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Original Research

First-line liposomal irinotecan with oxaliplatin, 5-fluorouracil and leucovorin (NALIRIFOX) in pancreatic ductal adenocarcinoma: A phase I/II study☆,☆☆

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Abstract ***Background:*** This open-label, phase I/II study evaluated safety and efficacy for first-line liposomal irinotecan + oxaliplatin + 5-fluorouracil + leucovorin (NALIRIFOX). ***Methods:*** Patients (aged ≥18 years) had locally advanced/metastatic pancreatic ductal adenocarcinoma (mPDAC), with an Eastern Cooperative Oncology Group performance status score

☆ Prior presentation: The contents of this article satisfy the criteria for originality. Results from this final data cutoff have been presented at: the European Society for Medical Oncology World Congress on Gastrointestinal Cancer 2020 – Virtual, 1–4 July, 2020; and the European Society for Medical Oncology Virtual Congress 2020, 19–21 September 2020.

☆☆ Results from earlier data cutoff dates were presented at: the American Association for Cancer Research Special Conference on Pancreatic Cancer: Advances in Science and Clinical Care, 2019, Boston, MA, 6–9 September, 2019; the European Society for Medical Oncology World Congress on Gastrointestinal Cancer 2019, Barcelona, Spain, 3–6 July, 2019; and the American Society of Clinical Oncology Annual Conference, Chicago, IL, 1–5 June, 2018.

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'Irinotecan');
Locally advanced pancreatic adenocarcinoma;
Metastatic pancreatic adenocarcinoma (MeSH: 'pancreatic neoplasms', 'carcinoma, pancreatic ductal', 'neoplasm metastasis');
Clinical trial (MeSH: 'clinical trials as topic')

of 0/1 and adequate organ function. Primary objectives were to determine the maximum tolerated dose (MTD) and to evaluate safety and tolerability. Treatment-emergent adverse events (TEAEs) were graded using National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. Efficacy end-points included progression-free survival (PFS) and overall survival (OS); disease assessments used Response Evaluation Criteria in Solid Tumors 1.1.
Results: The MTD (liposomal irinotecan 50 mg/m^2 [free-base equivalent], oxaliplatin 60 mg/m^2, 5-fluorouracil 2400 mg/m^2, leucovorin 400 mg/m^2 every 2 weeks) was based on dose-limiting toxicities and cumulative safety data in four dose-exploration cohorts. The MTD was received by 32 of 56 patients, seven during dose exploration and 25 during dose expansion (median age 58.0 years [range, 39–76], 28 [87.5%] with metastatic disease at diagnosis [29 at study entry], and one receiving study treatment at data cutoff [26 February 2020]). Of these patients, 22 of 32 had grade ≥3 treatment-related TEAEs, most commonly neutropenia (31.3%), febrile neutropenia (12.5%) and hypokalaemia (12.5%); ten had serious treatment-related TEAEs; and three died from TEAEs considered unrelated to treatment. Median PFS and OS were 9.2 (95% CI: 7.69–11.96) and 12.6 (8.74–18.69) months, respectively.
Conclusion: First-line NALIRIFOX for patients with locally advanced/mPDAC was generally manageable and tolerable. A randomised, controlled phase III study is underway.

