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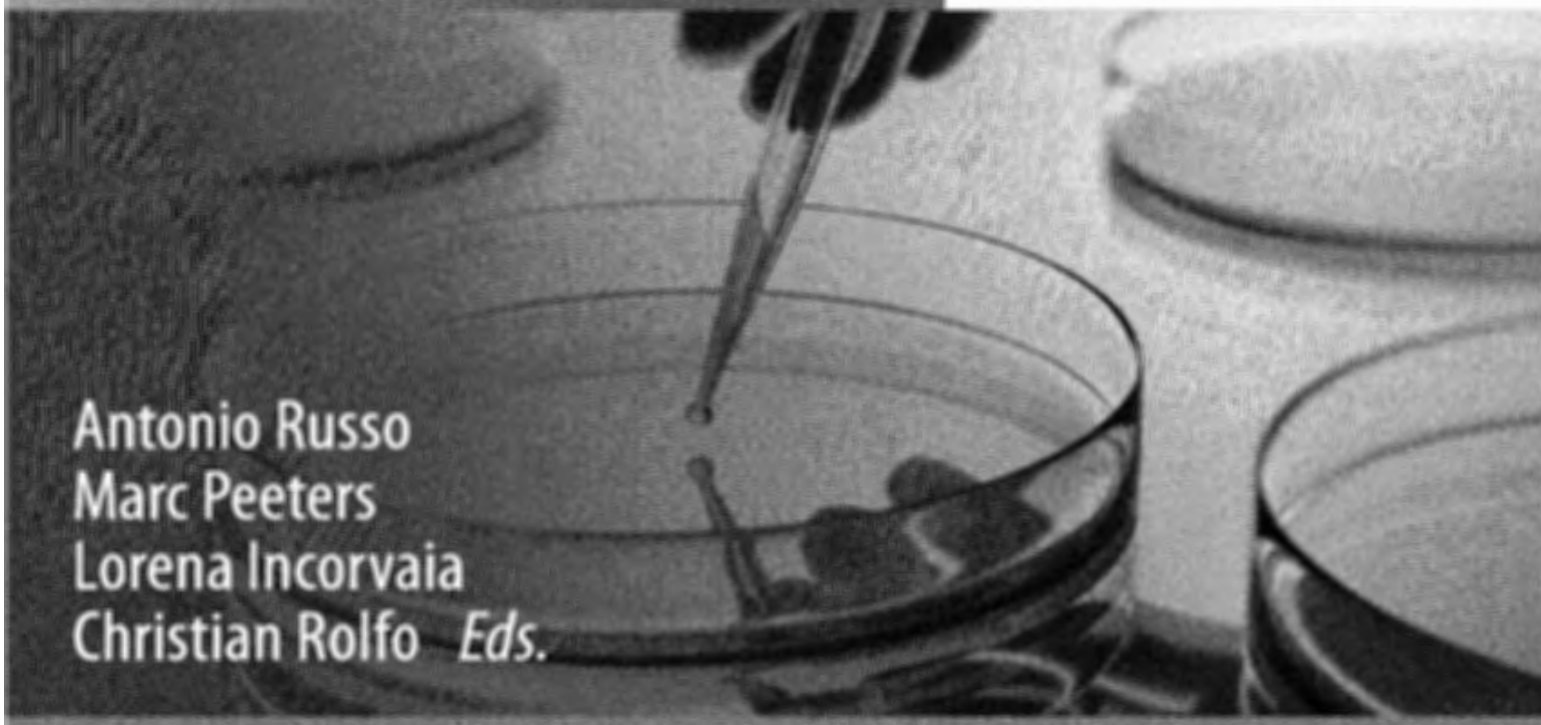

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Marc Peeters
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Christian Rolfo *Eds.*

Practical Medical Oncology Textbook

UNIVERSITÀ DEGLI STUDI DI PALERMO

Springer

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Practical Medical Oncology Textbook

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Preface

Clinical oncology is a rapidly evolving field. Within just a few years, increase in understanding of the molecular and immunological basis of cancer provided a strong base to clinical development of novel treatment options for patients across many cancer types. Several targeted therapies and immunotherapy are changing the clinical landscape and the natural history of many tumors, with an impact on patients survival. To maximize the patient benefit, prognostic and predictive biomarkers are under investigation to identify patients who will likely benefit from therapy, and multimodal diagnostic tools, such as liquid biopsy, are opening new frontiers to cancer diagnosis, screenings and therapeutic decisions.

In this textbook, many specialists in the field have covered many aspects of medical oncology. The first general section provides a comprehensive overview and background information on tumor biology and genetics, innovative technologies for clinical and translational research, and covers introductory topics on the main treatment modalities in the care of cancer patients. The following chapters are included in the clinical section on tumor presentations, diagnosis, prognosis, until the current state-of-the-art of medical treatment. It provides a systematic overview of all types of solid tumors, including epidemiology and cancer prevention, genetic aspects of hereditary cancers, differential diagnosis, typical signs and symptoms, diagnostic strategies and staging, and treatment modalities. Special attention is given to new and innovative treatments for cancer patients, such as targeted therapy and immunotherapy.

This textbook combines, therefore, essential information on clinical cancer medicine with a guide to the latest advances in molecular oncology and tumor biology. Expert commentaries at the end of each chapter highlight key points, offer hints for deeper insights, suggest further reading and discuss clinical application through the description of cases.

This textbook offers an invaluable, practice-oriented tool for medical students just beginning their clinical oncology studies, as well as medical oncology residents and young professionals.

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Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CAMPTOSAR safely and effectively. See full prescribing information for CAMPTOSAR.

CAMPTOSAR® (Irinotecan) Injection, intravenous infusion
Initial U.S. Approval: 1996

WARNING: DIARRHEA and MYELOSUPPRESSION
See full prescribing information for complete boxed warning.

- **Early and late forms of diarrhea can occur. Early diarrhea may be accompanied by cholinergic symptoms which may be prevented or ameliorated by atropine. Late diarrhea can be life threatening and should be treated promptly with loperamide. Monitor patients with diarrhea and give fluid and electrolytes as needed. Institute antibiotic therapy if patients develop ileus, fever, or severe neutropenia. Interrupt CAMPTOSAR and reduce subsequent doses if severe diarrhea occurs.**
- **Severe myelosuppression may occur.**

INDICATIONS AND USAGE

CAMPTOSAR is a topoisomerase inhibitor indicated for:

- First-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic carcinoma of the colon or rectum. (1)
- Patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy. (1)

DOSAGE AND ADMINISTRATION

- Colorectal cancer combination regimen 1: CAMPTOSAR 125 mg/m^2 intravenous infusion over 90 minutes on days 1, 8,15, 22 with LV 20 mg/m^2 intravenous bolus infusion on days 1, 8, 15, 22 followed by 5-FU intravenous bolus infusion on days 1, 8, 15, 22 every 6 weeks. (2.1)
- Colorectal cancer combination regimen 2: CAMPTOSAR 180 mg/m^2 intravenous infusion over 90 minutes on days 1, 15, 29 with LV 200 mg/m^2 intravenous infusion over 2 hours on days 1, 2, 15, 16, 29, 30 followed by 5-FU 400 mg/m^2 intravenous bolus infusion on days 1, 2, 15, 16, 29, 30 and 5-FU 600 mg/m^2 intravenous infusion over 22 hours on days 1, 2, 15, 16, 29, 30. (2.1)
- Colorectal cancer single agent regimen 1: CAMPTOSAR 125 mg/m^2 intravenous infusion over 90 minutes on days 1, 8, 15, 22 then 2-week rest. (2.2)
- Colorectal cancer single agent regimen 2: CAMPTOSAR 350 mg/m^2 intravenous infusion over 90 minutes on day 1 every 3 weeks. (2.2)

DOSAGE FORMS AND STRENGTHS

CAMPTOSAR Injection is available in three single-dose sizes:

- 2 mL-fill vial containing 40 mg irinotecan hydrochloride injection
- 5 mL-fill vial containing 100 mg irinotecan hydrochloride injection
- 15 mL-fill vial containing 300 mg irinotecan hydrochloride injection

CONTRAINDICATIONS

- Hypersensitivity to CAMPTOSAR or its excipients (4)

WARNINGS AND PRECAUTIONS

- **Diarrhea and Cholinergic Reactions**: Early diarrhea (occurring during or shortly after infusion of CAMPTOSAR) is usually transient and may be accompanied by cholinergic symptoms. Consider prophylactic or therapeutic administration of 0.25 mg to 1 mg of intravenous or subcutaneous atropine (unless clinically contraindicated). Late diarrhea (generally occurring more than 24 hours after administration of CAMPTOSAR) can occur. Monitor and replace fluid and electrolytes. Treat with loperamide. Use antibiotic support for ileus and fever. Interrupt CAMPTOSAR and reduce subsequent doses if severe diarrhea occurs. (5.1)
- **Myelosuppression**: Manage promptly with antibiotic support. Interrupt CAMPTOSAR and reduce subsequent doses if necessary. (5.2)
- **Patients with Reduced UGT1A1 Activity:** Individuals who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia following initiation of CAMPTOSAR treatment. (5.3)
- **Hypersensitivity:** Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed. Discontinue CAMPTOSAR if this occurs. (5.4)
- **Renal Impairment/Renal Failure:** Rare cases of renal impairment and acute renal failure have been identified, usually in patients who became volume depleted from severe vomiting and/or diarrhea. (5.5)
- **Pulmonary Toxicity:** Interstitial Pulmonary Disease (IPD)-like events, including fatalities, have occurred. Interrupt for new or progressive dyspnea, cough, and fever pending evaluation. If IPD diagnosed, discontinue and institute appropriate treatment as needed. (5.6)
- **Toxicity of the 5 Day Regimen:** CAMPTOSAR should not be used in combination with a regimen of 5-FU/LV administered for 4-5 consecutive days every 4 weeks outside of a clinical study. (5.7)
- **Embryofetal Toxicity:** CAMPTOSAR can cause fetal harm when administered to a pregnant woman. (5.9)
- **Patients with Hepatic Impairment:** In clinical trials, CAMPTOSAR has not been administered to patients with serum bilirubin > 2.0 mg/dL, or transaminases > 3 times ULN if no liver metastases, or transaminases > 5 times ULN if liver metastases. With the weekly dosage schedule, patients with total bilirubin levels 1.0-2.0 mg/dL had greater likelihood of grade 3-4 neutropenia. (5.10)

ADVERSE REACTIONS

Common adverse reactions (≥30%) observed in combination therapy clinical studies are: nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, mucositis, neutropenia, leukopenia (including lymphocytopenia), anemia, thrombocytopenia, asthenia, pain, fever, infection, abnormal bilirubin, alopecia. (6.1)

Common adverse reactions (≥30%) observed in single agent therapy clinical studies are: nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, neutropenia, leukopenia (including lymphocytopenia), anemia, asthenia, fever, body weight decreasing, alopecia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc at 1-800-438-1985 or www.pfizer.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP3A4 Inducers: Do not administer strong CYP3A4 inducers with CAMPTOSAR. (7.2)
- Strong CYP3A4 Inhibitors: Do not administer strong CYP3A4 inhibitors with CAMPTOSAR. (7.3)

USE IN SPECIFIC POPULATIONS

- **Nursing Mothers:** Discontinue nursing when receiving therapy with CAMPTOSAR. (8.3)
- **Geriatric Use:** Closely monitor patients greater than 65 years of age because of a greater risk of early and late diarrhea in this population. (8.5)
- **Patients with Renal Impairment:** Use caution and do not use in patients on dialysis. (8.6)
- **Patients with Hepatic Impairment:** Use caution. (2.1, 5.10, 8.7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: DIARRHEA and MYELOSUPPRESSION

- **Early and late forms of diarrhea can occur. Early diarrhea may be accompanied by cholinergic symptoms which may be prevented or ameliorated by atropine. Late diarrhea can be life threatening and should be treated promptly with loperamide. Monitor patients with diarrhea and give fluid and electrolytes as needed. Institute antibiotic therapy if patients develop ileus, fever, or severe neutropenia. Interrupt CAMPTOSAR and reduce subsequent doses if severe diarrhea occurs.**
- **Severe myelosuppression may occur.**

1 INDICATIONS AND USAGE

- CAMPTOSAR Injection is indicated as a component of first-line therapy in combination with 5-fluorouracil (5-FU) and leucovorin (LV) for patients with metastatic carcinoma of the colon or rectum.

- CAMPTOSAR is indicated for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Colorectal Cancer Combination Regimens 1 and 2

Administer CAMPTOSAR as a 90-minute intravenous infusion followed by LV and 5-FU. The currently recommended regimens are shown in Table 1.

A reduction in the starting dose by one dose level of CAMPTOSAR may be considered for patients with any of the following conditions: prior pelvic/abdominal radiotherapy, performance status of 2, or increased bilirubin levels. Dosing for patients with bilirubin >2 mg/dL cannot be recommended because there is insufficient information to recommend a dose in these patients.

Table 1. Combination-Agent Dosage Regimens and Dose Modifications[a]

Regimen 1 6-wk cycle with bolus 5-FU/LV (next cycle begins on day 43)	CAMPTOSAR LV 5-FU	125 mg/m^2 intravenous infusion over 90 minutes, days 1,8,15,22 20 mg/m^2 intravenous injection bolus, days 1,8,15,22 500 mg/m^2 intravenous injection bolus, days 1,8,15,22		
		Starting Dose & Modified Dose Levels (mg/m^2)		
		Starting Dose	Dose Level -1	Dose Level -2
	CAMPTOSAR	125	100	75
	LV	20	20	20
	5-FU	500	400	300
Regimen 2 6-wk cycle with infusional 5-FU/LV (next cycle begins on day 43)	CAMPTOSAR LV 5-FU Bolus 5-FU Infusion[b]	180 mg/m^2 intravenous infusion over 90 minutes, days 1,15,29 200 mg/m^2 intravenous infusion over 2 hours, days 1,2,15,16,29,30 400 mg/m^2 intravenous injection bolus, days 1,2,15,16,29,30 600 mg/m^2 intravenous infusion over 22 hours, days 1,2,15,16,29,30		
		Starting Dose & Modified Dose Levels (mg/m^2)		
		Starting Dose	Dose Level -1	Dose Level -2
	CAMPTOSAR	180	150	120
	LV	200	200	200
	5-FU Bolus	400	320	240
	5-FU Infusion[b]	600	480	360

[a]Dose reductions beyond Dose Level –2 by decrements of ≈ 20% may be warranted for patients continuing to experience toxicity. Provided intolerable toxicity does not develop, treatment with additional cycles may be continued indefinitely as long as patients continue to experience clinical benefit.
[b]Infusion follows bolus administration.

Dosing for patients with bilirubin >2 mg/dL cannot be recommended because there is insufficient information to recommend a dose in these patients *[see Warnings and Precautions (5.10), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

Dose Modifications

Based on recommended dose levels described in Table 1, Combination Regimens of CAMPTOSAR and Dose Modifications, subsequent doses should be adjusted as suggested in Table 2, Recommended Dose Modifications for Combination Regimens. All dose modifications should be based on the worst preceding toxicity.

Table 2. Recommended Dose Modifications for CAMPTOSAR/5-Fluorouracil (5-FU)/Leucovorin (LV) Combination Schedules

Patients should return to pre-treatment bowel function without requiring antidiarrhea medications for at least 24 hours before the next chemotherapy administration. A new cycle of therapy should not begin until the granulocyte count has recovered to ≥1500/mm^3, and the platelet count has recovered to ≥100,000/mm^3, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing therapy.

Toxicity NCI CTC Grade[a] (Value)	During a Cycle of Therapy	At the Start of Subsequent Cycles of Therapy[b]
No toxicity	Maintain dose level	Maintain dose level
Neutropenia		
1 (1500 to 1999/mm^3)	Maintain dose level	Maintain dose level
2 (1000 to 1499/mm^3)	↓ 1 dose level	Maintain dose level
3 (500 to 999/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level	↓ 1 dose level
4 (<500/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 2 dose levels	↓ 2 dose levels
Neutropenic fever	Omit dose until resolved, then ↓ 2 dose levels	
Other hematologic toxicities	Dose modifications for leukopenia or thrombocytopenia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.	
Diarrhea		
1 (2-3 stools/day > pretx[c])	Delay dose until resolved to baseline, then give same dose	Maintain dose level
2 (4-6 stools/day > pretx)	Omit dose until resolved to baseline, then ↓ 1 dose level	Maintain dose level
3 (7-9 stools/day > pretx)	Omit dose until resolved to baseline, then ↓ 2 dose levels	↓ 1 dose level
4 (≥10 stools/day > pretx)		↓ 2 dose levels
Other nonhematologic toxicities[d]		
1	Maintain dose level	Maintain dose level
2	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level	Maintain dose level
3	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level	↓ 1 dose level
4	Omit dose until resolved to ≤ grade 2, then ↓ 2 dose levels	↓ 2 dose levels
	For mucositis/stomatitis decrease only 5-FU, not CAMPTOSAR	*For mucositis/stomatitis decrease only 5-FU, not CAMPTOSAR.*

[a] National Cancer Institute Common Toxicity Criteria (version 1.0)
[b] Relative to the starting dose used in the previous cycle
[c] Pretreatment
[d] Excludes alopecia, anorexia, asthenia

2.2 Colorectal Single Agent Regimens 1 and 2

Administer CAMPTOSAR as a 90-minute intravenous infusion. The currently recommended regimens are shown in Table 3.

A reduction in the starting dose by one dose level of CAMPTOSAR may be considered for patients with any of the following conditions: prior pelvic/abdominal radiotherapy, performance status of 2, or increased bilirubin levels. Dosing for patients with bilirubin >2 mg/dL cannot be recommended because there is insufficient information to recommend a dose in these patients.

Table 3. Single-Agent Regimens of CAMPTOSAR and Dose Modifications

Regimen 1 (weekly)[a]	125 mg/m^2 intravenous infusion over 90 minutes, days 1,8,15,22 then 2-week rest		
	Starting Dose and Modified Dose Levels[c] **(mg/m^2)**		
	Starting Dose	Dose Level -1	Dose Level -2
	125	100	75
Regimen 2 (every 3 weeks)[b]	350 mg/m^2 intravenous infusion over 90 minutes, once every 3 weeks[c]		
	Starting Dose and Modified Dose Levels (mg/m^2)		
	Starting Dose	Dose Level -1	Dose Level -2
	350	300	250

[a] Subsequent doses may be adjusted as high as 150 mg/m^2 or to as low as 50 mg/m^2 in 25 to 50 mg/m^2 decrements depending upon individual patient tolerance.

[b] Subsequent doses may be adjusted as low as 200 mg/m^2 in 50 mg/m^2 decrements depending upon individual patient tolerance.

[c] Provided intolerable toxicity does not develop, treatment with additional cycles may be continued indefinitely as long as patients continue to experience clinical benefit.

Dose Modifications

Based on recommended dose-levels described in Table 3, Single-Agent Regimens of CAMPTOSAR and Dose Modifications, subsequent doses should be adjusted as suggested in Table 4, Recommended Dose Modifications for Single-Agent Schedules. All dose modifications should be based on the worst preceding toxicity.

Table 4: Recommended Dose Modifications For Single-Agent Schedules[a]

A new cycle of therapy should not begin until the granulocyte count has recovered to ≥1500/mm^3, and the platelet count has recovered to ≥100,000/mm^3, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing CAMPTOSAR.

Worst Toxicity NCI Grade[b] (Value)	**During a Cycle of Therapy**	**At the Start of the Next Cycles of Therapy (After Adequate Recovery), Compared with the Starting Dose in the Previous Cycle[a]**	
	Weekly	Weekly	Once Every 3 Weeks
No toxicity	Maintain dose level	↑ 25 mg/m^2 up to a maximum dose of 150 mg/m^2	Maintain dose level
Neutropenia			
1 (1500 to 1999/mm^3)	Maintain dose level	Maintain dose level	Maintain dose level
2 (1000 to 1499/mm^3)	↓ 25 mg/m^2	Maintain dose level	Maintain dose level
3 (500 to 999/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 25 mg/m^2	↓ 25 mg/m^2	↓ 50 mg/m^2
4 (<500/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 50 mg/m^2	↓ 50 mg/m^2	↓ 50 mg/m^2
Neutropenic fever	Omit dose until resolved, then ↓ 50 mg/m^2 when resolved	↓ 50 mg/m^2	↓ 50 mg/m^2
Other hematologic toxicities	Dose modifications for leukopenia, thrombocytopenia, and anemia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.		
Diarrhea			
1 (2-3 stools/day > pretx[c])	Maintain dose level	Maintain dose level	Maintain dose level
2 (4-6 stools/day > pretx)	↓ 25 mg/m^2	Maintain dose level	Maintain dose level
3 (7-9 stools/day > pretx)	Omit dose until resolved to ≤ grade 2, then ↓ 25 mg/m^2	↓ 25 mg/m^2	↓ 50 mg/m^2
4 (≥10 stools/day > pretx)	Omit dose until resolved to ≤ grade 2 then ↓ 50 mg/m^2	↓ 50 mg/m^2	↓ 50 mg/m^2
Other nonhematologic[d] toxicities			
1	Maintain dose level	Maintain dose level	Maintain dose level
2	↓ 25 mg/m^2	↓ 25 mg/m^2	↓ 50 mg/m^2
3	Omit dose until resolved to ≤ grade 2, then ↓ 25 mg/m^2	↓ 25 mg/m^2	↓ 50 mg/m^2
4	Omit dose until resolved to ≤ grade 2, then ↓ 50 mg/m^2	↓ 50 mg/m^2	↓ 50 mg/m^2

[a] All dose modifications should be based on the worst preceding toxicity
[b] National Cancer Institute Common Toxicity Criteria (version 1.0)
[c] Pretreatment
[d] Excludes alopecia, anorexia, asthenia

2.3 Dosage in Patients with Reduced UGT1A1 Activity

When administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele *[see Dosage and Administration (2.1 and 2.2) and Warnings and Precautions (5.3)]*. However, the precise dose reduction in this patient population

is not known, and subsequent dose modifications should be considered based on individual patient tolerance to treatment (see Tables 1-4).

2.4 Premedication

It is recommended that patients receive premedication with antiemetic agents. In clinical studies of the weekly dosage schedule, the majority of patients received 10 mg of dexamethasone given in conjunction with another type of antiemetic agent, such as a 5-HT^3 blocker (e.g., ondansetron or granisetron). Antiemetic agents should be given on the day of treatment, starting at least 30 minutes before administration of CAMPTOSAR. Physicians should also consider providing patients with an antiemetic regimen (e.g., prochlorperazine) for subsequent use as needed. A similar antiemetic regimen should be used with Camptosar in combination therapy.

Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms.

2.5 Preparation of Infusion Solution

Inspect vial contents for particulate matter and discoloration and repeat inspection when drug product is withdrawn from vial into syringe.

CAMPTOSAR Injection 20 mg/mL is intended for single use only and any unused portion should be discarded.

CAMPTOSAR Injection must be diluted prior to infusion. CAMPTOSAR should be diluted in 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, to a final concentration range of 0.12 mg/mL to 2.8 mg/mL. Other drugs should not be added to the infusion solution.

The solution is physically and chemically stable for up to 24 hours at room temperature and in ambient fluorescent lighting. Solutions diluted in 5% Dextrose Injection, USP, and stored at refrigerated temperatures (approximately 2° to 8°C, 36° to 46°F), and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using 0.9% Sodium Chloride Injection, USP, is not recommended due to a low and sporadic incidence of visible particulates. Freezing CAMPTOSAR and admixtures of CAMPTOSAR may result in precipitation of the drug and should be avoided.

The CAMPTOSAR Injection solution should be used immediately after reconstitution as it contains no antibacterial preservative. Because of possible microbial contamination during dilution, it is advisable to use the admixture prepared with 5% Dextrose Injection, USP, within 24 hours if refrigerated (2° to 8°C, 36° to 46°F). In the case of admixtures prepared with 5% Dextrose Injection, USP, or Sodium Chloride Injection, USP, the solutions should be used within 4 hours if kept at room temperature. If reconstitution and dilution are performed under strict aseptic conditions (e.g., on Laminar Air Flow bench), CAMPTOSAR Injection solution should be used (infusion completed) within 12 hours at room temperature or 24 hours if refrigerated (2° to 8°C, 36° to 46°F).

2.6 Safe Handling

Care should be exercised in the handling and preparation of infusion solutions prepared from CAMPTOSAR Injection. The use of gloves is recommended. If a solution of CAMPTOSAR contacts the skin, wash the skin immediately and thoroughly with soap and water. If CAMPTOSAR contacts the mucous membranes, flush thoroughly with water. Several published guidelines for handling and disposal of anticancer agents are available.

2.7 Extravasation

Care should be taken to avoid extravasation, and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site with sterile water and applications of ice are recommended.

3 DOSAGE FORMS AND STRENGTHS

CAMPTOSAR Injection is available in three single-dose sizes:

- 2 mL-fill vial containing 40 mg irinotecan hydrochloride
- 5 mL-fill vial containing 100 mg irinotecan hydrochloride
- 15 mL-fill vial containing 300 mg irinotecan hydrochloride

4 CONTRAINDICATIONS

- CAMPTOSAR Injection is contraindicated in patients with a known hypersensitivity to the drug or its excipients.

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea and Cholinergic Reactions

Early diarrhea (occurring during or shortly after infusion of CAMPTOSAR) is usually transient and infrequently severe. It may be accompanied by cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping. Bradycardia may also occur. Early diarrhea and other cholinergic symptoms may be prevented or treated. Consider prophylactic or therapeutic administration of 0.25 mg to 1 mg of intravenous or subcutaneous atropine (unless clinically contraindicated). These symptoms are expected to occur more frequently with higher irinotecan doses.

Late diarrhea (generally occurring more than 24 hours after administration of CAMPTOSAR) can be life threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis. Grade 3-4 late diarrhea occurred in 23-31% of patients receiving weekly dosing. In the clinical studies, the median time to the onset of late diarrhea was 5 days with

3-week dosing and 11 days with weekly dosing. Late diarrhea can be complicated by colitis, ulceration, bleeding, ileus, obstruction, and infection. Cases of megacolon and intestinal perforation have been reported. Patients should have loperamide readily available to begin treatment for late diarrhea. Begin loperamide at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normal. One dosage regimen for loperamide is 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. Loperamide is not recommended to be used for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus. During the night, the patient may take 4 mg of loperamide every 4 hours. Monitor and replace fluid and electrolytes. Use antibiotic support for ileus, fever, or severe neutropenia. Subsequent weekly chemotherapy treatments should be delayed in patients until return of pretreatment bowel function for at least 24 hours without anti-diarrhea medication. Patients must not be treated with CAMPTOSAR until resolution of the bowel obstruction. If grade 2, 3, or 4 late diarrhea recurs, subsequent doses of CAMPTOSAR should be decreased *[see Dosage and Administration (2)]*.

Avoid diuretics or laxatives in patients with diarrhea.

5.2 Myelosuppression

Deaths due to sepsis following severe neutropenia have been reported in patients treated with CAMPTOSAR. In the clinical studies evaluating the weekly dosage schedule, neutropenic fever (concurrent NCI grade 4 neutropenia and fever of grade 2 or greater) occurred in 3% of the patients; 6% of patients received G-CSF for the treatment of neutropenia. Manage febrile neutropenia promptly with antibiotic support *[see Warnings and Precautions (5.2)]*. Hold CAMPTOSAR if neutropenic fever occurs or if the absolute neutrophil count drops $<1000/mm^3$. After recovery to an absolute neutrophil count $\geq 1000/mm^3$, subsequent doses of CAMPTOSAR should be reduced *[see Dosage and Administration (2)]*.

When evaluated in the trials of weekly administration, the frequency of grade 3 and 4 neutropenia was higher in patients who received previous pelvic/abdominal irradiation than in those who had not received such irradiation (48% [13/27] versus 24% [67/277]; p=0.04). Patients who have previously received pelvic/abdominal irradiation are at increased risk of severe myelosuppression following the administration of CAMPTOSAR. Based on sparse available data, the concurrent administration of CAMPTOSAR with irradiation is not recommended.

Patients with baseline serum total bilirubin levels of 1.0 mg/dL or more also had a greater likelihood of experiencing first-cycle grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL (50% [19/38] versus 18% [47/266]; p<0.001). Patients with deficient glucuronidation of bilirubin, such as those with Gilbert's syndrome, may be at greater risk of myelosuppression when receiving therapy with CAMPTOSAR.

5.3 Patients With Reduced UGT1A1 Activity

Individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) are at increased risk for neutropenia following initiation of CAMPTOSAR treatment.

In a study of 66 patients who received single-agent CAMPTOSAR (350 mg/m^2 once-every-3-weeks), the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was 50%, and in patients heterozygous for this allele (UGT1A1 6/7 genotype) the incidence was 12.5%. No grade 4 neutropenia was observed in patients homozygous for the wild-type allele (UGT1A1 6/6 genotype).

In a prospective study (n=250) to investigate the role of UGT1A1*28 polymorphism in the development of toxicity in patients treated with CAMPTOSAR (180 mg/m^2) in combination with infusional 5-FU/LV, the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was 4.5%, and in patients heterozygous for this allele the incidence was 5.3%. Grade 4 neutropenia was observed in 1.8% of patients homozygous for the wild-type allele.

In another study in which 109 patients were treated with CAMPTOSAR (100-125 mg/m^2) in combination with bolus 5-FU/LV, the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was 18.2%, and in patients heterozygous for this allele the incidence was 11.1%. Grade 4 neutropenia was observed in 6.8% of patients homozygous for the wild-type allele.

When administered in combination with other agents or as a single-agent, a reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele. However, the precise dose reduction in this patient population is not known and subsequent dose modifications should be considered based on individual patient tolerance to treatment *[see Dosage and Administration (2)]*.

UGT1A1 Testing

A laboratory test is available to determine the UGT1A1 status of patients. Testing can detect the UGT1A1 6/6, 6/7 and 7/7 genotypes.

5.4 Hypersensitivity

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed. Discontinue CAMPTOSAR if anaphylactic reaction occurs.

5.5 Renal Impairment/Renal Failure

Renal impairment and acute renal failure have been identified, usually in patients who became volume depleted from severe vomiting and/or diarrhea.

5.6 Pulmonary Toxicity

Interstitial Pulmonary Disease (IPD)-like events, including fatalities, have occurred in patients receiving irinotecan (in combination and as monotherapy). Risk factors include pre-existing lung disease, use of pneumotoxic drugs, radiation therapy, and colony stimulating factors. Patients with risk factors should be closely monitored for respiratory symptoms before and during CAMPTOSAR therapy. In Japanese studies, a reticulonodular pattern on chest x-ray was observed in a small percentage of patients. New or progressive, dyspnea, cough, and fever should prompt interruption of chemotherapy, pending diagnostic evaluation. If IPD is diagnosed, CAMPTOSAR and other chemotherapy should be discontinued and appropriate treatment instituted as needed *[see Adverse Reactions (6.1)]*.

5.7 Toxicity of the 5 Day Regimen

Outside of a well-designed clinical study, CAMPTOSAR Injection should not be used in combination with a regimen of 5-FU/LV administered for 4-5 consecutive days every 4 weeks because of reports of increased toxicity, including toxic deaths. CAMPTOSAR should be used as recommended in Table 2 *[see Dosage and Administration (2)]*.

5.8 Increased Toxicity in Patients with Performance Status 2

In patients receiving either irinotecan/5-FU/LV or 5-FU/LV in the clinical trials, higher rates of hospitalization, neutropenic fever, thromboembolism, first-cycle treatment discontinuation, and early deaths were observed in patients with a baseline performance status of 2 than in patients with a baseline performance status of 0 or 1.

5.9 Embryofetal Toxicity

CAMPTOSAR can cause fetal harm when administered to a pregnant woman. Irinotecan was embryotoxic in rats and rabbits at doses significantly lower than those administered to humans on a mg/m^2 basis. In rats, at exposures approximately 0.2 times those achieved in humans at the 125 mg/m^2 dose, irinotecan was embryotoxic and resulted in decreased learning ability and female fetal body weight in surviving pups; the drug was teratogenic at lower exposures (approximately 0.025 times the AUC in humans at the 125 mg/m^2 dose). There are no adequate and well-controlled studies of irinotecan in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with CAMPTOSAR.

5.10 Patients with Hepatic Impairment

The use of CAMPTOSAR in patients with significant hepatic impairment has not been established. In clinical trials of either dosing schedule, irinotecan was not administered to patients with serum bilirubin >2.0 mg/dL, or transaminase >3 times the upper limit of normal if no liver metastasis, or transaminase >5 times the upper limit of normal with liver metastasis. In clinical trials of the weekly dosage schedule, patients with modestly elevated baseline serum

total bilirubin levels (1.0 to 2.0 mg/dL) had a significantly greater likelihood of experiencing first-cycle, grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL (50% [19/38] versus 18% [47/226]; p<0.001) *[see Dosage and Administration (2.1), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)].*

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Common adverse reactions (≥30%) observed in combination therapy clinical studies are: nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, mucositis, neutropenia, leukopenia (including lymphocytopenia), anemia, thrombocytopenia, asthenia, pain, fever, infection, abnormal bilirubin, and alopecia.

Common adverse reactions (≥30%) observed in single agent therapy clinical studies are: nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, neutropenia, leukopenia (including lymphocytopenia), anemia, asthenia, fever, body weight decreasing, and alopecia.

Serious opportunistic infections have not been observed, and no complications have specifically been attributed to lymphocytopenia.

First-Line Combination Therapy

A total of 955 patients with metastatic colorectal cancer received the recommended regimens of irinotecan in combination with 5-FU/LV, 5-FU/LV alone, or irinotecan alone. In the two phase 3 studies, 370 patients received irinotecan in combination with 5-FU/LV, 362 patients received 5-FU/LV alone, and 223 patients received irinotecan alone *[see Dosage and Administration (2)].*

In Study 1, 49 (7.3%) patients died within 30 days of last study treatment: 21 (9.3%) received irinotecan in combination with 5-FU/LV, 15 (6.8%) received 5-FU/LV alone, and 13 (5.8%) received irinotecan alone. Deaths potentially related to treatment occurred in 2 (0.9%) patients who received irinotecan in combination with 5-FU/LV (2 neutropenic fever/sepsis), 3 (1.4%) patients who received 5-FU/LV alone (1 neutropenic fever/sepsis, 1 CNS bleeding during thrombocytopenia, 1 unknown) and 2 (0.9%) patients who received irinotecan alone (2 neutropenic fever). Deaths from any cause within 60 days of first study treatment were reported for 15 (6.7%) patients who received irinotecan in combination with 5-FU/LV, 16 (7.3%) patients who received 5-FU/LV alone, and 15 (6.7%) patients who received irinotecan alone. Discontinuations due to adverse events were reported for 17 (7.6%) patients who received irinotecan in combination with 5FU/LV, 14 (6.4%) patients who received 5-FU/LV alone, and 26 (11.7%) patients who received irinotecan alone.

In Study 2, 10 (3.5%) patients died within 30 days of last study treatment: 6 (4.1%) received irinotecan in combination with 5-FU/LV and 4 (2.8%) received 5-FU/LV alone. There was one potentially treatment-related death, which occurred in a patient who received irinotecan in combination with 5-FU/LV (0.7%, neutropenic sepsis). Deaths from any cause within 60 days of first study treatment were reported for 3 (2.1%) patients who received irinotecan in combination with 5-FU/LV and 2 (1.4%) patients who received 5-FU/LV alone. Discontinuations due to adverse events were reported for 9 (6.2%) patients who received irinotecan in combination with 5FU/LV and 1 (0.7%) patient who received 5-FU/LV alone.

The most clinically significant adverse events for patients receiving irinotecan-based therapy were diarrhea, nausea, vomiting, neutropenia, and alopecia. The most clinically significant adverse events for patients receiving 5-FU/LV therapy were diarrhea, neutropenia, neutropenic fever, and mucositis. In Study 1, grade 4 neutropenia, neutropenic fever (defined as grade 2 fever and grade 4 neutropenia), and mucositis were observed less often with weekly irinotecan/5-FU/LV than with monthly administration of 5-FU/LV.

Tables 5 and 6 list the clinically relevant adverse events reported in Studies 1 and 2, respectively.

Table 5. Study 1: Percent (%) of Patients Experiencing Clinically Relevant Adverse Events in Combination Therapies[a]

Adverse Event	Study 1					
	Irinotecan + Bolus 5-FU/LV weekly x 4 every 6 weeks N=225		Bolus 5-FU/LV daily x 5 every 4 weeks N=219		Irinotecan weekly x 4 every 6 weeks N=223	
	Grade 1-4	Grade 3&4	Grade 1-4	Grade 3&4	Grade 1-4	Grade 3&4
TOTAL Adverse Events	100	53.3	100	45.7	99.6	45.7
GASTROINTESTINAL						
Diarrhea	84.9	22.7	69.4	13.2	83.0	31.0
late	--	15.1	--	5.9	--	18.4
grade 3	--	7.6	--	7.3	--	12.6
grade 4	45.8	4.9	31.5	1.4	43.0	6.7
early						
Nausea	79.1	15.6	67.6	8.2	81.6	16.1
Abdominal pain	63.1	14.6	50.2	11.5	67.7	13.0
Vomiting	60.4	9.7	46.1	4.1	62.8	12.1
Anorexia	34.2	5.8	42.0	3.7	43.9	7.2
Constipation	41.3	3.1	31.5	1.8	32.3	0.4
Mucositis	32.4	2.2	76.3	16.9	29.6	2.2
HEMATOLOGIC						
Neutropenia	96.9	53.8	98.6	66.7	96.4	31.4
grade 3	--	29.8	--	23.7	--	19.3
grade 4	--	24.0	--	42.5	--	12.1
Leukopenia	96.9	37.8	98.6	23.3	96.4	21.5
Anemia	96.9	8.4	98.6	5.5	96.9	4.5
Neutropenic fever	--	7.1	--	14.6	--	5.8
Thrombocytopenia	96.0	2.6	98.6	2.7	96.0	1.7
Neutropenic infection	--	1.8	--	0	--	2.2

BODY AS A WHOLE						
Asthenia	70.2	19.5	64.4	11.9	69.1	13.9
Pain	30.7	3.1	26.9	3.6	22.9	2.2
Fever	42.2	1.7	32.4	3.6	43.5	0.4
Infection	22.2	0	16.0	1.4	13.9	0.4
METABOLIC & NUTRITIONAL						
Bilirubin	87.6	7.1	92.2	8.2	83.9	7.2
DERMATOLOGIC	0.9	0	3.2	0.5	0	0
Exfoliative dermatitis	19.1	0	26.5	0.9	14.3	0.4
Rash	43.1	--	26.5	--	46.1	--
Alopecia[b]						
RESPIRATORY						
Dyspnea	27.6	6.3	16.0	0.5	22.0	2.2
Cough	26.7	1.3	18.3	0	20.2	0.4
Pneumonia	6.2	2.7	1.4	1.0	3.6	1.3
NEUROLOGIC						
Dizziness	23.1	1.3	16.4	0	21.1	1.8
Somnolence	12.4	1.8	4.6	1.8	9.4	1.3
Confusion	7.1	1.8	4.1	0	2.7	0
CARDIOVASCULAR	9.3	0.9	5.0	0	9.0	0
Vasodilatation	5.8	1.3	2.3	0.5	5.8	1.7
Hypotension	9.3	--	11.4	--	5.4	--
Thromboembolic events[c]						

[a] Severity of adverse events based on NCI CTC (version 1.0)

[b] Complete hair loss = Grade 2

[c] Includes angina pectoris, arterial thrombosis, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, embolus lower extremity, heart arrest, myocardial infarct, myocardial ischemia, peripheral vascular disorder, pulmonary embolus, sudden death, thrombophlebitis, thrombosis, vascular disorder.

Table 6. Study 2: Percent (%) of Patients Experiencing Clinically Relevant Adverse Events in Combination Therapies[a]

Adverse Event	Study 2			
	Irinotecan + 5-FU/LV infusional days 1&2 every 2 weeks N= 145		5-FU/LV infusional days 1&2 every 2 weeks N=143	
	Grades 1-4	Grades 3&4	Grades 1-4	Grades 3&4
TOTAL Adverse Events	100	72.4	100	39.2
GASTROINTESTINAL				
Diarrhea	72.4	14.4	44.8	6.3
late	--	10.3	--	4.2
grade 3	--	4.1	--	2.1
grade 4	28.3	1.4	0.7	0
Cholinergic syndrome[b]	66.9	2.1	55.2	3.5
Nausea	17.2	2.1	16.8	0.7
Abdominal pain	44.8	3.5	32.2	2.8
Vomiting	35.2	2.1	18.9	0.7
Anorexia	30.3	0.7	25.2	1.4
Constipation	40.0	4.1	28.7	2.8
Mucositis				
HEMATOLOGIC	82.5	46.2	47.9	13.4
Neutropenia	--	36.4	--	12.7
grade 3	--	9.8	--	0.7
grade 4	81.3	17.4	42.0	3.5
Leukopenia	97.2	2.1	90.9	2.1
Anemia	--	3.4	--	0.7
Neutropenic fever	32.6	0	32.2	0
Thrombocytopenia	--	2.1	--	0
Neutropenic infection				
BODY AS A WHOLE	57.9	9.0	48.3	4.2
Asthenia	64.1	9.7	61.5	8.4
Pain	22.1	0.7	25.9	0.7
Fever	35.9	7.6	33.6	3.5
Infection				
METABOLIC AND NUTRITIONAL	19.1	3.5	35.9	10.6
Bilirubin				
DERMATOLOGIC	10.3	0.7	12.6	0.7
Hand and foot syndrome	17.2	0.7	20.3	0
Cutaneous signs	56.6	--	16.8	--
Alopecia[c]				
RESPIRATORY	9.7	1.4	4.9	0
Dyspnea				

CARDIOVASCULAR	3.4	1.4	0.7	0
Hypotension	11.7	--	5.6	--
Thromboembolic events[d]				

[a] Severity of adverse events based on NCI CTC (version 1.0)
[b] Includes rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, abdominal cramping or diarrhea (occurring during or shortly after infusion of irinotecan)
[c] Complete hair loss = Grade 2
[d] Includes angina pectoris, arterial thrombosis, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, embolus lower extremity, heart arrest, myocardial infarct, myocardial ischemia, peripheral vascular disorder, pulmonary embolus, sudden death, thrombophlebitis, thrombosis, vascular disorder.

Second-Line Single-Agent Therapy

Weekly Dosage Schedule

In three clinical studies evaluating the weekly dosage schedule, 304 patients with metastatic carcinoma of the colon or rectum that had recurred or progressed following 5-FU-based therapy were treated with CAMPTOSAR. Seventeen of the patients died within 30 days of the administration of CAMPTOSAR; in five cases (1.6%, 5/304), the deaths were potentially drug-related. One of the patients died of neutropenic sepsis without fever. Neutropenic fever occurred in nine (3.0%) other patients; these patients recovered with supportive care.

One hundred nineteen (39.1%) of the 304 patients were hospitalized because of adverse events; 81 (26.6%) patients were hospitalized for events judged to be related to administration of CAMPTOSAR. The primary reasons for drug-related hospitalization were diarrhea, with or without nausea and/or vomiting (18.4%); neutropenia/leukopenia, with or without diarrhea and/or fever (8.2%); and nausea and/or vomiting (4.9%).

The first dose of at least one cycle of CAMPTOSAR was reduced for 67% of patients who began the studies at the 125-mg/m^2 starting dose. Within-cycle dose reductions were required for 32% of the cycles initiated at the 125-mg/m^2 dose level. The most common reasons for dose reduction were late diarrhea, neutropenia, and leukopenia. Thirteen (4.3%) patients discontinued treatment with CAMPTOSAR because of adverse events. The adverse events in Table 7 are based on the experience of the 304 patients enrolled in the three studies described in *Clinical Studies (14.1)*.

Table 7. Adverse Events Occurring in >10% of 304 Previously Treated Patients with Metastatic Carcinoma of the Colon or Rectum[a]

Body System & Event	% of Patients Reporting	
	NCI Grades 1-4	NCI Grades 3 & 4
GASTROINTESTINAL		
Diarrhea (late)[b]	88	31
7-9 stools/day (grade 3)	—	(16)
≥10 stools/day (grade 4)	—	(14)
Nausea	86	17
Vomiting	67	12
Anorexia	55	6
Diarrhea (early)[c]	51	8
Constipation	30	2
Flatulence	12	0
Stomatitis	12	1
Dyspepsia	10	0
HEMATOLOGIC		
Leukopenia	63	28
Anemia	60	7
Neutropenia	54	26
500 to <1000/mm^3 (grade 3)	—	(15)
<500/mm^3 (grade 4)	—	(12)
BODY AS A WHOLE		
Asthenia	76	12
Abdominal cramping/pain	57	16
Fever	45	1
Pain	24	2
Headache	17	1
Back pain	14	2
Chills	14	0
Minor infection[d]	14	0
Edema	10	1
Abdominal enlargement	10	0
METABOLIC AND NUTRITIONAL		
↓ Body weight	30	1
Dehydration	15	4
↑ Alkaline phosphatase	13	4
↑ SGOT	10	1
DERMATOLOGIC		
Alopecia	60	NA[e]
Sweating	16	0
Rash	13	1
RESPIRATORY		
Dyspnea	22	4
↑ Coughing	17	0
Rhinitis	16	0
NEUROLOGIC		
Insomnia	19	0
Dizziness	15	0
CARDIOVASCULAR		
Vasodilation (flushing)	11	0

Table 7. Adverse Events Occurring in >10% of 304 Previously Treated Patients with Metastatic Carcinoma of the Colon or Rectum[a]

[a] Severity of adverse events based on NCI CTC (version 1.0)
[b] Occurring >24 hours after administration of CAMPTOSAR
[c] Occurring ≤24 hours after administration of CAMPTOSAR
[d] Primarily upper respiratory infections
[e] Not applicable; complete hair loss = NCI grade 2

Once-Every-3-Week Dosage Schedule

A total of 535 patients with metastatic colorectal cancer whose disease had recurred or progressed following prior 5-FU therapy participated in the two phase 3 studies: 316 received irinotecan, 129 received 5-FU, and 90 received best supportive care. Eleven (3.5%) patients treated with irinotecan died within 30 days of treatment. In three cases (1%, 3/316), the deaths were potentially related to irinotecan treatment and were attributed to neutropenic infection, grade 4 diarrhea, and asthenia, respectively. One (0.8%, 1/129) patient treated with 5-FU died within 30 days of treatment; this death was attributed to grade 4 diarrhea.

Hospitalizations due to serious adverse events occurred at least once in 60% (188/316) of patients who received irinotecan, 63% (57/90) who received best supportive care, and 39% (50/129) who received 5-FU-based therapy. Eight percent of patients treated with irinotecan and 7% treated with 5-FU-based therapy discontinued treatment due to adverse events.

Of the 316 patients treated with irinotecan, the most clinically significant adverse events (all grades, 1-4) were diarrhea (84%), alopecia (72%), nausea (70%), vomiting (62%), cholinergic symptoms (47%), and neutropenia (30%). Table 8 lists the grade 3 and 4 adverse events reported in the patients enrolled to all treatment arms of the two studies described in *Clinical Studies (14.1)*.

Table 8: Percent Of Patients Experiencing Grade 3 & 4 Adverse Events In Comparative Studies Of Once-Every-3-Week Irinotecan Therapy[a]

	Study 1		Study 2	
Adverse Event	**Irinotecan N=189**	**BSC [b] N=90**	**Irinotecan N=127**	**5-FU N=129**
TOTAL Grade 3/4 Adverse Events	79	67	69	54
GASTROINTESTINAL				
Diarrhea	22	6	22	11
Vomiting	14	8	14	5
Nausea	14	3	11	4
Abdominal pain	14	16	9	8
Constipation	10	8	8	6
Anorexia	5	7	6	4
Mucositis	2	1	2	5
HEMATOLOGIC				
Leukopenia/Neutropenia	22	0	14	2
Anemia	7	6	6	3
Hemorrhage	5	3	1	3
Thrombocytopenia	1	0	4	2
Infection				
without grade 3/4 neutropenia	8	3	1	4
with grade 3/4 neutropenia	1	0	2	0
Fever				
without grade 3/4 neutropenia	2	1	2	0
with grade 3/4 neutropenia	2	0	4	2
BODY AS A WHOLE				
Pain	19	22	17	13
Asthenia	15	19	13	12
METABOLIC AND NUTRITIONAL				
Hepatic [c]	9	7	9	6
DERMATOLOGIC				
Hand and foot syndrome	0	0	0	5
Cutaneous signs [d]	2	0	1	3
RESPIRATORY [e]	10	8	5	7
NEUROLOGIC [f]	12	13	9	4
CARDIOVASCULAR [g]	9	3	4	2
OTHER [h]	32	28	12	14

[a] Severity of adverse events based on NCI CTC (version 1.0)
[b] BSC = best supportive care
[c] Hepatic includes events such as ascites and jaundice
[d] Cutaneous signs include events such as rash
[e] Respiratory includes events such as dyspnea and cough
[f] Neurologic includes events such as somnolence
[g] Cardiovascular includes events such as dysrhythmias, ischemia, and mechanical cardiac dysfunction
[h] Other includes events such as accidental injury, hepatomegaly, syncope, vertigo, and weight loss

The incidence of akathisia in clinical trials of the weekly dosage schedule was greater (8.5%, 4/47 patients) when prochlorperazine was administered on the same day as CAMPTOSAR than when these drugs were given on separate days (1.3%, 1/80 patients). The 8.5% incidence of akathisia, however, is within the range reported for use of prochlorperazine when given as a premedication for other chemotherapies.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of CAMPTOSAR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Myocardial ischemic events have been observed following CAMPTOSAR therapy. Thromboembolic events have been observed in patients receiving CAMPTOSAR.

Symptomatic pancreatitis, asymptomatic pancreatic enzyme elevation have been reported. Increases in serum levels of transaminases (i.e., AST and ALT) in the absence of progressive liver metastasis have been observed.

Hyponatremia, mostly with diarrhea and vomiting, has been reported.

Transient dysarthria has been reported in patients treated with CAMPTOSAR; in some cases, the event was attributed to the cholinergic syndrome observed during or shortly after infusion of irinotecan.

Interaction between CAMPTOSAR and neuromuscular blocking agents cannot be ruled out. Irinotecan has anticholinesterase activity, which may prolong the neuromuscular blocking effects of suxamethonium and the neuromuscular blockade of non-depolarizing drugs may be antagonized.

7 DRUG INTERACTIONS

7.1 5-Fluorouracil (5-FU) and Leucovorin (LV)

In a phase 1 clinical study involving irinotecan, 5-fluorouracil (5-FU), and leucovorin (LV) in 26 patients with solid tumors, the disposition of irinotecan was not substantially altered when the drugs were co-administered. Although the C_{max} and AUC_{0-24} of SN-38, the active metabolite, were reduced (by 14% and 8%, respectively) when irinotecan was followed by 5-FU and LV administration compared with when irinotecan was given alone, this sequence of administration was used in the combination trials and is recommended *[see Dosage and Administration (2)]*. Formal *in vivo* or *in vitro* drug interaction studies to evaluate the influence of irinotecan on the disposition of 5-FU and LV have not been conducted.

7.2 Strong CYP3A4 Inducers

Exposure to irinotecan or its active metabolite SN-38 is substantially reduced in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin, phenobarbital, carbamazepine, or St. John's wort. The appropriate starting dose for patients taking these or other strong inducers such as rifampin and rifabutin has not been defined. Consider substituting non-enzyme inducing therapies at least 2 weeks prior to initiation of CAMPTOSAR therapy. Do not administer strong CYP3A4 inducers with CAMPTOSAR unless there are no therapeutic alternatives.

7.3 Strong CYP3A4 or UGT1A1 Inhibitors

Irinotecan and its active metabolite, SN-38, are metabolized via the human cytochrome P450 3A4 isoenzyme (CYP3A4) and uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1), respectively, *[see Clinical Pharmacology (12.3)]*. Patients receiving concomitant ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased exposure to irinotecan and its active metabolite SN-38. Coadministration of CAMPTOSAR with other inhibitors of CYP3A4 (e.g., clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole) or UGT1A1 (e.g., atazanavir, gemfibrozil, indinavir) may increase systemic exposure to irinotecan or SN-38. Discontinue strong CYP3A4 inhibitors at least 1 week prior to starting CAMPTOSAR therapy. Do not administer strong CYP3A4 or UGT1A1 inhibitors with CAMPTOSAR unless there are no therapeutic alternatives.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.9)]*

CAMPTOSAR can cause fetal harm when administered to a pregnant woman. Radioactivity related to ^{14}C-irinotecan crosses the placenta of rats following intravenous administration of 10 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about 3 and 0.5 times, respectively, the corresponding values in patients administered 125 mg/m^2). Intravenous administration of irinotecan 6 mg/kg/day to rats and rabbits during the period of organogenesis resulted in increased post-implantation loss and decreased numbers of live fetuses. In separate studies in rats, this dose produced an irinotecan C_{max} and AUC of about 2 and 0.2 times, respectively, the corresponding values in patients administered 125 mg/m^2. In rabbits, the embryotoxic dose was about one-half the recommended human weekly starting dose on a mg/m^2 basis. Irinotecan was teratogenic in rats at doses greater than 1.2 mg/kg/day and in rabbits at 6.0 mg/kg/day. In separate studies in rats, this dose produced an irinotecan C_{max} and AUC about 2/3 and 1/40th, respectively, of the corresponding values in patients administered 125 mg/m^2. In rabbits, the teratogenic dose was about one-half the recommended human weekly starting dose on a mg/m^2 basis. Teratogenic effects included a variety of external, visceral, and skeletal abnormalities. Irinotecan administered to rat dams for the period following organogenesis through weaning at doses of 6 mg/kg/day caused decreased learning ability and decreased female

body weights in the offspring. There are no adequate and well-controlled studies of irinotecan in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with CAMPTOSAR.

8.3 Nursing Mothers

Radioactivity appeared in rat milk within 5 minutes of intravenous administration of radiolabeled irinotecan and was concentrated up to 65-fold at 4 hours after administration relative to plasma concentrations. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CAMPTOSAR, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The effectiveness of irinotecan in pediatric patients has not been established. Results from two open-label, single arm studies were evaluated. One hundred and seventy children with refractory solid tumors were enrolled in one phase 2 trial in which 50 mg/ m^2 of irinotecan was infused for 5 consecutive days every 3 weeks. Grade 3-4 neutropenia was experienced by 54 (31.8%) patients. Neutropenia was complicated by fever in 15 (8.8%) patients. Grade 3-4 diarrhea was observed in 35 (20.6%) patients. This adverse event profile was comparable to that observed in adults. In the second phase 2 trial of 21 children with previously untreated rhabdomyosarcoma, 20 mg/m^2 of irinotecan was infused for 5 consecutive days on weeks 0, 1, 3 and 4. This single agent therapy was followed by multimodal therapy. Accrual to the single agent irinotecan phase was halted due to the high rate (28.6%) of progressive disease and the early deaths (14%). The adverse event profile was different in this study from that observed in adults; the most significant grade 3 or 4 adverse events were dehydration experienced by 6 patients (28.6%) associated with severe hypokalemia in 5 patients (23.8%) and hyponatremia in 3 patients (14.3%); in addition Grade 3-4 infection was reported in 5 patients (23.8%) (across all courses of therapy and irrespective of causal relationship).

Pharmacokinetic parameters for irinotecan and SN-38 were determined in 2 pediatric solid-tumor trials at dose levels of 50 mg/m^2 (60-min infusion, n=48) and 125 mg/m^2 (90-min infusion, n=6). Irinotecan clearance (mean ± S.D.) was 17.3 ± 6.7 L/h/m^2 for the 50mg/m^2 dose and 16.2 ± 4.6 L/h/m^2 for the 125 mg/m^2 dose, which is comparable to that in adults. Dose-normalized SN-38 AUC values were comparable between adults and children. Minimal accumulation of irinotecan and SN-38 was observed in children on daily dosing regimens [daily x 5 every 3 weeks or (daily x 5) x 2 weeks every 3 weeks].

8.5 Geriatric Use

Patients greater than 65 years of age should be closely monitored because of a greater risk of early and late diarrhea in this population *[see Clinical Pharmacology (12.3)* and *Adverse Reactions (6.1)]*. The starting dose of CAMPTOSAR in patients 70 years and older for the once-

every-3-week-dosage schedule should be 300 mg/m^2 *[see Clinical Pharmacology (12.3) and Dosage and Administration (2)]*.

The frequency of grade 3 and 4 late diarrhea by age was significantly greater in patients ≥65 years than in patients <65 years (40% [53/133] versus 23% [40/171]; p=0.002). In another study of 183 patients treated on the weekly schedule, the frequency of grade 3 or 4 late diarrhea in patients ≥65 years of age was 28.6% [26/91] and in patients <65 years of age was 23.9% [22/92].

8.6 Renal Impairment

The influence of renal impairment on the pharmacokinetics of irinotecan has not been evaluated. Therefore, use caution in patients with impaired renal function. CAMPTOSAR is not recommended for use in patients on dialysis.

8.7 Hepatic Impairment

Irinotecan clearance is diminished in patients with hepatic impairment while exposure to the active metabolite SN-38 is increased relative to that in patients with normal hepatic function. The magnitude of these effects is proportional to the degree of liver impairment as measured by elevations in total bilirubin and transaminase concentrations. Therefore, use caution when administering CAMPTOSAR to patients with hepatic impairment. The tolerability of irinotecan in patients with hepatic dysfunction (bilirubin greater than 2 mg/dl) has not been assessed sufficiently, and no recommendations for dosing can be made *[see Dosage and Administration (2.1), Warnings and Precautions (5.10) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In U.S. phase 1 trials, single doses of up to 345 mg/m^2 of irinotecan were administered to patients with various cancers. Single doses of up to 750 mg/m^2 of irinotecan have been given in non-U.S. trials. The adverse events in these patients were similar to those reported with the recommended dosage and regimen. There have been reports of overdosage at doses up to approximately twice the recommended therapeutic dose, which may be fatal. The most significant adverse reactions reported were severe neutropenia and severe diarrhea. There is no known antidote for overdosage of CAMPTOSAR. Maximum supportive care should be instituted to prevent dehydration due to diarrhea and to treat any infectious complications.

11 DESCRIPTION

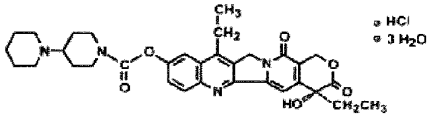
CAMPTOSAR Injection (irinotecan hydrochloride injection) is an antineoplastic agent of the topoisomerase I inhibitor class.

CAMPTOSAR is supplied as a sterile, pale yellow, clear, aqueous solution. Each milliliter of solution contains 20 mg of irinotecan hydrochloride (on the basis of the trihydrate salt), 45 mg of

sorbitol, NF, and 0.9 mg of lactic acid, USP. The pH of the solution has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. CAMPTOSAR is intended for dilution with 5% Dextrose Injection, USP (D5W), or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion. The preferred diluent is 5% Dextrose Injection, USP.

Irinotecan hydrochloride is a semisynthetic derivative of camptothecin, an alkaloid extract from plants such as *Camptotheca acuminata* or is chemically synthesized.

The chemical name is *(**S**)*-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo1***H***-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate, monohydrochloride, trihydrate. Its empirical formula is $C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$ and molecular weight is 677.19. It is slightly soluble in water and organic solvents. Its structural formula is as follows:



Irinotecan Hydrochloride

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Irinotecan is a derivative of camptothecin. Camptothecins interact specifically with the enzyme topoisomerase I, which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent religation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38. Mammalian cells cannot efficiently repair these double-strand breaks.

12.2 Pharmacodynamics

Irinotecan serves as a water-soluble precursor of the lipophilic metabolite SN-38. SN-38 is formed from irinotecan by carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and the dipiperidino side chain. SN-38 is approximately 1000 times as potent as irinotecan as an inhibitor of topoisomerase I purified from human and rodent tumor cell lines. *In vitro* cytotoxicity assays show that the potency of SN-38 relative to irinotecan varies from 2- to 2000-fold; however, the plasma area under the concentration versus time curve (AUC) values for SN-38 are 2% to 8% of irinotecan and SN-38 is 95% bound to plasma proteins compared to approximately 50% bound to plasma proteins for irinotecan *[see Clinical Pharmacology (12.3)]*. The precise contribution of SN-38 to the activity of CAMPTOSAR is

thus unknown. Both irinotecan and SN-38 exist in an active lactone form and an inactive hydroxy acid anion form. A pH-dependent equilibrium exists between the two forms such that an acid pH promotes the formation of the lactone, while a more basic pH favors the hydroxy acid anion form.

Administration of irinotecan has resulted in antitumor activity in mice bearing cancers of rodent origin and in human carcinoma xenografts of various histological types.

12.3 Pharmacokinetics

After intravenous infusion of irinotecan in humans, irinotecan plasma concentrations decline in a multiexponential manner, with a mean terminal elimination half-life of about 6 to 12 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 to 20 hours. The half-lives of the lactone (active) forms of irinotecan and SN-38 are similar to those of total irinotecan and SN-38, as the lactone and hydroxy acid forms are in equilibrium.

Over the recommended dose range of 50 to 350 mg/m^2, the AUC of irinotecan increases linearly with dose; the AUC of SN-38 increases less than proportionally with dose. Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion of irinotecan. Pharmacokinetic parameters for irinotecan and SN-38 following a 90-minute infusion of irinotecan at dose levels of 125 and 340 mg/m^2 determined in two clinical studies in patients with solid tumors are summarized in Table 9:

Table 9. Summary of Mean (±Standard Deviation) Irinotecan and SN-38 Pharmacokinetic Parameters in Patients with Solid Tumors

Dose (mg/m^2)	Irinotecan					SN-38		
	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	$t_{1/2}$ (h)	V_z (L/m^2)	CL (L/h/m^2)	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	$t_{1/2}$ (h)
125 (N=64)	1,660 ±797	10,200 ±3,270	5.8[a] ±0.7	110 ±48.5	13.3 ±6.01	26.3 ±11.9	229 ±108	10.4[a] ±3.1
340 (N=6)	3,392 ±874	20,604 ±6,027	11.7[b] ±1.0	234 ±69.6	13.9 ±4.0	56.0 ±28.2	474 ±245	21.0[b] ±4.3

C_{max} - Maximum plasma concentration
AUC_{0-24} - Area under the plasma concentration-time curve from time 0 to 24 hours after the end of the 90-minute infusion
$t_{1/2}$ - Terminal elimination half-life
V_z - Volume of distribution of terminal elimination phase
CL - Total systemic clearance
[a] Plasma specimens collected for 24 hours following the end of the 90-minute infusion.
[b] Plasma specimens collected for 48 hours following the end of the 90-minute infusion. Because of the longer collection period, these values provide a more accurate reflection of the terminal elimination half-lives of irinotecan and SN-38.

Distribution
Irinotecan exhibits moderate plasma protein binding (30% to 68% bound). SN-38 is highly bound to human plasma proteins (approximately 95% bound). The plasma protein to which irinotecan and SN-38 predominantly binds is albumin.

Metabolism

Irinotecan is subject to extensive metabolic conversion by various enzyme systems, including esterases to form the active metabolite SN-38, and UGT1A1 mediating glucuronidation of SN-38 to form the inactive glucuronide metabolite SN-38G. Irinotecan can also undergo CYP3A4-mediated oxidative metabolism to several inactive oxidation products, one of which can be hydrolyzed by carboxylesterase to release SN-38. *In vitro* studies indicate that irinotecan, SN-38 and another metabolite aminopentane carboxylic acid (APC), do not inhibit cytochrome P-450 isozymes. UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism. Approximately 10% of the North American population is homozygous for the UGT1A1*28 allele (also referred to as UGT1A1 7/7 genotype). In a prospective study, in which irinotecan was administered as a single-agent (350 mg/m^2) on a once-every-3-week schedule, patients with the UGT1A1 7/7 genotype had a higher exposure to SN-38 than patients with the wild-type UGT1A1 allele (UGT1A1 6/6 genotype) *[see Warnings and Precautions (5.3) and Dosage and Administration (2.3)]*. SN-38 glucuronide had 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using two cell lines *in vitro*.

Excretion

The disposition of irinotecan has not been fully elucidated in humans. The urinary excretion of irinotecan is 11% to 20%; SN-38, <1%; and SN-38 glucuronide, 3%. The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of irinotecan in two patients ranged from approximately 25% (100 mg/m^2) to 50% (300 mg/m^2).

Effect of Age

The pharmacokinetics of irinotecan administered using the weekly schedule was evaluated in a study of 183 patients that was prospectively designed to investigate the effect of age on irinotecan toxicity. Results from this trial indicate that there are no differences in the pharmacokinetics of irinotecan, SN-38, and SN-38 glucuronide in patients <65 years of age compared with patients ≥65 years of age. In a study of 162 patients that was not prospectively designed to investigate the effect of age, small (less than 18%) but statistically significant differences in dose-normalized irinotecan pharmacokinetic parameters in patients <65 years of age compared to patients ≥65 years of age were observed. Although dose-normalized AUC_{0-24} for SN-38 in patients ≥65 years of age was 11% higher than in patients <65 years of age, this difference was not statistically significant. No change in the starting dose is recommended for geriatric patients receiving the weekly dosage schedule of irinotecan *[see Dosage and Administration (2)]*.

Effect of Gender

The pharmacokinetics of irinotecan do not appear to be influenced by gender.

Effect of Race

The influence of race on the pharmacokinetics of irinotecan has not been evaluated.

Effect of Hepatic Impairment
Irinotecan clearance is diminished in patients with hepatic impairment while exposure to the active metabolite SN-38 is increased relative to that in patients with normal hepatic function. The magnitude of these effects is proportional to the degree of liver impairment as measured by elevations in total bilirubin and transaminase concentrations. However, the tolerability of irinotecan in patients with hepatic dysfunction (bilirubin greater than 2 mg/dl) has not been assessed sufficiently, and no recommendations for dosing can be made *[see Dosage and Administration (2.1), Warnings and Precautions (5.10) and Use in Specific Populations (8.7)]*.

Effect of Renal Impairment
The influence of renal impairment on the pharmacokinetics of irinotecan has not been evaluated. Therefore, caution should be undertaken in patients with impaired renal function. CAMPTOSAR is not recommended for use in patients on dialysis *[see Use in Specific Populations (8.6)]*.

Drug Interactions
Dexamethasone, a moderate CYP3A4 inducer, does not appear to alter the pharmacokinetics of irinotecan.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies with irinotecan were not conducted. Rats were, however, administered intravenous doses of 2 mg/kg or 25 mg/kg irinotecan once per week for 13 weeks (in separate studies, the 25 mg/kg dose produced an irinotecan C_{max} and AUC that were about 7.0 times and 1.3 times the respective values in patients administered 125 mg/m^2 weekly) and were then allowed to recover for 91 weeks. Under these conditions, there was a significant linear trend with dose for the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas. Irinotecan was clastogenic both *in vitro* (chromosome aberrations in Chinese hamster ovary cells) and *in vivo* (micronucleus test in mice). Neither irinotecan nor its active metabolite SN-38 was mutagenic in the *in vitro* Ames assay.

No significant adverse effects on fertility and general reproductive performance were observed after intravenous administration of irinotecan in doses of up to 6 mg/kg/day to rats and rabbits; however, atrophy of male reproductive organs was observed after multiple daily irinotecan doses both in rodents at 20 mg/kg and in dogs at 0.4 mg/kg. In separate studies in rodents, this dose produced an irinotecan C_{max} and AUC about 5 and 1 times, respectively, of the corresponding values in patients administered 125 mg/m^2 weekly. In dogs this dose produced an irinotecan C_{max} and AUC about one-half and 1/15th, respectively, of the corresponding values in patients administered 125 mg/m^2 weekly.

14 CLINICAL STUDIES

Irinotecan has been studied in clinical trials in combination with 5-fluorouracil (5-FU) and leucovorin (LV) and as a single agent *[see Dosage and Administration (2)]*. When given as a component of combination-agent treatment, irinotecan was either given with a weekly schedule of bolus 5-FU/LV or with an every-2-week schedule of infusional 5-FU/LV. Weekly and once-every-3-week dosage schedules were used for the single-agent irinotecan studies. Clinical studies of combination and single-agent use are described below.

14.1 Metastatic Colorectal Cancer

First Line Therapy in Combination with 5-FU/LV: Studies 1 and 2

Two phase 3, randomized, controlled, multinational clinical trials support the use of CAMPTOSAR Injection as first-line treatment of patients with metastatic carcinoma of the colon or rectum. In each study, combinations of irinotecan with 5-FU and LV were compared with 5-FU and LV alone. Study 1 compared combination irinotecan/bolus 5-FU/LV therapy given weekly with a standard bolus regimen of 5-FU/LV alone given daily for 5 days every 4 weeks; an irinotecan-alone treatment arm given on a weekly schedule was also included. Study 2 evaluated two different methods of administering infusional 5-FU/LV, with or without irinotecan. In both studies, concomitant medications such as antiemetics, atropine, and loperamide were given to patients for prophylaxis and/or management of symptoms from treatment. In Study 2, a 7-day course of fluoroquinolone antibiotic prophylaxis was given in patients whose diarrhea persisted for greater than 24 hours despite loperamide or if they developed a fever in addition to diarrhea. Treatment with oral fluoroquinolone was also initiated in patients who developed an absolute neutrophil count (ANC) $<500/mm^3$, even in the absence of fever or diarrhea. Patients in both studies also received treatment with intravenous antibiotics if they had persistent diarrhea or fever or if ileus developed.

In both studies, the combination of irinotecan/5-FU/LV therapy resulted in significant improvements in objective tumor response rates, time to tumor progression, and survival when compared with 5-FU/LV alone. These differences in survival were observed in spite of second-line therapy in a majority of patients on both arms, including crossover to irinotecan-containing regimens in the control arm. Patient characteristics and major efficacy results are shown in Table 10.

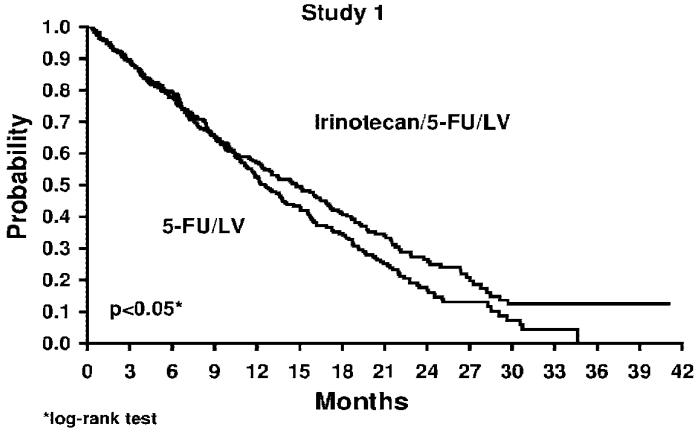
Table 10. Combination Dosage Schedule: Study Results

	Study 1			Study 2	
	Irinotecan + Bolus 5-FU/LV weekly x 4 every 6 weeks	**Bolus 5-FU/LV daily x 5 every 4 weeks**	**Irinotecan weekly x 4 every 6 weeks**	**Irinotecan + Infusional 5-FU/LV**	**Infusional 5-FU/LV**
Number of patients	231	226	226	198	187
Demographics and treatment administration					
Female/Male (%)	34/65	45/54	35/64	33/67	47/53
Median age in years (range)	62 (25-85)	61 (19-85)	61 (30-87)	62 (27-75)	59 (24-75)
Performance status (%)					
0	39	41	46	51	51
1	46	45	46	42	41
2	15	13	8	7	8
Primary tumor (%)					
Colon	81	85	84	55	65
Rectum	17	14	15	45	35
Median time from diagnosis to randomization (months, range)	1.9 (0-161)	1.7 (0-203)	1.8 (0.1-185)	4.5 (0-88)	2.7 (0-104)
Prior adjuvant 5-FU therapy (%)					
No	89	92	90	74	76
Yes	11	8	10	26	24
Median duration of study treatment[a] (months)	5.5	4.1	3.9	5.6	4.5
Median Relative Dose Intensity (%)[a]					
Irinotecan	72	—	75	87	—
5-FU	71	86	—	86	93
Efficacy Results					
Confirmed objective tumor response rate[b] (%)	39	21 ($p<0.0001$)[c]	18	35	22 ($p<0.005$)[c]
Median time to tumor progression[d] (months)	7.0	4.3 ($p=0.004$)[d]	4.2	6.7	4.4 ($p<0.001$)[d]
Median survival (months)	14.8	12.6 ($p<0.05$)[d]	12.0	17.4	14.1 ($p<0.05$)[d]

[a] Study 1: N=225 (irinotecan/5-FU/LV),N=219 (5-FU/LV),N=223 (irinotecan)
Study 2: N=199 (irinotecan/5-FU/LV),N=186 (5-FU/LV)
[b] Confirmed ≥ 4 to 6 weeks after first evidence of objective response
[c] Chi-square test
[d] Log-rank test

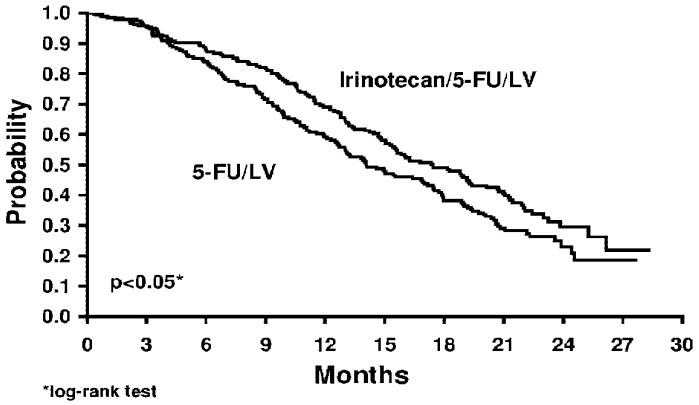
Improvement was noted with irinotecan-based combination therapy relative to 5-FU/LV when response rates and time to tumor progression were examined across the following demographic and disease-related subgroups (age, gender, ethnic origin, performance status, extent of organ involvement with cancer, time from diagnosis of cancer, prior adjuvant therapy, and baseline laboratory abnormalities). Figures 1 and 2 illustrate the Kaplan-Meier survival curves for the comparison of irinotecan/5-FU/LV versus 5-FU/LV in Studies 1 and 2, respectively.

Figure 1. Survival
First-Line Irinotecan/5-FU/LV vs 5-FU/LV
Study 1



*log-rank test

Figure 2. Survival
First-Line Irinotecan/5-FU/LV vs 5-FU/LV
Study 2



*log-rank test

Second-Line Therapy After 5-FU-Based Treatment

4 Weekly Doses on a 6-Week Cycle: Studies 3, 4, and 5

Data from three open-label, single-agent, clinical studies, involving a total of 304 patients in 59 centers, support the use of CAMPTOSAR in the treatment of patients with metastatic cancer of the colon or rectum that has recurred or progressed following treatment with 5-FU-based therapy. These studies were designed to evaluate tumor response rate and do not provide information on effects on survival and disease-related symptoms. In each study, CAMPTOSAR was administered in repeated 6-week cycles consisting of a 90-minute intravenous infusion once weekly for 4 weeks, followed by a 2-week rest period. Starting doses of CAMPTOSAR in these trials were 100, 125, or 150 mg/m^2, but the 150-mg/m^2 dose was poorly tolerated (due to high rates of grade 4 late diarrhea and febrile neutropenia). Study 3 enrolled 48 patients and was

conducted by a single investigator at several regional hospitals. Study 4 was a multicenter study conducted by the North Central Cancer Treatment Group. All 90 patients enrolled in Study 4 received a starting dose of 125 mg/m^2. Study 5 was a multicenter study that enrolled 166 patients from 30 institutions. The initial dose in Study 5 was 125 mg/m^2 but was reduced to 100 mg/m^2 because the toxicity seen at the 125-mg/m^2 dose was perceived to be greater than that seen in previous studies. All patients in these studies had metastatic colorectal cancer, and the majority had disease that recurred or progressed following a 5-FU-based regimen administered for metastatic disease. The results of the individual studies are shown in Table 11.

Table 11. Weekly Dosage Schedule: Study Results

	Study			
	3	4	5	
Number of Patients	48	90	64	102
Starting Dose (mg/m^2/week x 4)	125[a]	125	125	100
Demographics and Treatment Administration				
Female/Male (%)	46/54	36/64	50/50	51/49
Median Age in years (range)	63 (29-78)	63 (32-81)	61 (42-84)	64 (25-84)
Ethnic Origin (%)				
White	79	96	81	91
African American	12	4	11	5
Hispanic	8	0	8	2
Oriental/Asian	0	0	0	2
Performance Status (%)				
0	60	38	59	44
1	38	48	33	51
2	2	14	8	5
Primary Tumor (%)				
Colon	100	71	89	87
Rectum	0	29	11	8
Unknown	0	0	0	5
Prior 5-FU Therapy (%)				
For Metastatic Disease	81	66	73	68
≤ 6 months after Adjuvant	15	7	27	28
> 6 months after Adjuvant	2	16	0	2
Classification Unknown	2	12	0	3
Prior Pelvic/Abdominal Irradiation (%)				
Yes	3	29	0	0
Other	0	9	2	4
None	97	62	98	96
Duration of Treatment with CAMPTOSAR (median, months)	5	4	4	3
Relative Dose Intensity[b] (median %)	74	67	73	81

Table 11. Weekly Dosage Schedule: Study Results

Efficacy				
Confirmed Objective Response Rate (%)[c] (95% CI)	21 (9.3 - 32.3)	13 (6.3 - 20.4)	14 (5.5 - 22.6)	9 (3.3 - 14.3)
Time to Response (median, months)	2.6	1.5	2.8	2.8
Response Duration (median, months)	6.4	5.9	5.6	6.4
Survival (median, months)	10.4	8.1	10.7	9.3
1-Year Survival (%)	46	31	45	43

[a] Nine patients received 150 mg/m^2 as a starting dose; two (22.2%) responded to CAMPTOSAR.

[b] Relative dose intensity for CAMPTOSAR based on planned dose intensity of 100, 83.3, and 66.7 mg/m^2/wk corresponding with 150, 125, and 100 mg/m^2 starting doses, respectively.

[c] Confirmed ≥ 4 to 6 weeks after first evidence of objective response.

In the intent-to-treat analysis of the pooled data across all three studies, 193 of the 304 patients began therapy at the recommended starting dose of 125 mg/m^2. Among these 193 patients, 2 complete and 27 partial responses were observed, for an overall response rate of 15.0% (95% Confidence Interval [CI], 10.0% to 20.1%) at this starting dose. A considerably lower response rate was seen with a starting dose of 100 mg/m^2. The majority of responses were observed within the first two cycles of therapy, but responses did occur in later cycles of treatment (one response was observed after the eighth cycle). The median response duration for patients beginning therapy at 125 mg/m^2 was 5.8 months (range, 2.6 to 15.1 months). Of the 304 patients treated in the three studies, response rates to CAMPTOSAR were similar in males and females and among patients older and younger than 65 years. Rates were also similar in patients with cancer of the colon or cancer of the rectum and in patients with single and multiple metastatic sites. The response rate was 18.5% in patients with a performance status of 0 and 8.2% in patients with a performance status of 1 or 2. Patients with a performance status of 3 or 4 have not been studied. Over half of the patients responding to CAMPTOSAR had not responded to prior 5-FU. Patients who had received previous irradiation to the pelvis responded to CAMPTOSAR at approximately the same rate as those who had not previously received irradiation.

Once-Every-3-Week Dosage Schedule

Single Arm Study: Study 6

Data from an open-label, single-agent, single-arm, multicenter, clinical study involving a total of 132 patients support a once every-3-week dosage schedule of irinotecan in the treatment of patients with metastatic cancer of the colon or rectum that recurred or progressed following treatment with 5-FU. Patients received a starting dose of 350 mg/m^2 given by 30-minute intravenous infusion once every 3 weeks. Among the 132 previously treated patients in this trial, the intent-to-treat response rate was 12.1% (95% CI, 7.0% to 18.1%).

Randomized Studies: Studies 7 and 8
Two multicenter, randomized, clinical studies further support the use of irinotecan given by the once-every-3-week dosage schedule in patients with metastatic colorectal cancer whose disease has recurred or progressed following prior 5-FU therapy. In Study 7, second-line irinotecan therapy plus best supportive care was compared with best supportive care alone. In Study 8, second-line irinotecan therapy was compared with infusional 5-FU-based therapy. In both studies, irinotecan was administered intravenously at a starting dose of 350 mg/m^2 over 90 minutes once every 3 weeks. The starting dose was 300 mg/m^2 for patients who were 70 years and older or who had a performance status of 2. The highest total dose permitted was 700 mg. Dose reductions and/or administration delays were permitted in the event of severe hematologic and/or nonhematologic toxicities while on treatment. Best supportive care was provided to patients in both arms of Study 7 and included antibiotics, analgesics, corticosteroids, transfusions, psychotherapy, or any other symptomatic therapy as clinically indicated. In both studies, concomitant medications such as antiemetics, atropine, and loperamide were given to patients for prophylaxis and/or management of symptoms from treatment. If late diarrhea persisted for greater than 24 hours despite loperamide, a 7-day course of fluoroquinolone antibiotic prophylaxis was given. Patients in the control arm of the Study 8 received one of the following 5-FU regimens: (1) LV, 200 mg/m^2 IV over 2 hours; followed by 5-FU, 400 mg/m^2 IV bolus; followed by 5-FU, 600 mg/m^2 continuous IV infusion over 22 hours on days 1 and 2 every 2 weeks; (2) 5-FU, 250 to 300 mg/m^2/day protracted continuous IV infusion until toxicity; (3) 5-FU, 2.6 to 3 g/m^2 IV over 24 hours every week for 6 weeks with or without LV, 20 to 500 mg/m^2/day every week IV for 6 weeks with 2-week rest between cycles. Patients were to be followed every 3 to 6 weeks for 1 year.

A total of 535 patients were randomized in the two studies at 94 centers. The primary endpoint in both studies was survival. The studies demonstrated a significant overall survival advantage for irinotecan compared with best supportive care (p=0.0001) and infusional 5-FU-based therapy (p=0.035) as shown in Figures 3 and 4. In Study 7, median survival for patients treated with irinotecan was 9.2 months compared with 6.5 months for patients receiving best supportive care. In Study 8, median survival for patients treated with irinotecan was 10.8 months compared with 8.5 months for patients receiving infusional 5-FU-based therapy. Multiple regression analyses determined that patients' baseline characteristics also had a significant effect on survival. When adjusted for performance status and other baseline prognostic factors, survival among patients treated with irinotecan remained significantly longer than in the control populations (p=0.001 for Study 7 and p=0.017 for Study 8). Measurements of pain, performance status, and weight loss were collected prospectively in the two studies; however, the plan for the analysis of these data was defined retrospectively. When comparing irinotecan with best supportive care in Study 7, this analysis showed a statistically significant advantage for irinotecan, with longer time to development of pain (6.9 months versus 2.0 months), time to performance status deterioration (5.7 months versus 3.3 months), and time to > 5% weight loss (6.4 months versus 4.2 months). Additionally, 33.3% (33/99) of patients with a baseline performance status of 1 or 2 showed an improvement in performance status when treated with irinotecan versus 11.3% (7/62) of patients receiving best supportive care (p=0.002). Because of the inclusion of patients with non-measurable disease, intent-to-treat response rates could not be assessed.

Figure 3. Survival
Second-Line Irinotecan vs Best Supportive Care (BSC)
Study 7

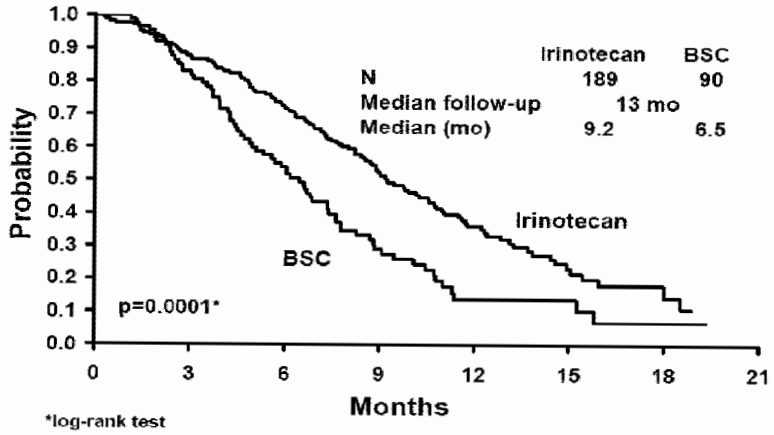


Figure 4. Survival
Second-Line Irinotecan vs Infusion 5-FU
Study 8

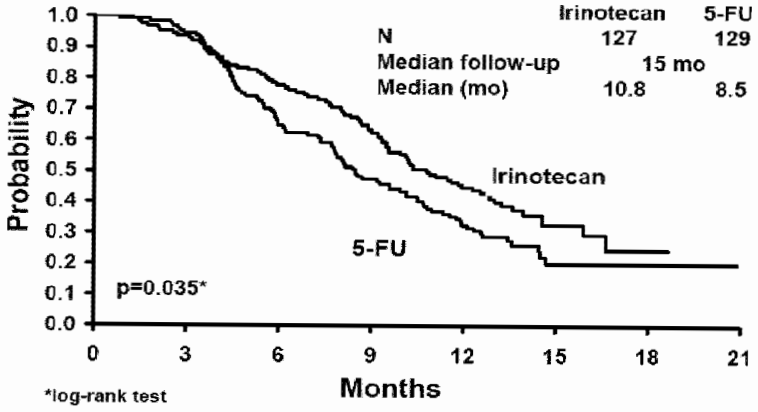


Table 12. Once-Every-3-Week Dosage Schedule: Study Results

	Study 7		Study 8	
	Irinotecan	BSC[a]	Irinotecan	5-FU
Number of patients	189	90	127	129
Demographics and treatment administration				
Female/Male (%)	32/68	42/58	43/57	35/65
Median age in years (range)	59 (22-75)	62 (34-75)	58 (30-75)	58 (25-75)
Performance status (%)				
0	47	31	58	54
1	39	46	35	43
2	14	23	8	3
Primary tumor (%)				
Colon	55	52	57	62
Rectum	45	48	43	38
Prior 5-FU therapy (%)				
For metastatic disease	70	63	58	68
As adjuvant treatment	30	37	42	32
Prior irradiation (%)	26	27	18	20
Duration of study treatment (median, months) (Log-rank test)	4.1	--	4.2 (p=0.02)	2.8
Relative dose intensity (median %)[b]	94	--	95	81-99
Survival				
Survival (median, months) (Log-rank test)	9.2 (p=0.0001)	6.5	10.8 (p=0.035)	8.5

[a] BSC = best supportive care

[b] Relative dose intensity for irinotecan based on planned dose intensity of 116.7 and 100 mg/m^2/wk corresponding with 350 and 300 mg/m^2 starting doses, respectively.

In the two randomized studies, the EORTC QLQ-C30 instrument was utilized. At the start of each cycle of therapy, patients completed a questionnaire consisting of 30 questions, such as "Did pain interfere with daily activities?" (1 = Not at All, to 4 = Very Much) and "Do you have any trouble taking a long walk?" (Yes or No). The answers from the 30 questions were converted into 15 subscales, that were scored from 0 to 100, and the global health status subscale that was derived from two questions about the patient's sense of general well being in the past week. The results as summarized in Table 13 are based on patients' worst post-baseline scores. In Study 7, a multivariate analysis and univariate analyses of the individual subscales were performed and corrected for multivariate testing. Patients receiving irinotecan reported significantly better results for the global health status, on two of five functional subscales, and on four of nine symptom subscales. As expected, patients receiving irinotecan noted significantly more diarrhea than those receiving best supportive care. In Study 8, the multivariate analysis on all 15 subscales did not indicate a statistically significant difference between irinotecan and infusional 5-FU.

Table 13. EORTC QLQ-C30: Mean Worst Post-Baseline Score[a]

QLQ-C30 Subscale	Study 7			Study 8		
	Irinotecan	BSC	p-value	Irinotecan	5-FU	p-value
Global health status	47	37	0.03	53	52	0.9
Functional scales						
Cognitive	77	68	0.07	79	83	0.9
Emotional	68	64	0.4	64	68	0.9
Social	58	47	0.06	65	67	0.9
Physical	60	40	0.0003	66	66	0.9
Role	53	35	0.02	54	57	0.9
Symptom Scales						
Fatigue	51	63	0.03	47	46	0.9
Appetite loss	37	57	0.0007	35	38	0.9
Pain assessment	41	56	0.009	38	34	0.9
Insomnia	39	47	0.3	39	33	0.9
Constipation	28	41	0.03	25	19	0.9
Dyspnea	31	40	0.2	25	24	0.9
Nausea/Vomiting	27	29	0.5	25	16	0.09
Financial impact	22	26	0.5	24	15	0.3
Diarrhea	32	19	0.01	32	22	0.2

[a] For the five functional subscales and global health status subscale, higher scores imply better functioning, whereas, on the nine symptom subscales, higher scores imply more severe symptoms. The subscale scores of each patient were collected at each visit until the patient dropped out of the study.

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16 HOW SUPPLIED/STORAGE AND HANDLING

CAMPTOSAR Injection is available in single-dose brown glass vials in the following package sizes:

2 mL NDC 0009-7529-02
5 mL NDC 0009-7529-01

CAMPTOSAR Injection is available in single-dose amber colored polypropylene CYTOSAFE® vials in the following package sizes:

2 mL	NDC 0009-7529-04
5 mL	NDC 0009-7529-03
15 mL	NDC 0009-7529-05

Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light. Keep the vial in the carton until the time of use.

Inspect the vial for damage and visible signs of leaks before removing from the carton. If damaged, incinerate the unopened package.

17 PATIENT COUNSELING INFORMATION

- Patients and caregivers should be informed of gastrointestinal complications, such as nausea, vomiting, abdominal cramping, and diarrhea. Patients should have loperamide readily available to begin treatment for late diarrhea (generally occurring more than 24 hours after administration of CAMPTOSAR). Begin loperamide at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normal. One dosage regimen for loperamide is 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. Loperamide is not recommended to be used for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus. During the night, the patient may take 4 mg of loperamide every 4 hours. Patients should contact their physician if any of the following occur: diarrhea for the first time during treatment; black or bloody stools; symptoms of dehydration such as lightheadedness, dizziness, or faintness; inability to take fluids by mouth due to nausea or vomiting; or inability to get diarrhea under control within 24 hours.
- Patients should be warned about the potential for dizziness or visual disturbances which may occur within 24 hours following the administration of CAMPTOSAR.
- Explain the significance of routine blood cell counts. Instruct patients to monitor their temperature frequently and immediately report any occurrence of fever or infection.
- CAMPTOSAR may cause fetal harm. Advise patients to avoid becoming pregnant while receiving this drug.
- Patients should be alerted to the possibility of alopecia.
- Contains sorbitol.

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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/Dawn MacPherson
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First Named Inventor	Eliel Bayever
Art Unit	1612
Examiner Name	Gollamundi S. KISHORE
Attorney Docket Number	01208-0007-01US

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	Art Unit	1612
	Examiner Name	Gollamundi S. KISHORE
	Attorney Docket Number	01208-0007-01US

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	Art Unit	1612
	Examiner Name	Gollamundi S. KISHORE
	Attorney Docket Number	01208-0007-01US

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	Art Unit	1612
	Examiner Name	Gollamundi S. KISHORE
	Attorney Docket Number	01208-0007-01US

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Signature	/Mary R. Henninger/	Date (YYYY-MM-DD)	2022-03-10
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We evaluated the influence of RAS status (RAS wild-type or RAS mutant), prior targeted therapy (prior anti-EGFR or prior anti-VEGF), age (≤70 years or >70 years) and gender on the effectiveness and safety of aflibercept plus FOLFIRI in daily practice.

Methods: QoLiTrap is a large international, prospective, non-interventional study evaluating the quality of life (QoL), effectiveness, and safety of aflibercept plus FOLFIRI. The primary endpoint was QoL as assessed by EORTC QLQ-C30 questionnaire. Secondary endpoints included overall survival (OS), progression-free survival (PFS), tumor response rate (complete + partial) and safety. Patients who had a QoL questionnaire at baseline and at least 2 post-baseline were evaluated. Safety was analyzed in all patients exposed to at least one dose of study drug.

Results: 1277 patients with mCRC were treated (≥70 years 38.5%, males 64.8%, RAS mutant 50.7%, right colon tumor 27.6%, liver metastases 53.2%, ECOG 0-1 84.7%) mainly in second-line (50.3%) but also in third-line (23.1%) and fourth-line (11.9%) setting. Median duration of treatment was 12 weeks. Overall, 872 patients were evaluable for the efficacy analysis. At baseline, the global health (mean) score was 58.7 and the mean change from baseline over 12 weeks was -4.6%. Overall, 868 and 869 patients were evaluated for PFS and OS respectively. In the overall population, median PFS and OS (95%, confidence interval) were 8.8 (8.0-9.4) and 19.5 (14.4-23.6) months, respectively. For RAS wild-type vs RAS mutant patients, median PFS was 9.4 (7.6-10.1) vs 8.1 (7.7-9.0) months and median OS was 23.6 (14.2-31.6) vs 18.1 (13.2-21.0) months, respectively. For patients treated with prior anti-EGFR vs prior anti-VEGF therapy, median PFS was 12.9 (7.7-28.5) vs 8.0 (7.3-8.75) months and median OS was 29.0 (14.3-33.7) vs 18.1 (13.4-22.3) months, respectively. For patients ≤70 years vs >70 years, median PFS was 8.7 (7.8-9.4) vs 9.0 (7.6-10.2) months and median OS was 19.5 (15.2-27.0) vs 14.4 (10.8-29.0) months, respectively. For males vs females, median PFS was 9.0 (8.0-10.0) vs 8.5 (7.3-9.4) months and median OS was 14.9 (14.0-27.0) vs 21.0 (15.4-33.4), respectively. Overall, tumor response rate was 22% and ranged from 21% to 26% in the subgroups previously described; highest values were observed in patients with prior anti-EGFR (26%) and those aged >70 years (24%). Most common all-grade adverse events were diarrhea (34.2%), nausea (17.9%), fatigue (17.2%), stomatitis (17.2%), and hypertension (11.6%).

Conclusions: Aflibercept plus FOLFIRI, mainly prescribed in second-line mCRC, retains its activity irrespective of RAS status, prior targeted therapy, age, or gender. The safety profile was manageable.

Clinical trial identification: Registration number: AIO-LQ-0113.

Legal entity responsible for the study: Sanofi Aventis Deutschland GmbH.

Funding: Sanofi.

Disclosure: R. Hofheinz: Honoraria (self): Amgen, BMS, MSD, Sanofi, Merck, Lilly, Roche; Advisory / Consultancy: Amgen, BMS, MSD, Sanofi, Merck, Lilly, Roche. All other authors have declared no conflicts of interest.

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PD-4 A phase I trial of trifluridine/tipiracil in combination with nanoliposomal irinotecan in advanced GI cancers

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Background: Trifluridine/tipiracil (FTD/TPI, TAS-102) is a combination of a nucleoside analogue and a thymidine phosphorylase inhibitor, with treatment activity in 5FU-resistant colorectal cancer (CRC). Nanoliposomal-irinotecan (Nal-IRI, Onivyde©) has been shown to achieve higher intra-tumor concentrations compared to irinotecan (142-fold) and its major metabolite, SN-38 (9-fold). Nal-IRI has superior anti-tumor activity compared to free irinotecan in multiple tumor xenografts. Clinical trials have demonstrated activity of Nal-IRI combined with 5FU/LV in pancreatic cancer. Therefore, the combination of Nal-IRI with the more potent nucleoside analogue TAS-102 may result in a more effective systemic therapy regimen in gastrointestinal (GI) cancers, including CRC and pancreatic ductal adenocarcinoma (PDAC). We designed this study to define the recommended phase II dose (RP2D) of the combination therapy.

Methods: The trial design was standard 3+3. The original study included the combination of TAS-102 given orally in four dose levels of 25, 25, 30, and 35 mg/m2 bid on days 1-5, and Nal-IRI at corresponding dose levels of 50, 70, 70, and 70mg/m2 IV on day 1, in 14-day cycles. After dose-limiting toxicities were experienced at dose level 2 (DL2 = 25mg/m2 TAS-102 + 70mg/m2 Nal-IRI), dose levels for Nal-IRI were amended as follows: 50, 60, 60, 60 mg/m2. Supportive therapy such as diarrhea and nausea management were planned per institutional guidelines. Eligible patients included those with stage IV or locally advanced unresectable GI adenocarcinomas, who had disease progression after at least one prior therapy; age ≥18 years, ECOG PS 0-1 and measurable disease per RECIST 1.1. Patients who were homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) were excluded from the dose-escalation phase of the trial. Primary endpoint was recommended phase II doses (RP2D) of the chemotherapy combination, and secondary endpoints included safety and tolerability.

Results: A total of 24 treatment-refractory patients were enrolled in the study; 58% male, median age 66.5 years. Diagnoses included 18 CRC, 4 PDAC, 1 biliary tract cancer (BTC), and 1 esophageal adenocarcinoma (EA). Two DLTs (neutropenic fever, and grade 3 steroid induced altered mentation) were observed on DL2 pre-amend study plan. Following protocol amendment, we enrolled three patients each on dose levels 1b-3b without any observed DLTs. The maximum tolerated doses which were adopted as RP2D were TAS-102: 35mg/m2 bid on days 1-5 and Nal-IRI: 60mg/m2 IV on day 1, given in 14-day cycles. Disease control rate was 62.5%. One CRC patient who had progression of disease after 4 lines of therapy, achieved and maintained partial response (55% reduction in tumor volume) for 12 months of the study. Fourteen additional patients (EA=1, BTC=1, CRC=10 and PDAC=2) had stable disease as best response. Most common treatment-related toxicities included nausea (G3; n=2), fatigue, diarrhea, vomiting, and anorexia (G3; n=1 each).

Conclusions: The combination of TAS102 and Nal-IRI had an acceptable safety profile. Clinical responses were observed in treatment-refractory patients with multiple locally advanced, unresectable, or metastatic GI adenocarcinomas. A dose expansion phase II of this study is currently enrolling CRC and PDAC patients.

Clinical trial identification: Clinical trial information: NCT03368963.

Legal entity responsible for the study: The authors.

Funding: Ipsen and Taiho Oncology, Inc.

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PD-5 Retrospective comparative analysis of K-ras G12C vs other K-ras mutations in metastatic colorectal cancer patients treated with first-line chemotherapy doublet + bevacizumab

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Background: Treatment choices in metastatic colorectal cancer (mCRC) patients are based on several factors: K-ras mutations define a subset of tumors who have primary resistance to anti-EGFR based therapy. Data concerning whether different isoforms of K-ras mutations may also have prognostic value are lacking. Furthermore, novel K-ras G12C isoform inhibitors are currently in development. The aim of our analysis was to compare response rates (RR) in patients treated with first-line chemotherapy doublet + bevacizumab among different K-ras isoforms.

Methods: Patients with K-ras mutated mCRC treated with either FOLFIRI/FOLFOX/XELOX+bevacizumab were eligible for enrollment. Propensity score matching (nearest method, 2:1 ratio) was used to define the two different groups of patients for comparison (K-ras G12C mutated vs other K-ras isoforms). ECOG PS, sex, metastatic site of involvement, synchronous vs metachronous metastatic disease, tumor sidedness, mucinous histology, primary tumor surgery, and radical surgery of metastases were used as matching factors. RR was calculated by RECIST 1.1 criteria. Categorical variables were compared by Fisher exact test for binomial variables and by chi-square test for all other instances. Level of statistical significance p was set at 0.05 for all tests.

Results: 120 patients were enrolled. 15/120 (12%) were K-ras G12C mutated. 59/120 (49%) had PR, 42/120 (35%) had SD, 19/120 (16%) had PD as best response. In K-ras G12C patients 4/15 (27%) had PR, 6/15 (40%) had SD and the remaining 5/15 (33%) had PD as best response. In patients with other K-ras mutations, 55/105 (52%) had PR, 37/105 (35%) had SD and the remaining 13/105 (12%) had PD as best response. The difference in RR between the two groups of patients was statistically significant (p=0.017). Even after matching, in patients with K-ras mutations different from G12C (30 patients), 16/30 (53%) had PR, 11/30 (37%) had SD and 3/30 (10%) had PD as best response. The difference in outcome remained statistically significant (p=0.046). K-ras G12C mutations were not associated with differences in sites of metastatic involvement (p=1 for liver metastases, p=0.56 for lung metastases and p=0.51 for peritoneal metastases), sex (p=0.06), ECOG PS (p=0.21). On the other hand, synchronous vs metachronous metastatic disease (p=0.039), age > 75 years (p=0.043) and mucinous histology (p=0.008) were more frequent in G12C mutated tumors compared with other K-ras mutations.

Conclusions: K-ras G12C mutations are associated with worse response rates compared to other K-ras isoforms when treated with standard chemotherapy doublet+bevacizumab. New agents, such as G12C selective inhibitors, or different treatment strategies (such as using FOLFOXIRI+bevacizumab) should be tested in this patient population to improve these results.

Legal entity responsible for the study: The authors.

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HEAD AND NECK CANCER

A phase 2 study of liposomal irinotecan with 5-fluorouracil and leucovorin in squamous cell carcinoma of head and neck or esophagus after prior platinum-based chemotherapy or chemoradiotherapy.

