PFS?			Yes			Yes		Yes			Yes	Yes

PFS in the pooled population 50/60

- Classical subtype: range 7.7–17.8 months (n = 8)
- Basal-like subtype: 9.6 months (n = 1)

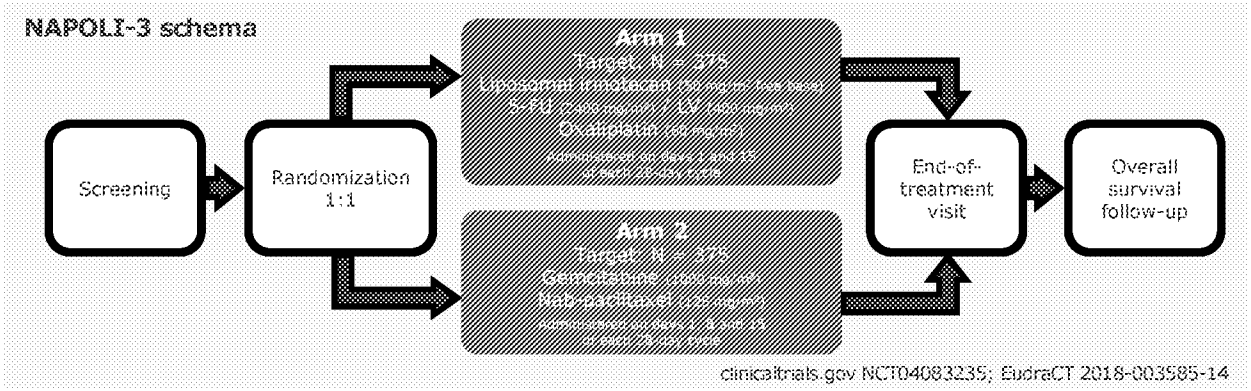
Ex, dose-expansion part; PFS, progression-free survival

Conclusions

Findings from this phase 1/2 study suggest that NALIRIFOX is tolerable for patients with previously untreated locally advanced or mPDAC

Regimen: liposomal irinotecan, 50 mg/m^2 (free base), 5-FU 2400 mg/m^2, LV 400 mg/m^2, OX 60 mg/m^2 on days 1 and 15 of each 28-day cycle

- No new safety signals were identified
- Antitumour activity (secondary outcome) was promising
  - Median PFS of 9.2 months (95% CI: 7.69–11.96)
  - Median OS of 12.6 months (95% CI: 8.74–18.69)
- The observed antitumour activity warrants further investigation
- Efficacy is the primary objective of the ongoing NAPOLI-3 phase 3 study in adults with previously untreated mPDAC



CI, confidence interval; LV, leucovorin; mPDAC, metastatic pancreatic ductal adenocarcinoma; NALIRIFOX, liposomal irinotecan + 5-FU/LV + OX; 5-FU, 5-fluorouracil; LV, leucovorin; OS, overall survival; OX, oxaliplatin; PFS, progression-free survival

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