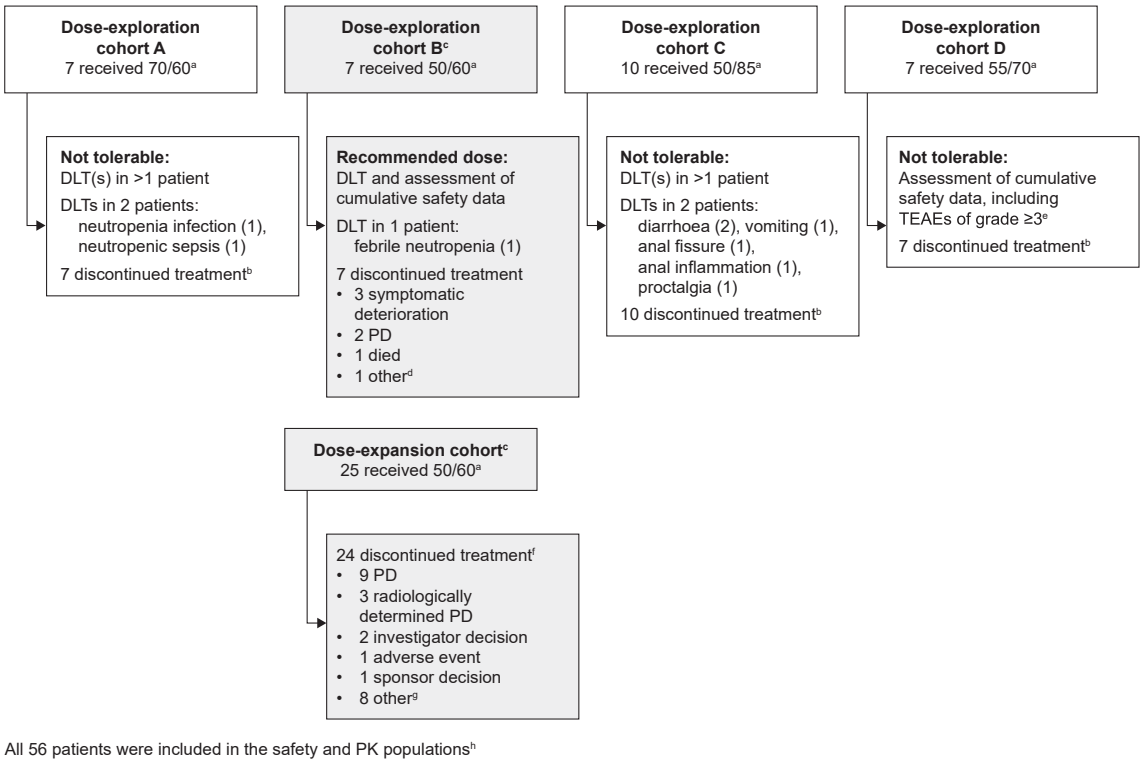

Fig. 1. Flow of patients through the study. [a] Dose of liposomal irinotecan (free-base equivalent)/dose of oxaliplatin expressed in mg/m^2 to be administered in combination with 5-fluorouracil 2400 mg/m^2 and leucovorin 400 mg/m^2 on days 1 and 15 of each 28-day cycle. [b] Reasons for discontinuation are provided in Table A2. [c] Cohorts receiving the recommended dose were included in the pooled population 50/60 for the analysis of efficacy and safety. [d] Owing to patient decision. [e] All TEAEs of grade ≥3 are provided in Table A3. [f] One patient was still receiving treatment at the data cutoff. [g] Owing to patient decision (four patients), clinical progression (two patients), consent withdrawn (one patient) and lack of clinical benefit/adverse event (one patient). [h] All patients in the enrolled population (completed screening successfully with documented enrolment date) were included in the safety and PK populations. Abbreviations: DLT, dose-limiting toxicity; PD, progressive disease; PK, pharmacokinetic.

Table 1
Demographic and disease characteristics at baseline.