Li-Yuan Bai, Muh-Hwa Yang, Nai-Jung Chiang, Shang-Yin Wu, Chen-Yuan Lin, Ming-Yu Lien, Jia-Hong Chen, Mu-Hsin Chang, Ching-Yun Hsieh, Rusy-Long Hong, Hsiang-fong Kao, Ren-Hua Ye, Shang-Hung Chen, Chin-Fu Hsiao, Li-Tzong Chen, Tsang-Wu Liu

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Abstract Disclosures

Abstract

6025

Background: Liposomal irinotecan (nal-IRI) + 5-FU/LV has been approved and used in treating patients with metastatic pancreatic cancer after gemcitabine-based therapy through the NAPOLI-1 study result. This phase 2 trial evaluated the activity of NAPOLI-1 regimen in patients with squamous cell carcinoma (SCC) of head and neck (H&N) or esophagus that progressed on or recur after platinum-based chemotherapy or concurrent chemoradiotherapy. **Methods:** Patients with histologically confirmed SCC of H&N or esophagus whose disease progressed while on or progressed/recurred within 6 months after platinum-based chemotherapy or chemoradiotherapy, and unsuitable for further surgical or radiation intervention were eligible. Prior anti-EGFR or anti-PD1/anti-PDL1 treatment was allowed. The regimen consisted of nal-IRI 70 mg/m^2 (irinotecan free base) followed by LV 400 mg/m^2 and 5-FU 2400 mg/m^2, every 2 weeks. A Simon's 2-stage design was used with planned 30 evaluable patients in the first stage and 52 evaluable patients in total. The primary endpoint is objective tumor response. **Results:** From December 2018 to April 2020, 59 subjects were enrolled, including 16 with esophagus cancer and 43 with H&N cancer. Thirty-seven (63%) patients had metastatic disease at enrollment. The mean of treatment cycles were

5 (range, 1-21). Among the total 59 enrolled subjects, 53 subjects (14 esophagus cancer, 39 H&N cancer) were evaluable for objective tumor response. The disease control rate in esophagus cancer was 50% (7 SD, intent-to-treat (ITT) population 43.8%). For H&N patients, 1 CR, 4 PR, and 23 SD resulted in the response rate 12.8% (11.6% in ITT population) and disease control rate 72% (65% in ITT population). The median progression free survival (N = 59) was 2.5 months (esophagus/H&N: 1.5/2.7 months) and the median overall survival was 5.9 months (esophagus/H&N: 4.2/7.3 months). Seventy-eight percent of patients had ≥grade 3 treatment-related adverse events. The most frequent ≥grade 3 toxicities were decreased lymphocyte count (50.8%), decreased neutrophil count (42.4%), and decreased white blood count (33.9%). Only 3 patients (5%) had grade 3 diarrhea during the treatment period.

Conclusions: This study showed the modest efficacy and manageable toxicity profile of nal-IRI+5-FU/LV in platinum-refractory locally advanced or metastatic H&N or esophagus cancer patients. Clinical benefits including complete tumor response were noted in H&N patients. The role of this regimen in selective patients and the efficacy of combination with immunotherapeutic agents warrant further explorations. Clinical trial information: NCT03712397.

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P196

Safety and effectiveness of prospective observational postmarketing surveillance study for pancreatic adenocarcinoma treated by liposomal irinotecan plus 5-fluorouracil/leucovorin in Korea

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Background/Purpose Liposomal irinotecan (nal-IRI) plus 5-fluorouracil/ leucovorin (5-FU/LV) is considered as a standard treatment option after failure of gemcitabine-based chemotherapy in patients with metastatic pancreatic adenocarcinoma. After NAPOLI-1 trial suggested the evidence of an effective regimen, several real-world data showed comparable or better results. All real-world data were based on retrospective analyses with chart review, so this prospective, observational, and multi-center, post-marketing surveillance (PMS) study in Korea will be able to show another value of evidence. **Methods** Nal-IRI was registered on August 29, 2017. This PMS started in May 2018, with the enrollment period occurring from May 2018 to June 2020; the PMS was continued until December 2020, where the follow-up period was 6 months. The basic design of the PMS aimed to assess safety of the nal-IRI; however, any effectiveness data gathered incidentally were also analyzed. Variables were described in a narrative way, and for evaluating factors affecting effectiveness, a univariate analysis was used. **Results** Ninety-four patients were enrolled; 3 dropped out due to no administration of nal-IRI. The Karnofsky performance status for the patients was > 80, with most patients having stave IV disease at enrollment (81.3%). Male patients were 55.0% of total analysis set, and patients and/over 65 years were 42.9% with median age of 61 years old. The most common site of metastasis was the liver (63 patients; 69.2%). 31 patients received ≥ 6 cycles of nal-IRI+5-FU/LV, whereas 60 patients discontinued before 6 cycles. During the regimen, 86 patients (95.5%) were treated with medicines for supportive care. The most common adverse event was nausea (27.5%) followed by neutropenia (18.7%). Grade 3-4 neutropenia was recorded in 14 patients (15.4%). mPFS was 3.5 months and associated factors were concomitant medication for supportive care and longer cycles of treatment (≥ 6 cycles), which resulted in longer PFS. **Conclusion** Korean PMS explained consistent safety and effectiveness results, compared with real-world data and NAPOLI-1 trial. Quality of life of patients treated with nal-IRI+5-FU/ LV was relatively well preserved, and well-established supportive care during the cycles can give modest effectiveness outcomes.

this patient population, with a focus on related hospitalizations and costs. ***Methods:*** Men receiving ADT with ≥2 claims for a diagnosis of PC were identified in the Marketscan Commercial and Medicare Supplemental Database (1/1/2009-12/31/2018). Index date was the first ADT claim. Patients were required to be continuously enrolled 6-months pre- and ≥2 months post-index. Patients with a major adverse cardiovascular event (MACE: myocardial infarction, cerebrovascular accident, unstable angina, percutaneous coronary intervention, and/or coronary bypass graft) post index and insurance eligibility for ≥30 days after MACE were identified. Thirty-day (30) post-MACE hospitalizations and MACE-related costs (2018 USD) were assessed. ***Results:*** The study included 49,155 men with PC on ADT; 8,102 patients (16.5%) experienced a MACE during the whole study period. A total of 6,754 (13.7%) qualified for the post-MACE analysis; most had Medicare (86.6%) coverage. In the 30-days post-event, a high proportion of patients incurred a MACE-related hospitalizations (Medicare: 46.6%; Commercial: 45.1%); inpatient costs among patients with ≥1 admission were $36,185 (SD: $62,654) and $55,322 (SD: $69,539) in Medicare and commercial patients, respectively. ***Conclusions:*** PC patients treated with GnRH agonists are at increased risk of CV events. When MACE occurs, patients likely require a hospitalization associated with substantial inpatient costs. ADTs that lower CV risk have the potential to improve patient outcomes while reducing healthcare costs.

PCN152
THE BURDEN OF SKELETAL-RELATED EVENTS IN FOUR LATIN AMERICAN COUNTRIES: ARGENTINA, BRAZIL, COLOMBIA, AND MEXICO

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Objectives: Limited data are available regarding the burden of skeletal-related events (SREs) in Latin America. The purpose of this study was to estimate the current and future economic burden of SREs in adult patients with cancer in Argentina, Brazil, Colombia, and Mexico. ***Methods:*** Model inputs were informed by a comprehensive literature review and expert opinion. Country-specific inputs were used, where possible. For each country, we estimated the prevalence of patients with bone metastasis from prostate cancer, breast cancer, and other solid tumors, as well as patients with multiple myeloma and bone lesions, and the annual number of SREs for each patient group. Aggregate SRE management costs for vertebral fractures, non-vertebral fractures, radiation to bone, spinal cord compression, and surgery to bone were obtained from country-specific sources. Productivity losses were also calculated. Costs were expressed in 2020 USD for the total annual burden, annual burden per 1,000 at risk, and projected five-year burden. ***Results:*** The estimated total number of SREs was 251,503 in 2020, resulting in a total annual cost of approximately $1.4 billion. The projected five-year cost was approximately $6.9 billion. Annual costs were highest in Brazil ($779.1 million), followed by Mexico ($281.8 million), Argentina ($174.6 million), and Colombia ($120.1 million). The average annual burden per 1,000 at risk was greatest in Brazil ($3.6 million), followed by Mexico ($3.4 million), Colombia ($2.9 million), and Argentina ($2.7 million). ***Conclusions:*** Over the next five years, patients will experience approximately 1,282,594 SREs in Argentina, Brazil, Colombia, and Mexico. Based on expert input and market research, 35%-70% of patients with advanced solid tumors currently do not receive treatment for the prevention of SREs. Early detection of bone metastases and SREs, and the use of the most effective preventative treatments are needed to decrease the clinical and economic burden of SREs.

PCN153
USING A BUDGET IMPACT MODEL (BIM) AS A DECISION-MAKING TOOL AT THE HOSPITAL LEVEL IN FRANCE: AN EXAMPLE OF CPX-351 IN PATIENTS WITH NEWLY DIAGNOSED THERAPY-RELATED AML (T-AML) OR AML WITH MYELODYSPLASIA-RELATED CHANGES (AML-MRC)

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Objectives: In France, Diagnosis-related Groups (DRG)–based payment is the main hospital funding system. For hospital-restricted products with an acquisition cost >30% of the DRG payment and without external funding through the "liste-en-sus," there is an affordability issue. One hospital-restricted product that falls in this category is CPX-351 (Vyxeos® Liposomal), a dual-drug liposomal encapsulation of cytarabine/daunorubicin at a synergistic 5:1 molar ratio that is indicated for patients with newly diagnosed t-AML and AML-MRC. The objective of this study was to develop a BIM to assess affordability at the hospital level. ***Methods:*** We developed a BIM comparing CPX-351 to conventional cytarabine/daunorubicin chemotherapy (7+3 regimen). The BIM followed a dynamic cohort entering the model every year over 3 years. Hospital data (PMSI) recommended by the French HTA were used to estimate costs and revenues related to the interventions and patient pathway (induction, consolidation, and hematopoietic cell transplantation [HCT]). All costs and revenues were assessed from a hospital perspective. All relevant clinical parameters (target population and patient pathway) are editable to enable adaptation at the hospital level. Model base case parameters/inputs are based on Study 301 (Lancet J, Clin Oncol 2018;36:2684-2692) and French real-world data. ***Results:*** At a national level, the introduction of CPX-351 increases total costs (+36%) and total revenues (+10%) for the hospitals . Costs are driven by the acquisition cost of CPX-351 and revenues by HCT. The use of CPX-351 results in more patients proceeding to transplant versus 7+3, generating more transplant-related revenue (+31%) for hospitals. ***Conclusions:*** Economic assessment of a new healthcare intervention, including the BIM, is a relevant decision-support tool for many stakeholders within the health system. At the hospital level, it helps to evaluate the affordability of new products, which may lead to greater accessibility across the country.

PCN154
BUDGET IMPACT ANALYSIS OF LIPOSOMAL IRINOTECAN FOR TREATMENT OF METASTATIC ADENOCARCINOMA OF PANCREAS FOLLOWING PROGRESSION ON GEMCITABINE-BASED THERAPIES FROM GREEK PAYER'S PERSPECTIVE

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Objectives: To estimate the budgetary impact from the introduction of liposomal Irinotecan as a treatment option for patients with metastatic pancreatic cancer (mPDAC) who have previously received gemcitabine-based regimens in Greek health system. ***Methods:*** A budget impact model was developed from third-party payer perspective over a 5-year time horizon to estimate the financial impact of liposomal Irinotecan by obtaining market shares from available treatments options. Based on local experts, patients with mPDAC are currently treated with FOLFOX, FOLFIRI, FOLFIRINOX, capecitabine and nab-paclitaxel, which represent the common clinical practice in the absence of any other recommendation. The model framework considered market share scenarios with and without liposomal Irinotecan and reimbursed costs of treatment applied to the eligible patient population. Data on the number of eligible patients were estimated from the published literature and local experts, while the projected uptake of liposomal Irinotecan was provided by Servier. Drug acquisition costs were considered in the analysis and were retrieved from the Greek Ministry of Health. The model measured outcome was incremental budget impact from the introduction of liposomal Irinotecan as a treatment option in the patients with mPDAC ***Results:*** Over the 5-year horizon, the number of eligible patients was 485 and the number of patients who received liposomal Irinotecan was 19, 116, 189, 210 and 210 in the years 1 to 5, respectively. The annual incremental costs associated with the introduction of liposomal Irinotecan were €118,641, €728,491, €1,186,407, €1,321,695 and €1,321,695 for years 1 to 5 respectively, resulting in a total 5-year budget impact of €4,676,928. ***Conclusions:*** The regimen of liposomal Irinotecan plus 5-FU/LV as a treatment option for patients with mPDAC after disease progression following gemcitabine-based therapies, provides survival benefits. The analysis suggests that, those clinical benefits are associated with additional costs which may be considered as reasonable and bearable from the Greek payer perspective.

PCN155
HEALTHCARE RESOURCE USE AND ASSOCIATED COSTS IN PATIENTS DIAGNOSED WITH ACUTE MYELOID LEUKEMIA IN HOSPITAL DISTRICT OF SOUTHWEST FINLAND

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Objectives: To estimate health care resource utilization (HRCU) and costs in different disease stages of acute myeloid leukemia (AML) in Finland. ***Methods:*** Real world data of adult patients (≥18 years) diagnosed with AML (ICD-10 C92.0) 2004-2016 was collected from Auria Biobank. Data on HCRU (secondary healthcare visits, medical procedures, laboratory tests, AML-related hospital drugs) were collected from the medical records of Turku university hospital. The unit costs were extracted from the 2020 hospital price list. Drug costs are not included in the cost calculation. Costs are reported as average cost per patient. ***Results:*** A total of 191 diagnosed patients (56% men) were identified. FLT3-mutation status was available from 120 patients, including 23 cases (19%) of FLT3-ITD and 5 cases (4%) of FLT3-TKD mutations. 119 patients (62%) received standard intensive chemotherapy, with 71% reaching complete remission (CR) after the 1st induction. Allogenic stem cell transplantation (SCT) was given to 57 patients (30%), out of which 33% were later diagnosed with graft versus host disease. The costs of induction (1st month of follow-up) were 32,605€, consolidation (1st month from the beginning of consolidation phase) 26,829€, CR after consolidation (6th-7th month of the follow-up) 4,500€, post

Risk Adjustment and Total Cost of Care per Month of Overall Survival Among Medicare Fee-for-Service (FFS) Patients Receiving NCCN Category-1 Treatments for Metastatic Pancreatic Cancer

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PURPOSE: Hierarchical Condition Category (HCC) risk scores are widely used by payers to assess the relative health status of Medicare beneficiaries and predict future healthcare costs. HCC risk score models use beneficiary information including age, sex, prior-year diagnosis codes, and social determinants of health. There is limited research evaluating the relationship between risk scores and costs for metastatic pancreatic cancer (m-PANC) patients receiving chemotherapy.

METHODS: We identified patients with m-PANC using ICD-10 diagnosis codes in the 2016-2019 Medicare Parts A/B/D 100% Research Identifiable Files. Study patients had 2+ claims with a pancreatic cancer diagnosis and Medicare FFS coverage for 6 months pre- and 3 months post-metastasis diagnosis. A line of therapy (LOT) was assigned based on the order and number of therapies used. Sequences of NCCN Category 1 regimen LOTs were created for patients that received FOLFIRINOX, gemcitabine/nab-paclitaxel, gemcitabine + erlotinib, gemcitabine monotherapy, or 5-FU + leucovorin + liposomal irinotecan (patients with multiple regimens in the same LOT were excluded). Mean HCC risk scores were calculated for patients in each sequence, and Kaplan-Meier methods were used to estimate median overall survival in months (OS). Median total cost of care (TCOC) per OS was normalized by HCC risk scores to assess variations among sequences. Results were summarized for the top 3 regimens with one, two, and three LOT sequences with at least 30 patients per sequence.

RESULTS: We identified 31,782 patients with m-PANC between 2016 and 2019, of which 14,900 (47%) were treated with the top 3 regimens for one, two, and three LOT sequences. 12,907 received one LOT consisting of gemcitabine/nab-paclitaxel, gemcitabine monotherapy, or FOLFIRINOX; 1,846 received two LOTs consisting of gemcitabine/nab-paclitaxel >> liposomal irinotecan + 5-FU/LV, FOLFIRINOX >> gemcitabine/nab-paclitaxel or gemcitabine/nab-paclitaxel >> FOLFIRINOX; 147 received three LOTs consisting of FOLFIRINOX >> gemcitabine/nab-paclitaxel >> liposomal irinotecan + 5-FU/LV or gemcitabine/nab-paclitaxel >> FOLFIRINOX >> liposomal irinotecan + 5-FU/LV. Patients in our study had a mean HCC risk score of 2.29 and median TCOC of $54,142. Mean HCC risk scores and median TCOC were lowest for patients receiving one LOT (2.24 and $47,417 respectively), followed by patients receiving two LOTs (2.62 and $120,618, respectively) and three LOTs (3.27 and $198,622, respectively). Risk-normalized median TCOC per OS decreased as the number of LOTs increased. These costs ranged from $6,615 to $12,118 for patients with one LOT (median $10,134), from $8,345 to $10,190 for patients with two LOTs (median $9,426) and from $6,926 to $8,524 for patients with three LOTs (median $7,054).

CONCLUSION: HCC risk scores suggest that monthly costs of care for patients with m-PANC (2.29) are predicted to be 129% higher than the average Medicare beneficiary (1.00). Patients with more LOTs were also expected to incur higher monthly costs of care: HCCs for patients with 2 and 3 LOTs were 17%

and 46% higher, respectively, than patients with only 1 LOT. After normalizing for HCCs, median total costs per month of overall survival remained flat or decreased with additional lines of therapy.

1477P Prognostic and predictive value of CA 19-9 in locally advanced pancreatic cancer treated with multi-agent induction chemotherapy: Results from a prospective, multicenter phase II trial (NEOLAP-AIO-PAK-0113)

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Background: The prognostic and predictive value of CA 19-9 in locally advanced pancreatic cancer (LAPC) has not yet been defined from prospective randomized controlled trials (RCT).

Methods: 165 patients LAPC were primarily treated for 4 months with multi-agent induction chemotherapy (either nab-Paclitaxel/Gemcitabine alone or nab-Paclitaxel/Gemcitabine followed by FOLFIRINOX) followed by surgical exploration of all patients without evidence of disease progression. CA 19-9 was evaluated at baseline and during induction chemotherapy (week 8 and 16) and correlated with overall survival (OS) and secondary R0 resection rate.

Results: From the total enrolled and treated NEOLAP study population (n=165) 133 patients (81%) were evaluable for CA 19-9 baseline and 81 patients for week 16 measurement. Median OS in the CA 19-9 cohort (N=133) was 16.2 months (95% CI 13.0-19.4) and R0 resection (31 of 133 patients; 23%) was associated with a significant survival benefit (40.8 [95% CI 21.4-52.7] months vs. 14.2 [95% CI 12.0-17.4] months; $p<0.0001$). After completion of induction chemotherapy (week 16) the majority of patients showed a CA 19-9 response (median change from baseline: -82%; any decrease: 98%; decrease $\geq$ 20%: 93%; decrease $\geq$ 60%: 78%; decrease $\leq$ 50 U/ml: 43%). Robust CA 19-9 response (decrease $\leq$ 50 U/ml) was significantly associated with mOS (27.8 [95% CI 18.4-37.2] vs 16.5 [95% CI 11.7-21.2] months; $p=0.013$), whereas CA 19-9 baseline levels were not prognostic for OS. CA 19-9 non-responders (<20% decrease) had no chance for successful R0 resection (NPV 100%). However, the best cut-off of CA 19-9 decrease ($\leq$ 61 U/ml by ROC-analysis) yielded a sensitivity of 72% and specificity of 62% for successful R0 resection.

Conclusions: In contrast to CA 19-9 baseline levels CA 19-9 response after induction chemotherapy provides prognostic information on overall survival in LAPC. CA 19-9 decrease may serve as a useful predictive biomarker for achieving R0 resection after multi-agent induction chemotherapy.

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1478P Trends in treatment patterns among Medicare fee-for-service (FFS) patients receiving treatment for metastatic pancreatic cancer

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Background: There is limited research evaluating trends in the use of regimen sequences among patients (pts) with metastatic pancreatic cancer (m-PANC).

Methods: We identified pts with m-PANC using ICD-10 diagnosis codes in the 2016-2019 Medicare Parts A/B/D 100% Research Identifiable Files. Study pts had 2+ claims with a pancreatic cancer diagnosis and Medicare FFS coverage for 6 months pre- and 3 months post-metastasis diagnosis. A line of therapy (LOT) was assigned based on the order and number of therapies used in each sequence (first, second, or third-line). Regimen sequences had no subsequent chemotherapy following the last regimen within a sequence. We examined one-line, two-line, and three-line sequences.

Results: We identified 31,782 total pts with 21,304 one-line sequences, 7,352 two-line sequences, and 3,126 three-line sequences between 2016 and 2019. Of these, 69% received chemotherapy in 2019, compared to 56% in 2016. In 2019, fewer pts used one-line sequences (41%) and more pts used two- or three-line sequences (28%), compared to 47% and 9%, respectively, in 2016. Among pts receiving two-line sequences, sequences consisting of FOLFIRINOX (FFX) to gemcitabine/nab-paclitaxel (gem/nab) or gem/nab to liposomal irinotecan had the largest increase (from 10% and 5%, respectively, in 2016 to 14% and 11% in 2019). Among pts receiving three-line sequences, the sequences with the largest increase in utilization were FFX to gem/nab to liposomal irinotecan or gem/nab to liposomal irinotecan to FOLFOX (1% and 0% respectively, of all pts with three-line sequences in 2016, compared to 4% and 5% in 2019).

Conclusions: The use of two- and three- line sequences increased consistently from 2016 to 2019. Sequences containing liposomal irinotecan in second and third line are the primary drivers of this increase.

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1479P Exploring second-line therapy outcome in pancreatic ductal adenocarcinoma (PDAC) patients with germlineBRCA1-2 pathogenic variants (gBRCA1-2pv)

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Background: Pancreatic Ductal Adenocarcinoma (PDAC) harboring germlineBRCA1-2 pathogenic variants (gBRCA1-2pv) is emerging as a distinct entity, benefitting from specific treatments (platinum agents, PARP-inhibitors). Information on second-line therapy (2LT) outcome in this setting is lacking.

Methods: Clinical data of stage IV PDAC patients (pts) carrying gBRCA1-2pv receiving a 2LT were retrospectively collected from 23 Italian Centers and descriptively analyzed, focusing on RECIST response and survival outcome. Progression-free and Overall survival2 (PFS2 and OS2) were calculated from 2LT start to 2nd progression or death, respectively.

Results: 49 out of 63 pts treated with first-line therapy (1LT) between December 2008 and July 2020 had Progressive Disease (PD) at time of database lock: 7 pts (4 treated without platinum) did not receive subsequent therapies, while 42 (86%) started a 2LT, whose outcome was assessable in 40 pts (2 had immature follow-up). ECOG Performance Status at diagnosis was ≤ 1 in 38 (95%) pts, 32 (80%) had liver metastases, median age was 62 (39-84) years. RECIST responses of the 19 and 18 pts receiving platinum- and non-platinum-based multidrug 2L were 47% vs 28% partial responses, 21% vs 33% stable diseases and 32% vs 39% PD, respectively. Median PFS for 1LT ($mPFS_1$), $mPFS_2$, mOS_2 and total median OS (mOS_{tot}) are shown in the Table.

Table: 1479P **Clinical characteristics and survival outcomes**

Variable	N	mPFS2 (mo)	mOS2 (mo)	mPFS1 (mo)	mOStot (mo)
All patients	40	5.3	9.8	7.5	19.9
Germline BRCA pathogenic variant 1 2	8 32	3.0 6.6	6.0 11.3	5.3 7.9	12.7 20.9
Gender male female	17 23	6.2 4.3	10.4 8.4	8.5 6.2	17.4 20.1
Age (years) $\leq$ 65 > 65	29 11	6.5 3.1	12.5 6.8	8.5 5.9	21.1 12.8
I line chemotherapy Nab-paclitaxel + Gemcitabine (m) FOLFIRINOX/PAXG/PEXG GEMOX/ FOLFOX Gemcitabine	18 14 6 2	8.1 5.3 2.6 2.4	11.8 11.4 2.8 3.6	6.0 11.6 5.3 3.9	19.9 26.8 10.8 8.1
II line chemotherapy Platinum NO Platinum Gemcitabine or Capecitabine	19 18 3	8.7 5.3 2.4	12.0 7.4 4.9	5.9 9.5 3.5	21.1 18.7 9.7
Previous PFS1 (mo) $\leq$ 6 > 6	16 24	6.8 5.3	10.6 8.8	- -	14.7 21.5

mo: months

Conclusions: Keeping in mind the small sample size of our series, gBRCA1pv and > 65 years pts yielded limited benefit from 2LT. Platinum-based 2LT obtained longer PFS_2 and OS_2 as opposed to platinum-free 2LT. Pts with $PFS_1 \leq 6$ months had longer PFS_2 and OS_2, but shorter OS_{tot} if compared to pts with $PFS_1 > 6$ months. Overall, 2L data confirm that platinum is the backbone of treatment for gBRCA1-2pv stage IV PDAC pts, but first-line use should be preferred.

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1480P Real-world progression outcomes among patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with liposomal irinotecan-based regimens in the United States

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Background: The NAPOLI-1 study, a randomized phase III study in pts with mPDAC previously treated with gemcitabine-based therapy, demonstrated an improvement in progression-free survival (PFS) with liposomal irinotecan + 5-fluorouracil/ leucovorin (5-FU/LV) vs. 5-FU/LV. Pts treated with liposomal irinotecan + 5-FU/LV in NAPOLI-1 had a median age of 63 years at treatment (tx) initiation, 97% had performance scores (PS) equivalent to ECOG 0-1, and 34% had at least 2 prior lines of therapy. This study examines the characteristics and real-world (rw) PFS of pts with mPDAC treated with liposomal irinotecan regimens.

Journal of Clinical Oncology
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Trends in use of one, two, and three-line NCCNcategory 1 regimens among Medicare fee-for-service (FFS) patients receiving treatment for metastatic pancreatic cancer.

Gabriela Dieguez, Samantha Tomicki, David DeStephano, Paul Cockrum

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Milliman, Inc., New York, NY; Ipsen, Cambridge, MA

Abstract Disclosures

Abstract

COMPANION ARTICLES

No companion articles

ARTICLE CITATION

DOI: 10.1200/JCO.2020.39.28_suppl.297
Journal of Clinical Oncology 39, no. 28_suppl (October 01, 2021) 297-297.

Published online September 21, 2021.

Background: There is limited research evaluating the share of patients (pts) with metastatic pancreatic cancer (m-PANC) treated according to NCCN guidelines. **Methods:** We identified pts with m-PANC using ICD-10 diagnosis codes in the 2016-2019 Medicare Parts A/B/D 100% Research Identifiable Files. Study pts had 2+ claims with a pancreatic cancer diagnosis and Medicare FFS coverage for 6 months pre- and 3 months post-metastatic disease diagnosis. A line of therapy (LOT) was assigned based on the order and number of therapies used. Pts with one, two, or three LOTs were defined as treated according to NCCN Category 1 guidelines if, in each LOT, pts used one of the following regimens: FOLFIRINOX (FFX), gemcitabine/nab-paclitaxel (gem/nab), gemcitabine + erlotinib, gemcitabine monotherapy, or 5-FU + leucovorin + liposomal irinotecan. Multi-drug LOTs were excluded from the analysis. **Results:** We identified 31,782 pts with m-PANC. 21,304 received one LOT, 7,352 received two LOTs, and 3,126 received three LOTs between 2016 and 2019. Among pts who received one or two LOTs, a higher portion were treated according to NCCN Category 1 guidelines in 2019 (72% and 43%, respectively) than in 2016 (64% and 33%, respectively). Among pts who received three LOTs, a higher portion were treated according to NCCN Category 1 guidelines in 2019 (17%) than in 2017 (12%); too few pts were treated in 2016 to make a comparison. From 2016 to 2019, FFX had the largest increase in share of pts receiving only one NCCN Category 1 LOT (11% to 27%) and gem-mono had the largest decrease (30% to 17%). Among pts receiving two NCCN Category 1 LOTs, gem/nab to liposomal irinotecan sequences had the largest increase in share of pts (18% to 32%) and gem/nab to FFX had the largest decrease (17% to 10%). Among pts receiving three NCCN Category 1 LOTs,

patient share for FFX to gem/nab to Liposomal irinotecan was 35% in 2019, while gem/nab to FFX to Liposomal was 8%; pt counts in earlier years were too small to calculate patient share. **Conclusions:** The use of NCCN Category 1 therapies increased consistently from 2016 to 2019 among pts that received one, two, and three lines of therapy. FFX drove increases in NCCN Category 1 utilization among patients receiving one line of therapy, and gem/nab to liposomal irinotecan sequences were the primary drivers of the increase among patients receiving two lines of therapy. FFX to gem/nab to liposomal irinotecan was the primary driver of increase among patients receiving three lines of therapy.

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PANCREATIC CANCER

Comparison of first-line (1L) treatment (tx) patterns and overall survival by age at diagnosis among patients with metastatic

pancreatic ductal adenocarcinoma (mPDAC).

Rawad Elias, Paul Cockrum, Andy Surinach, Shu Wang, Bong Chul Chu

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Hartford Healthcare Cancer Institute, Hartford, CT; Ipsen, Cambridge, MA; Genesis Research, Hoboken, NJ

Abstract Disclosures

Abstract

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Background: Pancreatic cancer is mostly diagnosed in patients (pts) aged ≥ 65 years and the mortality rate is the highest among older adults. As the population ages, it is expected that there will be a significant rise in the number of older pts with mPDAC but guidance regarding their management is limited as these pts are under-represented in clinical trials. The oncological care of older adults in daily practice is challenged by various age-related conditions. Therefore, a better understanding of the real-world population will help in the development of more effective tx strategies. This study describes the proportion of pts with mPDAC who were treated, the types of regimens received, and the associated survival outcomes by age at diagnosis. **Methods:** Data were extracted for pts diagnosed with

COMPANION ARTICLES

No companion articles

ARTICLE CITATION

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Published online January 22, 2021.

WE RECOMMEND

A randomized phase II study of gemcitabine/cisplatin, gemcitabine fixed dose rate infusion, gemcitabine/docetaxel, or gemcitabine/irinotecan in patients with metastatic pancreatic cancer (CALGB 89904)
M. H. Kulke et al., J Clin Oncol, 2004

Adjuvant nab-paclitaxel plus gemcitabine versus gemcitabine in resected pancreatic ductal adenocarcinoma: A Chinese single institution experience.
Zhuzeng Yin et al., JCO Global Oncology, 2019

A phase II trial of carboplatin and gemcitabine with exisulind (IND # 65,056) in patients with advanced non-small cell lung cancer: Eastern Cooperative Oncology Group Trial 1501

mPDAC between Jan 2015 and Mar 2020 from the Flatiron Health database. Pts were stratified into three age groups at diagnosis: <70y, 70-79y, and ≥ 80y. The proportion of pts was evaluated who received 1L tx and the types of regimens received in the metastatic setting. ECOG performance scores (PS) at tx initiation were described. Overall survival (OS) from the start of 1L was estimated using Kaplan-Meier methods. **Results:** Overall, of the 8,382 pts identified, 71.3% (n=5,973) received tx. Among pts who received tx, 55.5% (n=3,313) were aged <70y at diagnosis, 33.0% (n=1,972) were 70-79y, and 11.5% (n=688) were 80y+. Among those with data available, ECOG PS ≥2 was observed in 15.9% (n=381) of pts <70y, 21.0% (n=309) of pts 70-79y, and 29.9% (n=147) of pts 80y+($p < 0.001$). The proportion of pts who received tx decreased with increasing age at diagnosis: 74.9%, 70.9%, and 58.5% for pts aged <70y, 70-79y, and 80y+, respectively. Gemcitabine monotherapy (gem-mono) and gemcitabine + nab-paclitaxel (GNP) accounted for > 70% of regimens prescribed to pts aged 80y+. The median OS (mOS) for patients treated with GNP, gem-mono, FOLFIRINOX, and liposomal irinotecan-based regimens are presented in the table. **Conclusions:** This study of treatment patterns among pts with mPDAC found that older pts were more likely to have a decreased performance status and are less likely to receive treatment. However, older adults who received systemic therapy had comparable survival outcomes to younger pts treated with a similar regimen. The results of this large descriptive analysis suggest that the treatment strategy of mPDAC should not be based on age but rather on an overall assessment of the

performance/functional status and geriatric profile of older pts.

	<70y		70-79y		≥80y		p-value
	mOS	95% CI	mOS	95% CI	mOS	95% CI	
Overall 1L	7.9	7.6 - 8.3	6.8	6.3 - 7.2	6.2	5.5 - 6.8	<0.001
GNP	6.9	6.4 - 7.5	6.5	5.8 - 7.1	6.8	5.9 - 8.7	0.25
FOLFIRINOX	9.8	9.0 - 10.4	9.6	8.1 - 11.2	6.6	2.3 - 13.6	0.064
Gem-mono	3.0	2.2 - 4.1	4.0	3.1 - 5.2	4.4	3.3 - 5.7	0.72
Liposomal irinotecan-based	7.0	4.7 - 12.8	6.9	5.3 - 8.6	6.8	4.5 - NR	0.75

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advanced non-small cell lung cancer: a real-world retrospective observational cohort study from the I-O optimise initiative
Michael Snee et al., BMJ Open, 2021

The Clinical Management of Pancreatic Cancer
R. Brigg Turner et al., US Pharmacist, 2014

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former going on to receive auto-SCT. ***Conclusions:*** Despite the introduction of new therapies, unmet need remains for R/R cHL patients in the UK. Significant heterogeneity was observed among the populations of the included trials, particularly with regards to prior treatment. These between study differences pose challenges for conducting comparisons between interventions based on published results.

PCN13
QUALITY-OF-LIFE (QOL) RESULTS FROM THE PHASE 3 RAINBOW-ASIA STUDY OF RAMUCIRUMAB PLUS PACLITAXEL (RAM/PTX) VERSUS PLACEBO PLUS PACLITAXEL (PBO/PTX) IN PATIENTS WITH ADVANCED GASTRIC OR GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA (AGC)

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Objectives: In RAINBOW-Asia study (NCT02898077), a bridging study of RAINBOW, RAM/PTX compared with PBO/PTX demonstrated consistent efficacy benefit [PFS: 4.14 vs. 3.15 months, Hazard ratio (HR)=0.765, p=0.0184; OS: 8.71 vs. 7.92 months, HR=0.963] and safety profile with RAINBOW study in a predominantly Chinese population with AGC as 2nd-line therapy. Here we will present results of QoL of the study. ***Methods:*** Patients with AGC who previously received fluoropyrimidine- and platinum-based therapy were randomized at 2:1 ratio to receive RAM/PTX or PBO/PTX. Patients completed the EORTC QLQ-C30 (v3) at baseline, first day of each 4-week cycle and at discontinuation. Scores were classified as improved or deteriorated if changed by ≥10 points (on 100-point scale) relative to baseline, otherwise classified as stable. Time to deterioration in QoL parameters was defined as duration from randomization to first deterioration. HRs and 95% confidence interval (CI) were estimated using stratified Cox proportional hazard model. ***Results:*** Of 440 patients randomized, 272/294 (92.5%) of RAM/PTX and 133/146 (91.1%) of PBO/PTX patients provided both baseline and post-baseline data. Percentage of compliance was high (>95% in most cycles) and similar between arms. For all QoL parameters, the proportion of patients reporting improved or stable scores was generally similar between arms at all on-therapy assessment times. For time to deterioration, HRs for 11 of the 15 QoL scales had 95% CI that included 1, indicating no significant difference in those scales between arms. HRs for 4 symptom scales including dyspnea, insomnia, appetite loss, and diarrhea did not favor RAM/PTX arm, which was consistent with slightly higher incidence of all-grade (primarily low-grade) treatment-emergent adverse events in this arm. ***Conclusions:*** Similar proportion of patients reported improved or stable QoL scores between arms and no evidence of detriment to QoL in majority of scales by treatment with RAM/PTX as 2nd-line therapy in this population.

PCN15
INCREASING DISEASE COMPLEXITY POSES CHALLENGES FOR INDIRECT TREATMENT COMPARISONS: AN EXAMPLE IN RELAPSED AND REFRACTORY MULTIPLE MYELOMA (RRMM)

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Objectives: Quality health economics and outcomes research relies on direct evidence gathered from randomized controlled trials. In the absence of head-to-head clinical trials, indirect treatment comparisons (ITC) are used to assess the comparative effectiveness of treatments. The validity of ITCs relies on the assumption of transitivity which assumes patient populations are interchangeable between studies. To ensure the transitivity assumption is satisfied, studies included in the ITC network should have similar trial designs and patient baseline characteristics. This work aims to summarize the considerations and consequences of increasing disease complexity on ITC in RRMM. ***Methods:*** Phase 2 and 3 studies in the RRMM patient population were identified via a comprehensive systematic literature review of the Medline, Embase, and Cochrane databases from 2010 to Nov 2020. A transitivity assessment was conducted to identify study designs and population characteristics that may impact the validity of indirect treatment comparisons. ***Results:*** A total of 7,802 records were identified, and 47 studies were deemed appropriate for inclusion in the ITC. While trial designs were similar between studies, significant variation was observed in number and types of previous lines of therapy (LOT) and the proportion of relapsed vs. refractory patients in each trial. Inclusion criteria ranged 1 to 4+ prior LOT with median prior LOT ranging from 1 to 5, and up to 11 prior LOT. The proportion of patients with refractory disease ranged from 4% to 100%. Additionally, the proportion of patients with prior proteasome inhibitor or immunomodulatory agents varied significantly. Effectiveness data stratified by LOT and refractoriness were inconsistently reported. ***Conclusions:*** RRMM is a heterogenous disease. Prior LOT, type of prior therapy, and refractory status are characteristics that have been shown to significantly impact clinical outcomes. Therefore, robust ITC require stratified analyses (e.g., by line of therapy), population matching techniques, or covariate adjustment to account for differences in patient populations.

PCN17
REAL-WORLD IMPACT OF PRIOR SURGERY ON OUTCOMES OF PATIENTS WITH METASTATIC DUCTAL ADENOCARCINOMA (MPDAC) TREATED WITH LIPOSOMAL IRINOTECAN-BASED REGIMENS

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Objectives: This study seeks to describe demographic and clinical characteristics and treatment outcomes based on prior surgery in a real-world setting among patients with mPDAC treated with liposomal irinotecan-based regimens. ***Methods:*** This retrospective study utilized the Flatiron Health database. Data were analyzed for adult patients with mPDAC treated with liposomal irinotecan-based regimens between January 2015 and February 2020. Patients were stratified based on surgery prior to initiating a liposomal irinotecan-based regimen. Median overall survival (mOS) from treatment initiation and metastatic diagnosis was derived using Kaplan-Meier analyses. ***Results:*** 608 patients (median age 68 years (y), IQR: 61-74) with mPDAC and treated with a liposomal irinotecan-based regimen were included. 154 patients (25.3%) underwent prior surgery and of these patients, 118 (76.6%) underwent the Whipple procedure. Among patients with prior surgery (median age 70y (IQR: 62-74)), 61.0% had an ECOG score of 0-1, 32.5% had two or more lines of prior treatment. Among patients without surgery (median age 68y (IQR: 61-74)), 59.2% had an ECOG score of 0-1, 39.4% had two or more lines of prior treatment. mOS from liposomal irinotecan-based treatment for patients with prior surgery was 5.2 months (mos) (95% CI: 4.4-6.8) and 4.4 months (95% CI: 4.0–5.3) among patients with no prior surgery. mOS from metastatic diagnosis for patients with prior surgery was 16.1 months (95% CI: 13.1-19.0) and 14.4 months (95% CI: 13.3–15.7) among patients with no prior surgery ($p = 0.3$). Overall, mOS for patients treated with liposomal irinotecan-based regimens in first-, second-, and third line plus was 6.9 months (5.6 – 8.4), 5.0 months (4.2–6.2), and 3.8 months (3.3–4.4), respectively ($p < 0.0001$). ***Conclusions:*** Our results suggest patients with prior surgery had similar outcomes compared to those without prior surgery. Further studies are needed to understand the impact of liposomal irinotecan-based treatments among patients with previously resected pancreatic cancer.

PCN18
CETUXIMAB VERSUS BEVACIZUMAB IN METASTATIC COLORECTAL CANCER: A COMPARATIVE EFFECTIVENESS AND PATIENT-REPORTED OUTCOMES MULTICOHORT STUDY

Marques RP,[1] Heudtlass P,[2] Godinho AR,[2] Pais HL,[1] Quintela A,[1] Lopes da Cruz JP,[1] Martins AP[3]

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Objectives: Uncertainty exists regarding comparative effectiveness of cetuximab versus bevacizumab in metastatic colorectal cancer (mCRC), due to conflicting efficacy evidence of previous randomised clinical trials and the absence of Quality of Life (HRQoL) studies. We conducted a mainly retrospective head-to-head multi-cohort study comparing clinical outcomes from both antibodies, in which was nested a smaller prospective cohort study for measuring patient-reported outcomes (PROs). ***Methods:*** Retrospective cohorts were defined by treatment line, and subgroups by (K)RAS status and tumour sidedness. Among other effectiveness outcomes, we compared response rates, progression-free (PFS) and overall survival (OS). PROs were measured prospectively through EORTC disease-specific instruments. Methods and reporting followed STROBE guidelines and SISAQOL / SPIRIT-PRO recommendations. ***Results:*** Between 2010 and 2018, 311 patients were included in overall analysis. 44 were further allocated to PROs nested cohorts. Except for (K)RAS mutation status, baseline characteristics were balanced across groups. In full analyses, PFS (first-line: HR=0.85; P=0.26; second-line: HR=1.16; P=0.51) and OS (first-line: HR=0.83; P=0.26; second-line: HR=0.88; P=0.58) were similar between treatment arms. In subgroup analyses (first-line), we found a survival difference favouring bevacizumab in right-sided tumours (PFS: HR=0.52; P=0.025; OS: HR=0.60; P=0.11), but not in left-sided or (K)RAS wild-type tumours. Response rates were higher for bevacizumab in patients bearing right-sided primaries and similar across other comparisons. During initial 12 weeks of treatment, a higher proportion of patients in cetuximab arm experienced clinically meaningful (≥10%) deterioration of HRQoL: 53.8% *vs* 18.2% at 6 weeks and 66.7% *vs* 12.5% at 12 weeks. We also observed increased scoring on symptom scales in cetuximab cohort. ***Conclusions:*** This study provides evidence suggesting bevacizumab and cetuximab-containing regimens result in similar clinical effectiveness outcomes in mCRC, except for right-sided tumours, where bevacizumab performed better. Cetuximab led to a progressive negative impact on HRQoL, when compared to baseline and bevacizumab. These findings should be further explored through randomised studies.

POSTER PRESENTATIONS - PROFFERED ABSTRACTS | JULY 01 2021

Abstract 765: Real-world serum CA19-9 level monitoring patterns and its association with clinical outcomes among patients with metastatic pancreatic ductal adenocarcinoma (mPDAC)

Ben George; Matthew Kent; Andy Surinach; Neil Lamarre; Paul Cockrum; Aleksander Chudnovsky

+ Author & Article Information

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Abstract

Background: Pancreatic cancer is expected to be the third deadliest cancer in the US in 2020. Evaluation of treatment response in patients (pts) with mPDAC necessitates scheduled clinical and radiographic assessments along with monitoring serum CA 19-9 levels. Currently available single-institution data examining the importance of CA 19-9 monitoring cannot be generalized to real-world settings. We investigated the impact of serum CA19-9 monitoring and its association with clinical outcomes in pts with mPDAC in a population-based setting.

Methods: Data were extracted from the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database for pts diagnosed with mPDAC between January 1, 2014 and June 30, 2020. Serum CA19-9 levels at baseline – defined as the values obtained ≤ 60 days 1L initiation and during first-line (1L) treatment were extracted. CA 19-9 levels > 40 IU/mL were considered elevated. Data regarding patient exposure to second (2L) and third-line (3L) systemic therapies were collected. Survival analysis was performed using Kaplan-Meier methods. Categorical measures were compared with the chi-square test and survival outcomes with the log-rank test.

Results: Among the 6,118 pts identified, median age at treatment initiation was 68 years (IQR: 61 – 75), 55% were male, 67% were white, and 73% had a baseline serum CA 19-9 level available. Among 4,486 pts with baseline CA 19-9 levels available, 701 (15%) had a normal (< 40 U/mL) level. Among 3,867 pts with elevated CA 19-9 at baseline, 534 (14%) had a single 1L assay and 2,448 (63%) had > 1 assay during 1L treatment. The proportions of pts who received 2L/3L treatment were 25%/7.6% among pts with no CA 19-9 assays performed at any time, 14%/3.7% among pts

with only baseline CA 19-9 assays, 31%/9.7% among pts with a single CA 19-9 assay during 1L treatment (with or without a baseline assay), and 50%/17% if they had more than one CA 19-9 assay performed during the course of their 1L treatment ($p < 0.001$). Median OS (mOS) for pts who had no baseline serum CA 19-9 measurement, a normal baseline CA 19-9 level or an elevated baseline CA 19-9 level were 6.3 months, 8.8 months and 7.2 months, respectively ($p < 0.001$). The mOS of pts with no baseline CA 19-9 assay, only baseline assays, a single assay during 1L and > 1 assay during 1L was 3.8, 1.9, 4.2, and 11 months, respectively ($p < 0.001$).

Conclusions: In one of the largest, contemporary, real-world studies of patients with mPDAC to date, elevated CA 19-9 level at diagnosis demonstrated a prognostic impact. Routine serial monitoring of CA 19-9 levels during 1L treatment may be warranted, in addition to clinical and radiographic assessment, and may translate into better patient outcomes. Further validation studies are needed to understand the generalizability of these results.

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GASTROINTESTINAL CANCER—GASTROESOPHAGEAL, PANCREATIC, AND HEPATOBILIARY

The association between real-world CA19-9 level monitoring patterns and with clinical outcomes among patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) in the second- and third-line of therapy.

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Abstract Disclosures

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Abstract

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Background: Pancreatic cancer has an aggressive disease course, mandating close clinical monitoring while on treatment. Evaluation of treatment response in patients with mPDAC necessitates scheduled clinical and radiographic assessments along with monitoring serum CA 19-9 levels. We investigated the impact of serum CA 19-9 monitoring and its association with clinical outcomes in patients with mPDAC who received second- (2L) and third line (3L) in a population-based setting. **Methods:** Data were extracted from the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database for patients diagnosed with mPDAC and subsequently treated in the 2L or 3L setting between January 1, 2014 and June 30, 2020. Serum CA 19-9 levels at baseline were extracted – defined as the values obtained ≤ 60 days of treatment initiation and during treatment. CA 19-9 levels > 40 IU/mL were considered elevated. Survival analysis was performed using Kaplan-Meier methods. Categorical measures were compared with a chi-square test and survival outcomes with a log-rank test. **Results:** There were 2,402 patients who received 2L and 790 patients who received 3L treatment included in the study. Among the 2L cohort, median age at treatment initiation was 67 years (IQR: 60 – 73), 54% were male, 57% had an ECOG score of 0-1, and 82% had a baseline serum CA 19-9 level available. Among the 3L cohort, median age at treatment initiation was 67 years (IQR: 60 – 73), 53% were male, 58% had an ECOG score of 0-1, and 84% had a baseline CA 19-9 level available. Most patients in the 2L and 3L cohorts had an elevated CA 19-9 at baseline, 85.2% and 82.0%, respectively. Among the 2L and 3L cohorts, 38.5% and 31.9% had CA

19-9 levels decrease/remain stable during treatment and 27.6% and 31.4% had levels increase during treatment, respectively. Patients with normal baseline CA 19-9 experienced longer survival than patients with elevated levels [2L: 7.2 months (95% CI: 6.1 – 9.2) vs 5.2 months (4.9 – 5.6), p < 0.001; 3L: 6.1 months (5.4 – 9.1) vs 3.9 months (3.4 – 4.3), p < 0.001]. Similarly, patients with decreasing/stable CA 19-9 during treatment had longer survival than patients who had their CA 19-9 levels increase [2L: 8.2 months (7.7 – 8.5) vs 4.3 months (4.1 – 4.7), p < 0.001; 3L: 7.5 months (6.6 – 9.2) vs 3.7 months (3.4 – 4.3), p < 0.001]. **Conclusions:** In this large, contemporary, real-world study of patients with mPDAC, CA 19-9 levels at treatment initiation had a prognostic value across later lines of therapy. Routine serial monitoring of CA 19-9 levels during treatment, in addition to clinical and radiographic assessment, may help with timely additional diagnostic testing and treatment intervention. Further validation studies are needed to understand the generalizability of these results.

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Shohei Fukuda et al., jitc, 2021

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PCN107
COST-EFFECTIVENESS ANALYSIS OF LORLATINIB IN PATIENTS PREVIOUSLY TREATED WITH ANAPLASTIC LYMPHOMA KINASE INHIBITORS FOR NON-SMALL CELL LUNG CANCER IN GREECE

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Objectives: Lorlatinib is a potent 3rd generation anaplastic lymphoma kinase (ALK) inhibitor approved for the treatment of patients with ALK positive advanced non-small cell lung cancer (NSCLC) previously treated with one or more ALK tyrosine kinase inhibitors (TKIs). The present study assessed the cost-effectiveness of Lorlatinib versus pemetrexed with platinum combination of carboplatin or cisplatin (platinum based ChT) in Greece. ***Methods:*** A partitioned survival model with three health states, referring to pre-progression, progressed disease and death, was locally adapted from a Greek payer perspective over a lifetime horizon. Clinical and safety data as well as utility values applied in the model were extracted from the literature. A matching-adjusted indirect comparison of Lorlatinib and platinum based ChT was performed. Resource consumption data were obtained from a medical expert and only direct medical costs reflecting the year 2020 were included in the analysis (€). Primary outcomes were patients' life years (LYs), quality-adjusted life years (QALYs), total costs and incremental cost-effectiveness ratios (ICERs) per QALY and LY gained. All future outcomes were discounted at 3.5% per annum. A probabilistic sensitivity analysis (PSA) was conducted to account for model uncertainty. ***Results:*** The analysis showed that, over a lifetime horizon, total cost of Lorlatinib and platinum based ChT was estimated to be €81,754 and €12,343, respectively. Lorlatinib was more effective than platinum based ChT with 2.4 and 1.5 more LYs and QALYs gained, respectively. The generated ICERs of Lorlatinib compared to platinum based ChT were €28,613 per LY gained and €46,102 per QALY gained. PSA confirmed the deterministic results. ***Conclusions:*** The present analysis suggests that Lorlatinib may be considered a cost-effective option over platinum based ChT in Greece, for the treatment of patients with ALK positive advanced NSCLC who have progressed after one or more ALK TKIs, while covering a significant unmet medical need.

PCN108
THE COST-EFFECTIVENESS OF LIPOSOMAL IRINOTECAN AND 5-FLUOROURACIL (5-FU)/ LEUCOVORIN (LV) FOR THE TREATMENT OF PATIENTS WITH METASTATIC ADENOCARCINOMA OF PANCREAS WHO HAVE PROGRESSED FOLLOWING THE USE OF GEMCITABINE-RELATED THERAPIES IN GREECE

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Objectives: To evaluate the cost-effectiveness of the liposomal Irinotecan (nal-IRI) plus 5-Fluorouracil (5-FU)/ Leucovorin (LV) compare to 5-FU/LV alone for the treatment of patients with metastatic pancreatic cancer (mPDAC) who have previously received gemcitabine-based regimens in Greece. ***Methods:*** A partitioned survival model was locally adapted from a public payer perspective over a 10-year time horizon. Utility values, efficacy and safety data applied in the model, were extracted from the literature. Resource consumption data were obtained from local experts using a questionnaire, developed for the purposes of the study, and were combined with unit costs (in €2019) obtained from official sources. Primary outcomes were patients' life years (LYs), quality-adjusted life years (QALYs), total-costs, and incremental cost-effectiveness ratio (ICER) per QALY and LY gained. Both costs and outcomes were discounted at 3.5% per annum. A one-way sensitivity analysis (OWSA) was undertaken to test the robustness of the results and a probabilistic sensitivity analysis (PSA) was conducted to account for uncertainty in the model. ***Results:*** The analysis revealed that, the total cost per patient was estimated to be €21,468 and €4,758 for nal-IRI+5-FU/LV and 5-FU/LV respectively. In terms of health outcomes, nal-IRI+5-FU/LV was associated with 0.58 QALYs and 0.85 LYs, while patients who received 5-FU/LV alone accrued 0.43 QALYs and 0.64 LYs. The incremental analysis showed that nal-IRI+5-FU/LV resulted in an ICER of €114,153 per QALY gained and €79,799 per LY gained versus 5-FU/LV alone. OWSA results indicated that the most influential parameter on the model was utility values assigned to the pre-progression state. PSA confirmed the deterministic results. ***Conclusions:*** The present economic evaluation suggests that nal-IRI+5-FU/LV, a therapy that provides survival benefits to patients with mPDAC after disease progression following gemcitabine-based treatment, was estimated to be a good value for money treatment option for the Greek patients.

PCN110
COST-UTILITY ANALYSIS OF ADJUVANT TRASTUZUMAB EMTANSINE VERSUS TRASTUZUMAB IN PATIENTS WITH HER2+ EARLY BREAST CANCER WITH RESIDUAL INVASIVE DISEASE AFTER NEOADJUVANT THERAPY IN SPAIN

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Objectives: Trastuzumab emtansine (T-DM1) in the adjuvant treatment of patients with HER2-positive early breast cancer (HER2+ eBC) with residual invasive disease (RD) after neoadjuvant taxane-based and HER2-targeted therapy demonstrated a clinically and statistically significant improvement in invasive disease-free survival (iDFS) compared to trastuzumab in the KATHERINE trial. The aim of this study is to determine the efficiency of T-DM1 versus trastuzumab as adjuvant treatment of HER2+ eBC with RD in Spain through a cost-utility analysis. ***Methods:*** A six-state Markov model (iDFS, local recurrence, iDFS after local recurrence, metastatic-relapse [1L], metastatic-relapse [2L], and death) was adapted over a lifetime horizon (specifically 38 years), considering the Spanish National Healthcare System (SNHS) perspective. KATHERINE iDFS data were fitted with a log-normal distribution to extrapolate iDFS beyond the trial follow-up. Transition probabilities and costs (list prices of medicines considered and, for the adjuvant treatment, trastuzumab biosimilar price assumed; €2019) were obtained from literature and national databases. Utilities were based mainly on the 5Q-5D outcomes from KATHERINE trial. Model inputs were validated by an expert panel. A 3% annual discount rate was applied to both effects and costs. Deterministic and probabilistic sensitivity analyses (SA) were performed to explore uncertainties. ***Results:*** The incremental cost-utility ratio (ICUR) for T-DM1 versus trastuzumab was €6,748 per quality-adjusted life-year (QALY). Compared to trastuzumab, T-DM1 provided 1.702 additional QALYs at an additional cost of €11,485. SA confirmed the robustness of the model. In the probabilistic analysis, the probability of T-DM1 being cost-effective when considering a threshold of €30,000/QALY was >95%. ***Conclusions:*** T-DM1 is a more efficient therapeutic alternative than trastuzumab as adjuvant treatment of HER2+ eBC with residual invasive disease for the SNHS.

PCN111
COST-EFFECTIVENESS ANALYSIS OF IXAZOMIB PLUS LENALIDOMIDE-DEXAMETHASONE VERSUS DARATUMUMAB PLUS LENALIDOMIDE-DEXAMETHASONE IN MULTIPLE MYELOMA PATIENTS RECEIVED MORE THAN ONE PRIOR TREATMENT IN CHINA

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Objectives: With the approval of Daratumumab by the China National Medical Product Administration in 2019, this study aims to compare the cost-effectiveness of Ixazomib plus lenalidomide-dexamethasone (IRd) with Daratumumab plus lenalidomide-dexamethasone (DRd) among previously treated multiple myeloma patients in China. ***Methods:*** A partition survival model with three health states (progression-free survival, post-progression and death) was constructed from a societal perspective in China. The relative effectiveness of comparators was derived from a network meta-analysis synthesizing results of TOURMALINE-MM1 trial and POLLUX trial due to the lack of head-to-head trial data. Both direct (drug and administration, lab testing, health resource utilization, adverse event management and post-progression treatment) and indirect costs were considered in the analysis. Data inputs were obtained from published literature and clinical experts' interviews. Cost and effectiveness were discounted at 5% and a half-cycle correction was applied. Primary model outcomes included total costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratio (ICERs). One way and probabilistic sensitivity analyses (PSA) were performed to assess the robustness of the model estimates. ***Results:*** In the base case of a lifetime horizon, our estimation showed that to achieve a 0.561 QALY gain from IRd (3.429 QALYs) to DRd (3.990 QALYs), an additional CNY 521,318 is required, which can be translated into an ICER of CNY 930,047/QALY for DRd versus IRd. Model results were sensitive to the hazard ratio of IRd and DRd compared with lenalidomide-dexamethasone in overall survival from the NMA results. PSA further demonstrated that DRd did not show a significant advantage over IRd, assuming a willingness to pay threshold of CNY 212,676 (triple GDP per capita in China in 2019). ***Conclusions:*** Compared to IRd, DRd is not considered as a cost-effective treatment under current prices from a societal perspective among previously treated multiple myeloma patients in China.

PCN112
ESTIMATING RESOURCES UTILIZATION AND HEALTH CARE COSTS RELATED TO COLORECTAL CANCER PATIENTS IN SAUDI ARABIA

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Objectives: This study aimed to estimate the resources utilization and costs of colorectal cancer in Saudi Arabia. ***Methods:*** A retrospective single-centered cohort study of all CRC patient from January 2016 to December 2019, all patient's information was extracted from the Electronic Health Record of King Khalid University Hospital (KKUH). The study included all medical management cost of CRC in patients

PCN24
EVALUATING THE SURROGACY OF OBJECTIVE RESPONSE RATE FOR OVERALL SURVIVAL IN ONCOLOGY CLINICAL TRIALS: A METHODOLOGIC REVIEW

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Objectives: Overall survival (OS) is considered the gold-standard primary endpoint in oncology clinical trials. Protective OS treatment effects demonstrate clear patient benefits; however, large sample sizes and extensive follow-up are required, potentially delaying access to novel therapeutics. The use of intermediate endpoints such as objective response rate (ORR) as surrogates for OS offers a solution to these challenges but requires validation. A variety of techniques are available to conduct surrogate endpoint validation. We sought to compare the approaches used to assess the surrogacy of ORR for OS in oncology clinical trials. ***Methods:*** The PubMed and Cochrane Systematic Reviews databases were queried from 2010 to 2020 to identify studies that assessed ORR as a surrogate for OS. Analytical strategies were reviewed and extracted to compare OS endpoints (median, hazard ratio [HR]), ORR endpoints (percentage, odds ratio [OR], relative risk [RR]), correlation types, regression models, surrogate threshold effects (STE), and controlling for patient crossover. ***Results:*** The review identified 24 meta-analysis studies in 12 solid tumor and hematologic oncology populations. Median OS and OS HR were the primary endpoints in 9/24 (37.5%) and 17/24 (70.8%), respectively. Choice of ORR measure varied among studies; absolute ORR was used in 9/24 (37.5%), ORR OR in 15/24 (62.5%), and ORR RR in 6/24 (25.0%), with several studies employing multiple analyses. Furthermore, these measures were logarithmically transformed in 11/24 (45.8%) studies. Correlations were estimated in 15/24 (62.5%), and associations were modeled using regression techniques in 23/24 (95.8%). Few studies estimated the STE (20.8%) or attempted to control for patient crossover (16.7%). ***Conclusions:*** Methodologies to validate ORR as a surrogate endpoint for OS varied between studies. Further research is required to understand the impact of analytical methodology on the validation of surrogate endpoints, which may inform best practices for future studies.

PCN25
SYSTEMATIC LITERATURE REVIEW OF TREATMENT PATTERNS, LONG-TERM EFFICACY, AND SAFETY OF DASATINIB THERAPY FOR PATIENTS WITH CHRONIC MYELOID LEUKEMIA

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Objectives: The tyrosine kinase inhibitors (TKIs) imatinib, dasatinib, and nilotinib are approved for the treatment of chronic myeloid leukemia (CML). It is important to evaluate differences in efficacy and safety of TKIs to help guide first-line (1L) treatment decisions. The objective of this review was to assess treatment patterns, long-term efficacy, and safety of dasatinib compared with imatinib and nilotinib in CML. ***Methods:*** A systematic literature review (SLR) was conducted by searching Embase®, MEDLINE®, and Cochrane databases (Jan 2010 – Jul 2020). Searches of key congress abstracts (2017–2020) were performed using PRISMA guidelines and the Population, Intervention, Comparator, Outcome (PICO) criteria. Eligible interventional and real-world evidence (RWE) studies describing treatment and switching patterns, efficacy, and safety were selected. ***Results:*** Of 224 records identified, 119 reported switching or discontinuation in ≥1L settings and 128 reported safety and efficacy of 1L dasatinib. Discontinuation rates for dasatinib were lower than imatinib and nilotinib (17/22 studies). Dasatinib elicited a faster, deeper molecular response than imatinib (3/3 studies) but similar response to nilotinib (4/4 studies). Achieving an early molecular response at 3 months (n=6) or major molecular response (MMR) at 12 months (n=7) correlated with increased 5-year overall survival (R^2=0.5946 and 0.8415, respectively). Sustained use of 1L dasatinib led to improved MMR and survival. Hematologic adverse events (AEs) were similar between dasatinib and imatinib in RWE studies (n=4; 15–50% vs 15–40% grade 3 AEs, respectively), but certain hematolgic AEs (e.g. thrombocytopenia) were higher in clinical trials (n=4). Across all studies, cardiovascular and gastrointestinal AEs were higher in patients receiving nilotinib than dasatinib. ***Conclusions:*** This SLR demonstrates that dasatinib remains an effective long-term option for 1L treatment of patients with CML with a lower incidence of non-hematologic AEs compared with imatinib or nilotinib. Moreover, patients were more likely to remain on dasatinib, leading to improved outcomes.

PCN27
REAL-WORLD CHARACTERISTICS AND OUTCOMES OF PATIENTS WITH METASTATIC DUCTAL ADENOCARCINOMA (MPDAC) TREATED WITH LIPOSOMAL IRINOTECAN-BASED REGIMENS BY RACE

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Objectives: Racial disparities persist in outcomes for patients with pancreatic cancer in the United States, with Black or African American patients having higher age-adjusted incidence and mortality than White patients. Similarly, results from the pivotal phase 3 study, NAPOLI-1, and recent literature suggest that participants of East Asian ethnic origin experience better outcomes than other ethnic groups with liposomal irinotecan+5-fluorouracil/leucovorin following gemcitabine. This study seeks to describe clinical characteristics and treatment outcomes based on race. ***Methods:*** This retrospective observational study utilized the Flatiron Health EHR-derived de-identified database from over 280 cancer clinics in the US. Data were analyzed for adult patients with mPDAC treated with liposomal irinotecan-based regimens between January 2015 and February 2020. Patients were stratified based on their self-reported race. Median overall survival (OS) from treatment initiation was derived using Kaplan-Meier analysis. ***Results:*** Of the included 608 patients (median age 68 years (y), IQR: 61–74) with mPDAC and treated with a liposomal irinotecan-based regimen, 448 patients (73.7%) were White, 48 patients (7.9%) were Black or African American, 13 (2.1%) were Asian, and 99 (16.3%) were of other race or the data were missing. White patients had a median age at metastatic diagnosis of 69y (IQR: 61–74), Black patients, 64y (60–71), and Asian patients 65y (63–72). ECOG scores of 0–1 were reported for 61.6% of White patients, 58.3% of Black patients, and 61.5% of Asian patients. Overall, median OS was 4.7 months (95% CI: 4.2–5.4). Median OS was 4.6 months 4.1–5.6) among White patients, 3.8 months (3.1–5.6) among Black patients, and 12 months (3.4–NR) among Asian patients. ***Conclusions:*** This analysis found racial disparities may persist in survival outcomes among patients with mPDAC treated with liposomal irinotecan-based regimens. Further studies are needed to characterize and understand the biological and socio-economic factors contributing to these disparate outcomes.

PCN28
NETWORK META-ANALYSIS (NMA) OF ONCE WEEKLY SELINEXOR-BORTEZOMIB-DEXAMETHASONE (XVD) IN PREVIOUSLY TREATED MULTIPLE MYELOMA (MM)

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Objectives: A Bayesian NMA was developed from a systematic literature review (SLR) to evaluate the efficacy of XVd relative to other therapies in previously treated MM. ***Methods:*** Ovid was systematically searched for phase II–III randomized clinical trials (RCTs) that assessed progression-free survival (PFS), overall survival (OS) and overall response rates (ORR). As treatment line is an important factor in MM, two population subsets were assessed: second-line patients (2L) and third-line or greater patients (3L+). Fixed and random effect models were assessed for each outcome. Base case results compared all regimens against twice weekly bortezomib and dexamethasone (Vd) as the anchored comparator regimen. ***Results:*** 47 RCTs met inclusion. For 2L PFS, OS and ORR, XVd had, on average out of all iterations, the 6th (out of 21), 4th (out of 15), and 5th (out of 20) best result, respectively, versus Vd. This translated to a 24.5%, 68.6%, and 50.1% probability that XVd would be a top-5 ranked regimen. For 3L+ PFS, OS and ORR, XVd had the 12th (out of 24), 11th (out of 22), and 8th (out of 25) best result, respectively, versus Vd. This translated to a 7.6%, 12.8%, and 27.8% probability that XVd would be a top-5 ranked regimen. There was no statistically significant difference between XVd and other top-ranking therapies for PFS, OS, and ORR in either 2L and 3L+. except for daratumumab/bortezomib/dexamethasone [DVd] favorable versus XVd (2L PFS); however, XVd uses once-weekly Vd (versus twice-weekly in DVd). ***Conclusions:*** Results for XVd were more favorable in 2L, having a higher probability of being a top 5 regimen, compared with 3L+ therapies. The addition of XVd to the treatment landscape for previously treated MM provides a novel, oral regimen that may potentially be noninferior to other top 5 regimens in both 2L and 3L+ settings.

PCN31
MATCHING ADJUSTED INDIRECT TREATMENT COMPARISON OF FGFR2+ PATIENTS IN THE FIGHT-202 TRIAL VS. PATIENTS WITH UNSPECIFIED FGFR2 STATUS RECEIVING STANDARD OF CARE TREATMENTS

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Objectives: In the single-arm trial FIGHT-202, patients with advanced *FGFR2* translocation-positive cholangiocarcinoma treated with pemigatinib have shown a sustained response. As this trial has no comparator, unanchored indirect treatment comparisons are required to assess the overall survival (OS) and progression-free survival (PFS) gains seen for patients treated with pemigatinib compared to those treated with standard of care (SoC). ***Methods:*** A systematic literature review identified suitable sources of comparator data. Eight SoC treatment arms, from five different studies, were considered eligible for comparison with FIGHT-202. Endpoints of interest were OS and PFS. Covariates used for matching, based on clinical expert opinion and availability in published studies, were: age, sex, Eastern Cooperative Oncology Group performance status, and albumin levels. FGFR2 translocation status, which retrospective studies have suggested could be associated with positive prognosis in the patient population of interest was not reported in any of the

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PANCREATIC CANCER

Real-world one-year overall survival among patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with liposomal irinotecan in the NAPOLI-1 based regimen.

George P. Kim, Paul Cockrum, Andy Surinach, Laith I. Abushahin

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Abstract Disclosures

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Abstract

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Background: Pancreatic cancer remains one of the most lethal cancers in the United States (US) with a 5-year relative survival of 9%. Among patients who received liposomal irinotecan + 5-fluorouracil (5-FU) and leucovorin in the NAPOLI-1 study, a randomized phase 3 study in patients with mPDAC previously treated with gemcitabine-based therapy, 25% (n = 29) were alive at ≥ 1 year. This study examines the real world one-year survival of patients with mPDAC treated with liposomal irinotecan as a doublet with 5-FU in the NAPOLI-1 based regimen.

Methods: This retrospective observational study utilized the Flatiron Health EHR database from over 280 cancer clinics in the US. Data were analyzed for adult patients with mPDAC treated with liposomal irinotecan-based regimens between November 2015 and July 2020. Patient characteristics and one-year overall survival (OS) based on Kaplan-Meier estimates were assessed. Cycles were defined as unique days with an administration of liposomal irinotecan.

Results: There were 669 patients (median age: 69y, IQR: 62-75) included in the study. ECOG performance status (PS) of 0-1 and 2+ were reported for 78.3% (n = 396) and 21.7% (n = 110) of patients, respectively. ECOG PS was not captured for 24.4% (n = 163) of patients. 16.3% (n = 109) of patients initiated liposomal irinotecan-based in the first line (1L) metastatic setting, 47.5% (n = 318) in second line (2L), and 36.2% (n = 242) in the third line or later (3L+). The median number of cycles received was 4 (IQR: 2 – 8). Among all patients, one-year OS was 17.2% (95% CI: 14.3% - 20.7%). One-year OS was 31.5% (22.1% – 41.3%) for patients treated in 1L, 16.4% (12.2% - 21.1%) for patients treated in 2L, and 12.2% (7.5% - 18.0%) for patients treated in 3L. The median number of cycles for

1L, 2L, and 3L were 5, 4, and 3, respectively. One-year OS increased as patients were able to receive more cycles of liposomal irinotecan. Patients who received at least 2 cycles of liposomal irinotecan (n = 551) had a one-year OS of 20.4% (16.8% - 24.2%). Among patients who received at least 4 cycles (n = 359) and at least 8 cycles (n = 170), the one-year OS estimates were 29.1% (24.0% - 34.3%) and 47.9% (39.7% - 55.7%), respectively. **Conclusions:** In this real-world cohort of patients with mPDAC treated with liposomal irinotecan, as expected, one-year OS increased as patients remained on therapy. Patients in this cohort were older, had more prior lines of therapy, worse ECOG PS, and similar exposure to treatment compared with patients in the registrational phase 3 NAPOLI-1 study. Among patients who received at least 4 cycles of liposomal irinotecan, one-year OS (29%) was similar to both the intent-to-treat (25%) and per protocol treated patient populations in the NAPOLI-1 trial (34%). Further studies are needed to understand the predictors of long-term survival among patients with mPDAC.

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Conclusions: The use of two- and three- line sequences increased consistently from 2016 to 2019. Sequences containing liposomal irinotecan in second and third line are the primary drivers of this increase.

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1479P Exploring second-line therapy outcome in pancreatic ductal adenocarcinoma (PDAC) patients with germlineBRCA1-2 pathogenic variants (gBRCA1-2pv)

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Background: Pancreatic Ductal Adenocarcinoma (PDAC) harboring germlineBRCA1-2 pathogenic variants (gBRCA1-2pv) is emerging as a distinct entity, benefitting from specific treatments (platinum agents, PARP-inhibitors). Information on second-line therapy (2LT) outcome in this setting is lacking.

Methods: Clinical data of stage IV PDAC patients (pts) carrying gBRCA1-2pv receiving a 2LT were retrospectively collected from 23 Italian Centers and descriptively analyzed, focusing on RECIST response and survival outcome. Progression-free and Overall survival2 (PFS2 and OS2) were calculated from 2LT start to 2nd progression or death, respectively.

Results: 49 out of 63 pts treated with first-line therapy (1LT) between December 2008 and July 2020 had Progressive Disease (PD) at time of database lock: 7 pts (4 treated without platinum) did not receive subsequent therapies, while 42 (86%) started a 2LT, whose outcome was assessable in 40 pts (2 had immature follow-up). ECOG Performance Status at diagnosis was ≤ 1 in 38 (95%) pts, 32 (80%) had liver metastases, median age was 62 (39-84) years. RECIST responses of the 19 and 18 pts receiving platinum- and non-platinum-based multidrug 2L were 47% vs 28% partial responses, 21% vs 33% stable diseases and 32% vs 39% PD, respectively. Median PFS for 1LT ($mPFS_1$), mPFS $_2$, mOS_2 and total median OS (mOS_{tot}) are shown in the Table.

Table: 1479P **Clinical characteristics and survival outcomes**

Variable	N	mPFS2 (mo)	mOS2 (mo)	mPFS1 (mo)	mOStot (mo)
All patients	40	5.3	9.8	7.5	19.9
Germline BRCA pathogenic variant 1 2	8 32	3.0 6.6	6.0 11.3	5.3 7.9	12.7 20.9
Gender male female	17 23	6.2 4.3	10.4 8.4	8.5 6.2	17.4 20.1
Age (years) $\leq$ 65 > 65	29 11	6.5 3.1	12.5 6.8	8.5 5.9	21.1 12.8
I line chemotherapy Nab-paclitaxel + Gemcitabine (m) FOLFIRINOX/PAXG/PEXG GEMOX/ FOLFOX Gemcitabine	18 14 6 2	8.1 5.3 2.6 2.4	11.8 11.4 2.8 3.6	6.0 11.6 5.3 3.9	19.9 26.8 10.8 8.1
II line chemotherapy Platinum NO Platinum Gemcitabine or Capecitabine	19 18 3	8.7 5.3 2.4	12.0 7.4 4.9	5.9 9.5 3.5	21.1 18.7 9.7
Previous PFS1 (mo) $\leq$ 6 > 6	16 24	6.8 5.3	10.6 8.8	- -	14.7 21.5

mo: months

Conclusions: Keeping in mind the small sample size of our series, gBRCA1pv and > 65 years pts yielded limited benefit from 2LT. Platinum-based 2LT obtained longer PFS_2 and OS_2 as opposed to platinum-free 2LT. Pts with $PFS_1 \leq 6$ months had longer PFS_2 and OS_2, but shorter OS_{tot} if compared to pts with $PFS_1 > 6$ months. Overall, 2L data confirm that platinum is the backbone of treatment for gBRCA1-2pv stage IV PDAC pts, but first-line use should be preferred.

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1480P Real-world progression outcomes among patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with liposomal irinotecan-based regimens in the United States

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Background: The NAPOLI-1 study, a randomized phase III study in pts with mPDAC previously treated with gemcitabine-based therapy, demonstrated an improvement in progression-free survival (PFS) with liposomal irinotecan + 5-fluorouracil/ leucovorin (5-FU/LV) vs. 5-FU/LV. Pts treated with liposomal irinotecan + 5-FU/LV in NAPOLI-1 had a median age of 63 years at treatment (tx) initiation, 97% had performance scores (PS) equivalent to ECOG 0-1, and 34% had at least 2 prior lines of therapy. This study examines the characteristics and real-world (rw) PFS of pts with mPDAC treated with liposomal irinotecan regimens.

Methods: This retrospective study utilized the Flatiron Health EHR-derived database. Data were analyzed for adult pts with mPDAC treated with liposomal irinotecan-based regimens between January 2016 and October 2020. Pt and clinical characteristics evaluated included age, sex, stage at diagnosis, ECOG PS, and the number of prior lines of therapy at the time of tx initiation. rwPFS was assessed from the start of tx until progression or death. Median rwPFS was derived utilizing Kaplan-Meier methods.

Results: 675 pts with mPDAC treated with a liposomal irinotecan-based regimen were included. Of these, 54% were initially diagnosed with stage IV disease, 52% were male, and 62% initiated liposomal irinotecan in the 1L or 2L setting. Median age at tx initiation was 69 (IQR: 62 — 75) years. 91.5% of pts were treated in the community setting. Among pts with available ECOG PS (n=509), 77.4% had a PS of 0-1 and 22.6% had a PS of 2+. Overall, median rwPFS was 2.8 mos [95%CI: 2.5—3.1]. Median rwPFS among pts treated in 1L (n=101), 2L (n=318), and third line plus (3L+, n = 254) were 3.8 mos [2.9—4.8], 3.2 mos [2.8—3.5], and 2.1 mos [1.9—2.3], respectively.

Conclusions: In this real-world study of pts with mPDAC treated with a liposomal irinotecan-based regimen, median rwPFS was similar to the median PFS of the pivotal phase III trial despite the fact that pts in the real-world were older, had worse performance scores, and more prior lines of therapy than pts included in the clinical trial. Further studies are needed to characterize factors that influence PFS among pts treated with liposomal irinotecan.

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1481P Predictors for 30-day readmission in patients with pancreatic cancer who had DNR code status

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Background: Pancreatic cancer is a lethal malignancy, and most patients present with advanced disease. There is little known about the 30-day readmission rate in patients with Do-not resuscitate (DNR) code status in pancreatic cancer.

Methods: This retrospective study of a nationally representative cohort of hospitalized pancreatic cancer patients. The database was obtained from the Agency for Healthcare Research and Quality's (AHRQ) Healthcare Cost and Utilization Project (HCUP) national readmission (NRD) dataset files between 2016 — 2018. The study aims to look for predictors of mortality and 30-day readmission among patients with pancreatic cancer who had DNR code status. We evaluated readmission in pancreatic cancer with DNR code status in multivariable linear regression models.

Results: There were 240,107 index hospitalizations with pancreatic cancer (PAC) for the years 2016-2018. There were 51,451 (21.4%) PAC patients who had DNR code status during the index hospitalization. Patients with DNR status had a mean age of 68. The PAC patients with DNR status had significantly higher numbers of inpatient mortality (22% (DNR status) vs 3 % (full code) (OR 4.24 (95% CI 3.9-4.6; P <0.001), higher rate of cardiac arrhythmia (26% vs. 19%; p<0.001). The adjusted odd's ratio (Table) to look for significant readmission predictors for DNR status in PAC included chronic heart failure (OR 1.24, p <0.001), renal failure (OR 1.27, p<.001), and liver disease (OR 2.13, p <0.001). Most patients were treated in urban teaching hospitals, and Medicare was the primary payor in 70.4.

Table: 1481P **The adjusted odds ratio of a pancreatic cancer patient has DNR status**

Outcomes	Adjusted OR (95% CI)	p-valve
Heart failure Absent present	reference 1.24 (1.13-1.35)	<0.001
Cardiac arrhythmia Absent Present	- 1.39 (1.31-1.48)	<0.001
Hypertension Absent Present	- 0.78 (0.73-0.83)	<0.001
Renal failure Absent Present	- 1.27 (1.14-1.41)	<0.001
Liver disease Absent Present	- 2.13 (1.98-2.29)	<0.001
Diabetes Absent Present	- 0.97 (0.92-1.02)	0.22
Alcohol abuse Absent Present	- 0.88 (0.77-1.00)	0.06
Obesity Absent Present	- 0.87 (0.78-0.97)	0.01
Service payer Medicare Medicaid Private Self-pay	- 1.28 (1.14-1.43) 1.38 (1.26-1.51) 2.0 (1.80-2.41)	<0.001 <0.001 <0.001

Conclusions: This large nationwide study observed higher inpatient mortality and readmission rates in pancreatic cancer who have DNR code status utilizing hospital resources and healthcare costs. This suggests that patients with advanced pancreas cancer who adopt DNR status be offered early hospice care to avoid inpatient mortality. There is a need to look for data based on racial and ethnic differences.

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1482P Landscape of germline pathogenic variants beyond BRCA in pancreatic cancer patients

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Background: Compelling evidence suggests that up to 15% of PC may be due to germline Pathogenic Variants (PV) in high-risk genes. Because of this, international guidelines recommend multigene germline testing for all PC patients. However, the precise contribution of additional susceptibility genes other than *BRCA* is still to be clarified, as different panel were used among different studies.

Methods: We aimed to evaluate the prevalence of PVs in DNA Damage Repair (DDR) and other candidate susceptibility genes through an oncologist-led Multiple Gene Panel (MGP) testing in a retrospective series of unselected PC patients treated at our cancer center. We investigated the impact of these PVs on outcomes. The germline MGP tested 53 genes, selected according to the recent literature. Only PVs and Likely Pathogenetic Variants (LPVs) were included in the analyses. Student's t-test, chi square and log-rank test were used to test the association with age, stage and Overall Survival (OS), respectively.

Results: A total of 185 patients were included in the analyses. We found either a PV or LPV in 43/185 patients (23.2%), with PVs in 17.3% and LPVs in 7% of the patients. A *BRCA1/2* PV or LPV was found in 8/185 patients (4.3%). The most frequent altered genes other than *BRCA* were *CDKN2A* (3.7%), *CHEK2* and *ATM* (2.7%), *COL7A1* (4.8%). Median age (56 yrs overall, range 14-84) and stage IV frequency at diagnosis did not differ in Wild-Type (WT) and PV+LPV patients. Median OS (mOS) was 11 months. A trend towards better survival was observed among PV+LPV (12.9 mOS) than among WT cases (9.4 mOS), although not statistically significant (p=0.17). Among the 17 patients who survived for longer than 20 months, there were one *COL7A1* LPV, 2 *CDKN2A* and 2 *ATM* PV carriers, one of whom is still alive at 57 months from diagnosis and start of neoadiuvant gemcitabine-abraxane chemotherapy. Few data available about chemotherapy regimens do not allow further analyses.

Conclusions: A high PV and LPV overall frequency was found (23%), with a 4.3% of *BRCA* PV rate, in line with the literature. Interestingly, we found a 3.5 month longer mOS in PV+LPV as compared to WT patients, although not statistically significant. Encouraging good prognosis was observed for some 'outliers' with PVs and LPVs.

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Disclosure: S. Sciallero: Non-Financial Interests, Personal and Institutional, Invited Speaker: Amgen; Non-Financial Interests, Personal and Institutional, Invited Speaker: Servier; Non-Financial Interests, Personal and Institutional, Invited Speaker: Merck; Non-Financial Interests, Personal, Other, Participation at congresses: Novartis; Non-Financial Interests, Personal, Other, Participation at congresses: Ipsen. All other authors have declared no conflicts of interest.

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1483P Cell-free DNA dominant clone allele frequency associates with poor outcomes in advanced pancreatic cancer

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Background: Circulating cell-free tumor DNA (ctDNA) is an emerging tool under investigation in pancreatic cancer (PC). This study aimed to evaluate the prognostic value of ctDNA variant allele frequency (VAF) in advanced PC collected at diagnosis.

Methods: Patients with advanced pancreatic cancer and ctDNA collected at time of initial diagnosis were retrospectively evaluated. For analysis we considered the detected gene with highest VAF as the dominant clone allele frequency (DCAF). The

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Real-world safety and medication use of second-line (2L) 5-fluorouracil (5-FU)–based regimens among patients (pts) with

metastatic pancreatic ductal adenocarcinoma (mPDAC).

George P. Kim, Paul Cockrum, Andy Surinach, Shu Wang, Zev A. Wainberg

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Abstract Disclosures

Abstract

e16248

Background: Chemotherapy-related adverse events (AEs) can negatively impact the treatment of pts. Managing and preventing these toxicities often require additional medications. This study examined the proportion of pts with mPDAC treated with 5-FU–based regimens in 2L who experienced AEs during treatment, and the proportion who received medication to manage those AEs. **Methods:** Data were extracted for pts diagnosed with mPDAC who initiated 2L treatment Jan 2016 to Aug 2020 from the Flatiron Health database. Pts included were treated with FOLFIRINOX (FFX), FOLFOX, FOLFIRI, or liposomal irinotecan (nal-IRI). The occurrence of grade 3 (G3) and grade 4 (G4) neutropenia and G3/G4 thrombocytopenia were determined using lab

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WE RECOMMEND

Caring for heavily pretreated patients with metastatic breast cancer (MBC): Carboplatin (CBDCA) - gemcitabine (GCB) combination is effective and well tolerate
C. Catania et al., J Clin Oncol, 2004

A phase I study of carboplatin plus oral topotecan in advanced malignancies
E. Kim et al., J Clin Oncol, 2004

Phase I trial of pemetrexed plus paclitaxel administered every 21 days in patients with advanced solid tumors
A. Awada et al., J Clin Oncol, 2016

Phase I/II study of carboplatin and weekly paclitaxel for advanced non-small cell lung cancer
N. Ohashi et al., J Clin Oncol, 2004

Metastatic soft tissue sarcomas (MSTS): Second line chemotherapy

results and the grading criteria from the CTCAE v4.03. The occurrence of diarrhea and nausea/vomiting (N/V) were identified via ICD-10-CM codes. The use of atropine and granulocyte colony stimulating factor (G-CSF) during treatment was assessed. Duration of therapy (DOT) was assessed for each regimen. Descriptive statistics for AEs, medication use, and DOT were reported. **Results:** Of the 825 eligible pts, 29.0% (n=239) received FFX, 40.2% (n=332) received regimens containing nal-IRI, 24.0% (n=198) received FOLFOX, and 6.8% (n=56) received FOLFIRI. The median DOT (IQR) was 15.1 weeks (wks) (7.1 – 30.1), 12.9 wks (6.0 – 24.8), 11 wks (6.4 – 24.0), and 12.7 wks (8.3 – 24.6) for pts who received FFX, nal-IRI, FOLFOX, and FOLFIRI, respectively. G3/G4 thrombocytopenia (<50,000/mm^3) presented in 9.6%, 2.4%, 8.1%, and 14.3% of pts treated with FFX, nal-IRI, FOLFOX, and FOLFIRI, respectively. G3/G4 neutropenia (<1000/mm^3) presented in 22.6%, 12.3%, 14.6%, and 19.6% of pts treated with FFX, nal-IRI, FOLFOX, and FOLFIRI, respectively. The median (Q1-Q3) cumulative dose of the G-CSF pegfilgrastim was 18mg (12 – 45), 18mg (12 – 48), 24mg (12 – 36), and 30mg (13 – 48) for pts treated with FFX, nal-IRI, FOLFOX, and FOLFIRI, respectively. Atropine use was higher in pts treated with FFX and FOLFIRI (90.8% and 94.6%, respectively) than for pts treated with nal-IRI (75.6%). The full study results are reported in the table. **Conclusions:** In this study of AEs among pts with mPDAC treated in 2L, pts who received liposomal irinotecan had the lowest proportion of thrombocytopenia and neutropenia. Diarrhea was similar across the cohorts despite the high proportion of use in atropine for pts treated with FFX and FOLFIRI.

Outcome	FOLFIRINOX (n=238)	Nal-IRI-containing (n=332)	FOLFOX (n=198)	FOLFIRI (n=68)
G3/G4 Thrombocytopenia	9.6%	2.4%	8.1%	14.3%
G3/G4 Neutropenia	22.6%	12.4%	14.7%	19.6%
Diarrhea	12.6%	10.2%	4.6%	12.5%
N/V	15.9%	13.0%	12.6%	12.5%
Atropine	90.8%	75.6%	1.0%	94.6%
Median pegfilgrastim cumulative dose (IQR)	18 mg (12-45)	18 mg (12-48)	24 mg (12-36)	30 mg (13-48)

Leucovorin for Colorectal Cancer"

Yanhong Deng et al.,
Gastroenterology Report, 2021

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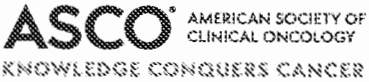

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Meeting Abstract | 2021 Gastrointestinal Cancers Symposium

PANCREATIC CANCER

Real-world safety data and differentiation of second-line (2L) 5-fluorouracil (5-FU) based regimens among patients with

metastatic pancreatic ductal adenocarcinoma (mPDAC).

George P. Kim, Paul Cockrum, Aleksander Chudnovsky, Andy Sutnach, Zev A. Wainberg, Shu Wang, Amin Yakubu

George Washington University, Division of Hematology & Oncology, Washington, DC; Ipsen, Cambridge, MA; Genesis Research, Hoboken, Nj; UCLA Medical Center - Cancer Care - Santa Monica, Los Angeles, CA

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Abstract Disclosures

Abstract

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Background: Chemotherapy related adverse events (AEs) can impact the treatment of patients, reducing quality of life and leading to dose delays and treatment discontinuation. This study examined the proportion of patients (pts) with mPDAC treated with 5-FU-based regimens in the 2L setting who experienced AEs during treatment. **Methods:** Data were extracted for pts diagnosed with mPDAC who initiated 2L treatment between January 2016 and July 2020 from the Flatiron Health electronic health database. Pts included in the study were treated with FOLFIRINOX (FFX), FOLFOX, FOLFIRI, or a regimen containing liposomal irinotecan. The occurrence of grade 3 (G3) and grade 4 (G4) neutropenia, G3/G4 elevated alanine transaminase (ALT) and anemia

COMPANION ARTICLES

No companion articles

ARTICLE CITATION

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Journal of Clinical Oncology 39, no. 3_suppl (January 20, 2021) 390-390.

Published online January 22, 2021.

WE RECOMMEND

Caring for heavily pretreated patients with metastatic breast cancer (MBC): Carboplatin (CBDCA) - gemcitabine (GCB) combination is effective and well tolerate
C. Catania et al., J Clin Oncol, 2004

Paclitaxel injectable emulsion: phase 2a study of weekly administration in patients with metastatic or locally advanced unresectable or recurrent urothelial transitional cell cancer (TCC)
A. Gorelov et al., J Clin Oncol, 2004

Oxaliplatin (L-OHP) in combination with 5-fluorouracil (5-FU)/l-leucovorin (l-LV) on modified Roswell Park regimen as first-line treatment of advanced colorectal cancer (ACRC): A phase I/II study
Y. Miyata et al., J Clin Oncol, 2004

where transfusion was indicated were determined using lab results and the grading criteria from the Common Terminology Criteria for Adverse Events v4.03. The occurrence of diarrhea, fatigue, nausea and vomiting (N/V), and neuropathy were identified from structured diagnosis records through ICD-10-CM codes. Duration of therapy (DOT) was assessed for each regimen. Descriptive statistics for AEs and DOT were reported. **Results:** Of the 804 pts included in the study, 28.4% (n=228) received FFX, 39.8% (n=320) received regimens containing liposomal irinotecan, 24.8% (n=199) received FOLFOX, and 7.1% (n=57) received FOLFIRI. The median DOT (IQR) was 86 days (d) (43 – 206), 79d (41 – 169), 72d (43 – 166), and 84d (46 – 148) for pts who received FFX, liposomal irinotecan, FOLFOX, and FOLFIRI, respectively. G3/G4 neutropenia (<1000/mm3) presented in 28.1% (n=64) of pts treated with FFX, 11.9% (n=38) of pts treated with liposomal irinotecan, 17.1% (n=34) of pts treated with FOLFOX, and 36.8% (n=21) of pts treated with FOLFIRI. NV occurred in 14.9% (n=34), 13.1% (n=42), 12.6% (n=25), and 10.5% (n=6), respectively. The full AE results are summarized in the table. **Conclusions:** In this assessment of often dose-limiting AEs among pts with mPDAC treated in 2L, pts who received liposomal irinotecan had the lowest proportion of neutropenia. No clear pattern was noted for N/V, neuropathy, fatigue, anemia, and elevated ALT. Further research is necessary to determine the real-world cost implications of AEs in this patient population.

Adverse event	FOLFIRINOX (n=238)	Liposomal irinotecan containing (n=320)	FOLFOX (n=199)	FOLFIRI (n=67)
G3 Neutropenia	42 (18.4%)	31 (9.7%)	24 (12.1%)	10 (17.5%)
G4 Neutropenia	29 (12.7%)	14 (4.4%)	13 (6.5%)	12 (21.1%)
G3/G4 Neutropenia	64 (28.1%)	38 (11.9%)	34 (17.1%)	21 (36.8%)
Anemia: transfusion indicated	30 (13.2%)	33 (10.3%)	24 (12.1%)	9 (15.8%)
G3/G4 Elevated ALT	9 (3.9%)	9 (2.8%)	5 (2.5%)	2 (3.5%)
Diarrhea	25 (11%)	30 (9.4%)	8 (4%)	7 (12.3%)
Fatigue	25 (11%)	25 (7.8%)	19 (9.5%)	6 (10.5%)
Nausea and vomiting	34 (14.9%)	42 (13.1%)	25 (12.6%)	6 (10.5%)
Neuropathy	6 (2.6%)	12 (3.8%)	4 (2%)	3 (5.3%)

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clinical oncology unit where both radiotherapy and chemotherapy are practised. Patient records were retrieved from a prospectively maintained database, and their demographic and clinical details were recorded.

Results: Between 2011 and 2020, a total of 35194 patients were registered. Their characteristics are detailed in the table. The most common sites were head and neck (42%), gynaecological (18%), and gastrointestinal (15%). The median (interquartile range, IQR) age in years for head and neck, breast, gynaecological, and rectal cancers were as follows: 47 (38-58), 45 (38-53), 50 (40-58), and 40 (29-53), respectively. The mean distance travelled by a patient to the hospital was 110.6 kilometres (68.7 miles). Most patients had no formal education (64%). Only 8% patients had received higher education: undergraduate (6%) and postgraduate (2%). Approximately 70% of patients had an annual income of less than INR 35,000 (USD 500).

Table: **1511P**

	No	Percent	Age, yrs	
			Median	IQR
Head Neck	14945	42	47	38-58
Oral	8109	23		
Oropharynx	3197	9		
Hypopharynx	646	2		
Larynx	2109	6		
Nasopharynx	162	<1		
Paranasal Sinus	311	1		
Salivary Gland	224	1		
Other	187	1		
Breast	3107	9	45	38-53
Lung	1044	3	55	48-65
Gynaecology	6451	18	50	40-58
Endometrium	272	1		
Cervix	5677	16		
Vulva	73	<1		
Vagina	29	<1		
Ovary	400	1		
Gastrointestinal	5118	15	50	42-58
Oesophagus	1184	3		
OG Junction, Stomach	393	1		
Colon	275	1		
Rectum	976	3		
Anus	226	1		
Pancreas	199	1		
Biliary Tract	1716	5		
Liver	149	<1		
Urology	822	2	60	50-67
Kidney	63	<1		
Ureter	6	<1		
Bladder	349	1		
Prostate	184	1		
Testis	109	<1		
Penis	111	<1		
CNS	1190	3	32	14-50
Haematology	743	2	20	12-35
Skin	84	<1	59	42-61
STS	226	1	50	34-58
Bone sarcoma	428	1	16	11-22
Thyroid	35	<1	50	40-56
Other	1001	3		

Conclusions: Oncology patients in developing countries represent a unique but large sub-group, often with a younger median age of presentation, low levels of formal education, distressed finances, and the need to travel significant distances to obtain specialised cancer care. Most guidelines originating from high HDI countries neither consider the financial nor logistical feasibility for these patients, and there is a profound unmet need to address the same.

Legal entity responsible for the study: The authors.

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Disclosure: All authors have declared no conflicts of interest.

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1512P Assessing the impact of anti PD-1/PD-L1 inhibitors on cancer care health and budget in Ireland

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Background: In Ireland, the incidence of cancer was estimated to be 30,272 in 2018, with the incidence expected to rise over the next 5 years by 39% in males and 27% in females. Despite chemotherapy being considered the standard of care (SOC) in many malignancies, it is associated with high levels of toxicity. Immunuotherapy has revolutionized cancer care, offering improved health outcomes. Many treatment options with the potential for use in several cancer types has led to concerns around the long-term affordability of these products. The objective of the study is to estimate and inform discussion around the potential public health and economic impact of PD-1/PD-L1 inhibitors in Ireland.

Methods: The Health Impact Projection (HIP) model estimates the key clinical health and economic outcomes of PD-1/PD-L1 inhibitors in 8 high incidence cancers, over a 5-year period (2020—2024) compared to the SOC. It includes an assessment of the relative health benefits such as life-years gained, and utility-adjusted life years gained and draws on budget impact analysis for its structure and methods. The HIP compares the economic and health outcomes in a world without anti PD-1/PD-L1 treatments versus a world where patients are treated with a mix of SOC and anti PD-1/PD-L1 treatments.

Results: The model shows that over 5 years, the clinical benefits offered by the introduction of anti PD-1/PD-L1s include an additional 3,194 life-years, 2,411 progression-free life years, 2,638 quality-adjusted life years and the avoidance of 92 adverse events. PD-1/PD-L1 inhibitors produce an average annual budget impact that is equivalent to 0.32% of total healthcare expenditure. Amongst this figure is a reduced burden of indirect costs and end of life costs — both of which fall with anti PD-1/PD-L1s on the market.

Conclusions: Ireland faces uncertainty in cancer care with pressure to reduce costs — the HIP helps demonstrate the value of anti PD-1/PD-L1s. Anti PD-1/PD-L1s are predicted to improve outcomes in Ireland with PFS gains being the largest. By projecting budget impact over a five-year period, this model should help inform multi-annual budget planning for innovative oncology medicines. This model informs planning by helping quantify the impact of immuno-oncology treatments on health and budget in different scenarios.

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1513P Real-world treatment discontinuation patterns among patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with liposomal irinotecan-based regimens in the United States

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Background: The most common reasons for treatment discontinuation (d/c) among patients treated in the liposomal irinotecan + 5-fluorouracil/ leucovorin (5-FU/LV) arm of the NAPOLI-1 study, a randomized phase 3 study in pts with mPDAC previously treated with gemcitabine-based therapy, were disease progression (55.3%), patient decision (13.6%), and clinical deterioration (12.6%). Real-world (RW) data lack detailed information regarding reasons for d/c of systemic treatment. This study examined the characteristics and reasons for treatment d/c of pts with mPDAC treated with liposomal irinotecan.

Methods: This retrospective study used the Flatiron Health EHR-derived database. Data were analyzed for adult pts with mPDAC treated with liposomal irinotecan-based regimens between January 2016 and October 2020. Pt and clinical characteristics evaluated included age, sex, stage, and the number of prior lines of therapy at the time of treatment initiation. Reasons for treatment d/c were abstracted from patient records.

Results: 675 pts (median age: 69 years (IQR: 62 — 75)) with mPDAC treated with a liposomal irinotecan-based regimen were included. 54% were initially diagnosed with stage IV disease, 52% were male, and 62% initiated liposomal irinotecan in the 1L or 2L setting. Across all lines of therapy, there were 555 patients with at least one reason for d/c recorded. Progression was the most common reason recorded (n=317, 57.1%), followed by toxic effect of therapy (n=102, 18.4%), disease related symptoms not due to therapy (n=92, 16.6%), and patient request (n=35, 6.3%).

Conclusions: In this RW study of patients with mPDAC treated with a liposomal irinotecan-based regimen, progression while on therapy was the most common reason

cited for treatment d/c similar to the pivotal phase 3 trial. The proportion of d/cs due to patient requests was smaller in the RW than in the trial (6.3% vs 13.6%); disease related symptoms/clinical deterioration were similar (16.6% vs 12.6%) and toxic effects of therapy/adverse events were higher in the RW (18.4% vs 9.4%). Further studies are needed to understand the clinical context that leads patients to discontinue treatment.

Legal entity responsible for the study: Ipsen.

Funding: Ipsen.

Disclosure: G. Kim: Financial Interests, Personal, Advisory Role: Ipsen. A. Surinach: Financial Interests, Institutional, Advisory Role: Ipsen. S. Wang: Financial Interests, Institutional, Advisory Role: Ipsen. N. Lamarre: Financial Interests, Institutional, Advisory Role: Ipsen. P. Cockrum: Financial Interests, Personal, Full or part-time Employment: Ipsen; Financial Interests, Personal, Stocks/Shares: Ipsen.

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1514P Age at diagnosis of Breast Cancer in Albania

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Background: The notion that breast cancer in developing countries is characterized by young age appears to be true in Albania. This review aims to evaluate and document the age pattern of breast cancer at diagnosis in a developing country.

Methods: This review was undertaken at "Mother Teresa" University Hospital Center, in Tirana, Albania between January 2010 to December 2019. Medical records and pathology reports of 1563 breast cancer patients were thoroughly reviewed with an emphasis on age at diagnosis.

Results: The total number of evaluated breast cancer patients was 1563. Age ranged from 23 to 88 years old with a median age of 55 years old. There was no noticeable change in age at diagnosis between the years. Most of the patients were within the age range of 40 -59 accounting for 55% of all breast cancer patients. It was also noted that 36.9% of cases were below the age of 50 years. The lower occurrence was demonstrated in the lower and higher age groups.

Conclusions: Contrary to the reported age pattern of breast cancer in high-income countries which can easily be explained by the older population as compared to the Albanian population, Albanian women tend to be diagnosed at a younger age than women in developed countries. This review had shown that 55% of cases were in the age range of 40 - 59 years. Special attention and consideration should be directed to this group of women during screening and breast imaging for symptomatic presentations.

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Disclosure: All authors have declared no conflicts of interest.

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1515P Common presenting symptoms in cancer patients that mimic tuberculosis leading to erroneous diagnosis in Pakistan

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Background: Tuberculosis (TB) is a common disease worldwide and nearly 10 million people succumb to this disease annually. It is endemic to certain areas including South Asia. A lot of cancer patients at presentation have symptoms that mimic TB as a consequence of which they get misdiagnosed and treated initially for TB. The rationale of this study was to determine the presenting symptoms of cancer patients that are akin in both diseases leading to wrong diagnosis as TB and patients get treated for TB before presenting to oncologists.

Methods: In a cross-sectional study 213 patients were recruited from Oncology outpatient and inpatient of Mayo Hospital Lahore and were interviewed via a preformed valid questioner. Data was entered and analyzed using SPSS version 23. Descriptive analysis and intergroup analysis performed using chi- square ($p < 0.05$ taken as significant).

Results: 213 patients, minimum age 14 and maximum age 93 with an average of 45 (SD $\pm$ 15) were taken (51.2% males and 48.8% females). Chi-square analysis ($p< 0.05$ significant) of groups showed that a lot of presenting symptoms in cancer patients mimic TB and patients get erroneous diagnosis. Most significant symptoms in both diseases which mimic and lead to fallacious diagnosis were weight loss,107 patients (69.48%,p=0.00, Cramer's V=0.5); anorexia, 99 patients having this symptom (66%, p=0.00,Cramer's V=0.4); fever, 93 patients (65%, p=0.00, Cramer's V=0.4); night sweats, 52 patients (77%, p=0.00, Cramer's V=0.3); cough, 61 patients (77%, p=0.0, Cramer's V=0.3); rigors and chills, 30 patients (71%, p =0.01, Cramer's V=0.2); all were given wrong diagnosis. Another strong factor for wrong diagnosis was contact of patient with a known case of TB, 54 patients (85%, p=0.0, Cramer's V=0.4).

Conclusions: A lot of presenting symptoms are similar in both diseases which lead to wrong diagnosis of cancer patients as TB and these patients continue taking treatment of TB until deterioration. Suspicion must be kept high while taking history of patients presenting with aforementioned symptoms and physician must be prudent enough while advising investigations on basis of history and examination so that cancer patients get diagnosed appropriately.

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1516P Core variables for managed entry agreements, regarding clinical outcomes and patient reported measures, in cancer

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Background: The aim was to define a core set of outcomes, the Cancer Standard Set, that would serve as a guide to innovative outcome measurement initiatives, such as in the application of managed entry agreements or risk-sharing agreements.

Methods: We present a literature search in MEDLINE (for the three most common cancers) to identify baseline characteristics, treatment patterns and outcomes to guide discussions of the working group composed by oncologists, pathologists, radiotherapy specialists, surgeons, pharmacists, nurses and hospital managers to review existing data and practices. The group has had structured meetings to share evidence and expert opinions. We explain which outcomes are essential, respecting the proposal of Porter's three-tiers of hierarchy (Health status achieved/retained, Process of recovery and Sustainability of health), in his value-based healthcare framework.

Results: We include baseline characteristics such as: birth date, death date, admission date, main diagnosis and respective date, ECOG performance status, comorbidities, sex, topographic location, behaviour, histological type, genetic markers/biomarkers and cancer stage. Treatments can be surgical, pharmacological and/or radiotherapy/brachytherapy. In all types of treatment, patient-reported QOL outcomes should be periodically applied, as per appropriate protocol. In the surgical treatment the outcomes include: surgery date, beginning and ending date of hospitalization, procedure, radicality of surgery, radicality of anatomy, need for unplanned reintervention, unwanted postoperative occurrence, relevant devices and their cost. Both in pharmacological treatment and in radiotherapy/brachytherapy the outcomes include: beginning and ending treatment date, cycles number of, name of the protocol/medication/procedure, toxicity and complications, evaluation of the response and its date. Regarding pharmacological treatment, the date of disease progression and the medicines cost should also be included.

Conclusions: We set forward a base for cancer-related research and management of entry agreements. The systematic collection of this set of outcomes will generate insights for future decisions and improve healthcare.

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SYMPTOMS AND SURVIVORSHIP

Psychometric properties of patient reported outcome (PRO) instruments in patients with small cell lung cancer (SCLC) in RESILIENT part 1.

Jaba Kokhreidze, Veleka Allen, Cristina Ivanescu, Xiaopan Valerie Yao, Bin Zhang, Brooke Harrow

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Ipsen, Boston, MA; IQVIA, New York, NY; IQVIA, Durham, NC; Ipsen Bioscience, Boston, MA; Ipsen Inc, Cambridge, MA

Abstract Disclosures

Abstract

ARTICLE CITATION

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e24027

Background: The ongoing two-part phase 2/3 RESILIENT study (NCT03088813) is investigating the efficacy and safety of liposomal irinotecan monotherapy in patients with SCLC who have progressed on or after first line platinum-based chemotherapy. This exploratory analysis from RESILIENT part 1 was conducted to confirm the psychometric properties of established PRO instruments that had not previously been validated in patients with SCLC. **Methods:** Patients completed the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) Core 30 (C30) and the EORTC QLQ Lung Cancer 13 (LC13) before treatment assignment (baseline), every 6 weeks thereafter, at treatment discontinuation and at the 30-day follow-up visit. Psychometric methods included descriptive statistics (items and scales), correlations (item-to-item and item-to-total), internal consistency (Cronbach's α), test-retest reliability (intraclass correlation coefficient [ICC], two-way random effects model), construct validity and sensitivity to change. The analysis included patients who received at least one dose of study drug and completed at least one PRO assessment. **Results:** Thirty patients were enrolled in RESILIENT part 1 and included in the analysis. At baseline, 68% of patients reported 'not severe' or 'mild' symptoms. Floor effects (i.e. more than 25% of responses of 'not at all') were observed for several of the functioning/impact and symptom scales of the EORTC QLQ C30 and LC13. Moderate to strong correlations were found among most questionnaire items within their respective scales. Acceptable evidence for internal consistency and good test-retest reliability were observed. Selected results for the EORTC QLQ LC13, including dyspnea scales, are shown in the Table. The magnitude of correlations among PRO instruments supported evidence for convergent validity in this sample.

Conclusions: In RESILIENT part 1, patients experienced low and tolerable symptoms at enrollment, limiting the potential for further improvement. Overall, these PRO instruments had acceptable psychometric properties (e.g. construct validity, reliability and ability to detect change) in this sample. However, these analyses should be repeated in a larger sample using data from RESILIENT part 2.Clinical trial information: NCT03088813.

Selected results for the EORTC QLQ LC13.

Item-total correlations	All items showed acceptable correlations with total scale for the two dyspnea scales, except shortness of breath while rested (r = 0.332 for dyspnea and r = 0.365 for dyspnea alternate[a])
Internal consistency	Good reliability (α > 0.7) was observed for both dyspnea scales
Test-retest reliability	Good test-retest reliability was observed for the dyspnea (ICC 0.752 [95% CI −0.555, 0.854]), pain in arm (0.625 [−0.086, 0.922] and pain in chest (0.625 [−0.245, 0.926]) scales

[a]Scale created by combining EORTC QLQ C30 and LC13 items

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Dispersion in total cost of care for Medicare fee-for-service (FFS) patients with metastatic pancreatic cancer receiving FDA-approved/NCCN Category 1 regimens at 340B verus non-340B institutions.

Helen Latimer, Samantha Tomicki, Gabriela Dieguez, Paul Cockrum, George P. Kim

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Milliman, Inc., New York, NY; Ipsen, Cambridge, MA; George Washington University, Washington, DC

Abstract Disclosures

Abstract

ARTICLE CITATION

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e18843

Background: The Department of Health and Human Services (HHS) designed the 340B drug pricing program to allow institutions that service specialty populations to acquire drugs at lower prices. Objective: To analyze the dispersion in total cost of care (TCOC) for Medicare FFS patients (pts) with metastatic pancreatic cancer (m-PANC) treated at 340B or non-340B institutions, by NCCN Category 1 regimen. **Methods:** We identified pts with m-PANC using ICD-10 diagnosis codes in the 2016-18 Medicare Parts A/B/D 100% Research Identifiable Files. Study pts had 2+ claims with a pancreatic cancer diagnosis and Medicare FFS coverage for 6 months pre- and 3 months post-metastasis diagnosis. Study pts were treated with NCCN Category 1 regimens: 1L gemcitabine monotherapy (gem-mono), 1L gemcitabine/nab-paclitaxel (gem-nab), 1L FOLFIRINOX (FFX), and 2L liposomal irinotecan-based regimen (nal-IRI). Pts were attributed to 340B or non-340B institutions based on plurality of chemotherapy claims. TCOC reflects insurer-paid services per line of therapy (LOT) for 3 categories: chemotherapy/supportive drugs (chemo/Rx), inpatient care (IP), and other outpatient care (OP). We grouped pts by quartile (qrt) and evaluated drivers of TCOC and mean rates of admissions (admits/pt). **Results:** We identified 2,697 (340B) and 3,839 (non-340B) pts taking NCCN Category 1 regimens. Gem-mono represented 1% and 4% of all pts in 340B and non-340B institutions, respectively. Gem-nab accounted for 72% of pts in both cohorts. For gem-nab, FFX, and nal-IRI pts, median TCOC was similar in both cohorts, although mean TCOC by qrt was lower at 340B institutions than non-340B institutions, except for gem-nab in the 1st qrt. The components of TCOC were similar between 340B and non-340B institutions in all qrts. In both cohorts, % IP costs increased between the 1st and 4th qrt (340B:15% to 23%,

non-340B:14% to 25%). From the 1st to the 4th qrt, admits/pt increased in both cohorts. In the 340B cohort, nal-IRI pts had the lowest admits/pt while gem-nab pts had the highest in all qrts. In the non-340B cohort, nal-IRI pts had the lowest admits/pt except for in the 1st qrt. **Conclusions:** Median TCOC was lower at 340B institutions than non-340B institutions for all regimens, and the range of TCOC dispersion was also smaller at 340B institutions. Across qrts, chemotherapy accounted for approximately half the TCOC; however, IP costs were proportionally higher in the 4th qrt. Comparing regimens, despite 2L nal-IRI pts being more heavily pretreated, median costs in each cohort were similar to 1L gem-nab and 1L FFX, while admits/pt were generally lower than 1L gem-nab and 1L FFX across qrts and cohorts.

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GASTROINTESTINAL CANCER—GASTROESOPHAGEAL, PANCREATIC, AND HEPATOBILIARY

Dispersion in total cost of care for Medicare fee-for-service (FFS) patients with metastatic pancreatic cancer receiving FDA-approved/NCCN Category 1 regimens at teaching versus non-teaching institutions.

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Abstract Disclosures

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Abstract

e16244

Background: Teaching institutions receive additional funding from Medicare & Medicaid Services (CMS) to provide specialized, quality care. Objectives: To analyze the dispersion in total cost of care (TCOC) for Medicare FFS patients (pts) with metastatic pancreatic cancer (m-PANC) treated at teaching (teach) or non-teaching (non-teach) institutions. **Methods:** We identified pts with m-PANC using ICD-9/10 diagnosis codes in the 2016-18 Medicare Parts A/B/D 100% Research Identifiable Files. Study pts had 2+ claims with a pancreatic cancer diagnosis and Medicare FFS coverage for 6 months pre- and 3 months post-metastasis diagnosis. Study pts were treated with NCCN Category 1 regimens: 1L gemcitabine monotherapy (gem-mono), 1L gemcitabine/nab-paclitaxel (gem-nab), 1L FOLFIRINOX (FFX), and 2L liposomal irinotecan-based regimen (nal-IRI). Pts were attributed to teach or non-teach institutions based on plurality of chemotherapy claims. TCOC reflects insurer-paid services per line of therapy (LOT) for 3 categories: chemotherapy/supportive drugs (chemo/Rx), inpatient care (IP), and other outpatient care (OP). We grouped pts by quartile (qrt), evaluated drivers of TCOC, and mean rates of admissions (admits/pt). **Results:** We identified 3,908 (teach) and 2,632 (non-teach) pts taking NCCN Category 1 regimens. There was a similar mix of patients in both cohorts, with gem-mono pts making up only 3% of the sample. Gem-nab accounted for 73% and 70% of pts in teach and non-teach institutions, respectively. For gem-nab, FFX, and nal-IRI pts, median TCOC was similar in both cohorts. However, median TCOC for the two non-generic drugs in our study, gem-nab (teach: $36,332; non-teach: $40,135) and nal-IRI (teach: $31,526;

Adjuvant nab-paclitaxel plus gemcitabine versus gemcitabine in resected pancreatic ductal adenocarcinoma: A Chinese single institution experience.
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Gemcitabine (GEM), cisplatin (P) and methylprednisolone: A salvage regimen in relapsed Hodgkin's disease and non-Hodgkin's lymphoma
J. Waters et al., J Clin Oncol, 2004

Phase I/II study of a docetaxel (DOC) and gemcitabine (GEM) combination for early recurrent (≤12 months)(ER) or refractory (R) epithelial ovarian cancer (EOC): Kansai Clinical Oncology Group, Japan
Y. Itani et al., J Clin Oncol, 2004

A phase II trial of carboplatin and gemcitabine with exisulind (IND # 65,056) in patients with advanced non-small cell lung cancer: Eastern Cooperative Oncology Group Trial 1501
G. A. Masters et al., J Clin Oncol, 2004

Gemcitabine (GEM) as salvage therapy in patients (pts) with advanced colorectal cancer (CRC) refractory to 5-fluorouracil (FU), irinotecan (IRI) and oxaliplatin (OXA)
S. Lonardi et al., J Clin Oncol, 2004

731 Costs of care for first-line (1L) treatment of advanced non-small cell lung cancer (aNSCLC): a real-world claims analysis
Jonathan Kish et al., Jitc, 2020

562 Real-world assessment of current treatment patterns and clinical outcomes among patients

non-teach: $39,360), were lower at teach institutions than non-teach institutions. The components of TCOC are similar between teach and non-teach institutions in all qrts. In both cohorts, % IP costs for all regimens increased between the first and fourth qrt (teach:14% to 23%, non-teach:14% to 26%). In the teach cohort, nal-IRI pts had the lowest admits/pt in all qrts. In the non-teach cohort, there was no discernable pattern, although nal-IRI pts had the lowest admits/pt in the second and fourth qrt. **Conclusions:** For non-generic regimens like nal-IRI and gem-nab, median TCOC was lower at teach institutions than non-teach institutions. There were no consistent differences in TCOC dispersion or admissions between cohorts. Across qrts, chemotherapy accounted for approximately half the TCOC. However, IP costs were proportionally higher in the fourth qrt, especially for non-teach institutions. Despite nal-IRI pts being on the second LOT, both median TCOC and admits/pt across qrts were lower than gem-nab and FFX in teach institutions. In the non-teach cohort, median TCOC were similar among nal-IRI, gem-nab, and FFX.

with EGFR and ALK wild type non-small cell lung cancer (NSCLC) in the US
Lyudmila Bazhenova et al., jitc, 2021

Costs of care similar or lower at teaching hospitals compared to non-teaching hospitals
MedicalXpress, 2019

Assessing GCSF Agent Guidelines
By staff, US Pharmacist, 2019

Rates of major CV procedures differ between Medicare Advantage and fee-for-service beneficiaries
MedicalXpress, 2013

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Diabetes/Endocrine/Metabolic Disorders - Clinical Outcomes

PDB1
EVALUATION OF HEALTH-RELATED QUALITY OF LIFE OF PATIENTS WITH TYPE 2 DIABETES MELLITUS AT A TERTIARY CARE HOSPITAL IN ETHIOPIA

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Objectives: Type 2 diabetes mellitus (T2DM) and its treatment adversely affect patients' health-related quality of life (HRQoL). This study aimed to assess HRQoL and its predictors among T2DM patients at a tertiary care hospital in Ethiopia. ***Methods:*** A paper-based, face-to-face cross-sectional study was conducted among patients with T2DM at Tikur Anbessa Specialized Hospital in Ethiopia. We collected data using a validated Amharic version of 5-level EuroQol-5 dimensions (EQ-5D-5L) instrument. Descriptive statistics were used to present patient demographic and clinical characteristics. Kruskal-Wallis and Mann-Whitney U tests were performed to identify factors associated with patients' HRQoL. Utility scores were calculated using disutility coefficients of the Ethiopian general population. Statistical significance was determined at $p < 0.05$. ***Results:*** A total of 352 patients responded (response rate of 97.8%) with a mean (SD) age of 64.43 (10.61) years. Reported health problems were mostly in the pain/discomfort (67.3%) domain followed by mobility (60.5%), whereas the usual activities domain (34.1%) was the least health problem being reported. The mean (SD) utility and EQ-VAS scores were 0.87 (0.17) and 76.38 (13.85), respectively. Older age, higher educational level, longer duration since diagnosis of diabetes, uncontrolled blood sugar level, use of insulin injection, and diabetes-related complications were significantly associated with lower utility scores, while higher monthly household income was related to better health utility and EQ-VAS scores ($p < 0.05$). ***Conclusions:*** Overall, patients with T2DM had lower HRQoL than the general population. The health utility values generated in this study can be useful to assess clinical outcomes and perform economic evaluations to inform decisions about alternative interventions for T2DM patients.

Diabetes/Endocrine/Metabolic Disorders - Economic Evaluation

PDB2
TOTAL COST OF CARE AND UTILIZATION AMONG MEDICARE FEE-FOR-SERVICE (FFS) PATIENTS WITH METASTATIC PANCREATIC CANCER TREATED WITH FDA-APPROVED/NCCN® CATEGORY 1 REGIMENS AT TEACHING VS. NON-TEACHING HOSPITALS

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Objectives: To compare total cost of care (TCOC) and utilization for Medicare FFS patients (pts) with metastatic pancreatic cancer (m-PANC) treated at teaching or non-teaching hospitals, by NCCN® Category 1 regimen. ***Methods:*** We identified pts with m-PANC using ICD-9/10 diagnosis codes in the 2016-18 Medicare Parts A/B/D 100% Research Identifiable Files. Study pts had 2+ claims with a pancreatic cancer diagnosis and Medicare FFS coverage for 6 months pre- and 3 months post-metastasis diagnosis. Teaching hospitals were identified using CMS Fiscal Year IPPS Final Rule and Correction Notices. Pts were attributed to teaching or non-teaching hospitals based on plurality of chemotherapy claims. TCOC was the sum of mean paid services by the insurer per line of therapy. We calculated mean rates of hospital admissions (admits/pt) and readmissions. Study pts were treated with NCCN® Category 1 regimens: 1L gemcitabine monotherapy (gem-mono), 1L gemcitabine/nab-paclitaxel (gem-nab), 1L FOLFIRINOX (FFX), and 2L liposomal irinotecan-based regimen (Nal-IRI). ***Results:*** We identified 7,594 and 4,959 pts in teaching and non-teaching cohorts, respectively. There were no significant differences in TCOC, admits/pt, or readmissions between teaching and non-teaching hospitals. In both cohorts, gem-mono had the lowest TCOC (teaching: $19,476, $P<.05$; non-teaching: $22,298, $P<.05$), while Nal-IRI had the highest (teaching: $49,776, $P<.05$;, non-teaching: $48,191, $P>.05$). In both cohorts, Nal-IRI had the lowest admits/pt (teaching: 0.69, $P<.05$; non-teaching: 0.77 $P>.05$) and readmissions (teaching: 12%, $P>.05$; non-teaching: 13%, $P>.05$) while gem-nab had the highest admits/pt (teaching: 1.21, $P>.05$; non-teaching: 1.15, $P>.05$) and readmissions (teaching: 19%, $P>.05$; non-teaching: 17%, $P>.05$). ***Conclusions:*** Despite teaching hospitals receiving add-on payments, there were no consistent differences in TCOC between teaching and non-teaching hospitals. Additionally, admits/pt and readmissions by regimen were similar among cohorts. However, across cohorts TCOC was lowest for gem-mono and highest for Nal-IRI and admits/pt and readmissions were lowest for Nal-IRI and highest for gem-nab.

PDB3
TRENDS IN PRICES OF INSULIN MARKETED IN THE U.S.

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Objectives: The cost of diabetes drugs has risen steadily since 80s. The increase in out-of-pocket cost lead to a reduction in treatment adherence. This study evaluated trends in insulin prices in the period 01/01/1983-01/01/2021 and analyzed the effect of follow-on and authorized generic competition on insulin prices. ***Methods:*** Data of marketed insulin products was derived from the FDA, the wholesale acquisition cost from the RedBook (IBM Micromedex), and the consumer price index from the U.S. Bureau of Labor Statistics. Descriptive statistics and linear spline regression analyses were performed. ***Results:*** There were 70 insulins and analogs marketed in the U.S. in the period 01/01/1983-01/01/2021. The study analytical sample included 51 injectable insulins, including 41(80.4%) brand products, 7(13.7%) authorized generics, and 3(5.9%) follow-on insulins. The first human insulin entered the market with a WAC 30-defined daily dose (DDD) of $12.42. It increased 14.4 times to $178.44 by 1/1/2021, representing 5.4 times the CPI increase. The rest of the insulins and analogs exhibited similar price trends. We identified four statistically significant different periods ($p<0.05$): 1983-1999 (the prices for human insulins increased by $0.53/year); 2000-2009 ($2.32/year increase for human insulins and $6.56/year for long-acting and rapid/intermediate combination analogs); 2010-2017 ($16.60/year and $22.37/year increase for insulins and analogs, respectively); and 2018-2020($2.40/year decrease for human insulins, and $5.00/year increased for analogs). These price trends may be related with the Medicaid Drug Rebate (1999), the Affordable Care Act (2010), and the social and political pressure on pharmaceutical companies to lower insulin prices, and the introduction of follow-on and authorized generic competition that occurred in 2018-2020. ***Conclusions:*** Prices of insulins and analogs increased significantly above the the inflation rate from 1/1/1983 to 1/1/2021. Changes in insulin prices occurred after the Medicaid Drug Rebate enactment (1999), the Affordable Care Act (2010), and the social pressure to reduce prices and market competition in 2018-2020.

PDB5
DETERMINATION OF PAYER BUDGET IMPACT FROM USING AN INNOVATIVE IN VITRO DIAGNOSTIC IN THE MANAGEMENT OF DIABETIC KIDNEY DISEASE

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Objectives: To evaluate the budget impact from implementing a proactive testing regime for chronic kidney disease in patients with type-2 diabetes (T2D). PromarkerD is an innovative biomarker-based blood test that predicts risk of diabetic kidney disease (DKD) and renal decline in T2D patients. This research aims to assess whether PromarkerD could reduce costs to US payers (currently $50 billion to the US healthcare system). ***Methods:*** This four-year model evaluated potential net savings to US payers from covering the PromarkerD test versus standard-of-care (SOC) in T2D patients with no/mild DKD (KDIGO categories G1-3b). Parameters were derived from prior literature and clinical studies, and included costs and frequency of testing, costs associated with changes to patient treatment strategies, and savings from slowing DKD progression and ESRD interventions (dialysis and kidney transplants). Model assumptions included testing rates (annual for low-risk, biannual for high-risk), 80% adherence to preventative medications, and a 20% decline in progression through DKD stages. ***Results:*** Covering PromarkerD testing per million T2D patients could produce savings for US payers of $2.3 billion over four years, against costs of $1.5 billion (net savings: $846m). Savings arise from slower DKD stage progression ($1.4b), delayed dialysis and transplants ($667m), and fewer unplanned dialysis ($272m), while costs include testing ($665m), and preventative treatments in high-risk patients ($793m). Sensitivity analysis showed that if the decline in progression was set to 15%, net savings were still $353m. ***Conclusions:*** Changing SOC by implementing an alternative PromarkerD testing regime in T2D patients could reduce unnecessary adoption of new therapeutic interventions in low risk patients, and enable early intervention for high risk patients, thereby slowing progression and lessening the need for expensive dialysis and transplants. This study demonstrates substantial near-term savings to US payers in the treatment of DKD through early, accurate and cost-effective prognosis with the PromarkerD test.

PDB8
CHANGES IN COST OF ORAL ANTIDIABETIC DRUGS BY INTRODUCTION OF FORMULARIES IN JAPAN: A SIMULATION USING HEALTH INSURANCE CLAIMS DATABASE

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Objectives: Japan's National Health Insurance (NHI) has a nationwide list of drugs covered. A new reimbursement for the introduction of a formulary has been examined. However, nobody knows how much of the reimbursement would be appropriate, or even whether the introduction would reduce the National Health Expenditure (NHE) or not. This research would help the government's decision on the reimbursement by simulating a hypothetical change of the cost of Oral Antidiabetic Drugs (OADs) if the formularies were introduced. ***Methods:*** We analyzed an anonymously processed health insurance claims database of National Health Insurance provided by DeSC Healthcare. National Health Insurance is a type of NHI. The insurers are municipalities, and the insureds include self-employed and retirees. OAD claims in 2019 are identified by "A10" of the first 3 digits of ATC code associated to each drug claim. We calculated the cost per member per month (PMPM) of OADs, and simulated the PMPM if a formulary were introduced. Two formularies, one provided by UnitedHealth and the other by Kaiser Permanente for commercial HMO,

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Real-world patterns of pain medication use among patients with metastatic pancreatic ductal adenocarcinoma (mPDAC).

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Abstract Disclosures

Abstract

302

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Background: Helping patients manage cancer-related pain is an important aspect of supportive care. 80% of patients with mPDAC suffer from abdominal and/or back pain. Pancreatic cancer-related pain is typically treated pharmaceutically using pain medicines, which include opioids or narcotics. Previous studies have found that the presence of pain was associated with impaired survival in pancreatic cancer patients. The goal of this study was to assess the treatment patterns of pain medication usage and their association with duration of therapy (DOT) among patients with mPDAC treated in the real-world setting. **Methods:** This retrospective observational study utilized the IBM MarketScan Commercial and Medicare supplemental claims data. Data were analyzed for adult patients who were diagnosed with mPDAC and received treatment between January 2015 and March 2020. Patient characteristics and DOT were assessed. Opioid use during treatment including the number of prescriptions filled and average daily dose in morphine equivalents were summarized. Yearly and regional trends of opioid use were assessed. **Results:** There were 2,841 patients (median age: 61 years, IQR: 56-66) included in the study treated with first line (1L) therapies of interest. 55.6% (n = 1,579) of patients were male and 72.0% (2,046) had commercial insurance. The overall DOT in 1L was 78 days (IQR: 38 – 157). 54.3% of patients filled at least one prescription for opioids during treatment. The mean number of prescriptions filled during treatment was 2.2 (SD: 4.0) and the mean daily dose was 39.5mg morphine equivalents (SD: 134.6) The median DOT among patients who received at least one pain prescription was 92 days (IQR: 44 – 176) while those who did not receive pain medication experienced a DOT of 64 days (IQR: 29 – 135). Among the 1,248 patients who received second line treatment the median DOT was 60.5 days (IQR: 29 – 127). 50.6% (n = 632) filled at least one opioid

prescription during treatment. Median DOT among patients who received pain medication was 73.5 days (IQR: 42 – 141) and 47.5 days (IQR: 15 – 103.5) among those who did not. Across lines of therapy opioid use remained stable during the study period ranging from 54.2% among patients treated in 2015 to 51.1% among those who initiated treatment in 2019. No regional differences were observed in prescription patterns within the four US census regions (range: 50.2 – 54.4%). **Conclusions:** In this real-world cohort of patients with mPDAC nearly half were prescribed at least one opioid during treatment. Patients who received opioids experienced a longer duration of therapy compared to those who did not. Further studies are needed to understand the association of pain control with improved clinical outcomes among patients with mPDAC.

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GASTROINTESTINAL CANCER—GASTROESOPHAGEAL, PANCREATIC, AND HEPATOBILIARY

Real-world overall survival of patients diagnosed with recurrent versus de novo metastatic pancreatic ductal adenocarcinoma (PDAC).

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Abstract

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Background: PDAC is a lethal malignancy which accounted for the third most cancer related deaths in 2020. Patients (pts) who are initially diagnosed with stage I-III PDAC have a 5-year relative survival of 13.3 – 39.4%; those with metastatic disease at diagnosis have a 5-year relative survival of 2.9%. Limited data are published comparing the outcomes of pts with stage I-III who develop metastases (recurrent) compared to pts with de novo mPDAC (de novo). This analysis seeks to compare demographic, clinical characteristics, and survival outcomes of pts with recurrent versus de novo mPDAC in a community oncology setting. **Methods:** Using the Flatiron Health database, a retrospective observational study was conducted abstracting deidentified data from ≥280 US cancer clinics. Pts with mPDAC diagnosed from 01/2016 to 08/2020 with a known stage at initial diagnosis were included. Pts were stratified based on initial stage at diagnosis. Median overall survival (OS) from time of metastasis was derived using Kaplan-Meier analysis. Unadjusted and multivariable Cox proportional hazards models were used to compare survival between recurrent and de novo cohorts. **Results:** N = 6,543 pts analyzed; 70.1% (n = 4,586) had de novo mPDAC and 29.9% (n = 1,957) had recurrent mPDAC. Median age at time of metastasis was similar for both cohorts: 69 years (IQR: 62 – 76). The most common site of primary tumor location was head for both cohorts (recurrent mPDAC: 69.8%; de novo mPDAC: 40.3%). Approximately 45% of pts with recurrent mPDAC underwent a Whipple procedure (pre diagnosis of metastasis). A similar proportion of pts in both cohorts received treatment in the metastatic setting (recurrent mPDAC: 74.3%; de novo mPDAC: 77.3%). Pts with recurrent mPDAC had a longer median OS compared to the de novo cohort: 8.0 months (95% CI: 7.5 – 8.6) versus 6.1 (95% CI:

5.7 – 6.4) [unadjusted hazard ratio (HR): 0.79 (95% CI: 0.74 – 0.84); adjusted HR: 0.73 (0.68 – 0.78), p < 0.0001]. **Conclusions:** The results of this real-world study indicate that pts with recurrent mPDAC are more likely to have a head primary and to experience longer OS from time of metastasis than those with de novo mPDAC. These data suggest stratification for clinical trial enrollment for recurrent vs de novo is necessitated.

Lillie D Shockney RN et al., PracticeUpdate(US), 2019

308 Indirect treatment comparison of nivolumab versus placebo as adjuvant treatment for melanoma
Jeffrey Weber et al., Jitc, 2020

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GASTROINTESTINAL CANCER—GASTROESOPHAGEAL, PANCREATIC, AND HEPATOBILIARY

Impact of the COVID-19 pandemic on care delivery and outcomes for patients with metastatic pancreatic ductal adenocarcinoma (mPDAC).

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Abstract Disclosures

Abstract

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Background: The coronavirus disease 2019 (COVID-19) pandemic has caused abrupt changes to the US health system and disruption in cancer care delivery. Little has been reported on the impact of COVID-19 on patients with mPDAC and the care delivery. Our study aimed to characterize the impact of COVID-19 on healthcare utilization and outcomes for patients with mPDAC in the US in the community oncology setting. **Methods:** We performed a retrospective cohort study of adult patients diagnosed with mPDAC between March – September 2019 and March – September 2020 using the nationwide Flatiron Health EHR database, comprising data from over 280 (largely community based) cancer clinics. Patients were stratified into two cohorts based on the year of diagnosis (2019 vs. 2020). Clinical characteristics were summarized including age at metastatic diagnosis, stage at initial diagnosis, and ECOG performance score (PS). Overall survival (OS) from metastatic diagnosis was estimated using Kaplan-Meier methods. A sensitivity analysis limiting the follow-up time to November of each year was conducted. **Results:** Overall, 1,719 patients were included in the study (2019: n = 923, 2020: n = 796); both cohorts had similar demographic compositions in terms of age and sex (2019: median age = 70 (IQR: 62 – 76), 52.2% male; 2020: median age = 70 [IQR: 62 – 76], 53.5% male). In 2020, the number of newly diagnosed mPDAC patients decreased by 13.8% compared to 2019. A slightly higher proportion of patients were initially diagnosed with stage IV disease in 2020 (69.7%) vs 2019 (62.3%). A similar proportion of patients with ECOG PS 0-1 was observed between the two cohorts (2019: 48.5%; 2020: 47.9%). The number of visits recorded within the first 90 days after metastatic diagnosis was similar between the two cohorts (2019: median 8 [IQR: 3 – 14]; 2020: median 9 [IQR: 4 – 14]). For

both cohorts, the proportion of patients who received 1L treatment was similar (2019: 75.8%; 2020: 76.5%), and the most common 1L treatment regimen was gemcitabine plus nab-paclitaxel (2019: 37.6%; 2020: 40.9%). Of the 1L treated populations, 37.6% of patients diagnosed in 2019 received second line (2L) compared to 17.9% of the 2020 cohort; 16.9% of 1L treated patients in 2019 received 2L in the sensitivity analysis. Patients diagnosed in 2020 had a significantly lower median OS of 6.1 months (95% CI: 5.4 – 6.9) compared to patients diagnosed in 2019: 8.4 months (7.5 – 9.0) ($p < 0.001$). **Conclusions:** During the COVID-19 pandemic era, the diagnoses of de novo mPDAC appears to have been impacted, with a higher number of patients diagnosed with advanced stage at presentation. Our analysis suggests that while patients diagnosed in 2020 received a similar level of care as those in 2019, their survival outcomes were adversely affected. Further research is necessary to characterize the impact of the COVID-19 pandemic on cancer care and outcomes.

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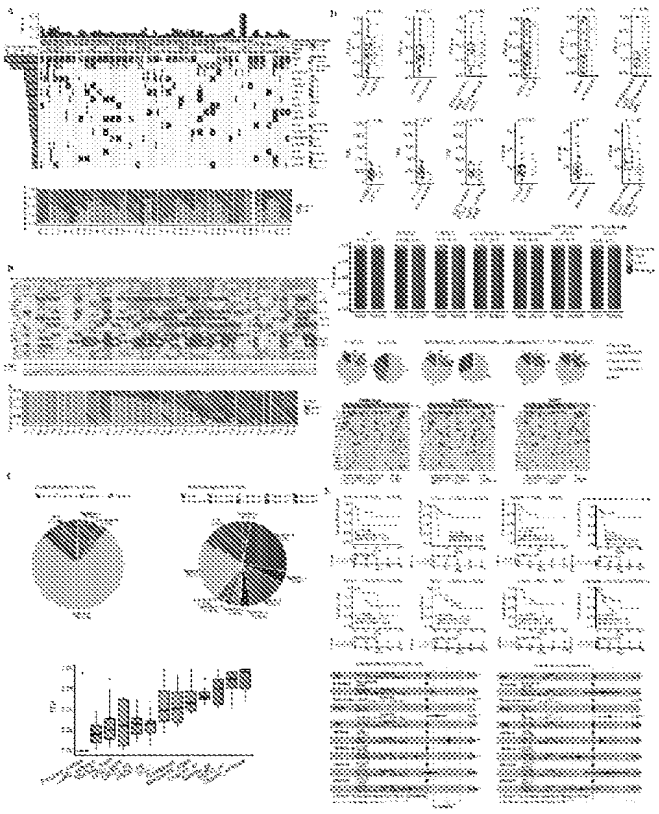
exhibited somatic copy number variation (CNV) across all patients. Using CNV ITH, an average of 0.49 (range 0.22~1 per sector) was found in SCLC (Fig.1B). The age-associated, tobacco-associated, and aflatoxin-associated signatures were major mutational signatures in these patients (Fig.1C). We found a medium mutational heterogeneity (0.50, range 0.22~1) in our SCLC cohort, in contrast to low ITH in previous reported NSCLC and LUAD cohort (Fig.1C). Combined SCLC patients behaved in much the same way as pure SCLC patients, both in terms of mutation distribution, ITH, TMB, mclone (number of tumor molecular clones) and gene signatures (Fig. 1D). This condition is also present in smoker patients and those with EGFR mutations. A higher CNV ITH was observed in stage I-II of SCLC than stage III ($p < 0.001$) (Fig.1E). Less mClone were associated with better DFS of SCLC (Fig. 1E).



Conclusion: Despite moderate mutation burden, SCLC showed a medium intratumoral heterogeneity with high genomic instability. CNV exhibited a high heterogeneity at early stage and mclone may serve as a prognostic biomarker for SCLC. **Keywords:** SCLC, heterogeneity, multi-regional exome sequencing

FP10.04
RESILIENT Part 1: Safety and Efficacy of Second-Line Liposomal Irinotecan in Patients with Small Cell Lung Cancer

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Introduction: Many patients with small cell lung cancer (SCLC) develop drug resistance to first-line platinum-based chemotherapy, and second-line therapies are limited. RESILIENT (ClinicalTrials.gov identifier NCT03088813) is a two-part phase 2/3 study assessing the safety, tolerability and efficacy of liposomal irinotecan monotherapy as second-line treatment for patients with SCLC. Here we report data from part 1 of the RESILIENT study (data cut off, 2 December 2019). **Methods:** RESILIENT part 1 was an open-label, single-arm study comprising dose-exploration and dose-expansion phases. Eligible patients with SCLC were aged ≥ 18 years, had progressed with platinum-based first-line therapy, had an Eastern Cooperative Oncology Group performance status score of 0 or 1, and had adequate organ function; prior exposure to immunotherapy was permitted. During dose exploration, participants received liposomal irinotecan 85 mg/m^2 or 70 mg/m^2 free base administered every 2 weeks; the identified recommended dose was used during dose expansion. Primary endpoints were safety and tolerability. Efficacy assessments included objective response rate (ORR), best overall response (BOR), progression-free survival (PFS), and overall survival (OS). **Results:** In total, 30 patients received liposomal irinotecan in RESILIENT part 1 (women, 56.7%; median age, 61.5 years). During dose exploration, four patients who received liposomal irinotecan 85 mg/m^2 experienced dose limiting toxicities, including diarrhea (n = 3) and abnormal liver function test (n = 1). Thus, this dose was not considered tolerable and enrollment into the 70 mg/m^2 cohort was initiated; a total of 25 patients (platinum resistant, 40%) received liposomal irinotecan 70 mg/m^2 (dose exploration, 12 patients; dose expansion, 13 patients). Among the 25 patients who received the recommended dose of 70 mg/m^2, 40% had one or more grade ≥ 3 treatment-related treatment-emergent adverse events (TEAEs), most commonly diarrhea (20%), neutropenia (16%), and anemia, thrombocytopenia, asthenia and abdominal sepsis (each 8%); 8% of patients discontinued treatment owing to TEAEs. Median (95% CI) PFS was 3.98 (1.45–4.24) months and OS was 8.08 (5.16–9.82) months. ORR (complete response + partial response) was 44% and BOR was: complete response, 4%; partial response, 40%; stable disease, 28%; progressive disease, 20%; non-evaluable, 8%.Thirty patients were treated in RESILIENT part 1. Full results to be presented in the updated abstract. **Conclusion:** In participants with SCLC who had progressed with platinum-based first-line therapy, liposomal irinotecan at the recommended dose of 70 mg/m^2 showed promising antitumor activity and safety findings were aligned with the known safety profile. RESILIENT part 2, an ongoing, phase 3, randomized controlled trial versus topotecan will provide further data regarding the efficacy and safety of liposomal irinotecan 70 mg/m^2 for the second-line treatment of patients with SCLC. **Keywords:** small-cell lung cancer, RESILIENT, liposomal irinotecan

FP10.05
A Prospective Phase II Study of Apatinib Plus Chemotherapy for Pretreated Patients With Advanced Small Cell Lung Cancer

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Introduction: Small-cell lung cancer (SCLC), which accounts for ~15% of all lung cancers, is characterised by its rapid proliferation. The clinical outcomes of second-line and above treatments are unsatisfactory, resulting in a median progression-free survival (PFS) of less than

tremelimumab + EP were significantly higher than EP (odds ratio 7.21, 95% credible interval 1.82, 52.47). **Conclusion:** The combination of ICIs and EP as first-line therapy for patients with untreated ES-SCLC significantly improved clinical outcomes. The regimen of nivolumab + EP was associated with the greatest survival benefits, but with higher grade 3-4 adverse events. **Keywords:** Immunotherapy, small-cell lung cancer, first-line

P48.14

RESILIENT Part 2: A phase 3 Study of Liposomal Irinotecan in Patients with Small-Cell Lung Cancer in the Second-Line Setting

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Introduction: Small cell lung cancer (SCLC) accounts for approximately 15% of lung cancers. SCLC is usually sensitive to established first-line therapies, but many patients relapse and develop resistance to platinum-based first-line treatment. Currently, the topoisomerase 1 inhibitor topotecan is the only approved second-line therapy for SCLC in the USA and Europe. Liposomal irinotecan is an intravenous formulation that encapsulates the topoisomerase 1 inhibitor irinotecan in a lipid-bilayer vesicle, leading to prolonged circulation. The safety, tolerability and efficacy of liposomal irinotecan monotherapy in patients with SCLC who progressed with platinum-based first-line therapy is being evaluated in RESILIENT (NCT03088813), a two-part phase 2/3 study. Preliminary data from the dose-ranging part of the study (part 1) indicated that liposomal irinotecan 70 mg/m^2 (free base equivalent) administered every 2 weeks was well tolerated and had promising antitumour activity.[1] Here, we present the design of RESILIENT part 2, which will assess the efficacy and safety of liposomal irinotecan versus topotecan in the same patient population. **References:** Paz-Ares L *et al.* Poster presented at the 2019 American Society of Clinical Oncology conference, May 31—June 4, 2019, Chicago, IL, USA. **Methods:** RESILIENT part 2 is a phase 3, open-label study with a planned sample size of 450. Participants are randomized 1:1 to intravenous liposomal irinotecan or intravenous topotecan. Liposomal irinotecan is administered at 70 mg/m2 every 2 weeks and topotecan is administered at 1.5 mg/m2 for 5 consecutive days every 3 weeks. A total of 254 patients have been randomized and received treatment to date (as of August 8, 2020). Tumour assessments are performed using the Response Evaluation Criteria in Solid Tumors version 1.1 and the Response Assessment in Neuro-oncology criteria for CNS lesions. Improvements in symptoms are measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13. Safety assessments include monitoring for adverse events. Overall survival is the primary endpoint of the study. Progression-free survival, objective response rate and proportion of patients reporting symptom improvement are secondary endpoints. Participants will continue study treatment until disease progression, unacceptable toxicity or study withdrawal. Participants will be followed for survival until death or study end, which is when all patients have died, withdrawn consent or are lost to follow-up. **Results:** Conclusion **Keywords:** liposomal irinotecan, small-cell lung cancer, RESILIENT

P48.15

A Case from a Single-Arm, Phase Two, Open Label Study Assessing Sindilimab Plus Metaformin in Chemotherapy Failed PD-L1 Positive Advanced SCLC

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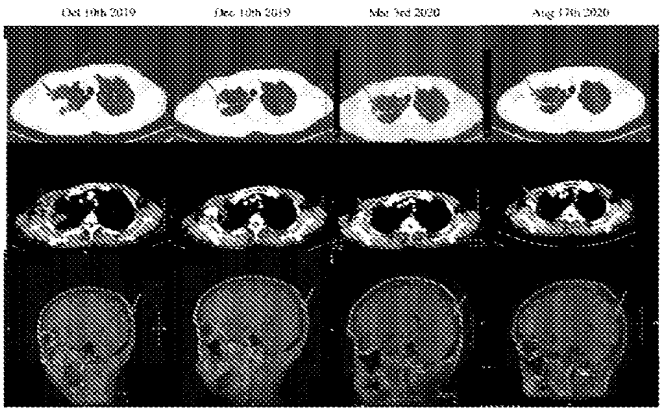
Introduction: Small cell lung cancer (SCLC) is relatively difficult in treatment and poor in prognosis. However immune checkpoint inhibitor (ICI) plus platinum based chemotherapy rewrote the SCLC NCCN guideline for the first time in past 2 decades. Metaformin is an oral tablets for type 2 diabete and was found to have potential anticancer effects through regulating T cell function, tumor oxygen consumption and AMPK pathway. Here we evaluated the efficacy and safety of ICI Sindilimab plus metaformin in chemotherapy failed PD-L1 positive SCLC. **Methods:** This single arm, phase two, open label study aimed to recruit SCLC patients failed standard first-line platinum-based or lines of chemotherapy. Tumor sample was required positive in PD-L1 expression (22C3, both tumor cells and stroma evaluated) . Sindilimab was administrated 200mg Q3w, metaformin was added at 500mg Bid on day 22, escalating to 1000mg Bid on day 29, until progression of disease, unbearable toxicity or receive one year treatment at most. The primary endpoint was objective response rate and second endpoints were progression free survival (PFS), overall survival (OS) and duration of response (DoR). This trial has been registered on ClinicalTrial.gov, NCT03994744, is ongoing. **Results:**



From Aug. 2019 to Mar. 2020, 8 in 40 (20%) SCLC patients were positive for PD-L1 expression, only two patients met the inclusion criteria and received Sindilimab and metaformin (S+M) treatment. One of these two patient (P004) showed favorable response. P004 was diagnosed with stage IVb SCLC and received EP chemotherapy with 8 month PFS. When assessed PD, he complained of back pain and CT scan showed a mass on

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LATE-BREAKING ABSTRACTS AND DEFERRED PUBLICATIONS

BILIARY TRACT CANCER, INCL. CHOLANGIOCARCINOMA

LBA10 **Nal-IRI with 5-fluorouracil (5-FU) and leucovorin or gemcitabine plus cisplatin in advanced biliary tract cancer: Final results of the NIFE-trial (AIO-YMO HEP-0315), a randomized phase II study of the AIO biliary tract cancer group**

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Background: Survival and treatment options in advanced biliary tract cancer (BTC) are limited with the current standard of care gemcitabine/cisplatin. The NIFE study examined nanoliposomal-irinotecan (nal-IRI)/5-FU/leucovorin (LV) as an alternative 1st-line treatment option in advanced BTC.

Methods: NIFE is a prospective, randomized, two-sided, phase II study. Advanced BTC patients were randomized (1:1) to receive either nal-IRI/5-FU/LV (arm A) or gemcitabine/cisplatin (arm B) with a stratification for tumor site (intrahepatic vs. extrahepatic), sex and ECOG (0 vs. 1). Arm A was planned as a Simon's optimal two-stage design and arm B served as an internal control for selection bias. As primary endpoint a 4 months (mo) progression free survival (PFS) rate ≥50% in the ITT-population was defined.

Results: Between 01/2018-09/2020 93 patients were randomly assigned in 21 German centers. Two patients violating inclusion criteria had to be excluded from the ITT population (n=91) due to inappropriate randomization. The NIFE trial met its primary endpoint with a PFS-rate of 51% at 4mo in the ITT population (arm A). Median PFS in arm A was 5.98mo (2.37-9.59) and in arm B 6.87mo (2.46-7.82). Provisional median overall survival (mOS) was 15.9mo (10.58-21.85) in arm A and 13.63mo (6.51-17.68) in arm B with ongoing follow-up at data closesure. Median PFS in intrahepatic (ICCA) vs. extrahepatic (ECCA) cholangiocarcinoma was 3.45mo (2.10-6.05) vs. 9.59mo (1.94-15.67) in arm A and 7.72mo (6.05-9.46) vs. 1.76mo (0.16-6.87) in arm B. Corresponding mOS times were ICCA 14.19/ECCA 18.23mo in arm A and ICCA 16.36/ECCA 6.34mo in arm B.

Conclusions: In the phase II NIFE trial nal-IRI/5-FU/LV showed efficacy as 1st-line treatment of advanced BTC with no new safety findings. ECCA and ICCA responded differently to drug interventions, with a clear benefit for nal-IRI/5-FU/LV in ECCA.

Clinical trial identification: AIO-YMO HEP-0315 (NIFE); EudraCT 2016-002467-34; NCT03044587.

Legal entity responsible for the study: AIO-Studien GmbH.

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Disclosure: M. Sinn: Financial Interests, Personal, Advisory Board: BMS; Financial Interests, Personal, Advisory Board: Incyte; Financial Interests, Personal, Advisory Board: Pfizer; Financial Interests, Personal, Advisory Board: AstraZeneca; Financial Interests, Personal, Advisory Board: Servier; Financial Interests, Personal, Advisory Board: Amgen; Financial Interests, Personal, Advisory Board: MSD; Financial Interests, Personal, Advisory Board: Sanofi. T.O. Goetze: Financial Interests, Personal, Advisory Board: Lilly; Financial Interests, Personal, Advisory Board: MSD Sharp Dohme; Financial Interests, Personal, Advisory Board: Bayer; Financial Interests, Personal, Advisory Board: Celgene; Financial Interests, Personal, Advisory Board: Servier; Financial Interests, Personal, Advisory Board: Roche; Financial Interests, Personal, Advisory Board: Ipsen; Financial Interests, Personal, Invited Speaker: Lilly; Financial Interests, Personal, Invited Speaker: MCI; Financial Interests, Personal, Invited Speaker: MSD Sharp Dohme; Financial Interests, Personal, Research Grant: AstraZeneca; Financial Interests, Personal, Research Grant: Incyte; Financial Interests, Personal, Research Grant: Lilly. D. Waldschmidt: Financial Interests, Personal, Advisory Board: AstraZeneca; Financial Interests, Personal, Advisory Board: Bayer; Financial Interests, Personal, Advisory Board: BMS; Financial Interests, Personal, Advisory Board: Celgene; Financial Interests, Personal, Advisory Board: Eisai; Financial Interests, Personal, Advisory Board: Incyte; Financial Interests, Personal, Advisory Board: Ipsen; Financial Interests, Personal, Advisory Board: Falk; Financial Interests, Personal, Advisory Board: MSD; Financial Interests, Personal, Advisory Board: Novartis; Financial Interests, Personal, Advisory Board: Roche; Financial Interests, Personal, Advisory Board: Servier; Financial Interests, Personal, Advisory Board: Shire Baxalta; Financial Interests, Personal, Advisory Board: Sirtex. T. Seufferlein: Financial Interests, Personal, Advisory Board: Sanofi; Financial Interests, Personal, Advisory Board: Pierre Fabre; Financial Interests, Personal, Advisory Board: Pfizer; Financial Interests, Personal, Advisory Board: Baxalta; Financial Interests, Personal, Advisory Board: Servier; Financial Interests, Personal, Speaker's Bureau: Sanofi; Financial Interests, Personal, Speaker's Bureau: Pierre Fabre; Financial Interests, Personal, Speaker's Bureau: Pfizer; Financial Interests, Personal, Speaker's Bureau: Baxalta; Financial Interests, Personal, Speaker's Bureau: Servier; Financial Interests, Personal, Research Grant: Boehringer; Financial Interests, Personal, Research Grant: Sanofi; Financial Interests, Personal, Research Grant: Celgene; Financial Interests, Personal, Research Grant: Amgen. T.J. Ettrich: Financial Interests, Personal, Advisory Board: AstraZeneca; Financial Interests, Personal, Advisory Board: Roche; Financial Interests, Personal, Advisory Board: Bayer; Financial Interests, Personal, Advisory Board: Amgen; Financial Interests, Personal, Advisory Board: MSD; Financial Interests, Personal, Invited Speaker: MSD; Financial Interests, Personal, Advisory Board: Merck; Financial Interests, Personal, Advisory Board: Ipsen; Financial Interests, Personal, Invited Speaker: Ipsen; Financial Interests, Personal, Advisory Board: Sanofi Aventis; Financial Interests, Personal, Invited Speaker: Eisai; Financial Interests, Personal, Advisory Board: Pierre-Fabre Pharma; Financial Interests, Personal, Advisory Board: Incyte; Financial Interests, Personal, Advisory Board: Lilly; Financial Interests, Personal, Advisory Board: Bristol Myers Squibb; Financial Interests, Institutional, Research Grant: Servier; Financial Interests, Institutional, Research Grant: Sanofi Aventis; Financial Interests, Institutional, Research Grant: Celgene. All other authors have declared no conflicts of interest.

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Table: LBA10

	ITT (n=91)	
	Arm A (n=49) Nal-IRI/5-FU/LV	Arm B (n=42) Gemcitabine/cisplatin
PFS rate at 4mo	51.0% ICCA (n=34) 41.2% ECCA (n=15) 73.3%	59.5% ICCA (n=32) 71.9% ECCA (n=10) 20.0%
mPFS	5.98mo (95% CI 2.37-9.59) ICCA (n=34) 3.45mo (95% CI 2.10-6.05) ECCA (n=15) 9.59mo (95% CI 1.94-15.67)	6.87mo (95% CI 2.46-7.82) ICCA (n=32) 7.72mo (95% CI 6.05-9.46) ECCA (n=10) 1.76mo (95% CI 0.16-6.87)
mOS	15.9mo (95% CI 10.58-21.85) ICCA (n=34) 14.19mo (95% CI 7.69-21.85) ECCA (n=15) 18.23mo (95% CI 8.67-30.95)	13.63mo (95% CI 6.51-17.68) ICCA (n=32) 16.36mo (95% CI 7.46-19.91) ECCA (n=10) 6.34mo (95% CI 0.16-NE)
ORR	24.5%	11.9%
DCR at 2mo	57.1%	57.1%

ICCA: intrahepatic CCA, ECCA: Extrahepatic CCA, NE: not estimable

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GASTROINTESTINAL CANCER—GASTROESOPHAGEAL, PANCREATIC, AND HEPATOBILIARY

A phase II, open-label pilot study evaluating the safety and activity of liposomal irinotecan (Nal-IRI) in combination with 5-FU and oxaliplatin (NALIRIFOX) in preoperative treatment of pancreatic adenocarcinoma (NEO-Nal-IRI study) (NCT03483038).

Sherise C. Rogers, Brian Hemendra Ramnaraign, Kathryn Hitchcock, Steven J. Hughes, Ji-Hyun Lee, Z. Hugh Fan, Carmen Joseph Allegra, Jose Trevino, Ahmad El-Far, Anita Ahmed Turk, Karen Bullock Russell, David L. DeRemer, Thomas J. George

University of Florida/UF Health Cancer Center, Gainesville, FL; University of Florida, Gainesville, FL; NSABP/NRG Oncology, and The University of Florida Health, Gainesville,

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Abstract Disclosures

Abstract

TPS4170

Background: Neoadjuvant treatment for potentially curable pancreatic cancer (PDAC) is increasing in acceptability, but a standard regimen has yet to be established. Multiple studies have demonstrated feasibility and effectiveness of the FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin and irinotecan) regimen in the perioperative setting. However, FOLFIRINOX often requires dose modifications, delays and growth factor support due to excessive toxicity which can complicate care delivery when given neoadjuvantly. Liposomal irinotecan injection (Nal-IRI) is FDA approved with a well-tolerated safety profile in relapsed, refractory metastatic PDAC. The current study aims to substitute Nal-IRI for traditional irinotecan in the standard FOLFIRINOX regimen (NALIRIFOX) and to demonstrate safe and effective neoadjuvant delivery. **Methods:** This phase 2, open-label, multicenter single-arm study focuses on patients (pts) with operable PDAC without metastatic disease. Other key eligibility criteria include age ≥18 years, resectability confirmed by multiD GI tumor board (resectable vs. borderline), adequate cardiac, renal, hepatic function and ECOG performance status of 0 to 1. Pts receive NALIRIFOX regimen as per the table every 2 weeks for four months followed by disease reassessment. Pts who remain surgical candidates will undergo surgical resection

within 4 to 8 weeks following last dose of therapy. The primary endpoint is to assess safety and feasibility of regimen in perioperative setting. Secondary endpoints include R0 resection rate, clinical, biochemical and radiological response rate and patient-reported quality of life during treatment as measured by the NCI validated FACT-G scale. Enrollment continues to a maximum of 28 evaluable pts to demonstrate a reduction in historical 30 day postoperative complication rate. NCT03483038. NALIRIFOX regimen components given intravenously (IV) every 14 days. Clinical trial information: NCT03483038.

Agent	Dose	Route/Duration
Nal-IRI	50 mg/m^2	IV over 90 minutes
Oxaliplatin	60 mg/m^2	IV over 120 minutes
Leucovorin	400 mg/m^2	IV over 120 minutes
5-fluorouracil infusion	2400 mg/m^2	IV continuous infusion for 46 hours

328 Phase 3 study of olaparib ± bevacizumab versus bevacizumab + fluorouracil in patients with unresectable or metastatic colorectal cancer not progressing on first-line FOLFOX + bevacizumab (LYNK-003)

Carlos Mayo et al., Jitc, 2020

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PANCREATIC CANCER

Real-world study of treatment patterns and outcomes among patients with metastatic pancreatic ductal adenocarcinoma (PDAC) in Europe.

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France; Servier Pharmaceuticals, Boston; Department of Medicine I, Hospital of the University Ulm, Ulm, Germany; Hospital Universitario Vall d'Hebron, Barcelona, Spain

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Abstract Disclosures

Abstract

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Background: Few data are available regarding real-world treatment patterns and outcomes for metastatic PDAC (mPDAC) in Europe. **Methods:** This retrospective, observational, chart-review study involved medical oncologists and gastroenterologists from France, Germany, Italy, Spain, and the UK. Physicians completed online patient (pt) reports for 20 consecutive pts diagnosed with PDAC between 01 and 10/2016. Here, the analysis is focused on treated pts diagnosed with mPDAC. Reports provided information on general disease and pt characteristics, diagnosis, and treatment of metastatic disease. Outcomes included median PFS and OS according to each line of metastatic therapy. In addition, how baseline performance status (PS) and treatment sequence affected OS and PFS were assessed. **Results:** 304 physicians (France [n=62], Germany [n=60], Italy [n=63], Spain [n=66], UK [n=53]) participated and enrolled 6,000 pts with PAC, of whom 3827 had mPDAC. Of the 3827, 3432 were treated for their metastatic disease. The most common first-line therapies were modified FOLFIRINOX (28.4%), gemcitabine + nab-paclitaxel (28.0%), and gemcitabine monotherapy (23.0%), while the most common second-line therapies were gemcitabine monotherapy (25.0%), 5-FU + oxaliplatin (21.8%), and gemcitabine + nab-paclitaxel (16.7%). The longest median PFS and OS were obtained when using mFOLFIRINOX as first-line therapy, with gemcitabine-based combinations as second-line therapy. However, pt characteristics were more favorable with

FOLFIRINOX compared with the other regimens used in first line. The most common treatment in first line for patients with a worse baseline PS (PS >1) was gemcitabine monotherapy (571 patients [46%]); in addition, having a worse baseline PS was predictive of shorter survival in second line. The most common reason for discontinuation of either line was disease progression. The study showed that the choice of first- and second-line treatment among European physicians is in accordance with current ESMO guidelines; in contrast, the choice of subsequent line was more heterogeneous, according to local practices. Additional data concerning first and second line OS and PFS per treatment regimen will be presented at the meeting. **Conclusions:** This large real-life study highlights a clear picture of treatment patterns in European real-world clinical practice and outcomes for metastatic PDAC, which may help in more effectively managing such patients in the future. Further univariate and multivariate analysis will complete this first description.

Research Sponsor:

Baxalta/Shire and Servier.

non–small cell lung cancer and a poor performance status
Joao V Alessi et al., jitc, 2020

Response to FOLFIRINOX neoadjuvant chemotherapy is associated with a high prevalence of Tbet expressing T cells in pancreatic cancer patients

Hui Peng et al., J Immunol, 2020

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SO-3 Treatment sequences and prognostic factors in metastatic pancreatic ductal adenocarcinoma: Univariate and multivariate analyses of a real-world study in Europe

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Background: As real-world data are limited concerning treatment sequences and prognostic factors for metastatic pancreatic adenocarcinoma (mPAC) in Europe, univariate and multivariate analyses of this retrospective, observational, chart-review study were performed to assess treatment patterns/sequences as well as outcomes. Here, we report on treatment sequencing and data from the multivariate analysis.

Methods: This study involved medical oncologists and gastroenterologists from France, Germany, Italy, Spain, and the UK who completed online patient reports for 20 consecutive patients diagnosed with PAC between January and October 2016 (n=6000), where the focus of this analysis was on those patients who were diagnosed with mPAC (n=3827). Reports provided information on treatment sequences of mPAC and how treatment sequences affected overall survival (OS). Univariate analysis and multivariate Cox regression of OS were also done on patients treated with one of six first- and second-line (1L+2L) treatment sequences of interest (n=915) to determine some prognostic factors. The treatment (trt) sequences were as follows: (trt1) gemcitabine + nab-paclitaxel followed by fluoropyrimidine combinations (n=286); (trt2) (m)FOLFIRINOX followed by gemcitabine combinations (n=263); (trt3) (m) FOLFIRINOX followed by gemcitabine monotherapy (n=228); (trt4) gemcitabine + nab-paclitaxel followed by fluoropyrimidine monotherapy (n=65); (trt5) gemcitabine monotherapy followed by fluoropyrimidine monotherapy (n=41); (trt6) gemcitabine monotherapy followed by fluoropyrimidine combinations (n=32).

Results: Of the patients with mPAC at diagnosis, 89.7% (3432) received a first-line (1L) treatment, with 35.5% (1218) receiving a second-line (2L) and 6.7% (229) a third-line. In terms of treatment sequencing (1L+2L), the most common sequences were (i) gemcitabine + nab-paclitaxel followed by fluoropyrimidine combinations (24%); (ii) modified (m)FOLFIRINOX followed by gemcitabine combinations (22%); and (iii) (m) FOLFIRINOX followed by gemcitabine monotherapy (19%). The patient characteristics were more favorable with (m)FOLFIRINOX compared with the other regimens used in first line. The median OS was 19.1 months for (m)FOLFIRINOX followed by gemcitabine combinations, 15.2 months for gem/nab-P followed by fluoropyrimidine combinations and 14.8 months for (m)FOLFIRINOX followed by gemcitabine monotherapy. Based on data from the univariate analysis, treatment, age, sex, body mass index, disease grade, liver metastases, lung metastases, comorbidities, tumour location, performance status (PS) and CA19-9 were selected as candidates for the multivariate analysis. The multivariate analysis showed that prognostic factors were (i) liver metastases (no vs yes: HR=0.397; $p < 0.0001$); (ii) treatments (1L+2L) ($p < 0.0001$) (trt2 vs 5: HR=0.424; trt1 vs 5: HR=0.601; trt4 vs 5: HR=0.645; trt3 vs 5: HR=0.665; trt6 vs 5: HR=0.787); (iii) PS (ECOG 0-1 vs $\geq$2: HR=0.448; $p < 0.0001$), (iv) CA19-9 ($<$ 400 U/ml [n=376] vs $\geq$400 [n=468]: HR=0.747; p=0.0004); (v) lung metastases (no vs yes: HR=0.789; p=0.0049) and (vi) sex (male [n=508] vs female [n=336]: HR=0.828; p=0.0228).

Conclusions: This large real-life study highlighted a clear picture of treatment sequences (first line followed by a second line) in European real-world clinical practice and outcomes for patients with mPAC. Treatment sequences were in accordance with the ESMO guidelines at the time of the study. Liver metastases, treatment sequences, PS, CA19-9, lung metastases and sex were significant independent prognostic factors of OS in this study.

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SO-4 Progression-free survival in patients with cholangiocarcinoma with FGFR2 fusions or rearrangements: A FIGHT-202 post-hoc analysis of prior systemic therapy response

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Background: Most cholangiocarcinoma (CCA) patients are diagnosed with advanced disease and are ineligible for surgery. First-line, standard-of-care therapy for patients with advanced/metastatic CCA not amenable to surgery is gemcitabine plus cisplatin. FGFR2 fusions or rearrangements are oncogenic drivers of CCA and are almost exclusive to intrahepatic CCA (iCCA; prevalence, 10—15%). However, the role of this alteration and how it impacts patient response to systemic therapy remains uncharacterized. FIGHT-202 is a phase 2 study of pemigatinib (a selective, potent, oral fibroblast growth factor receptor [FGFR]1—3 inhibitor) in patients with locally advanced or metastatic CCA with or without FGF/FGFR genomic alterations who progressed on $\geq$1 prior therapy (NCT02924376; Abou-Alfa et al. Lancet Oncol 2020;21:671—84). This post-hoc analysis evaluated progression free survival (PFS) to standard systemic therapy before FIGHT-202 study enrollment, in patients with CCA harboring FGFR2 fusions or rearrangements (FGFR2+).

Methods: In FIGHT-202, patients with locally advanced/metastatic CCA with documented disease progression following $\geq$1 previous systemic therapy were assigned to cohorts based on the presence and type of FGF/FGFR alterations. For this analysis, electronic case report forms from patients with FGFR2+ CCA enrolled in FIGHT-202 were reviewed to determine disease history and exposure to prior lines of systemic cancer therapies (LOSCT) in the advanced setting before receiving pemigatinib. Only patients with sufficient data on prior LOSCT were included in this analysis. Median PFS was calculated using the Kaplan-Meier method, defined as the date of initiation of that LOSCT until the date of progression.

Results: For the 108 patients with FGFR2+ CCA included in this analysis (April 2020 datacut), previous systemic therapy before pemigatinib most commonly included pyrimidine analogues (99.1%) or platinum compounds (96.3%), 99% had iCCA, median age was 55.5 years, and 61% were female. Median PFS on first-line therapy received prior to FIGHT-202 enrollment was 5.6 (95% confidence interval [CI]: 4.0, 8.3) months (n=104). Median PFS on second-line therapy received prior to FIGHT-202 enrollment was 4.4 (95% CI: 3.0, 5.3) months (n=40). For patients who had progressed after only 1 line of prior therapy and then received pemigatinib second-line during FIGHT-202, median PFS was 7.0 (95% CI: 4.9, 11.1) months (n=65). Median PFS on third-line therapy received prior to FIGHT-202 enrollment was 6.6 (95% CI: 2.7, 9.7) months (n=13). For patients who had progressed after 2 lines of prior therapies and then received pemigatinib third-line during FIGHT-202, median PFS was 8.9 (95% CI: 4.9, 13.1) months (n=30).

Conclusions: This post-hoc analysis provides data about PFS on standard systemic therapies received before pemigatinib for patients with FGFR2+ CCA. The short PFS on these standard therapies in patients with FGFR2+ CCA highlights the need for development of other options including targeted therapies to improve outcomes. Median PFS on second- or third-line pemigatinib for FGFR2+ CCA was longer than second- or third-line systemic therapy received prior to FIGHT-202 enrollment. Limitations of this analysis include retrospective examination of investigator reported data and small patient numbers for some analyses.

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PDB13
A COST OF CONTROL ANALYSIS OF LIRAGLUTIDE VERSUS OTHER ANTI-DIABETIC THERAPIES IN THE TREATMENT OF PATIENT WITH TYPE 2 DIABETES IN CHINA

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Objectives: The aim was to evaluate the cost of control for achieving composite treatment goals of blood glucose, weight and hypoglycaemia with liraglutide 1.2 mg once-daily versus other anti-diabetic therapies in Chinese patients with type 2 diabetes (T2D). ***Methods:*** Cost of control means the cost per patient successfully treated by anti-diabetic therapies, which was calculated by plotting relative treatment costs against efficacy. In this study, efficacy was measured by the proportions of patients reaching a composite treatment goal of HbA_{1c} <7.0% without weight gain and without hypoglycaemia. The clinical data were based on 'Liraglutide Effect and Action in Diabetes (LEAD)' clinical trial programme. Relevant comparators were glimepiride, rosiglitazone, insulin glargine and exenatide. The numbers needed to treat (NNTs) for patients achieving the composite endpoint at week 26 in each treatment group were calculated also. Treatment cost was captured from a Chinese healthcare perspective, which includes drug and needle cost. Drug dosage from LEAD project combined with price of drug and needle from averaged procurement of 2020 in China were used. ***Results:*** By calculation, NNTs for liraglutide 1.2mg (3.1) were lower compared to exenatide (4.0), insulin glargine (6.7), glimepiride (12.5) and rosiglitazone (16.7). In terms of the cost of control to achieve the composite endpoint, liraglutide 1.2mg costs less (¥16 405) compared to the other commonly used therapies. Cost with exenatide, insulin glargine, glimepiride, and rosiglitazone group was ¥18 732, ¥29 614, ¥31 253.9 and ¥50 523, consequently, amount spent on bringing per patient to composite endpoint was higher with 14%, 81%, 91% and 208% of corresponding groups compared to liraglutide 1.2 mg group. ***Conclusions:*** The efficacy-to-cost ratios with liraglutide 1.2 mg were superior to glimepiride, insulin glargine, rosiglitazone and exenatide on successfully treating patients in a Chinese setting, which represent as a cost-saving approach for patients with T2D in China.

PDB14
OBESITY AND THEIR COMORBIDITIES IN CHILE: AN OPEN DATABASE ANALYSIS TO SOLVE LOCAL GAPS IN CLINICAL INPUTS FOR ECONOMIC EVALUATIONS.

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Objectives: Obesity is a prevalent disease in Chile. The National Health Survey (NHS) presents general prevalence by disease, but not the association between diseases and Body Mass Index (BMI). The conditional prevalence of BMI for cardiovascular, kidney, and liver diseases and their attributable risk percent (AR%) were estimated to obtain local clinical inputs for economic evaluations. ***Methods:*** The NHS database was expanded to 14.519.582 observations, using the multiplicative inverse for the general probability of selecting a person-k in a dwelling-j in the i-th block of a commune-c of a stratum-h. The general prevalence of each nutritional status, comorbidities conditional to BMI and their AR% are estimated utilizing STATA IC 14.2 and R.STUDIO. Results are presented by disease and nutritional status subgroups. ***Results:*** The estimated prevalence for normal weight (NW), overweight (OW), grade I obesity (GIO) and grade 2 obesity (GIIO) were 24.35% (3,519,797), 39.83% (5,757,986), 23.39% (3,381,767) and 7.9% (1,142,556), respectively. For high blood pressure (HBP) prevalence was 11.5% (NW), 25% (OW), 29.6% (GIO), and 47% (GIIO). For type II diabetes (T2D), the prevalence by NW was 4.6%, 9.3% for OW, 14.2% for GIO, and 23% for GIIO. For chronic kidney disease (CKD) prevalence was 1.53% (NW), 1.52% (OW), 1.49% (GIO), and 2.98% (GIIO). The prevalence of cholelithiasis by NW was 11.45%, 25.11% (OW), 32.07% (GIO), and 36% (GIIO). For HBP, an AR% of 69.64% is obtained for GIIO (p-value<0.001). For GIIO, an AR% of 52.21% was calculated for acute myocardial infarction (p-value=0.001). In T2D, an AR% of 74.89% is obtained for GIIO (p-value<0.001). For cholelithiasis, an AR% of 54.97% (p-value<0.001), and 43.19% is obtained in the same subgroup (GIIO) for CDK (p-value=0.084). ***Conclusions:*** The AR% demonstrates the higher the BMI, the higher comorbidities. This database's statistical analysis provides new metadata for conducting local economic modeling by solving the gap of clinical inputs.

PDB15
COST-EFFECTIVENESS OF A NOVEL TREATMENT FOR DIABETIC FOOT ULCER AMONG PATIENTS WITH DIABETES: A MODELING STUDY

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Objectives: We evaluated the cost-effectiveness of a novel treatment - ON101 cream, which was recently introduced for treating diabetic foot ulcer (DFU) as add-on to standard care (SC), versus SC among diabetic patients from the healthcare sector perspective. ***Methods:*** A Markov model with six health states (i.e., uninfected DFU, infected DFU, healed DFU, history of amputation, gangrene, and all-cause death) was adopted to assess the cost-effectiveness of ON101 versus SC for treating DFU, with one-month cycle length for a 5-year simulation in the base-case analysis. Data from the ON101 phase 3 trial involving 236 DFU cases for a 16-week follow-up were used to generate efficacy parameters (transition probabilities between health states) for the model. Costs and health utilities associated with health states were drawn from published literature and estimated using Taiwan's National Health Insurance Research Database. Costs were expressed in 2020 U.S. dollars. Future costs and effectiveness were discounted at 3% annually. One-way and probabilistic sensitivity analyses were performed to examine the robustness of study results. ***Results:*** Attributed by a higher healing rate and shorter healing time of using ON101, the base-case analysis showed that ON101 treatment was associated with lower costs and higher quality-adjusted life years (QALYs) over 5 years. The total healthcare cost per ON101-treated patient was lower than that of a patient with SC (i.e., $14,270 versus $22,135), while QALYs per ON101-treated patient were higher than those of a patient with SC (i.e., 3.565 versus 3.545 QALYs). Results were robust across the sensitivity analyses. ***Conclusions:*** The novel treatment, ON101, versus SC would be cost-saving for DFU owing to its better efficacy.

PDB16
COST-EFFECTIVENESS OF ADD-ON THERAPIES TO METFORMIN: THE IMPACT OF MEDICATION ADHERENCE FOR TYPE 2 DIABETES MELLITUS

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Objectives: To evaluate the cost-effectiveness of sulfonylurea (SU), thiazolidinedione (TZD), dipeptidyl peptidase 4 inhibitors (DPP-4i), and sodium-glucose co-transporter-2 inhibitors (SGLT2i) as long-term add-on therapy with metformin for type 2 diabetes mellitus (T2DM) in US health care payer perspective and assess the effect of medication adherence on therapeutic effectiveness. ***Methods:*** The estimation of direct medical cost and quality-adjusted life years (QALYs) in 25-year time horizon was performed by using a one-year cycle Markov model with four health states. Cohorts, aged 60 years old, were treated with dual therapy when first-line metformin monotherapy failed. It then a triple therapy with insulin was given after the failure of dual therapy. Additionally, TZD were replaced with SGLT2i if heart failure occurs as a complication. Adherence to therapies were considered as weighting parameters of probabilities for treatment failure and diabetes complications. Costs, clinical outcomes, and utilities were retrieved from literature. Cost and effectiveness were discounted at 3% in 2020 value. ***Results:*** In scenario A (without considering medication adherence), DPP-4i increased 0.18 QALYs with incremental cost $13,842 compared to TZD, resulting in an ICER of $74,911 per QALY. In scenario B (considering medication adherence), DPP-4i increased 0.09 QALYs with incremental cost $5,073 compared to TZD, resulting in an ICER of $53,610 per QALY. The cost-effectiveness acceptability curves indicated that TZD gained highest probability as the most cost-effective strategy at willingness-to-pay (WTP) threshold $50,000 per QALY in both scenario A and B. Moreover, SGLT2i was the most cost-effective strategy at the threshold of $140,000 in scenario B. ***Conclusions:*** TZD was the most cost-effective alternative whether considering medication adherence or not. Although Dpp-4i and SGLT2i gained additional QALYs, compared to TZD, the benefit could not outweigh the tremendous health related expenditure. Our study will be valuable both for third-party payers and clinicians to make decisions in second-line T2DM therapies.

PDB17
TOTAL COST OF CARE AND UTILIZATION AMONG MEDICARE FEE-FOR-SERVICE (FFS) PATIENTS WITH METASTATIC PANCREATIC CANCER TREATED WITH FDA-APPROVED/NCCN® CATEGORY 1 REGIMENS AT 340B VS. NON-340B HOSPITALS

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Objectives: To compare total cost of care (TCOC) and utilization for Medicare FFS patients (pts) with metastatic pancreatic cancer (m-PANC) treated at 340B or non-340B hospitals, by NCCN® Category 1 regimen. ***Methods:*** We identified pts with m-PANC using ICD-9/10 diagnosis codes in the 2016-18 Medicare Parts A/B/D 100% Research Identifiable Files. Study pts had 2+ claims with a pancreatic cancer diagnosis and Medicare FFS coverage for 6 months pre- and 3 months post-metastasis diagnosis. 340B hospitals were identified using the 340B OPAIS database. Pts were attributed to 340B or non-340B hospitals based on plurality of chemotherapy claims. Mean TCOC includes all insurer-paid services per line of therapy (excluding patient cost share). We calculated mean rates of hospital admissions (admits/pt) and readmissions. Study pts were treated with NCCN® Category 1 regimens: 1L gemcitabine monotherapy (gem-mono), 1L gemcitabine/nab-paclitaxel (gem-nab), 1L FOLFIRINOX (FFX), and 2L liposomal irinotecan-based regimen (Nal-IRI). ***Results:*** We identified 5,098 (340B) and 7,450 (non-340B) pts. Across regimens, TCOC was higher at non-340B ($21,144-$53,127) than at 340B

hospitals ($18,544-$44,947). There were no consistent differences in admits/pt and readmission rate between cohorts. Gem-mono had the lowest TCOC (340B: $18,544, $P<.05$; non-340B: $21,144, $P<.05$) in both cohorts, while Nal-IRI had the highest (340B: $44,947, $P>.05$, non-340B: $53,127, $P<.05$); Nal-IRI pts also had the lowest admits/pt (340B: 0.72, $P>.05$; non-340B: 0.72, $P>.05$), while gem-nab had the highest (340B: 1.19, $P>.05$; non-340B: 1.18, $P>.05$). Gem-mono and Nal-IRI had the lowest readmission rate at 340B (7%, $P>.05$) and non-340B (9%, $P>.05$). ***Conclusions:*** While TCOC at 340B hospitals was 2%-15% lower than at non-340B hospitals overall, there was no consistent pattern of admits/pt and readmission rates. Among regimens, there were consistencies in both cohorts: TCOC was lowest for gem-mono and highest for Nal-IRI, while admits/pt were lowest for 2L Nal-IRI and highest for gem-nab.

Diabetes/Endocrine/Metabolic Disorders - Epidemiology & Public Health

PDB18
PREVALENCE AND CO-PREVALENCE OF COMORBIDITIES AMONG PATIENTS WITH TYPE 2 DIABETES MELLITUS LIVING IN PUERTO RICO, USA

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Objectives: To estimate the prevalence of common comorbidities and describe the healthcare utilization patterns in patients with type 2 diabetes mellitus (T2DM) in Puerto Rico. ***Methods:*** This is a descriptive study using healthcare claims data from patients with T2DM (based on ICD-9 diagnosis code) from most public and private healthcare insurance companies providing services in Puerto Rico in 2013 (representing more than 90% of insured population). Descriptive analyses by age, sex, type of insurance, health region, and type of medical encounter were done using frequency and percent for categorical data or means or median (with corresponding standard deviation or interquartile range) for continuous variables. ***Results:*** A total of 3,100,636 claims were identified from 485,866 adult patients with T2DM. Most patients were women (276,400; 57%), older than 65 years (235,390; 48%), from the Puerto Rico health regions of Caguas (79,604; 16%), Metro (66,280; 14%), or Bayamon (62,673; 13%) with private health insurance (371,806; 77%). The number of claims per patient ranged from 1 to 339. A mean of 6.3 claims (SD±9.99) and a median of 3 claims (Q1 1- Q3 8) per subject were identified. Of the 3,100,636 claims most (74%) were related to the diagnosis of diabetes (1,829,2015; 59%) or to cardiovascular diseases (458,219; 15%) and associated to outpatient services (2,722,727; 88%). The most prevalent comorbidities associated with healthcare utilization in these patients were hypertension (235,277; 48%), hyperlipidemia (197,449; 41%), neuropathy (100,471; 21%); renal disease (71,517; 15%), and retinopathy (61,837; 13%). ***Conclusions:*** A high prevalence of comorbidities and use of healthcare services were identified in patients with T2DM, especially in older adults. Since most comorbidities were due to diabetes-related conditions, this analysis highlights the importance of early diagnosis and adequate management of T2DM patients to avoid preventable burden to the patient and to the healthcare system.

Diabetes/Endocrine/Metabolic Disorders - Health Policy & Regulatory

PDB21
BUDGET IMPACT ANALYSIS OF A FLASH GLYCOSE MONITORING TECHNOLOGY IN GREECE

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Objectives: Flash Glycose Monitoring (FGM) is an innovative technology for glucose control that helps patients to avoid hypoglycemias and remain within Time in Range. Currently, only patients with DM1 are covered for using FGM by the National Organization for the Provision of Healthcare (EOPYY). Thus, we evaluated the economic consequences of FGM reimbursement expansion:a) in DM2 patients subjected to intensive insulin (N≥3 injections daily) b) in all insulin-treated patients with DM2. ***Methods:*** A Budget Impact Analysis Model (BIAM) was used, with a time horizon of three years. Resource utilization included the cost of all non-durables in regards to self-glycose monitoring and the cost of management of severe and non-severe hypoglycemia events. Analyses were conducted from the EOPYY perspective, taking into consideration a novel reimbursement model of progressive volume based price deduction for sensor and zero price for reader (as it is provided free of charge). ***Results:*** In the case of simultaneous coverage of FGM for both DM1 and DM2 patients, savings result from the very first year, increasing with the increase of the number of beneficiaries and peak during the third year. Specifically, savings reach the amount of a) € 1.9 million in the case of coverage of intensive insulin DM1 and DM2 patients and b) € 0.78 million in the case of coverage of all patients under insulin. The cumulative savings over three years amount to € 3.266 million for case (a) and € 1.3 million for case (b). ***Conclusions:*** Given the reduction of severe and non-severe hypoglycemia events for patients using the FGM technology, when compared with the SMBG (based on the relevant literature), and consequently, the cost savings achieved for EOPYY, the FGM technology is considered as of high value and, thus, the expansion of reimbursement coverage to DM2 patients is recommended.

PDB22
IMPLICATIONS FOR ACCESS TO INSULIN AND BIOSIMILARS: A SURVEY ON INSULIN PRICES, AVAILABILITY AND AFFORDABILITY IN THE PHILIPPINES

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Objectives: To evaluate the prices, availability and affordability of insulins and its biosimilars in the Philippines, following the 12% value-added tax exemption policy implemented in January 2019. ***Methods:*** The prices and availability of insulin and four oral antidiabetics, as comparator, were collected in August 2019 from 36 public and 36 private medicine outlets in six regions of the Philippines, using a modified WHO/HAI methodology. Insulin data was analyzed by type, manufacturer and presentation, and availability was reported in percentage. Insulin prices were compared with international reference price (IRP) to obtain the medicine price ratio. Affordability was measured by the number of days' wages needed for the lowest-paid unskilled government worker to purchase a monthly supply, 10mL 100IU/mL of insulin. ***Results:*** The mean availabilities of insulin originators and biosimilars were 2.8% and 50.0% in the public sector, and 63.9% and 61.1% in the private sector, respectively. Human insulin (55.6%) has higher mean availability versus analogue insulin (30.5%), with vial as the most available presentation. All insulin products were imported overseas, and three manufacturing companies dominated 65% of insulin available in the market. Insulin prices in the private sector were higher than the IRP (ranging from 1.05-3.66 times), while it is less than one in the public sector. Vials were mostly cheaper than pens and cartridges, and biosimilars were cheaper than originators. Purchasing 10mL of human and analogue insulin in the private sector would need 2-4 days and 4-8 days' wages, respectively. ***Conclusions:*** Insulins were affordable in public sector, but access was affected by low availability. High prices of insulin, despite tax exemption, influenced the affordability in the private sector with limited market competition. Effective measures should be taken to improve access to insulin, including bargaining lower prices with manufacturers, prioritizing the supply, and promoting the use of more affordable quality-assured biosimilars.

PDB23
INVESTIGATING INTERNISTSÂ€™ ENDOCRINOLOGISTSÂ€™ AND PAEDIATRICIANSÂ€™ ATTITUDES IN REGARDS TO THE VALUE OF INNOVATIVE DIABETES MELLITUS SELF-MONITORING TECHNOLOGIES IN GREECE

Siskou O,[1] Galanis P,[2] Konstantakopoulou O,[3] Karagkouni I,[4] Bargiota A,[4] Benroubi M,[5] Christoforidis A,[6] Delis D,[7] Didangelos T,[8] Dimitriadis G,[8] Doupis J,[9] Galli-Tsinopoulou A,[8] Ioannidis I,[10] Kanaka-Gantenbein C,[2] Kotsa K,[6] Koutsovasilis A,[11] Lambadiari V,[8] Papagianni M,[3] Papadimitriou DT,[12] Pappas A,[13] Souvatzoglou M,[14] Tentolouris N,[15] Tigas S,[16] Tsimihodimos V,[17] Mouslech Z,[18] Tsapas A,[19] Vazaiou A,[7] Vryonidou A,[12] Kaitelidou D[5]
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Objectives: Innovative technologies of continuous glucose monitoring (CGM) and flash glucose monitoring (FGM) contribute significantly to metabolic control and

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GASTROINTESTINAL CANCER—GASTROESOPHAGEAL, PANCREATIC, AND HEPATOBILIARY

Liposomal irinotecan (nal-IRI) in combination with fluorouracil (5-FU) and leucovorin (LV) for patients with metastatic biliary tract cancer (BTC) after progression on gemcitabine plus cisplatin (GemCis): Multicenter comparative randomized phase 2b study (NIFTY).

Changhoon Yoo, Kyu-Pyo Kim, Ilhwan Kim, Myoung Joo Kang, Jaekyung Cheon, Byung Woog Kang, Hyewon Ryu, Jae Ho Jeong, Ji Sung Lee, Kyung Won Kim, Baek-Yeol Ryoo

Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Inje University, Haeundae-Paik Hospital Medical Oncology,

COMPANION ARTICLES

No companion articles

ARTICLE CITATION

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Cancer Center, Busan, South Korea; Haeundae Paik Hospital, Busan, South Korea; Division of Hematology and Oncology, Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, South Korea; Department of Oncology/Hematology, Kyungpook National University Medical Center, Kyungpook National University School of Medicine, Daegu, South Korea; Division of Hematology and Oncology, Department of Internal Medicine, Chungnam National University Hospital, Daejeon, South Korea; Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Clinical Research Center, Asan Institute for Life Sciences, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Department of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

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Abstract Disclosures

Abstract

4006

Background: There is no globally established second-line therapy after progression on GemCis in BTC. Although ABC-06 trial showed the clinical benefit of mFOLFOX compared to active symptom control, further investigation is needed. **Methods:** NIFTY is an investigator-initiated, multicenter, open-label, randomized, phase 2b study. Pts with > 19 years, ECOG PS 0/1, histologically confirmed metastatic BTC, and disease progression on first-line GemCis were eligible. Pts were randomized 1:1 to nal-IRI (70 mg/m2, 90 min) plus 5-FU (2400 mg/m2, 46 hours)/LV (400 mg/m2, 30 min), every 2 weeks or 5-FU/LV, every 2 weeks until disease progression per investigator review or intolerable toxicities (stratification: primary tumor site, prior surgery and institution). Tumor response was evaluated per RECIST v1.1, every 6 weeks (fixed schedule). Primary endpoint is progression-free survival (PFS) per blinded independent central review (BICR). Secondary endpoints were PFS per investigator review, overall survival (OS) overall response rates (ORR), and safety. This study was designed to

improve median PFS from 2 months (P0) to 3.3 months (P1; HR 0.6) with 2-sided alpha of 0.05, power of 80% and follow-up loss rates of 10%; a total of 174 pts were required. **Results:** A total of 178 patients were enrolled between SEP 2018 and FEB 2020; with exclusion of 4 pts who did not receive any study treatment, 174 pts (88 for nal-IRI plus 5-FU/LV group and 86 for 5-FU/LV group) were included in the Full Analysis Set. Median age was 64 yrs (range 37-84); 99/75 pts were male/female; 74/47/53 pts had intrahepatic/extrahepatic/gallbladder cancers. Pts characteristics were well balanced between two arms. With median follow-up duration of 6.1 mo (IQR 3.5-11.2), median PFS per BICR in nal-IRI plus 5-FU/LV group and 5-FU/LV group was 7.1 mo (95% CI, 3.6-8.8) and 1.4 mo (1.2-1.5), respectively (HR=0.56 [0.39-0.81], p=0.0019); median PFS per investigator review was 3.9 mo (2.7-5.2) and 1.6 mo (1.3-2.2), respectively (HR=0.48 [0.34-0.69], p<0.0001). Median OS was 8.6 mo (5.4-10.5) and 5.5 mo (4.7-7.2), respectively (HR=0.68 [0.48-0.98], p=0.0349). ORR was 14.8% and 5.8% per BICR, respectively (p=0.0684) and 19.3% and 2.3% per investigator review, respectively (p=0.0002). Grade ≥3 adverse events (AEs) were reported in 68 pts (77.3%) of nal-IRI plus 5-FU/LV group and 27 pts (31.4%) of 5-FU/LV group. Most common grade ≥3 AEs in nal-IRI plus 5-FU/LV group were neutropenia (n=21, 23.9%), fatigue (7, 8.0%), and nausea (5, 5.7%). **Conclusion:** Nal-IRI plus 5-FU/LV significantly improved PFS and OS compared to 5-FU/LV in BTC pts who progressed on prior GemCis. Nal-IRI plus 5-FU/LV should be considered as standard second-line therapy for advanced BTC. ClinicalTrials.gov identifier: NCT03524508

Clinical trial information: NCT03524508.

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Liposomal irinotecan plus fluorouracil/leucovorin versus FOLFIRINOX as the second-line chemotherapy for patients with metastatic pancreatic cancer: a multicenter retrospective study of the Korean Cancer Study Group (KCSG)
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PANCREATIC CANCER

Population-based, real-world prognostic factors related to survival among patients with metastatic pancreatic ductal adenocarcinoma (mPDAC).

Kenneth H. Yu, Paul Cocknum, Andy Surinach, Shu Wang, Bong Chul Chu

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Memorial Sloan Kettering Cancer Center/Weill Cornell Medical College, New York, NY; Ipsen, Cambridge, MA; Genesis Research, Hoboken, NJ

Abstract Disclosures

Abstract

COMPANION ARTICLES

No companion articles

ARTICLE CITATION

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Background: Pancreatic cancer is expected to be the third deadliest cancer in the US in 2020. Many real-world studies of pts with mPDAC are restricted to single centers, limiting the generalizability of the insights they generate. There is a need to understand prognostic factors of survival in a broader setting to aid in tailoring treatment strategies for pts. This study aimed to identify important population-based predictors related to survival among pts diagnosed with mPDAC. **Methods:** Data were extracted for pts diagnosed with mPDAC between Jan 2017 and Dec 2019 from the Flatiron Health database. Predictive models for overall survival from the start of each treatment were developed using multivariable Cox proportional hazards regression. Treatment specific predictive models were generated for pts treated with first line (1L) gemcitabine + nab-paclitaxel (GNP), 1L FOLFIRINOX, 1L gemcitabine monotherapy (gem-mono), and 2L liposomal irinotecan-based regimens. The holdout method was used for cross-validation, splitting the data into 70% training / 30% validation. Age at diagnosis, sex, body mass index, smoking status, and ECOG performance score (PS) were included in all models due to clinical importance. Demographic, clinical characteristics, hematological labs, liver function tests (LFTs), and serum bilirubin levels were assessed for inclusion into the models. Uno's concordance statistic (c-statistic) was used to assess the predictive accuracy of the models. **Results:** Of the 3,572 pts included in the study, 44% (n = 1,557) received 1L GNP, 27% (n = 954) received 1L FOLFIRINOX, 7% (n = 265) received gem-mono, and 22% (n = 796) received other regimens. 38% (n = 1,345) pts received 2L and of those, 17% (n = 222) received liposomal irinotecan-based regimens. Among all 1L pts, the following were included in the final model: prior surgery, white blood cell (WBC) counts,

serum albumin, LFTs (ALP and ALT), serum bilirubin, and ascites (c-statistic: 0.65). The model for pts treated with GNP differed from the overall model via the addition of neutrophil counts and removal of serum bilirubin and ascites (c-statistic: 0.67). Stage at initial diagnosis was included in the model only for pts treated with 1L FOLFIRINOX (c-statistic: 0.68). Among pts treated with gem-mono the LFTs were not included in the model (c-statistic: 0.78). ALP, serum albumin, and WBC counts were important predictors of survival among pts treated with 2L liposomal irinotecan-based regimens (c-statistic: 0.70). Across all regimens the strongest predictors of survival were ECOG PS, serum albumin, and ALP. **Conclusions:** In one of the largest contemporary real-world studies of patients with mPDAC to date, important population predictors of survival in pts receiving systemic treatment were identified. Further validation studies are needed to understand the generalizability of these results.

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GASTROINTESTINAL CANCER—GASTROESOPHAGEAL, PANCREATIC, AND HEPATOBILIARY

Assessing real-world survival outcomes of patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with first-line FOLFIRINOX compared to patients from a phase 1/2 trial treated with NALIRIFOX.

Xuelian Zhu, Paul Cockrum, Bonny Shah, Craig Parzynski, Tamer Garawin, Fiona Maxwell, Andy Surinach

Genesis Research, Hoboken, NJ; Ipsen, Cambridge, MA

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Abstract Disclosures

ARTICLE CITATION

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Abstract

e16252

Background: Treatment options remain limited for pts newly diagnosed with mPDAC. NCCN and ASCO guidelines both recommend treatment with FOLFIRINOX or gemcitabine plus nab-paclitaxel in the first line (1L) setting for pts with mPDAC and good performance status. Over 80% of randomized clinical trials (RCTs) studying treatments for mPDAC have failed to meet their primary endpoints. Recently published analyses have utilized real-world (RW) data to compare outcomes between pts enrolled in clinical trials and RW pts. This study sought to identify the eligible population of pts with mPDAC treated with FOLFIRINOX in the 1L setting who would meet RCT eligibility criteria for the phase 1/2 study (NCT02551991) evaluating NALIRIFOX for pts with previously untreated locally advanced or mPDAC, and to assess their survival outcomes. **Methods:** This retrospective observational study utilized the Flatiron Health EHR database. Data were analyzed for adult pts diagnosed with mPDAC between January 2016 and February 2020 who initiated treatment with FOLFIRNOX in 1L within 90 days of their diagnosis for metastatic disease. Eligibility criteria from the phase 1/2 trial were applied to select a population of RW pts who may have been eligible to enter the RCT. Pts meeting the following criteria were included: good performance scores (ECOG 0-1), adequate hematological, hepatic, and renal function, were recovered from the effects of surgery, were untreated in the year prior to initiating 1L, and had no evidence of a different cancer in the last three years. Kaplan-Meier analyses were used to assess the median overall survival (mOS) from the start of 1L FOLFIRNOX treatment. **Results:** Of the 1,210 pts treated with 1L FOLFIRINOX, 652 pts (53.8%) met less stringent

versions of the RCT eligibility criteria in which missing values were deemed to indicate normal function/performance; 244 pts (20.2%) met the more stringent criteria and had complete data. The most restrictive selection criteria were the requirements for adequate hematological, hepatic, and renal function and having received prior therapy. The median age at treatment initiation among the 244 pts was 64 years (IQR: 58 – 70). 153 pts were male (62.7%), 158 were White (64.8%), and ECOG scores of 0 and 1 were split among the cohort 50%/50%. The mOS observed for the 244 pts was 10.1 months (95% CI: 9.1 – 11.3). The reported mOS from the phase 1/2 trial of NALIRIFOX was 12.6 months (8.7 – 18.7). **Conclusions:** This study demonstrates that RW data may be used to select a comparator cohort for a clinical trial. Initial estimates suggest NALIRIFOX pts from the RCT experienced longer survival than those receiving 1L FOLFIRINOX in the RW setting. Further analysis is necessary to minimize the effects of confounding and the differences in data collection between the RW and the RCT settings.

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Electronic Acknowledgement Receipt

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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
Customer Number:	153749
Filer:	Mary Rucker Henninger/Dawn MacPherson
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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	Gollamundi S. KISHORE
Attorney Docket Number	01208-0007-01US

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	1	BAI L, et al., "A Phase 2 Study of Liposomal Irinotecan With 5-Fluorouracil and Leucovorin in Squamous Cell Carcinoma of Head and Neck or Esophagus After Prior Platinum-Based Chemotherapy or Chemoradiotherapy," Poster presented at American Society of Clinical Oncology 2021 Meeting, June 4-8, 2021, 6 pages.
	2	DIEGUEZ G et al., "Risk Adjustment and Total Cost of Care Per Month of Overall Survival Among Medicare Fee-for-Service (FFS) Beneficiaries Receiving Treatment for Metastatic Pancreatic Cancer," Poster presented at American Society of Health-System Pharmacists (ASHP) Midyear Clinical Meeting & Exhibition, December 6-7, 2021, 6 pages.
	3	DIEGUEZ G, et al., "Trends in Treatment Patterns Among Medicare Fee-For-Service (FFS) Patients Receiving Treatment for Metastatic Pancreatic Cancer," Poster presented at European Society for Medical Oncology (ESMO) Congress 2021, September 16-21, 2021, 5 pages.
	4	DIEGUEZ G, et al., "Trends in Use of One, Two, and Three-Line NCCN Category 1 Regimens Among Medicare Fee-For-Service (FFS) Patients Receiving Treatment for Metastatic Pancreatic Cancer," Poster presented at ASCO Quality Care Symposium 2021, September 24-25, 2021, 5 pages.
	5	ELIAS R, et al., "Comparison of First-Line (1L) Treatment (Tx) Patterns and Overall Survival by Age at Diagnosis Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC)," Poster Presented at the American Society of Clinical Oncology Gastrointestinal Cancer Symposium (ASCO GI) 2021, January 15–17, 2021, Virtual Congress, 6 pages.
	6	GEORGE B, et al., "Real-World Impact of Prior Surgery on Outcomes of Patients With Metastatic Ductal Adenocarcinoma (mPDAC) Treated With Liposomal Irinotecan-Based Regimens," Presented at International Society for Pharmacoeconomics and Outcomes, May 17-19, 2021, Virtual poster, 10 pages.
	7	GEORGE B, et al., "Real-World Serum CA19-9 Level Monitoring Patterns and Its Association With Clinical Outcomes Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC)," Poster presented at the American Association for Cancer Research (AACR) 2021 Virtual Congress, April 10-15, 2021, 8 pages.
	8	KIM G, et al, "Real-World Characteristics and Outcomes of Patients With Metastatic Ductal Adenocarcinoma (mPDAC) Treated With Liposomal Irinotecan-Based Regimens by Race," Presented at International Society for Pharmacoeconomics and Outcomes, May 17-19, 2021, Virtual poster, 9 pages.
	9	KIM G, et al., "Real-World One-Year Overall Survival Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Treated With Liposomal Irinotecan in the NAPOLI-1 Based Regimen," Poster presented at the American Society of Clinical Oncology Gastrointestinal Cancer Symposium (ASCO GI) 2021, January 15–17, 2021, Virtual Congress, 6 printed pages.
	10	KIM G, et al., "Real-World Progression Outcomes Among Patients (pts) With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Treated With Liposomal Irinotecan-Based Regimens in the United States," Poster presented at European Society for Medical Oncology (ESMO) Congress,, Virtual Congress, September 16 -21, 2021, 5 pages.
	11	KIM G, et al., "Real-World Safety Data and Differentiation of Second-Line (2L) 5-Fluorouracil (5-FU) Based Regimens Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC)," Poster presented at the American Society of Clinical Oncology Gastrointestinal Cancer Symposium (ASCO GI) 2021, January 15–17, 2021, Virtual Congress, 7 pages.

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	12	KIM G, et al., "Real-World Treatment Discontinuation Patterns Among Patients (pts) With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Treated With Liposomal Irinotecan-Based Regimens in the United States," Presented at European Society for Medical Oncology (ESMO) Congress, Virtual Congress, September 16-21, 2021, 5 pages.
	13	LATIMER H, et al., "Total Cost of Care and Utilization Among Medicare Fee-For-Service (FFS) Patients With Metastatic Pancreatic Cancer Treated With FDA-Approved/NCCN® Category 1 Regimens at Teaching vs. Non-Teaching Hospitals," Presented at International Society for Pharmacoeconomics and Outcomes, May 17-19, 2021, Virtual poster, 11 pages.
	14	LAURSEN A, et al., "Real World Patterns of Pain Medication Use Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC)," Poster presented at ASCO Quality Care Symposium 2021. Boston, MA, Online, September 24 -25, 2021, 4 pages.
	15	PALURI R, et al., "Impact of the COVID-19 Pandemic on Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Care Delivery," Presented at the American Society for Clinical Oncology (ASCO) Annual Meeting: June 4 – 8, 2021; Virtual, 6 pages.
	16	PAZ-ARES L, et al., "RESILIENT Part 1: A Phase II Dose-Exploration and Dose-Expansion Study of Second-Line Liposomal Irinotecan Monotherapy in Adults With Small Cell Lung Cancer," Presented at World Conference on Lung Cancer, January 28-31, 2021, Virtual event, 12 pages.
	17	PAZ-ARES L, et al., "RESILIENT Part 2: A Phase III Study of Liposomal Irinotecan in Patients With Small-Cell Lung Cancer in the Second-Line Setting," Presented at World Conference on Lung Cancer, January 28-31, 2021, Virtual event, 9 pages.
	18	PERKHOFER L, et al., "Nal-IRI With 5-FU and Leucovorin or Gemcitabine Plus Cisplatin in Advanced Biliary Tract Cancer: Final Results of the Randomized Phase 2 NIFE Trial (AIO-YMO HEP-0315)," Presentation at the European Society for Medical Oncology (ESMO) Congress, Virtual Congress| September 16-21, 2021, 9 pages.
	19	RAMNARAIGN B, et al., "A Phase II, Open-Label Pilot Study Evaluating the Safety and Activity of Nal-IRI in Combination With 5-FU and Oxaliplatin (NALIRIFOX) in Preoperative Treatment of Pancreatic Adenocarcinoma (NEO-Nal-IRI study)," Poster presented at the American Society of Clinical Oncology Gastrointestinal Cancer Symposium (ASCO GI) 2021, January 15–17, 2021, Virtual Congress, 4 pages.
	20	TAIEB J, et al., "Real-World Study of Treatment Patterns and Outcomes Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma (PDAC) in Europe," Poster presented at the American Society of Clinical Oncology Gastrointestinal Cancer Symposium (ASCO GI) 2021, January 15-17, 2021, Virtual Congress, 6 pages.
	21	TOMICKI S, et al., "Total Cost of Care and Utilization Among Medicare Fee-For-Service (FFS) Patients With Metastatic Pancreatic Cancer Treated With FDA-Approved/NCCN® Category 1 Regimens at 340B vs. Non-340B Hospitals," Presented at International Society for Pharmacoeconomics and Outcomes, May 17-19, 2021, Virtual poster, 11 pages.
	22	YOO C, et al., "Liposomal Irinotecan (nal-IRI) in Combination With Fluorouracil (5-FU) and Leucovorin (LV) for Patients (pts) With Metastatic Biliary Tract Cancer (BTC) After Progression on Gemcitabine Plus Cisplatin (GemCis): Multicenter Comparative Randomized Phase 2B Study (NIFTY)," Presented at the American Society of Clinical Oncology 2021 Meeting, June 4-8, 2021, 18 pages.

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	23	YU K, et al., "Population-Based, Real-World Prognostic Factors Related to Survival Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC)," Poster presented at the American Society of Clinical Oncology Gastrointestinal Cancer Symposium (ASCO GI) 2021, January 15–17, 2021, Virtual Congress, 7 pages.

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

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)	2022-03-10
Name/Print	Mary R. Henninger	Registration Number	56992

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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

A Phase 2 Study of Liposomal Irinotecan with 5-Fluorouracil and Leucovorin in Squamous Cell Carcinoma of Head and Neck or Esophagus after Prior Platinum-based Chemotherapy or Chemoradiotherapy

L.Y. Bai[1], M.H. Yang [2], N.J. Chiang[3], S.Y. Wu[1], C.Y. Lin[1], Mi. Y. Lien[1], J.H. Chen[4], M.H. Chang[2], C.Y. Hsieh[1], R.L. Hong[5], H.F. Kao[5], R.H. Ye[4], S.H. Chen[3], C.F. Hsiao[6], L.T. Chen[6], T.W. Liu[6],
China Medical University Hospital, Taichung, Taiwan[1]; Taipei Veterans General Hospital, Taipei, Taiwan[2]; National Cheng-Kung University Hospital, Tainan, Taiwan[3]; Tri-Service General Hospital, Taipei, Taiwan[4]; National Taiwan University Hospital, Taipei, Taiwan[5]; National Health Research Institutes, Tainan, Taiwan[6]

INTRODUCTION

Background:

Nal-IRI is irinotecan hydrochloride encapsulated in a liposome drug delivery system. Nal-IRI + 5-FU/LV has been approved for patients with metastatic pancreatic cancer after gemcitabine-based therapy through the NAPOLI-1 study result.