Characteristic	Dose-exploration cohorts				Dose-expansion cohort	Pooled population
	A (70/60[a]) (n = 7)	B (50/60[a]) (n = 7)	C (50/85[a]) (n = 10)	D (55/70[a]) (n = 7)	(50/60[a]) (n = 25)	(50/60[a,b]) (n = 32)
Age, years						
Mean (SD)	66.7 (7.87)	60.4 (10.66)	65.5 (5.21)	63.1 (7.17)	56.8 (9.95)	57.6 (10.05)
Median (range)	64.0 (58–78)	57.0 (44–74)	66.5 (57–73)	61.0 (54–73)	58.0 (39–76)	58.0 (39–76)
Women, No. (%)	6 (85.7)	4 (57.1)	2 (20.0)	2 (28.6)	14 (56.0)	18 (56.3)
Race, No. (%)						
White	6 (85.7)	7 (100)	9 (90.0)	7 (100)	21 (84.0)	28 (87.5)
Black or African American	0	0	0	0	2 (8.0)	2 (6.3)
Asian	1 (14.3)	0	1 (10.0)	0	1 (4.0)	1 (3.1)
Missing	0	0	0	0	1 (4.0)	1 (3.1)
ECOG performance status score, No. (%)						
0	1 (14.3)	6 (85.7)	6 (60.0)	5 (71.4)	8 (32.0)	14 (43.8)
1	6 (85.7)	1 (14.3)	4 (40.0)	2 (28.6)	17 (68.0)	18 (56.3)
*UGT1A1*28* allele status, No. (%)						
Negative	4 (57.1)	3 (42.9)	5 (50.0)	3 (42.9)	11 (44.0)[c]	14 (43.8)[c]
Homozygous (7/7)	1 (14.3)	1 (14.3)	1 (10.0)	0	1 (4.0)	2 (6.3)
Heterozygous (7/6)	2 (28.6)	2 (28.6)	3 (30.0)	4 (57.1)	11 (44.0)	13 (40.6)
Missing	0	1 (14.3)	1 (10.0)	0	1 (4.0)	2 (6.3)
Tumour stage at diagnosis, No. (%)[d]						
IIA	0	0	0	0	1 (4.0)	1 (3.1)
III	3 (42.9)	1 (14.3)	2 (20.0)	2 (28.6)	2 (8.0)	3 (9.4)
IV	4 (57.1)	6 (85.7)	8 (80.0)	5 (71.4)	22 (88.0)	28 (87.5)
Tumour location, No. (%)						
Head	5 (71.4)	4 (57.1)	3 (30.0)	2 (28.6)	6 (24.0)	10 (31.3)
Body	0	2 (28.6)	6 (60.0)	3 (42.9)	2 (8.0)	4 (12.5)
Tail	1 (14.3)	1 (14.3)	0	1 (14.3)	8 (32.0)	9 (28.1)
Head and body	0	0	0	0	1 (4.0)	1 (3.1)
Body and tail	0	0	1 (10.0)	1 (14.3)	4 (16.0)	4 (12.5)
Missing	1 (14.3)	0	0	0	4 (16.0)	4 (12.5)
Metastatic lesion locations, No. (%)						
Liver	3 (42.9)	2 (28.6)	4 (40.0)	3 (42.9)	12 (48.0)	14 (43.8)
Lung	0	1 (14.3)	2 (20.0)	4 (57.1)	3 (12.0)	4 (12.5)
Lymph nodes	0	0	0	0	1 (4.0)	1 (3.1)
Other	2 (28.6)	4 (57.1)	4 (40.0)	1 (14.3)	16 (64.0)	20 (62.5)
Missing	4 (57.1)	1 (14.3)	4 (40.0)	3 (42.9)	4 (16.0)	5 (15.6)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.
[a] Dose of liposomal irinotecan (free-base equivalent)/dose of oxaliplatin expressed in mg/m^2 to be administered in combination with 5-fluorouracil 2400 mg/m^2 and leucovorin 400 mg/m^2 every on days 1 and 15 of each 28-day cycle.
[b] Comprises cohorts assigned to receive liposomal irinotecan 50 mg/m^2 and oxaliplatin 60 mg/m^2 during the dose-exploration or dose-expansion parts of the study.
[c] Excludes one patient with compound heterozygosity for the TA5 and TA7 polymorphisms.
[d] One patient in the dose-expansion cohort received a diagnosis of stage IIA disease but entered the study with stage IV disease.

1. Introduction

Advanced pancreatic cancer is associated with poor clinical outcomes [1]. Preferred first-line treatment options for patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) include gemcitabine + albumin-bound paclitaxel (gemcitabine/nab-paclitaxel) and non-liposomal irinotecan + oxaliplatin + 5-fluorouracil/leucovorin (5-FU/LV) (FOLFIRINOX) [2,3]. Although both regimens provided significant improvements in survival outcomes compared with gemcitabine monotherapy in clinical trials [4,5], survival rates for pancreatic cancer have remained low [6–8]. The research imperative for the treatment of patients with mPDAC therefore remains developing and testing new agents and new combinations in the first-line setting.