This phase 2 trial evaluated the activity of NAPOLI-1 regimen (Nal-IRI + 5-FU/LV) in patients with squamous cell carcinoma of head and neck (HNSCC) or esophagus (ESCC) that progressed on or recurred after platinum-based chemotherapy or concurrent chemoradiotherapy.

OBJECTIVES

- **Primary**
  - Objective tumor response rate
- **Secondary**
  - Disease control rate (DCR), duration of response (DoR), progression free survival (PFS), time to tumor progression (TTP), 1-year survival rate, overall survival (OS) and tumor marker response of serum SCC antigen
  - Treatment toxicities and safety profiles

METHODS

- **Study Design**
  - An open-label, single arm, multicenter study
  - A Simon's minimax two-stage was adopted.
    - The hypothesis is based on the improvement of response rate from 5% in the historical control to the 15% by Nal-IRI + 5-FU/LV with a power of 0.8 and one-sided type I error a 5%, which resulted in 30 evaluable patients in the first stage.
    - If ≥ 2 responders are observed in stage 1, another 22 patients will be recruited in stage 2 with a total of 52 subjects.

- **Study Regimen**
  - Nal-IRI 80 mg/m^2 for 90 minutes, leucovorin 400 mg/m^2 for 30 minutes and 5-FU 2400 mg/m^2 for 46 hours in sequence on day 1 every 14 days.
  - Modification of treatment dose according to the toxicities occurred in the previous treatment cycle.

PATIENTS

- **Key Inclusion Criteria**
  - Histologically confirmed HNSCC or ESCC with exclusion of nasopharyngeal carcinoma
  - Unresectable locally advanced, recurrent or metastatic diseases ineligible or unsuitable for further surgical or radiation
  - Documented disease progression within 6 months after treatment by prior platinum-based systemic chemotherapy or concurrent chemoradiotherapy.
- **Key Exclusion Criteria**
  - Received prior Nal-IRI or irinotecan therapy
  - Patient with liver cirrhosis with Child-Pugh score ≥ 8

RESULTS

- A total of 59 (ITT population) patients were enrolled from Dec. 2018 to Apr. 2020 (Table 1).
- DCR in ESCC was 43.8% (7 SD). For HNSCC, 1 CR, 4 PR, and 23 SD resulted in the response rate of 11.6% and DCR of 65.1%. (Table 2)
- More then 40% of patients had dose modification (Table 3).
- The most frequent ≥ grade 3 toxicities were shown in Table 4.

Table 1. Patient Demographic (n=59)

Sex, n (%)	
Male / Female	54 (91.5) / 5 (8.5)
Median age, years	55
ECOG performance status, n (%)	
0	21 (35.6)
1	38 (64.6)

Table 1. Patient Demographic (n=59) - (continue)

Stage, n (%)	
I	5 (8.5)
II	1 (1.7)
III	15 (25.4)
IV	38 (64.4)
Disease status, n (%)	
Metastatic diseases have disease progression after last dose of platinum-based chemotherapy	37 (62.7)
Locally advanced diseases have disease progression after last dose of platinum-based chemotherapy	20 (33.9)
Locally advanced diseases have a clinical complete response after last dose of platinum-based chemotherapy	2 (3.4)

Table 2. Efficacy- Response

	Overall	Esophagus	H&N
No. of Treated Patients	59	16	43
CR	1 (1.7%)	0	1 (2.3%)
PR	4 (6.8%)	0	4 (9.3%)
SD	30 (50.8%)	7 (43.8%)	23 (53.5%)
PD	18 (30.5%)	7 (43.8%)	11 (25.6%)
Disease control rate (DCR)	35 (59.3%)	7 (43.8%)	28 (65.1%)

Table 3. Dose Adjusted

	Overall (N= 59)		Esophagus (N=16)		H&N (N=23)	
	Nal-IRI	5-FU	Nal-IRI	5-FU	Nal-IRI	5-FU
No	35 (59.3%)	33 (55.9%)	12 (75.0%)	12 (75.0%)	23 (53.5%)	21 (48.8%)
Yes	24 (40.7%)	26 (44.1%)	4 (25.0%)	4 (25.0%)	20 (46.5%)	22 (51.2%)

Table 4. Treatment Related Toxicity (N= 59)

	G1-2	G3-4
Hemotology, n (%)		
Anemia	33 (55.9 %)	17 (28.8 %)
White blood cell decreased	21 (35.6 %)	20 (33.9 %)
Neutrophil count decreased	12 (20.3 %)	25 (42.3 %)
Lymphocyte count decreased	9 (15.3 %)	30 (50.8 %)
Non-Hemotology, n (%)		
Fatigue	43 (72.9 %)	3 (5.1 %)
Diarrhea	27 (45.8 %)	3 (5.1 %)
Nausea	26 (44.1 %)	4 (6.8 %)

Figure 1. Overall Survival

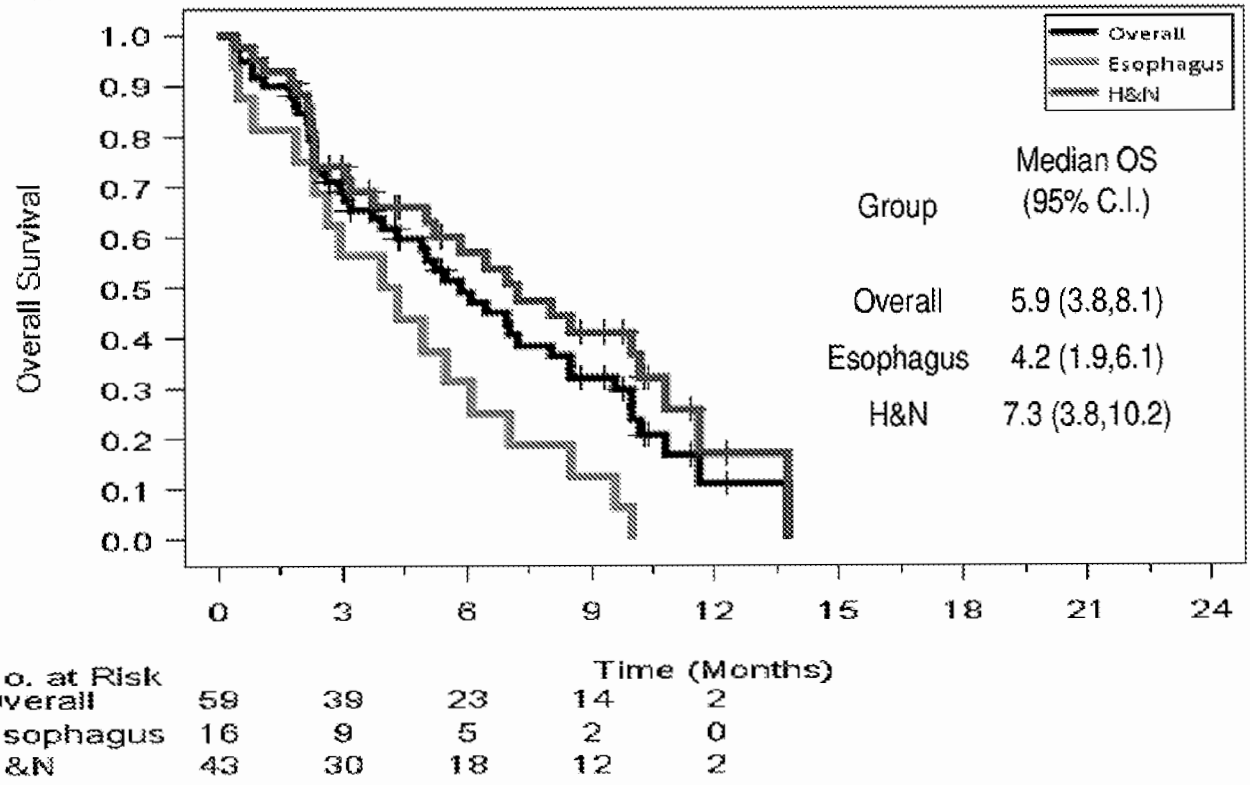
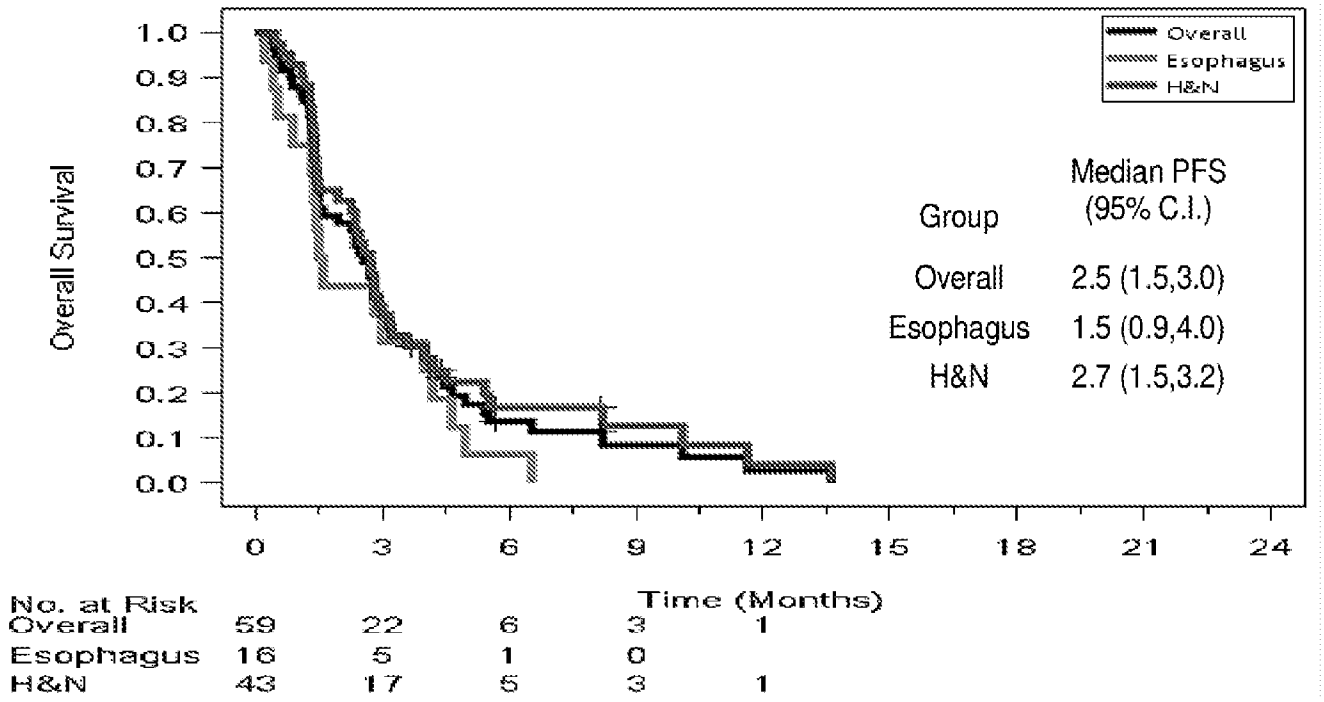


Figure 2. Progression Free Survival



CONCLUSIONS

- Nal-IRI in combination with 5-FU/LV showed modest efficacy in ESCC and HNSCC, with the response rate of 11.6% and DCR of 65.1% for the latter.
- Toxicities were moderate and manageable. Common grade 3/4 adverse effects are decreased lymphocyte count (50.8%), decreased neutrophil count (42.3%), decreased white blood cell (33.9%), and weight loss (33.9%).
- Nal-IRI plus 5-FU/LV warrants further investigation of combination with immunotherapeutic agents.

* Acknowledgements: All participating research staff, patients and their families; Nal-IRI drugs are provided by PharmaEngine, Inc.

A Phase 2 Study of Liposomal Irinotecan with 5-Fluorouracil and Leucovorin in Squamous Cell Carcinoma of Head and Neck or Esophagus after Prior Platinum-based Chemotherapy or Chemoradiotherapy

Study Regimen

Key Inclusion Criteria

Key Exclusion Criteria

Study Design

Figure 1. Overall Survival

Figure 2. Progression Free Survival

4-072

Risk Adjustment and Total Cost of Care per Month of Overall Survival Among Medicare Fee-for-Service (FFS) Beneficiaries Receiving Treatment for Metastatic Pancreatic Cancer

Dieguez G[1], Tomicki S[1], Destephano D[1], Cockrum P[2], Paluri R[1]
[1]Milliman, Inc., New York, NY; [2]Ipsen Biopharmaceuticals, Cambridge, MA; [3]Wake Forest Baptist Health, Winston-Salem, NC

Objective

There is limited research evaluating the relative health status of patients with metastatic pancreatic cancer. Hierarchical condition category (HCC) risk scores are widely accepted metrics of health status used to predict costs in the health insurance industry. We analyzed HCC risk scores and median costs per month of survival for NCCN® Category 1 regimens among Medicare fee-for-service (FFS) beneficiaries with metastatic pancreatic cancer.

Data Sourses

100% Medicare Research Identifiable (RIF) Claims Files (2016-2019)

- Contains all Medicare-paid Part A, B, and D claims for all FFS beneficiaries in the United States.
- Includes diagnosis, procedure, and diagnosis-related group (DRG) codes; beneficiary information, including age, sex, and eligibility status.

METHODS

Patient Identification

- Patients with metastatic pancreatic cancer were identified using International Classification of Disease (ICD)-10 diagnosis codes. We required:
  - Two or more claims with a pancreatic cancer diagnosis more than 30 days apart, and
  - One or more claims with a secondary malignancy (metastasis) diagnosis on or after the first pancreatic cancer diagnosis date.
- The “index date” was identified as the earliest metastasis diagnosis date.
- Patients were required to have six-month pre-index and three-month (or until death, if earlier) post-index Medicare FFS enrollment.
- Patients were excluded based on the presence of pre-index non-pancreatic malignancies.

Line of Therapy Assignment

- A line of therapy (LOT) was assigned based on the order of therapies used. The first LOT (1L) was defined as the first episode of an eligible therapy given in the 14 days preceding or after the patient’s index date, with the next LOT (2L) beginning the day after a patient switched to a new regimen.
- The end of the most recent LOT was defined as the earlier of 28 days after the most recent administration, visit date, or order for oral therapy (after the first date of chemotherapy), or date of death, if applicable.
- Patients with one, two, or three LOTs were defined as treated according to NCCN® Category 1 guidelines if, in each LOT, patients used one of the following regimens: FOLFIRINOX, gemcitabine/nab-paclitaxel, gemcitabine + erlotinib, gemcitabine

monotherapy, 5-FU + leucovorin + liposomal irinotecan, 2L+ liposomal irinotecan-based regimens
- Each LOT is assigned to the calendar year in which it begins. For example, patients with a third LOT that began in 2019 who received LOTs before 2019 would have only their third LOT assigned to calendar year 2019.

Regimen Sequence
- Regimen sequences were constructed as one-line, two-line, and three-line sequences.
- Regimen sequences had no subsequent chemotherapy following the last regimen within a sequence.
  - One-line sequences had no chemotherapy or change in therapy following the first line. Similar logic applied to two and three lines.
- Results were summarized for the top 3 regimens with one, two, and three LOT sequences with at least 30 patients per sequence.

Health Status and Survival
- Mean HCC risk scores were calculated for patients in each sequence.
  - HCC scores were generated using CMS's Hierarchical Condition Categories using the latest year that a patient with metastatic pancreatic cancer was alive.
- Kaplan-Meier methods were used to estimate median overall survival in months (OS).
  - Any patient that was alive past the study period was censored.
  - Patients that were lost in the data prior to the end of the study period were considered dead. Death dates were imputed to the 15th day of the month.

Risk Normalized Total Cost of Care
- Median total cost of care (TCOC) was first normalized by HCC risk score.
- The risk normalized TCOC was then divided by median months of OS.

TAKE-HOME MESSAGE

Based on HCC scores, patients with more lines of therapy are expected to incur higher monthly costs of care; after normalizing for HCCs, median TCOC per month of survival remain flat or decrease with additional lines of therapy.

Table 1. Risk Score and Total Cost of Care per Month of Overall Survival (OS) Among Medicare FFS Patients Receiving NCCN® Category 1 Regimens (2016-2019)

Regimen Sequences	Patients, no.	Median TCOC	Mean HCC Risk Score	HCC Risk-Normalized Median TCOC per Month of OS
All Patients with Chemotherapy	14,900	$54,142	2.29	$9,499
Top 3 One-line Regimens	12,907	$47,417	2.24	$10,134
gemcitabine/nab-paclitaxel	7,610	$54,758	2.24	$12,118
gemcitabine monotherapy	3,003	$28,845	2.63	$6,615
FOLFIRINOX	2,294	$52,738	1.71	$8,898

Top 3 Two-line Sequences	**1,846**	**$120,618**	**2.62**	**$9,426**
FOLFIRINOX >> gemcitabine/nab-paclitaxel	888	$115,047	2.51	$9,145
gemcitabine/nab-paclitaxel >> liposomal irinotecan + 5-FU/LV†	671	$132,463	2.71	$10,190
gemcitabine/nab-paclitaxel >> FOLFIRINOX	287	$113,234	2.76	$8,345
Top 2 Three-line Sequences	**147**	**$198,622**	**3.27**	**$7,054**
FOLFIRINOX >> gemcitabine/nab-paclitaxel >> liposomal irinotecan + 5-FU/LV†	115	$198,622	3.29	$6,926
gemcitabine/nab-paclitaxel >> FOLFIRINOX >> liposomal irinotecan + 5-FU/LV†	32	$195,598	3.19	$8,524

Conclusions

- HCC risk scores suggest that monthly costs of care for patients with metastatic pancreatic cancer (2.29) are predicted to be 129% higher than the average Medicare beneficiary (1.00).
- Patients with more LOTs were also expected to incur higher monthly costs of care, as predicted by their risk scores:
    - HCCs for patients with 2 and 3 LOTs were 17% and 46% higher, respectively, than patients with only 1 LOT.
- After normalizing for HCCs, median total costs per month of overall survival remained flat or decreased with additional lines of therapy.

Limitations

The data analyzed include the 2016-2019 Medicare FFS population. Analysis of different populations or time periods may yield different results. Our study used claims data and not electronic health records (EHRs), so we could not control for clinical covariates. Patient characteristics and regimen performance might influence which regimens patients receive. HCCs scores are designed to predict healthcare costs based on demographics and diagnosis codes; while cancer diagnosis are part of the HCCs, the model does not have enough granularity to discern severity of cancer. The HCC-normalized figures presented here are not meant to provide a head-to-head comparison.

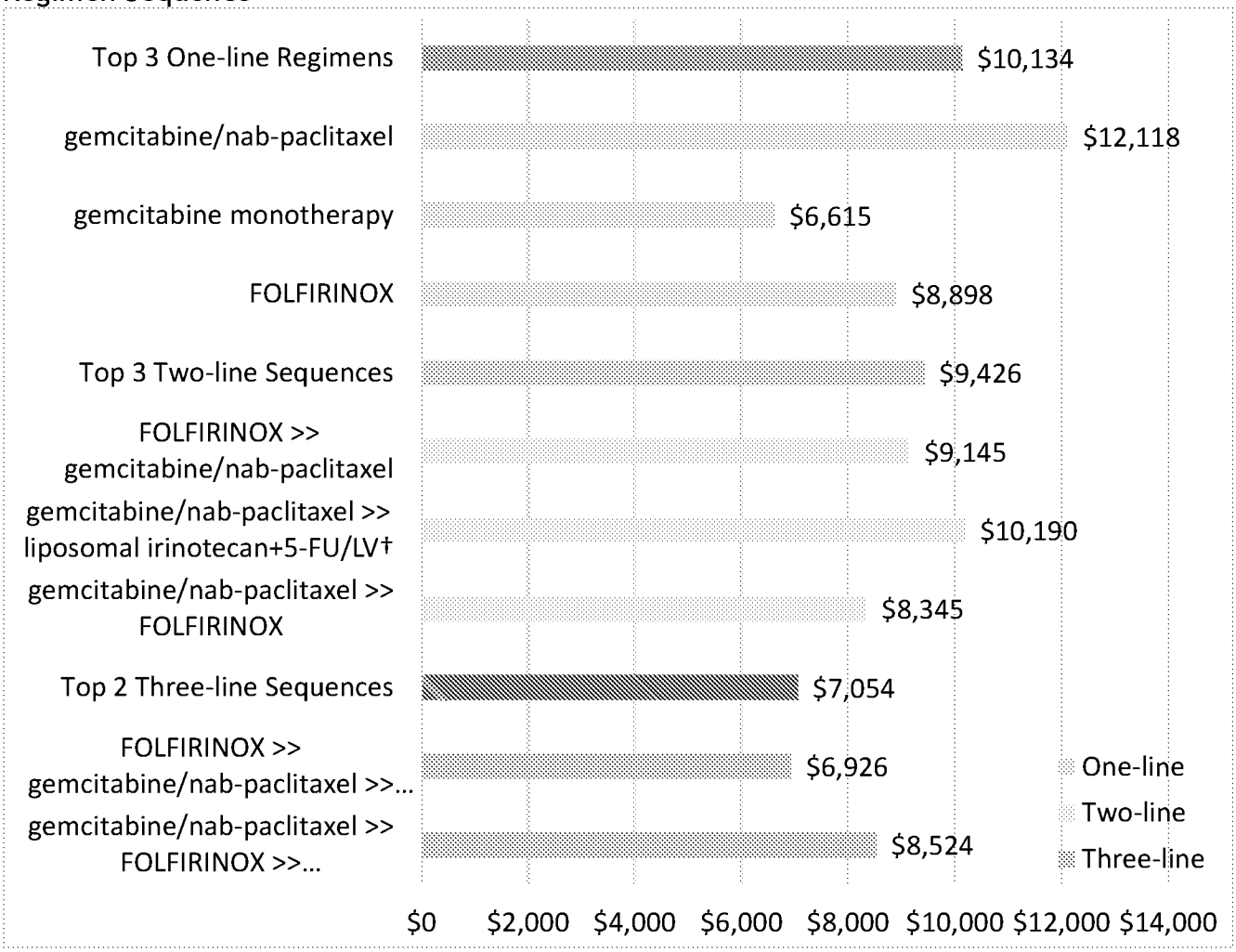
Results

- We identified 31,782 Medicare patients with metastatic pancreatic cancer between 2016 and 2019, of which 14,900 patients (47%) with one, two and three LOT sequences were further analyzed. **(Table 1)**
    - 12,907 patients received only one LOT consisting of gemcitabine/nab-paclitaxel, gemcitabine monotherapy, or FOLFIRINOX.

- 1,846 patients received two LOTs consisting of gemcitabine/nab-paclitaxel >> liposomal irinotecan + 5-FU/LV, FOLFIRINOX >> gemcitabine/nab-paclitaxel or gemcitabine/nab-paclitaxel >> FOLFIRINOX.
- 147 patients received three LOTs consisting of FOLFIRINOX >> gemcitabine/nab-paclitaxel >> liposomal irinotecan + 5-FU/LV or gemcitabine/nab-paclitaxel >> FOLFIRINOX >> liposomal irinotecan + 5-FU/LV.

- Mean HCC risk scores and median TCOC among patients who were treated with the top 3 regimens were lowest for patients receiving one LOT (2.24 and $47,417 respectively). Patients receiving two LOTs (2.62 and $120,618, respectively) and three LOTs (3.27 and $198,622, respectively) had higher mean HCC risk scores and median TCOC. **(Table 1)**
- Risk-normalized median TCOC per month of OS decreased as the number of LOTs increased: **(Figure 1)**
  - Among patients with one LOT, the median TCOC per OS for the top 3 regimens was $10,134 (ranged from $6,615 to $12,118).
  - For patients with two LOTs, the median TCOC per OS for the top 3 sequences was $9,426 (ranged from $8,345 to $10,190).
  - For patients with three LOTs, the median TCOC per OS for the top 2 sequences was $7,054 (ranged from $6,926 to $8,524).

Figure 1. HCC Risk-Normalized Median Total Cost of Care per Month of Overall Survival by Regimen Sequence



Author Contributions Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: [GD, ST, DD, PC, RP]; Drafting of the publication, or revising it critically for important intellectual content: [GD, ST, DD, PC, RP]; Final approval of the publication: [GD, ST, DD, PC, RP].

Disclosures [GD, ST, DD] : Employees of Milliman and received consulting fees from Ipsen. [PC] is employed by Ipsen and owns Ipsen stock. [RP] is employed by Wake Forest Baptist Health and received consulting fees from Ipsen.

This study was sponsored by Ipsen

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Risk Adjustment and Total Cost of Care per Month of Overall Survival Among Medicare Fee-for-Service (FFS) Beneficiaries Receiving Treatment for Metastatic Pancreatic Cancer

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Objective

There is limited research evaluating the relative health status of patients with metastatic pancreatic cancer. Hierarchical condition category (HCC) risk scores are widely accepted metrics of health status used to predict levels in the health insurance industry. We analyzed HCC risk scores and median costs per month of survival for NCCN® Category 1 regimens among Medicare fee-for-service (FFS) beneficiaries with metastatic pancreatic cancer.

Data Sources

100% Medicare Research Identifiable (RIF) Claims Files (2015-2018)

- Contains all reimbursement Parts A, B, and D claims for all FFS beneficiaries in the United States
- Includes diagnosis, procedure, and drug-level claims (DRG) before beneficiary identification, including age, sex, and eligibility status

Methods

Patient Identification

- Patients with metastatic pancreatic cancer were identified using International Classification of Diseases (ICD)-10 diagnosis codes. We required:
  - Two or more claims with a pancreatic cancer diagnosis more than 30 days apart, and
  - One or more claims with a secondary, subsequent (nonmetastatic) diagnosis for other than the first pancreatic cancer diagnosis date.
- The "index date" was determined as the earliest pancreatic diagnosis date.
- Patients were required to have demonstrated pre-index and follow-enrollment and health, a perfect proxy since Medicare FFS is continuous.
- Patients were excluded based on the presence of pancreatic neuroendocrine malignancies.

Line of Therapy Assignment

- A line of therapy (LOT) was developed based on the order of treatment used. The first LOT (1L) was defined as the first episode of an eligible therapy given within 30 days preceding or after the patient's index date, with the next LOT (2L) beginning the day after a patient switched to a new regimen.
- The end of the initial regimen LOT was defined as the earliest of 90 days after the most recent administration, switching, or death or last therapy (other than first date of discontinuation), or date of death, if applicable.
- Patients with one, two, or three LOTs were defined as treated according to NCCN® Category 1 guidelines if, in each LOT, patients used one of the following regimens: FOLFIRINOX, gemcitabine/nab-paclitaxel, gemcitabine + erlotinib, gemcitabine monotherapy, 5-FU + leucovorin + irinotecan liposome, 5-FU liposomal irinotecan based regimens.
- Each LOT is assigned to the calendar year in which it begins. For example, patients with a third LOT that began in 2018 were removed (90% reduce 2018 would have only their third LOT assigned to calendar year 2018).

Regimen Sequence

- Regimen sequences were summarized at one-, two-, and three-line assignment.
- Regimen sequences had no gaps (such as chemotherapy following the first line, switching regimens in second line).
  - One-line assignment had no chemotherapy or change in therapy following the first line, switching regimens in two and three lines.
- Analysis were summarized for the top 3 regimens with one, two, and three LOT sequences with at least 50 patients per sequence.

Health Status and Survival

- Mean HCC risk scores were calculated for patients in each sequence.
  - HCC scores were performed using CMS's Hierarchical Condition Categories using the latest year that a patient with metastatic pancreatic cancer was alive.
- Kaplan-Meier estimates were used to estimate median overall survival in months (mo).
  - Any patient that was alive, gain not really proven was censored.
  - Patients that were lost to the data prior to the end of the study period were considered dead. Death dates were captured to the following of the month.

Risk Normalized Total Cost of Care

- Median total cost of care (TCOC) was first normalized by HCC risk score.
- The risk normalized TCOC was then divided by median months of OS.

TAKE-HOME MESSAGE

Based on HCC scores, patients with more lines of therapy are expected to incur higher monthly costs of care; after normalizing for HCCs, median TCOC per month of survival remain flat or decreases with additional lines of therapy.

Table 1. Risk Score and Total Cost of Care per Month of Overall Survival (OS) Among Medicare FFS Patients Receiving NCCN® Category 1 Regimens (2015-2018)

Regimen Sequences	Patients, no.	Median TCOC	Mean HCC Risk Score	HCC Risk-Normalized Median TCOC per Month of OS
Top 3 One-Line Regimens	**10,907**	**$67,457**	**1.54**	**$46,104**
gemcitabine/nab-paclitaxel	7,640	$54,758	1.58	$42,116
gemcitabine monotherapy	3,093	$38,845	2.62	$6,615
FOLFIRINOX	2,294	$83,758	1.71	$8,806
Top 3 Two-Line Sequences	**1,345**	**$109,611**	**2.62**	**$41,431**
FOLFIRINOX >> gemcitabine/nab-paclitaxel	686	$118,647	2.55	$8,146
gemcitabine/nab-paclitaxel >> liposomal irinotecan + 5-FU/LV	673	$120,469	2.73	$10,169
gemcitabine/nab-paclitaxel >> FOLFIRINOX	287	$113,294	2.76	$8,340
Top 3 Three-Line Sequences	**117**	**$196,822**	**3.29**	**$7,804**
FOLFIRINOX >> gemcitabine/nab-paclitaxel >> liposomal irinotecan + 5-FU/LV	115	$196,822	3.29	$8,939
gemcitabine/nab-paclitaxel >> FOLFIRINOX >> liposomal irinotecan + 5-FU/LV	39	$165,999	3.16	$6,634

CONCLUSIONS

- HCC risk scores suggest that monthly costs of care for patients with metastatic pancreatic cancer (2.29) are predicted to be 129% higher than the average Medicare beneficiary (1.00).
- Patients with more LOTs were also expected to have higher monthly costs of care, as predicted by their risk scores.
  - HCCs for patients with 2 and 3 LOTs were 17% and 43% higher, respectively, than patients with only 1 LOT.
- After normalizing for HCCs, median total costs per month of overall survival remained flat or decreased with additional lines of therapy.

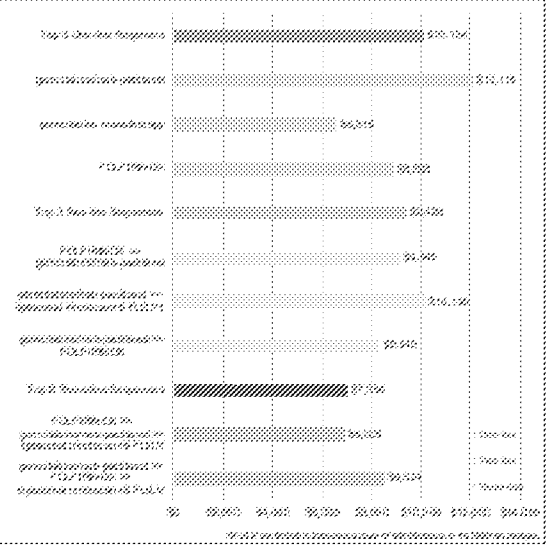
Limitations

The data analyzed includes the 2015-2018 Medicare FFS population. Adherence to different populations or data periods may yield different results. Our study used claims data and not laboratory results (Stage), as we do not have access to cancer biomarkers. Patient characteristics and regimen sequencing might influence which regimens patients receive. HCCs account for changes in patient healthcare needs based on demographics and diagnosis codes, which cancer diagnosis are part of the HCCs. We analyzed data for each strength separately to discuss severity of disease. The HCC-normalized figures presented here are not meant to promote a head-to-head comparison.

Results

- We identified 34,782 Medicare patients with metastatic pancreatic cancer between 2015 and 2018, of which 14,904 patients (43%) with one, two and three LOT sequences were further analyzed (Table 1):
  - 10,907 patients received only one LOT consisting of gemcitabine/nab-paclitaxel, gemcitabine monotherapy, or FOLFIRINOX.
  - 1,345 patients received two LOTs consisting of gemcitabine/nab-paclitaxel >> liposomal irinotecan + 5-FU/LV, FOLFIRINOX >> gemcitabine/nab-paclitaxel or gemcitabine/nab-paclitaxel >> FOLFIRINOX.
  - 117 patients received three LOTs consisting of FOLFIRINOX >> gemcitabine/nab-paclitaxel >> liposomal irinotecan + 5-FU/LV or gemcitabine/nab-paclitaxel >> FOLFIRINOX >> liposomal irinotecan + 5-FU/LV.
- Mean HCC risk scores and median TCOC among patients who were treated with the top 3 regimens were lowest for patients receiving one LOT (2.29 and $47,417 respectively). Patients receiving two LOTs ($107,611 and $109,619, respectively) and three LOTs ($196,822 and $196,822, respectively) had higher mean HCC risk scores and median TCOC (Table 1).
- Risk normalized median TCOC per month of OS also served as the number of LOTs increased (Figure 1):
  - Among patients with one LOT, the median TCOC per OS for the top 3 regimens was $46,104 (ranged from $6,615 to $42,116).
  - For patients with two LOTs, the median TCOC per OS for the top 3 sequences was $9,439 (ranged from $8,340 to $10,169).
  - For patients with three LOTs, the median TCOC per OS for the top 3 sequences was $7,804 (ranged from $6,634 to $8,939).

Figure 1. HCC Risk-Normalized Median Total Cost of Care per Month of Overall Survival by Regimen Sequence



Author Contributions: All authors contributed to study conceptualization, or acquisition/analysis/interpretation of data (GO, ST, DD, PC, RP); drafting of the publication, or revising it critically for important intellectual content (GO, ST, DD, PC, RP); final approval of the publication (GO, ST, DD, PC, RP).

Disclosures: GO, ST, DD, PC declare no conflicts of interest and received consulting fees from Novan (RP). RP is employed by Novan. Wake Forest Baptist Health and received consulting fees from Novan.

Presented at American Society of Health-System Pharmacists (ASHP) Midyear Clinical Meeting & Exhibition | December 6-7, 2021

This study was sponsored by Novan.

1478P

Trends in Treatment Patterns Among Medicare Fee-for-Service (FFS) Patients Receiving Treatment for Metastatic Pancreatic Cancer

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[1]Milliman, Inc., New York, NY; [2]Ipsen Biopharmaceuticals, Cambridge, MA; [3]George Washington University, Washington, DC

OBJECTIVE

There is limited research evaluating trends in the use of regimen sequences among patients with metastatic pancreatic cancer. We analyzed treatment by regimen sequence for Medicare fee-for-service (FFS) patients with metastatic pancreatic cancer.

DATA SOURCES

100% Medicare Research Identifiable (RIF) Claims Files (2016-2019)

- Contains all Medicare-paid Part A, B, and D claims for all FFS beneficiaries in the United States.
- Includes diagnosis, procedure, and diagnosis-related group (DRG) codes; site of service information; and beneficiary information, including age, sex, and eligibility status.

METHODS

Patient Identification

- Patients with metastatic pancreatic cancer were identified using International Classification of Disease (ICD)-10 diagnosis codes. We required:
  - Two or more claims with a pancreatic cancer diagnosis more than 30 days apart, and
  - One or more claims with a secondary malignancy (metastasis) diagnosis on or after the first pancreatic cancer diagnosis date.
- The "index date" was identified as the earliest metastasis diagnosis date.
- Patients were excluded based on the presence of pre-index non-pancreatic malignancies. Study patients had six-month pre-index and/or three-month (or until death, if earlier) post-index Medicare FFS enrollment.

Line of Therapy Assignment (Figure 1)

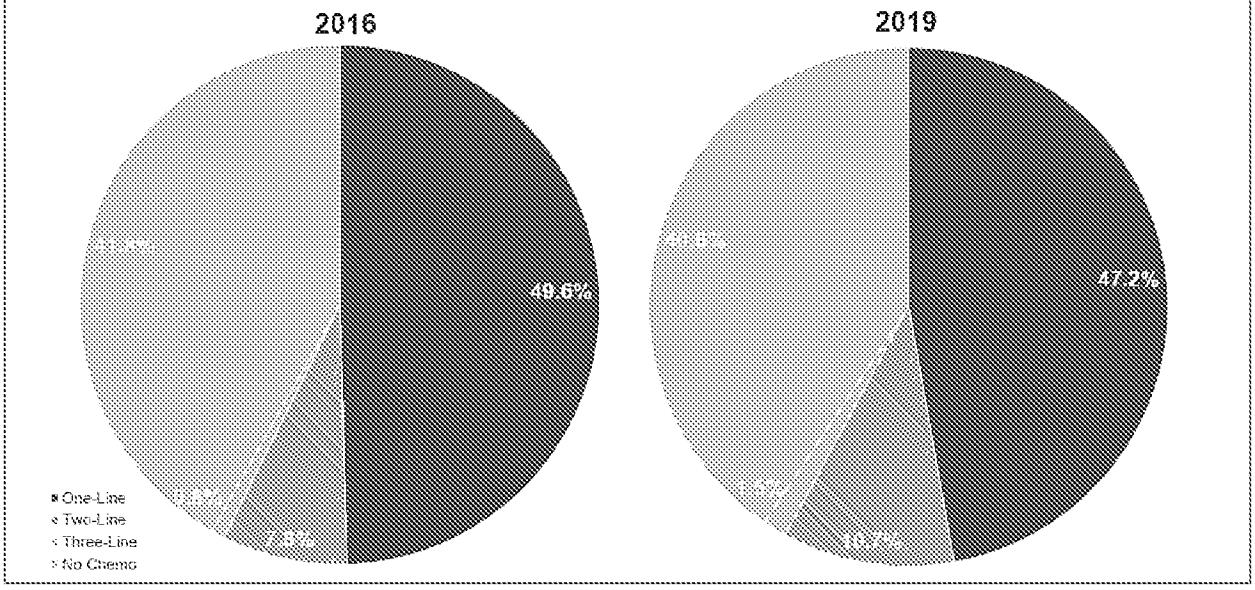
- A line of therapy (LOT) was assigned based on the order of therapies used. The first LOT (1L) was defined as the first episode of an eligible therapy given in the 14 days preceding or after the beneficiary's index date, with the next LOT (2L) beginning the day after a beneficiary switched to a new regimen.

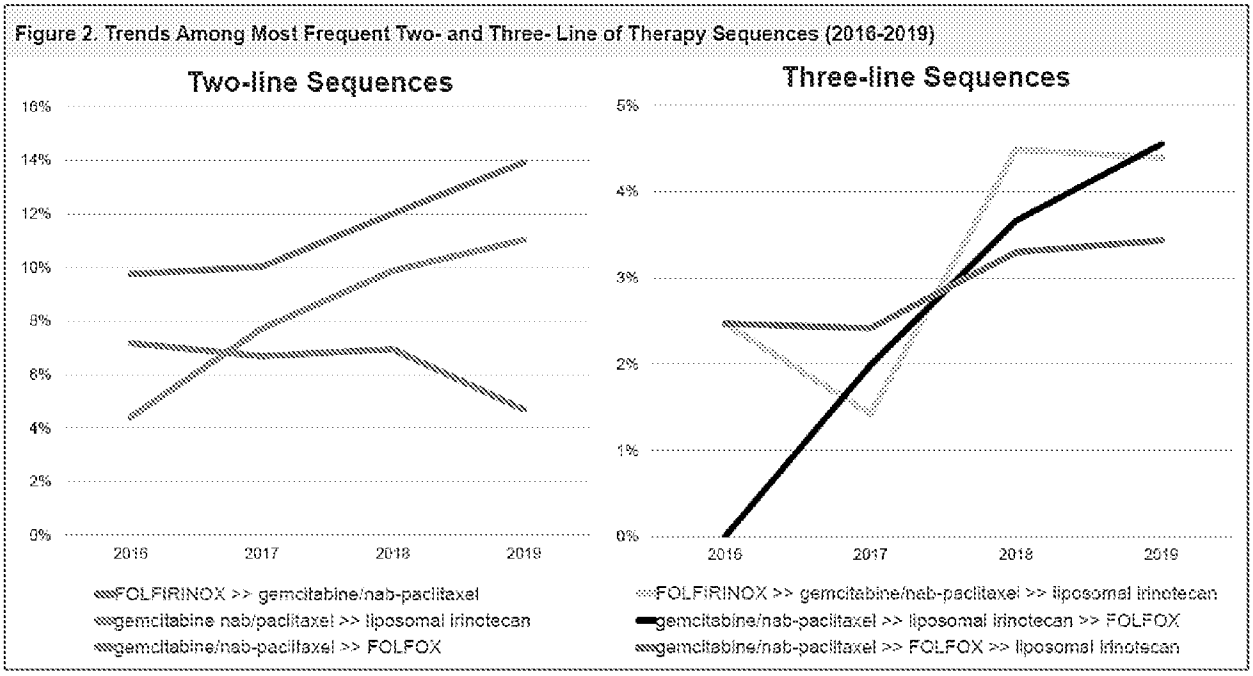
- The end of the most recent LOT was defined as the earlier of 28 days after the most recent administration, visit date, or order for oral therapy (after the first date of chemotherapy), or date of death, if applicable.
- Each LOT is assigned to the calendar year in which it begins.
- To ensure similar exposure periods for comparing the portion of patients with up to 3 LOTs (Figure 1), we excluded patients who initiated LOTs in multiple calendar years.

Regimen Sequence (Figure 2)

- Regimen sequences were constructed as two-line and three-line sequences, regardless of which calendar year the LOTs initiated in, based on the cumulative number of LOTs patients received. Patients with four or more LOTs were excluded from the analysis.
- Regimen sequences had no subsequent chemotherapy following the last regimen within a sequence.
  - One-line sequences had no chemotherapy or change in therapy following the first line. Similar logic applied to two- and three-lines.

Figure 1. Percent of Patients with Zero, One, Two, or Three Lines of Therapy in 2016 and 2019





RESULTS

- We identified 31,782 patients with metastatic pancreatic cancer in the Medicare population, with 21,304 one-line sequences, 7,352 two-line sequences, and 3,126 three-line sequences between 2016 and 2019.
- In 2019, fewer patients received no chemotherapy in 2016 (40.6%) and more patients received two- or three-line sequences (12.2%), compared to 41.8% and 8.6%, respectively, in 2016. (Figure 1)
- Among patients receiving two-line sequences, sequences consisting of FOLFIRINOX (FFX) to gemcitabine/nab-paclitaxel (gem/nab) or gem/nab to liposomal irinotecan had the largest increase (from 10% and 5%, respectively, in 2016 to 14% and 11% in 2019). (Figure 2)
- Among patients receiving three-line sequences, the sequences with the largest increase in utilization were FFX to gem/nab to liposomal irinotecan or gem/nab to liposomal irinotecan to FOLFOX (1% and 0% respectively, of all patients with three-line sequences in 2016, compared to 4% and 5% in 2019). (Figure 2)

CONCLUSIONS

- The number of patients with metastatic pancreatic cancer receiving chemotherapy increased from 2016 to 2019.
- From 2016 to 2019, the use of two- and three- line sequences increased consistently.
  - –Among Medicare FFS patients receiving two- and three-line sequences, those containing liposomal irinotecan in the second and third line were the primary drivers of this increase in utilization.

LIMITATIONS

The data analyzed include the 2016-2019 Medicare FFS population. Analysis of different populations or time periods may yield different results. Our study used claims data and not electronic health records (EHRs), so we could not control for clinical covariates. Patient characteristics and regimen performance might influence which regimens patients receive. We did not study whether liposomal irinotecan-based therapy patients received concomitant 5-fluorouracil (5-FU) or prior gemcitabine-based therapy.

Author Contributions Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: [GD, ST, DD, PC, GK]; Drafting of the publication, or revising it critically for important intellectual content: [GD, ST, DD, PC, GK]; Final approval of the publication: [GD, ST, DD, PC, GK].

Disclosures[GD, ST, DD] : Employees of Milliman and received consulting fees from Ipsen. [PC] is employed by Ipsen and owns Ipsen stock. [GK] is employed by George Washington University and received consulting fees from Ipsen.

This study was sponsored by Ipsen

Presented at European Society for Medical Oncology (ESMO) Congress 2021 | September 16-21, 2021

Trends in Treatment Patterns Among Medicare Fee-for-Service (FFS) Patients Receiving Treatment for Metastatic Pancreatic Cancer

1478P

Dergunt G[1], Tomaski S[2], Desilephano S[3], Cockram P[4], Kim G[5]

[1]Celgene, Inc., New York, NY, [2]Ipsen Biopharmaceuticals, Cambridge, MA, [3]George Washington University, Washington, DC

OBJECTIVE

There is limited research evaluating trends in the use of regimen sequences among patients with metastatic pancreatic cancer. We analyzed treatment by regimen sequence for Medicare fee-for-service (FFS) patients with metastatic pancreatic cancer.

DATA SOURCES

100% Medicare Research Identifiable (RIF) Claims Files (2016-2019):

- *Contains all Medicare-paid Part A, B, and D claims for all FFS beneficiaries in the United States*
- *Includes diagnosis, procedure, and diagnosis-related group (DRG) codes; date of service information; and beneficiary information, including age, sex, and eligibility status.*

METHODS

Patient Identification

- *Patients with metastatic pancreatic cancer were identified using International Classification of Disease (ICD)-10 diagnosis codes. We required:*
  - *Two or more claims with a pancreatic cancer diagnosis more than 30 days apart, and*
  - *One or more claims with a secondary malignancy (metastasis) diagnosis on or after the first pancreatic cancer diagnosis date.*
- *The "index date" was identified as the earliest metastasis diagnosis date.*
- *Patients were excluded based on the presence of pre-index non-pancreatic malignancies. Study patients had six-month pre-index and/or three-month (or until death, if earlier) post-index Medicare FFS enrollment.*

Line of Therapy Assignment (Figure 1)

- *A line of therapy (LOT) was assigned based on the order of therapies used. The first LOT (1L) was defined as the first episode of an eligible therapy given in the 14 days preceding or after the beneficiary's index date, with the next LOT (2L) beginning the day after a beneficiary switched to a new regimen.*
- *The end of the most recent LOT was defined as the earlier of 28 days after the most recent administration, visit date, or order for oral therapy (after the first date of chemotherapy); or date of death, if applicable.*
- *Each LOT is assigned to the calendar year in which it begins.*
- *To ensure similar exposure periods for comparing the portion of patients with up to 3 LOTs (Figure 1), we excluded patients who initiated LOTs in multiple calendar years.*

Regimen Sequence (Figure 2)

- *Regimen sequences were constructed as two-line and three-line sequences, regardless of which calendar year the LOTs initiated in, based on the cumulative number of LOTs patients received. Patients with four or more LOTs were excluded from the analysis.*
- *Regimen sequences had no subsequent chemotherapy following the last regimen within a sequence.*
  - *One-line sequences had no chemotherapy or change in therapy following the first line. Similar logic applied to two- and three-lines.*

Figure 1. Percent of Patients with Zero, One, Two, or Three Lines of Therapy in 2016 and 2019

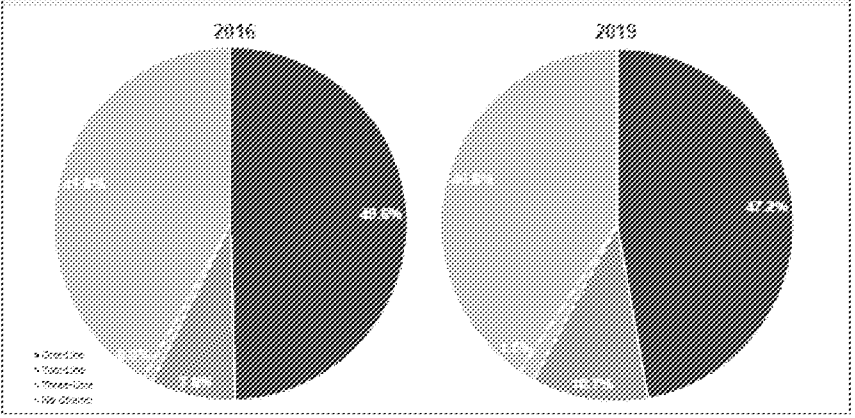
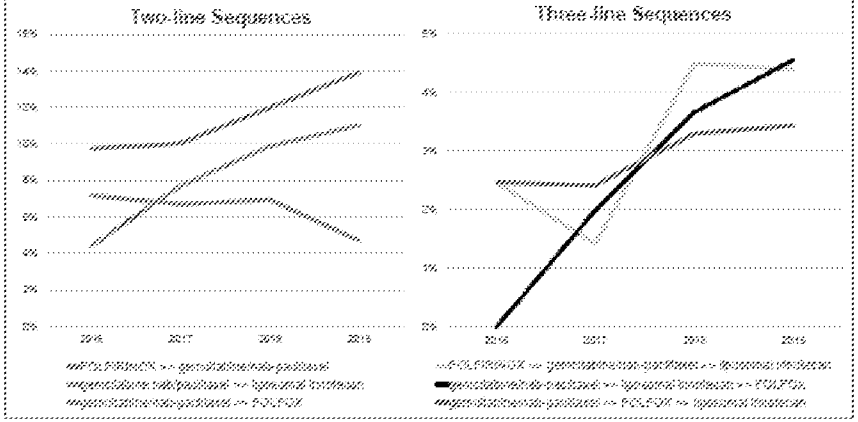


Figure 2. Trends Among Most Frequent Two- and Three- Line of Therapy Sequences (2016-2019)



RESULTS

- *We identified 31,702 patients with metastatic pancreatic cancer in the Medicare population, with 21,304 one-line sequences, 7,352 two-line sequences, and 3,126 three-line sequences between 2016 and 2019.*
- *In 2019, fewer patients received no chemotherapy in 2016 (42.6%) and more patients received two- or three-line sequences (12.2%), compared to 41.8% and 8.6%, respectively, in 2016. (Figure 1)*
- *Among patients receiving two-line sequences, sequences consisting of FOLFIRINOX (FFX) to gemcitabine/nab-paclitaxel (gem/nab) or gem/nab to liposomal irinotecan had the largest increase (from 10% and 6%, respectively, in 2016 to 14% and 11% in 2019). (Figure 2)*
- *Among patients receiving three-line sequences, the sequences with the largest increase in utilization were FFX to gem/nab to liposomal irinotecan or gem/nab to liposomal irinotecan to FOLFOX (1% and 0% respectively, of all patients with three-line sequences in 2016, compared to 4% and 5% in 2019). (Figure 2)*

CONCLUSIONS

- *The number of patients with metastatic pancreatic cancer receiving chemotherapy increased from 2016 to 2019.*
- *From 2016 to 2019, the use of two- and three- line sequences increased consistently.*
  - *Among Medicare FFS patients receiving two- and three-line sequences, those containing liposomal irinotecan in the second and third line were the primary drivers of this increase in utilization.*

LIMITATIONS

The data analyzed include the 2016-2019 Medicare FFS population. Analysis of different populations or time periods may yield different results. Our study used claims data and not electronic health records (EHRs), so we could not control for clinical covariates. Patient characteristics and regimen performance might influence which regimens patients receive. We did not study whether liposomal irinotecan-based therapy patients received concomitant 5-fluorouracil (5-FU) or prior gemcitabine-based therapy.

Author Contributions: Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: GD, ST, DD, PC, GK; Drafting of the publication, or revising it critically for important intellectual content: GD, ST, DD, PC, GK; Final approval of the publication: GD, ST, DD, PC, GK;

Disclosures: GD, ST, DD: Employees of Celgene and received consulting fees from Ipsen. PC: Is employed by Ipsen and owns shares stock. GK: Is employed by George Washington University and received consulting fees from Ipsen.

Presented at European Society for Medical Oncology (ESMO) Congress 2021 | September 16-21, 2021

This study was sponsored by Ipsen.

Trends in Use of One, Two, and Three-Line NCCN® Category 1 Regimens Among Medicare Fee-for-Service (FFS) Patients Receiving Treatment for Metastatic Pancreatic Cancer

Dieguez G[1], Tomicki S[1], Destephano D[1], Cockrum P[2]
[1]Milliman, Inc., New York, NY; [2]Ipsen Biopharmaceuticals, Cambridge, MA

OBJECTIVE

There is limited research evaluating the treatment of patients with metastatic pancreatic cancer according to NCCN® Category 1 guidelines. We analyzed trends in the use of NCCN® Category 1 regimens among Medicare fee-for-service (FFS) patients with metastatic pancreatic cancer receiving up to three lines of therapy.

DATA SOURSES

100% Medicare Research Identifiable (RIF) Claims Files (2016-2019)

- Contains all Medicare-paid Part A, B, and D claims for all FFS beneficiaries in the United States.
- Includes diagnosis, procedure, and diagnosis-related group (DRG) codes; beneficiary information, including age, sex, and eligibility status.

METHODS

Patient Identification

- Patients with metastatic pancreatic cancer were identified using International Classification of Disease (ICD)-10 diagnosis codes. We required:
  - Two or more claims with a pancreatic cancer diagnosis more than 30 days apart, and
  - One or more claims with a secondary malignancy (metastasis) diagnosis on or after the first pancreatic cancer diagnosis date.
- The "index date" was identified as the earliest metastasis diagnosis date.
- Patients were required to have six-month pre-index and three-month (or until death, if earlier) post-index Medicare FFS enrollment.
- Patients were excluded based on the presence of pre-index non-pancreatic malignancies.

Line of Therapy Assignment

- A line of therapy (LOT) was assigned based on the order of therapies used. The first LOT (1L) was defined as the first episode of an eligible therapy given in the 14 days preceding or after the patient's index date, with the next LOT (2L) beginning the day after a patient switched to a new regimen.
- The end of the most recent LOT was defined as the earlier of 28 days after the most recent administration, visit date, or order for oral therapy (after the first date of chemotherapy), or date of death, if applicable.
- Patients with one, two, or three LOTs were defined as treated according to NCCN® Category 1 guidelines if, in each LOT, patients used one of the following regimens:
  - FOLFIRINOX
  - Gemcitabine/nab-paclitaxel
  - Gemcitabine + erlotinib
  - Gemcitabine monotherapy

- 5-FU + leucovorin + liposomal irinotecan
- 2L+ Liposomal irinotecan-based regimens (5FU was not included in this analysis. See Limitations for further details.)

- Each LOT is assigned to the calendar year in which it begins. For example, patients with a third LOT that began in 2019 who received LOTs before 2019 would have only their third LOT assigned to calendar year 2019.

Regimen Sequence

- Regimen sequences were constructed as one-line, two-line, and three-line sequences. Patients with four or more lines of therapy were excluded from the analysis.
- Regimen sequences had no subsequent chemotherapy following the last regimen within a sequence.
  - One-line sequences had no chemotherapy or change in therapy following the first line. Similar logic applied to two and three lines.

Figure 1. Percent of Patients Treated with NCCN Category 1 Regimens by Line Sequence: One, Two, or Three Lines (2016 to 2019)

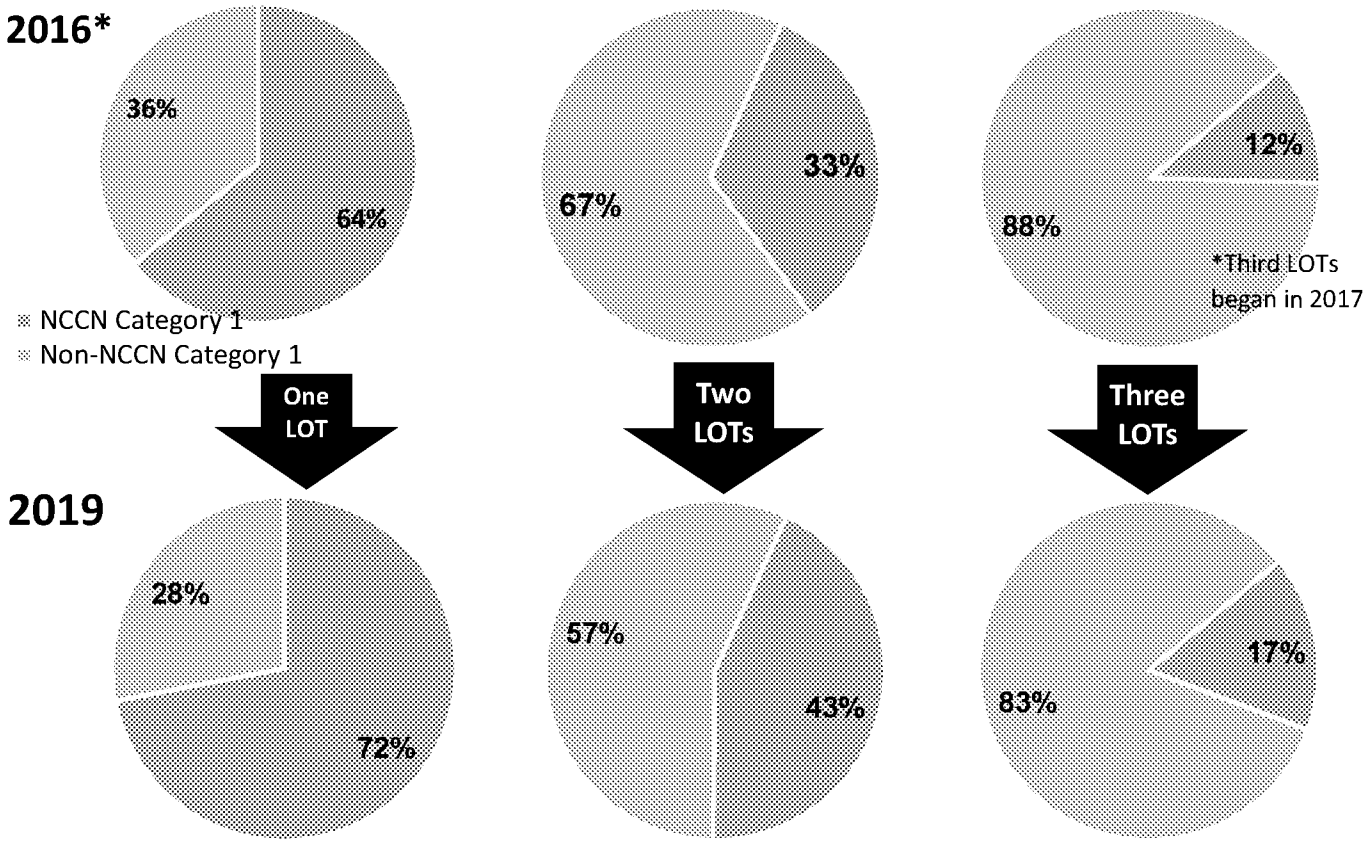
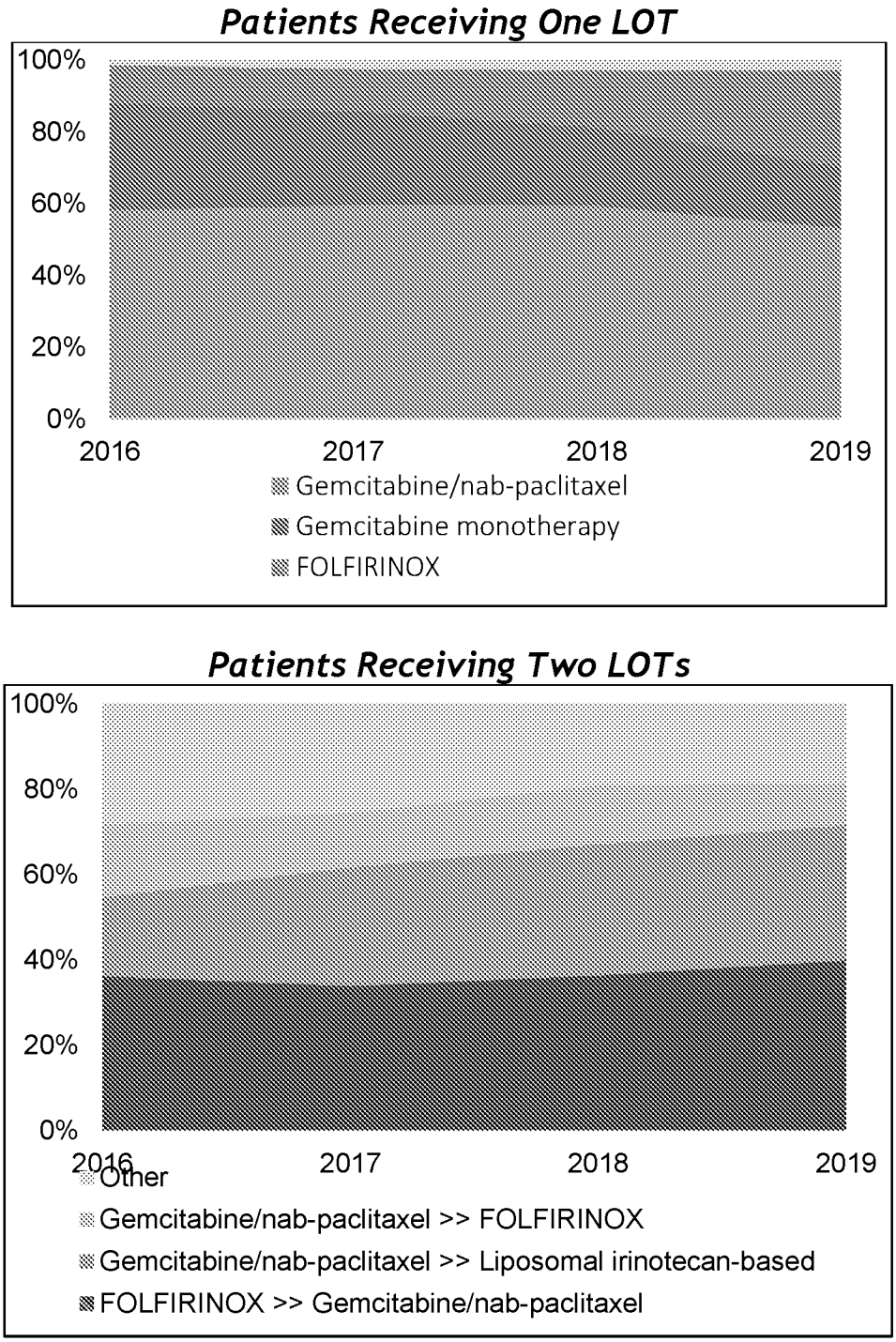


Figure 2. Top Sequences Among Patients with One and Two NCCN® Category 1 Line Sequences (2016-2019)



RESULTS

- We identified 31,782 Medicare beneficiaries with metastatic pancreatic cancer receiving one (21,304), two (7,352), and three (3,126) lines of therapy between 2016 and 2019.
- Among patients who received treatment, a higher portion were treated according to NCCN® Category 1 guidelines in 2019 than in 2016/2017. **(Figure 1)** The proportion of patients treated with an NCCN® Category 1 regimen increased:
    - From 64% in 2016 to 72% in 2019 for patients receiving 1 LOT.

    - From 33% in 2016 to 43% in 2019 for patients receiving 2 LOTs.
    - From 12% in 2017 to 17% in 2019 for patients receiving 3 LOTs.
- From 2016 to 2019, FOLFIRINOX had the largest increase in share of patients receiving one NCCN® Category 1 LOT (11% to 27%) and gemcitabine monotherapy had the largest decrease (30% to 17%). **(Figure 2)**
- Among patients receiving two NCCN® Category 1 LOTs, the sequence gemcitabine/nab-paclitaxel to liposomal irinotecan had the largest increase in share of patients (18% to 32%) and gemcitabine/nab-paclitaxel to FOLFIRINOX had the largest decrease (17% to 10%). **(Figure 2)**
- Among patients receiving three NCCN® Category 1 LOTs, patient share for FOLFIRINOX to gemcitabine/nab-paclitaxel to liposomal irinotecan was 35% in 2019, while gem/nab to FOLFIRINOX to liposomal irinotecan was 8%; patient counts in earlier years were too small to calculate patient share.

CONCLUSIONS

- The use of NCCN® Category 1 therapies increased consistently from 2016 to 2019 among patients that received one, two, and three lines of therapy.
    - FOLFIRINOX drove increases in NCCN® Category 1 utilization among patients receiving 1 line of therapy.
    - The sequence Gemcitabine/nab-paclitaxel => liposomal irinotecan was the primary driver of the increase among patients receiving 2 lines of therapy.
    - The sequence FOLFIRINOX => gemcitabine/nab-paclitaxel => liposomal irinotecan was the primary driver of increase among patients receiving 3 lines of therapy.

Limitations

The data analyzed include the 2016-2019 Medicare FFS population. Analysis of different populations or time periods may yield different results. Our study used claims data and not electronic health records (EHRs), so we could not control for clinical covariates. Patient characteristics and regimen performance might influence which regimens patients receive. We did not study whether liposomal irinotecan-based therapy patients received concomitant 5-fluorouracil (5-FU) or prior gemcitabine-based therapy.

Author Contributions Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: [GD, ST, DD, PC]; Drafting of the publication, or revising it critically for important intellectual content: [GD, ST, DD, PC]; Final approval of the publication: [GD, ST, DD, PC].

Disclosures [GD, ST, DD] : Employees of Milliman and received consulting fees from Ipsen. [PC] is employed by Ipsen and owns Ipsen stock.

This study was sponsored by Ipsen

Presented at ASCO Quality Care Symposium 2021 | September 24-25, 2021

Trends in Use of One, Two, and Three-Line NCCN® Category 1 Regimens Among Medicare Fee-for-Service (FFS) Patients Receiving Treatment for Metastatic Pancreatic Cancer

OBJECTIVE

DATA SOURCES

METHODS

Patient Identification

Line of Therapy Assignment

Regimen Sequence

Figure 1. Percent of Patients Treated with NCCN® Category 1 Regimens by Line Sequence: One, Two, or Three Lines (2016 to 2019)

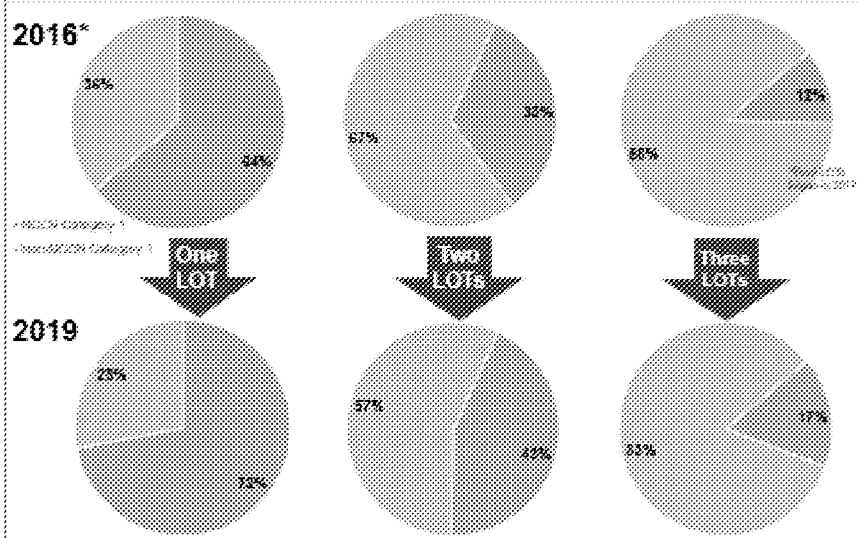
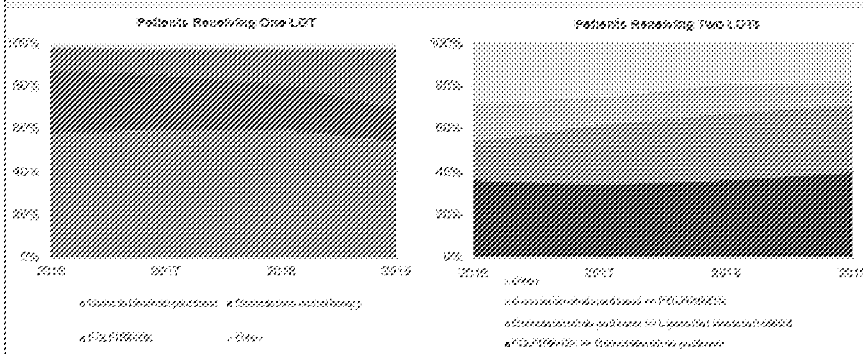


Figure 2. Top Sequences Among Patients with One and Two NCCN® Category 1 Line Sequences (2016-2019)



RESULTS

CONCLUSIONS

LIMITATIONS

Presented at ASCO Quality Care Symposium 2021 | September 24-25, 2021

This study was sponsored by Ipsen.

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Comparison of first line (1L) treatment (tx) patterns and overall survival by age at diagnosis among patients with metastatic pancreatic ductal adenocarcinoma (mPDAC)

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Introduction

- Pancreatic cancer incidence and mortality rates are highest in patients aged ≥65 years.
- Older adults are under-represented in clinical trials and their oncological care is complicated with various age-related conditions.
- There are limited data to guide the management of older patients with mPDAC. Therefore, a better understanding of the real-world population will help with the development of better treatment strategies for older patients with mPDAC.
- Our study aimed to describe the differences in treatment strategy and in survival outcomes for patients by age at diagnosis.

Methods

- Retrospective descriptive analysis was performed using the Flatiron Health® longitudinal database including data from over 280 cancer clinics
- This analysis identified and evaluated adult patients diagnosed with mPDAC between January 1, 2015 and March 31, 2020
- Eligible patients were at least 18 years old at treatment initiation for a mPDAC, had a recorded activity within 90 days of their metastatic diagnosis date, and had at least one recorded activity after the start of treatment

Measures and Statistical analyses

- Baseline patient demographics and clinical characteristics, proportion of treated patients by line of therapy, and overall survival from treatment initiation were assessed
- Outcomes were stratified by age at diagnosis (<70 years, 70 to 79 years, and ≥80 years) and by treatment regimen received in first line (1L)

Figure 1. Proportion of patients who received systemic treatment

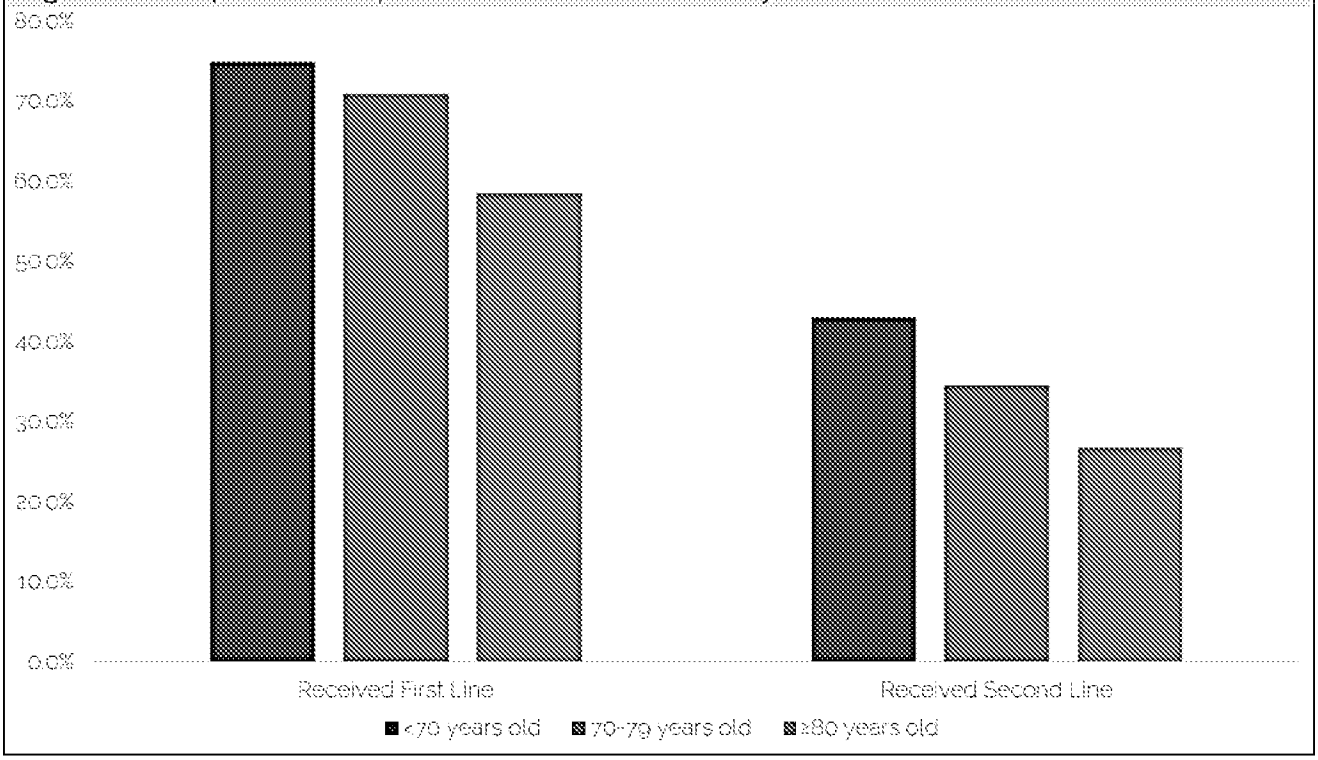


Figure 2. Most frequent 1L metastatic treatment regimens overall and by age at diagnosis

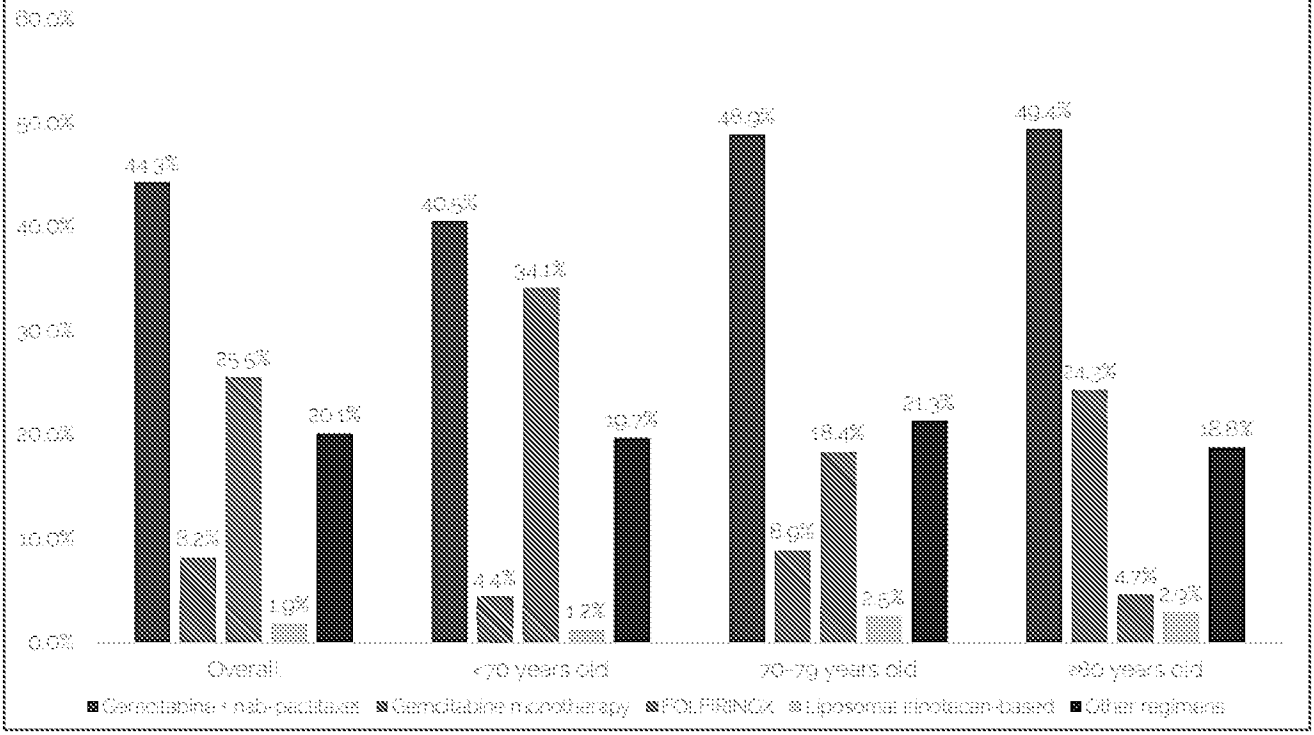


Figure 3. Overall survival by age at diagnosis

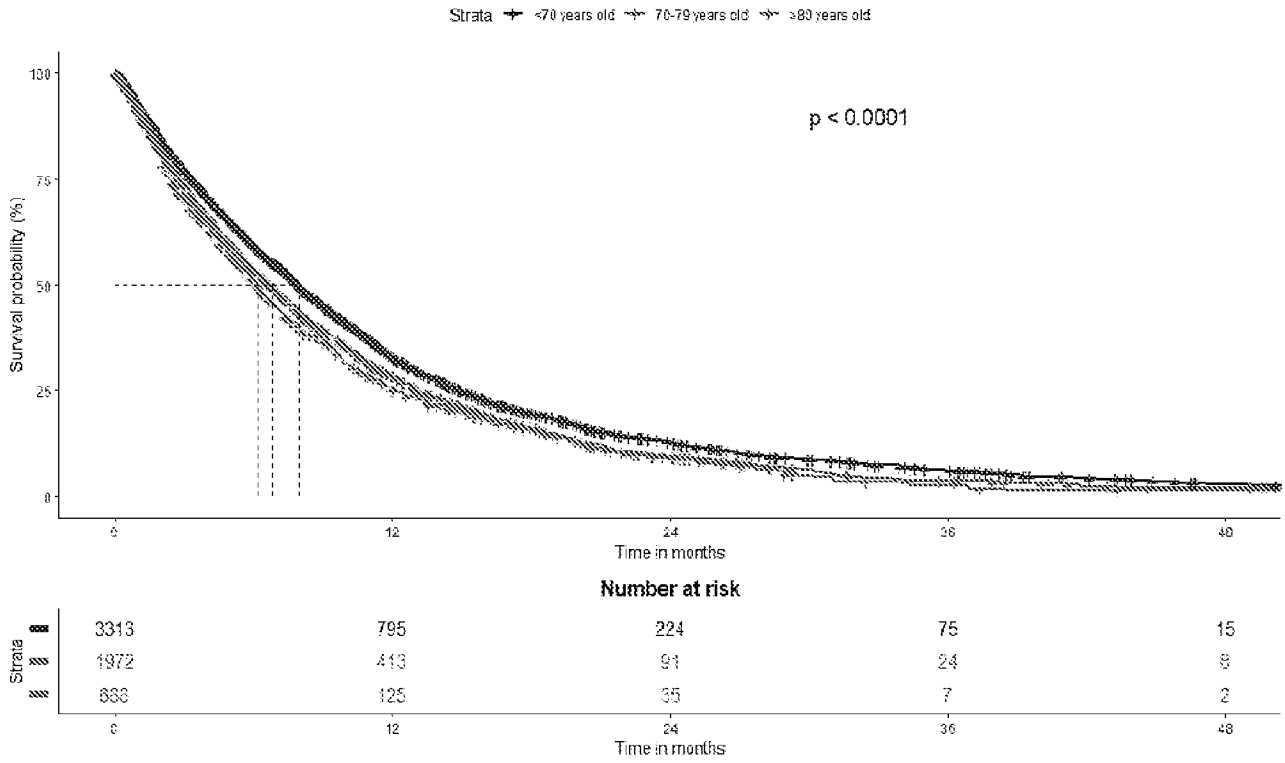


Table 1. Overall survival by 1L metastatic regimen

Treatment Regimen	<70 years mOS (95% CI)	70-79 years mOS (95% CI)	≥80 years mOS (95% CI)	p-value
Overall	7.9 (7.6 – 8.3)	6.8 (6.3 – 7.2)	6.2 (5.5 – 6.8)	<0.001
Gemcitabine + nab-paclitaxel	6.9 (6.4 – 7.5)	6.5 (5.8 – 7.1)	6.8 (5.9 – 8.7)	0.25
Gemcitabine monotherapy	3.0 (2.2 – 4.1)	4.0 (3.1 – 5.2)	4.4 (3.3 – 5.7)	0.72
FOLFIRINOX	9.8 (9.0 – 10.4)	9.6 (8.1 – 11.2)	6.6 (2.3 – 13.6)	0.004
Liposomal irinotecan-based	7.0 (4.7 – 12.8)	6.9 (5.3 – 8.6)	6.8 (4.5 – NP)	0.75

RESULTS

Treatment patterns and patient characteristics

- The proportion of patients who received treatment decreased by age at mPDAC diagnosis from 74.9% among patients who were <70 years old to 58.5% among patients who were ≥80 years (Figure 1)
- The most frequent 1L regimen overall was gemcitabine + nab-paclitaxel, accounting for 44.3% (n=2,647) of the cohort
- FOLFIRINOX was received by only 4.7% (n=32) of patients aged ≥80 years compared to 34.1% (n=1,131) of patients aged <70 years (Figure 2)

Overall Survival

- The median overall survival (mOS) for all 1L treated patients decreased with increased age: 7.9 months (95% CI: 7.6 – 8.3) for those aged <70 years vs 6.8 months (6.3 – 7.2) among patients aged 70-79years and 6.2 months (5.5 – 6.8) among patients aged ≥80 years ($p < 0.001$) (Figure 3)
- No significant differences in overall survival were observed by age group among patients treated with the same regimen (Table 1)

Conclusions

- This study of treatment patterns among patients with mPDAC found that older patients were less likely to receive first or subsequent line of therapies for pancreatic cancer.
- Older patients that received systemic therapy had similar survival outcomes to younger patients treated with a similar regimen.
- The results of this large descriptive analysis suggest that the treatment strategy of mPDAC should not be based on age but rather on an overall assessment of the performance/functional status and geriatric profile of older patients

Limitations

- Age at diagnosis is capped at 85 for patient privacy therefore outcomes among the oldest patients in the cohort could not described
- Overall survival results are not adjusted for important covariates

Conflicts of interest

R.W. has no conflicts to disclose; P.C. is an employee of and has stock in Ipsen; A.S., S.W., and B.C.C. are employees of Genesis Research, which receives consulting fees from Ipsen;

This study was sponsored by Ipsen

Presented at the American Society of Clinical Oncology Gastrointestinal Cancer Symposium (ASCO GI) 2021, January 15–17, 2021, Virtual Congress

Comparison of treatment (tx) patterns and overall survival by age at diagnosis among patients with metastatic pancreatic adenocarcinoma (mPDAC)

Introduction

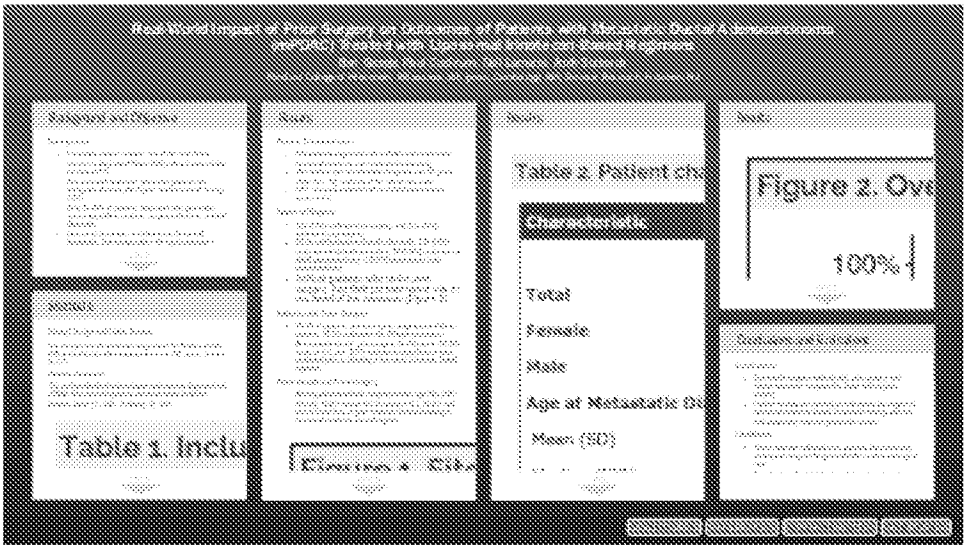
Methods

Results

Conclusions

Limitations

Real-World Impact of Prior Surgery on Outcomes of Patients with Metastatic Ductal Adenocarcinoma (mPDAC) Treated with Liposomal Irinotecan-Based Regimens



Ben George, Paul Cockrum, Neil Lamarre, Andy Surinach

Medical College of Wisconsin, Milwaukee, WI; Ipsen, Cambridge, MA; Genesis Research, Hoboken, NJ

PRESENTED AT:

Virtual Poster Symposium VIRTUAL ISPOR 2021

BACKGROUND AND OBJECTIVE

Background

- Pancreatic cancer remains one of the most lethal cancers in the United States (US) with a 5-year relative survival of 9%[1]
- Due to limited treatment options for patients with metastatic disease, the 5-year relative survival is only 2.9%[2]
- Only 15-20% of patients diagnosed with pancreatic cancer are able to undergo surgery at the time of initial diagnosis[3]
- Liposomal irinotecan, an intravenous liposomal formulation that encapsulates the topoisomerase 1 inhibitor irinotecan in a lipid-bilayer vesicle, is the only U.S. Food and Drug Administration and European Medicines Agency approved second-line/post-gemcitabine treatment in mPDAC that is National Comprehensive Cancer Network (NCCN) Category 1 [4,5]

Objective

This study sought to describe demographic and clinical characteristics and treatment outcomes based on prior surgery in a real-world setting among patients with mPDAC treated with liposomal irinotecan-based regimens

METHODS

Study Design and Data Source

This retrospective observational study utilized the Flatiron Health EHR-derived de-identified database from over 280 cancer clinics in the US.

Patient Selection

This analysis identified and evaluated adult patients diagnosed with mPDAC who received liposomal irinotecan-based treatment between January 1, 2015 – February 29, 2020

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	N
Patients diagnosed with mPDAC between January 1, 2014 and February 29, 2020	9748
Patients who had recorded activity in Flatiron network within 90 days of metastatic diagnosis date	8976
Patients who were least 18 years of age at metastatic diagnosis	8976
Patients treated with liposomal irinotecan-based regimen. The index date was the start date of the first line of therapy which contains this agent	695
Patients whose index date was between January 1, 2015 and February 29, 2020	610
Exclusion Criteria	**N**
Patients without activity in Flatiron network on or after the respective index date	610
Patients whose index date occurred after their death date (after assigning the 15th day of the month to derive date of death)	608

Measures and Statistical Analyses

- Patients were stratified based on surgery prior to initiating a liposomal irinotecan-based regimen
- Categorical variables including treatment patterns, and demographic/clinical characteristics were summarized using frequencies and percentages
- Continuous variables were summarized using means, standard deviations, medians, and interquartile ranges
- Median overall survival (mOS) from treatment initiation and metastatic diagnosis was derived using Kaplan-Meier analyses
- All data analyses were carried out using SAS 9.4

RESULTS

Patient Characteristics

- 608 patients diagnosed with mPDAC and treated with liposomal irinotecan were included in the study
- The median age at metastatic diagnosis was 68 years (IQR: 61 – 74) and 52% of the cohort was male
- 59% of overall patients had an ECOG performance score of 0-1

Types of Surgery

- 454 (75%) underwent no surgery, and 154 (25%) underwent any surgery
- Of the total patients included in the study, 118 (19%) underwent a Whipple procedure, 35 (5.8%) underwent a distal pancreatectomy, 1 (0.2%) underwent a total pancreatectomy
- 44% of patients who underwent surgery had their primary tumor site in the head of the pancreas (Figure 1)

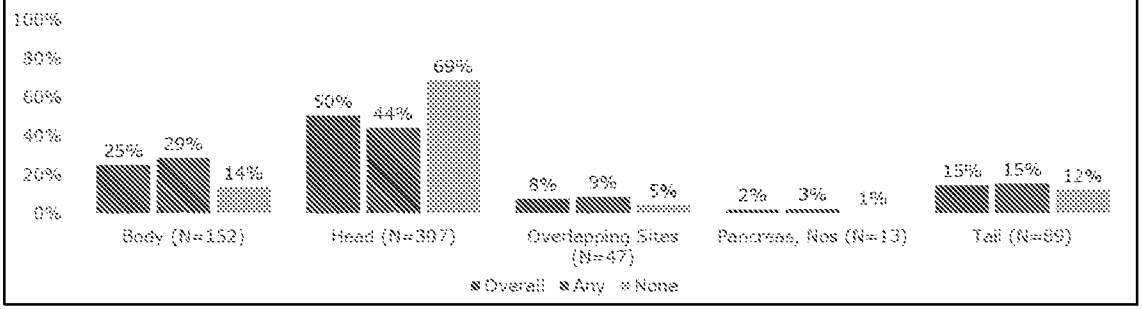
Patients with Prior Surgery

- 25.3% of patients underwent prior surgery and of these patients, 76.6% underwent the Whipple procedure.
- Among patients with prior surgery, 61.0% had an ECOG score of 0-1, and 32.5% had two or more lines of prior treatment prior to initiating a liposomal irinotecan-based regimen

Patients without Prior Surgery

- Among patients without surgery (median age 68y (IQR: 61-74)), 59.2% had an ECOG score of 0-1, 39.4% had two or more lines of prior treatment before initiating a liposomal irinotecan-based regimen

Figure 1. Site of Primary Tumor by Prior Surgery



RESULTS

Table 2. Patient characteristics

Characteristic	Overall	None	Any
	N (%)		
Total	608	454	154
Female	289 (48%)	214 (47%)	75 (49%)
Male	319 (52%)	240 (53%)	79 (51%)
Age at Metastatic Diagnosis			
Mean (SD)	67 (9)	67 (9)	67 (9)
Median (IQR)	68 (61 - 74)	68 (61 - 74)	70 (62 - 74)
Race			
Asian	13 (2.1%)	10 (2.2%)	3 (1.9%)
Black or African American	48 (7.9%)	38 (8.4%)	10 (6.5%)
Hispanic or Latino	4 (0.7%)	4 (0.9%)	0 (0%)
White	448 (74%)	335 (74%)	113 (73%)
Other Race	62 (10%)	39 (8.6%)	23 (15%)
Missing/Unknown	33 (5.4%)	28 (6.2%)	5 (3.2%)
Stave IV Initial Diagnosis	335 (55%)	332 (71%)	13 (8.4%)
ECOG			
0	100 (16%)	72 (16%)	28 (18%)
1	263 (43%)	197 (43%)	66 (43%)
2+	109 (18%)	81 (18%)	28 (18%)
Missing	136 (22%)	104 (23%)	32 (21%)
Prior Lines of Therapy			
0	90 (15%)	57 (13%)	33 (21%)
1	289 (48%)	218 (48%)	71 (46%)
2	177 (29%)	138 (30%)	39 (25%)
3+	52 (8.6%)	41 (9.0%)	11 (7.1%)

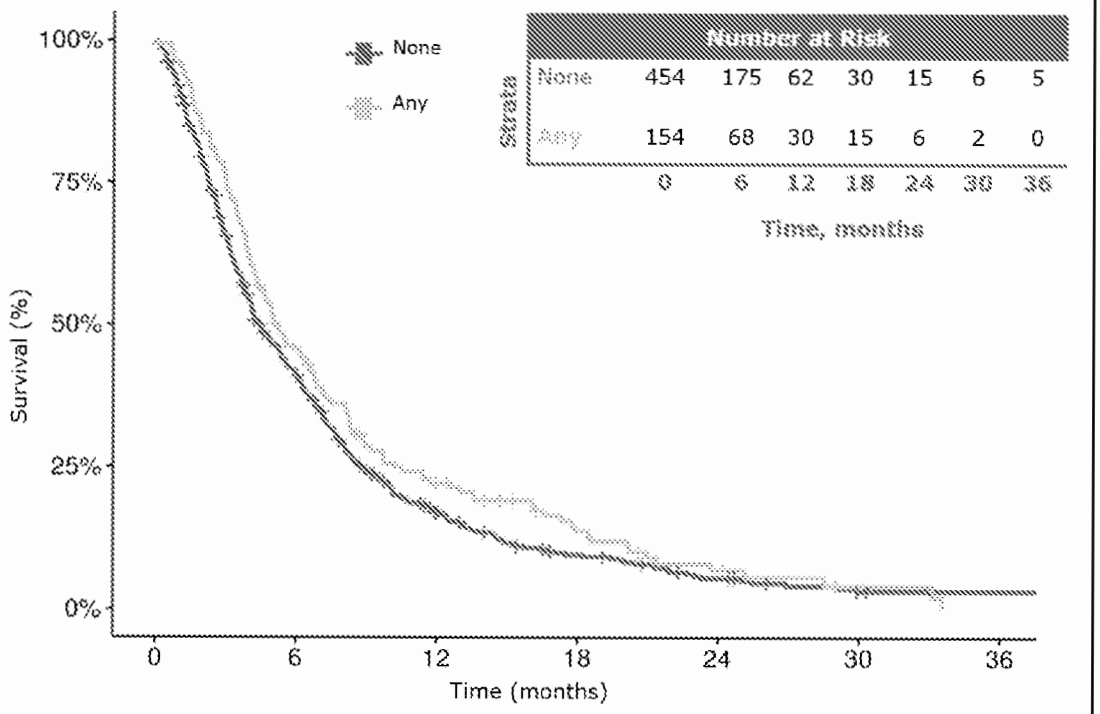
Overall Survival

- Median overall survival from the start of treatment for patients with prior surgery was 5.2 months (mos) (95% CI: 4.4-6.8) and 4.4 months (95% CI: 4.0–5.3) among patients with no prior surgery (p = 0.11)
- Median overall survival from metastatic diagnosis for patients with prior surgery was 16.1 months (95% CI: 13.1-19.0) and 14.4 months (95% CI: 13.3–15.7) among patients with no prior surgery (p = 0.3)

- Overall, median overall survival for patients treated with liposomal irinotecan-based regimens in first-, second-, and third line plus in the metastatic setting was 6.9 months (5.6 – 8.4), 5.0 months (4.2–6.2), and 3.8 months (3.3–4.4), respectively ($p < 0.0001$)

RESULTS

Figure 2. Overall Survival by Prior Surgery



CONCLUSIONS AND LIMITATIONS

Conclusions

- Our results suggest patients with prior surgery had similar outcomes compared to those without prior surgery
- Further studies are needed to understand the impact of liposomal irinotecan-based treatments among patients with previously resected pancreatic cancer

Limitations

- These data are collected from primarily the community setting and may not be generalizable to other settings of care
- Sensitivity and specificity of mortality data may impact survival estimates

DISCLOSURES

Medical Writing Support

Medical writing support was supported by Ipsen in accordance with GPP3

Conflicts of interest

BG serves in an advisory role for Ipsen. PC is an employee of Ipsen. AS and NL are employees of Genesis Research, which receives funding from Ipsen

This study was sponsored by Ipsen

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Real-world CA19-9 level monitoring patterns and its association with clinical outcomes among patients with metastatic pancreatic ductal adenocarcinoma (mPDAC)

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[1]Medical College of Wisconsin, Milwaukee, WI, USA; [2]Genesis Research, Hoboken, NJ, USA; [3]Ipsen, Cambridge, MA, USA

BACKGROUND

- Pancreatic cancer is predicted to account for 48,220 deaths in the United States in 2021, making it the 3rd deadliest cancer[1]
- Evaluation of treatment response in patients with mPDAC necessitates scheduled clinical and radiographic assessments along with monitoring serum CA 19-9 levels[2]
- The 5-year relative survival across all stages for patients with pancreatic cancer is 10%[3-4]
- CA 19-9 has shown to be an effective prognostic biomarker that can be used to aid in treatment decisions with mPDAC patients[5-11]

OBJECTIVE

- **The objective of this study is to assess the impact of serum CA19-9 monitoring and its association with clinical outcomes in patients with mPDAC 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, 2014 and June 30, 2020
- Index date was defined as the first-line (1L) treatment initiation date for mPDAC
- 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 1L systemic therapy
  - had at least one recorded activity after the start of treatment

Table 1. Patient characteristics at the start of therapy

Characteristic	Overall, N = 6,118	No Testing, N = 781	Baseline Only, N = 1,082	One Test During 1L, N = 896	Multiple 1L Tests, N = 3,359
Male, n (%)	3,336 (55%)	423 (54%)	619 (57%)	497 (55%)	1,797 (53%)
Age at Treatment Start, years, median (IQR)	68 [61 - 75]	68 [60 - 74]	70 [63 - 76]	69 [61 - 76]	68 [61 - 75]
ECOG PS, n (%)					
0	1,368 (22%)	122 (16%)	185 (17%)	167 (19%)	894 (27%)
1	2,045 (33%)	243 (31%)	357 (33%)	323 (36%)	1,122 (33%)
2+	795 (13%)	136 (17%)	227 (21%)	130 (15%)	302 (9.0%)
Missing	1,910 (31%)	280 (36%)	313 (29%)	276 (31%)	1,041 (31%)
Baseline CA19-9 Category					
Normal	701 (11%)	0 (0%)	197 (18%)	125 (14%)	379 (11%)
Elevated	3,867 (63%)	0 (0%)	885 (82%)	534 (60%)	2,448 (73%)
Missing	1,550 (25%)	781 (100%)	0 (0%)	237 (26%)	532 (16%)
Progressed to 2L	2,324 (38%)	196 (25%)	151 (14%)	282 (31%)	1,695 (50%)
Duration of 1L Therapy, weeks, Median [IQR]	10 [3 - 22]	4 [0 - 11]	1 [0 - 4]	5 [2 - 10]	18 [10 - 31]
Time between CA19-9 Tests, weeks, Median [IQR]	3.5 [2.1 - 5.6]	N/A	N/A	5.0 [2.0 - 9.9]	3.3 [2.1 - 4.9]

CA19-9, Cancer-associated antigen 19-9
ECOG PS, Eastern Cooperative Oncology Group Performance Score
IQR, Interquartile range
NOS, Not otherwise specified

Measures and Statistical analyses

- Baseline patient demographics and clinical characteristics, real-world overall survival (OS) and serum CA 19-9 levels were determined
- Serum CA19-9 levels at baseline and during 1L treatment were extracted
- CA 19-9 levels > 40 IU/mL were considered elevated
- Data regarding patient exposure to second (2L) systemic therapies were collected
- Categorical variables were described with counts and percentages, summary statistics (mean, SD, etc) were generated for continuous variables
- Kaplan-Meier methods were used to calculated median overall survival
- Analysis was conducted using R (version 4.0.0)

RESULTS

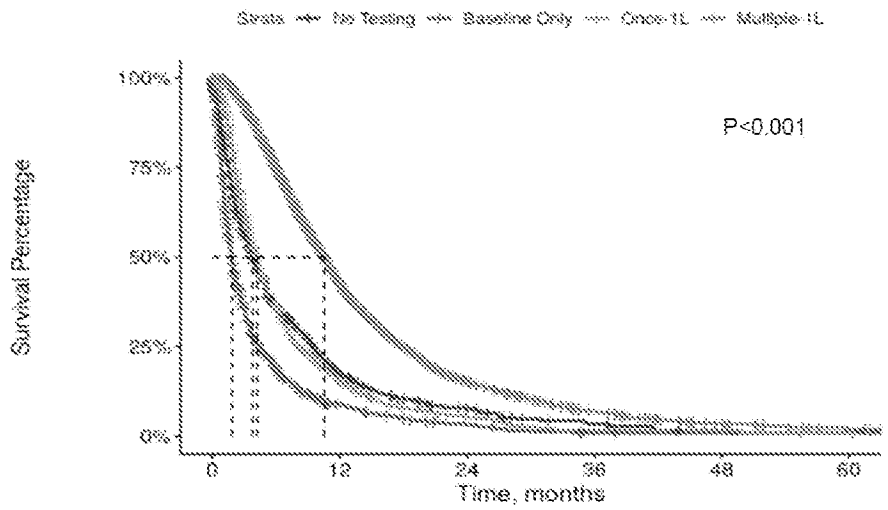
Patient Characteristics

- Total of 6,118 patients were included in the analysis
- The median age for the overall cohort was 68 years (IQR: 61 – 75); 54.5% were male and 67.1% were white
- The proportion of patients with ECOG PS 2+ was the lowest among patients who received multiple 1L testing (Table 1)

Testing Patterns

- 5,337 (87.2%) patients were tested for CA 19-9 prior to or during 1L treatment
    - Majority of these patients (62.9%; n=3,359) were tested for CA 19-9 multiple times during treatment
- Among patients who were evaluated for CA 19-9 level prior to starting 1L treatment, 84.6% had an elevated serum CA 19-9 (> 40 IU/mL)
- 63% of patients with elevated baseline CA 19-9 levels received multiple tests during treatment compared to 54% of patients with normal levels
- 1L Duration of therapy was similar across baseline CA 19-9 levels
    - Normal: 11 weeks (IQR: 4 – 24)
    - Elevated: 10 weeks (IQR: 3 – 23)
- The time between tests on average was lower among patients with elevated CA 19-9 than patients with normal CA 19-9 (4.1 weeks vs 6.6 weeks)

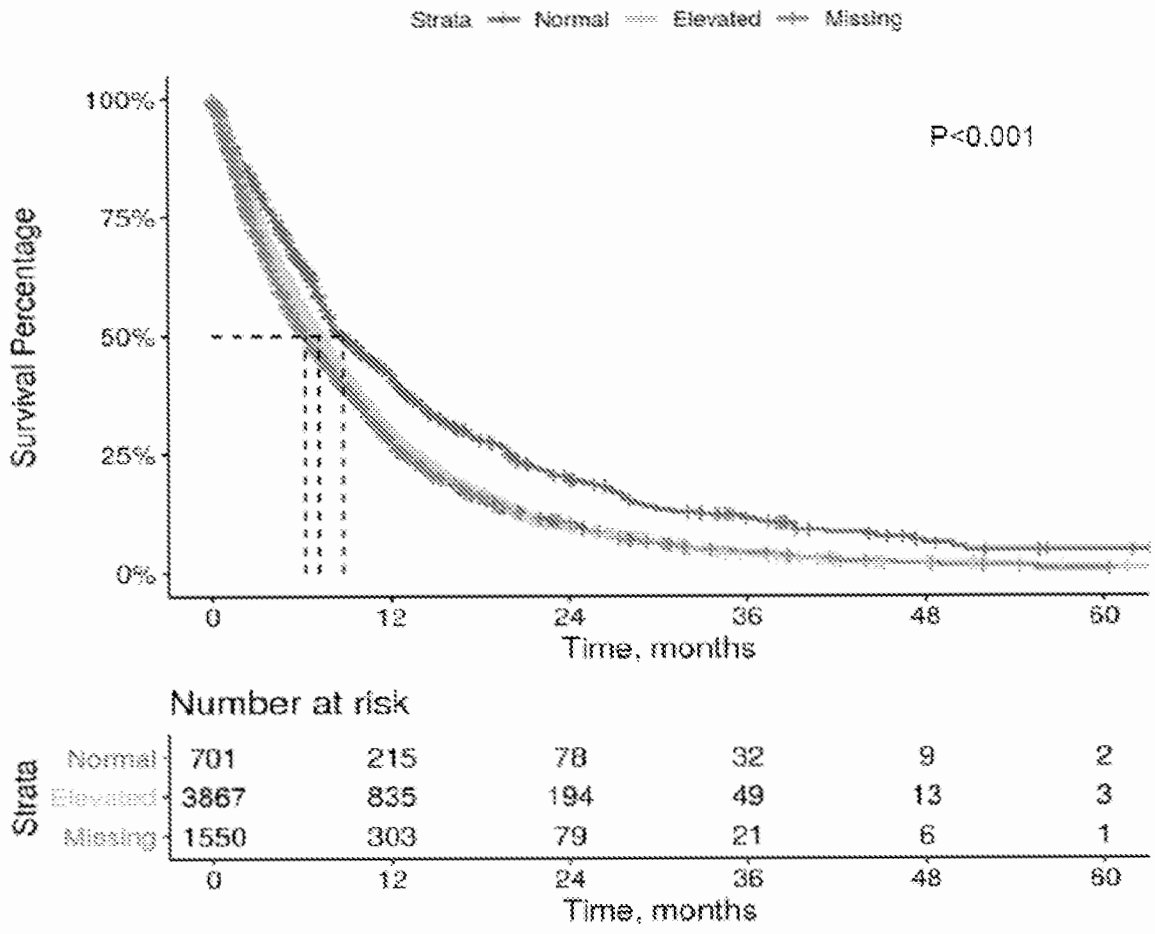
Figure 1. Overall Survival by CA19-9 Testing Status



Overall Survival

- The median OS (mOS) of patients with no baseline CA 19-9 assay, only baseline assays, a single assay during 1L and > 1 assay during 1L was 3.8, 1.9, 4.2, and 11 months, respectively ($p < 0.001$) (Figure 1)
- The mOS for patients who had no baseline serum CA 19-9 measurement result, a normal baseline CA 19-9 level or an elevated baseline CA 19-9 level were 6.3 months, 8.8 months and 7.2 months, respectively ($p < 0.001$) (Figure 2)

Figure 2. Overall Survival by Baseline CA19-9



Conclusions

- The prognostic utility of CA 19-9 for patients with mPDAC was demonstrated in one of the largest, contemporary, real-world studies of patients with mPDAC to date.
- Routine serial monitoring of CA 19-9 levels during 1L treatment may be warranted, in addition to clinical and radiographic assessment, and may translate into better patient outcomes.
- Further validation studies are needed to understand the generalizability of these results

Limitations

- EHR data are subject to possible entry errors and missing information which could have led to extreme or incorrect values
- This study did not evaluate how specific treatment regimens impacted CA 19-9 levels and further research is necessary to characterize individual treatment regimens
- 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
- These data are collected from primarily the community setting and may not be generalizable to other settings of care

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Medical Writing Support

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Conflicts of interest

BG serves in an advisory role for Ipsen. PC is an employee of Ipsen. At the time of the study AC was an employee of Ipsen. MK, AS, and NL are employees of Genesis Research, which receives funding from Ipsen

This study was sponsored by Ipsen

Presented at AACR 2021 | Virtual Congress | April 10-15, 2021

Real-world CA19-9 level monitoring patterns and its association with clinical outcomes among patients with metastatic pancreatic ductal adenocarcinoma (mPDAC)

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BACKGROUND

- Pancreatic cancer is predicted to account for 48,220 deaths in the United States in 2021, making it the 3rd deadliest cancer[1]
- Evaluation of treatment response in patients with mPDAC necessitates scheduled clinical and radiographic assessments along with monitoring serum CA 19-9 levels[2]
- The 5-year relative survival across all stages for patients with pancreatic cancer is 10%[3,4]
- CA 19-9 has shown to be an effective prognostic biomarker that can be used to aid in treatment decisions with mPDAC patients[5,6]

OBJECTIVE

- The objective of this study is to assess the impact of serum CA19-9 monitoring and its association with clinical outcomes in patients with mPDAC 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

- The analysis identified and evaluated adult patients diagnosed with mPDAC between January 1, 2014 and June 30, 2020
- Index date was defined as the first-line (1L) treatment initiation date for mPDAC
- 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 1L systemic therapy
  - had at least one recorded activity after the start of treatment

Table 1. Patient characteristics at the start of therapy

Characteristic	Overall, N = 5,118	No Testing, N = 779	Baseline Only, N = 2,780	Only Test During 1L, N = 1,559	Multiple 1L Tests, N = 1,780
Male, n (%)	3,239 (63.3)	482 (61.9)	1,769 (63.6)	987 (63.3)	1,081 (60.7)
Age at Treatment Start, years, median (IQR)	68 (61 – 75)	69 (60 – 76)	68 (61 – 75)	68 (61 – 75)	68 (61 – 74)
ECOG PS, n (%)					
0	1,668 (32.6)	181 (23.2)	1,022 (36.8)	189 (12.1)	276 (15.5)
1	2,566 (50.1)	343 (44.0)	1,357 (48.8)	921 (59.1)	945 (53.1)
2+	705 (13.8)	180 (23.1)	357 (12.8)	404 (25.9)	264 (14.8)
Unknown	179 (3.5)	75 (9.6)	44 (1.6)	45 (2.9)	315 (17.7)
Baseline CA19-9 Category					
<Normal	1,011 (19.8)	0 (0.0)	687 (24.7)	149 (9.6)	175 (9.8)
Elevated	3,861 (75.4)	0 (0.0)	2,093 (75.3)	1,410 (90.5)	1,358 (76.3)
Missing	246 (4.8)	779 (100.0)	0 (0.0)	0 (0.0)	247 (13.9)
Progressed to 2L	1,994 (39.0)	166 (21.3)	1,121 (40.3)	199 (12.8)	508 (28.5)
Duration of 1L Therapy, weeks, Median (IQR)	10 (5 – 17)	4 (2 – 8)	10 (5 – 16)	9 (5 – 15)	10 (6 – 21)
Time between CA19-9 Tests, weeks, Median (IQR)	5 (3.1 – 6.9)	N/A	N/A	5 (3.1 – 6.9)	5 (3.3 – 6.9)

Footnotes: Values may not add to 100% due to rounding; ECOG PS, Eastern Cooperative Oncology Group Performance Score; IQR, Interquartile range; N/A, Not applicable; SD, Standard deviation

Measures and Statistical analyses

- Baseline patient demographics and clinical characteristics, real-world overall survival (OS) and serum CA 19-9 levels were determined
- Serum CA19-9 levels at baseline and during 1L treatment were extracted
- CA 19-9 levels > 40 IU/mL were considered elevated
- Data regarding patient exposure to second (2L) systemic therapies were collected
- Categorical variables were described with counts and percentages, summary statistics (mean, SD, etc) were generated for continuous variables
- Kaplan-Meier methods were used to calculated median overall survival
- Analysis was conducted using R (version 4.0.0)

RESULTS

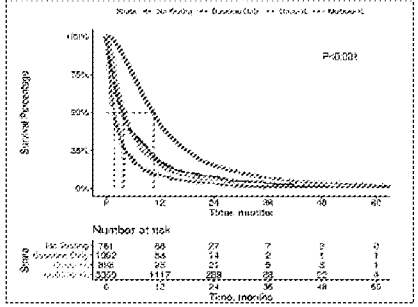
Patient Characteristics

- Total of 6,118 patients were included in the analysis
- The median age for the overall cohort was 68 years (IQR: 61 – 75); 54.5% were male and 67.1% were white
- The proportion of patients with ECOG PS 2+ was the lowest among patients who received multiple 1L testing (Table 1)

Testing Patterns

- 5,337 (87.2%) patients were tested for CA 19-9 prior to or during 1L treatment
  - Majority of these patients (62.5%; n=3,359) were tested for CA 19-9 multiple times during treatment
- Among patients who were evaluated for CA 19-9 level prior to starting 1L treatment, 84.6% had an elevated serum CA 19-9 (> 40 IU/mL)
- 63% of patients with elevated baseline CA 19-9 levels received multiple tests during treatment compared to 54% of patients with normal levels
- 1L Duration of therapy was similar across baseline CA 19-9 levels
  - Normal: 11 weeks (IQR: 4 – 24)
  - Elevated: 10 weeks (IQR: 3 – 23)
- The time between tests on average was lower among patients with elevated CA 19-9 than patients with normal CA 19-9 (4.1 weeks vs 6.6 weeks)

Figure 1. Overall Survival by CA19-9 Testing Status

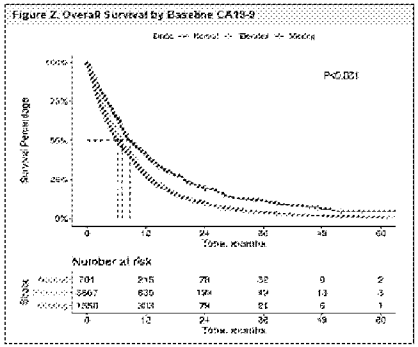


RESULTS (Continued)

Overall Survival

- The median OS (mOS) of patients with no baseline CA 19-9 assay, only baseline assays, a single assay during 1L and ≥ 1 assay during 1L was 3.8, 1.9, 4.2, and 11 months, respectively (p < 0.001) (Figure 1)
- The mOS for patients who had no baseline serum CA 19-9 measurement result, a normal baseline CA 19-9 level or an elevated baseline CA 19-9 level were 6.3 months, 8.8 months and 7.2 months, respectively (p < 0.001) (Figure 2)

Figure 2. Overall Survival by Baseline CA19-9



Conclusions

- The prognostic utility of CA 19-9 for patients with mPDAC was demonstrated in one of the largest, contemporary, real-world studies of patients with mPDAC to date.
- Routine serial monitoring of CA 19-9 levels during 1L treatment may be warranted, in addition to clinical and radiographic assessment, and may translate into better patient outcomes.
- Further validation studies are needed to understand the generalizability of these results

Limitations

- EHR data are subject to possible entry errors and missing information which could have led to extreme or incorrect values
- This study did not evaluate how specific treatment regimens impacted CA 19-9 levels and further research is necessary to characterize individual treatment regimens
- Age was limited to 89 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
- These data are collected from primarily the community setting and may not be generalizable to other settings of care

References

Medical Writing Support

Conflicts of Interest

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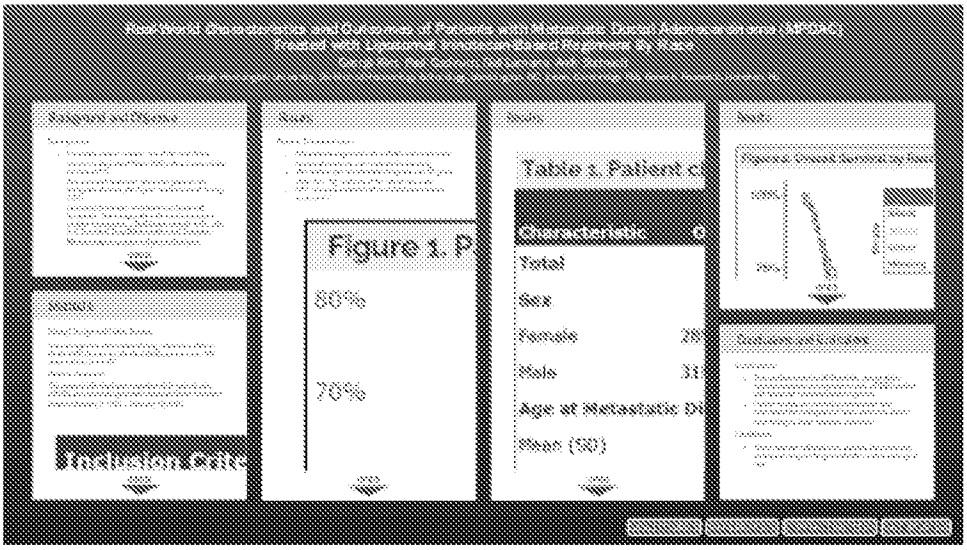
Real-World Characteristics and Outcomes of Patients with Metastatic Ductal Adenocarcinoma (MPDAC) Treated with Liposomal Irinotecan-Based Regimens By Race



George Kim, Paul Cockrum, Neil Lamarre, Andy Surinach

George Washington University, Division of Hematology & Oncology, Washington, DC; Ipsen, Cambridge, MA; Genesis Research, Hoboken, NJ

PRESENTED AT:

Virtual Poster Showcase

VIRTUAL ISPOR 2021

BACKGROUND AND OBJECTIVE

Background

- Pancreatic cancer remains one of the most lethal cancers in the United States (US) with a 5-year relative survival of 9%[1]
- Due to limited treatment options for patients with metastatic disease, the 5-year relative survival is only 2.9%[2]
- Liposomal irinotecan, an intravenous liposomal formulation that encapsulates the topoisomerase 1 inhibitor irinotecan in a lipid-bilayer vesicle, is the only U.S. Food and Drug Administration and European Medicines Agency approved second-line/post-gemcitabine treatment in mPDAC that is National Comprehensive Cancer Network (NCCN) Category 1 [3,4]
- Racial disparities persist in outcomes for patients with pancreatic cancer in the United States, with Black or African American patients having higher age-adjusted incidence and mortality than White patients.2
- Results from the pivotal phase 3 study, NAPOLI-1, and recent literature suggest that participants of East Asian ethnic origin experience better outcomes than other ethnic groups with liposomal irinotecan+5-fluorouracil/leucovorin following gemcitabine.[5]

Objective

This study sought to describe clinical characteristics and treatment outcomes based on race among patients with mPDAC treated with liposomal irinotecan-based regimens

METHODS

Study Design and Data Source

This retrospective observational study utilized the Flatiron Health EHR-derived de-identified database from over 280 cancer clinics in the US.

Patient Selection

This analysis identified and evaluated adult patients with mPDAC who received liposomal irinotecan-based treatment between January 1, 2015 – February 29, 2020.

Inclusion Criteria	N
Patients diagnosed with mPDAC between January 1, 2014 and February 29, 2020	9748
Patients who had recorded activity in Flatiron network within 90 days of metastatic diagnosis date	8976
Patients who were at least 18 years of age at metastatic diagnosis	8976
Patients treated with liposomal irinotecan-based regimen. The index date was the start date of the first line of therapy which contained this agent	695
Patients whose index date was between January 1, 2015 and February 29, 2020	610
Exclusion Criteria	**N**
Patients without activity in Flatiron network on or after the respective index date	610
Patients whose index date occurred after their death date (after assigning the 15th day of the month to derive date of death)	608

Measures and Statistical Analyses

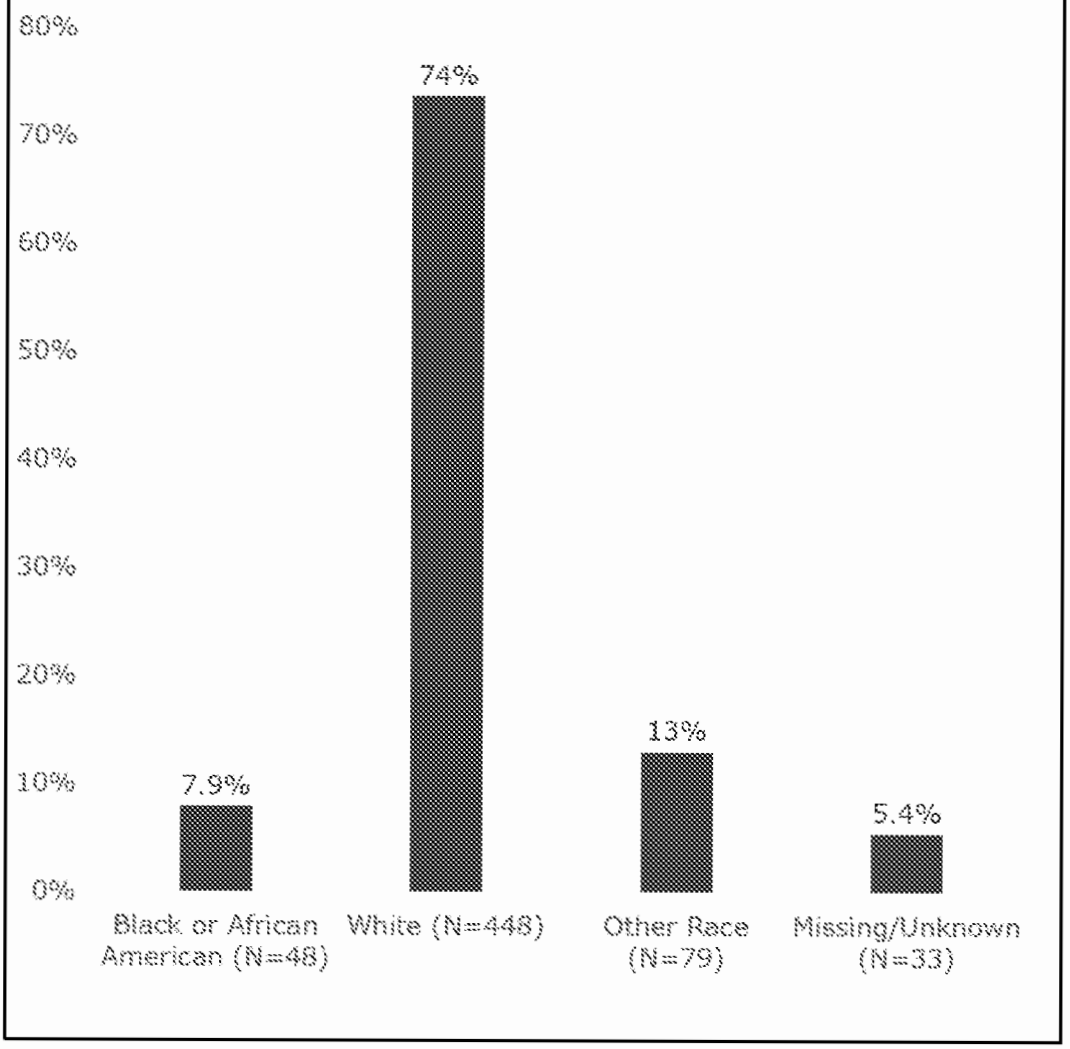
- Patients were stratified based on their self-reported race.
- Median overall survival (OS) from treatment initiation was derived using Kaplan-Meier analysis.
- Categorical variables including treatment patterns, and demographic/clinical characteristics were summarized using frequencies and percentages.
- Continuous variables were summarized using means, standard deviations, medians, and interquartile ranges.
- All data analyses were carried out using SAS 9.4

RESULTS

Patient Characteristics

- 608 patients diagnosed with mPDAC and treated with liposomal irinotecan were included in the study
- The median age at metastatic diagnosis was 68 years (IQR: 61 – 74) and 52% of the cohort was male
- 59% of overall patients had an ECOG performance score of 0-1

Figure 1. Patient Race



- Of the included patients with mPDAC and treated with a liposomal irinotecan-based regimen, 448 patients (73.7%) were White
- 48 patients (7.9%) were Black or African American, 79 patients (13.0%) were of other race (including Asian and Hispanic)
- 33 patients (5.4%) were missing race information
- White patients had a median age at metastatic diagnosis of 69y (IQR: 61–74), Black patients, 64y (60-71), and Other patients 67y (62 - 74)

RESULTS

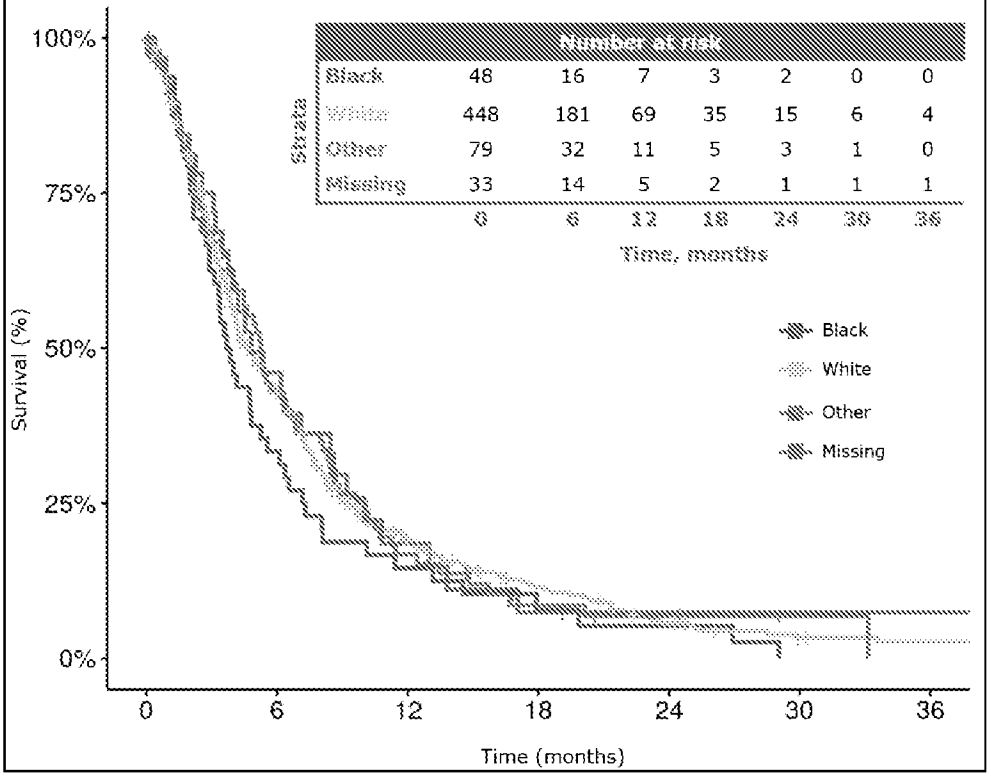
Table 1. Patient characteristics

Characteristic	Overall	Black or African American	White	Other Race	Missing/Unknown
Total	608	48	448	79	33
Sex					
Female	289 (48%)	31 (65%)	198 (44%)	43 (54%)	17 (52%)
Male	319 (52%)	17 (35%)	250 (56%)	36 (46%)	16 (48%)
Age at Metastatic Diagnosis					
Mean (SD)	67 (9)	65 (10)	68 (9)	67 (9)	67 (9)
Median (IQR)	68 (61 - 74)	64 (60 - 71)	69 (61 - 74)	67 (62 - 74)	68 (59 - 74)
Stage IV Initial Diagnosis	335 (55%)	29 (60%)	249 (56%)	34 (43%)	23 (70%)
Site of Primary Tumor					
Body	152 (25%)	12 (25%)	110 (25%)	18 (23%)	12 (36%)
Head	307 (50%)	22 (46%)	225 (50%)	44 (56%)	16 (48%)
Overlapping Sites	47 (7.7%)	6 (12%)	36 (8.0%)	4 (5.1%)	1 (3.0%)
Pancreas, Nos	13 (2.1%)	0 (0%)	12 (2.7%)	0 (0%)	1 (3.0%)
Tail	89 (15%)	8 (17%)	65 (15%)	13 (16%)	3 (9.1%)
ECOG (Closest to Index)					
0	100 (16%)	3 (6.2%)	82 (18%)	8 (10%)	7 (21%)
1	263 (43%)	25 (52%)	194 (43%)	33 (42%)	11 (33%)
2+	109 (18%)	8 (17%)	79 (18%)	18 (23%)	4 (12%)
Missing	136 (22%)	12 (25%)	93 (21%)	20 (25%)	11 (33%)
Prior Lines of Therapy					
0	90 (15%)	11 (23%)	61 (14%)	15 (19%)	3 (9.1%)
1	289 (48%)	21 (44%)	210 (47%)	40 (51%)	18 (55%)
2	177 (29%)	13 (27%)	134 (30%)	18 (23%)	12 (36%)
3+	52 (8.6%)	3 (6.2%)	43 (9.6%)	6 (7.6%)	0 (0%)

- Overall among patients treated with liposomal irinotecan, median OS was 4.7 months (95% CI: 4.2–5.4)
- Median OS was 4.6 months (95% CI: 4.1–5.6) among White patients, 3.8 months (3.1–5.6) among Black patients, and 5.3 months (4.1, 6.9) in patients identified as other
- Median OS was 12 months (3.4–NR) among Asian patients, a subset of the Other race group

RESULTS

Figure 2. Overall Survival by Race



CONCLUSIONS AND LIMITATIONS

Conclusions

- This analysis found racial disparities may persist in survival outcomes among patients with mPDAC treated with liposomal irinotecan-based regimens
- Further studies are needed to characterize and understand the biological and socio-economic factors contributing to these disparate outcomes

Limitations

- These data are collected from primarily the community setting and may not be generalizable to other settings of care

DISCLOSURES

Medical Writing Support

Medical writing support was supported by Ipsen in accordance with GPP3

Conflicts of interest

G.K. has an immediate family member who is an employee of and owns stock in Ipsen and has a consulting/advisory role with Ipsen and Celgene; P.C. is an employee of and has stock in Ipsen; N.L and A.S. are employees of Genesis Research, which receives consulting fees from Ipsen.

This study was sponsored by Ipsen

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Real-world one-year overall survival among patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with liposomal irinotecan in the NAPOLI-1 based regimen

George Kurn[1], Paul Cockrum[2], Andy Sumrall[3], Laith Abuzahrah[4]
[1]George Washington University, Division of Hematology & Oncology, Washington, DC, [2]Iqvia, Cambridge, MA, [3]Genesis Research, Hoboken, NJ, [4]The Ohio State University Comprehensive Cancer Center, Columbus, OH

BACKGROUND

- Pancreatic cancer remains one of the most lethal cancers in the United States (US) with a 5-year relative survival of 9%[1]
- Due to limited treatment options for patients with metastatic disease, the 5-year relative survival is only 2.9%[2]
- Liposomal irinotecan, an intravenous liposomal formulation that encapsulates the topoisomerase 1 inhibitor irinotecan in a lipid-bilayer vesicle, is the only U.S. Food and Drug Administration and European Medicines Agency approved second-line/post-gemcitabine treatment in mPDAC that is National Comprehensive Cancer Network (NCCN) Category 1 [3,4]
- Among patients who received liposomal irinotecan + 5-fluorouracil (5-FU) and leucovorin in the NAPOLI-1 study, a randomized phase 3 study in patients with mPDAC previously treated with gemcitabine-based therapy, 25% (n=29) were alive at ≥1 year[5]

OBJECTIVE

- To evaluate the one-year survival of patients with mPDAC treated with liposomal irinotecan + 5-FU in the real-world 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 comprising de-identified, patient-level structured and unstructured data, curated via technology-enabled abstraction. Flatiron Health includes data from over 280 cancer clinics

Patient Selection

- This analysis identified and evaluated adult patients diagnosed with mPDAC and treated with liposomal irinotecan between November 1, 2015 and July 31, 2020
- Eligible patients were those who:
  - were treated with a liposomal irinotecan + 5-FU based regimen in the metastatic setting
  - were at least 18 years old at treatment initiation
  - had at least one recorded activity after the start of treatment

Measures and Statistical Analyses

- Baseline patient demographics and clinical characteristics, the number of cycles of treatment, and real-world overall survival (OS), in months, were assessed
- One-year survival probability 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
- Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA)

RESULTS

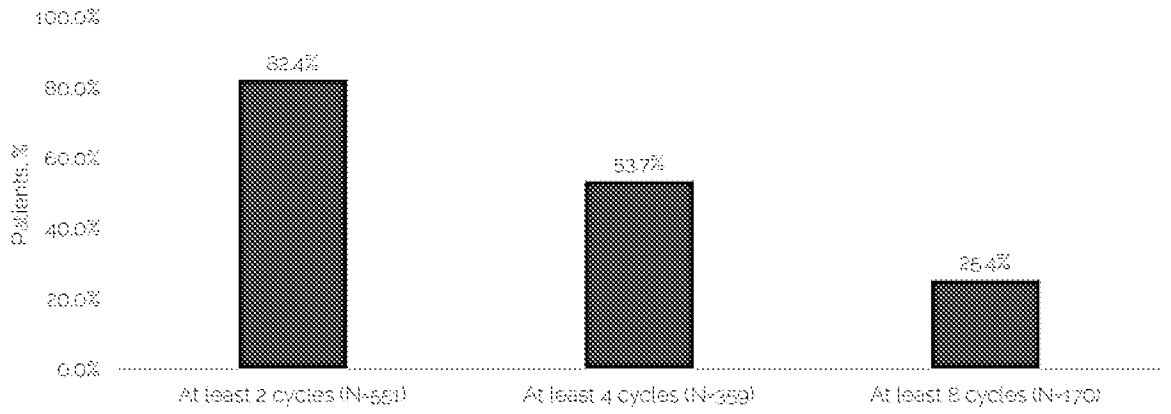
Patient Characteristics

- 669 patients diagnosed with mPDAC and treated with liposomal irinotecan + 5-FU were included in the study
- The median age at treatment initiation was 69 years (IQR: 62 – 75) and 53% of the cohort was male
- 57% of patients had an ECOG performance score of 0-1
- 47.5% of patients initiated treatment with liposomal irinotecan + 5-FU in the second line metastatic setting (Table 1)

Number of Treatment Cycles

- On average, patients received 6.2 cycles of treatment (SD: 7.5)
- The median number of cycles received was 4 (IQR: 2 – 8)
- The median number of cycles for 1L, 2L, and 3L were 5, 4, and 3, respectively
- The proportion of patients who received at least 2, 4, and 8 cycles are presented in Figure 1

Figure 1. Number of treatment cycles received



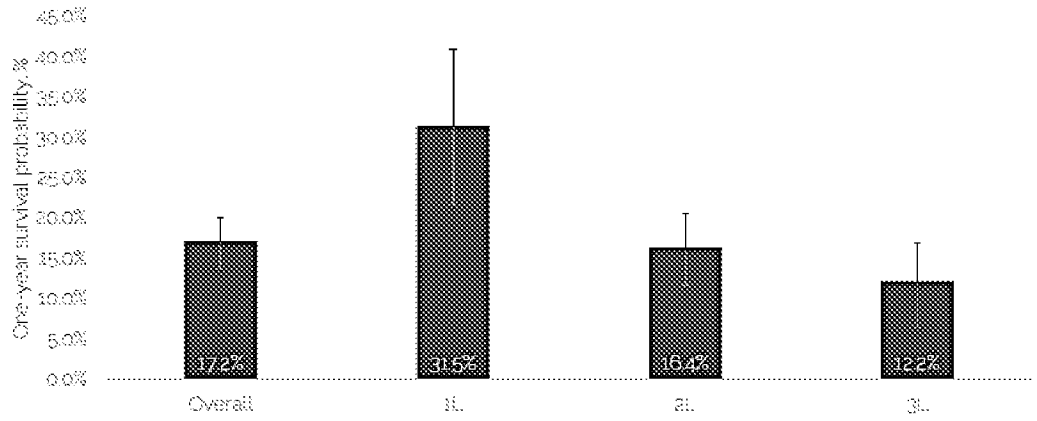
One-year Real-world OS

- Among all patients, one-year OS was 17.2% (95% CI: 14.3% - 20.7%) One-year OS was 31.5% (22.1% – 41.3%) for patients treated in 1L, 16.4% (12.2% - 21.1%) for patients treated in 2L, and 12.2% (7.5% - 18.0%) for patients treated in 3L (Figure 2)

Table 1. Patient characteristics at the start of treatment

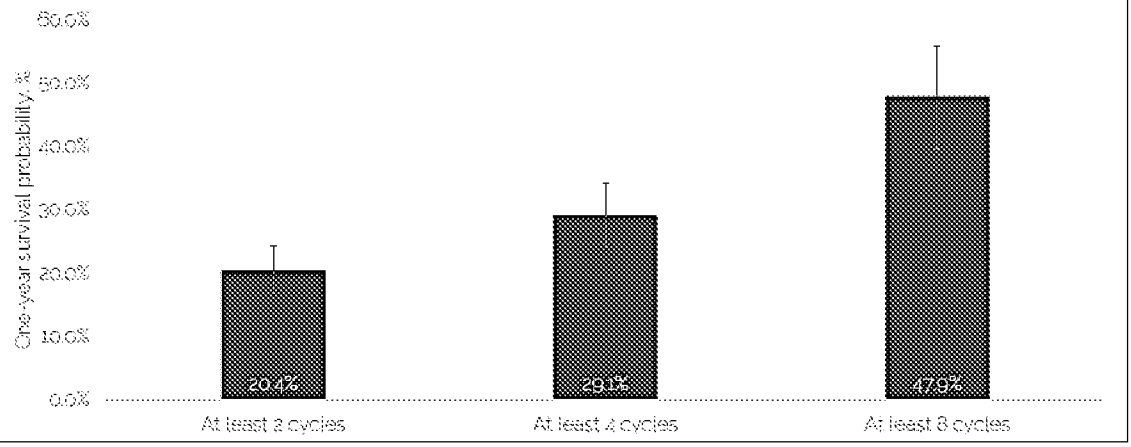
Characteristic	Liposomal Irinotecan + 5-FU Treated Patients
Total, n (%)	669 (100%)
Age at index, years	
Mean (SD)	68.3 (8.9)
Median (Q1-Q3)	69 (72 - 75)
Male, n(%)	353 (52.7%)
ECOG Score, n(%)	
0	115 (17.2%)
1	281 (42.0%)
2	110 (16.4%)
Missing/Unknown	163 (24.4%)
Race, n (%)	
Asian	14 (2.1%)
White	485 (72.5%)
Other Race/missing	170 (25.4%)
Geographic Region, n(%)	
Northeast	107 (16.0%)
Midwest	96 (14.4%)
South	301 (45.0%)
West	108 (16.1%)
Unknown	57 (8.5%)
Stage at initial diagnosis, n (%)	
Stage IV	363 (54.3%)
Other	306 (45.7%)
Line of therapy	
1L	109 (16.3%)
2L	318 (47.5%)
3L+	242 (36.2%)
Prior surgery, n(%)	182 (27.2%)

Figure 2. One-year survival overall and by line of therapy



- Patients who received at least 2 cycles of liposomal irinotecan had a one-year OS of 20.4% (16.8% - 24.2%)
- Among those who received at least 4 cycles and at least 8 cycles, the one-year OS estimates were 29.1% (24.0% - 34.3%) and 47.9% (39.7% - 55.7%), respectively. (Figure 3)

Figure 3. One-year survival by number of cycles received



Conclusions

- In this real-world cohort of patients with mPDAC treated with liposomal irinotecan + 5-FU based-regimen, as expected, one-year OS increased as patients remained on therapy
- Compared with the registrational phase 3 NAPOLI-1 study, patients were older, had more prior lines of therapy and worse ECOG PS, but received a similar number of treatment cycles (median 4)
- Among patients who received at least 4 cycles of liposomal irinotecan + 5-FU based-regimen, one-year OS (29%) was similar to both the intent-to-treat (25%) and per protocol treated patient populations in the NAPOLI-1 trial (34%)
- Further studies are needed to understand the predictors of long-term survival among patients with mPDAC

Limitations

- EHR data are subject to possible entry errors and missing information which could have led to extreme or incorrect values
- Sensitivity and specificity of mortality data may impact one-year survival estimates

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Conflicts of interest

G.K. has an immediate family member who is an employee of and owns stock in Ipsen and has a consulting/advisory role with Ipsen and Celgene; P.C. is an employee of and has stock in Ipsen; A.S. is an employee of Genesis Research, which receives consulting fees from Ipsen; L.A. receives consulting fees from Bionest.

Corresponding authors: George Kim (gmrpkim@gmail.com) and Paul Cockrum (paul.cockrum@ipsen.com)

Presented at the American Society of Clinical Oncology Gastrointestinal Cancer Symposium (ASCO GI) 2021, January 15–17, 2021, Virtual Congress

BACKGROUND

OBJECTIVE

METHODS

RESULTS

Conclusions

Limitations

References

3709P

Real-world progression outcomes among patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with liposomal irinotecan-based regimens in the United States

George Kim[1], Paul Cockrum[2], Andy Surinach[3], Shu Wang[3], Neil Lamarre[3]
[1]George Washington University, Division of Hematology & Oncology, Washington, DC; [2]Ipsen, Cambridge, MA; [3]Genesis Research, Hoboken, NJ

Background

- Pancreatic cancer is expected to be the third deadliest cancer in 2021 and account for more than 48,000 cancer-related deaths.[1]
- Liposomal irinotecan, an intravenous liposomal formulation that encapsulates the topoisomerase 1 inhibitor irinotecan in a lipid-bilayer vesicle, is the only US Food and Drug Administration and European Medicines Agency approved, in combination with fluorouracil and leucovorin, second-line/post-gemcitabine treatment in mPDAC that is National Comprehensive Cancer Network® (NCCN) Category 1. [2-3]
- The NAPOLI-1 study, a randomized phase 3 study in patients with mPDAC previously treated with gemcitabine-based therapy, demonstrated an improvement in progression-free survival (PFS) with liposomal irinotecan + 5-fluorouracil/ leucovorin (5-FU/LV) vs. 5-FU/LV, 3.1 months (95% CI: 2.7 – 4.2) vs 1.5 months (95% CI: 1.4 – 1.8), respectively.[4]
- Patients treated with liposomal irinotecan + 5-FU/LV in NAPOLI-1 had a median age of 63 years at treatment initiation, 97% had performance status (PS) equivalent to Eastern Cooperative Oncology Group (ECOG) PS 0-1, and 34% had at least 2 prior lines of therapy.[4]

Objective

To evaluate real-world progression outcomes among patients with mPDAC treated with liposomal irinotecan-based regimens.

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 evaluated adult patients diagnosed with mPDAC and treated with liposomal irinotecan between January 1, 2016 and October 31, 2020.
- Eligible patients were those who:
  - had a documented activity in the EHR within 90 days on or after their metastatic diagnosis date
  - were treated with a liposomal irinotecan-based regimen in the metastatic setting
  - were at least 18 years old at treatment initiation and had at least one recorded activity after the start of treatment
  - and if a death was recorded, it occurred after the start of treatment.

Measures and Statistical Analyses

- Baseline patient demographics and clinical characteristics and real-world progression-free survival (rwPFS) were assessed.
- Baseline characteristics included: age at treatment initiation, ECOG PS, stage at initial diagnosis, region, practice type, serum albumin, and the number of prior lines of therapy. Median rwPFS was determined via Kaplan-Meier analysis.
- rwPFS was defined as the time between the start of the index liposomal-irinotecan-based line of therapy and the first of the following:
  - Documented progression event that occurred >14 days after the start of the of line therapy.
  - Documented death that occurred at any point after the start of the line of therapy.
- Patients without a documented progression event were censored on the last day that a note from the clinic was documented.
- Patients whose last note occurred prior to the start of the index line of therapy were excluded from the rwPFS analysis.
- Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, US).

Figure 1. Overall rwPFS among patients treated with liposomal irinotecan

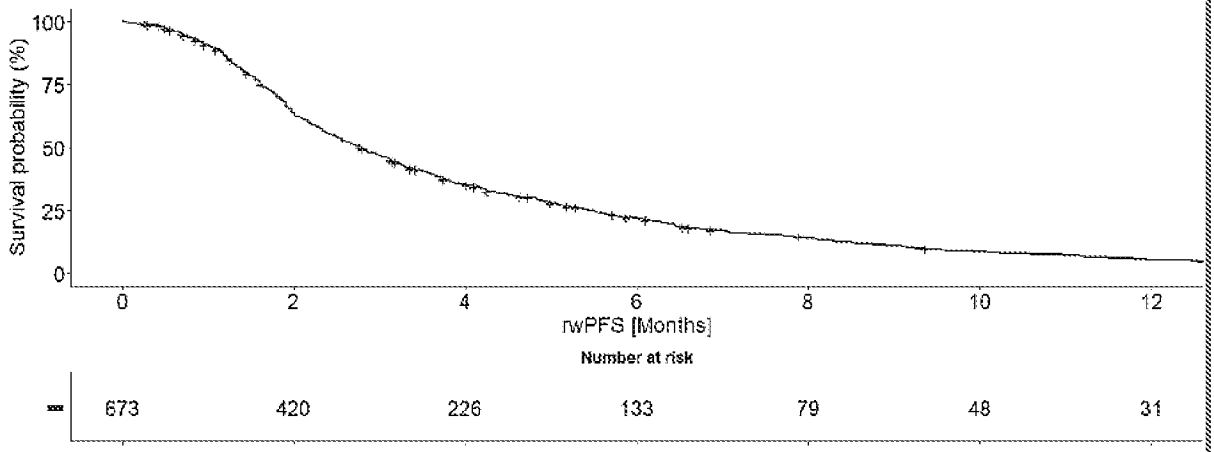
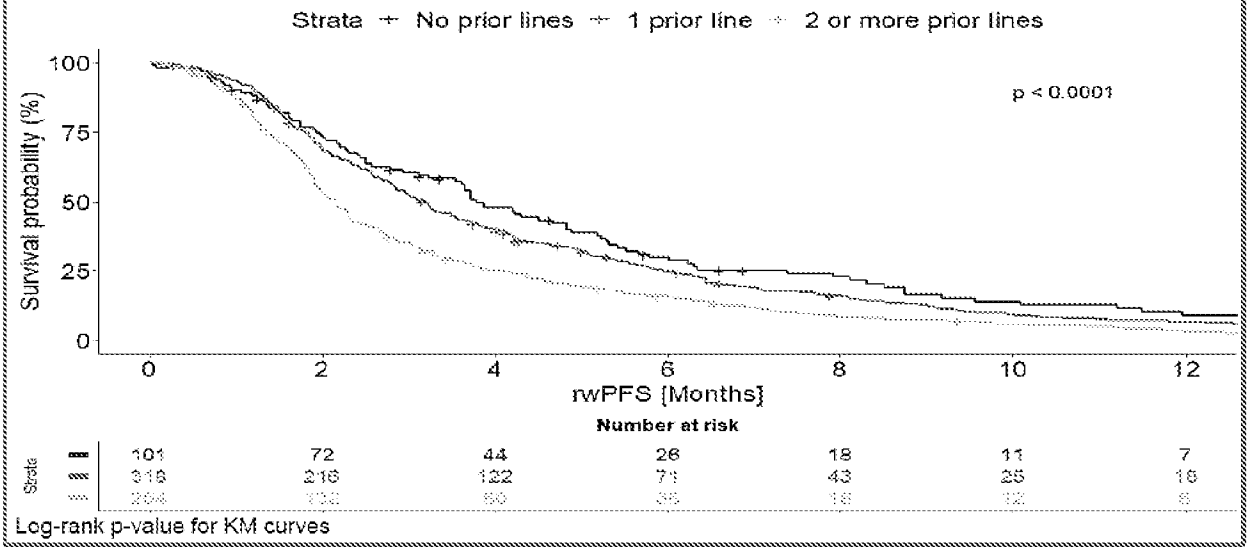


Figure 2. rwPFS by line of therapy



Log-rank p-value for KM curves

Results

Patient Characteristics

- 675 patients with mPDAC treated with liposomal irinotecan were included in the study.
- The median age at treatment initiation was 69 years (IQR: 62 – 75).
- 255 (37.8%) patients had two or more prior lines of therapy, 394 (58.4%) had an ECOG PS of 0-1, 115 (17.0%) had an ECOG score of 2+, and 166 (24.6%) had missing scores (Table 1).
- 368 (54.5%) patients were initially diagnosed with stage IV disease.

Real-world Progression-free Survival

- The overall median rwPFS (95% CI) for 673 patients was 2.8 months (2.5 – 3.1) (Figure 1) [2 patients were excluded due to lack of follow-up for the rwPFS analysis].
- As expected, rwPFS decreased in later lines of therapy (Figure 2)
- Median rwPFS among patients treated in 1L (n=101), 2L (n=318), and third line plus (3L+, n = 254) were 3.8 months (2.9–4.8), 3.2 months (2.8–3.5), and 2.1 months (1.9–2.3), respectively.

Table 1. Patient characteristics at the start of liposomal irinotecan treatment

Characteristics	Overall Cohort N = 675
Age at index, years, median (Q1-Q3)	69 (62 - 75)
Male, n (%)	349 (51.7%)
Stage IV at initial diagnosis, n (%)	368 (54.5%)
Year of treatment initiation, n (%)	
2016	117 (17.3%)
2017	123 (18.2%)
2018	181 (26.8%)
2019	163 (24.2%)
2020	91 (13.5%)
Geographic Region, n (%)	
Northeast	110 (16.3%)
Midwest	97 (14.4%)
South	296 (43.8%)
West	106 (15.7%)
Unknown	66 (9.8%)
ECOG PS, n(%)	
0	118 (17.5%)
1	276 (40.9%)
2+	115 (17.0%)
Missing	166 (24.6%)
Serum albumin, n (%)	
<40 g/L	493 (73.0%)
≥ 40g/L	122 (18.1%)
Unknown/Not Tested	60 (8.9%)
Previous Lines of therapy, n (%)	
0	101 (15.0%)
1	319 (47.3%)
2 or more	255 (37.8%)
Practice Type, n (%)	
Academic	57 (8.4%)
Community	618 (91.6%)

ECOG PS, Eastern Cooperative Oncology Group performance status

CONCLUSIONS

- In this real-world study of patients with mPDAC treated with a liposomal irinotecan-based regimen, median rwPFS was similar to the median PFS of the pivotal phase 3 trial despite the fact that patients in the real-world were older, had worse performance scores, and more prior lines of therapy than patients included in the clinical trial.
- Further studies are needed to characterize factors that influence PFS among patients treated with liposomal irinotecan.

Limitations

- Prior gemcitabine use could not be confirmed for all patients.
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- Asymptomatic progression is likely not captured in these data
- 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.

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This study was sponsored by Ipsen

Presented at European Society for Medical Oncology (ESMO) Congress | Virtual Congress| 16 -21 September,2021

Real-world progression outcomes among patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with liposomal irinotecan-based regimens in the United States

George Kim[1], Paul Frankel[2], Barry Sunwoo[3], Wei Wang[3], Neil Lamarre[3]
[1]Rutgers Robert Wood Johnson Medical School, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; [2]Cedars-Sinai Medical Center, Los Angeles, CA; [3]Janssen Research & Development, LLC, Titusville, NJ

1P060

Background

- Pancreatic cancer is expected to be the third deadliest cancer in 2021[1] and account for more than 48,000 cancer-related deaths.[1]
- Liposomal irinotecan, an intravenous liposomal formulation that encapsulates the topoisomerase 1 inhibitor irinotecan in a lipid-bilayer vesicle, is the only US Food and Drug Administration and European Medicines Agency approved, in combination with fluorouracil and leucovorin, second-line/post-gemcitabine treatment in mPDAC that is National Comprehensive Cancer Network® (NCCN) Category 1.[2,3]
- The NAPOLI-1 study, a randomized phase 3 study in patients with mPDAC previously treated with gemcitabine-based therapy, demonstrated an improvement in progression-free survival (PFS) with liposomal irinotecan + 5-fluorouracil/leucovorin (5-FU/LV) vs. 5-FU/LV; 3.1 months (95% CI: 2.7 – 4.2) vs 1.5 months (95% CI: 1.4 – 1.8), respectively.[4]
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To evaluate real-world progression outcomes among patients with mPDAC treated with liposomal irinotecan-based regimens.

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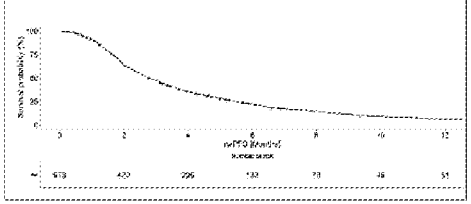

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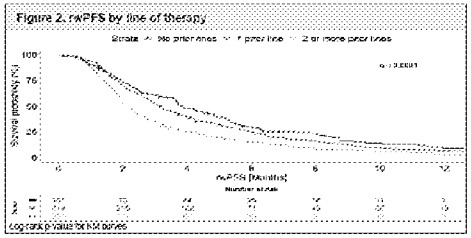

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Unknown	66 (9.8%)
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Serum albumin, n (%)	
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≥ 40g/L	123 (18.1%)
Unknown/Not Tested	59 (8.8%)
Previous Lines of therapy, n (%)	
0	101 (15.0%)
1	318 (47.2%)
2 or more	256 (37.9%)
Practice Type, n (%)	
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Community	618 (91.6%)

ECOG PS: Eastern Cooperative Oncology Group performance status

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390

Real-world safety data and differentiation of second-line (2L) 5-fluorouracil (5-FU) based regimens among patients with metastatic pancreatic ductal adenocarcinoma (mPDAC)

Georgia Kim[1], Paul Cockrum[2], Alexander Chudnovsky[2], Andy Sumroch[3], Jay Wanlong[2], Shu Wang[2], Amin Yonubul[2]
[1] Georgetown University, Division of Hematology & Oncology, Washington, DC; [2] Eisai, Carrington, MA; [3] Eisai Research, Hoboken, NJ; [4] University of California, Los Angeles, CA

BACKGROUND

- Pancreatic cancer remains one of the most lethal cancers in the United States (US) with a 5-year relative survival of 9%[1]
- Many of the National Comprehensive Cancer Network (NCCN) recommended regimens for the treatment of mPDAC in the second line (2L) setting are 5-FU-based including FOLFIRINOX, FOLFOX, and FOLFIRI[2]
- Due to limited treatment options for patients with metastatic disease, the 5-year relative survival is only 2.9%[3]
- Chemotherapy related adverse events (AEs) can impact the treatment of patients, reducing quality of life and leading to dose delays and treatment discontinuation

OBJECTIVE

- To evaluate the proportion of patients with mPDAC treated with 5-FU-based regimens in the 2L metastatic setting who experienced select AEs during treatment

METHODS

Study Design and Data Source

A retrospective descriptive analysis was performed using the Flatiron Health® longitudinal database, a demographically and geographically diverse database comprising de-identified patient-level structured and unstructured data, curated via technology-enabled abstraction. Flatiron Health includes data from over 280 cancer clinics

Patient Selection

- This analysis identified and evaluated adult patients diagnosed with mPDAC on or after January 1, 2014 and who initiated 2L therapy with FOLFIRINOX, FOLFOX, FOLFIRI, or a liposomal irinotecan-based regimen between January 1, 2016 and July 31, 2020
- Eligible patients were those who:
  - Had a recorded activity within 90 days of their metastatic diagnosis date
  - were at least 18 years old at 2L treatment initiation
  - had at least one recorded activity after the start of treatment

Measures and Statistical analyses

- Baseline patient demographics and clinical characteristics, duration of treatment, and the proportion of patients with an adverse event during treatment were evaluated
- The occurrence of grade 3 (G3) and grade 4 (G4) neutropenia, G3/G4 elevated alanine transaminase (ALT) and anemia where transfusion was indicated were determined using lab results and the grading criteria from the Common Terminology Criteria for Adverse Events v4.03[4]
- The occurrence of diarrhea, fatigue, nausea and vomiting (N/V), and neuropathy were identified from structured diagnosis records through ICD-10-CM codes
- Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA)

RESULTS

Patient Characteristics

- 804 patients were included in the study; 28.4% (n=228) received FOLFIRINOX, 39.8% (n=320) received regimens containing liposomal irinotecan, 24.8% (n=199) received FOLFOX, and 7.1% (n=57) received FOLFIRI

- The median age at treatment initiation was 66.5y, 70y, 71y, and 68y for patients treated with FOLFIRINOX, liposomal irinotecan-based regimens, FOLFOX, and FOLFIRI, respectively
- Males comprised 54.8% and 55.3% of the patients treated with FOLFIRINOX and liposomal irinotecan-based regimens, respectively (Table 1)
- Patients treated with FOLFOX had the highest proportion of ECOG performance scores of 2+ (19.1%)

Duration of treatment

- The median DOT (IQR) was 86 days (d) (43 – 206), 79d (41 – 169), 72d (43 – 166), and 84d (46 – 148) for pts who received FOLFIRINOX, liposomal irinotecan, FOLFOX, and FOLFIRI, respectively (Figure 1)

Figure 1. Duration of treatment by regimen

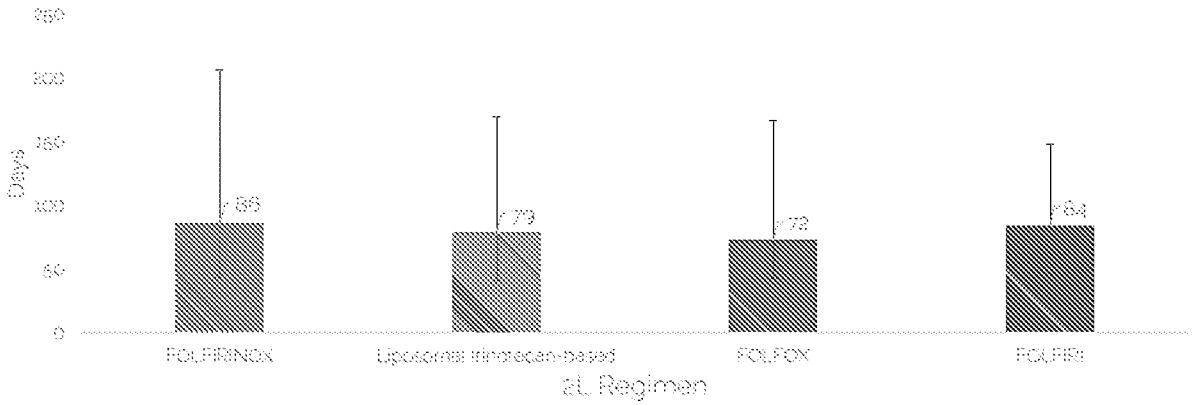


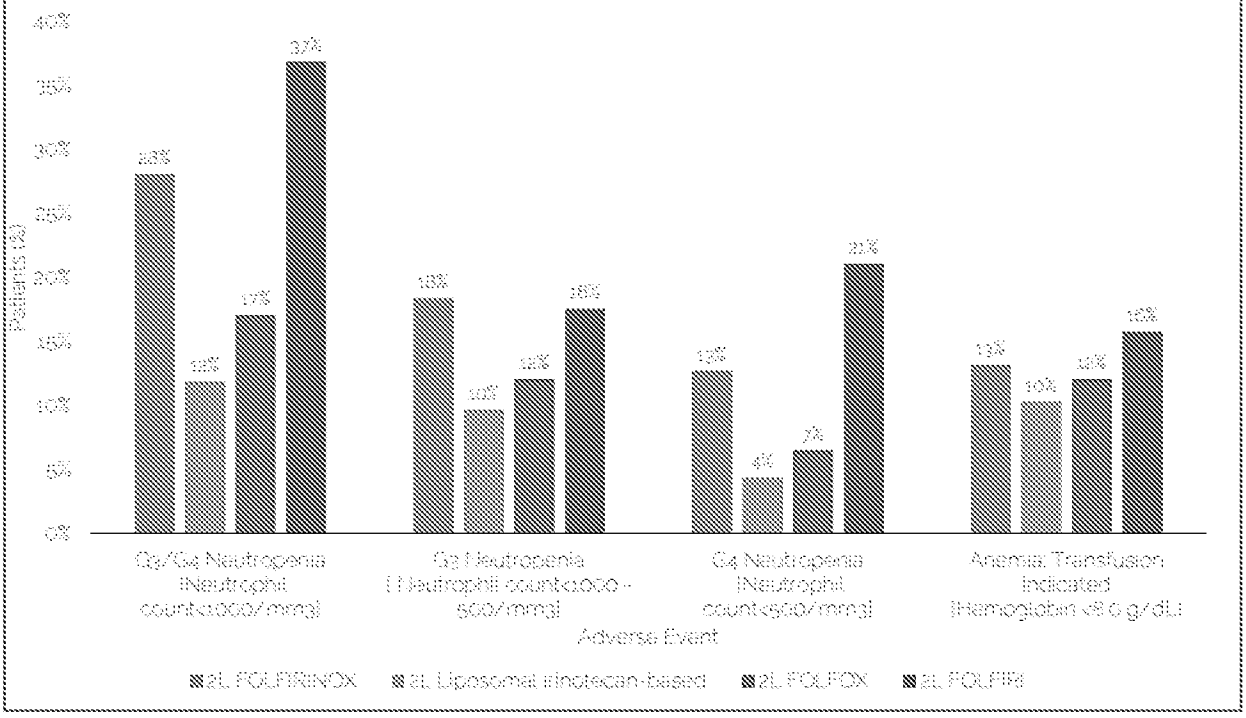
Table 1. Patient characteristics at the start of 2L treatment

Characteristic	FOLFIRINOX	Liposomal irinotecan-based	FOLFOX	FOLFIRI
Total, n (%)	228 (100%)	320 (100%)	199 (100%)	57 (100%)
Male, n (%)	125 (54.8%)	177 (55.3%)	90 (45.2%)	24 (42.1%)
Age, years				
Median (Q1-Q3)	66.5 (61 – 72)	70 (63 – 76)	71 (64 – 77)	68 (64 – 74)
ECOG Score				
0	49 (21.5%)	56 (17.5%)	29 (14.6%)	11 (19.3%)
1	83 (36.4%)	128 (40.0%)	70 (35.2%)	14 (24.6%)
2+	27 (11.8%)	55 (17.2%)	38 (19.1%)	8 (14.0%)
Missing	69 (30.3%)	81 (25.3%)	62 (31.2%)	24 (42.1%)

Adverse Events

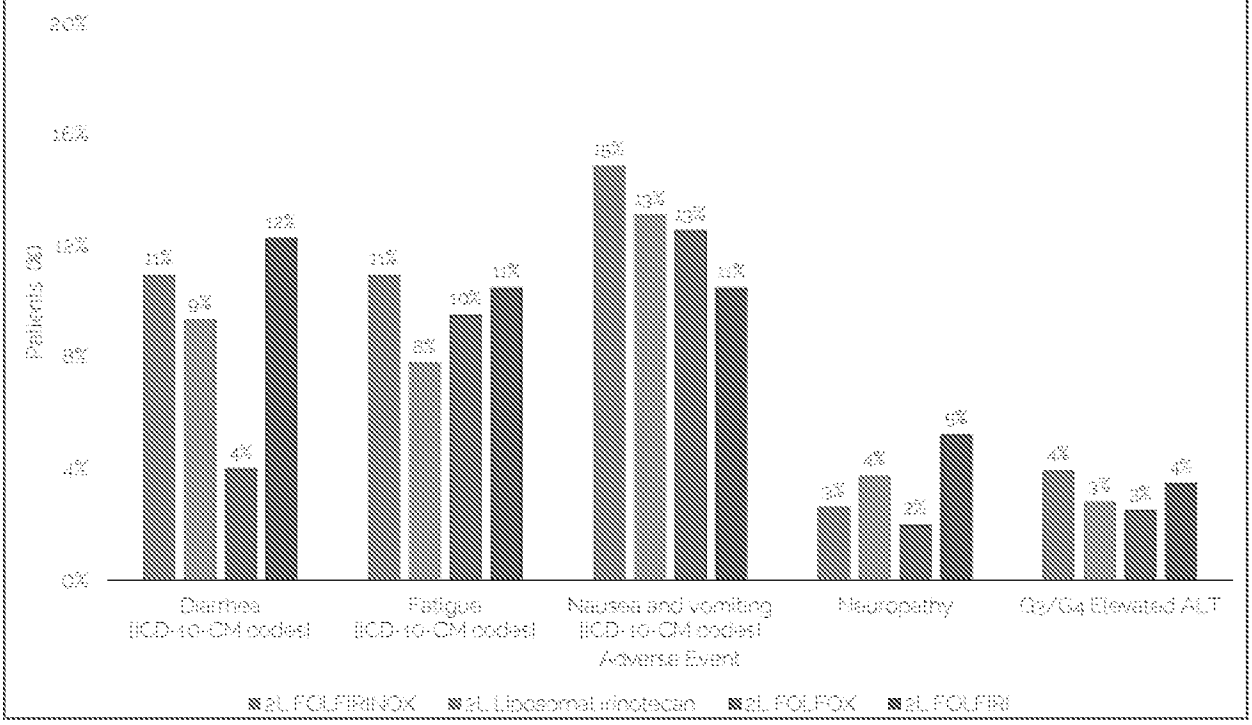
- G3/G4 neutropenia (<1000/mm^3) presented in 28.1% (n=64) of patients treated with FOLFIRINOX, 11.9% (n=38) of patients treated with liposomal irinotecan, 17.1% (n=34) of patients treated with FOLFOX, and 36.8% (n=21) of patients treated with FOLFIRI
- Other hematological adverse events (AEs) are presented in Figure 2

Figure 2. Proportion of patients with hematological AEs during treatment



- Nausea and vomiting occurred in 14.9% (n=34), 13.1% (n=42), 12.6% (n=25), and 10.5% (n=6) patients treated with FOLFIRINOX, liposomal irinotecan-based regimens, FOLFOX, and FOLFIRI, respectively Other select AEs observed during treatment are presented in Figure 3

Figure 3. Proportion of patients with other AEs during treatment



Conclusions

- In this assessment of often dose-limiting AEs among pts with mPDAC treated in 2L, pts who received liposomal irinotecan had the lowest proportion of G3 neutropenia, G4 neutropenia, and combined G3/G4 neutropenia
- No clear pattern was noted for N/V, neuropathy, fatigue, anemia, and elevated ALT
- Further research is necessary to determine the real-world cost implications of AEs in this patient population

Limitations

- EHR data are subject to possible entry errors and missing information which could have led to extreme or incorrect values
- Under coding may be present for symptomatic adverse events that are derived from ICD-9/10-CM diagnosis codes

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Conflicts of interest

G.K. has an immediate family member who is an employee of and owns stock in Ipsen and has a consulting/advisory role with Ipsen and Celgene; P.C. is an employee of and has stock in Ipsen; A.C. was an employee of Ipsen at the time of the study; A.S., S.W., and A.Y. are employees of Genesis Research, which receives consulting fees from Ipsen; Z.W has a consulting/advisory role with Ipsen, Array BioPharma, Five Prime Therapeutics, Novartis, Lilly, Merck, Merck KGaA, Bristol-Myers Squibb, Bayer, AstraZeneca/Medimmune, and Macrogenics, has been compensated for travel by Lilly, Merck, and Bayer, and his institution receives funding from Novartis, Plexxikon, Pfizer, Merck, Five Prime Therapeutics

This study was sponsored by Ipsen

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BACKGROUND

OBJECTIVE

METHODS

RESULTS

Conclusions

Limitations

References

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Real-world treatment discontinuation patterns among patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with liposomal irinotecan-based regimens in the United States

George Kim[1], Andy Surinach[2], Shu Wang[2], Neil Lamarre[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 is expected to account for over 60,000 new cases and more than 48,000 cancer-related deaths in 2021.[1]
- Liposomal irinotecan, an intravenous liposomal formulation that encapsulates the topoisomerase 1 inhibitor irinotecan in a lipid-bilayer vesicle, is the only US Food and Drug Administration and European Medicines Agency approved, in combination with fluorouracil and leucovorin, second-line/post-gemcitabine treatment in mPDAC that is National Comprehensive Cancer Network® (NCCN) Category 1.[2-3]
- Real-world data describing why patients discontinue liposomal irinotecan-based treatment are lacking.
- The most common reasons for treatment discontinuation among patients treated in the liposomal irinotecan + 5-fluorouracil/ leucovorin (5-FU/LV) arm of the NAPOLI-1 study, a randomized phase 3 study in patients with mPDAC previously treated with gemcitabine-based therapy, were disease progression (55.3%), patient decision (13.6%), and clinical deterioration (12.6%).[4]

Objective

To describe real-world reasons for treatment discontinuation among patients with mPDAC treated with liposomal irinotecan-based regimens.

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 evaluated adult patients diagnosed with mPDAC and treated with liposomal irinotecan between January 1, 2016 and October 31, 2020.
- Eligible patients were those who:
  - had a documented activity in the EHR within 90 days on or after their metastatic diagnosis date
  - were treated with a liposomal irinotecan-based regimen in the metastatic setting
  - were at least 18 years old at treatment initiation and had at least one recorded activity after the start of treatment
  - and if a death was recorded, it occurred after the start of treatment.

Measures and Statistical Analyses

- Baseline patient demographics and clinical characteristics were assessed.
- Baseline characteristics included: age at treatment initiation, Eastern Cooperative Oncology Group performance status (ECOG PS), stage at initial diagnosis, region, practice type, serum albumin, and the number of prior lines of therapy.
- Reasons for discontinuation were abstracted from the patient medical records for each line of therapy, multiple reasons could be noted for each line.
- Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, US).

RESULTS

Patient Characteristics

- 675 patients with mPDAC treated with liposomal irinotecan were included in the study.
- The median age at treatment initiation was 69 years (IQR: 62 – 75) (Table 1).

Table 1. Patient characteristics at the start of liposomal irinotecan treatment

Characteristics	Overall Cohort N = 675
Age at index, years, median (Q1-Q3)	69 (62 - 75)
Male, n (%)	349 (51.7%)
Stage IV at initial diagnosis, n (%)	368 (54.5%)
Year of treatment initiation, n (%)	
2016	117 (17.3%)
2017	123 (18.2%)
2018	181 (26.8%)
2019	163 (24.2%)
2020	91 (13.5%)
Geographic Region, n (%)	
Northeast	110 (16.3%)
Midwest	97 (14.4%)
South	296 (43.8%)
West	106 (15.7%)
Unknown	66 (9.8%)
ECOG PS, n(%)	
0	118 (17.5%)
1	276 (40.9%)
2+	115 (17.0%)
Missing	166 (24.6%)
Serum albumin, n (%)	
<40 g/L	493 (73.0%)
≥ 40g/L	122 (18.1%)
Unknown/Not Tested	60 (8.9%)
Previous Lines of therapy, n (%)	
0	101 (15.0%)
1	319 (47.3%)
2 or more	255 (37.8%)
Practice Type, n (%)	
Academic	57 (8.4%)
Community	618 (91.6%)

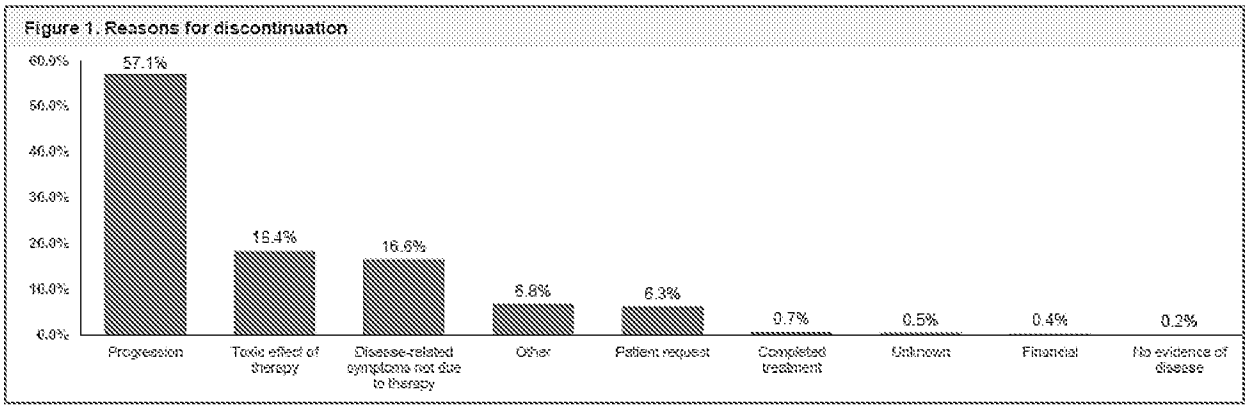
ECOG PS, Eastern Cooperative Oncology Group performance status

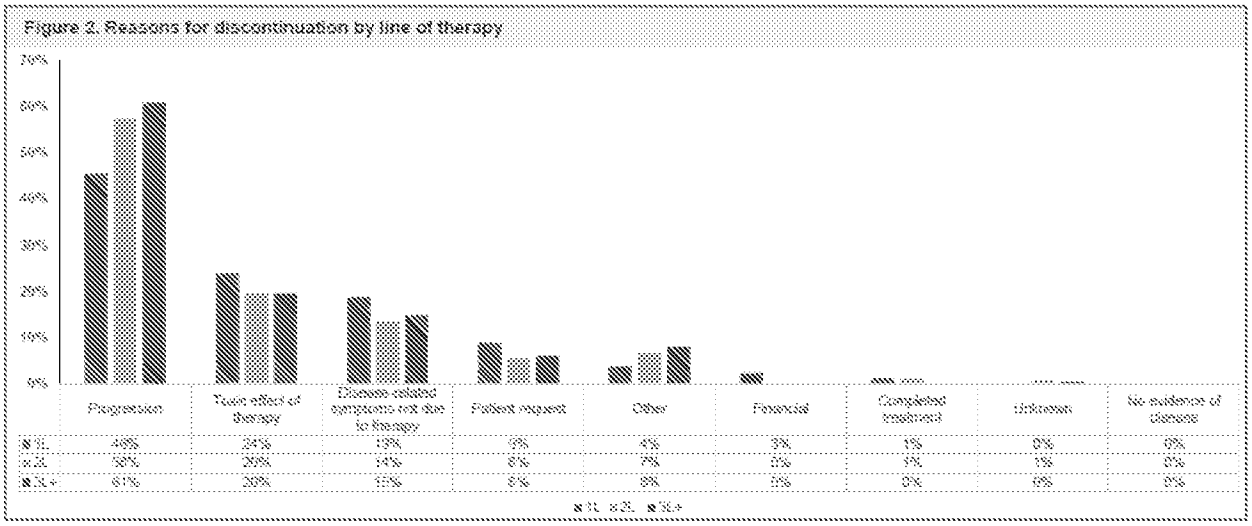
Patient Characteristics

- 101 (15.0%) patients received a liposomal irinotecan-containing regimen in the first line (1L) metastatic setting, 319 (47.3%) in the second line setting (2L), and 255 (37.8%) in the third line plus setting (3L+).
- 394 (58.4%) had an ECOG score of 0-1, 115 (17.0%) had an ECOG score of 2+, and 166 (24.6%) had missing scores.
- 368 (54.5%) patients were initially diagnosed with stage IV disease.
- The majority of patients were treated in community oncology centers (91.6%).

Reasons for discontinuation

- Across all lines of therapy, there were 555 patients with at least one reason for discontinuation recorded.
- Progression was the most common reason recorded (n=317, 57.1%), followed by toxic effect of therapy (n=102, 18.4%), disease related symptoms not due to therapy (n=92, 16.6%), and patient request (n=35, 6.3%). (Figure 1).
- Progression was increasingly the most common reason for discontinuation in later lines of therapy: 1L: 46%, 2L 56%, 3L+ 61% (Figure 2).
- A higher proportion of patients treated in the first line setting discontinued treatment due to toxic effects of therapy (24%) than in the third line plus setting (15%); 20% of patients treated in 2L discontinued for the same reason.





Conclusions

- In this real-world study of patients with mPDAC treated with a liposomal irinotecan-based regimen, progression while on therapy was the most common reason cited for treatment discontinuation similar to the pivotal phase 3 trial.
- The proportion of discontinuations due to patient requests was smaller in our study than in the trial (6.3% vs 13.6%); disease related symptoms/clinical deterioration were similar (16.6% vs 12.6%) and toxic effects of therapy/adverse events were higher in the real-world setting (18.4% vs 9.4%).
- Further studies are needed to understand the clinical context that leads patients to discontinue treatment.

Limitations

- Prior gemcitabine use could not be confirmed for all patients.
- Reasons for discontinuation may be documented differently by treating physicians and may not be representative of all patients receiving liposomal irinotecan-based therapy.
- These data are collected primarily from the community oncology setting and may not be generalizable to other practice types.

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Disclosures: G.K serves in an advisory role for Ipsen; A.S, S.W, and NL are employees of Genesis Research, which receives consulting fees from Ipsen; P.C. is an employee of and has stock in Ipsen.

This study was sponsored by Ipsen

Presented at European Society for Medical Oncology (ESMO) Congress | Virtual Congress| 16 -21 September,2021

Real-world treatment discontinuation patterns among patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with liposomal irinotecan-based regimens in the United States

George Kim[1], Andy Burkhardt[2], Rita Wang[2], Neil Lamarre[2], Paul Lindman[2]

[1]Fox Chase Cancer Center, Temple University Health System, Philadelphia, PA; [2]Ipsen, Cambridge, MA

Background

- Pancreatic cancer is expected to account for over 60,000 new cases and more than 48,000 cancer-related deaths in 2021.[1]
- Liposomal irinotecan, an intravenous liposomal formulation that encapsulates the topoisomerase I inhibitor irinotecan in a lipid-bilayer vesicle, is the only US Food and Drug Administration and European Medicines Agency approved, in combination with fluorouracil and leucovorin, second-line/post-gemcitabine treatment in mPDAC that is National Comprehensive Cancer Network® (NCCN) Category 1.[2,3]
- Real-world data describing why patients discontinue liposomal irinotecan-based treatment are lacking.
- The most common reasons for treatment discontinuation among patients treated in the liposomal irinotecan + 5-fluorouracil/leucovorin (5-FU/LV) arm of the NAPOLI-1 study, a randomized phase 3 study in patients with mPDAC previously treated with gemcitabine-based therapy, were disease progression (56.3%), patient decision (13.6%), and clinical deterioration (12.8%).[4]

Objective

To describe real-world reasons for treatment discontinuation among patients with mPDAC treated with liposomal irinotecan-based regimens.

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 evaluated adult patients diagnosed with mPDAC and treated with liposomal irinotecan between January 1, 2016 and October 31, 2020.
- Eligible patients were those who:
  - had a documented activity in the EHR within 90 days on or after their metastatic diagnosis date
  - were treated with a liposomal irinotecan-based regimen in the metastatic setting
  - were at least 18 years old at treatment initiation and had at least one recorded activity after the start of treatment
  - and if a death was recorded, it occurred after the start of treatment.

Measures and Statistical Analyses

- Baseline patient demographics and clinical characteristics were assessed.
- Baseline characteristics included: age at treatment initiation, Eastern Cooperative Oncology Group performance status (ECOG PS), stage at initial diagnosis, region, practice type, serum albumin, and the number of prior lines of therapy.
- Reasons for discontinuation were abstracted from the patient medical records for each line of therapy; multiple reasons could be noted for each line.
- Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, US).

Results

Patient Characteristics

- 675 patients with mPDAC treated with liposomal irinotecan were included in the study.
- The median age at treatment initiation was 66 years (IQR: 62 – 76) (Table 1).

Table 1. Patient characteristics at the start of liposomal irinotecan treatment

Characteristics	Overall Cohort N = 675
Age at index, years, median (Q1-Q3)	66 (62 - 76)
Male, n (%)	349 (51.7%)
Stage IV at initial diagnosis, n (%)	368 (54.5%)
Year of treatment initiation, n (%)	
2016	117 (17.3%)
2017	123 (18.2%)
2018	181 (26.8%)
2019	163 (24.2%)
2020	91 (13.5%)
Geographic Region, n (%)	
Northeast	110 (16.3%)
Midwest	97 (14.4%)
South	290 (43.0%)
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Unknown	66 (9.8%)
ECOG PS, n(%)	
0	118 (17.5%)
1	278 (41.9%)
2+	115 (17.0%)
Missing	166 (24.6%)
Serum albumin, n (%)	
<40 g/L	493 (73.0%)
≥ 40g/L	122 (18.1%)
Unknown/Not Tested	60 (8.9%)
Previous Lines of therapy, n (%)	
0	101 (15.0%)
1	319 (47.3%)
2 or more	255 (37.8%)
Practice Type, n (%)	
Academic	57 (8.4%)
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ECOG PS, Eastern Cooperative Oncology Group performance status

CONCLUSIONS

- In this real-world study of patients with mPDAC treated with a liposomal irinotecan-based regimen, progression while on therapy was the most common reason cited for treatment discontinuation similar to the pivotal phase 3 trial.
- The proportion of discontinuations due to patient requests was smaller in our study than in the trial (6.3% vs 13.6%); disease related symptoms/clinical deterioration were similar (18.6% vs 12.8%) and toxic effects of therapy/adverse events were higher in the real-world setting (18.4% vs 9.4%).
- Further studies are needed to understand the clinical context that leads patients to discontinue treatment.

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- Prior gemcitabine use could not be confirmed for all patients.
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- These data are collected primarily from the community oncology setting and may not be generalizable to other practice types.

Results (cont'd)

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- 101 (15.0%) patients received a liposomal irinotecan-containing regimen in the first line (1L) metastatic setting, 319 (47.3%) in the second line setting (2L), and 255 (37.8%) in the third line plus setting (3L+).
- 384 (56.4%) had an ECOG score of 0-1, 115 (17.0%) had an ECOG score of 2+, and 166 (24.6%) had missing scores.
- 369 (54.6%) patients were initially diagnosed with stage IV disease.
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Reasons for discontinuation

- Across all lines of therapy, there were 565 patients with at least one reason for discontinuation reported.
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- Progression was increasingly the most common reason for discontinuation in later lines of therapy: 1L: 48%, 2L: 58%, 3L+: 61% (Figure 2).
- A higher proportion of patients treated in the first line setting discontinued treatment due to toxic effects of therapy (24%) than in the third line plus setting (15%); 20% of patients treated in 2L discontinued for the same reason.

Figure 1. Reasons for discontinuation

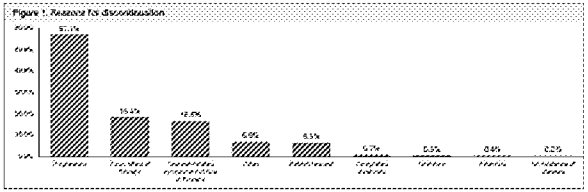
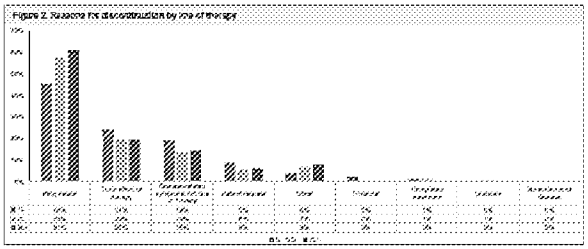


Figure 2. Reasons for discontinuation by line of therapy



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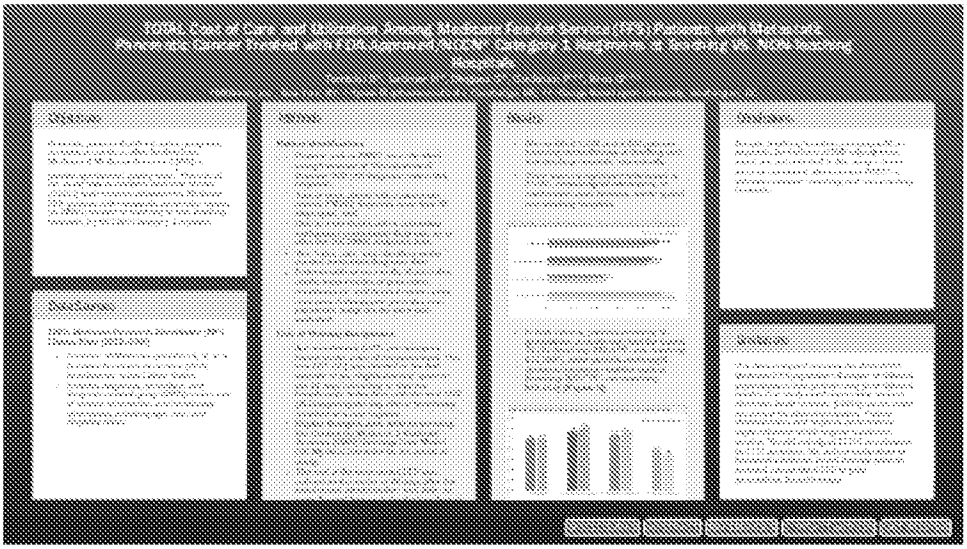
TOTAL Cost of Care and Utilization Among Medicare Fee-for-Service (FFS) Patients with Metastatic Pancreatic Cancer Treated with FDA-Approved/NCCN® Category 1 Regimens at Teaching VS. NON-Teaching Hospitals



Tomicki S*, Latimer H*, Dieguez G*, Cockrum P**, Kim G***

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PRESENTED AT:

Virtual Poster Symposium
VIRTUAL ISPOR 2021

OBJECTIVES

Hospitals partnered with education programs or research centers utilize funding from Medicare & Medicaid Services (CMS) to

provide specialized, quality care.[1] The aim of our study was to compare total cost of care (TCOC) and resource utilization for Medicare FFS patients with metastatic pancreatic cancer (m-PANC) treated at teaching or non-teaching hospitals, by NCCN® Category 1 regimen.

DATA SOURCES

100% Medicare Research Identifiable (RIF) Claims Files (2016-2018)

- Contains all Medicare-paid Part A, B, and D claims for all fee-for-service (FFS) beneficiaries in the United States.
- Includes diagnosis, procedure, and diagnosis-related group (DRG) codes; site of service information; and beneficiary information, including age, sex, and eligibility status.

METHODS

Patient Identification

- Patients with m-PANC were identified using International Classification of Disease (ICD)-10 diagnosis codes. We required:
- Two or more claims with a pancreatic cancer (PANC) diagnosis more than 30 days apart, and
- One or more claims with a secondary malignancy (metastasis) diagnosis on or after the first PANC diagnosis date.
- The "index date" was identified as the earliest metastasis diagnosis date.
- Patients without six months of pre-index and/or three months of post-index enrollment (or until death if earlier) were excluded. Patients with pre-index non-pancreatic malignancies were also excluded.

Line of Therapy Assignment

- A line of therapy (LOT) was assigned based on the order of therapies used. The first LOT (1L) was defined as the first episode of an "eligible therapy" given in the 14 days preceding or after the beneficiary's index date, with the next LOT (2L) beginning the day after a beneficiary switched to a new regimen.
- Eligible therapies were determined using the Centers for Medicare & Medicaid Services (CMS) Oncology Care Model (OCM) list of therapies for the period of study.[2]
- The end of the most recent LOT was defined as the earlier of 28 days after the most recent administration, visit date, or order for oral therapy (after the first date of chemotherapy), or date of death, if applicable.

Costs and resource utilization were summarized for the following NCCN® Category 1 drugs or regimens:

- 1L Gemcitabine monotherapy
- 1L Gemcitabine + nab-paclitaxel
- 1L Folinic acid + 5-fluorouracil + irinotecan + oxaliplatin (FOLFIRINOX)
- 2L Liposomal irinotecan + 5FU (5FU was not included in this analysis; see Limitations for further details.)

Teaching Hospital Identification

- Teaching hospitals were defined as those receiving indirect medical education (IME) adjustments to Medicare's prospective payment rates and were identified using CMS Fiscal Year IPPS Final Rule and Correction Notices.[3]
- Patients were attributed to teaching or non-teaching hospitals based on plurality of chemotherapy claims.

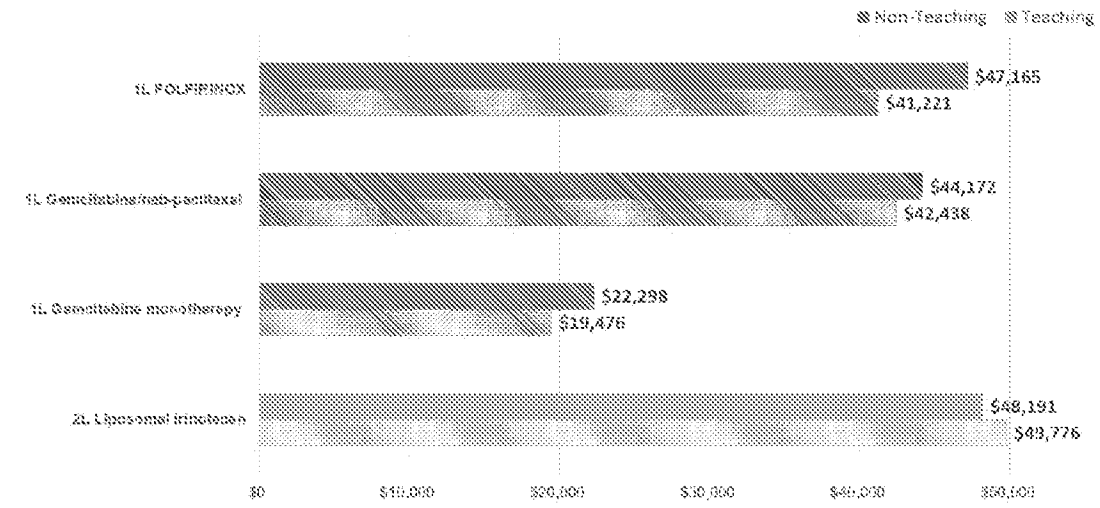
Cost Analysis and Resource Utilization

- Mean total cost of care (TCOC) was calculated as the average of the insurer paid amount excluding the patient cost-sharing per regimen/LOT.
- Mean hospital admissions were calculated as admissions per patient per regimen/LOT.
- Readmission rates were calculated as a percentage of total hospital admissions.
- We performed Tukey's Honestly Significant Difference (HSD) pairwise statistical testing for each regimen/LOT at 95% level of significance.

RESULTS

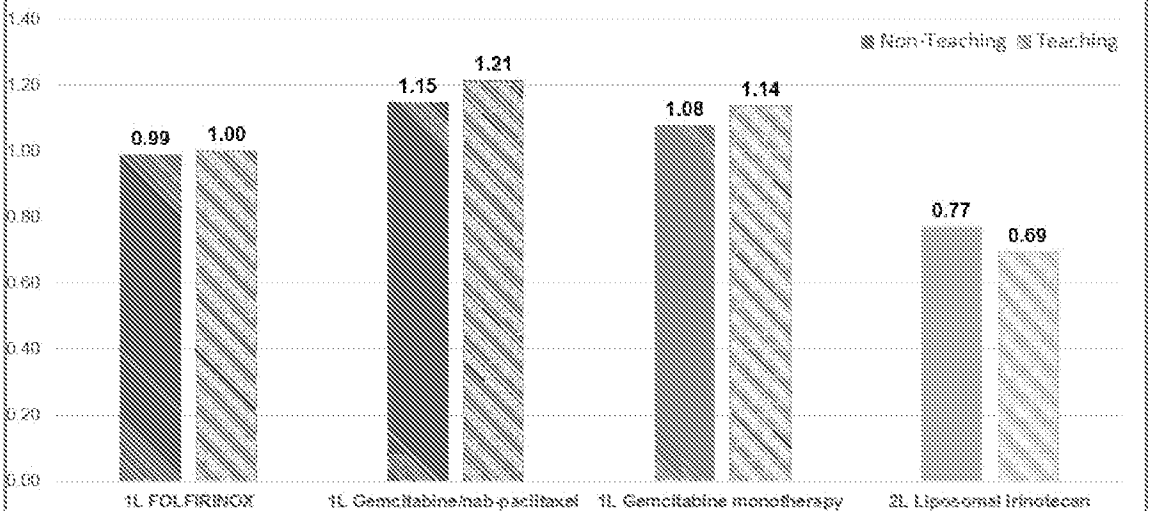
- We identified 7,594 and 4,959 patients receiving chemotherapy at teaching and non-teaching hospitals, respectively.
- There were no significant differences in TCOC, mean hospital admissions, or readmission rates between teaching and non-teaching hospitals.

Figure 1. Mean Total Cost of Care Per Patient Receiving Chemotherapy at Teaching Hospitals vs. Non-Teaching Hospitals

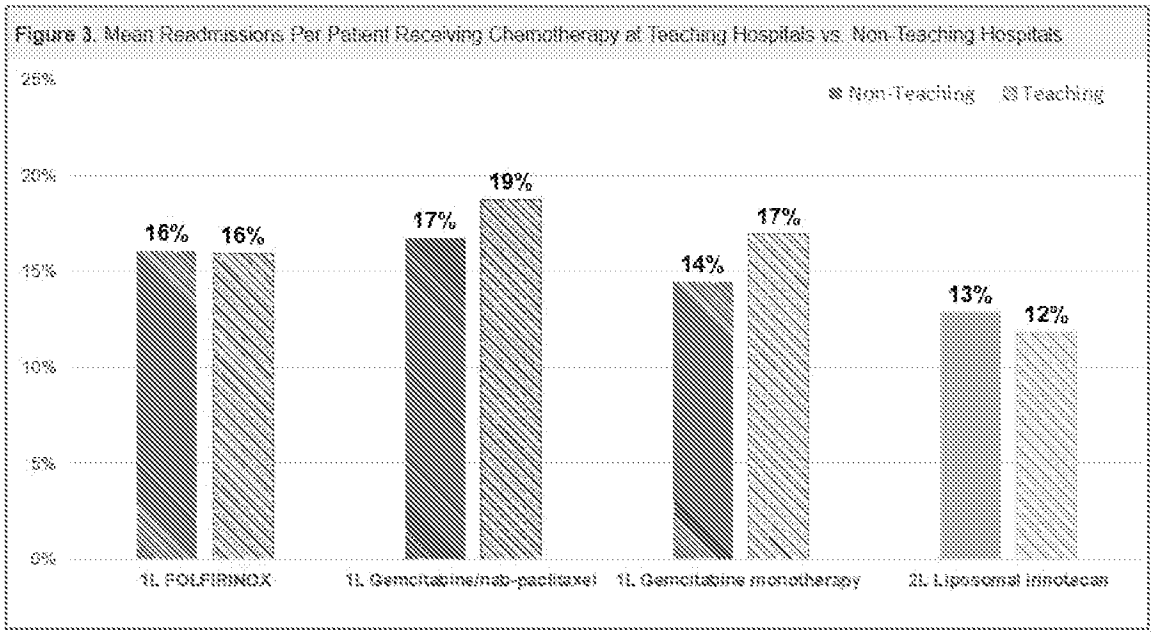


- In both cohorts, patients receiving 1L gemcitabine monotherapy had the lowest TCOC (teaching: $19,476*, non-teaching: $22,298*), while patients receiving 2L liposomal irinotecan had the highest (teaching: $49,776*, non-teaching: $48,191). [Figure 1]

Figure 2. Mean Admissions Per Patient Receiving Chemotherapy at Teaching Hospitals vs. Non-Teaching Hospitals



- In both cohorts, 2L liposomal irinotecan had the lowest mean hospital admissions (teaching: 0.69*, non-teaching: 0.77); while 1L gemcitabine/nab-paclitaxel had the highest (teaching: 1.21, non-teaching: 1.15). **[Figure 2]**



- Patients receiving 2L liposomal irinotecan also had the lowest readmission rates (teaching: 12%, non-teaching: 13%), while patients receiving 1L gemcitabine/nab-paclitaxel had the highest (teaching: 19%, non-teaching: 17%). {Figure 3}

Values with an * indicate statistical significance at $\alpha = 0.05$.

CONCLUSIONS

Despite teaching hospitals receiving add-on payments (in the form of IME adjustments, which are not reflected in this study[3]), there were no consistent differences in TCOC or utilization between teaching and non-teaching hospitals.

LIMITATIONS

The data analyzed included the 2016-2018 Medicare FFS population. Analysis of different populations or time periods may yield different results. Our study used claims data and not electronic health records (EHRs), so we could not control for clinical covariates. Patient characteristics and regimen performance might influence which regimens patients receive. We did not adjust TCOC or utilization for LOT durations. We did not study whether liposomal irinotecan-based therapy patients received concomitant 5FU or prior gemcitabine-based therapy.

DISCLOSURES

Author Contributions Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: [HL, ST, GD, PC, GK]; Drafting of the publication, or revising it critically for important intellectual content: [HL, ST, GD, PC, GK]; Final approval of the publication: [HL, ST, GD, PC, GK].

Disclosures [HL, ST, GD]: Employees of Milliman and received consulting fees from Ipsen. [PC] is employed by Ipsen and owns Ipsen stock. [GK] is employed by George Washington University and received consulting fees from Ipsen.

ABSTRACT

OBJECTIVES: To compare total cost of care (TCOC) and utilization for Medicare FFS patients (pts) with metastatic pancreatic cancer (m-PANC) treated at teaching or non-teaching hospitals, by NCCN® Category 1 regimen.

METHODS: We identified pts with m-PANC using ICD-9/10 diagnosis codes in the 2016-18 Medicare Parts A/B/D 100% Research Identifiable Files. Study pts had 2+ claims with a pancreatic cancer diagnosis and Medicare FFS coverage for 6 months pre- and 3 months post-metastasis diagnosis. Teaching hospitals were identified using CMS Fiscal Year IPPS Final Rule and Correction Notices. Pts were attributed to teaching or non-teaching hospitals based on plurality of chemotherapy claims. TCOC was the sum of mean paid services by the insurer per line of therapy. We calculated mean rates of hospital admissions (admits/pt) and readmissions. Study pts were treated with NCCN® Category 1 regimens: 1L gemcitabine monotherapy (gem-mono), 1L gemcitabine/nab-paclitaxel (gem-nab), 1L FOLFIRINOX (FFX), and 2L liposomal irinotecan-based regimen (Nal-IRI).

RESULTS: We identified 7,594 and 4,959 pts in teaching and non-teaching cohorts, respectively. There were no significant differences in TCOC, admits/pt, or readmissions between teaching and non-teaching hospitals. In both cohorts, gem-mono had the lowest TCOC (teaching: $19,476, P<.05; non-teaching: $22,298, P<.05), while Nal-IRI had the highest (teaching: $49,776, P<.05; non-teaching: $48,191, P>.05). In both cohorts, Nal-IRI had the lowest admits/pt (teaching: 0.69, P<.05; non-teaching: 0.77 P>.05) and readmissions (teaching: 12%, P>.05; non-teaching: 13%, P>.05) while gem-nab had the highest admits/pt (teaching: 1.21, P>.05; non-teaching: 1.15, P>.05) and readmissions (teaching: 19%, P>.05; non-teaching: 17%, P>.05).

CONCLUSION: Despite teaching hospitals receiving add-on payments, there were no consistent differences in TCOC between teaching and non-teaching hospitals. Additionally, admits/pt and readmissions by regimen were similar among cohorts. However, across cohorts TCOC was lowest for gem-mono and highest for Nal-IRI and admits/pt and readmissions were lowest for Nal-IRI and highest for gem-nab.

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302P

Real world patterns of pain medication use among patients with metastatic pancreatic ductal adenocarcinoma (mPDAC)

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Background

- An estimated 60,430 new cases of pancreatic cancer (PC) will be diagnosed, and 48,220 patients will die due to this disease in the United States (US) in 2021.[1]
- Pancreatic ductal adenocarcinoma (PDAC), accounts for more than 90% of PC diagnoses, and is the most common type of pancreatic cancer.[2]
- 80% of patients with advanced PC suffer from abdominal and/or back pain.[3]
- Pancreatic cancer-related pain is typically treated pharmaceutically using pain medicines, which include opioids or narcotics (morphine, oxycodone, hydromorphone, and fentanyl), acetaminophen (Tylenol®), and nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, ibuprofen (Advil® or Motrin®) and naproxen (Aleve®). [3,4]
- Previous studies have found that the presence of pain was associated with impaired survival in pancreatic cancer patients.[5,6]

Objective

The goal of this study was to assess the treatment patterns of pain medication usage and their association with duration of therapy among patients with mPDAC treated in the real-world setting.

Methods

Study Design and Data Source

A retrospective descriptive analysis was performed using the IBM MarketScan Commercial Claims and Encounter and Medicare Supplemental database.

Patient Selection

- This analysis evaluated adult patients diagnosed with mPDAC and treated with systemic therapy between January 1, 2015 and March 31, 2020
- Eligible patients were those who:
  - Had at least two diagnoses for PC (ICD-9-CM: 157.xx, ICD-10-CM: C25.xx) separated by at least 30 days but no more than 365 days apart
  - Had two claims for secondary malignancy (ICD-9-CM: 196-198.xx; ICD-10-CM: C77-C79.xx) after the initial PC diagnosis
  - Were at least 18 years old at metastatic diagnosis
  - Received systemic treatment indicated for mPDAC on or after the initial metastatic diagnosis date
  - And had 6 months of continuous enrollment prior to initiating treatment and 1-month post-treatment with no evidence of other primary cancers.

Measures and Statistical Analyses

- Baseline patient demographics and clinical characteristics and opioid medication use patterns were assessed.
  - Baseline characteristics included: age at treatment initiation, sex, insurance plan type, payer type, region, and year of treatment initiation.
- The duration of therapy (DOT), in days, of each line was summarized.
- Prescription opioid use was evaluated during the systemic line of therapy and following were assessed:
  - Receipt of an opioid prescription
  - Average daily dose (in morphine equivalents)
- Opioid use trends over time and region were summarized.
- Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Table 1. Patient characteristics at the start each line of therapy

Characteristics	First Line N = 2,841	Second Line N = 1,248	Third Line N = 375
Age, years, median (Q1-Q3)	61 (56 - 66)	61 (55 - 65)	61 (56 - 65)
Male, n (%)	1,579 (55.6%)	692 (55.5%)	196 (52.3%)
Geographic region, n (%)			
North Central	772 (27.2%)	311 (24.9%)	94 (25.1%)
Northeast	568 (20%)	279 (22.4%)	100 (26.7%)
South	1,115 (39.3%)	491 (39.3%)	137 (36.5%)
Unknown	6 (0.2%)	7 (0.6%)	0 (0%)
West	380 (13.4%)	160 (12.8%)	44 (11.7%)
Payer Type, n (%)			
Commercial	2,046 (72%)	969 (77.6%)	300 (80%)
Medicare	795 (28%)	279 (22.4%)	75 (20%)
Index Year, n (%)			
2015 - 2017	1,916 (67.4%)	757 (60.7%)	196 (52.3%)
2018 - 2020	925 (32.6%)	491 (39.3%)	179 (47.7%)

RESULTS

Patient Characteristics

- There were 2,841 patients (median age: 61 years, IQR: 56-66) included in the study treated with first line (1L) therapies of interest. 1,248 patients received second line (2L) treatment, and 375 patients received third line (3L) treatment.
- Patient characteristics are summarized in Table 1

Opioid Use and Duration of Therapy

- 54.6% of 1L treated, 50.6% of 2L treated patients, and 46.1% of 3L treated patients received at least one prescription for opioids (Figure 1).
- Duration of therapy was longer for patients who received a pain medication than for those who did not across all lines of therapy (Figure 2).

Figure 1. Opioid use by line of therapy

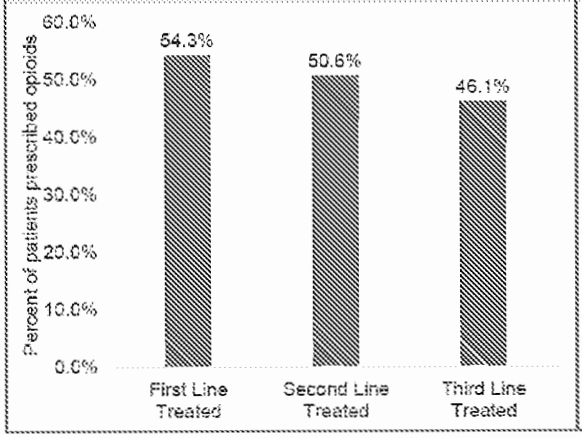
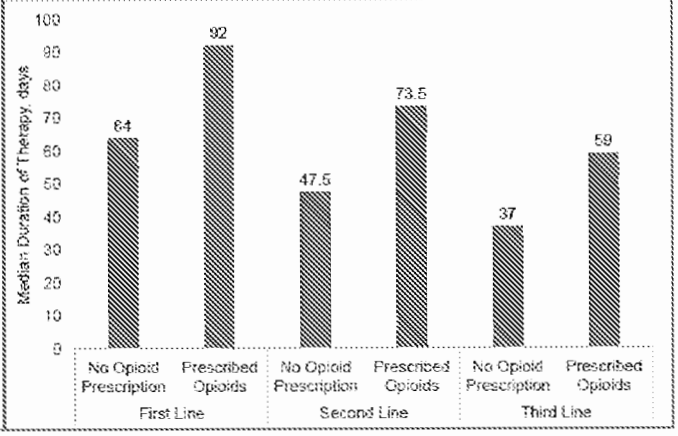


Figure 2. Duration of therapy by line of therapy and opioid use



Opioid Use and Duration of Therapy

- In 1L the mean daily dose was 39.5mg (SD: 134.6) morphine equivalents, in 2L it was 34.5mg (SD: 100.9), and in 3L it was 28.1mg (SD: 49.51).
- Across all lines of therapy opioid use remained stable during the study period ranging from 54.2% among patients treated in 2015 to 51.1% among those who initiated treatment in 2019 (Figure 3).
- No regional differences were observed in prescription patterns within the four US census regions (Figure 4).