The non-liposomal formulation of the topoisomerase I inhibitor irinotecan is a well-established component of various combination therapies [9], including FOLFIRINOX in mPDAC [2,10,11]. However, preclinical and clinical data suggest there may be additional benefits if liposomal irinotecan (ONIVYDE®; historically nal-IRI; Ipsen Biopharmaceuticals, Inc., Cambridge, MA, USA) is substituted for the non-liposomal formulation. Liposomal irinotecan (70 mg/m^2 free-base equivalent), in combination with 5-FU (2400 mg/m^2) and LV (400 mg/

Table 2
Duration of treatment, cumulative doses and overview of TEAEs.

	Dose-exploration cohorts				Dose-expansion cohort	Pooled population
	A (70/60[a]) (n = 7)	B (50/60[a]) (n = 7)	C (50/85[a]) (n = 10)	D (55/70[a]) (n = 7)	(50/60[a]) (n = 25)	(50/60[a,b]) (n = 32)
Duration of treatment in weeks,[c] mean (SD)						
Liposomal irinotecan	3.8 (5.02)	44.6 (49.26)	23.2 (31.62)	14.0 (16.20)	28.4 (20.36)	31.9 (28.93)
Oxaliplatin	3.8 (5.02)	44.6 (49.26)	15.1 (17.67)	14.0 (16.20)	25.8 (18.61)	29.9 (28.28)
5-Fluorouracil	4.1 (5.02)	44.9 (49.30)	23.5 (31.62)	14.3 (16.20)	28.7 (20.36)	32.2 (28.94)
Leucovorin	3.8 (5.02)	44.6 (49.26)	23.2 (31.62)	14.0 (16.20)	28.4 (20.36)	31.9 (28.94)
Cumulative doses in mg, median (range)						
Liposomal irinotecan	160.5 (79.1 −398.1)	620.5 (59.7 −3574.1)	185.8 (59.8 −2748.2)	326.5 (64.7 −794.3)	632.0 (58.8 −1683.2)	626.2 (58.8 −3574.1)
Oxaliplatin	120.3 (59.4 −359.6)	705.8 (59.7 −3087.7)	269.8 (84.8 −1636.5)	353.3 (69.7 −1221.1)	596.3 (58.8 −1440.4)	598.8 (58.8 −3087.7)
5-Fluorouracil	4813.7 (2373.9 −14444.4)	22844.1 (2400.0 −143350.5)	7867.6 (2400.0 −108238.0)	12081.1 (2388.1 −41865.3)	25347.4 (2352.9 −67326.2)	24862.7 (2352.9 −143350.5)
Leucovorin	802.3 (395.7 −2407.4)	4805.8 (400.0 −23926.0)	1406.8 (400.0 −17966.3)	2012.5 (394.2 −9170.1)	4953.8 (411.8 −12411.1)	4879.8 (400.0 −23926.0)
Any TEAE	7 (100)	7 (100)	10 (100)	7 (100)	25 (100)	32 (100)
Any treatment-related[d] TEAE	6 (85.7)	7 (100)	9 (90.0)	7 (100)	25 (100)	32 (100)
Grade ≥3	6 (85.7)	4 (57.1)	8 (80.0)	5 (71.4)	18 (72.0)	22 (68.8)
Any TEAE leading to dose discontinuation[e]	5 (71.4)	1 (14.3)	3 (30.0)	3 (42.9)	7 (28.0)	8 (25.0)
Any TEAE leading to dose adjustment[f]	2 (28.6)	4 (57.1)	7 (70.0)	4 (57.1)	22 (88.0)	26 (81.3)
Any serious TEAE	6 (85.7)	2 (28.6)	7 (70.0)	4 (57.1)	15 (60.0)	17 (53.1)
Leading to death[g]	0	1 (14.3)	1 (10.0)	1 (14.3)	2 (8.0)	3 (9.4)
Treatment-related[d]	4 (57.1)	1 (14.3)	5 (50.0)	4 (57.1)	9 (36.0)	10 (31.3)
TEAE of grade ≥3 occurring in ≥5% of the pooled population						
Neutropenia	1 (14.3)	2 (28.6)	3 (30.0)	1 (14.3)	8 (32.0)	10 (31.3)
Hypokalaemia	3 (42.9)	2 (28.6)	2 (20.0)	3 (42.9)	4 (16.0)	6 (18.8)
Diarrhoea	3 (42.9)	1 (14.3)	4 (40.0)	1 (14.3)	3 (12.0)	4 (12.5)
Neutrophil count decreased	1 (14.3)	0	1 (10.0)	0	4 (16.0)	4 (12.5)
Febrile neutropenia	0	1 (14.3)	0	0	3 (12.0)	4 (12.5)
Alanine aminotransferase increased	0	0	0	0	4 (16.0)	4 (12.5)
Vomiting	1 (14.3)	0	3 (30.0)	0	3 (12.0)	3 (9.4)
Anaemia	0	1 (14.3)	0	0	2 (8.0)	3 (9.4)
Nausea	0	0	3 (30.0)	0	3 (12.0)	3 (9.4)
Abdominal pain	0	0	0	1 (14.3)	3 (12.0)	3 (9.4)
Lymphocyte count decreased	0	0	0	0	3 (12.0)	3 (9.4)
Hypoalbuminemia	1 (14.3)	0	0	0	2 (8.0)	2 (6.3)
Back pain	0	1 (14.3)	0	0	1 (4.0)	2 (6.3)
Dyspnoea	0	0	0	0	2 (8.0)	2 (6.3)
Gamma-glutamyltransferase increased	0	0	0	0	2 (8.0)	2 (6.3)
Hyperglycaemia	0	0	0	0	2 (8.0)	2 (6.3)
Hyponatraemia	0	0	0	0	2 (8.0)	2 (6.3)
White blood cell count decreased	0	0	0	0	2 (8.0)	2 (6.3)