Figure 3: Opioid use by Year of Index

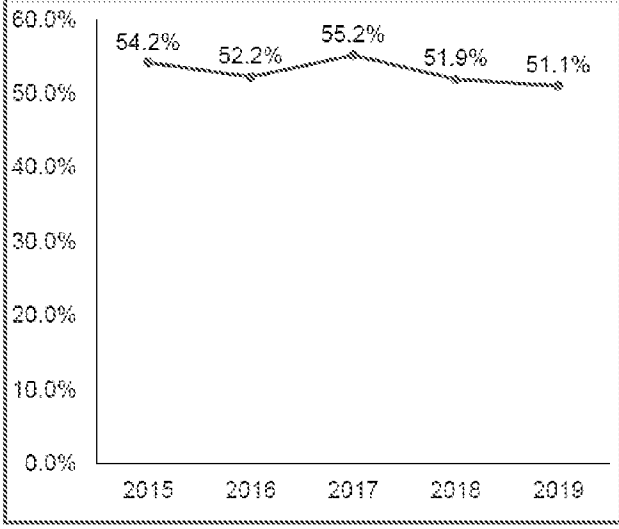
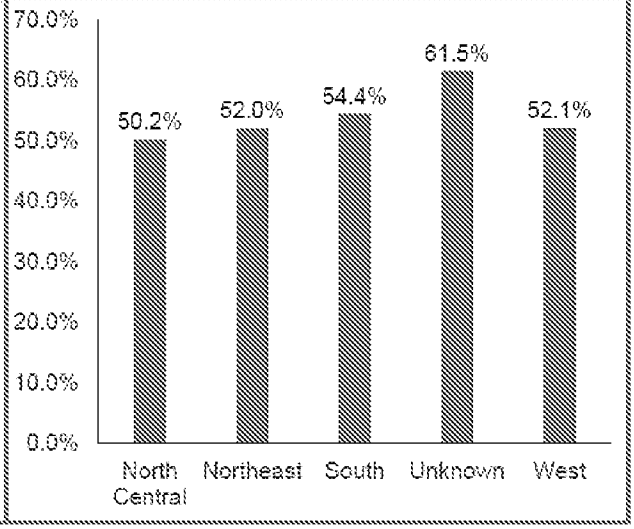


Figure 4: Opioid use by Region



Conclusions

- In this real-world cohort of patients with mPDAC nearly half were prescribed at least one opioid during treatment.
- Patients who received opioids experienced a longer duration of therapy compared to those who did not.
- Further studies are needed to understand the association of pain control with improved clinical outcomes among patients with mPDAC.

Limitations

- While patients are prescribed pain treatment, there is no way to confirm if the treatments were used as intended
- Other modalities for pain management (over-the-counter medications, cannabinoids) are not captured in claims data
- Reasons why patients were prescribed opioids were not available for our analysis

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Author Contributions Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: [AS;AS;SW;PC;BG]; Draftingof the publication or revising it critically for important intellectual content: [AS;AS;SW;PC;BG]; Final approval of the publication: [AS;AS;SW;PC;BG].

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Real world patterns of pain medication use among patients with metastatic pancreatic ductal adenocarcinoma (mPDAC)

Ashley Laurent[1], Andy Sumarsidi[1], Eric Wang[2], Paul Lindsmith[1], Dan George[3]
[1]Ipsen, Cambridge, MA; [2]Clinical Research Institute, M.D. Medical College of Wisconsin, Milwaukee, WI

Background

- An estimated 60,430 new cases of pancreatic cancer (PC) will be diagnosed, and 48,220 patients will die due to this disease in the United States (US) in 2021.[1]
- Pancreatic ductal adenocarcinoma (PDAC), accounts for more than 90% of PC diagnoses, and is the most common type of pancreatic cancer.[2]
- 80% of patients with advanced PC suffer from abdominal and/or back pain.[2]
- Pancreatic cancer-related pain is typically treated pharmaceutically using pain medicines, which include opioids or narcotics (morphine, oxycodone, hydromorphone, and fentanyl), acetaminophen (Tylenol®), and nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, ibuprofen (Advil® or Motrin®) and naproxen (Aleve®).[3,4]
- Previous studies have found that the presence of pain was associated with lessened survival in pancreatic cancer patients.[5,6]

Objective

The goal of this study was to assess the treatment patterns of pain medication usage and their association with duration of therapy among patients with mPDAC treated in the real-world setting.

Methods

Study Design and Data Source

A retrospective descriptive analysis was performed using the IBM MarketScan Commercial Claims and Encounter and Medicare Supplemental databases.

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- This analysis evaluated adult patients diagnosed with mPDAC and treated with systemic therapy between January 1, 2015 and March 31, 2020
- Eligible patients were those who:
  - Had at least two diagnoses for PC (ICD-9-CM: 157.xx, ICD-10-CM: C25.xx) separated by at least 30 days but no more than 365 days apart
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  - Were at least 18 years old at metastatic diagnosis
  - Received systemic treatment indicated for mPDAC on or after the initial metastatic diagnosis date
  - And had 6 months of continuous enrollment prior to initiating treatment and 1-month post-treatment with no evidence of other primary cancers.

Measures and Statistical Analyses

- Baseline patient demographics and clinical characteristics and opioid medication use patterns were assessed.
  - Baseline characteristics included: age at treatment initiation, sex, insurance plan type, payer type, region, and year of treatment initiation.
- The duration of therapy (DOT), in days, of each line was summarized.
- Prescription opioid use was evaluated during the systemic line of therapy and following were assessed:
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- Opioid use trends over time and region were summarized.
- Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Table 1. Patient characteristics at the start each line of therapy

Characteristics	First Line N = 2,941	Second Line N = 1,248	Third Line N = 575
Age, years, median (Q1-Q3)	61 (56 - 66)	61 (55 - 65)	61 (56 - 65)
Male, n (%)	1,579 (55.8%)	682 (55.5%)	355 (62.3%)
Geographic region, n (%)			
North Central	773 (27.2%)	311 (24.9%)	94 (25.1%)
Northeast	568 (20%)	279 (22.4%)	100 (25.7%)
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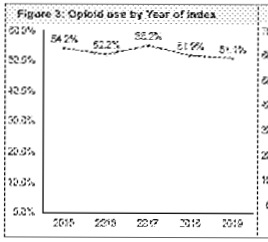
Commercial	2,046 (72%)	969 (77.8%)	302 (80%)
Medicare	795 (28%)	278 (22.4%)	75 (20%)
Index Year, n (%)			
2015 - 2017	1,918 (67.4%)	757 (60.7%)	186 (32.3%)
2018 - 2020	926 (32.6%)	491 (39.3%)	179 (47.7%)

Figure 3: Opioid use by Year of Index



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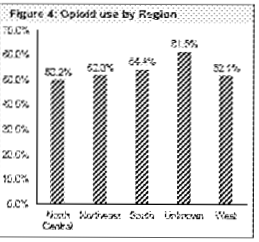

CONCLUSIONS

- In this real-world cohort of patients with mPDAC nearly half were prescribed at least one opioid during treatment.
- Patients who received opioids experienced a longer duration of therapy compared to those who did not.
- Further studies are needed to understand the association of pain control with improved clinical outcomes among patients with mPDAC.

Results

Patient Characteristics

- There were 2,941 patients (median age: 61 years, IQR: 56-66) included in the study treated with first line (1L) therapies of interest, 1,248 patients received second line (2L) treatment, and 575 patients received third line (3L) treatment.
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- 54.2% of 1L treated, 55.6% of 2L treated patients, and 48.1% of 3L treated patients received at least one prescription for opioids (Figure 1).
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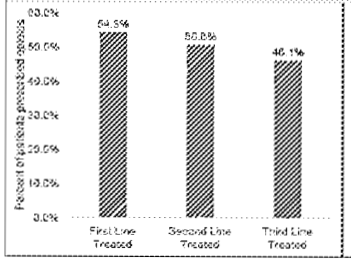

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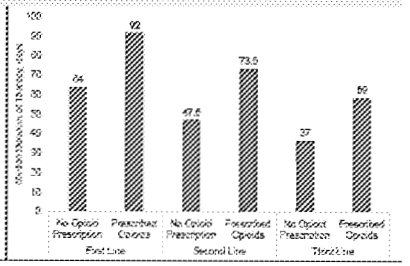

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- Across all lines of therapy opioid use remained stable during the study period ranging from 54.2% among patients treated in 2015 to 51.1% among those who initiated treatment in 2019 (Figure 3).
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Limitations

- While patients are prescribed pain treatment, there is no way to confirm if the treatments were used as intended
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Author Contributions: Substantial contributions to study conception design, or acquisition/analysis/interpretation of data. (AL/AS/EW/PG/EG); Drafting of the publication or revising it critically for important intellectual content. (AL/AS/EW/PG/EG); Final approval of the publication (AL/AS/EW/PG/EG)

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Impact of the COVID-19 pandemic on metastatic pancreatic ductal adenocarcinoma (mPDAC) care delivery

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BACKGROUND

- Recent studies have reported declines in medical encounters among patients with cancer and a decline in cancer screenings[1,2]
- The coronavirus disease 2019 (COVID-19) pandemic has caused abrupt changes to the US health system and disruption in cancer care delivery[1]
- Patients with cancer have reported concerns about the impact to their care due to the COVID-19 pandemic[3]
- Pancreatic cancer remains one of the most lethal cancers in the United States (US) with a 5-year relative survival of 9%[4]
- Due to limited treatment options for patients with metastatic disease, the 5-year relative survival is only 2.9%[5]
- There are no reports on the impact of care of patients with mPDAC due to COVID-19

OBJECTIVE

- Characterize the impact of COVID-19 on healthcare utilization and outcomes for patients with mPDAC in the US in the community oncology 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 comprising de-identified, patient-level structured and unstructured data, curated via technology-enabled abstraction. Flatiron Health includes data from over 280 cancer clinics

Patient Selection

- This analysis identified and evaluated adult patients diagnosed with mPDAC between March 1, 2019 – September 30, 2019 (Pre-COVID) and those diagnosed with mPDAC between March 1, 2020 – September 30, 2020 (Post-COVID)
- Additionally, eligible patients were those who:
  - were at least 18 years old at mPDAC diagnosis
  - had at least one recorded activity after diagnosis
  - had correctly specified death data

Measures and Statistical Analyses

- Baseline patient demographics and clinical characteristics at the metastatic diagnosis were assessed
- The proportion of patients who received systemic treatment, the time to treatment, and the most common treatment regimens were assessed
- Overall survival was assessed via Kaplan-Meier analysis
  - Patients without a death recorded in their follow-up were censored on the date of their last recorded activity
  - 60-, 90-, and 180-day survival were summarized
  - The log-rank test was used to compare survival between the cohorts
- Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA)

RESULTS

Patient Characteristics

- There were 923 patients diagnosed with mPDAC in the pre-COVID period and 796 diagnosed in the post-COVID period
- The median age at metastatic diagnosis was 70 years (IQR: 62 – 76) for both cohorts
- 48.5% of patients in the pre-COVID period had ECOG PS scores of 0-1 compared to 47.1% of patients in the post-COVID period (Table 1)

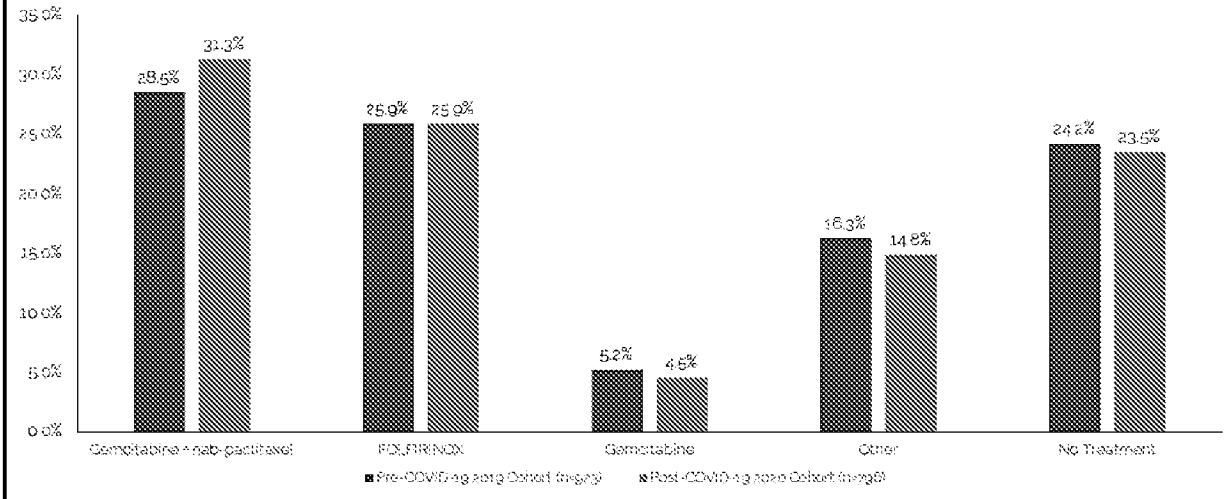
Treatment Patterns

- Slightly more patients were diagnosed initially with stage IV disease in the post-COVID period (69.7%) compared to the pre-COVID period (62.3%)
- A similar proportion of patients received first-line (1L) therapy in the pre- and post-COVID period, 75.8% and 76.5%, respectively
- The median number of days from metastatic diagnosis until the start of treatment was 21 (IQR: 13 – 40) and 19 (IQR: 12 – 32) for the pre-COVID and post-COVID period, respectively
- The most common 1L regimens were similar in both periods as shown in Figure 1

Overall Survival

- The median overall survival in the pre-COVID period was 8.4 months (95% CI: 7.5 – 9.0) and 6.11 months (95% CI: 5.4 – 6.9) in the post-COVID period ($p < 0.001$) as shown in Figure 2
- The 60-, 90-, and 180-day survival in the pre-COVID period were 86.2%, 77.0%, and 61.4% compared to 82.8%, 71.4%, and 51.4% in the post-COVID period

Figure 1. Most Frequent 1L Regimens



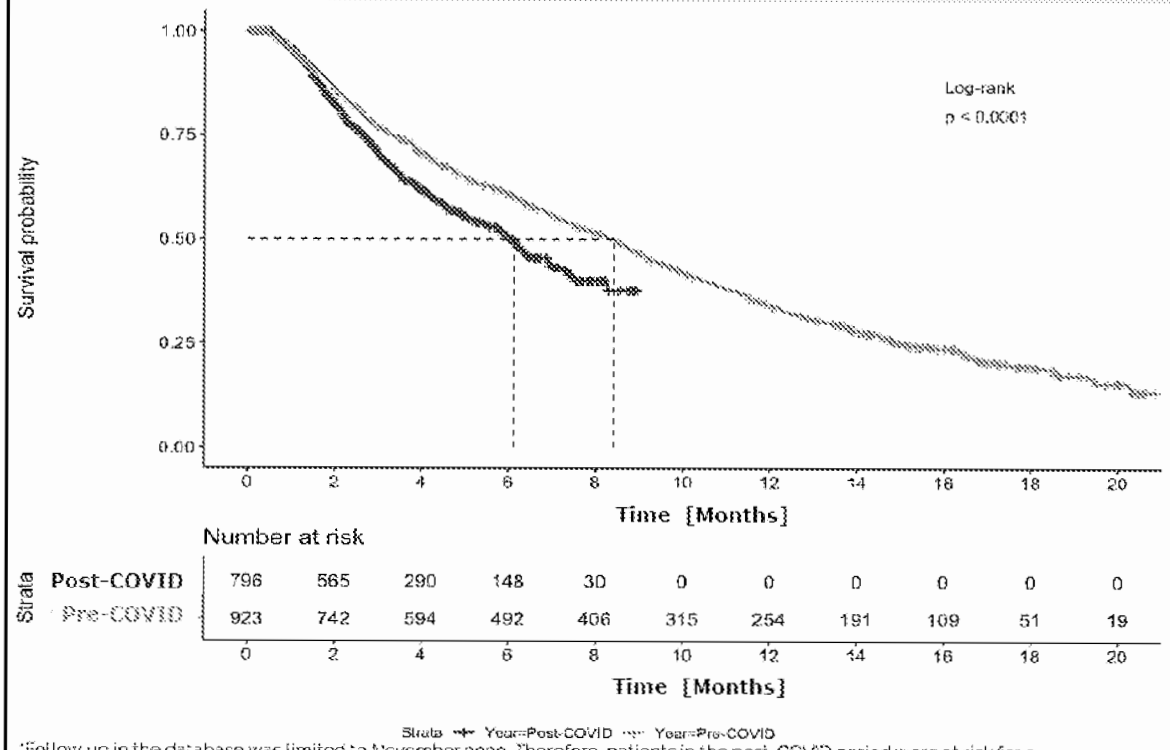
The top regimens included in the 'Other' category included FOLFOX (~3%), Clinical Study Drugs (~3%), Capecitabine (2-3%), and liposomal irinotecan + 5-FU/LV (~2%)

Table 1. Patient characteristics at metastatic diagnosis

Characteristic	Pre-COVID-19 2019 Cohort (N=923)	Post-COVID-19 2020 Cohort (N=796)
Age, y		
Median (IQR)	70 (62, 76)	70 (62, 76)
Gender, n (%)		
Male	482 (52.2)	426 (53.5)
Female	441 (47.8)	370 (46.5)
Race, n (%)		
White	532 (57.6)	419 (52.6)
Other	139 (15.1)	156 (19.6)
Black	81 (8.8)	66 (8.3)
Asian	18 (2.0)	19 (2.4)
Unknown	101 (10.9)	95 (11.9)
Region, n (%)		
South	393 (42.6)	343 (43.1)
Northeast	128 (13.9)	105 (13.2)
West	125 (13.5)	125 (15.7)
Midwest	93 (10.1)	84 (10.6)
Unknown	184 (19.9)	139 (17.5)
Stage at initial diagnosis, n (%)		
Stage I–III	283 (30.7)	202 (25.4)
Stage IV	575 (62.3)	555 (69.7)
Unknown	65 (7.0)	39 (4.9)
ECOG PS score, n (%)		
0	191 (20.7)	152 (19.1)
1	257 (27.8)	229 (28.8)
2+	75 (8.1)	87 (10.9)
Missing	400 (43.3)	328 (41.2)
Received 1L therapy, n (%)	700 (75.8)	609 (76.5)
Received 2L therapy, n (%)	263 (28.5)	109 (13.7)
Clinic visit within 90 days of mPDAC diagnosis, n (%)	872 (94.5)	782 (98.2)
Days to first clinic visit after metastatic diagnosis		
Median (IQR)	7 (2–14)	7 (2–14)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; IQR, interquartile range; mPDAC, metastatic pancreatic ductal adenocarcinoma; SD, standard deviation.

Figure 2. Overall Survival



*Follow up in the database was limited to November 2020. Therefore, patients in the post-COVID period were at risk for a maximum of 9 months leading to the truncated survival plot

Conclusions

- During the COVID-19 pandemic era, the diagnosis of de novo mPDAC appears to have been impacted with relatively higher number of patients diagnosed with advanced stage at presentation
- Our analysis suggests that while patients diagnosed in 2020 received a similar level of care as those in 2019, their survival outcomes were adversely affected

Limitations

- EHR data are subject to possible entry errors and missing information which could have led to extreme or incorrect values
- Sensitivity and specificity of mortality data may affect survival estimates

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Medical Writing Support

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Conflicts of interest

R.K.P has a consulting/advisory role with Ipsen and Exelis; A.L., J.G. and P.C. is are employee of and have stock in Ipsen; S.W. and A.S are employees of Genesis Research, which receives consulting fees from Ipsen.

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This study was sponsored by Ipsen

Presented at the American Society for Clinical Oncology (ASCO) Annual Meeting: June 4 – 8, 2021; Virtual.

Impact of the COVID-19 pandemic on metastatic pancreatic ductal adenocarcinoma (mPDAC) care delivery

[redacted]

4137

BACKGROUND

- Recent studies have reported declines in medical encounters among patients with cancer and a decline in cancer screenings[1,2]
- The coronavirus disease 2019 (COVID-19) pandemic has caused abrupt changes to the US health system and disruption in cancer care delivery[3]
- Patients with cancer have reported concerns about the impact to their care due to the COVID-19 pandemic[4]
- Pancreatic cancer remains one of the most lethal cancers in the United States (US) with a 5-year relative survival of 9%[5]
- Due to limited treatment options for patients with metastatic disease, the 5-year relative survival is only 2.9%[6]
- There are no reports on the impact of care of patients with mPDAC due to COVID-19

OBJECTIVE

- Characterize the impact of COVID-19 on healthcare utilization and outcomes for patients with mPDAC in the US in the community oncology 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 comprising de-identified, patient-level structured and unstructured data, curated via technology-enabled abstraction. Flatiron Health includes data from over 280 cancer clinics

Patient Selection

- This analysis identified and evaluated adult patients diagnosed with mPDAC between March 1, 2019 – September 30, 2019 (Pre-COVID) and those diagnosed with mPDAC between March 1, 2020 – September 30, 2020 (Post-COVID)
- Additionally, eligible patients were those who
  - were at least 18 years old at mPDAC diagnosis
  - had at least one recorded activity after diagnosis
  - had correctly specified death data

Measures and Statistical Analyses

- Baseline patient demographics and clinical characteristics at the metastatic diagnosis were assessed
- The proportion of patients who received systemic treatment, the time to treatment, and the most common treatment regimens were assessed
- Overall survival was assessed via Kaplan–Meier analysis
  - Patients without a death recorded in their follow-up were censored on the date of their last recorded activity
  - 60-, 90-, and 180-day survival were summarized
  - The log-rank test was used to compare survival between the cohorts
- Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA)

RESULTS

Patient Characteristics

- There were 923 patients diagnosed with mPDAC in the pre-COVID period and 796 diagnosed in the post-COVID period
- The median age at metastatic diagnosis was 70 years (IQR: 62 – 76) for both cohorts
- 48.5% of patients in the pre-COVID period had ECOG PS scores of 0-1 compared to 47.1% of patients in the post-COVID period (Table 1)

Treatment Patterns

- Slightly more patients were diagnosed initially with stage IV disease in the post-COVID period (69.7%) compared to the pre-COVID period (62.3%)
- A similar proportion of patients received first-line (1L) therapy in the pre- and post-COVID period, 75.8% and 76.5%, respectively
- The median number of days from metastatic diagnosis until the start of treatment was 21 (IQR: 13 – 40) and 19 (IQR: 12 – 32) for the pre-COVID and post-COVID period, respectively
- The most common 1L regimens were similar in both periods as shown in Figure 1

Overall Survival

- The median overall survival in the pre-COVID period was 8.4 months (95% CI: 7.5 – 9.0) and 8.11 months (95% CI: 6.4 – 8.9) in the post-COVID period ($p < 0.001$) as shown in Figure 2
- The 60-, 90-, and 180-day survival in the pre-COVID period were 86.2%, 77.0%, and 61.4% compared to 82.8%, 71.4% and 51.4% in the post-COVID period

Table 1. Patient characteristics at metastatic diagnosis

Characteristic	Pre-COVID-19 Era Cohort (N = 923)	Post-COVID-19 Era Cohort (N = 796)
Age, y		
Median (IQR)	70 (62, 76)	70 (62, 76)
Gender, n (%)		
Male	482 (52.2)	426 (53.5)
Female	441 (47.8)	370 (46.5)
Race, n (%)		
White	533 (57.8)	459 (57.7)
Other	139 (15.1)	126 (15.8)
Black	51 (5.5)	66 (8.3)
Asian	16 (1.7)	19 (2.4)
Unknown	184 (19.9)	126 (15.8)
Region, n (%)		
South	392 (42.5)	343 (43.1)
Northeast	178 (19.3)	165 (20.7)
West	175 (19.0)	125 (15.7)
Midwest	93 (10.1)	84 (10.6)
Unknown	184 (19.9)	139 (17.5)
Stage at initial diagnosis, n (%)		
Stage I-III	283 (30.7)	208 (26.1)
Stage IV	575 (62.3)	555 (69.7)
Unknown	65 (7.0)	33 (4.1)
ECOG PS score, n (%)		
0	191 (20.7)	152 (19.1)
1	257 (27.8)	239 (28.8)
2+	75 (8.1)	87 (10.9)
Missing	400 (43.3)	318 (39.9)
Received 1L therapy, n (%)	700 (75.8)	609 (76.5)
Received 2L therapy, n (%)	262 (28.4)	193 (24.2)
Clinic visit within 90 days of mPDAC diagnosis, n (%)	872 (94.5)	782 (98.2)
Days to first clinic visit after metastatic diagnosis		
Median (IQR)	7 (3, 14)	7 (3, 14)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; IQR, interquartile range; mPDAC, metastatic pancreatic ductal adenocarcinoma; SD, standard deviation.

Figure 1. Most Frequent 1L Regimens

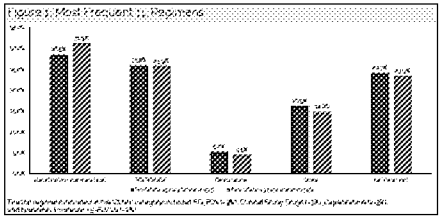
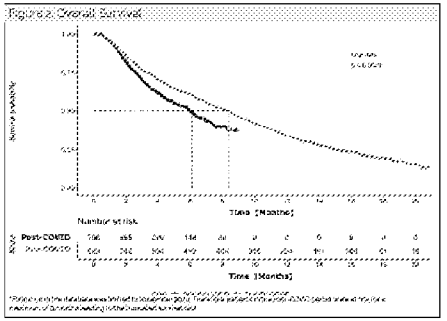


Figure 2. Overall Survival



Conclusions

- During the COVID-19 pandemic era, the diagnosis of de novo mPDAC appears to have been impacted with relatively higher number of patients diagnosed with advanced stage at presentation
- Our analysis suggests that while patients diagnosed in 2020 received a similar level of care as those in 2019, their survival outcomes were adversely affected

Limitations

- EHR data are subject to possible entry errors and missing information which could have led to extreme or incorrect values
- Sensitivity and specificity of mortality data may affect survival estimates

References

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]

Medical Writing Support

Medical writing support was supported by Ipsen in accordance with GPP3.

Conflicts of Interest

[redacted] has a consulting relationship with Ipsen and Optum, Inc. [redacted] are employees of and have stock in Optum, Inc. and AbbVie, employers of Genesis Research, which receives consulting fees from Ipsen.

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CONQUERING THORACIC CANCERS WORLDWIDE

RESILIENT part 1: a phase II dose-exploration and dose-expansion study of second-line liposomal irinotecan monotherapy in adults with small cell lung cancer

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Author	Disclosure(s)
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David R Spigel	Consultant: AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Clovis Oncology, Eli-Lilly, Genentech/Roche, Novartis, Pfizer; research/grant funding (institution): Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Clovis Oncology, Daiichi Sankyo, Eli-Lilly, Genentech/Roche, Merck, Novartis, Peregrine Pharmaceuticals, Pfizer, OncoGenex, OncoMed, Verastem Oncology, University of Texas Southwestern Medical Center - Simmons Cancer Center; other: Bristol Myers Squibb
Yuanbin Chen	Honorarium: Array BioPharma, AstraZeneca, Bristol Myers Squibb, Eli-Lilly, Genentech, Guardant Health, Heron Therapeutics, Merck, Novartis, Pfizer, Takeda; consultant: Array BioPharma, AstraZeneca, Bristol Myers Squibb, Genentech, Heron Therapeutics, Novartis, Pfizer, Takeda; speaker's bureau: AstraZeneca, Bristol Myers Squibb, Eli-Lilly, Genentech, Guardant Health, Merck, Novartis, Takeda; research/grant funding (institution): AstraZeneca, Bristol Myers Squibb, Guardant Health, Helsinn, Ipsen, Roche; expert testimony: AstraZeneca, Takeda; clinical trials: AstraZeneca, Bristol Myers Squibb, Ipsen, Roche
Maria Jove	Consultant: Boehringer Ingelheim; travel and accommodation support: Bristol Myers Squibb, MSD, Roche
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Patricia Rich, Theresa Hayes, Vanesa Gutiérrez Calderón	Nothing to disclose
Reyes Bernabe Caro	Consultant: AstraZeneca, Bristol Myers Squibb, Roche; travel and accommodation support: Bristol Myers Squibb, Roche
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Santiago Ponce	Consultant: Roche; speaker's bureau: Bristol Myers Squibb; travel and accommodation support: RSD Pharma
Paul Bunn	Consultant: AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Eli-Lilly, Genentech, Merck, Merrimack Pharmaceuticals, Novartis, Pfizer; other: AstraZeneca, Bristol Myers Squibb, Genentech, Merck, Pfizer
Bin Zhang, Yan Moore, Xiaopan Valerie Yao, Jaba Kokhreidze	Employment: Ipsen

Introduction

- Liposomal irinotecan (ONIVYDE pegylated liposomal) encapsulates irinotecan in a lipid-bilayer vesicle, leading to prolonged circulation, and protection from hydrolysis and rapid metabolic conversion[1]
- Preliminary data from part 1 of the phase II/III RESILIENT trial (ClinicalTrials.gov Identifier: NCT03088813) indicated that second-line liposomal irinotecan 70 mg/m^2 (free base) every 2 weeks was well tolerated and had promising antitumor activity in patients with SCLC[2]
- Here, we report long-term follow-up results (data cut: August 20, 2020) from RESILIENT part 1

SCLC, small cell lung cancer

1. Drummond D *et al. Cancer Res* 2006;66:3271–7; 2. Paz-Ares L *et al.* Poster presented at the 2019 World Conference on Lung Cancer (WCLC), September 7–10, 2019, Barcelona, Spain

Objectives

Primary objectives

- To describe the safety and tolerability of liposomal irinotecan monotherapy
- To determine the recommended dose (85 mg/m² or 70 mg/m²; free base) for RESILIENT part 2

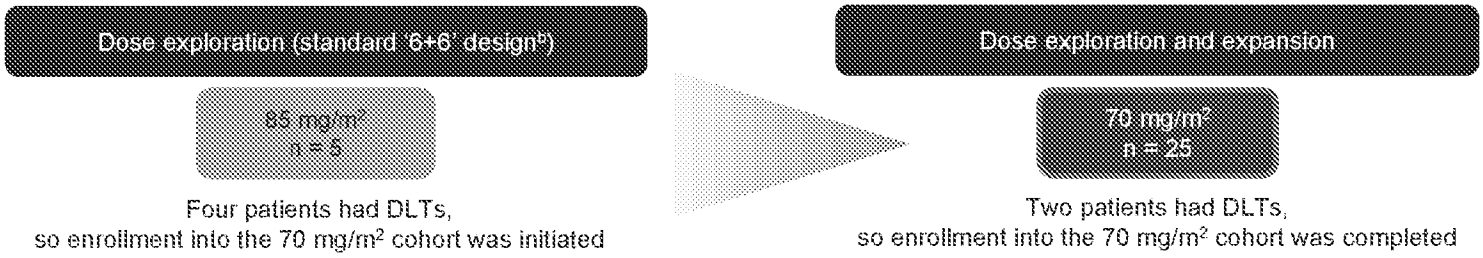
Secondary objectives

- To assess the preliminary efficacy of liposomal irinotecan monotherapy:
  - ORR
  - PFS
  - OS

ORR, objective response rate; OS, overall survival; PFS, progression-free survival

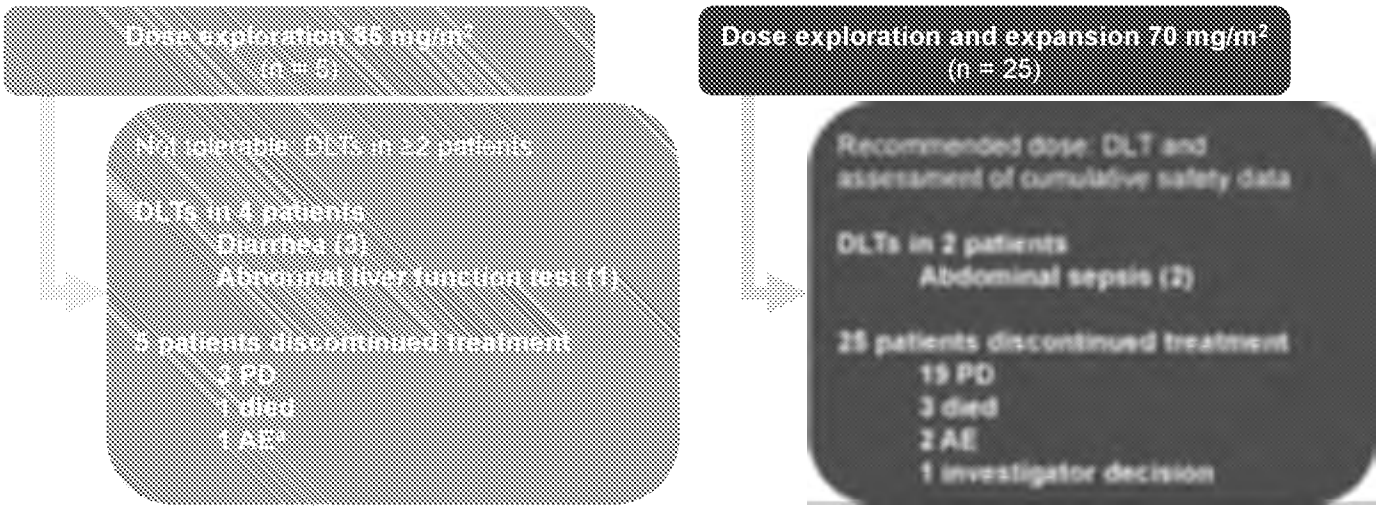
Methods

- An open-label, single-arm, safety run-in of liposomal irinotecan administered every 2 weeks in patients with SCLC who had progressed on or after platinum-based first-line therapy
- Patients were aged ≥18 years with an ECOG Performance Status of 0 or 1
- The study comprised two parts: dose exploration and dose expansion
- Patients received i.v. liposomal irinotecan over 90 minutes, every 2 weeks in 6-week cycles[a]
- The dose selected for expansion was based on DLTs and safety data from dose exploration



[a]Treatment was until progressive disease or unacceptable toxicity; [b]if fewer than two of the first six patients in the 85 mg/m2 cohort had DLTs, a further six patients were enrolled, otherwise enrollment into the 70 mg/m² cohort was initiated.
DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; i.v., intravenous; SCLC, small cell lung cancer

Patient disposition



- FPFT occurred in May 2018; as of August 20, 2020, two patients (one in each dose group) were in long-term follow-up (95% CI for OS, 5.16–9.82 months)

[a]Study drug-related AE prior to disease progression. AE, adverse event; CI, confidence interval; DLT, dose-limiting toxicity; FPFT, first patient first treatment; OS, overall survival; PD, progressive disease

Baseline characteristics

	35 mg/m² n = 5	70 mg/m² n = 25	All patients N = 30
Age, years			
Median (range)	62.0 (59–72)	59.0 (48–73)	61.5 (48–73)
Gender, n (%)			
Male	3 (60.0)	9 (36.0)	12 (40.0)
Race, n (%)			
White	5 (100)	25 (100)	30 (100)
Disease status, n (%)			
Locally advanced	0	2 (8.0)	2 (6.7)
Metastatic	5 (100)	23 (92.0)	28 (93.3)
Baseline ECOG Performance Status, n (%)			
Fully active (ECOG 0)	1 (20.0)	3 (12.0)	4 (13.3)
Restricted activity (ECOG 1)	4 (80.0)	22 (88.0)	26 (86.7)
Best response to previous therapies, n (%)			
Complete response	0	1 (4.0)	1 (3.3)
Partial response	2 (40.0)	16 (64.0)	18 (60.0)
Stable disease	1 (20.0)	2 (8.0)	3 (10.0)
Progressive disease	2 (40.0)	3 (12.0)	5 (16.7)
Unknown	0	3 (12.0)	3 (10.0)

ECOG, Eastern Cooperative Oncology Group

Treatment exposure and safety

	35 mg/m² n = 5	70 mg/m² n = 25	All patients N = 30
Duration of treatment, weeks, mean (SD)	12.3 (9.19)	17.7 (14.94)	16.8 (14.17)
Total dose received, mg, median (range)	687.0 (160.0–1109.4)	714.0 (148.0–2295.8)	696.0 (148.0–2295.8)
Any TEAE, n (%)	5 (100)	25 (100)	30 (100)
Leading to discontinuation of treatment	1 (20.0)	2 (8.0)	3 (10.0)
Leading to dose reduction	4 (80.0)	7 (28.0)	11 (36.7)
Any treatment-related TEAE, n (%)	5 (100)	24 (96.0)	29 (96.7)
Grade ≥3	5 (100)	10 (40.0)	15 (50.0)
Any treatment-related serious TEAE, n (%)	2 (40.0)	3 (12.0)[a]	5 (16.7)
Grade ≥3 treatment-related TEAEs occurring in ≥5% of patients, n (%)			
Diarrhea	3 (60.0)	5 (20.0)	8 (26.7)
Neutropenia	1 (20.0)	4 (16.0)	5 (16.7)
Abdominal sepsis	0	2 (8.0)[a]	2 (6.7)
Anemia	0	2 (8.0)	2 (6.7)
Asthenia	0	2 (8.0)	2 (6.7)
Thrombocytopenia	0	2 (8.0)	2 (6.7)
Fatigue	1 (20.0)	1 (4.0)	2 (6.7)
Hypokalemia	1 (20.0)	1 (4.0)	2 (6.7)
Hypomagnesemia	1 (20.0)	1 (4.0)	2 (6.7)

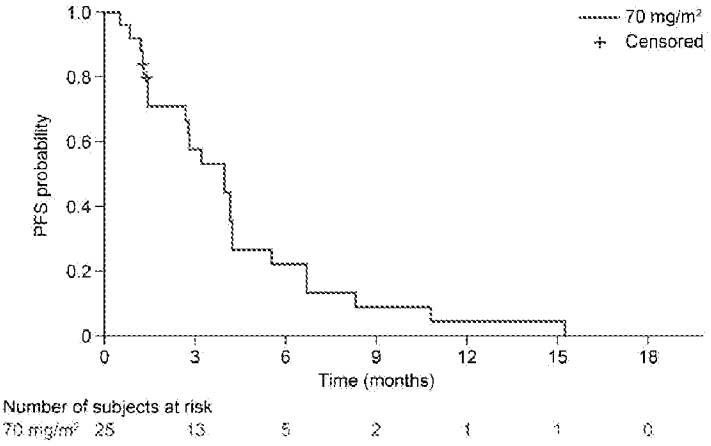
[a]Abdominal sepsis related to treatment led to death in two patients. SD, standard deviation; TEAE, treatment-emergent adverse event

Clinical efficacy (1/2)

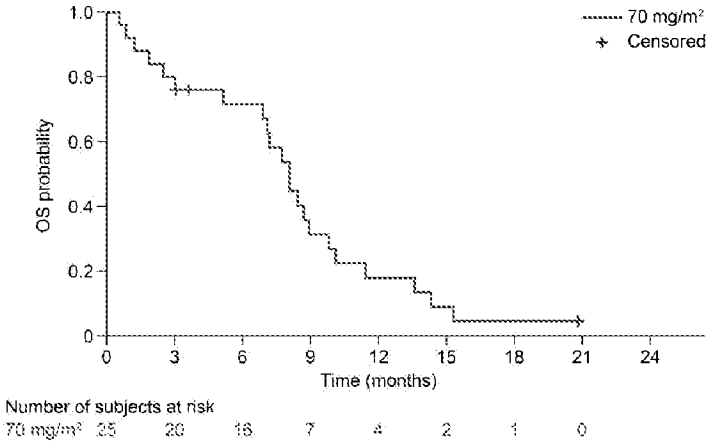
	35 mg/m² n = 5	70 mg/m² n = 25	All patients N = 30
Best overall response, n (%)			
Complete response	0	1 (4.0)	1 (3.3)
Partial response	2 (40.0)	10 (40.0)	12 (40.0)
Stable disease	1 (20.0)	7 (28.0)	8 (26.7)
Progressive disease	1 (20.0)	5 (20.0)	6 (20.0)
Non-evaluable	1 (20.0)	2 (8.0)	3 (10.0)
Objective response, % (95% CI)			
Complete response + partial response	40.0 (5.27–85.34)	44.0 (24.40–65.07)	43.3 (25.46–62.57)
Duration of response			
Median, months (95% CI)	8.80 (4.11–NE)	2.99 (2.37–7.03)	3.78 (2.43–7.03)

CI, confidence interval; NE, not estimable

Clinical efficacy (2/2)



Median PFS: 3.98 months
(95% CI: 1.45–4.24)



Median OS: 8.08 months
(95% CI: 5.16–9.82)

CI, confidence interval; OS, overall survival; PFS, progression-free survival

Conclusions

- In participants with SCLC who had progressed with platinum-based first-line therapy, liposomal irinotecan at the recommended dose of 70 mg/m^2 (free base) demonstrated:
  - safety and tolerability findings that were aligned with the known safety profile of liposomal irinotecan
  - promising antitumor activity (ORR, 44%; mPFS, 3.98 months; mOS, 8.08 months)
- The efficacy and safety of liposomal irinotecan 70 mg/m^2 in patients with SCLC is being evaluated in RESILIENT part 2, an ongoing, phase III, randomized, controlled trial versus topotecan

mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; SCLC, small cell lung cancer

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Thank you for listening!

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CONQUERING THORACIC CANCERS WORLDWIDE

RESILIENT part 2: a phase III study of liposomal irinotecan in patients with small cell lung cancer in the second-line setting

Luis G Paz-Ares,[1] David R Spigel,[2] Yuanbin Chen,[3] Maria Jove,[4] Oscar Juan-Vidal,[5] Patricia Rich,[6] Theresa Hayes,[7] Vanesa Gutiérrez Calderón,[8] Reyes Bernabe Caro,[9] Alejandro Navarro,[10] Afshin Dowlati,[11] Bin Zhang,[12] Yan Moore,[12] Xiaopan Valerie Yao,[12] Jaba Kokhreidze,[12] Santiago Ponce,[1] Paul Bunn[13]

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David R Spigel	Consultant: AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Clovis Oncology, Eli-Lilly, Genentech/Roche, Novartis, Pfizer; research/grant funding (institution): Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Clovis Oncology, Daiichi Sankyo, Eli-Lilly, Genentech/Roche, Merck, Novartis, Peregrine Pharmaceuticals, Pfizer, OncoGenex, OncoMed, Verastem Oncology, University of Texas Southwestern Medical Center - Simmons Cancer Center; other: Bristol Myers Squibb
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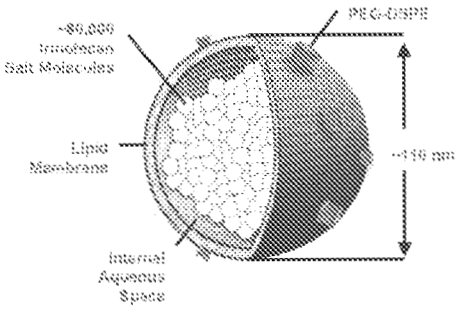
Maria Jove	Consultant: Boehringer Ingelheim; travel and accommodation support: Bristol Myers Squibb, MSD, Roche
Oscar Juan-Vidal	Consultant: Boehringer Ingelheim, Bristol Myers Squibb, Merck; research/grant funding (institution): AstraZeneca, Bristol Myers Squibb; travel and accommodation support: Boehringer Ingelheim, Merck, Roche
Patricia Rich, Theresa Hayes, Vanesa Gutiérrez Calderón	Nothing to disclose
Reyes Bernabe Caro	Consultant: AstraZeneca, Bristol Myers Squibb, Roche; travel and accommodation support: Bristol Myers Squibb, Roche
Alejandro Navarro	Consultant: Boehringer Ingelheim, Bristol Myers Squibb, Pfizer, Roche; expert testimony: Oryzon Genomics; travel and accommodation support: Boehringer Ingelheim, Pfizer
Afshin Dowlati	Consultant: Abbvie/Stemcentrx, ARIAD Pharmaceuticals; research/grant funding (institution): Amgen, Bristol Myers Squibb, Eli-Lilly/ImClone Systems, EMD Serono, MedImmune, OncoMed
Santiago Ponce	Consultant: Roche; speaker's bureau: Bristol Myers Squibb; travel and accommodation support: RSD Pharma
Paul Bunn	Consultant: AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Eli-Lilly, Genentech, Merck, Merrimack Pharmaceuticals, Novartis, Pfizer; other: AstraZeneca, Bristol Myers Squibb, Genentech, Merck, Pfizer
Bin Zhang, Yan Moore, Xiaopan Valerie Yao, Jaba Kokhreidze	Employment: Ipsen

Introduction

- Liposomal irinotecan is an intravenous formulation that encapsulates the topoisomerase 1 inhibitor irinotecan in a lipid-bilayer vesicle, leading to prolonged circulation[1]
- The safety, tolerability, and efficacy of second-line liposomal irinotecan in SCLC is being evaluated in RESILIENT, a two-part phase II/III study[2]
  - Preliminary data from part 1 (dose exploration and expansion) indicated that liposomal irinotecan 70 mg/m^2 (free base) every 2 weeks was well tolerated and had promising antitumour activity[3]

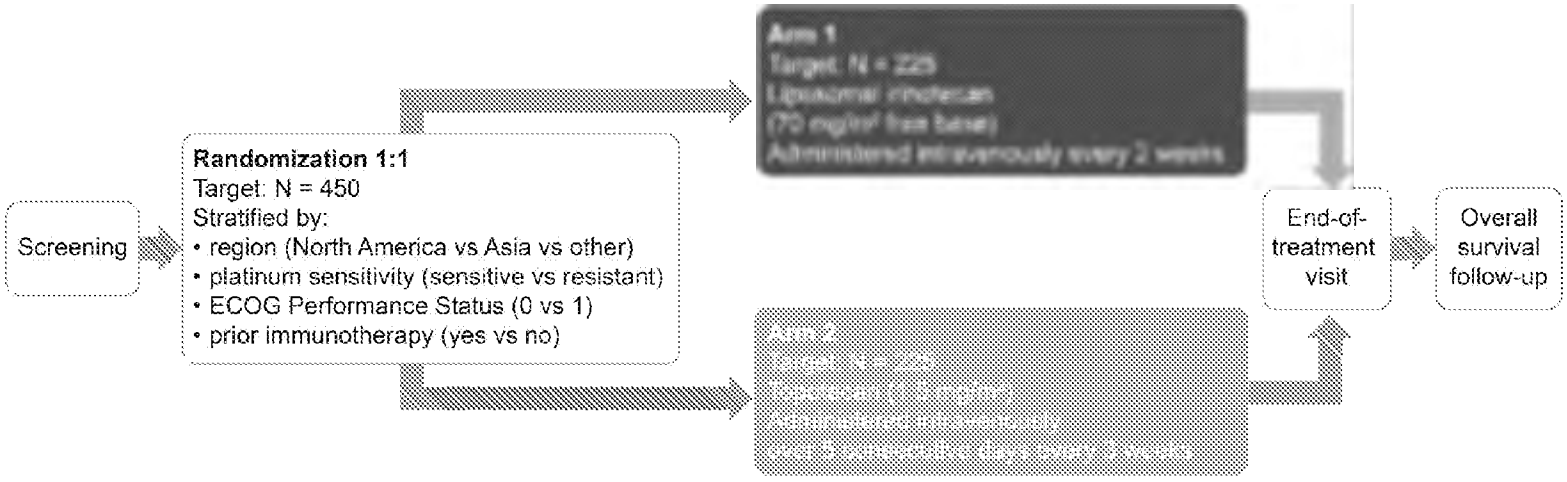


- Here, we present the design of RESILIENT part 2, which will assess the efficacy and safety of liposomal irinotecan versus topotecan in the same patient population

SCLC, small cell lung cancer.
1. Drummond D *et al. Cancer Res* 2006;66:3271–7; 2. ClinicalTrials.gov. NCT03088813. Available from: https://clinicaltrials.gov/ct2/show/NCT03088813 (Accessed November 2020); 3. Paz-Ares L *et al.* Poster presented at the 2019 World Conference on Lung Cancer (WCLC), September 7–10, 2019, Barcelona, Spain

Study design

- An open-label, randomized, multicenter, phase III study comparing second-line liposomal irinotecan (arm 1) with second-line topotecan (arm 2) in adults with SCLC



ECOG, Eastern Cooperative Oncology Group; SCLC, small cell lung cancer

Objectives

Primary objective	
Overall survival	Time from randomization to death by any cause
Secondary objectives	
Progression-free survival	Time from randomization to first documented objective disease progression as per RECIST v1.1 or death by any cause, whichever occurs first
Objective response rate	Proportion of patients with a BOR of complete or partial response as per RECIST v1.1 (or RANO-BM criteria for CNS lesions); BOR is defined as the best response from treatment initiation to disease progression
Symptom improvement	Proportion of patients with symptom improvement measured using patient-reported EORTC-QLQ-30 and EORTC-QLQ-LC-13 symptom scales
Safety	Severity of AEs and serious AEs graded according to NCI-CTCAE v5.0; proportion of patients with TEAEs (any grade), grade ≥ 3 TEAEs, study-drug related TEAEs, serious TEAEs, and TEAEs leading to dose reduction, study drug discontinuation or death; laboratory parameters

AE, adverse event; BOR, best overall response; CNS, central nervous system; EORTC-QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; LC, lung cancer; NCI-CTCAE; US National Cancer Institute-Common Terminology Criteria for Adverse Events; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RECIST, Response Evaluation Criteria in Solid Tumors; TEAE, treatment-emergent adverse event

Patients

- Eligible patients are those aged ≥18 years with:
  - histologically or cytologically confirmed SCLC as per IASLC classification
  - evaluable disease as per RECIST v1.1
  - radiologically-confirmed progression on or after platinum-based first-line therapy; in addition to platinum-based therapy, one line of immunotherapy (monotherapy or combination therapy) is allowed
  - ECOG performance status of 0 or 1
  - life expectancy >12 weeks
  - adequate hematologic, hepatic, and renal function
  - an ECG without clinically significant findings
- Patients will be stratified according to region (North America vs Asia vs other), platinum sensitivity (sensitive vs resistant), ECOG performance status (0 vs 1), and prior immunotherapy (yes vs no)

ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; IASLC, International Association for the Study of Lung Cancer; RECIST, Response Evaluation Criteria in Solid Tumors; SCLC, small cell lung cancer

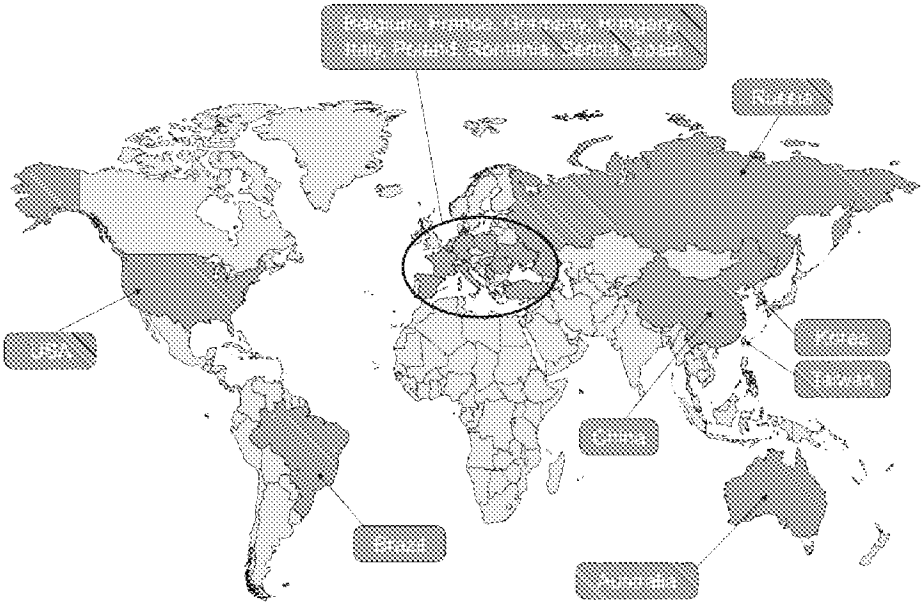
Data collection and analysis

- Patients will receive 6-week cycles of treatment until disease progression or toxicity
  - Thirty days after permanent discontinuation from study treatment, patients will undergo a 30-day follow-up assessment and will be observed for survival status every month until death or study end (when all patients have died or withdrawn consent, or are lost to follow-up)
- Tumor assessments will be performed by computed tomography or magnetic resonance imaging every 6 weeks using RECIST v1.1 guidelines and RANO-BM criteria for CNS lesions
- OS and PFS will be assessed using Kaplan–Meier methodology and differences between treatments will be evaluated using a stratified log-rank test (one-sided significance level, 0.025)
  - The primary OS analysis will be performed when at least 350 events are observed, providing at least 87% power to detect a true HR of ≤0.714
- Differences between treatments in overall response rate will be compared using the Cochran–Mantel–Haenszel method

CNS, central nervous system; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases

Trial status

- Recruitment is ongoing or planned in:
  - North America
  - South America
  - Europe
  - Asia
  - Australia
- The estimated study completion date is December 2022



Acknowledgments

- The authors thank all patients involved in the study, as well as their caregivers

Medical writing support

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Funding

- The study was funded by Ipsen

Thank you for listening!

ESMO Congress 16-21 SEPTEMBER 2021

17:30 - 18:30 Mini oral session - Gastrointestinal tumours, non-colorectal

CHAIRS: YELENA JANJIGIAN, CHANG-HOON YOO

ESMO Congress AIO

NaI-IRI with 5-FU and leucovorin or gemcitabine plus cisplatin in advanced biliary tract cancer

Final results of the randomized phase 2 NIFE trial

(AIO-YMO HEP-0315)

L. Perkhofer, J. Strieffer, M. Sinn, B. Opitz, Y. Goetze, E. Gallmeier, L. Fischer von Weikersthal, L. Jacobasch, D. Waldschmidt, M. Niedermeier, M. Sohn, D. Sackthal, A. Berger, A. Bendel, T. Seufferlein, T. J. Ettrich

On behalf of the AIO Biliary Tract Cancer Group and AIO Young Medical Oncologists

NCT03486067

Lukas Perkhofer

17:30 - 18:30 Mini oral session - Gastrointestinal tumours, non-colorectal

CHAIRS: YELENA JANJIGIAN, CHANGHOON YOO

AIO NIFE Trial – Rationale

- Standard of care first-line treatment of metastatic biliary tract cancer (BTC): Gemcitabine/Cisplatin (phase 3: mPFS 8.0mo, mOS 11.7mo)[1], Gemcitabine/Oxaliplatin (phase 2: mPFS 5.5mo, mOS 12.4mo)[2]
- Nal-IRI/5-FU/LV showed significant PFS and OS benefit in second-line treatment of BTC[3] and metastatic pancreatic cancer[4] compared to 5-FU/LV
- **NIFE** is an open-label, non-comparative, randomized, multicenter phase 2 trial evaluating nal-irinotecan/5-FU/leucovorin (Arm A) and gemcitabine/cisplatin (Arm B) as palliative first-line treatment of advanced BTC patients

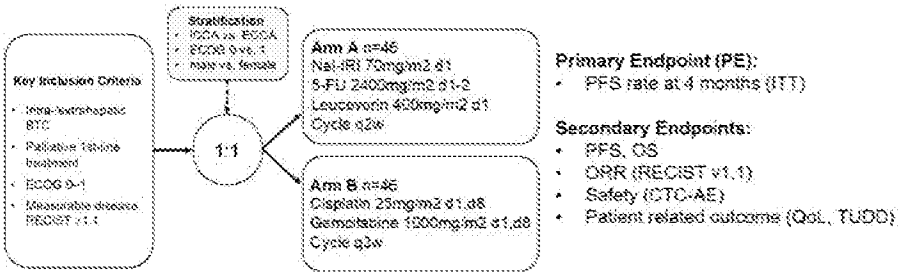
Lukas Perkhofer

Ulm, Germany

17:30 - 18:30 Mini oral session - Gastrointestinal tumours, non-colorectal

CHAIRS: YELENA JANJIGIAN, CHANGHOON YOO

AIO NIFE Trial – Design and statistical assumptions



Primary Endpoint (PE):
- PFS rate at 4 months (ITT)

Secondary Endpoints:
- PFS, OS
- ORR (RECIST v1.1)
- Safety (CTC-AE)
- Patient related outcome (QoL, TUDD)

- Arm A Simon's optimal two-stage design, standard arm B internal control for selection bias
- PE: ≥50% of patients of the ITT are progression-free by 4mo of nal-IRI/5-FU/LV, power 90%, α0.1.

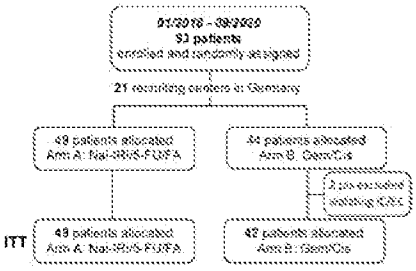
Lukas Perkhofer

[redacted]

17:30 - 18:30 Mini oral session - Gastrointestinal tumours, non-colorectal

CHAIRS: YELENA JANJIGIAN, CHANG-HOON YOO

AIO NIFE Trial – Baseline Characteristics



	Arm A Nal-IRI/5-FU/FA (n=49) n (%)	Arm B GemCis (n=42) n (%)
Male	36 (57.1)	25 (59.5)
Female	21 (42.9)	17 (40.5)
Age, median years (range)	65.0 (33-80)	66.5 (35-80)
ECOG 0	28 (57.1)	28 (66.7)
ECOG 1	21 (42.9)	14 (33.3)
Intrahepatic CCA (iCCA)	34 (69.4)	32 (76.2)
Extrahepatic CCA (eCCA)	15 (30.6)	10 (23.8)
Well differentiated (G1)	3 (6.1)	0
Fairly differentiated (G2)	22 (44.9)	16 (38.1)
Poorly differentiated (G3)	5 (10.2)	3 (7.0)
Undifferentiated (G4)	1 (2.0)	0
Not specified (Gx)	18 (36.7)	18 (42.9)
Previous adjuvant therapy, n (%)		
Tumor resection	11 (22.4)	12 (28.6)
Adjuvant chemotherapy	1 (2.0)	2 (4.8)
Adjuvant radio-chemoradiotherapy	2 (4.1)	0

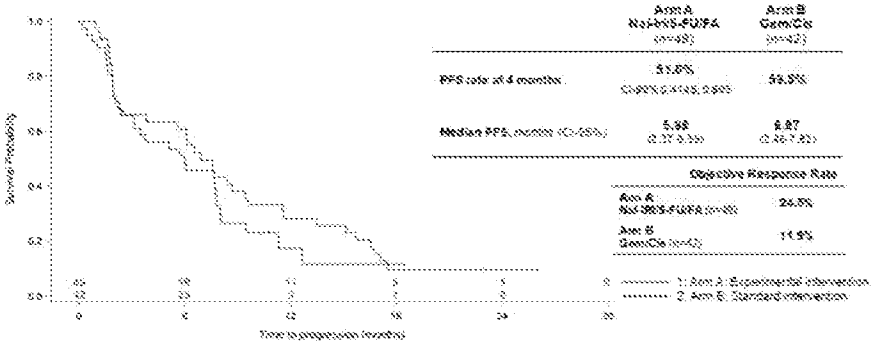
Lukas Perkhofer

Nal-IRI with 5-fluorouracil (5-FU) and leucovorin or gemcitabine plus cisplatin in advanced biliary tract cancer – final results of the NIFE trial (AIO-HEP-0218) – a randomized phase II study of the AIO biliary tract cancer group

17:30 - 18:30 Mini oral session - Gastrointestinal tumours, non-colorectal

CHAIRS: YELENA JANJIGIAN, CHANDRIKHA YOO

Primary Endpoint - PFS



NIFE met its primary endpoint with 51% of patients being progression-free at 4 months

Lukas Perkhofer

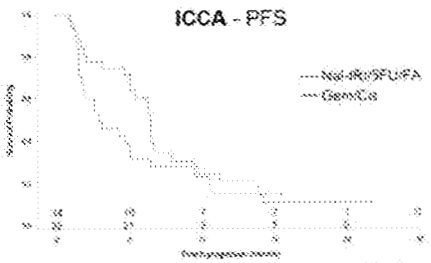
Ulm, Germany

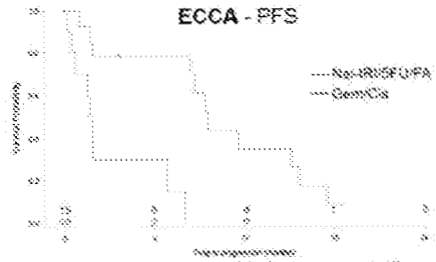
Nalirifl with 5-fluorouracil (5-FU) and liposomal irinotecan plus oxaliplatin in advanced biliary tract cancer - final results of the NIFE trial (ZIO-PAN-HBP-0313) - a randomized phase II study of the AIO biliary tract cancer group

17:30 - 18:30 Mini oral session - Gastrointestinal tumours, non-colorectal

CHAIRS: YELENA JANJIGIAN, CHANG-HOON YOO

Prespecified Subgroup Analysis





Intrahepatic CCA (ICCA)	Arm A Nal-IRI/5-FU/FA (n=34)	Arm B Gem/Cis (n=32)
mPFS (mo) (95%-CI)	5.45 (2.10-8.05)	7.72 (5.65-9.66)
mOS (mo) (95%-CI)	14.18 (7.53-21.85)	16.36 (7.46-19.81)

Extrahepatic CCA (ECCA)	Arm A Nal-IRI/5-FU/FA (n=15)	Arm B Gem/Cis (n=10)
mPFS (mo) (95%-CI)	9.59 (3.94-15.67)	1.76 (1.18-6.67)
mOS (mo) (95%-CI)	18.23 (8.67-30.55)	8.34 (2.10-NE)

Test for heterogeneity (Cox regression): PFS p=0.0018; OS p=0.0019

Lukas Perkhofer

Nal-IRI with 5-fluorouracil (5-FU) and folinic acid or gemcitabine plus cisplatin in advanced biliary tract cancer – final results of the NIFE oral AIO-HEP-0121-trial – a randomized phase II study of the AIO Biliary tract cancer group

17:30 - 18:30 Mini oral session - Gastrointestinal tumours, non-colorectal

CHAIRS: YELENA JOLIGIAN, CHANGHOON YOO

Safety

Adverse Events grade 3-4	Arm A NaLiri5-FU/FA (n=49)	Arm B GemCis (n=42)
Anemia	4.1%	26.2%
Neutropenia	18.2%	21.4%
Thrombocytopenia	2.0%	9.5%
Mucositis	2.0%	0%
Diarrhea	22.4%	2.4%
Nausea	12.2%	0%
Fatigue	4.1%	2.4%

- Arm A more GI toxicity
- Arm B more hematotoxicity

	Arm A NaLiri5-FU/FA (n=49)	Arm B GemCis (n=42)
Duration of protocol treatment (mo)	5.8	5.5

Lukas Perkhofer

17:30 - 18:30 Mini oral session - Gastrointestinal tumours, non-colorectal

CHAIRS: VELENA JANJIGIAN, CHANGHOON YOO

AIO NIFE Trial – Conclusion

- Nal-IRI/5-FU/LV achieved a 51.02% PFS rate at 4 months, therefore NIFE met its primary endpoint
- Nal-IRI/5-FU/LV showed promising effectivity in BTC, above all a particular effect on extrahepatic cholangiocarcinoma (mPFS: Arm A 9.59mo, Arm B 1.76mo; mOS: Arm A 18.23mo, Arm B 6.34mo)
- Adverse events of Nal-IRI/5-FU/LV were consistent with previously published data[1]
- Particularly, the effectivity of Nal-IRI/5-FU/LV in ECCA warrants further investigation

Lukas Perkhofer

17:30 - 18:30 Mini oral session - Gastrointestinal tumours, non-colorectal

CHAIRS: YELENA JANJIGIAN, CHANG-ON YOO

AIO NIFE Trial – Acknowledgements

We want to thank…

…all patients and their families

…all contributors

…AIO Studien gGmbH

…SERVIER

…IKF Frankfurt

Lukas Perkhofer

[illegible] • first results of the NIFE trial (AIO-YMO-0219) • a double-blind phase II study of the AIO biliary tract cancer group

A Phase II, Open-label Pilot Study Evaluating the Safety and Activity of Nal-IRI in Combination with 5-FU and Oxaliplatin in Preoperative Treatment of Pancreatic Adenocarcinoma (NEO-Nal-IRI Study)

Brian H. Ramnaraign[1], Steven J. Hughes5, Kathryn Hitchcock[3], Ji-Hyun Lee[6], Sherise C. Rogers[1], Z. Hugh Fan[4], Carmen J. Allegra[1], Jose G. Trevino[5], Ahmad El-Far[7], Karen B. Russell[8], Anita A. Turk[9], David L. DeRemer[2], Thomas J. George[1]

[1]Dept of Medicine; [2]Dept of Pharmacy; [3]Dept of Radiation Oncology; [4]College of Engineering; [5]Dept of Surgery; [6]Dept of Biostatistics; University of Florida, Gainesville, FL [7]Orlando Health Cancer Institute, Orlando, FL; [8]Tallahassee Memorial Hospital, Tallahassee, FL; [9]Indiana University Simon Cancer Center, Indianapolis, IN

BACKGROUND

- Neoadjuvant treatment for borderline resectable pancreatic cancer (PCa) is increasing in acceptability, but an optimal regimen has yet to be established.
- Multiple studies have demonstrated feasibility and effectiveness of FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin and irinotecan) in the perioperative setting.
- However, FOLFIRINOX often requires dose modifications, delays and growth factor support due to excessive toxicity which can complicate care delivery when given neoadjuvantly.
- Irinotecan liposomal injection (Nal-IRI) is FDA approved with a well-tolerated safety profile in relapsed, refractory metastatic PCa.
- The current study aims to substitute Nal-IRI for traditional irinotecan in the standard FOLFIRINOX regimen and demonstrate safe and effective neoadjuvant delivery (NALIRIFOX).

METHODS

- Phase 2, open-label, single-arm multicentered study for newly diagnosed patients with borderline resectable or resectable PCa without overt metastatic disease.
- Other key eligibility criteria include age ≥18 years, measurable disease by RECIST v1.1, adequate cardiac, renal, hepatic function and ECOG PS of 0 or 1.
- Patients receive NALIRIFOX regimen as per **Table 1** every 2 weeks for four months followed by reassessment.

- Patients who remain surgical candidates will undergo resection within 4 to 8 weeks following last dose of therapy.

- Radiotherapy is allowed pre or post-operatively if surgical margins are believed to be compromised.

Table 1. NALIRIFOX treatment regimen

Agent	Dose	Infusion Duration
Nal-IRI	50 mg/m^2	90 min
Oxaliplatin	60 mg/m^2	120 min
Leucovorin	400 mg/m^2	120 min
5-fluorouracil	2400 mg/m^2	Continuous infusion for 46 hours
Each agent is given by IV infusion every 14 days		

Table 2. Study objectives

Primary Objective
Assess safety and feasibility of regimen in perioperative setting
Secondary Objectives
R0 resection rate
Clinical, biochemical and radiological response rates
Patient-reported quality of life during treatment as measured by the NCI validated FACT-G scale.
Exploratory Objectives
Collect tissues and blood for post-hoc exploratory biomarker, CTC, ctDNA, microbiome, pharmacogenomic, tumor mutational profile assessments as well as potential PDX development.

STATISTICAL PLAN

- Evaluable patients are defined as those who complete surgery.
- A total of 28 evaluable patients will be needed to achieve the primary endpoint (**Table 2**).
- This is based on the assumption of a 66% reduction (HR 0.34) in the 30-day post-operative complication rate from 30% (historical data) to 10% (expected). (alpha = 0.05; beta = 0.20), using a one-sided exact test of binomial proportion.
- This pilot phase II study and this sample size, while not definitive, will allow determination of safety, feasibility, compliance, toxicity, and generation of robust clinicopathologic outcome assessment to serve as a benchmark control for subsequent comparative studies.

TRIAL STATUS

- Active enrollment continues.
- Additional sites are being activated.
- No unexpected toxicities have thus far been identified.
- NCT03483038

REFERENCES

1. Conroy T, et al. *NEJM.* 2011; 364(19): 1817-1825.
2. Birkmeyer JD, et al. *NEJM.* 2002; 346(15): 1128.
3. Hosein PJ, et al. *BMC Cancer.* 2012; 12(1): 199.
4. Ferrone C, et al. *Annals of Surg.* 2015; 261(1): 12.
5. Kim SS, et al. *J of Surg Onc.* 2016; *114*(5): 587-596.
6. Blazer M, et al. *Annals Surgical Onc.* 2015; 22(4): 1153-1159.
7. Wang-Gillam A, et al. *Lancet.* 2016; 387(10018):545-57.

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University of Florida Health Cancer Center

Funding for trial provided by Ipsen Pharmaceuticals and University of Florida Health Cancer Center

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Ipsen Pharmaceuticals and
University of Florida Health Cancer Center

Abstract #391
Presented at: ASCO GI January 15-17, 2021, Virtual

Real-world study of treatment patterns and outcomes among patients with metastatic pancreatic ductal adenocarcinoma in Europe

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KEY TAKE-AWAYS

- This large chart review exploring metastatic pancreatic ductal adenocarcinoma (mPAC) in the real-world setting demonstrated that the choice of 1L and 2L treatment among European physicians was in accordance with ESMO guidelines at the time of the study in 2016.
- Longest median progression-free survival (mPFS) was observed with modified (m)FOLFIRINOX as 1L therapy in patients with performance status (PS) 0/1 and PS ≥2 (8.1 and 6.2 mo, respectively); however, patient characteristics were more favorable with (m)FOLFIRINOX vs. other 1L regimens.
- Longest median overall survival (mOS) was observed with 5-FU + OX (14.5 mo) and (m)FOLFIRINOX (14.3 mo), followed by gem + nab-pac (13.0 mo), as 1L therapy in patients with PS 0/1.
- Longest mOS was observed with 1L (m)FOLFIRINOX in patients with PS ≥2 (10.0 mo), indicating that patients with PS ≥2 can benefit from intensified treatment.
- For patients with PS 0/1, the longest mPFS (6.7 mo) and mOS (10.3 mo) were observed with 2L gem + nab-pac; for patients with PS ≥2, longest mOS (6.3 mo) was observed with 2L 5-FU+OX and longest mPFS (4.6 mo) was observed with 2L gem-based therapy.
- Having a worse baseline PS was predictive of shorter survival in 2L.

BACKGROUND

About mPAC

- mPAC has one of the lowest survival prognoses.[1]
- mPAC represents the 4th most frequent cause of cancer-related deaths in Europe.[2]
- Surgical resection is the only potentially curative treatment for patients with mPAC.[1,3]
- >80% of these patients have an unresectable tumor,[1,4] and sequential lines of chemotherapy are recommended by ESMO guidelines.[1,2]

About this study

- Few data are available regarding real-world treatment patterns and outcomes for mPAC in Europe.
- The objectives of this study were to assess treatment patterns to obtain more clarity on efficacy data (OS and PFS) in the general PAC population and in the metastatic setting.

METHODS

- This retrospective, observational, chart review involved medical oncologists and gastroenterologists from France, Germany, Italy, Spain, and the UK.
- Physicians completed online patient reports for 20 consecutive patients diagnosed with PAC between January and October 2016, including the entire patient history from diagnosis to 5 years or death.
- Chart reports provided information on general disease and patient characteristics, diagnosis, and treatment type.
- Outcomes included median PFS* and OS† according to each line of metastatic therapy, and baseline Eastern Cooperative Oncology Group Performance Status (ECOG PS) and treatment sequence according to PFS and OS.
- Kaplan-Meier survival analysis was used to evaluate PFS and OS for each line of therapy. All p-values are based on a log-rank test to compare treatment groups.

* PFS (months): time from date of first day of treatment until the date of disease progression or death due to any cause.
† OS (months): time from date of first day of treatment to the date of death or date last known alive.

RESULTS

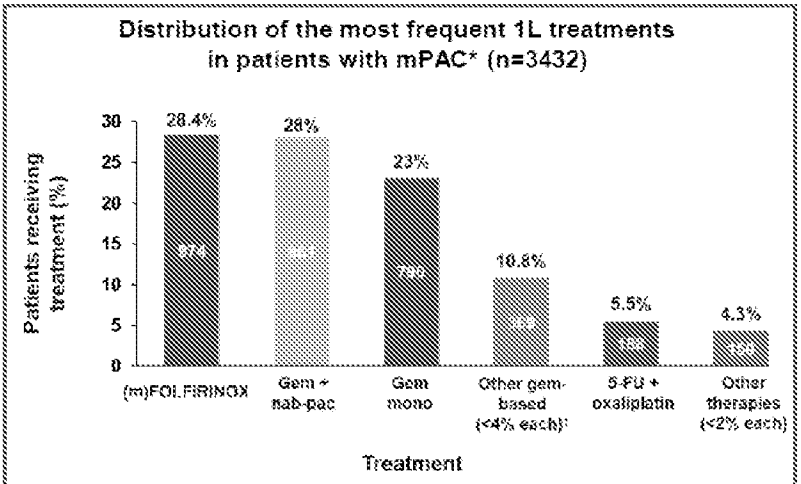
- 304 physicians (France [n=62], Germany [n=60], Italy [n=63], Spain [n=66], UK [n=53]) participated and enrolled 6,000 patients with PAC, of whom 3827 had mPAC, of the 3827, 3432 were treated for their metastatic disease, and data for these 3432 patients are presented here.
- Physicians were recruited from a range of regions and settings to ensure a balanced representation of each country (see table, data shown as percentages):

Academic/teaching/university hospital	53.0
General hospital	26.3
Private hospital/clinic	9.5
Office	4.9
Other	6.3

ALL PATIENTS

1L TREATMENT

Baseline characteristics	
Male, %	59.5
Female, %	40.5
Median age, years	65.3
CA19-9 ≥400, %	57.1
CA19-9 <400, %	42.9
Head, %	40.0
Body, %	22.9
Head/body, %	19.0
Tail, %	8.7
Body/tail, %	8.5
Unknown	1.0
ECOG PS, %	
0	10.7
1	53.3
2	31.1
3	4.3
4	0.5
Unknown	0.1



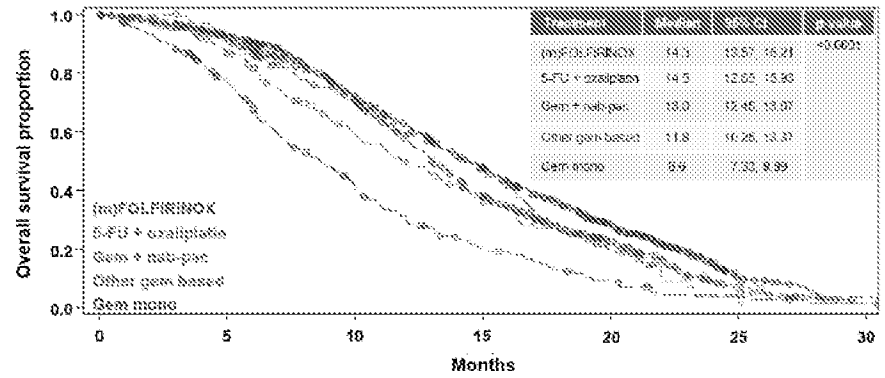
* Metastatic PAC at initial diagnosis. † Other gemcitabine-based chemotherapies: gemcitabine-erlotinib, gemcitabine-capecitabine, gemcitabine-oxaliplatin, gemcitabine-cisplatin.

Most common 1L therapies: (m)FOLFIRINOX, gemcitabine + nab-paclitaxel and gemcitabine monotherapy

Abbreviations: 5-FU, fluorouracil; CA19-9, Cancer antigen 19-9; ECOG, Eastern Cooperative Oncology Group; gem: gemcitabine; nab-pac: nab-paclitaxel; PS: Performance Status.

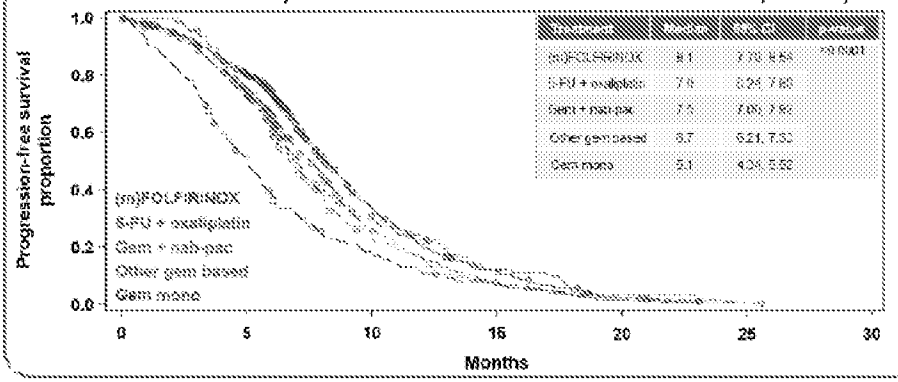
PATIENTS WITH ECOG PS 0/1

OS in mPAC patients with 1L treatment and ECOG PS 0/1 (n=2127)



Longest mOS was observed with 5-FU + OX (14.5 mo) and (m)FOLFIRINOX (14.3 mo), followed by gem + nab-pac (13.0 mo) as 1L therapy

PFS in mPAC patients with 1L treatment and ECOG PS 0/1 (n=2127)

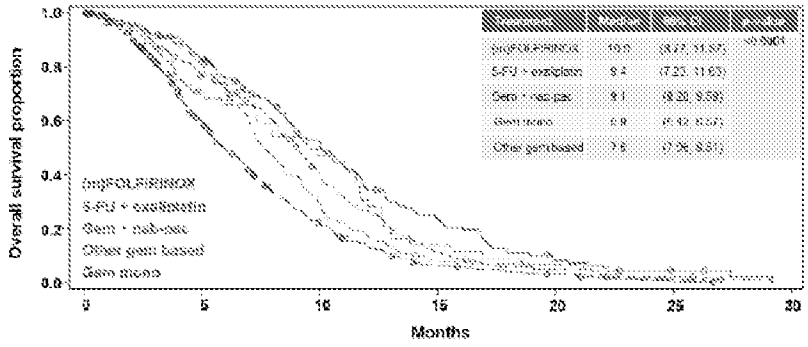


Longest mPFS (8.1 mo) was observed with (m)FOLFIRINOX as 1L therapy

Conclusions limited by small sample size for 1L 'other gem based' and '5-FU + OX'

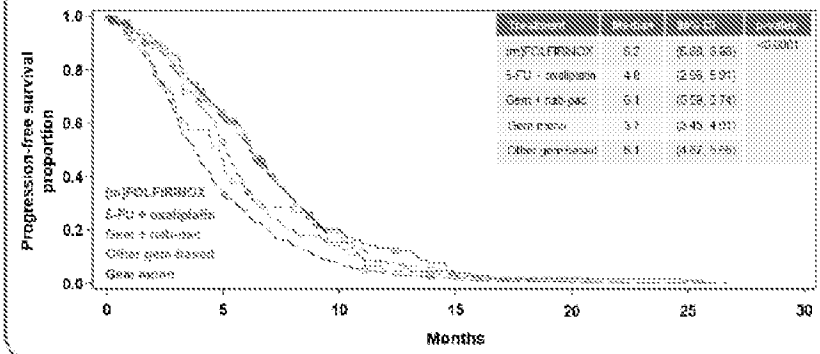
PATIENTS WITH ECOG PS ≥2

OS in mPAC patients with 1L treatment and ECOG PS ≥2 (n=1153)



Longest mOS (10.0 mo) and mPFS (6.2 mo) was observed with (m)FOLFIRINOX as 1L therapy

PFS in mPAC patients with 1L treatment and ECOG PS ≥2 (n=1153)

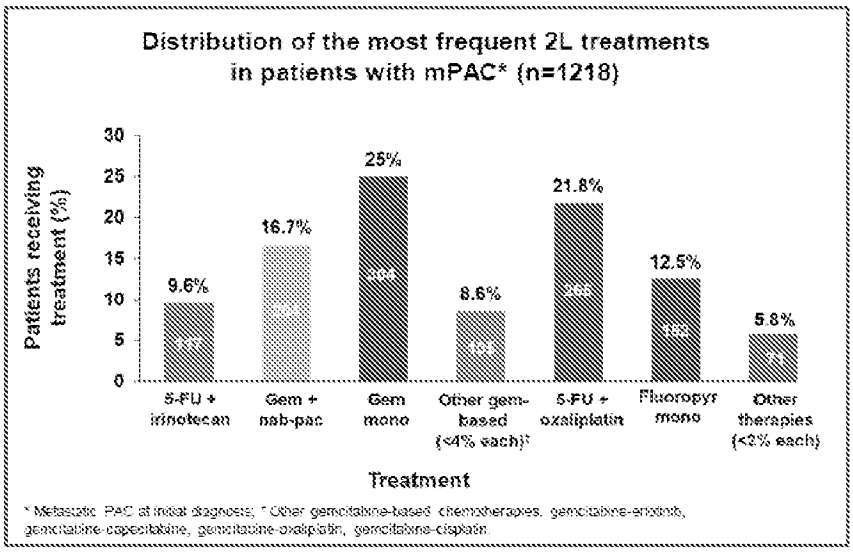


Conclusions limited by small sample size for 1L 'other gem based' and '5-FU + OX'

ALL PATIENTS

2L TREATMENT

Baseline characteristics	
Male, %	60.1
Female, %	39.9
Median age, years	63.2
CA19-9 ≥400, %	68.9
CA19-9 <400, %	31.1
Head, %	40.7
Body, %	22.9
Head/body, %	16.7
Tail, %	9.4
Body/tail, %	9.9
Unknown	0.3
ECOG PS, %	
0	3.9
1	46.6
2	44.6
3	4.7
4	0.2
Unknown	0



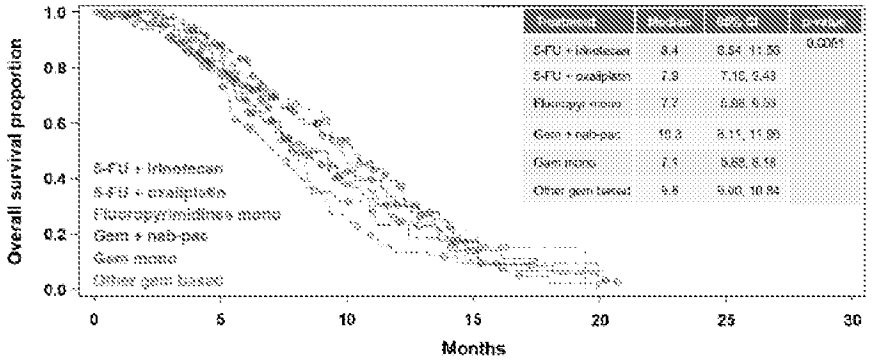
* Metastatic PAC at initial diagnosis; † Other gemcitabine-based chemotherapies: gemcitabine-erlotinib, gemcitabine-capecitabine, gemcitabine-oxaliplatin, gemcitabine-cisplatin

Most common 2L therapies: gemcitabine monotherapy, 5-FU + oxaliplatin, and gemcitabine + nab-paclitaxel

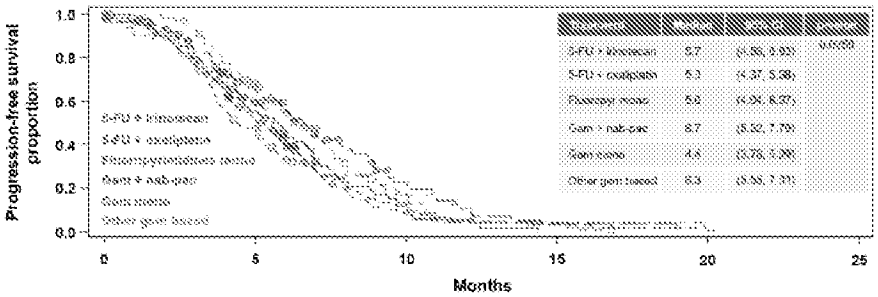
Abbreviations: 5-FU: fluorouracil; CA19-9: Cancer antigen 19-9; ECOG: Eastern Cooperative Oncology Group; fluoropyr mono: fluoropyrimidines monotherapy; gem: gemcitabine; PS: Performance Status.

PATIENTS WITH ECOG PS 0/1

OS in mPAC patients with 2L treatment and ECOG PS 0/1 (n=563)



PFS in mPAC patients with 2L treatment and ECOG PS 0/1 (n=563)

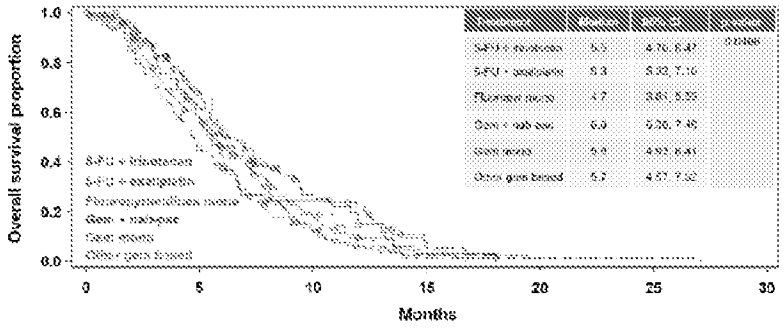


Longest mOS (10.3 mo) and mPFS (6.7 mo) were observed with gem + nab-pac as 2L therapy

Conclusions limited by small sample size for 2L 'other gem-based' and '5-FU + irinotecan'

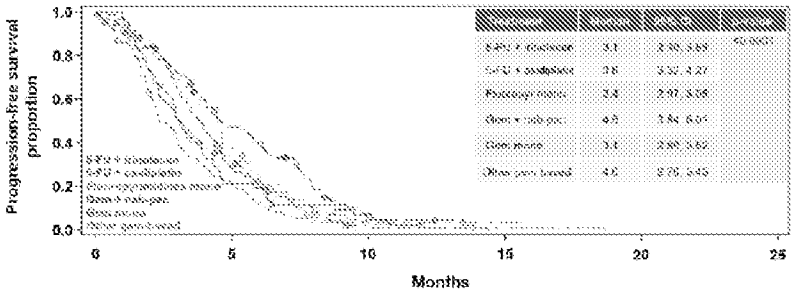
PATIENTS WITH ECOG PS ≥2

OS in mPAC patients with 2L treatment and ECOG PS ≥2 (n=584)



Longest mOS (6.3 mo) was observed with 5-FU + oxaliplatin as 2L therapy

PFS in mPAC patients with 2L treatment and ECOG PS ≥2 (n=584)



Longest mPFS (4.6 mo) was observed with gem-based 2L therapy

Conclusions limited by small sample size for 2L 'other gem-based' and '5-FU + irinotecan'

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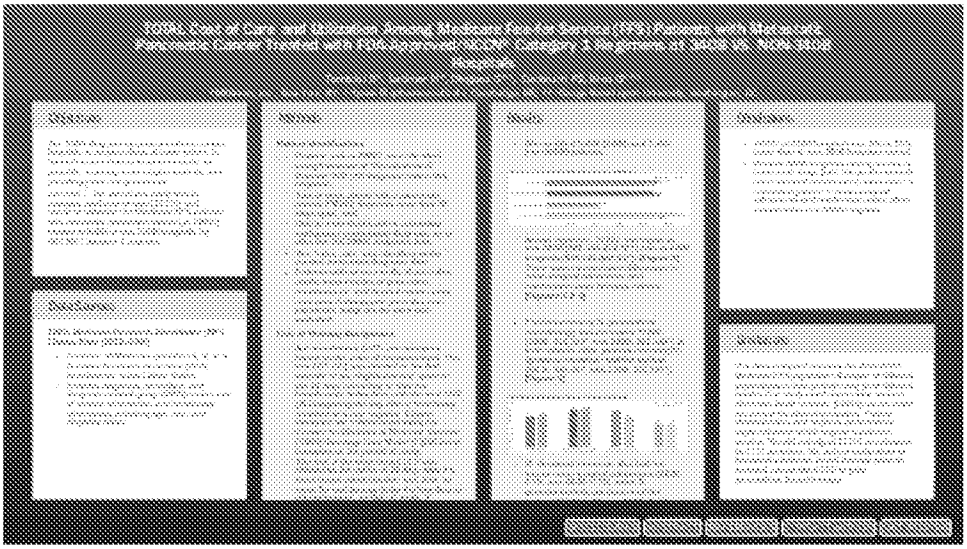
Real-world study of treatment patterns and outcomes among patients with metastatic pancreatic ductal adenocarcinoma in Europe

TOTAL Cost of Care and Utilization Among Medicare Fee-for-Service (FFS) Patients with Metastatic Pancreatic Cancer Treated with FDA-Approved/NCCN® Category 1 Regimens at 340B VS. NON-340B Hospitals



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PRESENTED AT:

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OBJECTIVES

The 340B drug pricing program allows certain hospitals to acquire drugs at lower prices, to "stretch scarce federal resources as far as possible, reaching more eligible patients and providing more comprehensive

services".[1] The aim of our study was to compare total cost of care (TCOC) and resource utilization for Medicare FFS patients with metastatic pancreatic cancer (m-PANC) treated at 340B or non-340B hospitals, by NCCN® Category 1 regimen.

DATA SOURCES

100% Medicare Research Identifiable (RIF) Claims Files (2016-2018)

- Contains all Medicare-paid Part A, B, and D claims for all fee-for-service (FFS) beneficiaries in the United States.
- Includes diagnosis, procedure, and diagnosis-related group (DRG) codes; site of service information; and beneficiary information, including age, sex, and eligibility status.

METHODS

Patient Identification

- Patients with m-PANC were identified using International Classification of Disease (ICD)-10 diagnosis codes. We required:
- Two or more claims with a pancreatic cancer (PANC) diagnosis more than 30 days apart, and
- One or more claims with a secondary malignancy (metastasis) diagnosis on or after the first PANC diagnosis date.
- The "index date" was identified as the earliest metastasis diagnosis date.
- Patients without six months of pre-index and/or three months of post-index enrollment (or until death if earlier) were excluded. Patients with pre-index non-pancreatic malignancies were also excluded.

Line of Therapy Assignment

- A line of therapy (LOT) was assigned based on the order of therapies used. The first LOT (1L) was defined as the first episode of an "eligible therapy" given in the 14 days preceding or after the beneficiary's index date, with the next LOT (2L) beginning the day after a beneficiary switched to a new regimen. Eligible therapies were determined using the Centers for Medicare & Medicaid Services (CMS) Oncology Care Model (OCM) list of therapies for the period of study.[2]
- The end of the most recent LOT was defined as the earlier of 28 days after the most recent administration, visit date, or order for oral therapy (after the first date of chemotherapy), or date of death, if applicable.

Costs and resource utilization were summarized for the following NCCN® Category 1 drugs or regimens:

- 1L Gemcitabine monotherapy
- 1L Gemcitabine + nab-paclitaxel
- 1L Folinic acid + 5-fluorouracil + irinotecan + oxaliplatin (FOLFIRINOX)
- 2L Liposomal irinotecan + 5FU (5FU was not included in this analysis; see Limitations for further details.)

340B Hospital Identification

- 340B hospitals were identified using the 340B OPAIS database.[3]
- Patients were attributed to 340B or non-340B hospitals based on plurality of chemotherapy claims.

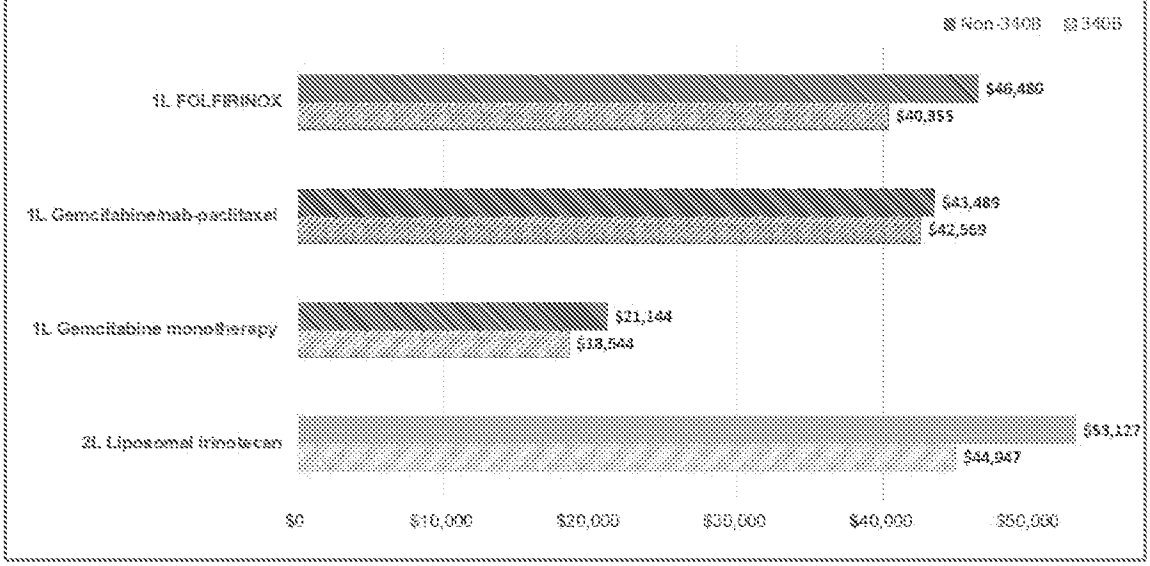
Cost Analysis and Resource Utilization

- Mean total cost of care (TCOC) was calculated as the average of the insurer paid amount excluding the patient cost-sharing per regimen/LOT.
- Mean hospital admissions were calculated as admissions per patient per regimen/LOT.
- Readmission rates were calculated as a percentage of total hospital admissions.
- We performed Tukey's Honestly Significant Difference (HSD) pairwise statistical testing for each regimen/LOT at 95% level of significance.

RESULTS

- We identified 5,098 (340B) and 7,450 (non-340B) patients.

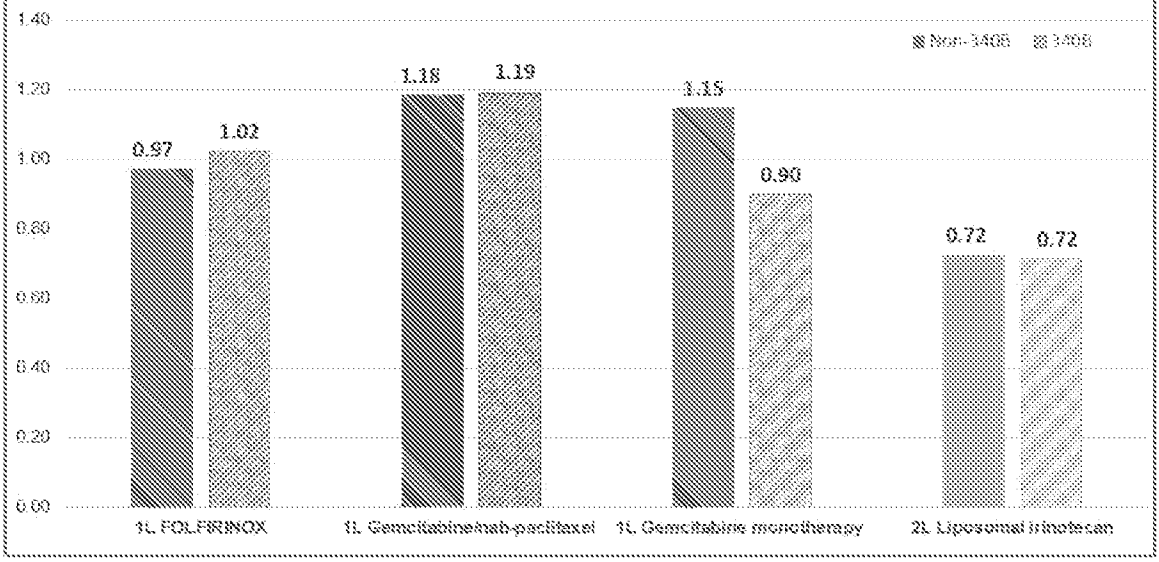
Figure 1. Mean Total Cost of Care Per Patient Receiving Chemotherapy at 340B Hospitals vs. Non-340B Hospitals



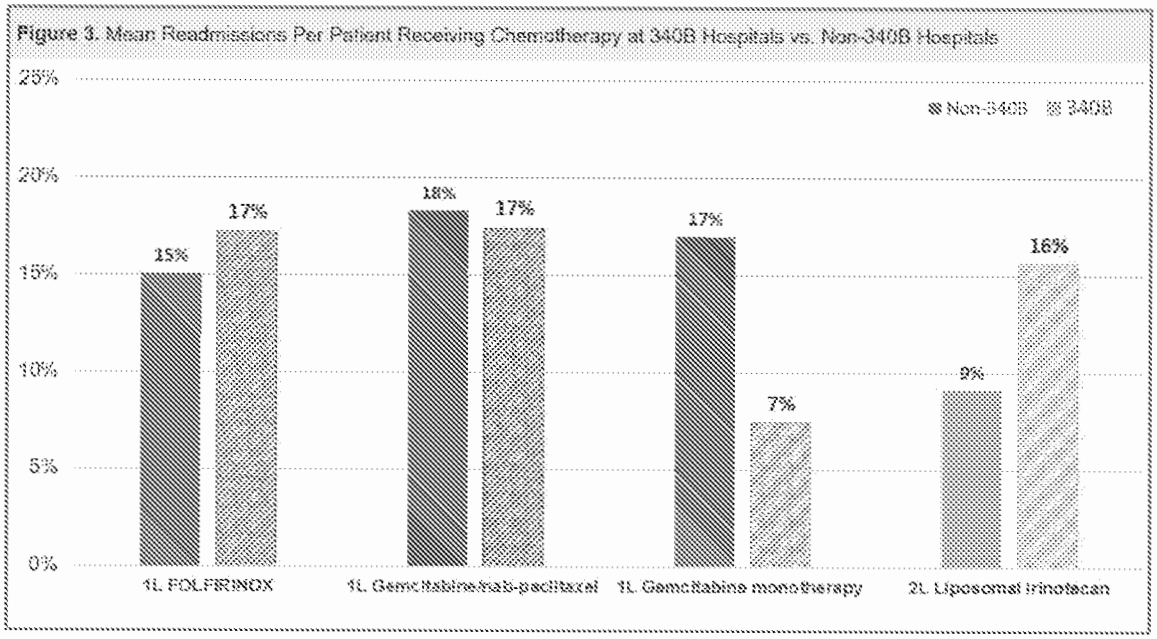
- Across regimens, TCOC was higher at non-340B ($21,144-$53,127) than at 340B hospitals ($18,544-$44,947). **[Figure 1]**

- Patients receiving 1L gemcitabine monotherapy had the lowest TCOC (340B: $18,544*, non-340B: $21,144*) in both cohorts, while patients receiving 2L liposomal irinotecan had the highest (340B: $44,947, non-340B: $53,127*). **[Figure 1]**

Figure 2. Mean Admissions Per Patient Receiving Chemotherapy at 340B Hospitals vs. Non-340B Hospitals



- 2L liposomal irinotecan also had the lowest mean hospital admissions (340B: 0.72, non-340B: 0.72), while 1L gemcitabine/nab-paclitaxel had the highest (340B: 1.19, non-340B: 1.18). [Figure 2]



- Patients receiving 1L gemcitabine monotherapy and 2L liposomal irinotecan had the lowest readmission rates at 340B (7%) and non-340B (9%), respectively. [Figure 3] There were no consistent differences in mean hospital admissions and readmission rates between cohorts. **[Figures 2 & 3]**

Values with an * indicate statistical significance at $\alpha = 0.05$.

CONCLUSIONS

- TCOC at 340B hospitals was 2% to 15% lower than at non-340B hospitals overall.
- Despite 340B hospitals having access to lower-cost drugs (with the goal to provide more comprehensive care), there was no consistent pattern in mean hospital admissions and readmission rates when compared to non-340B hospitals.

LIMITATIONS

The data analyzed included the 2016-2018 Medicare FFS population. Analysis of different populations or time periods may yield different results. Our study used claims data and not electronic health records (EHRs), so we could not control for clinical covariates. Patient characteristics and regimen performance might influence which regimens patients receive. We did not adjust TCOC or utilization for LOT durations. We did not study whether liposomal irinotecan-based therapy patients received concomitant 5FU or prior gemcitabine-based therapy.

DISCLOSURES

Author Contributions Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: [ST, HL, GD, PC, GK]; Drafting of the publication, or revising it critically for important intellectual content: [ST, HL, GD, PC, GK]; Final approval of the publication: [ST, HL, GD, PC, GK].

Disclosures [HL, ST, GD]: Employees of Milliman and received consulting fees from Ipsen. [PC] is employed by Ipsen and owns Ipsen stock. [GK] is employed by George Washington University and received consulting fees from Ipsen.

ABSTRACT

OBJECTIVES: To compare total cost of care (TCOC) and utilization for Medicare FFS patients (pts) with metastatic pancreatic cancer (m-PANC) treated at 340B or non-340B hospitals, by NCCN® Category 1 regimen.

METHODS: We identified pts with m-PANC using ICD-9/10 diagnosis codes in the 2016-18 Medicare Parts A/B/D 100% Research Identifiable Files. Study pts had 2+ claims with a pancreatic cancer diagnosis and Medicare FFS coverage for 6 months pre- and 3 months post-metastasis diagnosis. 340B hospitals were identified using the 340B OPAIS database. Pts were attributed to 340B or non-340B hospitals based on plurality of chemotherapy claims. Mean TCOC includes all insurer-paid services per line of therapy (excluding patient cost share). We calculated mean rates of hospital admissions (admits/pt) and readmissions. Study pts were treated with NCCN® Category 1 regimens: 1L gemcitabine monotherapy (gem-mono), 1L gemcitabine/nab-paclitaxel (gem-nab), 1L FOLFIRINOX (FFX), and 2L liposomal irinotecan-based regimen (Nal-IRI).

RESULTS: We identified 5,098 (340B) and 7,450 (non-340B) pts. Across regimens, TCOC was higher at non-340B ($21,144-$53,127) than at 340B hospitals ($18,544-$44,947). There were no consistent differences in admits/pt and readmission rate between cohorts. Gem-mono had the lowest TCOC (340B: $18,544, P<.05; non-340B: $21,144, P<.05) in both cohorts, while Nal-IRI had the highest (340B: $44,947, P>.05, non-340B: $53,127, P<.05); Nal-IRI pts also had the lowest admits/pt (340B: 0.72, P>.05; non-340B: 0.72, P>.05), while gem-nab had the highest (340B: 1.19, P>.05; non-340B: 1.18, P>.05). Gem-mono and Nal-IRI had the lowest readmission rate at 340B (7%, P>.05) and non-340B (9%, P>.05).