Data are no. (%) of patients from the safety population unless stated otherwise. Events were coded in accordance with the preferred terms in the Medical Dictionary for Regulatory Activities version 20.1 and toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Abbreviations: SD, standard deviation; TEAE, treatment-emergent adverse event.

[a] Dose of liposomal irinotecan (free-base equivalent)/dose of oxaliplatin expressed in mg/m^2 to be administered in combination with 5-fluorouracil 2400 mg/m^2 and leucovorin 400 mg/m^2 on days 1 and 15 of each 28-day cycle.

[b] Comprises cohorts assigned to receive liposomal irinotecan 50 mg/m^2 and oxaliplatin 60 mg/m^2 during the dose-exploration or dose-expansion parts of the study.

[c] Duration of treatment (in days) was calculated as (date of last exposure − date of first exposure) + 1, before being converted to weeks.

[d] Comprises TEAEs considered by the investigator to be related to any of the four treatments administered or for which the relationship was missing.

[e] Refers to discontinuation of oxaliplatin alone or all four treatments administered, as described in the protocol. In the PP 50/50, TEAEs leading to discontinuation were peripheral neuropathy (two patients); abdominal pain, biliary dilatation, enterocolitis, malignant gastrointestinal obstruction, neurotoxicity, decreased platelet count, thrombocytopenia, upper gastrointestinal haemorrhage and decreased white blood cell count (one patient in each case); in some patients more than one TEAE contributed to discontinuation.

[f] Refers to an adjustment in the dose of any of the four treatments administered.

[g] TEAEs leading to death, considered unrelated to treatment: cohort B, upper gastrointestinal haemorrhage (n = 1); cohort C, subdural haematoma (n = 1), dose-expansion cohort, malignant gastrointestinal obstruction (n = 1, considered unrelated to treatment), disease progression (n = 1, considered unrelated to treatment); considered related to treatment: cohort D, colitis (n = 1).