CONCLUSION: While TCOC at 340B hospitals was 2%-15% lower than at non-340B hospitals overall, there was no consistent pattern of admits/pt and readmission rates. Among regimens, there were consistencies in both cohorts: TCOC was lowest for gem-mono and highest for Nal-IRI, while admits/pt were lowest for 2L Nal-IRI and highest for gem-nab.

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3 .Health Resources & Services Administration Office of Pharmacy Affairs Information System (340B OPAIS). Accessed on November 3, 2020. Available at: https://340bopais.hrsa.gov/CoveredEntitySearch/000110065

2021 ASCO
ANNUAL MEETING

Liposomal Irinotecan (nal-IRI) in combination with Fluorouracil (5-FU) and Leucovorin (LV) for Patients (pts) with Metastatic Biliary Tract Cancer (BTC) after Progression on Gemcitabine plus Cisplatin (GemCis): Multicenter Comparative Randomized Phase 2B study (NIFTY)

Changhoon Yoo[1], Kyu-pyo Kim[1], Ilhwan Kim[2], Myoung Joo Kang[3], Jaekyung Cheon[3], Byung Woog Kang[4], Hyewon Ryu[5], Jae Ho Jeong[4], Ji Sung Lee[4], Kyung Won Kim[1], Baek-Yeol Ryoo[1]

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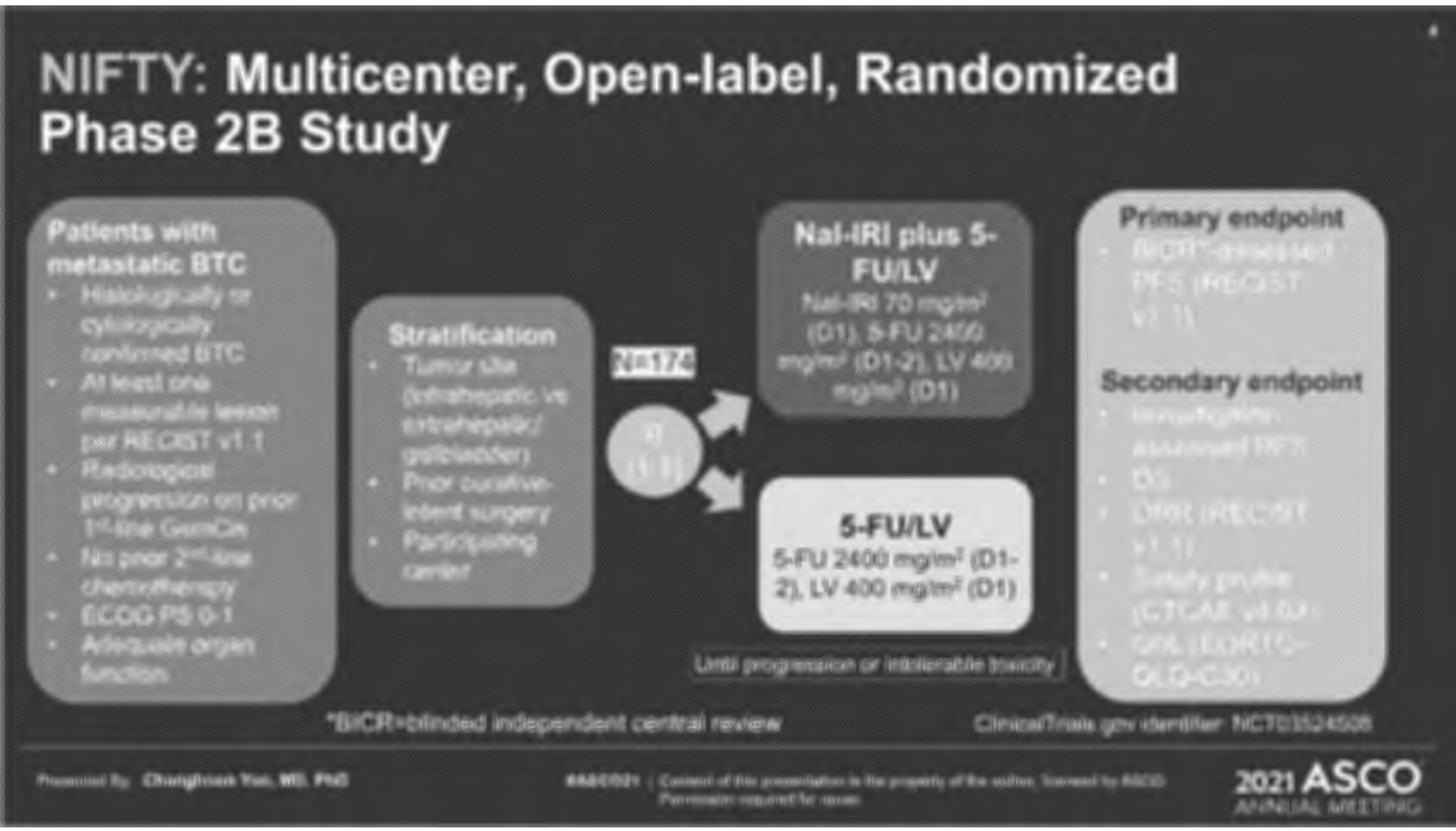
Introduction

- GemCis is the standard first-line chemotherapy for patients with unresectable or metastatic BTC.
- For patients progressed on GemCis, there was no globally established second-line chemotherapy. However, fluoropyrimidine-based therapy has been widely used in daily practice, despite the lack of data based on the randomized trial.[1-3]
- Although FGFR and IDH-1 inhibitors have demonstrated clinical benefit in BTC patients harboring *FGFR2* gene fusions or IDH-1 mutations, respectively, only up to 20% of patients could be benefited with these targeted agents.[3-4]
- Recently, the ABC-06 trial demonstrated the survival benefit of second-line FOLFOX compared with active symptom control, but further investigation is necessary in this clinical setting.[5]

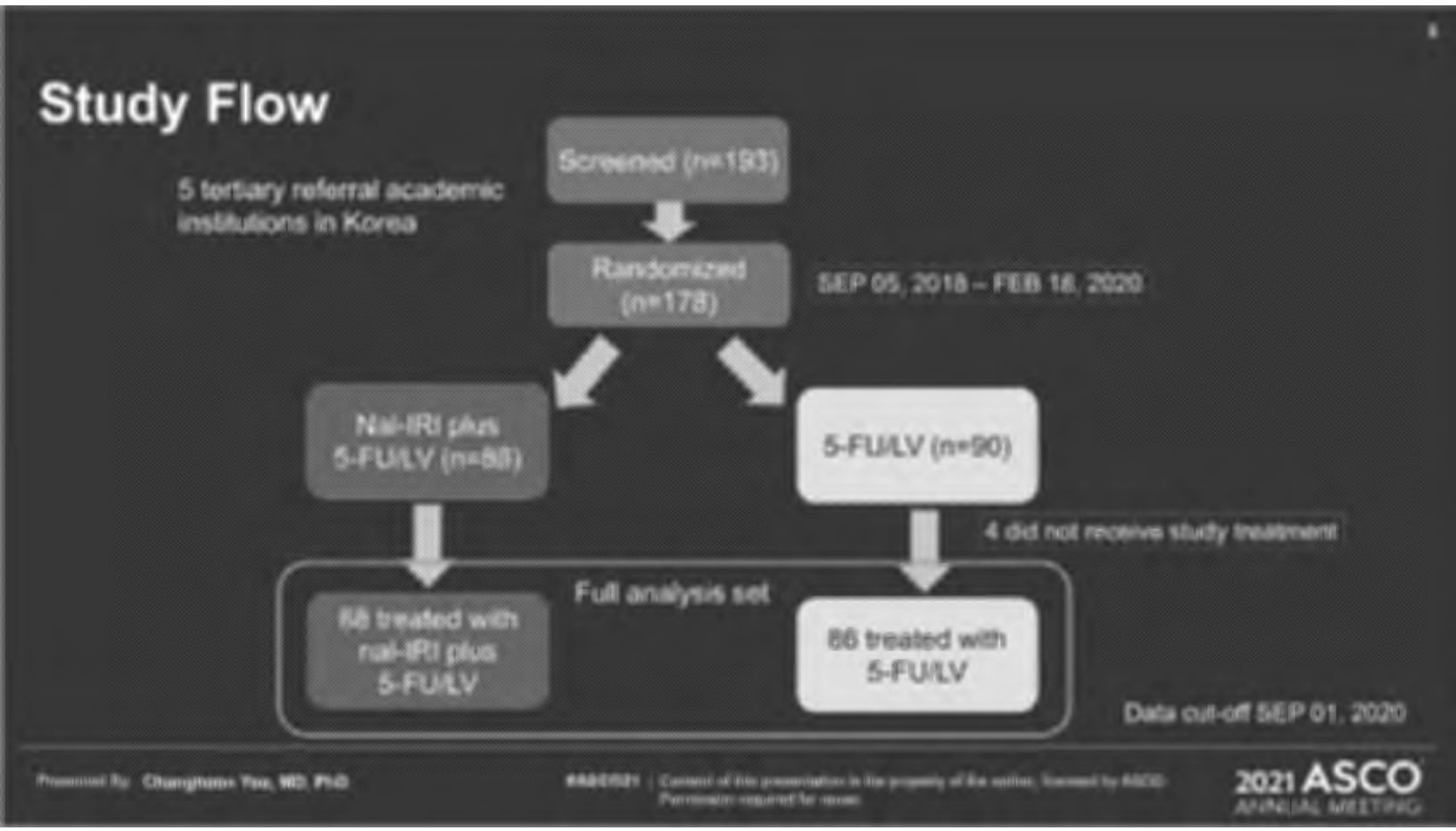
Liposomal Irinotecan (nal-IRI) and Aim of the Study

- Nal-IRI is a topoisomerase inhibitor featuring a liposomal formulation of irinotecan, which has an advantage in enhanced tumor exposure of active metabolite, SN-38.[1]
- Nal-IRI plus 5-FU/LV showed significant PFS and OS improvement compared with 5-FU/LV for patients with gemcitabine-refractory pancreatic cancer in the phase 3 NAPOLI-1 trial.[2]
- Given that BTC also has enriched stroma similar to pancreatic cancer, nal-IRI may be active in BTC.[3]
- **The NIFTY trial is an investigator-initiated, multicenter, randomized, phase 2B study comparing nal-IRI plus 5-FU/LV and 5-FU/LV as second-line therapy after progression on first-line GemCis in patients with metastatic BTC.**
- This study was designed and initiated before the presentation of the results of the ABC-06 trial.



Assessment and Statistical Analysis

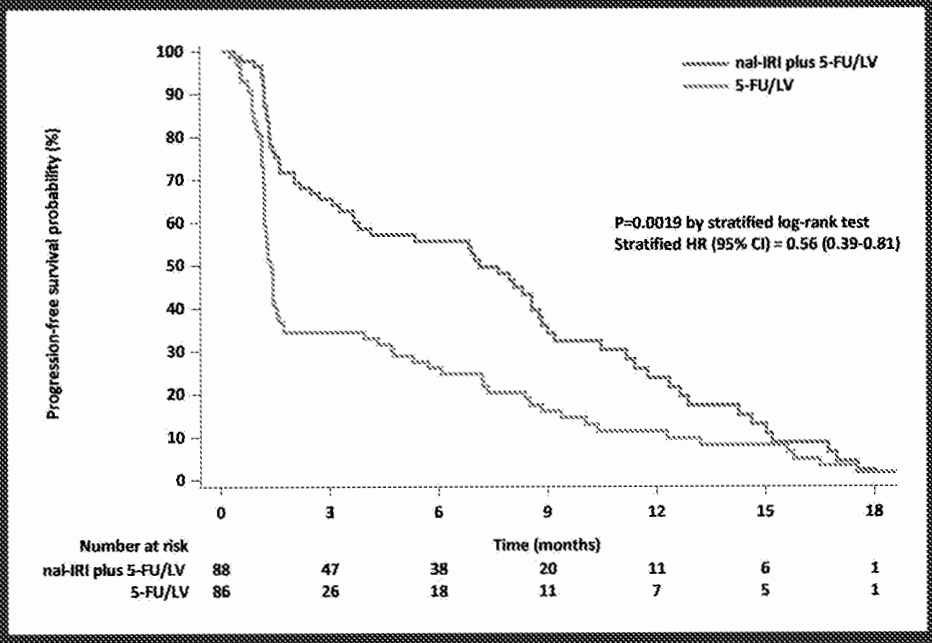
- Radiological tumor assessment (CT or MRI) was done **every 6 weeks on a fixed schedule (window period: 7 days) from C1D1**.
- **Treatment decisions were based on the local investigator's radiological assessment**. Blinded independent central review (BICR) did not perform real-time confirmation of locally determined radiographic progression and was conducted after data cut-off.
- For BICR, all imaging data were subsequently collected, anonymized, and **reviewed centrally in a double-blind manner by the independent radiological reviewers**.
- The study was designed to have **80% power, with two-sided type I error of 5%, to detect a hazard ratio (HR) of 0.6 (P1: median 3.3 months) for PFS** with the addition of nal-IRI to 5-FU/LV (**P0: median 2 months**). With an expected 10% loss to follow-up, **a total of 174 patients (87 per each treatment group) were required**.
- Data cut-off for the analysis was planned at 6 months' follow-up for the last enrolled patient.



Patient Baseline Characteristics

	Nal-IRI plus 5-FU/LV group (n=88)	5-FU/LV group (n=86)
Age (years), median (range)	63 (38-84)	65 (37-80)
Gender, n (%)		
Male	51 (58.0%)	48 (55.8%)
Female	37 (42.0%)	38 (44.2%)
ECOG performance status, n (%)		
0	23 (26.1%)	15 (17.4%)
1	65 (73.9%)	71 (82.6%)
Primary tumor site, n (%)		
Intrahepatic	35 (39.8%)	39 (45.3%)
Extrahepatic	22 (25.0%)	25 (29.1%)
Gallbladder	31 (35.2%)	22 (25.6%)
Disease extent at screening, n (%)		
Metastatic	88 (100%)	86 (100%)
Duration of first-line GemCis, n (%)		
< Median (5.1 months)	48 (54.5%)	39 (45.3%)
≥ Median (5.1 months)	40 (45.5%)	47 (54.7%)
Prior curative-intent surgery, n (%)		
Yes	26 (29.5%)	29 (33.7%)
No	62 (70.5%)	57 (66.3%)
Serum 19-9 level, n (%)		
< Median (172 U/mL)	48 (54.5%)	39 (45.3%)
≥ Median (172 U/mL)	40 (45.5%)	47 (54.7%)

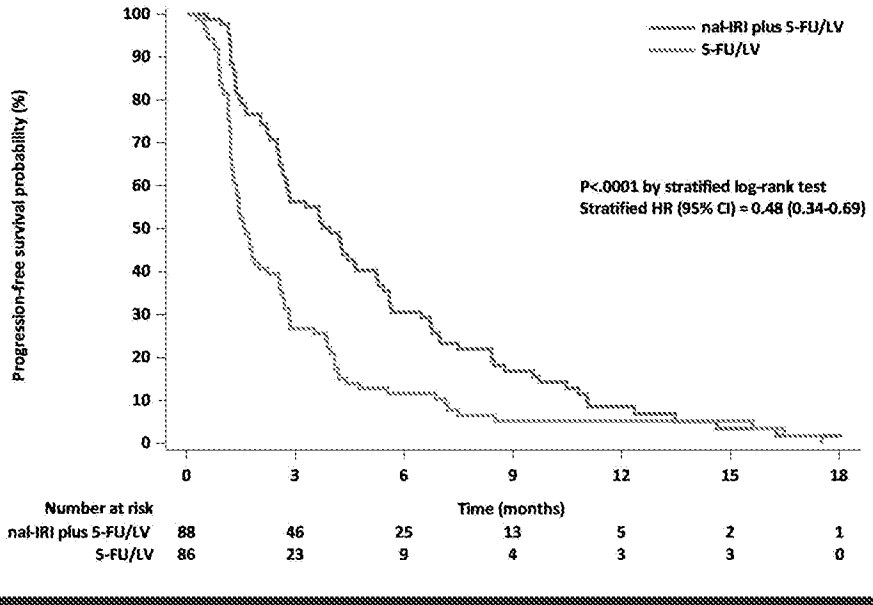
Primary Endpoint: BICR-Assessed PFS



Median follow-up period: 11.8 months (IQR 7.7-18.7)

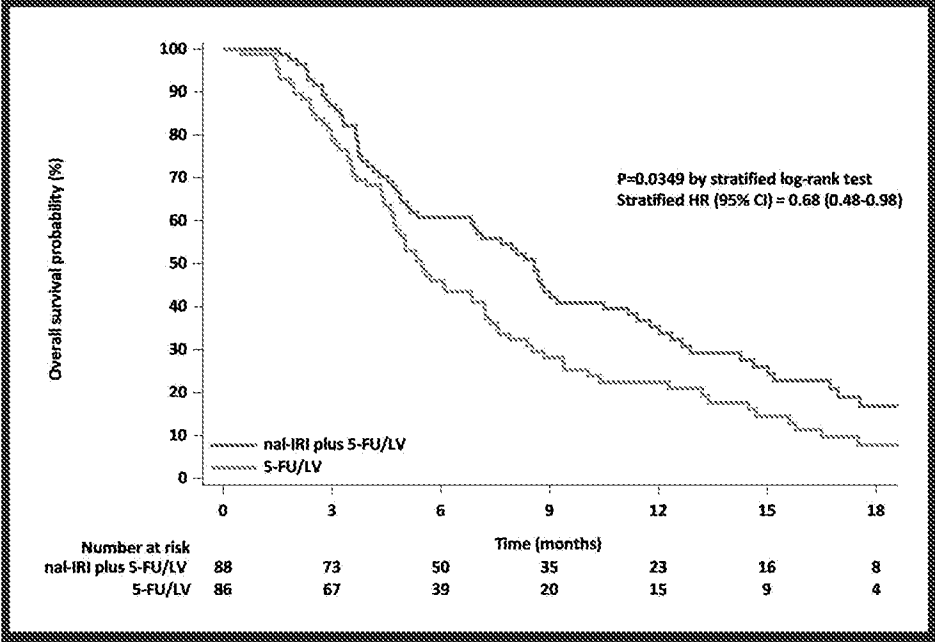
	nal-IRI + 5-FU/LV (n=88)	5-FU/LV (n=86)
No. of events, n (%)	64 (72.7%)	79 (91.9%)
mPFS, months (95% CI)	7.1 (3.6-8.8)	1.4 (1.2-1.5)
	HR, 0.56 95% CI, 0.39-0.81 *P*=0.0019	
6-month PFS rate, % (95% CI)	55.7% (44.7-66.6)	26.2% (16.6-35.8)

Secondary Endpoint: Investigator Review-Assessed PFS



	nal-IRI + 5-FU/LV (n=88)	5-FU/LV (n=86)
No. of events, n (%)	79 (89.8%)	84 (97.7%)
mPFS, months (95% CI)	3.9 (2.7-5.2)	1.6 (1.3-2.2)
	HR, 0.48 95% CI, 0.34-0.69 *P*<0.0001	
6-month PFS rate, % (95% CI)	30.6% (20.6-40.5)	11.6% (4.9-18.4)

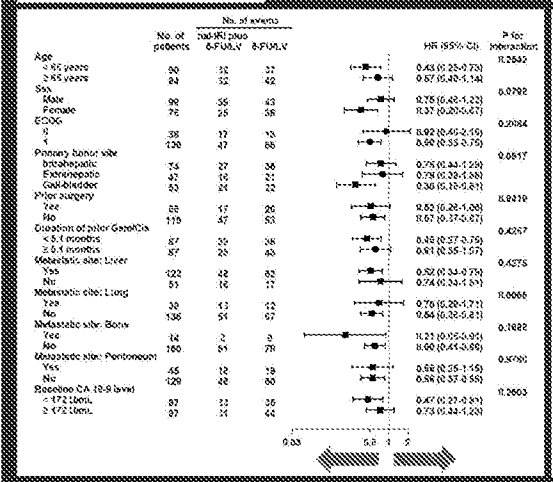
Secondary Endpoint: Overall Survival



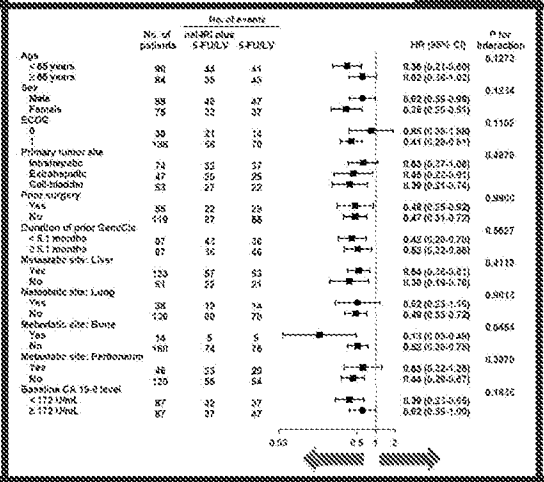
	nal-IRI + 5-FU/LV (n=88)	5-FU/LV (n=86)
No. of events, n (%)	64 (72.7%)	74 (86.0%)
mOS, months (95% CI)	6.6 (5.4-10.5)	5.5 (4.7-7.2)
	HR, 0.68 95% CI, 0.48-0.98 *P*=0.0349	
6-month OS rate, % (95% CI)	60.7% (50.3-71.2)	45.9% (35.3-56.5)
1-year OS rate, % (95% CI)	35.4% (24.9-45.9)	22.4% (13.1-31.7)

Subgroup Analysis for PFS and OS

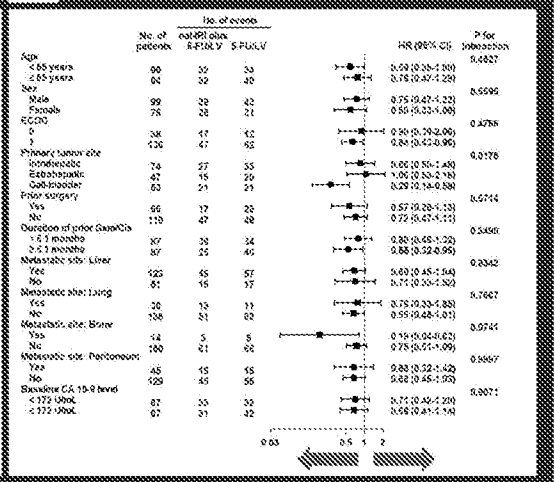
BICR-assessed PFS



Investigator review–assessed PFS



OS

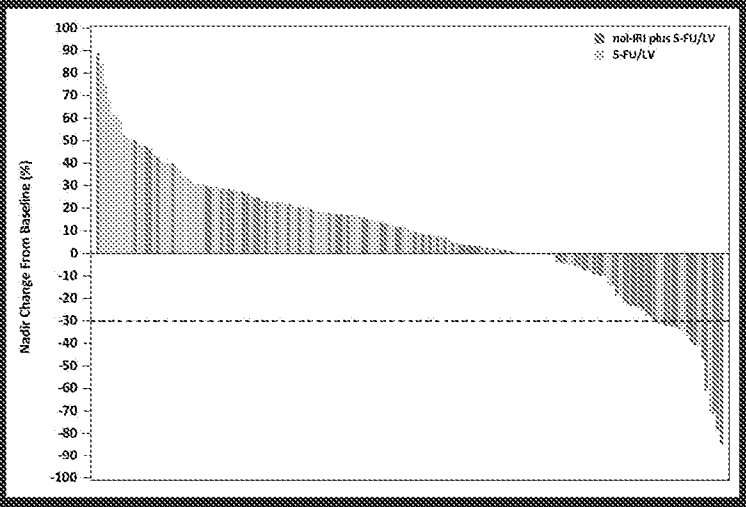


Secondary Endpoint: Overall Response Rates

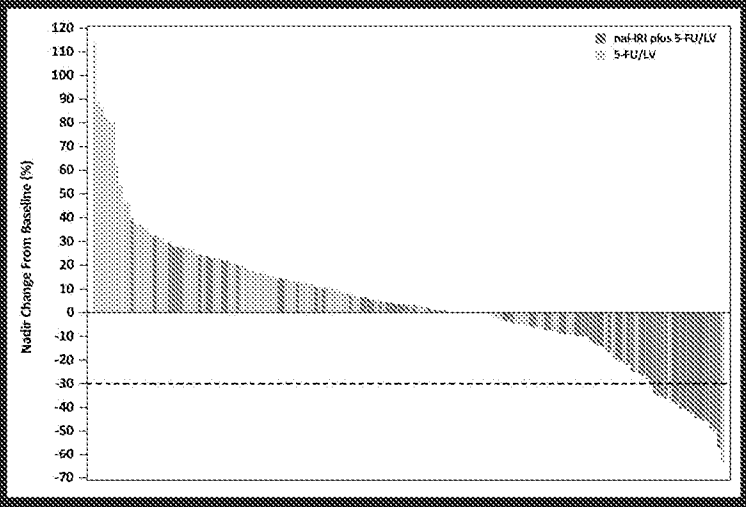
Response per RECIST v1.1	BICR-assessed response		Investigator review-assessed response	
	[illegible]	5-FU/LV	[illegible]	5-FU/LV
Objective response	14.8%	5.8%	18.3%	2.3%
	P=0.0004		P=0.0002	
CR	0	0	0	0
PR	14.8%	5.8%	18.3%	2.3%
SD	60.5%	29.1%	53.4%	47.7%
PD	20.5%	64.0%	21.8%	48.8%
Not evaluable	5.7%	1.2%	5.7%	1.2%

Maximum Changes in Tumor Size

BICR-assessed



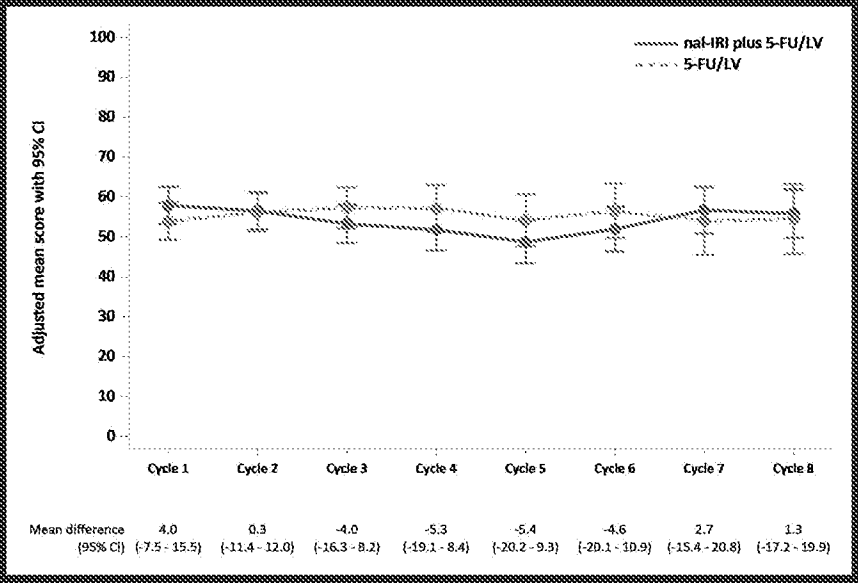
Investigator review-assessed



Adverse Events Occurring in >10% of Patients

	Nal-IRI plus 5-FU/LV (n=89)		5-FU/LV (n=86)	
	Any grade (%)	Grade 3-4 (%)	Any grade (%)	Grade 3-4 (%)
With at least one AE	87 (98.9)	68 (77.3)	74 (86.0)	29 (33.7)
Hematological				
Anemia	13 (14.8)	8 (9.1)	5 (5.8)	3 (3.5)
Febrile neutropenia	2 (2.3)	2 (2.3)	0 (0)	0 (0)
Neutropenia	29 (33.0)	21 (23.9)	3 (3.5)	1 (1.2)
Thrombocytopenia	3 (3.4)	0 (0)	1 (1.2)	1 (1.2)
Non-hematological				
Nausea	22 (25.0)	5 (5.7)	14 (16.3)	1 (1.2)
Vomiting	9 (10.2)	0 (0)	4 (4.7)	1 (1.2)
Abdominal pain	22 (25.0)	4 (4.5)	14 (16.3)	3 (3.5)
Constipation	26 (29.5)	0 (0)	19 (22.1)	0 (0)
Diarrhea	20 (22.7)	4 (4.5)	9 (10.5)	0 (0)
Dyspepsia	20 (22.7)	0 (0)	12 (14.0)	0 (0)
Stomatitis	14 (15.9)	2 (2.3)	10 (11.6)	0 (0)
Fatigue/Asthenia	27 (30.7)	11 (12.5)	17 (19.8)	3 (3.5)
Pyrexia	15 (17.0)	0 (0)	8 (9.3)	1 (1.2)
Decreased appetite	24 (27.3)	1 (1.1)	16 (18.6)	0 (0)

Patient-Reported Quality of Life: Global Health Status



Post-Study Treatment

	[illegible]	[illegible]
Any anti-cancer therapy	30 (34.9%)	27 (31.8%)
Fluoropyrimidine plus cisplatin or oxaliplatin	15 (17.4%)	9 (10.6%)
Fluoropyrimidine monotherapy	10 (11.6%)	6 (7.1%)
Pembrolizumab	9 (10.5%)	10 (11.8%)
Investigational Drug	1 (1.2%)	3 (3.5%)
Gemcitabine plus cisplatin or oxaliplatin	2 (2.3%)	2 (2.4%)
FOLFIRI	1 (1.2%)	2 (2.4%)

Conclusion

- Nal-IRI plus 5-FU/LV significantly **improved PFS, assessed by BICR and investigator, OS, and investigator-assessed ORR** in patients with metastatic BTC after progression on GemCis. PFS and OS benefits were consistent across subgroups.
- **Adverse events of nal-IRI plus 5-FU/LV were well manageable** and consistent with the safety profile shown in the NAPOLI-1 trial for pancreatic cancer. There was no significant difference in QoL between the two groups.
- Given that the study was conducted in Korea only, global generalization of the data may be limited. However, this study is **appropriately powered to compare two treatment groups and designed for meticulous tumor response evaluation** (6-week fixed evaluation and blinded central image review).
- **Nal-IRI plus 5-FU/LV should be considered as one of standard treatments for patients with advanced BTC who failed on GemCis.**

Acknowledgements

- All patients and their families
- All investigators and research nurses
- Asan Academic Research Office (ARO) for study monitoring, maintenance and data management
- Asan Image Metrics (AIM) for independent imaging review
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- HK inno.N provided palonosetron.

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Population-based real-world prognostic factors related to survival among patients with metastatic pancreatic ductal adenocarcinoma (mPDAC)

Kenneth H. Yu[1], Fiau Cocoeum[2], Andy Sumroch[2], Shu Wang[2], Bong Chu Chu[2]
[1]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, New York; [2]Flatiron Health, Inc., Cambridge, MA; [3]Genesis Research, Hoboken, NJ

BACKGROUND

- Pancreatic cancer is expected to be the third deadliest cancer in the US in 2020[1]
- Many real-world studies of patients with mPDAC are restricted to single centers, limiting the generalizability of the insights they generate
- Prior studies, Song et al[2] and Gargiulo et al[3], have identified age, race/ethnicity, tumor location and stage. Aspartate transaminase (ASAT), low performance status, increased derived neutrophil to lymphocyte ratio, increased Carbohydrate Antigen 19-9 (CA 19-9), low hemoglobin, presence of pain, presence of metastasis and increased alkaline phosphatase (ALP) as predictors of mortality
- There is a need to understand prognostic factors of survival in a real-world setting to aid in tailoring treatment strategies for patients

OBJECTIVE

- To identify important population-based predictors related to overall survival after treatment initiation in the metastatic setting among patients diagnosed with mPDAC

METHODS

Study Design and Data Source

A retrospective descriptive analysis was performed using the Flatiron Health® longitudinal database, a demographically and geographically diverse database comprising de-identified patient-level structured and unstructured data, curated via technology-enabled abstraction. Flatiron Health includes data from over 280 cancer clinics

Patient Selection

- This analysis identified and evaluated adult patients diagnosed with mPDAC between January 1, 2017 and December 31, 2019
- Eligible patients were those who:
  - Had a recorded activity within 90 days of their metastatic diagnosis date
  - Were treated with 1L Gemcitabine + nab-paclitaxel (GNP), 1L FOLFIRINOX, 1L gemcitabine monotherapy (gem-mono), or 2L liposomal irinotecan-based regimens
  - Were at least 18 years old at treatment initiation
  - Had at least one recorded activity after the start of treatment

Measures and Statistical Analyses

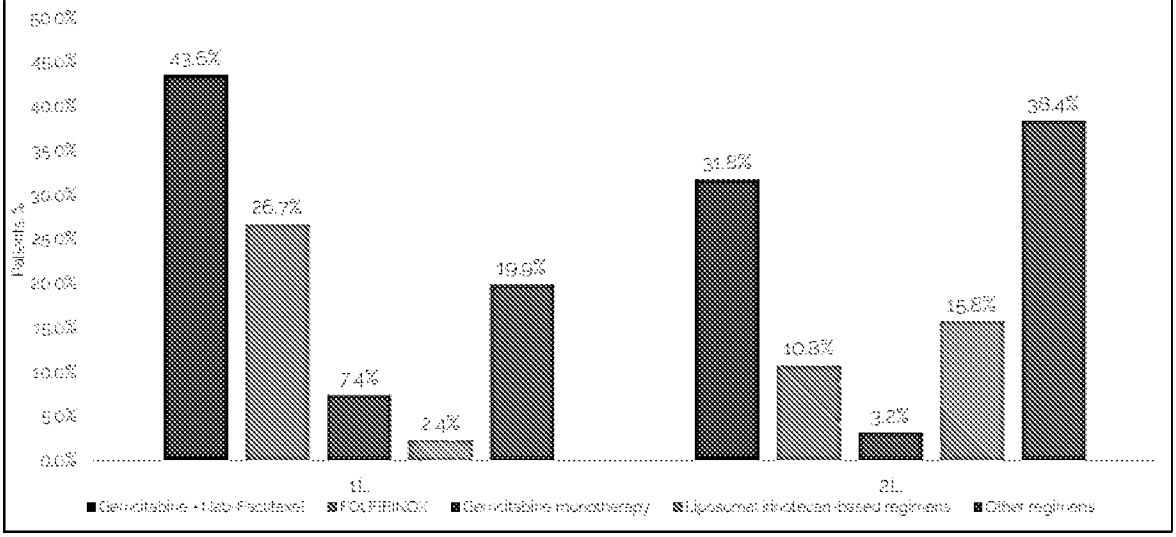
- Baseline patient demographics and clinical characteristics were assessed at the start of treatment
- Predictive models for overall survival from the start of each treatment were developed using multivariable Cox proportional hazards regression
- The holdout method was used for cross-validation, splitting the data into 70% training / 30% validation
- Age at diagnosis, sex, body mass index, smoking status, and ECOG performance score (PS) were included in all models due to clinical importance
- Demographic, clinical characteristics, hematological labs, liver function tests (LFTs), and serum bilirubin levels were assessed for inclusion into the models
- Uno's concordance statistic (c-statistic) was used to assess the predictive accuracy of the models
- Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA)

RESULTS

Treatment Patterns

- There were 3,572 patients with mPDAC treated in 1L and 1,345 treated in 2L included in the study
- Gemcitabine + nab-paclitaxel and FOLFIRINOX were the most common 1L treatments accounting for 44% and 27% of patients, respectively
- Gemcitabine + nab-paclitaxel and liposomal irinotecan-based regimens were the most common 2L treatments accounting for 32% and 16% of patients, respectively (Figure 1)

Figure 1. mPDAC 1L and 2L Treatment Patterns



Prognostic Models

- Among all patients treated with therapy in the front-line setting, the following were included in the final model: prior surgery, white blood cell (WBC) counts, serum albumin, LFTs (ALP and ALT), serum bilirubin, and ascites (c-statistic: 0.65)
- The included variables for specific regimens are presented in (Table 1)

Table 1. Included variables for Prognostic Survival Models by Regimen

mPDAC predictive models	Overall 1L	1L Gemcitabine + Nab-Paclitaxel	1L FOLFIRINOX	1L Gemcitabine Monotherapy	2L Liposomal Irinotecan-based regimens
C-Statistic	0.6534	0.6693	0.6833	0.7839	0.7004
Variables included due to clinical significance					
Age (categories)					
Gender					
BMI					
Smoking status					
ECOG Performance Score					
Prior Line of therapy*					
Variables kept during model building					
Prior Surgery					
Disease Stage					
Neutrophils					
Lymphocytes					
White Blood					
Albumin					
ALT					
AST					
ALP					
LDH					
Bilirubin					
HbA1C					
Presence of Ascites					
Number of Metastatic sites					

A green cell indicates that the variable was included in the final predictive model for a given regimen.
*Prior Line of therapy was used only for the 2L treated patients

- Across all 1L regimens the strongest predictors of survival were ECOG performance score, serum albumin, and ALP
- Among all 1L patients the adjusted hazard ratio (HR) for survival for patients with an ECOG score of 2+ was 1.66 (95% CI: 1.46-1.88) relative to patients with an ECOG score of 0 (66% increased risk of death)
- Similarly, patients with abnormal serum albumin lab values had an adjusted HR of 1.55 (1.42 – 1.7) relative to patients with normal lab values (55% increased risk of death)
- Patients with abnormal ALP lab reading at baseline had an adjusted HR of 1.45 (1.33 – 1.58) relative to patients with a normal value (45% increased risk of death)
- The hazard ratios by regimen are presented in Table 2

Table 2. Adjusted Mortality Hazard Ratios for Included Regimens

Variable	1L Gemcitabine + Nab-Paclitaxel	1L FOLFIRINOX	1L Gemcitabine Monotherapy	2L Liposomal Irinotecan-based regimens
ECOG Score	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
0 (Reference)				
1	1.20 (1.03 - 1.39)	1.44 (1.19 - 1.75)	1.04 (0.64 - 1.7)	1.14 (0.72 - 1.82)
2+	1.46 (1.21 - 1.76)	1.64 (1.21 - 2.23)	1.42 (0.87 - 2.31)	2.06 (1.21 - 3.52)
Missing	1.21 (1.01 - 1.44)	1.20 (0.96 - 1.51)	1.57 (0.94 - 2.63)	0.81 (0.47 - 1.43)
Serum Albumin				
Normal (Reference)				
Abnormal	1.47 (1.3 - 1.66)	1.64 (1.35 - 1.98)	1.76 (1.27 - 2.44)	1.74 (1.24 - 2.44)
Unknown/Not tested	1.38 (0.89 - 2.13)	0.95 (0.49 - 1.85)	2.01 (1.17 - 3.47)	6.17 (0.79 - 48.25)
ALP				
Normal (Reference)				
Abnormal	1.68 (1.48 - 1.92)	1.28 (1.08 - 1.53)		1.39 (0.99 - 1.94)
Unknown/Not tested	2.13 (0.7 - 6.42)	2.57 (0.9 - 7.36)		0.81 (0.28 - 2.33)

Conclusions

- In one of the largest contemporary real-world studies of patients with mPDAC to date, important population predictors of survival in patients receiving systemic treatment were identified
- The strongest predictors for survival identified across all regimens were ECOG performance score and serum albumin
- Further validation studies are needed to understand the generalizability of these results

Limitations

- EHR data are subject to possible entry errors and missing information which could have led to extreme or incorrect values
- Under coding may be present for ascites and sites of metastases that are derived from ICD-10-CM diagnosis codes
- Lab testing patterns may differ by site of care and impact availability of data
- Sensitivity and specificity of mortality data may impact survival estimates

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Conflicts of interest

K.H.Y has received research funding from Bristol-Myers Squibb and Halozyme, and compensation for advisory services from Ipsen. A.S., S.W., and B.C.C. are employees of Genesis Research, which receives consulting fees from Ipsen. P.C. is an employee of and has stock in Ipsen.

Corresponding authors: Kenneth Yu (YuK1@mskcc.org)

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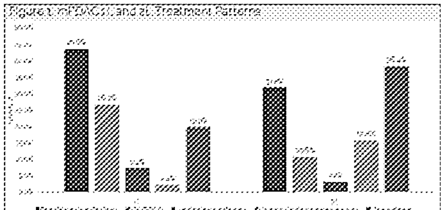
- Gemcitabine + nab-paclitaxel and liposomal irinotecan-based regimens were the most common 2L treatments accounting for 32% and 18% of patients, respectively (Figure 1)

Figure 1. mPDAC 1L and 2L Treatment Patterns



Prognostic Models

- Among all patients treated with therapy in the front-line setting, the following were included in the final model: prior surgery, white blood cell (WBC) counts, serum albumin, LFTs (ALP and ALT), serum bilirubin, and ascites (c-statistic: 0.69)
- The included variables for specific regimens are presented in (Table 1)

Table 1. Included Variables for Prognostic Survival Models by Regimen

mPDAC predictive models	Overall 1L	1L Gemcitabine + Nab-Paclitaxel	1L FOLFIRINOX	1L Gemcitabine Monotherapy	2L Liposomal Irinotecan-based regimens
C-Statistic	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Variables included due to clinical significance					
Age (categorical)					
Gender					
BMI					
Smoking status					
ECOG Performance Score					
Prior Line of therapy					
Variables kept during model building					
Prior surgery					
[illegible]					
Neutrophils					
Lymphocytes					
White blood					
Albumin					
ALT					
AST					
ALP					
[illegible]					
Sodium					
[illegible]					
Presence of Ascites					
Number of Metastatic sites					

[illegible]

- Across all 1L regimens the strongest predictors of survival were ECOG performance score, serum albumin and ALP
- Among all 1L patients the adjusted hazard ratio (HR) for survival for patients with an ECOG score of 2+ was 1.[illegible] (95% CI: 1.[illegible]) relative to patients with an ECOG score of 0 ([illegible]% increased risk of death)
- Similarly, patients with abnormal serum albumin lab values had an adjusted HR of 1.[illegible] relative to patients with normal lab values ([illegible]% increased risk of death)
- Patients with abnormal ALP lab reading at baseline had an adjusted HR of 1.[illegible] relative to patients with a normal value ([illegible]% increased risk of death)
- The hazard ratios by regimen are presented in Table 2

Table 2. Adjusted Mortality Hazard Ratios for Included Regimens

Variable	1L Gemcitabine + Nab-Paclitaxel	1L FOLFIRINOX	1L Gemcitabine Monotherapy	2L Liposomal Irinotecan-based regimens
ECOG Score	[illegible]	[illegible]	[illegible]	[illegible]
0 (Reference)				
1	[illegible]	[illegible]	[illegible]	[illegible]
2+	[illegible]	[illegible]	[illegible]	[illegible]
Missing	[illegible]	[illegible]	[illegible]	[illegible]
Serum Albumin				
Normal (Reference)				
Abnormal	[illegible]	[illegible]	[illegible]	[illegible]
Unknown/Not tested	[illegible]	[illegible]	[illegible]	[illegible]
ALP				
Normal (Reference)				
Abnormal	[illegible]	[illegible]		[illegible]
Unknown/Not tested	[illegible]	[illegible]		[illegible]

Conclusions

- In one of the largest contemporary real-world studies of patients with mPDAC to date, important population predictors of survival in patients receiving systemic treatment were identified
- The strongest predictors for survival identified across 1L regimens were ECOG performance score and serum albumin
- Further validation studies are needed to understand the generalizability of these results

Limitations

- EHR data are subject to possible entry errors and missing information which could have led to extreme or incorrect values
- Under coding may be present for ascites and sites of metastases that are derived from ICD-10-CM diagnosis codes
- Lab testing patterns may differ by site of care and impact availability of data
- Sensitivity and specificity of mortality data may impact survival estimation

References

[illegible]

Conflicts of Interest

[illegible]

Corresponding author: [illegible]

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International Application Number:	
Confirmation Number:	5137
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First Named Inventor/Applicant Name:	Eliel Bayever
Customer Number:	153749
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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	Gollamundi S. KISHORE
Attorney Docket Number	01208-0007-01US

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	1	MARSH R, et al., "Pancreatic Cancer and FOLFIRINOX: A New Era and New Questions," Cancer Med. 4(6):853-63 (2015).
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	Application Number	15809815
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	First Named Inventor	Eliel Bayever
	Art Unit	1612
	Examiner Name	Gollamundi S. KISHORE
	Attorney Docket Number	01208-0007-01US

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Cancer Medicine

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REVIEW

Pancreatic cancer and FOLFIRINOX: a new era and new questions

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Chemotherapy, FOLFIRINOX, genomics, modifications, pancreatic cancer, toxicity

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Abstract

FOLFIRINOX (FFX) was introduced to clinical practice in 2010 following publication of the PRODIGE 4/ACCORD 11 study, which compared this novel regimen to gemcitabine in metastatic pancreatic cancer. Median overall survival, progression-free survival, and objective responses were all superior with FFX and there was improved time to definitive deterioration in quality of life. Despite initial concerns over toxicity, there has been rapid uptake of this regimen, both revolutionizing management and opening the door to innovative research. As experience with FFX has accrued, many questions have arisen including the management of toxicities, the impact of frequent modifications, the optimal number of cycles, integration with other regimens and modalities, interpretation of radiologic and serologic response, utility of molecular signatures, and potential benefit in unique clinical settings such as pre- and postsurgery. This review will closely examine these issues, not only to summarize current knowledge but also to fuel scientific debate.

Introduction

Historical context

Previously published studies have suggested that combination therapy could be an improvement on gemcitabine alone. These include the phase III study of gemcitabine versus gemcitabine plus erlotinib [1], the phase III study of gemcitabine versus gemcitabine plus capecitabine [2], and the phase II study of GTX (gemcitabine, taxotere, and capecitabine) [3, 4]. In the first study, overall survival (OS) (median 6.24 vs. 5.91 months, HR = 0.82, 95% CI = 0.69–0.99; $P = 0.038$), 1-year survival (23% vs. 17%; $P = 0.023$), and progression-free survival (HR = 0.77, 95% CI = 0.64–0.92; $P = 0.004$) were better with gemcitabine plus erlotinib. In the second study, objective response rate (19.1% vs. 12.4%; $P = 0.034$) and progression-free survival (HR = 0.78; 95% CI = 0.66–0.93; $P = 0.004$) favored the combination and there was a trend toward improved OS (7.1 vs. 6.2 months, HR = 0.86, 95% CI = 0.72–1.02; $P = 0.08$). In the GTX study, median progression-free survival of responders was 6.3 months (95% CI = 4.4–10.4 months) and median survival was 11.2 months (95% CI = 8.1–15.1 months). While certainly of interest, the clinical benefit of these regimens was either marginal, of uncertain impact on quality of life, or achieved in very small numbers, resulting in sporadic and unenthusiastic uptake.

FOLFIRINOX

Promising phase II results with FOLFIRINOX (FFX) [5] (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, irinotecan 180 mg/m^2, bolus 5-fluorouracil 5FU) (400 mg/m^2, infu-

sional 5FU 2400 mg/m^2 over 46 h, every 14 days) were confirmed in a sentinel phase III study (PRODIGE 4/ACCORD 11) [6], which randomized patients ≤75 years of age with metastatic pancreatic cancer and an ECOG PS of 0 or 1, to receive either gemcitabine or FFX. With a median follow-up of 26.6 months and with 171 patients in each arm (38% of patients had lesions in the head of the pancreas with 14.3% requiring biliary stents), the median survival with FFX was 11.1 months versus 6.8 months for gemcitabine ($P < 0.001$, HR = 0.57, 95% CI = 0.45–0.73). More impressively, 1-year survival was 48.4% versus 20.6%, respectively, and this difference was sustained at 18 months, 18.6% versus 6%. Quality of life measures, equally, strongly favored the FFX group [7].

While toxicity was not inconsequential (45.7% grade 3 or 4 neutropenia, 5.4% febrile neutropenia, 12.7% diarrhea, 9.1% thrombocytopenia, 9.0% sensory neuropathy), oncologists rapidly adopted the FFX regimen following the 2010 ASCO meeting [8]. Many questions have now arisen such as: best management of common and uncommon toxicities; potential impact of adjustments to the original regimen; number of cycles administered for optimal results; innovative strategies in early disease; radiologic and serologic assessment of response; evolving data on integration into overall treatment planning; and utility of molecular profiling.

In order to derive the data used in this review, all relevant papers in Medline, CANCERLIT, and Index Medicus together with meeting abstracts from ASCO, ASTRO, and AACR since 1990, were examined. No ethnic or racial group or gender was excluded. Approximately 65% of discovered references have been included based on relevance, timeliness, and quality of data.

How is Toxicity of FFX Best Managed?

As with usual practice, reduction in individual drug dosing is a standard approach for many of the common complications such as low blood counts, fever, infection, diarrhea, weight loss, and fatigue. However, some problems engendered by FFX are either idiosyncratic, not dose related, or not manageable with simple dose reduction and may require more innovative strategies (Table 1).

If platelet counts are problematic despite dose modifications, then splenectomy, either surgical [9] or by endovascular means using an embolic approach [10], can help in selected patients. The typical phenotype would be someone who is responding to chemotherapy, with a good functional status, but who has isolated thrombocytopenia (<90 × 10^3/μL). In the surgical series, counts increased significantly ($P < 0.01$) with a mean value of 87 × 10^3/μL prior to treatment and 425 × 10^3/μL on discharge (average 3 days later). All patients were able to resume chemotherapy within a median of 11.5 days (range 6–27). The IR procedure could be particularly useful in those either too frail for surgery or for whom surgery is relatively contraindicated (e.g., disease in the splenic hilum or carcinomatosis). Complications of postoperative pain and splenic abscess are limiting factors [11] and relative efficacy is unknown.

Infusion reactions are common and desensitizing protocols may be needed [12]. A significant hypercholinergic response with excess salivation, cramping, and sweating, related to the piperidine structure of irinotecan, which mimics a cholinergic drug when metabolized by esterases to form SN-38, is not unusual [13]. The potentiating role of oxaliplatin is real but not well understood [14]. Slowing of the infusion, aggressive medication with atropine, and a proton pump inhibitor may be required.

The common problems of oral dysesthesia and thick tongue, and the rare complication of total body weakness, near paralysis and even coma from oxaliplatin may be difficult to manage. Slowing the infusion and a warm drink works best for the former, while aggressive correction of serum potassium and calcium prior to, and following, the infusion may resolve the latter [15, 16].

Table 1. Management of FOLFIRINOX toxicity.

Toxicity	Strategy	Concern
Low blood counts, fatigue, diarrhea, mucositis	Decrease doses of one or more of the drugs; lomotil/pegfilgrastim	Decreased efficacy of therapy; bone pain
Low platelet counts despite appropriate dose reduction	Splenectomy—surgical or via interventional radiology	Pain; abscess formation; treatment delay
Acute allergic reaction to oxaliplatin infusion	Desensitization protocol and possible discontinuation	Ineffective to resolve problem; resources
Hypercholinergic reaction with cramping and sweating	Slow infusion rate and premedicate with atropine	Prolonged treatment time; resources
Oral dysesthesia with sense of swollen tongue	Slow infusion rate and warm drink	Prolonged treatment time; anxiety; resources
Weakness, paralysis, and even coma	Maintenance of normal potassium and calcium prior to and during infusion	Patient anxiety; staff anxiety; imperfect results

Do Modifications to the FFX Regimen Matter?

Oncologists in the United States and elsewhere were anxious to use FFX, but initially concerned about toxicity, particularly in patients with lesions in the head of the pancreas and with biliary stents. A Canadian report suggested that there could be considerable toxicity when the regimen is used outside of a clinical study and in community centers [17]. In their series of 46 patients, there were 3 (7%) treatment-related deaths, 54% of patients were hospitalized with sepsis, 33% had neutropenia grade ≥3, 15% had diarrhea grade ≥3, and 4 (9%) patients had febrile neutropenia.

With this scenario in mind, many modifications have been made (Table 2). Initially, physicians removed the bolus of 5FU, which is notably myelosuppressive, with some adding pegfilgrastim 6 mg on day 3 or 4. Commonly referred to as "mFOLFIRINOX," this seems to be the way it is often used today [18]. Historically, a bolus of 5FU has been used in the majority of fluoropyrimidine regimens, together with a more prolonged infusion to maximize total exposure [19]. A Japanese study shows that the bolus contributes significantly to the overall exposure to 5FU via AUC [20]. In addition, 5FU functions differently depending on how it is administered [21] and thus, theoretically, the omission of the bolus could lead to loss of efficacy. Data reported at the 2014 GI ASCO meeting suggest, however, that this may not be the case, and longer follow-up will be needed for clarification [22].

A further dilemma concerns the omission of leucovorin, should the bolus of 5FU be removed. Previous dose-finding studies of infusional 5FU with leucovorin clearly demonstrated that there is considerable synergy, and that omission of leucovorin results in less toxicity [23], suggesting that efficacy could equally be impacted. Absent real data, and given the low cost of leucovorin, it seems reasonable to leave it untouched.

Ohio State physicians reported their experience with limiting irinotecan to 165 mg/m^2 in addition to these changes, in either locally advanced or borderline resectable disease. They concluded that the modified regimen was effective and well tolerated with no episodes of grade 3 or 4 neutropenia/thrombocytopenia, but with 46% of patients requiring a dose reduction for other toxicities [24]. Similarly, physicians at Yale reported that in their hands dose reductions were common (relative dose intensities: oxaliplatin 88%, irinotecan 64%, bolus 5FU 57%, infusional 5FU 100%, compared to oxaliplatin 78%, irinotecan 81%, and 5FU 82%—PRODIGE 4/ACCORD 11) [25]. Despite these modifications, efficacy was comparable to that of the original regimen—response (CR + PR 33% —similar to historical data 31.6%; $P = 0.21$), and toxicity was notably less (grade 3 or 4 neutropenia 6.4%, $P < 0.0001$; fatigue 9.6%, $P < 0.02$).

For frail and elderly patients, additional adjustments have been made. In a series of 19 patients over age 65,

Table 2. FOLFIRINOX dose modifications and results.

Author	Modification	Results/comments
Mahaseth et al. [18]	Drop 5FU bolus	Grade 4 neutropenia 3%
	Add pegfilgrastim 6 mg	Grade 3/4 diarrhea 13%, fatigue 13%
		OS 9.0 months, PFS 8.5 months
Blazer et al. [24]	Drop 5FU bolus	Grade 3/4 neutropenia or thrombocytopenia 0%
	Decrease irinotecan to 165 mg/m^2	46% further dose reductions for other toxicities
	Add pegfilgrastim 6 mg	
Gunturu et al. [25]	Median dose intensity 5FU bolus 57%	Grade 3/4 neutropenia 6.4%
	Median dose intensity oxaliplatin 88%	Grade 3/4 fatigue 9.6%
	Median dose intensity irinotecan 64%	CR plus PR 31.6%
Metges et al. [27]	Median dose intensity 5FU bolus 82%	Grade 3/4 hematologic and neurotoxicity 32%
	Median dose intensity oxaliplatin 78%	Response rate 39%
	Median dose intensity irinotecan 81%	PFS 6.5 months
		OS 10.9 months
Alessandretti et al. [26]	Drop 5FU bolus	Grade 3/4 neutropenia 21% or thrombocytopenia 5%
	Decrease 5FU infusion to 2000 mg/m^2	Grade 3/4 fatigue 15.7%
	Decrease oxaliplatin to 50 mg/m^2	CR plus PR 31.7%
	Decrease irinotecan to 135 mg/m^2	OS and PFS not reached at 4 months
	Add pegfilgrastim 6 mg	
James et al. [22]	Decrease 5FU bolus 25%	Grade 3/4 neutropenia 17% or thrombocytopenia 11.3%
	Decrease irinotecan 25%	Grade 3/4 fatigue 11.3%
	Add pegfilgrastim 6 mg	CR plus PR 29%

the bolus of 5FU was dropped and doses of both oxaliplatin and irinotecan were lowered (5FU 2000 mg/m^2 over 46 h, oxaliplatin 50 mg/m^2, irinotecan 135 mg/m^2) [26]. Grade 3/4 toxicities were reported in 10 patients: nausea/vomiting in one, diarrhea in one, fatigue in three, neutropenia in four, thrombocytopenia in one, and febrile neutropenia in three—all manageable. A follow-up study by the original investigators in the PRODIGE 4/ACCORD 11 study, based on their established criteria, showed that 81% of 242 patients required a dose reduction, but that this did not affect results (response rate 39% vs. 32%, PFS 6.5 vs. 6.4 months and OS 10.9 vs. 11.1 months) [27].

A biologically based refinement, using genotype-derived dosing of irinotecan via UGT1A1, the enzyme that inactivates SN-38 (the active metabolite of irinotecan) showed that those with a *28*28 genotype are at highest risk of severe neutropenia, *1*28 at intermediate risk, and *1*1 at lowest risk [28]. Initial doses of irinotecan could be adjusted accordingly.

A close examination of clinicaltrials.gov confirms that the majority of regimens presently under investigation incorporate some modification of FFX.

How is the Number of Treatment Cycles with FFX Determined?

The optimal number of treatment cycles is not well understood, but the goal of therapy (i.e., curative vs. palliative) is critical in this regard. The disease should be unambiguously defined as either resectable, borderline resectable, locally advanced unresectable, or metastatic. This has implications for ensuring that treatment is not unnecessarily modified, or conversely, that excessive treatment (and toxicity) is not given. This is simplest in a palliative setting, where duration and intensity of treatment is determined by response and quality of life. The median number of cycles in the original PRODIGE 4/ACCORD 11 study was 10, with a range of 1–47 [6]. In locally advanced and borderline resectable disease, it is common to use four cycles of FFX (± chemo/RT) in a neoadjuvant strategy (e.g., ALLIANCE/Intergroup study A021101). This is based on very limited data, and an alternative approach might be to treat to maximal response and/or maximum-tolerated dose. A retrospective study of this strategy in borderline (60%) and locally advanced, unresectable (40%) disease examined outcomes in 18 patients [29]. An R0 resection was ultimately possible in 44% of patients, with a median number of six cycles (range 5–17) prior to surgery. A report on FFX plus chemo/RT in 22 patients with locally advanced, unresectable disease, examined use of an initial four cycles with an additional four cycles prior to chemo/RT, if disease was either stable or improved [30]. A median of eight cycles was administered, with 12 patients taken to the OR and 5 (42%) were able to have an R0 resection. However, three patients developed distant recurrence within 81 days, confirming their dismal prognosis.

Steatohepatitis (irinotecan) and sinusoidal obstructive syndrome (oxaliplatin) are dose-related complications which effect outcome in liver resection for colorectal cancer [31]. A Whipple operation, in and of itself, leads to an increase in hepatic steatosis [32]. Further, a BMI exceeding 25 kg/m^2, diabetes mellitus, and preexisting steatosis all significantly increase the risk of steatohepatitis and postoperative morbidity [33]. These data suggest that the number of cycles be limited to the minimum necessary, as the effects on patients undergoing a Whipple operation are as yet unknown.

Complicating matters further, pancreatic cancer is clearly a heterogeneous disease [34]. Aggressive subsets (if they do respond) may require three or four cycles of therapy before showing a decline in CA 19-9, implying response, and may conceivably require further cycles of chemotherapy prior to surgery.

In locally advanced (arterial encasement) or metastatic disease, initial intensive therapy could be followed by omission of either oxaliplatin or irinotecan (depending on which is more problematic) for continuation of a "maintenance program," as this is strictly palliative therapy. While there are few publications on the efficacy of FOLFOX or FOLFIRI, those that do exist are positive [35–37].

Is Preoperative or Postoperative FFX the Optimal Strategy for Potentially Resectable Disease?

One of the most intriguing questions currently under study is whether FFX will improve on results in the adjuvant therapy of resectable pancreatic cancer. A recent update of the CONKO-001 study shows that median OS is 22.8 months in the gemcitabine group versus 20.2 months in the observation group (HR = 0.76, $P = 0.01$) [38]. OS at 5 and 10 years is 20.7% versus 12.2% and 10.4% versus 7.7%, respectively—all dismal numbers.

Studies comparing gemcitabine with combination therapy, and even vaccine therapy, have failed to improve on these results [39–41]. There are no data as yet on FFX in the adjuvant setting (PRODIGE 24/ACCORD 24—gemcitabine vs. mFFX; and Marsh et al.—four cycles of mFFX pre- and postsurgery, are in progress) (clinicaltrials.gov). The latter approach is intriguing as early systemic treatment, prior to surgical intervention, is attractive for many reasons: better selection of patients for surgery based on the exclusion of those with rapidly progressive disease; better tumor exposure to chemotherapy prior to disrup-

tion of the vasculature; ability to gauge response; better tolerance of chemotherapy prior to debilitating surgery; and increased R0 resections. Furthermore, pancreatic cancer has been shown to be systemic from the earliest stages [42–44] and thus an early systemic approach is not only logical but may also be essential.

Previous studies of neoadjuvant therapy in resectable patients include gemcitabine plus radiation (73/86 were taken to surgery, with 64/86 undergoing successful surgery) [45]; and gemcitabine plus nab-paclitaxel (14/25 completing the planned three cycles, with surgery in 20/25, 19/20 R0) [46]; (9/16 undergoing surgery at the time of reporting, with 8/9 R0 resections) [47].

The University of Michigan reported improved 1- and 3-year OS, lower margin and node positivity, and minimal additional perioperative toxicity in a retrospective review of various neoadjuvant regimens in borderline resectable disease [48]. University of Washington similarly reported almost doubling of OS in a small series of patients with both resectable and borderline resectable disease (neoadjuvant GTX vs. historical controls) [49], and Columbia was able to convert 57% of inoperable patients to operable with 49% R0 resections [50]. Finally, the Medical College of Wisconsin reported on mFFX followed by radiation therapy in borderline resectable disease and found this approach both safe and favorable compared to historical controls [51]. The ALLIANCE/Intergroup A021101 study is examining the feasibility of mFFX for four cycles followed by RT with oral capecitabine in a multi-institutional setting. Gemcitabine is given in the adjuvant space. The primary endpoint is 1-year OS and there are multiple levels of quality control to ensure validity (clinicaltrials.gov).

How Best Can Response to FFX Therapy be Assessed?

Both serologic and radiographic response to therapy has come under increasing scrutiny. CA 19-9 has been used for decades as a serum marker in pancreatic cancer in Lewis antigen-positive individuals [52, 53]. However, this is complicated by the fact that biliary obstruction, pancreatitis, intestinal inflammation, and even elevated blood glucose [54] all lead to an increase in CA 19-9. While there is evidence that there is a difference in outcome between no responders and stable or good responders [55, 56], there are opposing findings suggesting that there may be no correlation [57], and additional data are awaited.

Change in tumor dimensions, as assessed on CT scan and/or MRI, is both challenging to measure and often insignificant [58]. In a study of 129 patients with borderline resectable tumors, post therapy, presurgical imaging suggested that only 1% had been down staged, 78% had no change, and 21% had progressive disease [59]. In fact, 66% were able to undergo resection with 95% R0 resections. Provided the patient has acceptable performance status and no evidence of metastatic disease, even where there is no obvious radiographic response, surgery should proceed as pathology may indicate clear-cut treatment effect [60]. Whether pathologic response has any meaning in the clinical context awaits further clarification, but initial reports suggest that more than 5% viable cells in the final specimen portends a bad outcome [61, 62].

While endoscopic ultrasound can be valuable [63], novel ways of imaging the tumor, such as perfusion imaging [64], dynamic PET scans [65] and routine CT scan derived mass transport parameters, are increasingly being incorporated into investigational algorithms [66].

How is FFX Optimally Combined with Radiation Therapy?

Many protocols in borderline and locally advanced, unresectable disease switch to radiation therapy following initial FFX [51]. However, the precise role of radiation in these settings is the subject of ongoing debate. The LAP 07 study found that in locally advanced disease, chemo/radiation had no effect on OS compared to continued chemotherapy alone (over 40% of patients developed metastatic disease prior to being randomized to radiation or not) in those patients stable after an initial phase of gemcitabine ± erlotinib [67]. Updated results in 2014 suggested less local recurrence in the CRT arm (34% vs. 65%, $P < 0.0001$). The true impact of radiation may not be fully evaluable until systemic disease control improves further. An upcoming study will re-explore this question: the three-arm randomized phase II RTOG 1201 study, which is evaluating systemic chemotherapy alone (gemcitabine plus nab-paclitaxel) versus capecitabine plus standard versus intensified local RT (50.4 Gy vs. 63 Gy) preceded and followed by systemic therapy. Given that FFX is notably more active than gemcitabine in metastatic disease [6], the combination of radiation with FFX deserves to be examined and novel approaches such as SBRT [68, 69], may make it possible to do so.

How Best to Combine FFX with Other Regimens?

Recently, the MPACT study reported on gemcitabine plus nab-paclitaxel (GN) versus gemcitabine in 861 patients with metastatic pancreatic cancer [56]. Median OS was 8.5 versus 6.7 months (HR for death, 0.72; 95% CI = 0.62–0.83; $P < 0.001$), and progression-free survival was 5.5 versus 3.7 months (HR = 0.69, 95% CI = 0.58–0.82; $P < 0.0001$). While less than that of FFX in the

Table 3. Selected current studies using FOLFIRINOX in all stages of pancreatic cancer.

Setting	Study	Regimen	Goal	Opened
Resectable neoadjuvant	NorthShore/University of Chicago Pilot study	mFFX—no 5FU bolus—four cycles pre- and postop	Assess safety and efficacy (R0, ORR, PFS, and OS)	August 2012
Resectable neoadjuvant	Indiana University Phase II study	Standard full dose FFX—four cycles preoperatively	Assess safety and efficacy (Path CR, DFS, OS, ORR)	June 2014
Resectable neoadjuvant	Yale/NCI Phase II study	mFFX—no 5FU bolus—six cycles pre and post op	Assess safety and efficacy (R0, path CR, PFS, and OS)	January 2014
Resectable adjuvant	PRODIGE 24/ACCORD 24 Phase III	mFFX—no 5FU bolus—versus gemcit, each for 24 weeks	DFS, OS, specific survival	February 2012
Resectable adjuvant	Krankenhaus Nordwest Phase II/III	Standard full dose FFX—six cycles pre and postop vs. gemcit postop	Assess safety and efficacy (OS, PFS, R0, path CR)	Opening pending
Resectable adjuvant	Sidney Kimmel Comprehensive Cancer Center Pilot Study	SBRT plus Vaccine (GVAX)/cyclophosphamide then standard full dose FFX—six cycles with GVAX	Toxicity, safety, OS, DFS, TTF	April 2012
Borderline resectable	ALLIANCE A021101 Pilot study	mFFX—no 5FU bolus—four cycles, then RT/cape gemcit postop	Accrual rate, toxicity, CR/PR, completion of all therapy, R0/R1	March 2013
Borderline resectable	Medical University of South Carolina Phase II	mFFX—no 5FU bolus—six cycles then RT/cape	R0/R1 resection (OS, TTR, ORR, path CR) and safety	August 2012
Borderline resectable	University of Maryland Pilot Study	mFFX—no 5FU bolus—four cycles then SBRT	Resectability, DFS, OS, TTR, path CR and safety	September 2013
Locally advanced	UNC LINEBERGER Phase II	Standard full dose FFX	Assess safety and efficacy (OS, PFS, ORR)	September 2012
Locally advanced	Foundation for Liver Research/Erasmus Medical Center Phase II	Standard full dose FFX—four cycles then SBRT	OS, radiologic RR, Resection rate, PFS, Biologic predictive markers	July 2014
Locally advanced	Massachusetts General Hospital/NCI Phase II	Standard full dose FFX—eight cycles plus losartan then proton beam RT	Feasibility, PFS, OS, toxicity, downstaging, gene mutations	March 2013
Metastatic disease	University of Chicago Phase II	Modified FFX—irinotecan dose determined by UGT1A1 status; no 5FU bolus	DLT in course 1; RR, cumulative dose intensity of irinotecan	July 2012
Metastatic disease	Institut Cancerologie de l'Ouest Phase II	Modified FFX—irinotecan dose determined by UGT1A1 status; 5FU dose by DPD expression	Safety, toxicity and efficacy (OS, PFS)	May 2014
Metastatic disease	Centre Val d'Aurelle—Paul Lamarque Phase I–II	Standard Gemcitabine plus nab-paclitaxel followed by standard FFX	MTD; Phase II dosing; RR	August 2013

ORR, overall response rate; PFS, progression-free survival; OS, overall survival; CR, complete remission; gemcit, gemcitabine; SBRT, stereotactic body radiation therapy; TTF, time-to-treatment failure; cape, capecitabine; TTR, time to response; DLT, dose-limiting toxicity; DPD, dihydropyrimidine dehydrogenase; MTD, maximum-tolerated dose; FFX, FOLFIRINOX; postop, postoperative.

PRODIGE 4/ACCORD 11 study—11.1 months [6], median OS is significant enough to be of major interest, raising the issue of how best to integrate these two regimens in a comprehensive treatment plan. One of the more interesting questions is whether there is synergism, and whether pretreatment with GN would alter the cancer-associated stroma such that FFX would be more effective. A recent phase II study used up to six cycles of GN followed by consolidation with FFX for up to 12 cycles and was deemed feasible [70]. A case report from Germany, reported success with this approach in locally advanced disease [71].

The efficacy of GN following failure of FFX is unknown. In a retrospective study from Yale, 23 patients were so treated with an estimated time-to-treatment failure of 11 weeks, about half of that in first-line GN [72]. Interestingly, dose densities of only 56.9% and 63.5% for nab-paclitaxel and gemcitabine, respectively, were achieved which suggest that alternative dosing schedules should be examined.

Innovative approaches currently under investigation include addition of a Hedgehog inhibitor to FFX [73]; combination of FFX, SBRT, and GVAX as adjuvant therapy; and a combination of FFX and hyperacute vaccine in borderline and locally advanced disease. As we learn more, it is hoped that future study design will be based on biology and molecular profiling of tumors, rather than empiricism or intuition.

How Do We Use Molecular Signatures in Planning FFX Treatment?

There is an increasing interest in the molecular profiling of cancers. Certainly, patients testing positive for a BRCA 1 or BRCA 2 mutation might have increased sensitivity to a platin [74], but this has uncertain practical value. PARP inhibitors might be more effective [75]. From the Pancreatic Cancer Genome Project, we know that pancreatic cancers contain an average of 63 genetic alterations, the majority of which are point mutations [76]. A core set of 12 cellular signaling pathways and processes are defined by these alterations in 67–100% of tumors. KRAS, Hedgehog, Wnt/Notch, SMAD4, and TGF-β signaling pathways are key, with abnormalities of one or more of these pathways in 100% of cancers. The effects on therapy with FFX are as yet unknown.

Candidates for future study include predictors of drug metabolism and toxicity—ERCC1 expression (oxaliplatin) [77], UGT 1A1 genotype (irinotecan) [28], thymidylate synthase expression (5FU) [78], HENT-1 expression (gemcitabine—both positive and negative studies) [79, 80] and SPARC expression—both nab-paclitaxel [81] and gemcitabine [82].

What Important Clinical Studies are Currently Underway in Pancreatic Cancer Using FFX Alone or in Combination?

As a final note, it is relevant to include a table of selected current and ongoing studies using FFX in all stages of pancreatic cancer (Table 3). These studies have been selected from many for their potentially significant impact on the use of this regimen in the future. It may once again be noted that FFX is very frequently modified.

Summary

FFX has had a major impact on the treatment of pancreatic cancer. As experience with this regimen has accrued, and as we have learned how to manage the toxicities, we have been presented with a new set of questions: the effect of frequent modifications; optimal use in all stages of pancreatic cancer; integration with both established and emerging therapies; how to evaluate response; and the incorporation of evolving molecular data. Furthermore, while metastasectomy in pancreatic cancer has historically been fraught with futility and failure, the markedly improved activity of FFX [5, 6] could mean that the time to study surgery plus FFX (in highly selected patients) is near [83, 84]. The next few years should prove to be exciting for all working to improve the outlook for this challenging group of patients.

Conflict of Interest

None declared.

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The Role of Tumor Size in the Radiosurgical Management of Patients with Ambiguous Brain Metastases

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OBJECTIVE: To identify a size cutoff below which it is safe to observe obscure brain lesions suspected of being metastases so that treatment of nonmetastases can be avoided.

METHODS: Medical records from patients who underwent linear accelerator-based radiosurgery from August 1991 to October 2001 were reviewed. Inclusion criteria were defined as brain metastasis tumor volume less than 5 cm^3 (diameter, ~2.1 cm) treated with a dose of 20 Gy or more. One hundred thirty-five patients had 153 evaluable brain metastases with follow-up imaging that met inclusion criteria. Median age was 54 years (range, 18–79 yr). Lesion primaries were non-small-cell lung (n = 39), melanoma (n = 44), renal (n = 37), breast (n = 18), colon (n = 3), sarcoma (n = 5), other (n = 5), and unknown primary (n = 2). Median tumor volume was 0.67 cm^3 (range, 0.06–4.58 cm^3). The minimum peripheral dose was 20 Gy (n = 132) or 21 to 24 Gy (n = 21). At the time of analysis, the median follow-up for all patients was 10 months (range, 0.2–99 mo).

RESULTS: The 1- and 2-year actuarial local control rates for all of the lesions were 69 and 46%, respectively. For lesions of 1 cm (0.5 cm^3) or less, the corresponding local control rates were 86 and 78%, respectively, which was significantly higher than the corresponding rates of 56 and 24%, respectively, for lesions larger than 1 cm (0.5 cm^3) ($P = 0.0016$).

CONCLUSION: A convincing brain metastasis measuring less than 1 cm should be pursued aggressively. If the suspected brain metastasis is ambiguous, observation is proposed up to a diameter of 1 cm. This is the first study in the literature to identify a 1-cm cutoff for radiosurgical control of small brain metastases, and validation by additional studies is required.

KEY WORDS: Brain metastases, Prognostic factors, Size, Stereotactic radiosurgery, Timing

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In the maturing field of stereotactic radiosurgery (SRS), numerous studies have demonstrated its value in the management of metastatic brain disease (1, 2). However, the role of SRS continues to evolve, because important questions still remain in terms of defining the precise indications for its use. One such question that needs to be addressed is the optimum timing of performance of SRS for obscure lesions shown by magnetic resonance imaging (MRI) that are not obvious brain metastases and for which the patient is asymptomatic. Such lesions may mimic blood vessels in cross section when tiny, may be ill-defined when uptake of contrast is poor, or may be at the limit of MRI resolution. SRS relies critically on computed tomography and MRI, both of which have received continual refinements in technique, giving an improved ability to detect and treat smaller, previously occult brain metastases (20). With such refinements, screening of cancer patients with MRI can now routinely detect asymptomatic brain metastases that are only several millimeters in size (20). Unfortunately, such improvements in sensitivity can create a diagnostic dilemma because they are associated with an increased rate of false-positive readings from better vi-

sualization of blood vessels, nontumor enhancement such as in vascular malformations, and detected artifacts (17). In addition, there can be difficulty with defining the SRS target volume for ill-defined lesions. The risk of diagnostic error in the absence of histological studies has been reported to be as high as 10 to 15% for the single metastasis (8, 11). This error rate may be even higher for a tiny, ill-defined single brain metastasis.

For patients at the University of Texas M. D. Anderson Cancer Center (UTMDACC) who are referred for consideration of SRS for obscure lesions, it has been our policy to observe such poorly defined lesions with serial MRI studies. SRS treatment is given only if subsequent imaging convincingly demonstrates enlarging brain metastases. Although this strategy may help avoid inadvertent treatment of nonmetastases mimicking brain metastases, it is unknown whether observation may unintentionally undermine tumor control. The aim of this study was to try to identify a size cutoff below which it is safe to observe obscure brain lesions suspected of being metastases so that inappropriate treatment of nonmetastases can be avoided.

PATIENTS AND METHODS

This retrospective study on 135 selected patients (216 total brain metastases) with 169 small (<2 cm) brain metastases treated with linear accelerator-based SRS spans the 10-year period from the inception of the SRS program at UTMDACC in August 1991 to October 2001. At the outset of the study, inclusion criteria required that study patients have a brain metastasis tumor volume of less than 5.0 cm^3 (equivalent to a spherical lesion diameter of ~2.1 cm, where the volume of a sphere = $4/3 \times \pi \times$ radius cubed) and treatment to a minimum peripheral dose of 20 Gy or more. These inclusion criteria were specified so that a relatively homogeneous group of patients with respect to dose could be used to study the effect of lesion size on local tumor control. Size assessment was based solely on volumetric data recorded by the Tyco-Radionics (Burlington, MA) treatment planning software. In each case, contrast-enhanced tumor was outlined on 1.5-mm-thick computed tomographic slices. Data from all 135 patients who met these inclusion criteria are included in the survival analyses, but data from only 169 of 216 metastatic brain tumors were eligible for analysis on the basis of these criteria. Of these 169 eligible tumors, 153 were lesions evaluable for tumor control analysis on the basis of having follow-up imaging performed after SRS. Data from five patients were not evaluable because the patients did not have follow-up imaging and died within 1 month after SRS. The remaining unevaluable tumors were from patients who failed to return for follow-up imaging. The patients' characteristics and their primary tumors are listed in *Table 1*. The radiation treatment parameters and the treatment sequence of whole-brain radiation therapy (WBRT) and SRS are categorized for all patients in *Table 2*.

Follow-up data on vital status were completed for all 135 patients. Methods of follow-up included review of the hospital medical records and the UTMDACC tumor registry, mailing of follow-up letters to all study patients and their families, telephone follow-up when necessary, and review of publicly available death registries. At the time of analysis, the median

TABLE 1. Patient characteristics[a]

Patients	
No.	135
Total lesions	216
Eligible lesions	169
Evaluable lesions	153
Age (yr)	
Range	18–79
Median	54
KPS	
60–70	38% (51/135)
80–90	40% (54/135)
100	22% (30/135)
Median	80
RPA	
I	8.1% (11/135)
II	86.7% (117/135)
III	5.2% (7/135)
Primary site	
Non-small-cell lung	28.1% (38/135)
Melanoma	29.6% (40/135)
Renal	23.7% (32/135)
Breast	8.9% (12/135)
Colon	1.5% (2/135)
Sarcoma	3.7% (5/135)
Other	3.0% (4/135)
Unknown primary	1.5% (2/135)
Status of primary during SRS	
Controlled	61.5% (83/135)
Uncontrolled	38.5% (52/135)
Extracranial disease	
Present	80% (108/135)
Liver	18
Lung	71
Bone	29
Adrenal	9
Other	4
Absent	20% (27/135)
No. of initially diagnosed brain metastases	
1	60% (81/135)
2	25.2% (34/135)
≥3	14.8% (20/135)

[a] KPS, Karnofsky Performance Scale score; RPA, recursive partitioning analysis; SRS, stereotactic radiosurgery.

TABLE 2. Treatment characteristics[a]

SRS dose	
Minimum peripheral dose (Gy)	
20	86% (132/153)
21–24	14% (21/153)
Median isocenter	23.53 Gy
Median isodose	85% (70–100%)
Cone diameter (cm)	
Range	1.0–3.25
Median	1.75
Tumor volume (cm^3)	
Median	0.68
Range	0.06–4.58
WBRT	
Median dose	30 Gy
Range	22.5–40 Gy
Treatment sequence by patient	
SRS first	
SRS only	52.6% (71/135)
SRS + WBRT	11.1% (15/135)
SRS + salvage WBRT	11.1% (15/135)
WBRT first	
WBRT + SRS	1.5% (2/135)
WBRT + salvage SRS	23.7% (32/135)

[a] SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

duration of follow-up from time of SRS was 10 months for all patients (range, 0.2–99 mo), 14 months for those who were still alive, and 7.6 months for those who had died. Median duration of follow-up from diagnosis of brain metastasis was 13 months for all patients and 17 months for those still alive.

In general, routine follow-up was performed 1 month after SRS. MRI subsequent to this was ordered at the discretion of the multidisciplinary team composed of the neurosurgeon, radiation oncologist, and primary medical oncologist. The median duration of imaging follow-up for all lesions from the date of SRS was 5.7 months (range, 0.2–32.2 mo). Local treatment failure for a lesion was defined as any one of the following comprehensive criteria: 1) 25% radiographic increase in largest tumor diameter, 2) tumor progression of an SRS-treated lesion that required surgery, and 3) SRS-related complications including significant edema with mass effect (e.g., herniation, midline shift) and hemorrhage or necrosis requiring surgery. The occurrence of post-SRS hemorrhage was determined by review of the precontrast T1-weighted MRI scan for the presence of hyperintensity in the lesion that was not present before SRS.

The emphasis of the study was on identifying a size cutoff below which it is safe to observe obscure brain lesions suspected of being metastases, which requires determining the local tumor control of individual SRS-treated lesions. Therefore, we did not define distant brain failure as an end point. To identify a volumetric size cutoff for SRS treatment of small metastases, two distinct statistical techniques were applied. 1) Univariate Cox regression analysis yielded hazard ratios and their significance for tumor volumes ranging from 0.2 to 1.0 cm^3 in 0.1-cm^3 increments and from 1.0 to 4.0 cm^3 in 1.0-cm^3 increments (*Table 3*). With this method of statistical analysis, 0.5 cm^3 (1 cm) represented a cutoff volume that had the greatest hazard ratio of 4.3, which was highly significant ($P = 0.001$) for tumors less than 1 cm (*Table 3*). On the basis of this statistical analysis of the entire volumetric data set, 1 cm (0.5 cm^3) seemed to be the most appropriate cutoff. 2) Regression tree analysis confirmed the use of 0.5 cm^3 as a cutoff. An almost identical cutoff of 0.49 cm^3 was identified as the most significant cutoff volume, with a hazard ratio of 4.19 ($P < 0.001$). All lesions analyzed had been uniformly treated with minimum peripheral doses of between 20 and 24 Gy. Survival and local tumor control were also analyzed according to treatment sequence (WBRT followed by SRS, called "WBRT first"; or SRS followed by WBRT, called "SRS first"). Actuarial local tumor control from the time of SRS was analyzed for all 153 lesions.

Both recursive partitioning analysis (RPA) derived from the Radiation Therapy Oncology Group (RTOG) database (6) and the Score Index for Radiosurgery in Brain Metastases (SIR) classifications described by Weltman et al. (18) (*Table 4*) were used to evaluate their prognostic value as it relates to survival. Actuarial local control of each lesion from the time of the SRS

TABLE 3. Hazard ratios for tumor control failure according to tumor volume[a]

Tumor volume (cm^3)	Hazard ratio (95% CI)	*P* value
≥0.2	7.1 (0.96–52)	0.055
≥0.3	3.1 (1.1–8.9)	0.035
≥0.4	3.9 (1.5–10.2)	0.005
≥0.5[b]	4.3 (1.8–10.3)	0.001
≥0.6	2.7 (1.3–5.8)	0.010
≥0.7	1.8 (0.92–3.6)	0.084
≥0.8	1.7 (0.88–3.4)	0.115
≥0.9	2.5 (1.3–4.9)	0.009
≥1.0	2.0 (0.97–3.9)	0.059
≥2.0	2.8 (1.1–7.2)	0.037
≥3.0	5.2 (1.2–21.9)	0.026
≥4.0	11.1 (1.4–86.6)	0.022

[a] CI, confidence interval.
[b] 1 cm.

TABLE 4. Prognostic variable marks to compose Score Index for Radiosurgery[a]

	SIR score		
	0	1	2
Age (yr)	≥60	51–59	≤50
KPS	≤50	60–70	>70
Systemic disease	PD	PR–SD	CR–NED
Largest lesion (cm^3)	>13	5–13	<5
No. of lesions	>3	2	1

[a] SIR, Score Index for Radiosurgery; KPS, Karnofsky Performance Scale score; PD, progressive disease; PR, partial remission; SD, stable disease; CR, complete clinical remission; NED, no evidence of disease. The SIR index is based on the classification system of Weltman et al. (18).

procedure was determined by Kaplan-Meier analysis. Comparison using the log-rank test was used to assess the equality of survivor functions across groups. χ^2 analysis was used to assess and compare groups with respect to prognostic factors. Both univariate and multivariate analyses using Cox regression analyses were performed for prognostic factors for tumor control and survival by use of Stata 8.0 software (16). The Institutional Review Board at UTMDACC approved the conduct of this study involving retrospective chart review and a waiver of informed consent.

RESULTS

Local Control

The 1- and 2-year actuarial local control rates for all of the lesions, according to the comprehensive criteria defining local treatment failure, were 69 and 46%, respectively, with lesions censored at time of last imaging follow-up. To assess whether observation of tiny, obscure lesions was a viable strategy for lesions suspected to be brain metastases, comparisons were made of the incidence of tumor control for lesions greater than or less than a cutoff volume of 0.5 cm^3. The 1- and 2-year local control rates (56 and 24%, respectively) for lesions greater than 0.5 cm^3 were significantly inferior to the 1- and 2-year control rates for lesions smaller than 0.5 cm^3 (86 and 78%, respectively; $P = 0.0016$) (*Fig. 1*). The 1-year tumor control rate for melanoma brain metastases treated with SRS was lower than for brain metastases from all other primaries, but the difference did not achieve statistical significance (62 versus 72%; $P = 0.11$). The median time to local tumor failure for evaluable tumors was 23.3 months. The 1-year actuarial local control rates by histological type were lung, 84%; melanoma, 63%; renal cell carcinoma, 65%; breast, 75%; and others (colon cancer, sarcoma, and unknown primary), 50%.

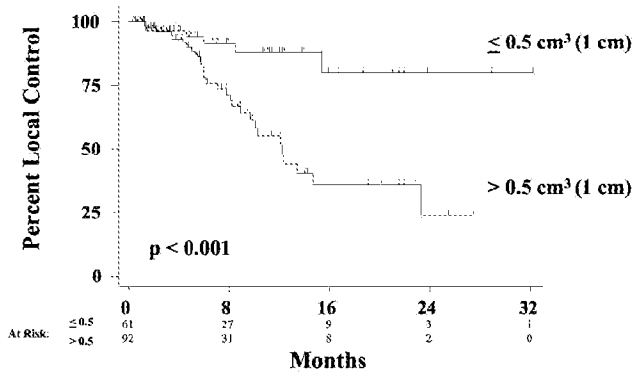

FIGURE 1. *Graph showing actuarial tumor control (size ≤0.5 versus >0.5 cm^3).*

Survival

For the entire study population, the median survival time from the time of SRS was 11.4 months, with 1- and 2-year survival rates of 48 and 19%, and the median survival time from the time of initial diagnosis of brain metastasis was 14.9 months. Median survival from the time of diagnosis of brain metastasis was significantly worse in melanoma patients (12.2 mo) than in nonmelanoma patients (17 mo; $P = 0.0018$). The median survival from time of SRS was also worse for melanoma patients (7.2 mo) than for nonmelanoma patients (12.3 mo; $P = 0.014$). Patients with Karnofsky Performance Scale (KPS) scores of 80 or more fared better than those with KPS scores of less than 80, with median survival times from time of SRS of 12 months compared with 7.6 months, respectively ($P = 0.0391$). Differences in the initial number of lesions treated with SRS (1 versus 2 versus 3 or more) did not affect survival ($P = 0.77$). For patients with a controlled primary tumor, median survival time was significantly longer than for patients whose primary disease was not controlled (12.1 versus 9.3 mo; $P = 0.0264$).

Prognostic Factors and Scoring Systems

Prognostic factors for tumor control with SRS, which included age, KPS score, primary cancer histology, treatment sequencing (WBRT first or SRS first), SIR, dose, tumor volume, cone diameter, and number of lesions, were examined by univariate and multivariate analyses. Cox regression analyses and prognostic factors are listed in *Table 5*. Results showed that tumor volume greater than 0.5 cm^3 (1 cm) and cone diameter greater than 2 cm were significant risk factors for local tumor treatment failure according to univariate analysis. Results of multivariate analysis found that only tumor volume greater than 0.5 cm^3 remained as an independent risk factor for local treatment failure, with a hazard ratio of 3.53 (95% confidence interval, 1.53–8.13) ($P = 0.003$).

For survival, univariate Cox regression analysis found that melanoma histology, a KPS score of 70 or more, uncontrolled primary disease, and the presence of extracranial disease were

TABLE 5. Univariate and multivariate Cox regression analysis of prognostic factors for local tumor control and survival[a]

	Hazard ratio (95% CI)	P value
Tumor control		
Univariate analysis		
Tumor volume >0.5 cm³	3.5 (1.5–8.1)	0.003
Dose >20 Gy	0.29 (0.068–1.2)	0.089
Melanoma	1.8 (0.87–3.8)	0.11
Cone diameter >2 cm	2.8 (1.3–6.3)	0.010
Isodose	0.97 (0.94–1.0)	0.15
Multivariate analysis		
Tumor volume >0.5 cm³	3.5 (1.5–8.1)	0.003
Survival		
Univariate analysis		
Melanoma	1.7 (1.1–2.5)	0.015
KPS ≤70	1.5 (1.0–2.3)	0.041
Primary not controlled	1.6 (1.0–2.3)	0.028
Extracranial disease	1.7 (1.0–2.9)	0.046
Lung metastases	1.4 (0.96–2.1)	0.082
Multivariate analysis		
Melanoma	1.6 (1.1–2.5)	0.018
KPS ≤70	1.5 (1.0–2.2)	0.050
Primary not controlled	1.5 (1.0–2.3)	0.038

[a] KPS, Karnofsky Performance Scale score; CI, confidence interval. Only factors with $P < 0.2$ are listed in the table.

significant risk factors. In contrast, multivariate Cox regression analysis showed that melanoma, a KPS score of 70 or more, and uncontrolled primary disease were significant risk factors for death (*Table 5*). Application of the SIR scoring system to the study populations produced distinct survival curves that indicated statistically significant separation of treatment groups ($P = 0.0162$), with median survivals of 4.7 months for patients with SIR scores of 1 to 3, 10.5 months for patients with SIR scores of 4 to 7, and 12.3 months for those with SIR scores of 8 to 10. By contrast, application of the RPA classification did not produce statistically significant separation of survival curves; median survival time for RPA 1 was 13.1 months; for RPA 2, 10.5 months; and for RPA 3, 6.4 months ($P = 0.64$). The reason for this may be the highly selected study population forming the basis of this study, whereas the RPA classification is derived from the RTOG database, which contains a more general brain metastasis population.

SRS Dose

Higher 1- and 2-year local control rates of 87 and 87% were observed for the 21- to 24-Gy dose group compared with 66 and 36% for the 20-Gy group, respectively, and these differences approached statistical significance ($P = 0.069$). Because tumor size of 0.5 cm^3 or smaller was found to be a significant factor favorably influencing tumor control in this study, the two dose groups were compared with respect to tumor size of 0.5 cm^3 or less versus greater than 0.5 cm^3 by χ^2 analysis. There was a statistically significantly higher percentage of tumors of less than 0.5 cm^3 among patients in the 21- to 24-Gy group compared with the 20-Gy group (71 versus 35%; $P = 0.001$). This fact probably influenced the tumor control results for the 21- to 24-Gy group favorably. Therefore, it is unclear whether the trend toward improved tumor control with higher doses is related to dose or just a result of imbalances in tumor size at baseline.

Sequencing of WBRT and SRS

To determine the optimal sequence of SRS and WBRT, patients were divided into two categories, either SRS first or WBRT first (*Table 2*). Analysis on the basis of treatment sequence revealed no statistically significant difference between SRS first and WBRT first with respect to either local tumor control ($P = 0.97$) or survival ($P = 0.94$) (*Fig. 2*).

Failure-associated Complications

Complications arising in post-SRS-treatment brain metastases were scored as treatment failures. The most frequent failure-associated complication for any histological type appreciable on either MRI or pathology was significant edema with mass effect, which occurred at a rate of 14%, of which 64% required surgery. Pathologically proven necrosis was rare and was observed in 1.3% of SRS-treated lesions. The average rate of hemorrhage among lesions for which therapy failed was 4.6%, and the rate of hemorrhage was increased among melanoma (11%) and sarcoma (20%) lesions, although the sarcoma numbers (2 of 5 lesions) are small. The median time to hemorrhage for all lesions that bled after SRS was short, at 1.3 months (range, 0.7–14.7 mo). For those lesions that developed hemorrhage, surgical management with resection was required for 71% of the patients.

Within histological categories, the rates of resection by lesion after SRS were higher for melanomas (14%), renal cell carcinoma (16%), and sarcomas (40%) than for non-small-cell

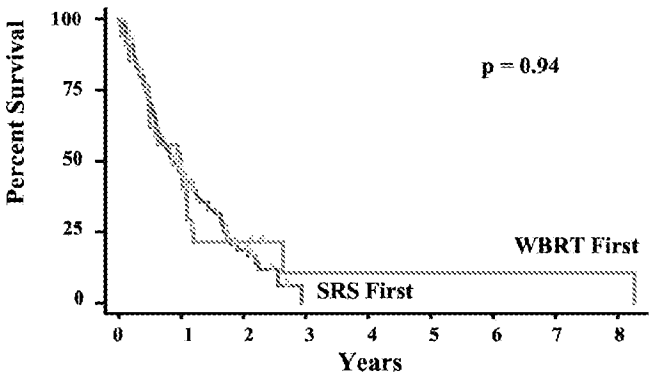

FIGURE 2. *Graph showing actuarial survival as determined on the basis of therapy sequence: WBRT first versus SRS first.*

carcinoma of the lung (7.7%). Of the 19 patients requiring post-SRS resection, 74% (14 of 19 patients) had so-called "radioresistant" tumors, including melanomas, renal cell carcinomas, and sarcomas. The characteristics of lesions requiring surgical salvage are listed in *Table 6*. For those lesions surgically resected, the median time to resection from time of SRS was 8 months (range, 1–23 mo), whereas median survival time from surgical salvage was 10 months (range, 5–30 mo).

Illustrative Case

This 46-year-old man had a history of malignant melanoma of the left thigh. On a routine brain MRI follow-up study, he was found to have a new tiny nodule of enhancement measuring 3 × 3 × 3 mm in the right anterior internal capsule just adjacent to the right caudate head that had not been present on an MRI scan obtained 4 years earlier. This lesion, initially thought to possibly represent a new brain metastasis, was followed up during a 21-month period, with seven subsequent MRI studies (*Fig. 3*). The lesion size and appearance did not change on any subsequent MRI examination. On the basis of the stability of the lesion, it was thought that the nodule represented a vascular finding rather than a brain metastasis.

DISCUSSION

A size cutoff for safe observation of an obscure brain lesion suspected of being a brain metastasis has not been defined previously in the literature. The goal of this study was to identify a tumor size below which it is safe to observe ambiguous brain metastases. In the subcentimeter range, opposing forces exist in that aggressive pursuit of metastatic lesions is necessary to maximize chances for tumor control, whereas inadvertent treatment of a nonmetastasis or imaging artifact is

TABLE 6. Characteristics of stereotactic radiosurgery-treated metastatic lesions requiring surgical salvage[a]

Lesion	Location	Primary	Interval from SRS to failure (mo)	Size (cm^3)	Reason for surgery	Survival from surgery (mo)	Pathology
1	Cerebellum	Ad	20	0.95	RP	15	Mix
2	Periventricular	L	6	1.00	E	9	A
3	Temporal	R	9	1.10	RN, E, ME	10[b]	N
4	Occipital	L	8	0.57	E, SFH, RP	9	A
5	Occipital	R	10	3.19	E, H	6	R
6	Occipital	R	1.5	0.56	E	21	R
7	Frontal	R	6	0.71	E, H, RP	8	N
8	Insula	M	15	1.44	H, E	5	M
9	Frontal	Cd	5	4.29	RP, E, W	25	A
10	Frontal	L	23	1.44	W, E, RN	30[b]	Mix
11	Parietal	M	10	1.84	E, RN	10	M
12	Temporal	M	13	0.88	RP	17	Mix
13	Cerebellum	M	8	0.95	GI, RP	9	M
14	Insula	M	6	0.63	H, RP	14	M
15	Parietal	Sar	8	1.20	RP, E, ME, H	3	Sar
16	Frontal	R	1	0.21	RP, E, HP, S	20	R
17	Periventricular	R	10	1.20	E, HP, RP	10[b]	R
18	Frontal	Sar	4	0.78	RP, S	8[b]	Sar
19	Insular	M	3	0.50	H, RP, E	4	M

[a] SRS, stereotactic radiosurgery; Ad, adenoid cystic carcinoma; L, lung adenocarcinoma; R, renal cell carcinoma; M, melanoma; Cd, collecting duct adenocarcinoma; Sar, sarcoma; RP, radiographic progression; E, significant edema; RN, radiographic necrosis; ME, mass effect; SFH, subfalcine herniation; H, hemorrhage; W, symptomatic weakness; GI, gait instability; HP, hemiplegia; S, seizures; Mix, mixed tumor and necrosis; A, adenocarcinoma; N, pathology-proven pure necrosis; [b], alive at time of analysis.

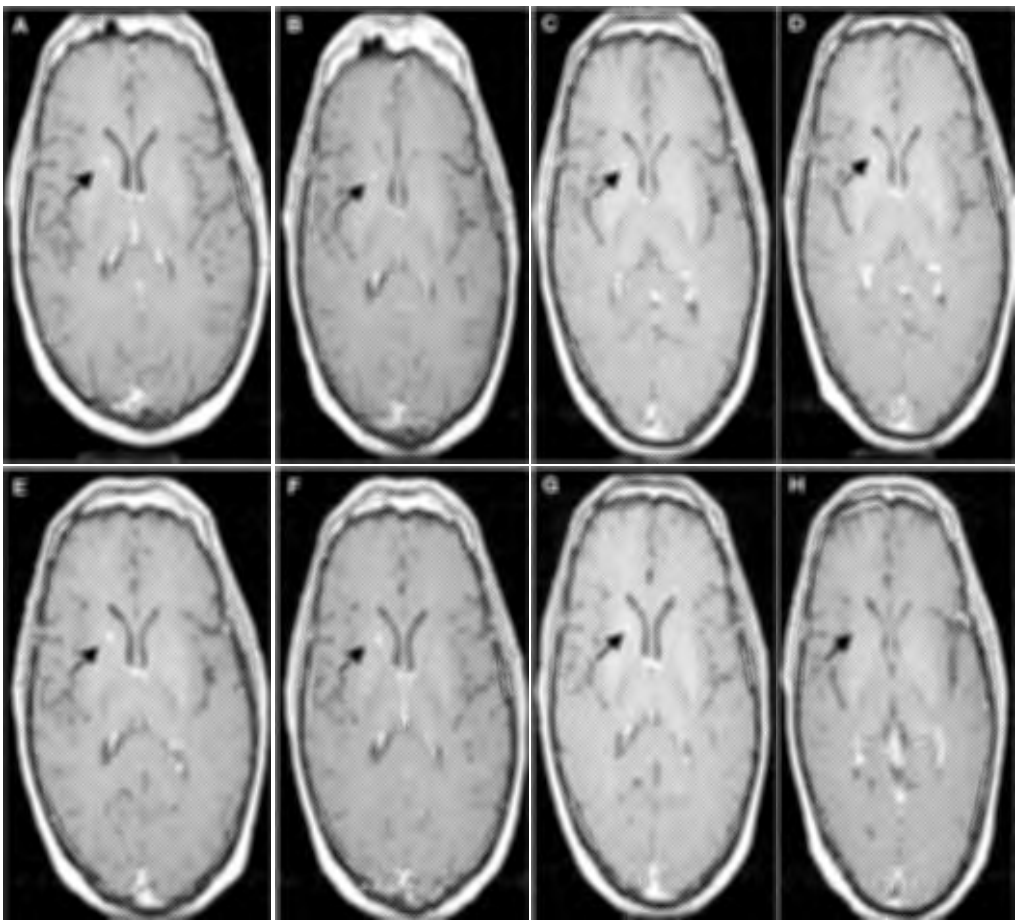

FIGURE 3. *MRI scans. The tiny lesion (arrows) was initially suspected to be a brain metastasis, but it remained stable during a 21-month period in a patient with melanoma.* A, *baseline;* B, *1 mo;* C, *3 mo;* D, *5 mo;* E, *8 mo;* F, *11 mo;* G, *14 mo;* H, *21 mo.*

to be avoided. A size cutoff of 1 cm is intended to allow observation of an ambiguous lesion without significantly compromising tumor control if it is a true metastasis. The possibility of inadvertently treating a vascular lesion with SRS is highlighted in the illustrative case of a patient with melanoma presenting with a new 3-mm enhancing brain lesion initially suspected of being a metastasis (*Fig. 3*).

At UTMDACC, our policy, when feasible, has been to closely observe ambiguous lesions with MRI until subsequent imaging convincingly demonstrates the presence of metastasis. A 1-cm cutoff diameter permitting ambiguous lesions to be safely observed and easily assessed is proposed. It should be emphasized that observation should be reserved only for the special circumstance of the equivocal brain metastasis. This is especially relevant for cancer patients who are in the process of being diagnosed with an asymptomatic solitary metastasis. For the vast majority of cases that present with convincing brain metastasis, we advocate aggressive treatment as early as possible to maximize the chances for tumor control.

In previous studies, confounding effects of dose were encountered when trying to analyze the effect of size on tumor control, because dose and size were always interrelated, with dose serving as a dependent variable. According to the RTOG, higher SRS doses are typically prescribed for smaller lesions because of higher maximum tolerated doses (13). The University of California at San Francisco group reported that they were unable to demonstrate an important effect of volume based on multivariate analysis because dose and volume were not independent in their series (15). In a Harvard study, univariate analysis indicated that tumor volume greater than 3 cm^3 (versus those $\leq$3 cm^3) was significantly associated with local control, but multivariate analysis did not show this result (10), presumably for the same reason. In our study, emphasizing the influence of size on local tumor control, an effort was made to minimize the confounding effect of dose by defining a relatively homogeneous group of lesions in which the majority of lesions (132 of 153 lesions) received 20 Gy and the remainder (21 of 153 lesions) received 21 to 24 Gy. Evaluable lesions were limited to 5 cm^3 or less.

This study has identified a size cutoff for small brain metastases using two different statistical techniques. The data strongly suggest that allowing a tumor to grow beyond the cutoff of 1 cm (0.5 cm^3) will lower the absolute tumor control by up to 30%. Conversely, the data suggest that treating a tumor smaller than 0.5 cm^3 will result in tumor control rates that compare favorably with the 2-year local control rates reported from the Cleveland Clinic of 52 to 80%, depending on whether WBRT was given. It appears that obscure brain lesions that are suspected metastases may be safely observed up to 1 cm (0.5 cm^3).

In our retrospective study, the 1- and 2-year actuarial local control rates for all of the lesions were 69 and 46%, respectively. These results are somewhat lower than what has been generally reported in the literature. The reason may be the conservative approach to our analysis, which includes a

stricter definition of local treatment failure. Other studies have reported local control rates in terms of freedom from progression as measured by imaging only. They do not necessarily include treatment failures or complications requiring surgery (n = 19 lesions in the present study), which we scored as treatment failures. Local control is also reported actuarially in our study, unlike the crude local control rates used in some series. Crude rates may be artificially inflated, especially if there is a high risk of early death, as is true for patients with brain metastases (15). Censorship at time of death rather than at time of last imaging follow-up may also artificially increase tumor control rates because of the possibility of incorrectly assuming that a tumor is controlled beyond the last available imaging follow-up. Such an assumption in our series would significantly alter our results, because our median duration of imaging follow-up was 5.7 months, 4.3 months shorter than the median follow-up of 10 months for all patients. Therefore, in our analysis, it was decided that censorship for local control was most appropriately performed at the time of last imaging follow-up and not at the time of death.

The optimal sequencing of SRS and WBRT is not well defined for patients with one to three brain metastases. Lesions were categorized according to whether they underwent WBRT first or SRS first to evaluate the effect of treatment sequence on tumor control. The 1-year local tumor control rate for patients receiving WBRT first was 77%, which was not significantly different from the SRS-first control rate of 67% ($P = 0.996$). Likewise, giving WBRT first or SRS first did not significantly affect duration of survival ($P = 0.9377$). Thus, our data indicate that the sequence of WBRT and SRS did not have an effect on local tumor control or overall survival rates. This finding is consistent with that of the University of California at San Francisco study, in which no significant differences were noted in local freedom from progression among lesions undergoing SRS for recurrence after previous radiotherapy, SRS alone as initial treatment, or SRS boost (15).

The median survival time of 11.4 months in our study was comparable to the more favorable results of treatment with SRS for brain metastases reported in the literature from several institutions, including the Cleveland Clinic (10.5 mo) (5), Harvard (10.5 mo) (1), a multi-institutional study (11 mo) (2), and the University of California at San Francisco (11.3 mo) (15). Two prognostic survival classifications for brain metastases, RPA used by the RTOG and SIR used by Weltman et al. (18), were applied to the data. The SIR scheme was able to separate the patient groups into prognostically distinct survival curves ($P = 0.016$), whereas the RPA scheme was not ($P = 0.64$). A possible reason for the inability of RPA to effectively separate our data into significantly distinct survival groups may be that the RPA scheme was derived from the RTOG database, which contains a much more generic brain metastasis population treated with WBRT only. It may lose its prognostic value when applied to a highly selected patient population such as that used in this study. For instance, the most favorable RPA Class 1 for RTOG is associated with a median survival of 7.1 months, but the median survival for the highly selected patients in our study is 11.4 months. The SIR, conversely, takes into account additional information, including largest tumor volume and number of lesions, and is derived from an SRS data set (*Table 4*). Interestingly, a KPS score of 70 or less and uncontrolled primary status were both statistically significant prognostic factors for survival, suggesting that systemic disease remains the overriding factor in determining patient survival.

In terms of histology, melanoma patients as a group fared worse than patients in all other histological groups examined. The median survival time for melanoma patients was 7.2 months, versus 12.3 months for all others ($P = 0.014$). The 1-year actuarial tumor control rate was lower, but not significantly so, for melanoma brain metastases compared with all others (62 versus 72%; $P = 0.107$). These results are consistent with those of six other melanoma brain metastasis series, which had survival rates ranging from 7 to 9.7 months, whereas crude local control rates ranged from 57 to 100% (3, 4, 7, 9, 12, 19).

The maximum tolerated SRS dose to be applied to lesions 2 cm or smaller was defined in the final report of the RTOG 90-05 study (13), which stated that the maximum tolerated dose of single-fraction radiosurgery was 24 Gy for lesions 2 cm or smaller. However, investigators from the University of Kentucky recently concluded, in abstract form, that 20 Gy is the optimal SRS dose for brain metastases 2 cm or smaller (14). They found no obvious improvement in local control and the appearance of higher RTOG Grade IV neurotoxicity (5.9 versus 1.9%; $P = 0.078$) with doses greater than 20 Gy. The rate of pathology-proven pure necrosis in our series was 1.3%. Our dose prescription at the UTMDACC was consistent with the findings reported in the University of Kentucky abstract in that a dose of 20 Gy was prescribed for the majority of tumors 2 cm or smaller in our series. A dose of 20 Gy was administered to 86% of lesions, and a dose of 21 to 24 Gy was delivered to 14%. A comparison of local control rates for lesions treated with 20 Gy versus those treated with 21 to 24 Gy showed a trend toward improved local control at doses of 21 to 24 Gy. However, this analysis is confounded by selection bias for small tumor size, given that there was a significantly greater percentage of tumors of less than 0.5 cm^3 in the 21- to 24-Gy group ($P = 0.001$; χ^2 analysis). Because of the favorable effect on tumor control conferred by tumor size less than 0.5 cm^3, as identified in this study, no conclusion can be drawn from these data regarding the use of doses greater than 20 Gy in our series.

CONCLUSION

A convincing brain metastasis measuring less than 1 cm should be pursued aggressively. If the suspected brain metastasis is ambiguous, observation is proposed up to a diameter of 1 cm. This is the first study in the literature to identify a 1-cm cutoff for radiosurgical control of small brain metastases, and it will require validation by additional studies.

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COMMENTS

The authors have reviewed a series of 135 patients with brain metastases who underwent stereotactic radiosurgery (SRS) during a 10-year period. The aim of the study was to determine whether small lesions suspected of being brain metastases could be observed without treatment. The authors conclude that in those patients with lesions that display characteristics typical of metastases, aggressive treatment should be sought. For lesions that may be equivocal on the basis of imaging studies and that are less than 1 cm in diameter, serial observation is reasonable. If such a lesion were to grow, then the diagnosis of metastasis should be considered.

The authors also have found on the basis of their data that patients with controlled primary disease fared better and that patients with melanomas fared worse than other patients. Other groups have made this discovery. Interestingly, median survival after SRS was 11.4 months in this series, which is much better than the 7-month survival after SRS that they identified in their previous comparison of SRS with resection.

Patients increasingly are being identified with small brain metastases on the basis of staging studies. When the imaging result is typical for metastasis at my institution, my colleagues and I advocate SRS. The smallest lesions demonstrate the best response. It is in the treatment of such small lesions that clinicians have the greatest opportunity to help patients avoid the neurological symptoms and deficits that occur with larger tumors. SRS may be the most effective way to maintain patients' quality of life.

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Pittsburgh, Pennsylvania

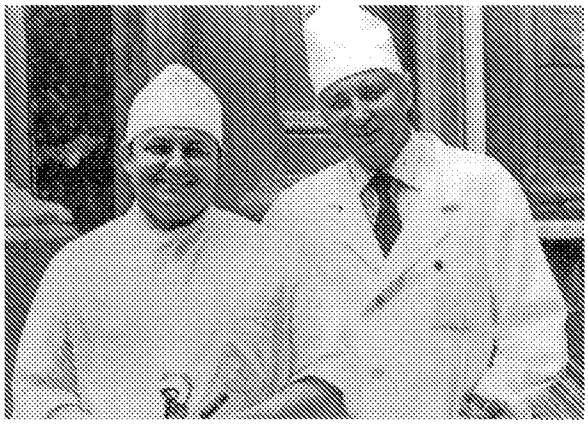
Retrospective studies provide potentially useful preliminary information the detail of which is generally difficult to sort out, but by drawing our attention in general, these investigations may lead the way to higher-quality work. The authors have retrospectively evaluated 135 patients with brain metastases after the patients underwent either SRS alone or a combination of SRS

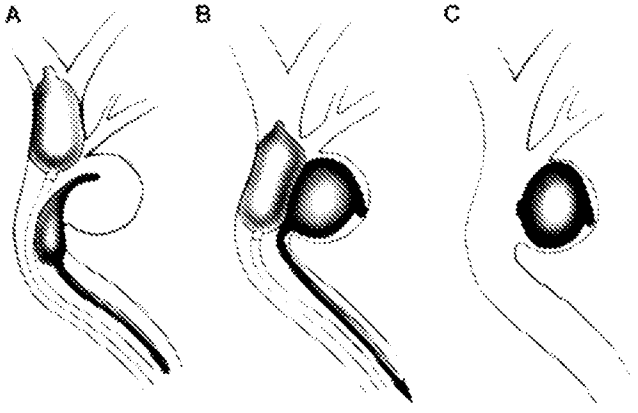
and whole-brain radiation therapy. One- and two-year actuarial local control rates for the entire cohort were 69 and 46%, and local control rates for lesions smaller than 0.5 cm^3 were superior to those for patients with lesions larger than 0.5 cm^3. Only two stereotactic radiation dosages were administered, which limits the confounding effects of this treatment variable (as the authors indicate, other confounding variables are present in this investigation), and 71% of patients were managed with SRS only. The authors conclude that lesions smaller than 0.5 cm^3 can be observed and that lesions that are at least 0.5 cm^3 are best treated. Although this conclusion seems reasonable and one that the tumor board at my institution would support, one might ask whether all small brain metastases require treatment simply because they exist. According to *Table 6*, neurological decline was observed in only 4 of 17 patients, and although the rate of radiation-related complications or failure was only 14 and 22% at 1- and 2-year follow-up for patients with small lesions, one still might wonder whether treatment is necessary for patients with asymptomatic lesions, even those with radiographic progression. The authors note the negative impact of advanced systemic disease status on survival, the lack of positive correlation between survival and lesion volume, and the lengthy tails on the survival curves. Once again, it is clear that although some of these patients do well long after being diagnosed with brain metastases, systemic disease needs to remain the primary factor guiding treatment decisions. Therefore, one might readily argue for earlier treatment of larger lesions in those patients with stable systemic disease and for avoiding treatment altogether in patients with progressive systemic disease.

Jack P. Rock
Detroit, Michigan

In this study, Chang et al. have culled a large retrospective database of SRS cases at the University of Texas M. D. Anderson Cancer Center. They state that the intent of the article is to determine whether small, ambiguous, asymptomatic lesions found on magnetic resonance imaging scans can safely be observed. The authors proceed to demonstrate that metastases smaller than 0.5 cm^3 (1 cm) are controlled better with SRS than are metastases that are 1 to 2 cm^3. The authors use this data to conclude that small metastases can be observed until they reach 1 cm^3, and then they should be treated before they become larger than this "magic" number. There are several problems with this logic. First, if smaller lesions are easier to control than larger lesions, it makes sense to treat lesions when they are smaller and not to observe them. Because the 0.5 cm^3 cutoff is somewhat arbitrary, it also seems apparent that smaller lesions (i.e., less than 0.4 cm^3) are controlled better than lesions that are larger than 0.4 cm^3, and so forth. On the basis of the authors' conclusions, one should observe a lesion when it is 0.4 cm^3 and then perform repeat magnetic resonance imaging at a later date. If the lesion is 0.6 cm^3, the treating physician has suddenly lost a window of opportunity for better tumor control. This makes no sense. If the authors wanted to draw any sort of conclusion about which lesions can be observed, they should have included a treatment arm to study lesions that were observed. All lesions in this study were treated; therefore, it is impossible to draw any conclusions about observation.

Theodore H. Schwartz
Philip H. Gutin
New York, New York





Left, *Fedor Serbinenko (right) with friend and pupil Victor Shcheglov in 1979.* Right, *aneurysm balloon embolization technique inspired by Serbinenko and used by Shcheglov. Two balloon catheters are advanced into the internal cartoid artery. A, the nondetachable balloon catheter is advanced beyond the cerebral aneurysm and acts as a "shepherd balloon" that guides the detachable balloon into the aneurysm sac. The detachable balloon has a heavy metal tip, which aids its maneuverability. B, once the detachable balloon is filled with silicone polymer (thus occluding flow into the aneurysm), the shepherd balloon can brace it in place and facilitate separation from its delivery catheter. The shepherd balloon may also be used to occlude the parent vessel if the aneurysm ruptures inadvertently during these manipulations. C, final endosaccular deployment of the inflated balloon (both pictures from, Teitelbaum GP, Larsen DW, Zelman V, Lysachev AG, Likhterman LB: A tribute to Dr. Fedor A. Serbinenko, founder of endovascular neurosurgery. **Neurosurgery** 46:462–470, 2000).*

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Phase I and Pharmacokinetic Study of the Camptothecin Derivative Irinotecan, Administered on a Weekly Schedule in Cancer Patients[1]

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ABSTRACT

Irinotecan (CPT-11) is a novel water-soluble, semisynthetic derivative of camptothecin, with inhibitory effects on mammalian DNA topoisomerase I, high cytotoxic activity *in vitro* and anticancer activity in animal models. Fifty-nine patients, with cancer refractory to conventional therapy, were entered in this phase I study, using a weekly schedule administration. A total of 304 weekly doses were administered at dose levels ranging from 50 to 145 mg/m^2 (30–90 min i.v. infusion). Leukoneutropenia and diarrhea were the dose-limiting toxicities and appeared to be dose related, reversible and noncumulative. However, interpatient variability of toxic effects was substantial. Prolongation of the infusion time from 30 min to 90 min appeared to decrease the diarrhea. Other toxicities included moderate emesis, asthenia, alopecia, abdominal pain, and anemia. CPT-11 plasma disposition was bi- or triphasic with a terminal half-life of 9.3 h. CPT-11 area under the plasma concentration *versus* time curves increased linearly with dose ($r = 0.87$, $P < 0.01$). The active metabolite area under the plasma concentration *versus* time curve correlated significantly with that of CPT-11, but not with that of CPT-11 dose. Both CPT-11 and 7-ethyl-10-hydroxycamptothecin areas under the plasma concentration *versus* time curve correlated significantly with leukoneutropenia and diarrhea. One partial and 4 minor responses were observed at dose levels of 130 and 145 mg/m^2. Using this weekly schedule, recommended doses for phase II studies are 100 mg/m^2 in high risk patients and 115 mg/m^2 in others.

INTRODUCTION

CPT[4] is a cytotoxic plant alkaloid, isolated from the Chinese tree *Camptotheca acuminata* (Nyssaceae) (1). In spite of a strong antitumor activity *in vitro* (2, 3) and in animal solid tumor models (4), this compound has not produced favorable results in clinical investigations, because of its low therapeutic index and severe toxicity to the intestinal mucosae, bladder, and hematological system (5–10). However, renewed interest in CPT, as a potential clinical antitumor drug, has come from the elucidation of its presumed mechanism of action against DNA topoisomerase I, and the hemisynthesis of derivatives with higher activity and less toxicity.

Early observations demonstrated that treatment of mammalian cells with CPT results in a reversible fragmentation of DNA (11–13), a potent inhibition of DNA and RNA synthesis (14, 15), and a subsequent impairment of cell division. Recently, mammalian DNA topoisomerase I has been suggested as one intracellular target of CPT (16, 17). DNA topoisomerases are enzymes that regulate the superhelical density of DNA by transiently nicking either one (type I) or two (type II) strands of the DNA helix. They are supposed to be involved in many aspects of DNA metabolism, including replication, transcription, recombination, and chromosome segregation (18, 19). CPT inhibits type I topoisomerase through the formation of stable topoisomerase I-DNA cleavable complexes (20–22). The DNA single-strand breaks in S phase may interfere or block the replication fork, resulting in cell death (23, 24).

Various derivatives of CPT have been semisynthesized to improve its water solubility, decrease its toxicity, and increase its antitumoral activity without opening the lactone ring needed for activity (25–27). Among the water-soluble CPT analogues, CPT-11 (Fig. 1) emerged as a potent anticancer drug in a broad spectrum of experimental tumor models (28–30).

A prior Japanese phase I study, using a single i.v. dose administration of CPT-11, established the MTD at 250 mg/m^2 and myelosuppression as the dose-limiting toxicity (31). Early phase II trials started in Japan, with different schedules (mainly using a weekly dose of 100–145 mg/m^2), have shown encouraging response rates in patients with untreated non-small cell lung cancer (32), refractory leukemia and lymphoma (33), small cell lung cancer (34), colon cancer, and gynecological cancer (35). In 1990, phase I studies have been initiated in France, exploring 3 different schedules in an attempt to determine the optimal administration scheme for CPT-11 (single dose weekly, single dose every 3 weeks, and daily dose for 3 days every 3 weeks) and to define possible schedule dependency of the side effects.

We report here the results of the phase I trial using a weekly CPT-11 administration as a 30–90 min i.v. infusion. The aims of this study were to determine the MTD, to identify and quantify the adverse effects, to assess the pharmacokinetic features of CPT-11 and its main active metabolite SN-38 (36) (Fig. 1), and to obtain preliminary evidence on CPT-11 antitumoral activity.

PATIENTS AND METHODS

Patients

Between July 1990 and November 1991, 59 adult patients, admitted at Hospital Saint Louis (Paris) or at Centre Claudius Régaud (Toulouse), were entered in this study according to the following criteria (*a*) histologically confirmed malignant solid tumor, refractory to standard therapy, or for which no established therapy exists; (*b*) no chemotherapy or radiotherapy 4 weeks before entry (6 weeks for nitrosoureas and mitomycin C); (*c*) age between 18 and 75 years; (*d*) performance status of 0–2, according to the Eastern Cooperative Oncology Group scale; (*e*) life expectancy of at least 3 months; (*f*) adequate hematological parameters (WBC $\geq$4000/μl, platelet count $\geq$100,000/μl, and hemoglobin $\geq$10 g/dl), hepatic function (bilirubin and transaminase level $\leq$2-fold upper limit of normal values), and renal function (creatinine $\leq$120 μmol/liter); (*g*) no evidence of cardiac dysfunction; (*h*) no previous anaphylactic reactions; (*i*) informed consent was obtained for all patients, according to institutional guidelines.

Prior to the first CPT-11 course, each patient had a medical history, physical examination, complete blood cell count, serum chemistry for electrolytes, renal and hepatic functions assessment, urinalysis, and chest X-ray. The complete

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[4] The abbreviations used are: CPT, camptothecin; CPT-11, irinotecan, or 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin; SN-38, 7-ethyl-10-hydroxycamptothecin; MTD, maximal tolerated dose; AUC, area under the plasma concentration *versus* time curve; C_{max}, maximum concentration; Vd_{SS}, volume of distribution at steady state; CL, total body clearance.

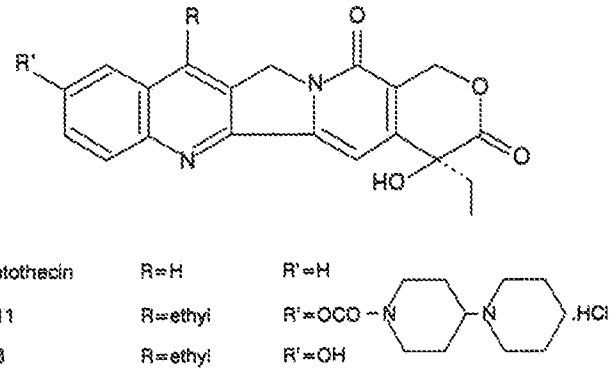

Fig. 1. Chemical structures of camptothecin, the analogue CPT-11, and its active metabolite SN-38.

blood cell counts were repeated at least twice weekly and other biological tests were performed once a week.

The toxic effects and tumor responses were classified according to the WHO criteria (37). Patients who received at least three weekly doses were considered evaluable for response.

Drug Administration

CPT-11 was prepared by Yakult Honsha Co., Ltd (Tokyo, Japan), and supplied by Laboratoire Roger-Bellon (Rhône-Poulenc Rorer, Antony, France) as a solution ready for clinical use, in 2- or 5-ml vials, containing 40 or 100 mg of the drug, respectively. The required dose was further diluted in 250 ml of 0.9% sodium chloride solution and administered as a 30-min i.v. infusion every week. In 21 patients, the infusion time was prolonged to 90 min in an attempt to alleviate acute gastrointestinal toxicities.

Dose Escalation Procedure

Based upon already reported phase I and II tolerance (31–35) the starting dose of CPT-11 was 50 mg/m^2 weekly for 3 consecutive weeks, followed by a 2-week rest period (one-fourth of the recommended dose in a previous phase I study, using a single i.v. dose every 4 weeks) (31). The doses were escalated to 66, 75, 85, 98, 115, 130, and 145 mg/m^2, in successive groups of patients. A minimum of three patients were studied at each dose level, with an accrual of at least three other patients, when a grade 3 toxicity occurred. No intrapatient dose escalation was allowed above the dose level of 100 mg/m^2. We considered that the MTD was reached when more than 50% of patients experienced grade 3–4 toxicity at a dose level affecting either one or more organs (with the exception of emesis and alopecia).

Pharmacokinetics

Chemicals. Pure standards of CPT-11, SN-38, and CPT were synthesized and kindly provided by Yakult Honsha Co., Ltd. (Tokyo, Japan). Solvents and reagents were of the highest purity available and were obtained from Farmitalia Carlo Erba (Milan, Italy).

Plasma and Urine Collection for Pharmacokinetics. Heparinized blood samples (2 ml) were collected immediately predose (time 0), and at the following times thereafter: 10, 20, and 30 min during the 30 min i.v. infusion; after the infusion at, 5, 10, 15, 30, 45, 60 min, 2, 4, 8, 12, and 24 h postinfusion. In addition, 15 patients in the 100–130-mg/m^2 dose range were sampled between 24 and 40 h, to determine more accurately the terminal half-life. Blood was immediately centrifuged at 2000 × *g* for 15 min, and the plasma was transferred to a 1.5-ml polypropylene tube and stored at −20°C until analysis. Urine was collected as 6-h fractions, the volume was measured, and an aliquot of 10 ml was stored at −20°C until analysis.

HPLC Determination of CPT-11 and SN-38 Levels. CPT-11 and SN-38 were assayed by reversed-phase high-performance liquid chromatography with fluorescence detection using a procedure that allowed the simultaneous determination of both compounds in the same run (38). Briefly, after addition of CPT as internal standard, plasma samples (100 μl) were extracted using a solid-phase (C_{18}) extraction step. The extracts were then chromatographed on a C_{18} reversed-phase analytical column using a mobile phase (1 ml/min) composed of 34% acetonitrile and 66% potassium dihydrogen phosphate (0.1 M) containing 3 mM sodium heptanesulfonic acid (pH 4). The fluorescence detector wavelengths were set at 380 nm (excitation) and 500 nm (emission). The calibration curves were linear over a wide range of concentrations (1 ng/ml to 10 μg/ml), and the lower limit of determination was 1 ng/ml for both CPT-11 and SN-38. The concentrations of CPT-11 and SN-38 were determined from peak area ratios of either compound to the internal standard (CPT), by reference to a calibration curve run daily.

Pharmacokinetic Parameter Determination. Both model-independent and model-dependent analyses were performed. Model-independent parameters included (39): the actual concentration at the end of i.v. infusion (C_{max}); the total AUC calculated by the trapezoidal method to infinity; the mean residence time which corresponds to the time for 63% of the drug to be eliminated; the volume of distribution at steady state (Vd_{ss}) calculated according to the statistical moment theory; and the total body clearance calculated as the dose/AUC. For model-dependent analysis, CPT-11 plasma concentrations were fitted to a two- or a three-compartment model with constant i.v. infusion, using a nonlinear regression program (PCNONLIN; Statistical Consultants, Inc., Lexington, KY). For the metabolite SN-38, the following parameters were determined: the maximum concentration achieved (C_{max}); the time of peak plasma level; the AUC calculated as above; and the terminal apparent half-life.

Statistical Analysis

Student's *t* test for paired data was applied to assess the difference between weeks for CL and AUC. To evaluate the significance between CPT-11 or SN-38 AUCs and clinical toxicities, Student's *t* test for the correlation coefficient *r* obtained by linear regression analysis was applied. The level accepted as significant was $P < 0.05$. The results are expressed as mean ± SEM.

RESULTS

Patients

The characteristics of the 59 patients enrolled in this phase I study are shown in Table 1. The median age was 54 years. The median

Table 1 *Patient characteristics (N = 59)*

Age in yr (median (range))	54 (24–75)
Sex	
Male	29
Female	30
ECOG[a] performance status	
0	19
1	26
2	14
Tumor type	
Colorectal	15
Soft tissue sarcoma	7
Unknown primary	5
Hepatocarcinoma	4
Ovary	4
Breast	3
Lung (NSCLC)	3
Esophagus	3
Pancreas	3
Cervix	2
Stomach	2
Head and neck	2
Kidney	2
Melanoma	2
Cholangiocarcinoma	1
Prostate	1
Prior treatment	
Chemotherapy	38
Chemoradiotherapy	17
Immunotherapy	1
Radiotherapy	1
Radioembolization	1
None	1

[a] ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung carcinoma.

performance status was 1. Only one patient had not received prior therapy. A total of 304 weekly doses were given at dose levels ranging from 50 to 145 mg/m^2. The number of patients entered at each dose level and the number of courses administered are presented in Table 2. Above the dose level of 98 mg/m^2, the CPT-11 infusion time was lengthened up to 90 min for 21 patients, in an attempt to alleviate acute side effects thus accounting for the size of this study.

Side Effects

Hematological Toxicity. In this phase I study, leukoneutropenia and gastrointestinal toxicity (see below), were the main side effects (Table 3). A wide interpatient variation in the degree of leukopenia was observed at each dose level, but a trend toward increased severity with highest dose levels was noted. However, grade 4 neutropenia occurred only in three patients treated at the two highest dose levels. The nadir count for granulocytes occurred on days 21–25, with a median recovery time of 5 days. Only one life-threatening septicemia was observed and no patient died of sepsis-related complication. Mild to moderate hemoglobin decrease was observed in 64% of patients and its association with highest dose levels suggested a dose-effect relationship. Thrombocytopenia (Table 6) can be considered a rare event, insofar as only three grade 1 and two grade 3 toxicities were observed. No clear-cut difference was observed between 30- and 90-min infusion times for hematological toxicities (data not shown).

Nonhematological Toxicities. Diarrhea was the dose-limiting effect (Table 4). Although its severity and duration seemed to be dose related, the interpatient susceptibility was substantial. For 18 of 36 (50%) patients receiving a dose superior or equal to 115 mg/m^2, a grade 3–4 diarrhea was experienced [*versus* 3 of 23 (13%) for patients treated at lower doses], with a duration superior to 4 days in 23 of 36 (64%) patients [*versus* 5 of 23 (22%) patients treated at lower doses]. Diarrhea was more frequent and more pronounced after the second and the third weekly doses of CPT-11. However, the incidence did not correlate with the total amount of CPT-11 administered. Transient grade 4 diarrhea was observed in two patients at the 145-mg/m^2 dose level after two weekly infusions, and the treatment was discontinued. In one patient, this toxicity was associated with a grade 4 neutropenia. In an attempt to prevent or reduce diarrhea, various compounds including loperamide hydrochloride, diphenoxylate, atropine sulfate, dismectide, codeine phosphate, or a somatostatin analogue (Octreotide) were used as curative or prophylactic treatments. None of these drugs displayed a clear-cut therapeutic value. However, high dose loperamide which was efficacious in another phase I study (40) was not used in this one. The incidence and severity of diarrhea were not related to tumor types. However, for CPT-11 dose levels of 115 and 130 mg/m^2, diarrhea appeared to be influenced by the number of prior chemotherapeutic treatments, inasmuch as 6 of 14 patients

Table 2 *Dose escalation*

CPT-11 (mg/m2)	No. of patients	No. of infusions
50	3	17
66	3	12
75	4	15
85	7	33
98	6	51
115	12	71
130	17	66
145	7	39
Total	59	304

Table 3 *Leukopenia and neutropenia (maximal grade/patients)*

Dose (mg/m^2)	Patients	Leukopenia					Neutropenia				
		0	1	2	3	4	0	1	2	3	4
50	3	2	1				2	1			
66	3	2		1			2		1		
75	4	1	3				4				
85	7	1	2	1	3		2	1	1	3	
98	6	3	1	1	1		5			1	
115	12	1	2	5	4		4	1	5	2	
130	17	7	3	4	2	1	9	2	2	2	2
145	7	0	1	2	3	1	1	2	3		1
Total	59 (100)[a]	17 (29)	13 (22)	14 (24)	13 (22)	2 (3)	29 (49)	7 (12)	12 (20)	8 (14)	3 (5)

[a] Number in parentheses, percentage.

Table 4 *Intestinal toxicity (diarrhea)*

Five of 23 patients receiving doses between 50 and 98 mg/m^2 had prolonged diarrhea (>4 days) as compared to 23 of 36 patients receiving dose between 115 and 145 mg/m^2.

Dose (mg/m^2)	Patients	Grade						Duration (days)		
		0	1	2	3	4	% with 3–4	2–4	>4	Hospitalization
50	3	3								
66	3	2	1					1		
75	4		2	1	1		25	2	2 (50)[a]	
85	7	2	1	3	1		14	3	2 (40)	
98	6	1	3	1	1		17	4	1 (20)	
115	12	1	3	2	6		50	3	8 (73)	3
130	17	5	1	3	8		47	2	10 (83)	
145	7	2		1	2	2	57		5 (100)	1
Total	59 (100)	16 (27)	11 (19)	11 (19)	19 (32)	2 (3)	(36)	15	28 (65)	4

[a] Numbers in parentheses, percentage.

Table 5 *Diarrhea according to perfusion time*

Dose (mg/m²)	Duration of perfusion (min)	No. of patients	No. of patients with diarrhea (WHO grade)					% with grade 3–4
			0	1	2	3	4	
115	30	6	1	1	1	3		50
	90	6		2	1	3		50
130	30	8				8		100
	90	9	5	1	3			
145	30	1					1	100
	90	6	2		1	2	1	50
Total	30	15	1	1	1	11	1	80
	90	21	7	3	5	5	1	28

Table 6 *Other toxicities*

	Grade 0	Grade 1–2	Grade 3–4
Nausea-vomiting	16	33	10 (17)[a]
Alopecia	26	17	6 (12)
Asthenia	26	30	3 (5)
Abdominal pain	46	11	2 (3)
Infection	53	4	2 (3)
Thrombocytopenia	54	3	2 (3)
Anemia	20	38	1 (2)
ALT, AST[b]	50	9	0
Cutaneous toxicity	51	5	0
Stomatitis	56	3	0

[a] Numbers in parentheses, percentage.
[b] ALT, alanine aminotransferase; AST, aspartate aminotransferase.

(43%) treated by 1 prior chemotherapy suffered grade 2–4 diarrhea, whereas this toxicity level was experienced by 13 of 15 patients (87%) treated by more than 1 prior chemotherapy. At dose level of 145 mg/m², all patients but one had received one prior chemotherapy and 5 of 7 patients (71%) had grade 2–4 diarrhea.

In an attempt to reduce the severity of diarrhea, the infusion time was prolonged from 30 to 90 min in 21 patients. A trend toward reduced diarrhea was indeed observed with increased infusion time (Table 5).

Other gastrointestinal toxicities included nausea and vomiting and abdominal pain without diarrhea (Table 6). Nausea and vomiting appeared mainly at the highest dose levels and were manageable by standard antiemetic therapy using metoclopramide or serotonin antagonists.

Other toxic effects, which were mainly observed at dose levels above 98 mg/m², included asthenia, alopecia, cutaneous erythema, and transient increase of hepatic enzymes (Table 6). No proteinuria or hemorrhagic cystitis occurred.

Although a 2-week rest period was allowed after 3 administrations, CPT-11 treatment had to be postponed for 1 week in 7 patients (11 courses) at the 115–145-mg/m² dose levels, due to leukoneutropenia (5 courses), diarrhea (5 courses), or both (1 course).

Pharmacokinetics

CPT-11 Pharmacokinetics. Pharmacokinetic data were obtained during 50 administrations of CPT-11 in 26 patients. Mean plasma concentration profiles of both CPT-11 and active metabolite SN-38 after a 30-min i.v. infusion of CPT-11 are depicted in Fig. 2. The mean CPT-11 peak plasma concentrations achieved at the end of the i.v. infusion ranged from 664 ng/ml for the lowest dose administered (50 mg/m²) to 2578 ng/ml at 115 mg/m² (Table 7). The mean peak plasma levels did not increase proportionally to the dose beyond 115 mg/m² because most patients in this dose range received the drug as a longer infusion time (1.5 h) in an attempt to alleviate acute toxicities (nausea/vomiting and diarrhea). CPT-11 plasma decay was either biphasic (28 data sets) or triphasic (22 data sets). The mean half-life of the first phase of the triphasic model was 6.6 min, the second phase

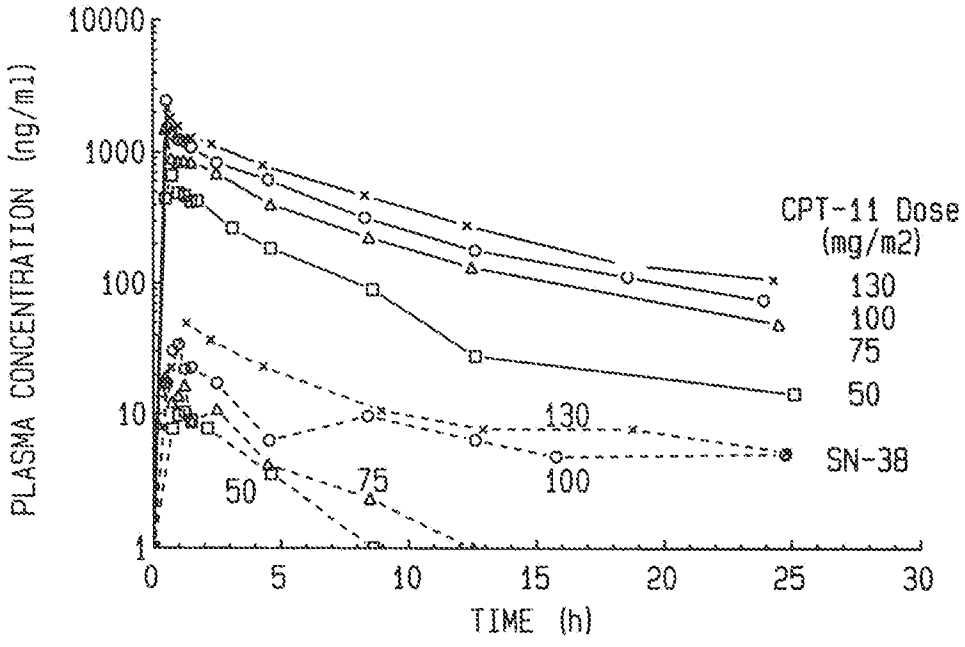

Fig. 2. Mean plasma concentration curves of CPT-11 (——) and active metabolite SN-38 (– – – –) at the indicated CPT-11 doses (mg/m²). CPT-11 was administered as a 30-min i.v. infusion, and CPT-11 and SN-38 levels were simultaneously assayed by high-performance liquid chromatography using fluorescence detection as described in "Patients and Methods." CPT-11 plasma concentrations (——) at 130 mg/m² (×), 100 mg/m² (○), 75 mg/m² (△), and 50 mg/m² (□). SN-38 plasma concentrations (– – – –) at indicated CPT-11 (×), doses: 130 mg/m² 100 mg/m² (○), 75 mg/m² (△), 50 mg/m² (□). Error bars are not shown for legibility.

Table 7 *CPT-11 and active metabolite SN-38 pharmacokinetic parameters*

		CPT-11								SN-38	
			Half-lives (h)								
Dose (mg/m²)	No.	C_{max} (ng/ml)	a	b	g	MRT[a] (h)	Vd_{ss} (liters/m²)	CL (liters/h/m²)	AUC (ng/h/ml)	C_{max} (ng/ml)	AUC (ng/h/ml)
50	2	664 ± 77[b]		1.6 ± 0.7	5.3 ± 0.4	8.0 ± 0.9	151 ± 9	18.9 ± 1.0	2,654 ± 144	10 ± 1	36 ± 2
66	6	1,552 ± 86	0.05 ± 0.02	1.6 ± 0.3	7.9 ± 0.3	8.4 ± 0.8	161 ± 8	19.8 ± 1.5	3,453 ± 305	16 ± 6	69 ± 24
75	6	1,733 ± 129	0.03 ± 0.01	2.1 ± 0.1	9.0 ± 1.0	9.9 ± 0.9	105 ± 3	11.2 ± 1.1	7,078 ± 751	23 ± 3	92 ± 21
85	7	2,008 ± 324		3.0 ± 0.6	7.7 ± 0.7	10.2 ± 1.9	101 ± 11	10.7 ± 1.1	8,437 ± 840	75 ± 23	443 ± 136
98	9	2,306 ± 353	0.03 ± 0.01	1.6 ± 0.3	11.2 ± 1.3	12.1 ± 1.5	167 ± 26	14.8 ± 2.0	8,482 ± 1,863	42 ± 8	170 ± 36
115	9	2,578 ± 546[c]	0.02 ± 0.01	1.3 ± 0.2	9.5 ± 0.7	9.4 ± 0.4	174 ± 20	18.5 ± 2.2	7,124 ± 1,038	44 ± 8	175 ± 35
130	7	2,072 ± 306[c]	0.15 ± 0.07	2.8 ± 0.7	10.8 ± 1.6	10.4 ± 1.3	124 ± 10	12.8 ± 1.6	10,941 ± 1,096	52 ± 24	313 ± 124
145	1	2,055[c]		1.0	5.9	7.3	122	16.6	8,720	33	164
Overall mean			0.11 ± 0.05	2.0 ± 0.2	9.3 ± 0.5	10.0 ± 0.5	142 ± 8	15.0 ± 0.8			

[a] MRT, mean residence time.
[b] Mean ± SEM.
[c] Includes 90-min. infusions.

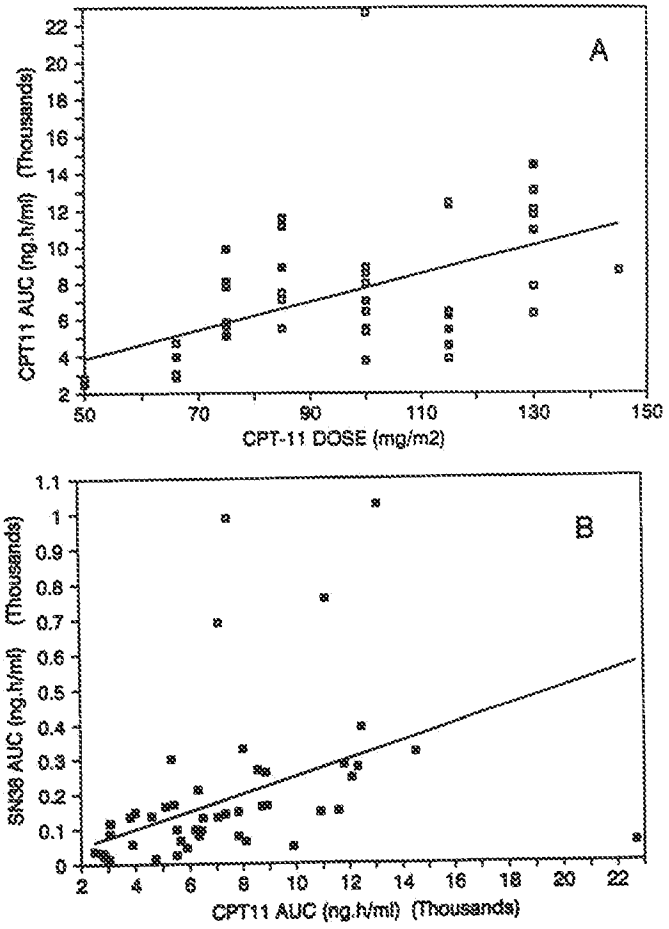

Fig. 3. Correlation between CPT-11 dose and CPT-11 AUC (*A*; $r = 0.47$, $P < 0.01$), and correlation between CPT-11 AUC and SN-38 AUC (*B*; $r = 0.32$, $P < 0.05$).

half-life (or the first phase of the biphasic model) was 2.0 h, and the terminal phase half-life was 9.3 h (Table 7). The model-independent mean residence time corresponding to the time needed for 63% of the drug to be eliminated was 10 h. The mean volume of distribution at steady state (Vd_{ss}) was large and remained stable as a function of dose with a mean value of 142 liters/m². Total body clearance (CL) did not vary with increased dosage (mean, 15 liters/h/m²) indicating linear pharmacokinetics within the dose range administered in this phase I trial (Table 7). CL also did not vary significantly between weeks. The total AUC increased proportionally to the dose ($r = 0.47$, $P < 0.01$) but as depicted in Fig. 3*A*, the interpatient variability was important.

Active Metabolite SN-38 Pharmacokinetics. Mean metabolite SN-38 peak levels ranged from 10 to 52 ng/ml (Table 7), and maximum levels were observed 0.6 h after the end of the 0.5-h CPT-11 i.v. infusion, *i.e.*, 1.1 h since the beginning. SN-38 plasma decay followed closely that of CPT-11 with a mean apparent half-life of about 7.7 ± 0.9 h (Fig. 2). Although the increase in SN-38 AUC as a function of CPT-11 dose did not reach statistical significance in this phase I trial ($r = 0.20$, P is not significant), we observed a statistically significant correlation between CPT-11 AUC and its corresponding SN-38 AUC (Fig. 3*B*) ($r = 0.32$, $P < 0.05$).

CPT-11 and SN-38 Urinary Excretion. Mean 24-h urinary excretion of CPT-11 accounted for 11.1 ± 1.2% (range, 1.4–33.3%) of the administered dose, and SN-38 excretion accounted for 0.18 ± 0.03% of the CPT-11 dose.

CPT-11 and SN-38 Biliary Secretion. Bile samples were available for the first and the third week in one patient at dose level of 100 mg/m², at 12, 24, and 36 h after the CPT-11 administration (Table 8). Mean CPT-11 and SN-38 bile levels were 113-fold and 40-fold higher compared to corresponding plasma levels, respectively. These high biliary secretion of both CPT-11 and SN-38 probably account for the relatively long half-life of both compounds.

Pharmacokinetic-Pharmacodynamic Relationships. Relationships between both CPT-11 and SN-38 AUC's with the main toxicities were noted. Table 9 presents the major findings of these pharmacokinetic-pharmacodynamic relationships. Particularly noteworthy were the significant correlations between CPT-11 AUC with both the percentage of decrease in WBC (Fig. 4) and neutrophils. The fitting of

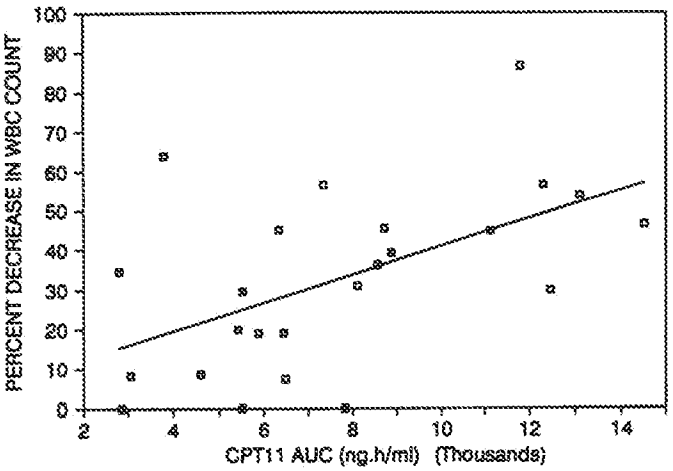

Fig. 4. Correlation between CPT-11 AUC and the percentage of decrease in WBC for the first week only ($r = 0.54$, $P < 0.01$).

Table 8 *CPT-11 and SN-38 bile/plasma ratios*

Week	Time (h)	Sample	CPT-11 Concentration (ng/ml)	CPT-11 Bile/plasma	SN-38 Concentration (ng/ml)	SN-38 Bile/plasma
1	12	Bile	22,377	67	485	24
		Plasma	334		20	
	24	Bile	11,337	80	366	35
		Plasma	141		11	
	36	Bile	5,044	63	203	27
		Plasma	80		8	
2	12	Bile	27,862	52	402	11
		Plasma	532		37	
	24	Bile	20,879	153	408	102
		Plasma	136		4	
	36	Bile	12,031	200	327	
		Plasma	(60)			
Bile/plasma ratio			113 ± 27[a]		40 ± 4	

[a] Mean ± SEM.

hematological toxicities and CPT-11 AUC was attempted with both the linear and the sigmoidal model but was found to be less adequate with the latter. The active metabolite SN-38 AUC also correlated significantly with both percentage decrease in WBC and neutrophil counts (Table 9). The intensity of diarrhea (grade) also correlated significantly with both CPT-11 and SN-38 AUCs, whereas no correlation was found for the intensity of nausea and vomiting (Table 9).

Table 9 *Pharmacokinetic-pharmacodynamic relationships*

Pharmacokinetic parameter	Correlation coefficients (*P*) % decrease[a] WBC	% decrease[a] Neutrophils	Diarrhea	Nausea and vomiting
First wk ($N = 24$)				
CPT11 AUC	0.54 (<0.01)[b]	0.62 (<0.01)	0.42 (<0.05)	0.21 (NS)[c]
SN-38 AUC	0.43 (<0.05)	0.51 (<0.05)	0.46 (<0.05)	0.36 (NS)
All weeks ($N = 47$)				
CPT11 AUC	0.43 (<0.01)	0.35 (<0.02)	0.31 (<0.05)	0.13 (NS)
SN-38 AUC	0.33 (<0.05)	0.42 (<0.01)	0.43 (<0.01)	0.23 (NS)

[a] Percentage of decrease in WBC and neutrophils on day 7 after CPT-11 administration, compared to predose values.
[b] Correlation coefficient *r* value followed by the *P* value in parentheses.
[c] NS, not significant.

Responses

A woman with cervical cancer, previously treated with surgery and radiotherapy, achieved a partial response lasting for 19 weeks. Four minor responses were noted in patients with colon, esophagus, and unknown primary cancer (Table 10).

DISCUSSION

In the search for new and better anticancer compounds, camptothecin and its derivatives with intact lactone ring, such as CPT-11, are promising agents. They are currently the only known and clinically assessed inhibitors of DNA topoisomerase I (16, 17, 41). Specifically, CPT-11 has been shown to possess strong antitumor activity against a broad spectrum of experimental tumor models (28–30).

Of particular interest is the lack of cross-resistance of CPT with the drugs affected by the multidrug resistance system (42). Precise mechanisms of resistance to CPT are not well understood. However, decreased activity of the target enzyme DNA topoisomerase I (43–45) and/or mutation of the enzyme with decreased binding of the drug (46) have been described in resistant cell lines.

We report here the results obtained in a phase I study of CPT-11 using a weekly schedule. The maximum tolerated dose was 145 mg/m^2, where 4 of 7 patients experienced grade 3–4 toxicities. At the highest dose levels (≥115 mg/m^2) severe diarrhea was observed in 50% of patients, a higher figure than the one described in a previous Phase I study using a weekly schedule (47), with a 90-min i.v. infusion, where the MTD was 100 mg/m^2, and 3 of 10 patients receiving 125–150 mg/m^2 experienced grade 3–4 diarrhea. Because CPT-11 treatment had to be postponed for 1 week in 7 of 36 patients (11 courses) at the 115–145 mg/m^2 dose levels, due to leukoneutropenia (5 courses), diarrhea (5 courses), or both (1 course), diarrhea and leukoneutropenia thus were the dose-limiting toxicities, as previously described in other studies (31–34, 40, 47–49). These toxicities appeared dose related, reversible, and noncumulative, although there was a wide interpatient variation in the degree of diarrhea and neutropenia at a given dose level. No clinical risk factor strongly predictive of diarrhea and leukoneutropenia has been clearly identified, with the possible exception of the number of prior chemotherapeutic regimen for diarrhea. The toxic mechanism of diarrhea is currently unknown, neither prolongation of infusion (21 patients) nor the different treatments used in this study had clear-cut efficacy, however, the intensive loperamide administration which have been reported to control the CPT-11-induced diarrhea (40) has been used in these patients. No cystitis, as described previously with CPT (5, 8), or pulmonary toxicity, as seen in recent phase II studies of CPT-11 (32, 34), were observed. The pharmacological studies showed that CPT-11 has a relatively long terminal half-life which could be of advantage for this S-phase-specific agent by allowing prolonged exposure time of tumor cells *in vivo*. This long disposition half-life is also probably responsible for the maintenance of cytotoxic concentrations of the active metabolite SN-38 *in vivo*. Interestingly, CPT-11 terminal half-life seems longer than that of topotecan, another CPT analogue currently under clinical development, which was reported to have a terminal half-life of about 3 h (50–53). It is also of interest that the CPT-11 terminal half-life is longer in humans (9 h) than in either mice (1.1 h) (54) or rats (1.2–2.4 h) (55). Also, contrary to reactions in rodents (54, 55), no dose dependency was observed for human CPT-11 pharmacokinetics, using the weekly schedule of administration.

Table 10 *CPT-11 antitumoral effects*

Primary tumor	No. of prior chemotherapy regimens	Dose level (mg/m^2)	Cumulative dose (mg/m^2)	Response	Duration (wk)
Cervix	0	145	870	Partial	19
Colon	1	145	1450	Minor	15
ACUP[a]	1	130	1300	Minor	8
ACUP	2	145	2560	Minor	>23
Esophagus	2	130	1560	Minor	16

[a] ACUP, adenocarcinoma of unknown primary.

Based on *in vitro* data, CPT-11 plasma concentrations achieved in patients at recommended phase II doses (100–115 mg/m^2) are potentially cytotoxic (2306–2578 ng/ml). For example, the 50% growth inhibition concentration values for KB and L1210 cells are 1100 and 5500 ng/ml, respectively (54). At the same CPT-11 dose levels, corresponding active metabolite SN-38 levels (42–44 ng/ml) were, however, more clearly above the 50% growth inhibition concentration values reported for KB and L1210 cells (0.37 and 3.6 ng/ml, respectively) (54). Therefore, biologically active plasma concentrations of both CPT-11 and SN-38 were achieved using this weekly administration schedule. Finally we have demonstrated the biliary excretion of CPT-11 and SN-38 which has also been observed in another trial (48). It is also of interest that CPT-11 appears to be metabolized to a greater extent than topotecan; since only 11% (range, 1.4–33.3%) of the former is excreted in a 24-h urinary collection, whereas 39–99% (range, 12–99%) is excreted in the urine for the latter (51, 52).

The significant pharmacokinetic-pharmacodynamic relationships between the AUCs of both CPT-11 and SN-38 with the percentage of WBC decrease may indicate that CPT-11 also, and not only the active metabolite SN-38, may be responsible for this hematological toxicity. In this study, we also noted that the severity of diarrhea correlated well with both CPT-11 and SN-38 AUCs. These data support the hypothesis that exposure to both CPT-11 and its metabolite SN-38 are responsible for the main toxicities of this compound. Whether or not there is a correlation between these pharmacokinetic parameters with the antitumor activity of CPT-11 remains to be established in phase II trials, but it is noteworthy that in this phase I trial, the antitumor responses were observed in the highest dose range administered (130–145 mg/m^2) where the highest AUCs of CPT-11 and SN-38 were observed.

Broader phase II trials of CPT-11 are now required to confirm the activity of the drug described in lymphoma and lung cancers (32–34). Recommended doses for phase II studies using a weekly schedule is 100 mg/m^2 (not different from the 98 mg/m^2 which was studied in this trial) in high risk patients (more than 1 prior chemotherapeutic regimen) and 115 mg/m^2 in others. Careful monitoring of gastrointestinal and hematological side effects is needed.

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Phase I and Pharmacokinetic Study of the Camptothecin Derivative Irinotecan, Administered on a Weekly Schedule in Cancer Patients

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Electronic Patent Application Fee Transmittal

Application Number:	15809815
Filing Date:	10-Nov-2017
Title of Invention:	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin
First Named Inventor/Applicant Name:	Eliel Bayever
Filer:	Mary Rucker Henninger/Deborah Barragan
Attorney Docket Number:	01208-0007-01US

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	260	260
		Total in USD ($)		**260**

Electronic Acknowledgement Receipt

EFS ID:	45210682
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/Deborah Barragan
Filer Authorized By:	Mary Rucker Henninger
Attorney Docket Number:	01208-0007-01US
Receipt Date:	11-MAR-2022
Filing Date:	10-NOV-2017
Time Stamp:	17:40:55
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$260
RAM confirmation Number	E20223AH43284579
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	2022-03-11_01208-0007-01US_IDS_Transmittal.pdf	128590 7b1d12259cf7cb2473f52bd0ef5ed1df19d8bd95	no	2
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	2022-03-11_01208-0007-01US_SB08.pdf	1282551 18190a06d785f41d74e99999bb7f8e9c6ce11204	no	4
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
3	Non Patent Literature	Marsh_2015.pdf	94733 35921130f14b96f49a947af94f624f5472241bdc	no	11
Warnings:					
Information:					
4	Non Patent Literature	Chang_2003.pdf	1442611 259b57ca99a19e630ea01681c061b8098e8367b3	no	10
Warnings:					
Information:					
5	Non Patent Literature	deForni_1994_.pdf	11264617 73dd3964d5270911cc6a08f79609db17b4bb6475	no	9
Warnings:					
Information:					

6	Fee Worksheet (SB06)	fee-info.pdf	38271 bac784b0214c9332c289f37ae805b36816799864	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	14251373

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Group Art Unit: 1612
Eliel BAYEVER et al.	
Application No.: 15/809,815	Examiner: Gollamudi S. Kishore
Filed: November 10, 2017	Confirmation No.: 5137
For: Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin	

VIA EFS-WEB
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97(c)

Pursuant to 37 C.F.R. §§ 1.56 and 1.97(c), Applicant brings to the attention of the Examiner the document listed on the enclosed IDS Form PTO/SB/08. This Information Disclosure Statement is being filed after the mailing of an Office Action on the merits, but to Applicant's knowledge, prior to the mailing of a Final Office Action, *ex parte Quayle* Action, or Notice of Allowance. This Information Disclosure Statement is accompanied by $260, as required by 37 C.F.R. §1.97(c).

Copies of the non-US patent publication documents are enclosed.

Applicant respectfully requests that the Examiner consider the listed documents and indicate that they were considered by making appropriate notations on the attached form.

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that each or all of the listed documents are material or constitute "prior art." If the Examiner applies any of the documents as prior art against any claim

in the application and Applicant determines that the cited documents do not constitute "prior art" under United States law, Applicant reserves the right to present to the U.S. Patent and Trademark Office the relevant facts and law regarding the appropriate status of such documents.

Applicant further reserves the right to take appropriate action to establish the patentability of the claimed invention over the listed documents, should one or more of the documents be applied against the claims of the present application.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account 506488.

Respectfully submitted,

McNeill Baur PLLC

Dated: March 11, 2022

By: /Mary R. Henninger/
Mary R. Henninger
Reg. No. 56,992
404-891-1400

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

153749 7590 03/25/2022

McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
125 Cambridge Park Drive
Suite 301
Cambridge, MA 02140

EXAMINER
KISHORE, GOLLAMUDI S

ART UNIT	PAPER NUMBER
1612	

DATE MAILED: 03/25/2022

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/809,815	11/10/2017	Eliel Bayever	01208-0007-01US	5137

TITLE OF INVENTION: Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	06/27/2022

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

153749 7590 03/25/2022

McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
125 Cambridge Park Drive
Suite 301
Cambridge, MA 02140

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/809,815	11/10/2017	Eliel Bayever	01208-0007-01US	5137

TITLE OF INVENTION: Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	06/27/2022

EXAMINER	ART UNIT	CLASS-SUBCLASS
KISHORE, GOLLAMUDI S	1612	424-450000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/809,815	11/10/2017	Eliel Bayever	01208-0007-01US	5137

153749 7590 03/25/2022

McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
125 Cambridge Park Drive
Suite 301
Cambridge, MA 02140

EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1612	

DATE MAILED: 03/25/2022

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 15/809,815	Applicant(s) Bayever et al.	
	Examiner GOLLAMUDI S KISHORE	Art Unit 1612	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 2-25-2922.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/GOLLAMUDI S KISHORE/
Primary Examiner, Art Unit 1612

Continuation of 3. The allowed claim(s) is/are: 1,4-15,18-19 and 21-23

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/809,815	Bayever et al.
	Examiner	**Art Unit**
	GOLLAMUDI S KISHORE	1612

CPC						
Symbol					**Type**	**Version**
A61K	/	31	/	519	F	2013-01-01
A61K	/	31	/	282	I	2013-01-01
A61K	/	31	/	4745	I	2013-01-01
A61K	/	31	/	513	I	2013-01-01
A61K	/	9	/	1271	I	2013-01-01
A61K	/	9	/	0019	I	2013-01-01
A61K	/	31	/	475	I	2013-01-01
A61K	/	31	/	436	I	2013-01-01
A61K	/	47	/	20	I	2013-01-01
A61K	/	9	/	127	I	2013-01-01
A61K	/	2300	/	00	A	2013-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
A61K	/	31	/	519	I	1	1	2013-01-01
A61K	/	2300	/	00	I	1	2	2013-01-01
A61K	/	31	/	4745	I	2	1	2013-01-01
A61K	/	2300	/	00	I	2	2	2013-01-01
A61K	/	31	/	282	I	3	1	2013-01-01
A61K	/	2300	/	00	I	3	2	2013-01-01
A61K	/	31	/	513	I	4	1	2013-01-01
A61K	/	2300	/	00	I	4	2	2013-01-01

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	18	
/GOLLAMUDI S KISHORE/ Primary Examiner, Art Unit 1612	16 March 2022	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	4A

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/809,815	Bayever et al.
	Examiner	**Art Unit**
	GOLLAMUDI S KISHORE	1612

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K31/519	/	31	/	519
A61K31/282	/	31	/	282
A61K31/4745	/	31	/	4745
A61K31/513	/	31	/	513
A61K9/127	/	9	/	127
A61K9/00	/	9	/	00
A61K31/475	/	31	/	475
A61K31/436	/	31	/	436
A61K47/20	/	47	/	20

NON-CLAIMED				
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US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE (Assistant Examiner) (Date)	**Total Claims Allowed:** 18	
/GOLLAMUDI S KISHORE/ Primary Examiner, Art Unit 1612 (Primary Examiner) 16 March 2022 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 4A

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/809,815	Bayever et al.
	Examiner	Art Unit
	GOLLAMUDI S KISHORE	1612

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	8	10	15	19										
	2	9	11		20										
	3	10	12	16	21										
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3	5	12	14	18	23										
4	6	13	15												
5	7		16												
6	8		17												
7	9	14	18												

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	18	
/GOLLAMUDI S KISHORE/ Primary Examiner, Art Unit 1612	16 March 2022	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	4A

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/809,815	Bayever et al.
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	GOLLAMUDI S KISHORE	1612

CPC - Searched*		
Symbol	**Date**	**Examiner**
(A61K31/519 or A61K9/1271 or A61K9/0019 or A61K31/475 or A61K31/436 or A61K47/20 or A61K31/282 or A61K31/4745 or A61K31/513 or A61K9/127 or A61K2300/00 or A61P43/00 or A61P35/04).cpc.	07/07/2021	GSK
(A61K31/519 or A61K9/0019 or A61K9/127 or A61K9/1271 or A61K31/282 or A61K31/436 or A61K31/4745 or A61K31/475 or A61K31/513 or A61K47/20 or A61K2300/00 or A61P35/04 or A61P43/00).cpc.	03/15/2022	GSK

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US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**

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Search Notes		
Search Notes	**Date**	**Examiner**
west and palm searches	02/21/2018	CR
west and palm searches	09/02/2018	CR
west and palm searches	07/01/2019	CR
west and palm searches	02/20/2020	CR
West, Google, Inventor name	07/07/2021	GSK
West	03/15/2022	GSK

/GOLLAMUDI S KISHORE/ Primary Examiner, Art Unit 1612	

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	15/809,815	Bayever et al.
	Examiner	Art Unit
	GOLLAMUDI S KISHORE	1612

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	((metastatic adj3 adenocarcinoma adj3 pancreas) and (liposom$ adj3 irinotecan) and oxaliplatin and leucovorin and $fluorouracil).clm.	03/16/2022	GSK

/GOLLAMUDI S KISHORE/ Primary Examiner, Art Unit 1612	

Refine Search

Search Results

Terms	Documents
((metastatic adj3 adenocarcinoma adj3 pancreas) and (liposom$ adj3 irinotecan) and oxaliplatin and leucovorin and $fluorouracil)	35

Database: Foreign Patent Retrieval

Search Type: (•) Prior Art ( ) Interference

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Order By	Set Name Side by Side	Query	Hit Count	Set Name Result Set	Set Name Grid	Set Name Classification
Prior Art Searches						
		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR				
Date	L2	((metastatic adj3 adenocarcinoma adj3 pancreas) and (liposom$ adj3 irinotecan) and oxaliplatin and leucovorin and $fluorouracil)	35	L2	L2	L2
Date	L1	((metastatic adj3 adenocarcinoma adj3 pancreas) and (liposom$ adj3 irinotecan) and oxaliplatin and leucovorin and $fluorouracil).clm.	2	L1	L1	L1

END OF SEARCH HISTORY

PTO/SB/08a (01-22)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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First Named Inventor	Eliel Bayever
Art Unit	1612
Examiner Name	Gollamundi S. KISHORE
Attorney Docket Number	01208-0007-01US

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EXAMINER SIGNATURE

Examiner Signature	/GOLLAMUDI S KISHORE/	Date Considered	03/16/2022

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	Attorney Docket Number	01208-0007-01US

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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	1	11052079	B2	2021-07-06	Hong et al.	
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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	Gollamundi S. KISHORE
	Attorney Docket Number	01208-0007-01US

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	1	EP3337478: Proprietor's Submission in Response to Oppositions, dated December 7, 2021, including main request and auxiliary requests 1-3, 62 pages.	
	2	EP3337478: Proprietor's Submission in Response to Oppositions, dated December 7, 2021, D18 (WAINBERG Z, et al., "First-line Liposomal Irinotecan With Oxaliplatin, 5-Fluorouracil and Leucovorin (NALIRIFOX) in Pancreatic Ductal Adenocarcinoma: A Phase I/II Study," Eur J Cancer. 151:14-24 (2021)).	
	3	EP3337478: Proprietor's Submission in Response to Oppositions, dated December 7, 2021, D19 (Declaration of Dr. Bin Zhang, including Annex A and Annex B, 15 pages).	
	4	EP3337478: Proprietor's Submission in Response to Oppositions, dated December 7, 2021, D20 (EISENHAUER E, et al., "New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (version 1.1)," Eur J Cancer. 45 (2):228-47 (2009)).	
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	9	EP3337478: Sandoz AG Response to Proprietor's Reply to the Notice of Opposition dated February 1, 2022, 17 pages.	
	10	EP3337478: Sandoz AG Response to Proprietor's Reply to the Notice of Opposition dated February 1, 2022, D25 (TSAI C, et al., "Nanovector-Based Therapies in Advanced Pancreatic Cancer," J Gastroint Oncol 2(3):185-94 (2011)).	

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	11	EP3337478: Sandoz AG Response to Proprietor's Reply to the Notice of Opposition dated February 1, 2022, D26 (YOO C, et al., "A Randomised Phase II Study of Modified FOLFIRI.3 vs Modified FOLFOX as Second-Line Therapy in Patients with Gemcitabine-Refractory Advanced Pancreatic Cancer," Br J Cancer. 101(10):1658-63 (2009)).
	12	EP3337478: Sandoz AG Response to Proprietor's Reply to the Notice of Opposition dated February 1, 2022, D27 (KALRA A, et al., "Preclinical Activity of Nanoliposomal Irinotecan Is Governed by Tumor Deposition and Intratumor Prodrug Conversion," Cancer Res. 74(23):7003-13 (2014)).
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	14	BRENDEL K, et al., "Population Pharmacokinetics of Liposomal Irinotecan in Patients With Cancer and Exposure–Safety Analyses in Patients With Metastatic Pancreatic Cancer," CPT Pharmacometrics Syst Pharmacol. 10 (12):1550-63, doi: 10.1002/psp4.12725 (2021).
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	16	GEORGE B, et al., "The Association of Real-World CA 19-9 Level Monitoring Patterns and Clinical Outcomes Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma," Front Oncol. 11:754687, doi: 10.3389/fonc.2021.754687, pages 1-8 (2021).
	17	PAZ-ARES L, et al., "RESILIENT Part 1: A Phase 2 Dose-Exploration and Dose-Expansion Study of Second-Line Liposomal Irinotecan in Adults With Small Cell Lung Cancer," Cancer. doi: 10.1002/cncr.34123, online ahead of print, pages 1-11 (2022).
	18	SACHDEV J, et al., "Phase I Study of Liposomal Irinotecan in Patients With Metastatic Breast Cancer: Findings from the Expansion Phase," Breast Cancer Res Treat..185(3):759-71 (2021), Epub 2020.
	19	TOMICKI S, et al., "Real-World Cost of Care for Commercially Insured Versus Medicare Patients With Metastatic Pancreatic Cancer Who Received Guideline-Recommended Therapies," Am Health Drug Benefits. 14(2):70-78 (2021).
	20	YOO C, et al., "Liposomal Irinotecan Plus Fluorouracil and Leucovorin Versus Fluorouracil and Leucovorin for Metastatic Biliary Tract Cancer After Progression on Gemcitabine Plus Cisplatin (NIFTY): A Multicentre, Open-Label, Randomized, Phase 2b Study," Lancet Oncol. 22(11):1560-1572, doi: 10.1016/S1470-2045(21)00486-1, pages 1-13 (2021).
	21	YU K, et al., "Clinical Outcomes Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma Treated With Liposomal Irinotecan," Front Oncol. 11:678070. doi: 10.3389/fonc.2021.678070, pages 1-9 (2021).

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	22	YU K, et al., "Real-World Prognostic Factors for Survival Among Treated Patients With Metastatic Pancreatic Ductal Adenocarcinoma," Cancer Med. 10(24):8934-43 (2021).
	23	U.S. Patent Application No. 15/664,976: 2021-04-21 Notice of Allowance including Examiner's Reasons for Allowance, 14 pages.
	24	U.S. Patent Application No. 15/809,815: 2021-08-26 Non-Final Office Action, 14 pages.
	25	U.S. Patent Application No. 16/012,351: 2021-03-08 Notice of Allowance including Examiner's Reasons for Allowance, 9 pages.
	26	U.S. Patent Application No. 16/012,372: 2021-02-11 Notice of Allowance including Examiner's Reasons for Allowance, 9 pages.
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	28	U.S. Patent Application No. 16/567,902: 2021-03-08 Notice of Allowance including Examiner's Reasons for Allowance and Examiner Interview Summary, 22 pages.
	29	U.S. Patent Application No. 16/711,072: 2021-12-10 Non-Final Office Action, 19 pages.
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Examiner Signature	/GOLLAMUDI S KISHORE/	Date Considered	03/16/2022

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	Attorney Docket Number	01208-0007-01US

CERTIFICATION STATEMENT

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)	2022-03-09
Name/Print	Mary R. Henninger	Registration Number	56992

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SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
15/809,815	11/10/2017	424	1612	01208-0007-01US

APPLICANTS

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Ashish Kalra, Belmont, MA;
Helen Lee, Arlington, MA;

**** CONTINUING DATA ***************************

This application is a CON of 15/241,106 08/19/2016 ABN
which claims benefit of 62/343,313 05/31/2016
and claims benefit of 62/323,245 04/15/2016
and claims benefit of 62/302,341 03/02/2016
and claims benefit of 62/281,473 01/21/2016
and claims benefit of 62/273,244 12/30/2015
and claims benefit of 62/216,736 09/10/2015
and claims benefit of 62/208,209 08/21/2015

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Foreign Priority claimed ❑ Yes ☑ No 35 USC 119(a-d) conditions met ❑ Yes ☑ No Verified and Acknowledged Celeste Roney (Examiner's Signature)	❑ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
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McNeill Baur PLLC/Ipsen
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Suite 301
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UNITED STATES

TITLE

Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin

FILING FEE	FEES: Authority has been given in Paper	❑ All Fees ❑ 1.16 Fees (Filing) ❑ 1.17 Fees (Processing Ext. of time)

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	1	BAI L, et al., "A Phase 2 Study of Liposomal Irinotecan With 5-Fluorouracil and Leucovorin in Squamous Cell Carcinoma of Head and Neck or Esophagus After Prior Platinum-Based Chemotherapy or Chemoradiotherapy," Poster presented at American Society of Clinical Oncology 2021 Meeting, June 4-8, 2021, 6 pages.
	2	DIEGUEZ G et al., "Risk Adjustment and Total Cost of Care Per Month of Overall Survival Among Medicare Fee-for-Service (FFS) Beneficiaries Receiving Treatment for Metastatic Pancreatic Cancer," Poster presented at American Society of Health-System Pharmacists (ASHP) Midyear Clinical Meeting & Exhibition, December 6-7, 2021, 6 pages.
	3	DIEGUEZ G, et al., "Trends in Treatment Patterns Among Medicare Fee-For-Service (FFS) Patients Receiving Treatment for Metastatic Pancreatic Cancer," Poster presented at European Society for Medical Oncology (ESMO) Congress 2021, September 16-21, 2021, 5 pages.
	4	DIEGUEZ G, et al., "Trends in Use of One, Two, and Three-Line NCCN Category 1 Regimens Among Medicare Fee-For-Service (FFS) Patients Receiving Treatment for Metastatic Pancreatic Cancer," Poster presented at ASCO Quality Care Symposium 2021, September 24-25, 2021, 5 pages.
	5	ELIAS R, et al., "Comparison of First-Line (1L) Treatment (Tx) Patterns and Overall Survival by Age at Diagnosis Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC)," Poster Presented at the American Society of Clinical Oncology Gastrointestinal Cancer Symposium (ASCO GI) 2021, January 15–17, 2021, Virtual Congress, 6 pages.
	6	GEORGE B, et al., "Real-World Impact of Prior Surgery on Outcomes of Patients With Metastatic Ductal Adenocarcinoma (mPDAC) Treated With Liposomal Irinotecan-Based Regimens," Presented at International Society for Pharmacoeconomics and Outcomes, May 17-19, 2021, Virtual poster, 10 pages.
	7	GEORGE B, et al., "Real-World Serum CA19-9 Level Monitoring Patterns and Its Association With Clinical Outcomes Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC)," Poster presented at the American Association for Cancer Research (AACR) 2021 Virtual Congress, April 10-15, 2021, 8 pages.
	8	KIM G, et al, "Real-World Characteristics and Outcomes of Patients With Metastatic Ductal Adenocarcinoma (mPDAC) Treated With Liposomal Irinotecan-Based Regimens by Race," Presented at International Society for Pharmacoeconomics and Outcomes, May 17-19, 2021, Virtual poster, 9 pages.
	9	KIM G, et al., "Real-World One-Year Overall Survival Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Treated With Liposomal Irinotecan in the NAPOLI-1 Based Regimen," Poster presented at the American Society of Clinical Oncology Gastrointestinal Cancer Symposium (ASCO GI) 2021, January 15–17, 2021, Virtual Congress, 6 printed pages.
	10	KIM G, et al., "Real-World Progression Outcomes Among Patients (pts) With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Treated With Liposomal Irinotecan-Based Regimens in the United States," Poster presented at European Society for Medical Oncology (ESMO) Congress,, Virtual Congress, September 16 -21, 2021, 5 pages.
	11	KIM G, et al., "Real-World Safety Data and Differentiation of Second-Line (2L) 5-Fluorouracil (5-FU) Based Regimens Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC)," Poster presented at the American Society of Clinical Oncology Gastrointestinal Cancer Symposium (ASCO GI) 2021, January 15–17, 2021, Virtual Congress, 7 pages.

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	12	KIM G, et al., "Real-World Treatment Discontinuation Patterns Among Patients (pts) With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Treated With Liposomal Irinotecan-Based Regimens in the United States," Presented at European Society for Medical Oncology (ESMO) Congress, Virtual Congress, September 16-21, 2021, 5 pages.
	13	LATIMER H, et al., "Total Cost of Care and Utilization Among Medicare Fee-For-Service (FFS) Patients With Metastatic Pancreatic Cancer Treated With FDA-Approved/NCCN® Category 1 Regimens at Teaching vs. Non-Teaching Hospitals," Presented at International Society for Pharmacoeconomics and Outcomes, May 17-19, 2021, Virtual poster, 11 pages.
	14	LAURSEN A, et al., "Real World Patterns of Pain Medication Use Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC)," Poster presented at ASCO Quality Care Symposium 2021. Boston, MA, Online, September 24 -25, 2021, 4 pages.
	15	PALURI R, et al., "Impact of the COVID-19 Pandemic on Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Care Delivery," Presented at the American Society for Clinical Oncology (ASCO) Annual Meeting: June 4 – 8, 2021; Virtual, 6 pages.
	16	PAZ-ARES L, et al., "RESILIENT Part 1: A Phase II Dose-Exploration and Dose-Expansion Study of Second-Line Liposomal Irinotecan Monotherapy in Adults With Small Cell Lung Cancer," Presented at World Conference on Lung Cancer, January 28-31, 2021, Virtual event, 12 pages.
	17	PAZ-ARES L, et al., "RESILIENT Part 2: A Phase III Study of Liposomal Irinotecan in Patients With Small-Cell Lung Cancer in the Second-Line Setting," Presented at World Conference on Lung Cancer, January 28-31, 2021, Virtual event, 9 pages.
	18	PERKHOFER L, et al., "Nal-IRI With 5-FU and Leucovorin or Gemcitabine Plus Cisplatin in Advanced Biliary Tract Cancer: Final Results of the Randomized Phase 2 NIFE Trial (AIO-YMO HEP-0315)," Presentation at the European Society for Medical Oncology (ESMO) Congress, Virtual Congress| September 16-21, 2021, 9 pages.
	19	RAMNARAIGN B, et al., "A Phase II, Open-Label Pilot Study Evaluating the Safety and Activity of Nal-IRI in Combination With 5-FU and Oxaliplatin (NALIRIFOX) in Preoperative Treatment of Pancreatic Adenocarcinoma (NEO-Nal-IRI study)," Poster presented at the American Society of Clinical Oncology Gastrointestinal Cancer Symposium (ASCO GI) 2021, January 15–17, 2021, Virtual Congress, 4 pages.
	20	TAIEB J, et al., "Real-World Study of Treatment Patterns and Outcomes Among Patients With Metastatic Pancreatic Ductal Adenocarcinoma (PDAC) in Europe," Poster presented at the American Society of Clinical Oncology Gastrointestinal Cancer Symposium (ASCO GI) 2021, January 15-17, 2021, Virtual Congress, 6 pages.
	21	TOMICKI S, et al., "Total Cost of Care and Utilization Among Medicare Fee-For-Service (FFS) Patients With Metastatic Pancreatic Cancer Treated With FDA-Approved/NCCN® Category 1 Regimens at 340B vs. Non-340B Hospitals," Presented at International Society for Pharmacoeconomics and Outcomes, May 17-19, 2021, Virtual poster, 11 pages.
	22	YOO C, et al., "Liposomal Irinotecan (nal-IRI) in Combination With Fluorouracil (5-FU) and Leucovorin (LV) for Patients (pts) With Metastatic Biliary Tract Cancer (BTC) After Progression on Gemcitabine Plus Cisplatin (GemCis): Multicenter Comparative Randomized Phase 2B Study (NIFTY)," Presented at the American Society of Clinical Oncology 2021 Meeting, June 4-8, 2021, 18 pages.

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	First Named Inventor	Eliel Bayever
	Art Unit	1612
	Examiner Name	Gollamundi S. KISHORE
	Attorney Docket Number	01208-0007-01US

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Name/Print	Mary R. Henninger	Registration Number	56992

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	1	MARSH R, et al., "Pancreatic Cancer and FOLFIRINOX: A New Era and New Questions," Cancer Med. 4(6):853-63 (2015).
	2	CHANG E, et al. "The Role of Tumor Size in the Radiosurgical Management of Patients with Ambiguous Brain Metastases," Neurosurgery. 53(2):272-280; discussion at 280-281 (2003).
	3	DE FORNI M, et al., "Phase I and Pharmacokinetic Study of the Camptothecin Derivative Irinotecan, Administered on a Weekly Schedule in Cancer Patients," Cancer Res. 54(16):4347-4354 (1994).

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	1	EP3337467: Sandoz AG Opposition dated September 9, 2021, 24 pages.
	2	EP3337467: Sandoz AG Opposition dated September 9, 2021, D1 (LORUSSO P, et al., "Phase I Study of the Safety, Pharmacokinetics (PK), and Pharmacodynamics (PD) of the Poly(ADP-ribose) Polymerase (PARP) Inhibitor Veliparib (ABT-888; V) in Combination with Irinotecan (CPT-11; Ir) in Patients (pts) with Advanced Solid Tumors," J Clin Oncol. 29(15) Suppl:3000 (2011), 2 pages).
	3	EP3337467: Sandoz AG Opposition dated September 9, 2021, D1a (LORUSSO P, et al., "Phase I Study of the Safety, Pharmacokinetics, and Pharmacodynamics of the Poly(ADP-ribose) Polymerase (PARP) Inhibitor Veliparib (ABT-888) in Combination with Irinotecan (CPT-11) in Patients with Advanced Solid Tumors," Presentation presented at American Society of Clinical Oncology 2011 Meeting, 37 pages).
	4	EP3337467: Sandoz AG Opposition dated September 9, 2021, D2 (BERLIN J, et al., "A Phase 1 Dose-Escalation Study of Veliparib with Bimonthly FOLFIRI in Patients with Advanced Solid Tumors," J Clin Oncol. 32(15) Suppl:2574 (2014), 4 pages).
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	6	EP3337467: Sandoz AG Opposition dated September 9, 2021, D4 (NEIJZEN R, et. al., "Irinophore C™, a Lipid Nanoparticle Formulation of Irinotecan, Improves Vascular Function, Increases the Delivery of Sequentially Administered 5-FU in HT-29 Tumors, and Controls Tumor Growth in Patient Derived Xenografts of Colon Cancer," J Control Release. 199:72-83 (2015), Epub 2014).
	7	EP3337467: Sandoz AG Opposition dated September 9, 2021, D5 (Clinical Trials Identifier NCT01770353: 2015-05-05 update submitted, "A Pilot Study in Patients Treated with MM-398 to Determine Tumor Drug Levels and to Evaluate the Feasibility of Ferumoxytol Magnetic Resonance Imaging to Measure Tumor Associated Macrophages." 5 pages).
	8	EP3337467: Sandoz AG Opposition dated September 9, 2021, D6 (SHAH M, et al., "The Relevance of Drug Sequence in Combination Chemotherapy," Drug Resist Updat. 3(6):335-356 (2000)).
	9	EP3337467: Sandoz AG Opposition dated September 9, 2021, D7 (O'SULLIVAN C, et al., "Beyond Breast and Ovarian Cancers: PARP Inhibitors for BRCA Mutation-Associated and BRCA-Like Solid Tumors," Front Oncol. 4:42 doi: 10.3389/fonc.2014.00042 (2014), 13 pages).
	10	EP3337467: Sandoz AG Opposition dated September 9, 2021, D8 (ONIVYDE package insert, revision October 22, 2015, 18 pages).
	11	EP3337467: Sandoz AG Opposition dated September 9, 2021, D9 (CARNEVALE J and KO A, "MM-398 (Nanoliposomal Irinotecan): Emergence of a Novel Therapy for the Treatment of Advanced Pancreatic Cancer," Future Oncol. 12(4):453-64 (2016). Epub 2015).

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	12	EP3337467: Sandoz AG Opposition dated September 9, 2021, D10 (Clinical Trials Identifier NCT02631733: 2015-12-15 submitted, "A Phase I Study of a Combination of MM-398 and Veliparib in Solid Tumors." 7 pages).
	13	EP3337467: Sandoz AG Opposition dated September 9, 2021, D11 (KOSHKARYEV A, et al., "Differential Tissue Clearance Results in Improved Therapeutic Index for Irinotecan Liposome Injection (ONIVYDE) When Combined with the PARP Inhibitor Veliparib in Preclinical Cervical Tumors," In: Proceedings of the 107th Annual Meeting of the American Association for Cancer Research; 2016 Apr 16-20; Cancer Res. 76(14 Suppl):Abstract nr 2075 (2016), 2 pages).
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	15	EP3337467: Proprietor's Submission in Response to Oppositions, dated February 3, 2022, including main request and auxiliary requests 1-23, 140 pages.
	16	EP3337467: Proprietor's Submission in Response to Oppositions, dated February 3, 2022, D13 (Written transcript of the presentation associated with D1a: LORUSSO P, et al., "Phase I Study of the Safety, Pharmacokinetics, and Pharmacodynamics of the Poly(ADP-ribose) Polymerase (PARP) Inhibitor Veliparib (ABT-888) in Combination with Irinotecan (CPT-11) in Patients with Advanced Solid Tumors," American Society of Clinical Oncology 2011 Meeting), 7 pages).
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	19	EP3337467: Proprietor's Submission in Response to Oppositions, dated February 3, 2022, D16 (Practical Medical Oncology Textbook, Eds. Russio A, et al., Springer Nature Switzerland AG, Table of Contents, pp I-XI (2021)).
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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	Gollamundi S. KISHORE
	Attorney Docket Number	01208-0007-01US

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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

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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)	2022-03-10
Name/Print	Mary R. Henninger	Registration Number	56992

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Attorney Docket Number	01208-0007-01US

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	2	EP2861210: Proprietor's response to opponent's reply to proprietor's grounds of appeal following opposition, dated June 30, 2021, D37 (Declaration of Carla Schoonderbeek) including D37A (Directive 2001/20/EC of the European Parliament and of the Counsel of 4 April 2001 ("the Clinical Trials Directive" or CTD)), 26 total pages.	
	3	EP2861210: Proprietor's response to opponent's reply to proprietor's grounds of appeal following opposition, dated June 30, 2021, D38 (Declaration of Grant H. Castle, Ph.D.) including D38A (European Commission: "Communication from the Commission – Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1)"), 23 total pages.	
	4	EP2861210: Communication of the Board of Appeals, Preliminary Opinion, dated August 9, 2021, 21 pages.	
	5	EP2861210: Proprietor Response to the Board of Appeals' Preliminary Opinion, dated December 21, 2021, 12 pages.	
	6	EP3266456: EPO Notice of Sandoz AG Opposition dated February 1, 2022, 6 pages.	
	7	EP3266456: Sandoz AG Opposition dated February 1, 2022, 23 pages.	
	8	EP3266456: EPO Notice of Teva Pharmaceuticals Industries Ltd. Opposition dated February 2, 2022, 6 pages.	
	9	EP3266456: Teva Pharmaceutical Industries Ltd. Opposition dated February 2, 2022, 12 pages.	
	10	EP3266456: EPO Notice of Generics [UK] Limited Opposition dated February 4, 2022, 5 pages.	

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	11	EP3266456: Generics [UK] Ltd. Opposition dated February 4, 2022, 13 pages.
	12	EP3266456: EPO Opposition Consolidated List of Citations, February 4, 2022, 2 pages.
	13	EP3266456: Consolidated Opposition dated February, 2022, D1 (CHEN L, et al., "Phase I Study of Liposome Irinotecan (PEP02) in Combination with Weekly Infusion of 5-FU/LV in Advanced Solid Tumors," J Clin Oncol. 28 (15_suppl):abstract e13024 (2010), 2 pages).
	14	EP3266456: Consolidated Opposition dated February, 2022, D2 (CHEN L, et al., "Phase I Study of Biweekly Liposome Irinotecan (PEP02, MM-398) in Metastatic Colorectal Cancer Failed on First-line Oxaliplatin-based Chemotherapy," J Clin Oncol. 30(4_suppl):Abstract 613 (2012), 2 pages).
	15	EP3266456: Consolidated Opposition dated February, 2022, D3 (KO A, et al., "A Multinational Phase II Study of Liposome Irinotecan (PEP02) for Patients with Gemcitabine-Refractory Metastatic Pancreatic Cancer," J Clin Oncol. 29 (4_suppl):Abstract 237 (2011), 2 pages).
	16	EP3266456: Consolidated Opposition dated February, 2022, D4 (CHEN L, et al., "Phase I Study of Liposome Encapsulated Irinotecan (PEP02) in Advanced Solid Tumor Patients," J Clin Oncol., 26(15_suppl):abstract 2565 (2008), 2 pages).
	17	EP3266456: Consolidated Opposition dated February, 2022, D5 ((Clinical Trials Identifier NCT01494506: 2012-05-29 version submitted, "A Randomized, Open Label Phase 3 Study of MM-398 Versus 5-Fluorouracil and Leucovorin in Patients With Metastatic Pancreatic Cancer." 6 pages).
	18	EP3266456: Consolidated Opposition dated February, 2022, D5a ((Clinical Trials Identifier NCT01494506: 2012-08-08 submitted, "A Randomized, Open Label Phase 3 Study of MM-398, With or Without 5-Fluorouracil and Leucovorin, Versus 5-Fluorouracil and Leucovorin in Patients with Metastatic Pancreatic Cancer Who Have Failed Prior Gemcitabine-based Therapy." 7 pages).
	19	EP3266456: Consolidated Opposition dated February, 2022, D6 ((Clinical Trials Identifier NCT01375816: 2011-06-16 version submitted, "A Randomized Phase II Study of PEP02 or Irinotecan in Combination with Leucovorin and 5-Fluorouracil in Second Line Therapy of Metastatic Colorectal Cancer." 6 pages).
	20	EP3266456: Consolidated Opposition dated February, 2022, D7 (TSAI C, et al., "Nanovector-Based Therapies in Advanced Pancreatic Cancer," J Gastroint Oncol 2(3):185-94 (2011)).
	21	EP3266456: Consolidated Opposition dated February, 2022, D8 (CAMPTOSAR package insert, 2009, 37 pages).

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	22	EP3266456: Consolidated Opposition dated February, 2022, D9 (FUSILEV package insert, 2008, 7 pages).
	23	EP3266456: Consolidated Opposition dated February, 2022, D10 (YOO C, et al., "A Randomised Phase II Study of Modified FOLFIRI.3 vs Modified FOLFOX as Second-Line Therapy in Patients with Gemcitabine-Refractory Advanced Pancreatic Cancer," Br J Cancer. 101(10):1658-63 (2009)).
	24	EP3266456: Consolidated Opposition dated February, 2022, D11 (DRUMMOND D, et al., "Development of a Highly Active Nanoliposomal Irinotecan Using a Novel Intraliposomal Stabilization Strategy," Cancer Res. 66(6):3271-77 (2006)).
	25	EP3266456: Consolidated Opposition dated February, 2022, D12 (BAKER J, et al., "Irinophore C, a Novel Nanoformulation of Irinotecan, Alters Tumor Vascular Function and Enhances the Distribution of 5-Fluorouracil and Doxorubicin," Clin Cancer Res. 14(22):7260-71 (2008)).
	26	EP3266456: Consolidated Opposition dated February, 2022, D13 (VENDITTO V, et al., "Cancer Therapies Utilizing the Camptothecins: A Review of the in Vivo Literature," Mol Pharm. 7(2):307-349 (2010)).
	27	EP3266456: Consolidated Opposition dated February, 2022, D14 (TARDI P, et. al., "Coencapsulation of Irinotecan and Floxuridine Into Low Cholesterol-Containing Liposomes That Coordinate Drug Release In Vivo," Biochim Biophys Acta. 1768(3):678–87 (2007). Epub 2006).
	28	EP3266456: Consolidated Opposition dated February, 2022, D15 (Opposition Division's decision to revoke EP2861210, dated August 28, 2019, 24 pages).
	29	EP3266456: Consolidated Opposition dated February, 2022, D16 (EP2861210: Communication of the Board of Appeals, Preliminary Opinion, dated August 9, 2021, 21 pages).
	30	EP3266456: Consolidated Opposition dated February, 2022, D17 (Clinical Trials Identifier NCT01494506: 2011-12-16 version, "A Randomized, Open Label Phase 3 Study of MM-398 Versus 5-Fluorouracil and Leucovorin in Patients With Metastatic Pancreatic Cancer." 2 pages).
	31	EP3266456: Consolidated Opposition dated February, 2022, D18 (HOSKINS J, et al., "UGT1A1*28 Genotype and Irinotecan-Induced Neutropenia: Dose Matters," J Natl Cancer Inst. 99(17):1290-95 (2007)).
	32	EP3266456: Consolidated Opposition dated February, 2022, D19 (BRIXI-BENMANSOUR H, et al., "Phase II Study of First-line FOLFIRI for Progressive Metastatic Well-differentiated Pancreatic Endocrine Carcinoma," Dig Liver Dis. 43 (11):912-6 (2011)).

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	33	EP3266456: Consolidated Opposition dated February, 2022, D20 (INFANTE J, et al., "Phase I and Pharmacokinetic Study of IHL-305 (PEGylated Liposomal Irinotecan) in Patients with Advanced Solid Tumors," Cancer Chemother Pharmacol. 70(5):699-705 (2012)).
	34	EP3266456: Consolidated Opposition dated February, 2022, D23 (European Commission Implementing Decision granting marketing authorisation for Onivyde, October 14, 2016, 39 pages).
	35	EP3266456: Consolidated Opposition dated February, 2022, D24 (WANG-GILLAM A, et al., "Nanoliposomal Irinotecan with Flourouracil and Folinic Acid in Metastatic Pancreatic Cancer After Previous Gemcitabine-Based Therapy (NAPOLI-1): A Global, Randomised, Open-Label, Phase 3 Trial," Lancet, 387(10018):545-57 (2016). Epub doi: 10.1016/S0140-6736(15)00986-1, pages 1-13 (2015)).
	36	EP3266456: Consolidated Opposition dated February, 2022, D25 (FDA News Release, "FDA Approves New Treatment for Advanced Pancreatic Cancer." http://ww.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm468654.htm, October 22, 2015, 3 pages).
	37	EP3266456: Consolidated Opposition dated February, 2022, D26 (MHRA Public Assessment Report for 5-Fluorouracil, 2006, 60 pages).
	38	EP3266456: Consolidated Opposition dated February, 2022, D27 (GEBBIA V, et al., "Irinotecan Plus Bolus/Infusional 5-Fluorouracil and Leucovorin in Patients With Pretreated Advanced Pancreatic Carcinoma: A Multicenter Experience of the Gruppo Oncologico Italia Meridionale," Am J Clin Oncol. 33(5):461-64 (2010)).
	39	EP3266456: Consolidated Opposition dated February, 2022, D28 (CHEN P, et al., "Comparing Routes of Delivery for Nanoliposomal Irinotecan Shows Superior Anti-Tumor Activity of Local Administration in Treating Intracranial Glioblastoma Xenografts," Neuro Oncol. 15(2):189-97 (2013), Epub December 21, 2012).

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Signature	/Mary R. Henninger/	Date (YYYY-MM-DD)	2022-03-10
Name/Print	Mary R. Henninger	Registration Number	56992

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-OR-

Fax to:
571-273-6500

INSTRUCTIONS: The issue fee must have been paid for the application(s) listed on this form. In addition, only an address represented by a Customer Number can be established as the fee address for maintenance fee purposes (hereafter, fee address). A fee address should be established when correspondence related to maintenance fees should be mailed to a different address than the correspondence address for the application.

When to check the first box below: If you have a Customer Number to represent the fee address.

When to check the second box below: If you have no Customer Number representing the desired fee address, in which case a completed Request for Customer Number (PTO/SB/125) must be attached to this form. For more information on Customer Numbers, see the Manual of Patent Examining Procedure (MPEP) § 403.

For the following listed application(s), please recognize as the "Fee Address" under the provisions of 37 CFR 1.363 the address associated with:

☑ Customer Number: 197

OR

☐ The attached Request for Customer Number form (PTO/SB/125)

PATENT NUMBER (if known)	APPLICATION NUMBER
	15/809,815

Completed by (check one):

☐ Applicant/Inventor

☑ Attorney or Agent of record 56992 (Reg. No.)

☐ Assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(c) (Form PTO/AIA/96) is enclosed or was filed on _____ (Date)

/Mary R. Henninger/
Signature

Mary R. Henninger
Typed or printed name

(404) 891-1400
Requester's telephone number

2022-04-01
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. If the assignee is a juristic entity, this form must be signed by a patent practitioner (attorney or agent) of record. Submit multiple forms if more than one signature is required, see below*.

☑ *Total of 1 forms are submitted

This collection of information is required by 37 CFR 1.363. The information is required to obtain or retain a benefit by the public, which is to indicate (and for the USPTO to process) a fee address. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 5 minutes to complete, including gathering, preparing, and submitting the completed form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND COMPLETED FORMS TO THE PREVIOUS ADDRESS. **SEND COMPLETED FORMS TO: Mail Stop Maintenance Fee, Director of the United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

153749 7598 03/25/2022
McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
125 Cambridge Park Drive
Suite 301
Cambridge, MA 02140

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/809,815	11/10/2017	Eliel Bayever	01208-0007-01US	5137

TITLE OF INVENTION: Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	06/27/2022

EXAMINER	ART UNIT	CLASS-SUBCLASS
KISHORE, GOLLAMUDI S	1612	424-450000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

☒ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 McNeill Baur PLLC
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Ipsen Biopharm Ltd.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Great Britain

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☒ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 506488

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Mary R. Henninger/ Date April 1, 2022

Typed or printed name Mary R. Henninger Registration 56992

Electronic Patent Application Fee Transmittal

Application Number:	15809815
Filing Date:	10-Nov-2017
Title of Invention:	Methods for Treating Metastatic Pancreatic Cancer Using Combination Therapies Comprising Liposomal Irinotecan and Oxaliplatin
First Named Inventor/Applicant Name:	Eliel Bayever
Filer:	Mary Rucker Henninger/Dawn MacPherson
Attorney Docket Number:	01208-0007-01US

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	1200	1200

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1200**

Electronic Acknowledgement Receipt

EFS ID:	45377145
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/Dawn MacPherson
Filer Authorized By:	Mary Rucker Henninger
Attorney Docket Number:	01208-0007-01US
Receipt Date:	01-APR-2022
Filing Date:	10-NOV-2017
Time Stamp:	16:00:22
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1200
RAM confirmation Number	E202241G03371722
Deposit Account	506488
Authorized User	Dawn MacPherson

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Change of Address	2022-04-01_01208-0007-01US_USPTO_FeeAddressIndicationForm.pdf	231581 2fe805c589ac198a56ad981918ca041c6086c079	no	2
Warnings:					
Information:					
2	Issue Fee Payment (PTO-85B)	2022-04-01_01208-0007-01US_Issue_Fee.pdf	77300 8f9b99cc9735a23f9d4dcc728dc0170bd131767f	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	38200 056f3593df296f5106bb7f461add940ffad4874f	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	347081		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PRINTER RUSH
(PTO ASSISTANCE)

Application: 15809815	**Examiner:** Kishore	**GAU:** 1612
From:	**Location:** IDC	**Creation Date:** 04/04/2022

Week Date: 3/21/2022

DOC CODE	DOC DATE	MISCELLANEOUS
[ ] 1449		[ ] Continuing Data
[ ] IDS		[ ] Foreign Priority
[X] CLM	02/25/2022	[ ] Document Legibility
[X] IIFW/FWCLM	03/25/2022	[ ] Fees
[ ] SRFW		[ ] Petition (TC)
[ ] DRW		[ ] Other
[ ] OATH		
[ ] 312		
[ ] SPEC		

[RUSH] Message:

Renumbered claims 12, 14 (original claims 14, 18) depends on renumbered claim 15 (original claim 19). A claim can not depend on a subsequent renumbered claim.

Thank you.

[XRUSH] Response:

Initials: _____

Examiner: PUBS contact - James Leija, (703) 756-1197
NOTE: This form will be included as part of the official USPTO record with the response document coded as XRUSH.
REV: AUG 16

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/809,815	11/10/2017	Eliel Bayever	01208-0007-01US	5137

153749 7590 04/11/2022

McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
125 Cambridge Park Drive
Suite 301
Cambridge, MA 02140

EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
04/11/2022	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mcneillbaur.com
eofficeaction@appcoll.com
patents.us@ipsen.com

CORRECTED ***Notice of Allowability***	**Application No.** 15/809,815	**Applicant(s)** Bayever et al.	
	Examiner GOLLAMUDI S KISHORE	**Art Unit** 1612	**AIA (FITF) Status** Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 4-6-2022.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☑ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/GOLLAMUDI S KISHORE/
Primary Examiner, Art Unit 1612

Continuation of 3. The allowed claim(s) is/are: 1,4-13,19 and 21-23

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in an interview with Victoria S. Lee on 4-6-2022.

The application has been amended as follows:

1) Claims 14, 15 and 18 have been canceled.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GOLLAMUDI S KISHORE whose telephone number is (571)272-0598. The examiner can normally be reached Monday through Friday 6:30 AM - 4:00 PM.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, FRED KRASS can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GOLLAMUDI S KISHORE/
Primary Examiner, Art Unit 1612

Examiner-Initiated Interview Summary	**Application No.** 15/809,815	**Applicant(s)** Bayever et al.		
	Examiner GOLLAMUDI S KISHORE	**Art Unit** 1612	**AIA (First Inventor to File) Status** Yes	**Page** 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
GOLLAMUDI S KISHORE	Primary Examiner	Telephonic
VICTORIA S. LEE	Attorney of Record	

Date of Interview: 06 April 2022

Issues Discussed:

Other

The Examiner indicated that claims 14 and 18 dependent from higher numbered claim 19. The attorney wanted these claims to be canceled. Since claim 15 depends from claim 14, claim 15 also to be canceled.

/GOLLAMUDI S KISHORE/ Primary Examiner, Art Unit 1612	04-06-2022

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/809,815	Bayever et al.
	Examiner	Art Unit
	GOLLAMUDI S KISHORE	1612

CPC							
Symbol						Type	Version
A61K	/	31	/	519		F	2013-01-01
A61K	/	31	/	282		I	2013-01-01
A61K	/	31	/	4745		I	2013-01-01
A61K	/	31	/	513		I	2013-01-01
A61K	/	9	/	1271		I	2013-01-01
A61K	/	9	/	0019		I	2013-01-01
A61K	/	31	/	475		I	2013-01-01
A61K	/	31	/	436		I	2013-01-01
A61K	/	47	/	20		I	2013-01-01
A61K	/	9	/	127		I	2013-01-01
A61K	/	2300	/	00		A	2013-01-01

CPC Combination Sets								
Symbol					Type	Set	Ranking	Version
A61K	/	31	/	519	I	1	1	2013-01-01
A61K	/	2300	/	00	I	1	2	2013-01-01
A61K	/	31	/	4745	I	2	1	2013-01-01
A61K	/	2300	/	00	I	2	2	2013-01-01
A61K	/	31	/	282	I	3	1	2013-01-01
A61K	/	2300	/	00	I	3	2	2013-01-01
A61K	/	31	/	513	I	4	1	2013-01-01
A61K	/	2300	/	00	I	4	2	2013-01-01

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	15	
/GOLLAMUDI S KISHORE/ Primary Examiner, Art Unit 1612	06 April 2022	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	4A

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/809,815	Bayever et al.
	Examiner	**Art Unit**
	GOLLAMUDI S KISHORE	1612

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K31/519	/	31	/	519
A61K31/282	/	31	/	282
A61K31/4745	/	31	/	4745
A61K31/513	/	31	/	513
A61K9/127	/	9	/	127
A61K9/00	/	9	/	00
A61K31/475	/	31	/	475
A61K31/436	/	31	/	436
A61K47/20	/	47	/	20

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE (Assistant Examiner) (Date)	**Total Claims Allowed:** 15	
/GOLLAMUDI S KISHORE/ Primary Examiner, Art Unit 1612 (Primary Examiner) 06 April 2022 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 4A

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/809,815	Bayever et al.
	Examiner	Art Unit
	GOLLAMUDI S KISHORE	1612

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	8	10	12	19										
	2	9	11		20										
	3	10	12	13	21										
2	4	11	13	14	22										
3	5		14	15	23										
4	6		15												
5	7		16												
6	8		17												
7	9		18												

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	15	
/GOLLAMUDI S KISHORE/ Primary Examiner, Art Unit 1612	06 April 2022	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	4A

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Application	Document	Mailroom Date	Attorney Docket No.
15809815	NOA	04/11/2022	01208-0007-01US
	EXIN	04/11/2022	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

	9	7850990	B2	2010-12-14	Tardi et al.	
	10	9511155	B2	2016-12-06	Drummond et al.	
Change(s) applied to document, /MJE/ 4/29/2022	11	9616081	B2	2017-04-11	~~Taiho Pharmaceutical Co., Ltd~~ Okabe	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20020035091	A1	2002-03-21	Govindarajan et al.	
	2	20040071768	A1	2004-04-15	Sarris et al.	
	3	20110104256	A1	2011-05-05	Wang et al.	
	4	20120034295	A1	2012-02-09	Spiegel et al.	
	5	20120282325	A1	2012-11-08	Tong et al.	
	6	20160058704	A1	2016-03-03	Tardi et al.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /G.S.K/

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/809,815	05/31/2022	11344552	01208-0007-01US	5137

153749 7590 05/11/2022

McNeill Baur PLLC/Ipsen
Ipsen Bioscience, Inc.
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ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

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Application	Document	Mailroom Date	Attorney Docket No.
15809815	ISSUE.NTF	05/11/2022	01208-0007-01US

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