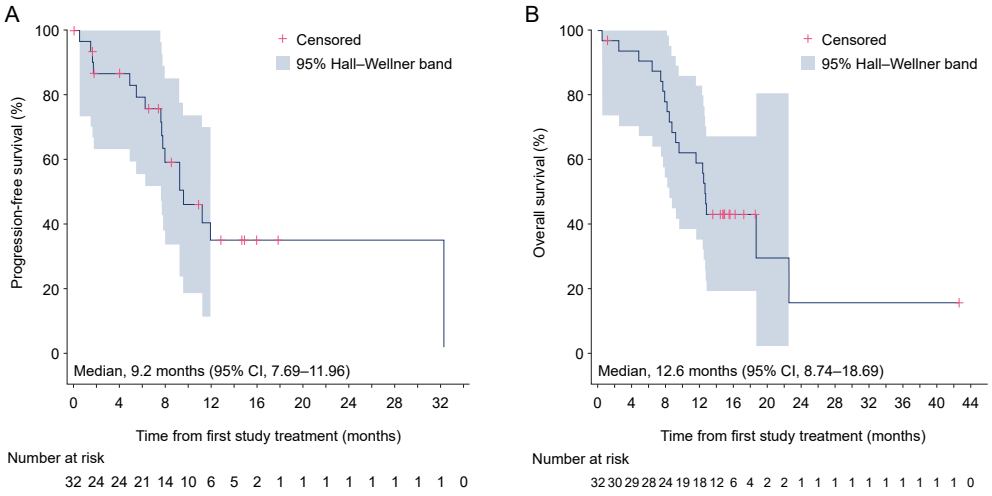

Fig. 2. (A) PFS and (B) OS in the pooled population of patients receiving the recommended dose (50/60[a]). Data are from the safety population (n = 32). Median PFS and OS were calculated using the Kaplan–Meier method, with 95% CIs calculated using Brookmeyer–Crowley methods. Confidence bands are 95% Hall–Wellner bands. One patient with minimal progressive disease per RECIST version 1.1 was approved for treatment continuation as the investigator believed there was a benefit from treatment. PFS for this patient ended at the date of minimal progressive disease. [a]Comprises cohorts assigned to receive liposomal irinotecan 50 mg/m^2 (free-base equivalent) and oxaliplatin 60 mg/m^2, in combination with 5-fluorouracil 2400 mg/m^2 and leucovorin 400 mg/m^2, on days 1 and 15 of each 28-day cycle during either the dose-exploration or dose-expansion parts of the study. Abbreviations: CI, confidence interval; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 3
Clinical response.

	Dose-exploration cohorts				Dose-expansion cohort	Pooled population
	A (70/60[a]) (n = 7)	B (50/60[a]) (n = 7)	C (50/85[a]) (n = 10)	D (55/70[a]) (n = 7)	(50/60[a]) (n = 25)	(50/60[a,b]) (n = 32)
Best overall response[c], No. (%)						
CR	0	0	0	0	1 (4.0)	1 (3.1)[d]
PR	0	3 (42.9)	3 (30.0)	1 (14.3)	7 (28.0)	10 (31.3)
SD	2 (28.6)	3 (42.9)	1 (10.0)	3 (42.9)	12 (48.0)	15 (46.9)
PD	1 (14.3)	0	2 (20.0)	1 (14.3)	3 (12.0)	3 (9.4)
Non-PD/non-CR[e]	1 (14.3)	0	0	0	0	0
Not evaluable	3 (42.9)	1 (14.3)	4 (40.0)	2 (28.6)	2 (8.0)	3 (9.4)
Overall response (CR + PR), rate [95% CI][f]	0 [0, 41.0]	42.9 [9.9, 81.6]	30.0 [6.7, 65.2]	14.3 [0.4, 57.9]	32.0 [14.9, 53.5]	34.4 [18.6, 53.2]
DCR at 16 weeks (CR + PR + SD), rate [95% CI][g]	42.9 [9.9, 81.6]	71.4 [29.0, 96.3]	40.0 [12.2, 73.8]	28.6 [3.7, 71.0]	72.0 [50.6, 87.9]	71.9 [53.3, 86.3]
Duration of response[h]	(n = 0)	(n = 3)	(n = 3)	(n = 1)	(n = 8)	(n = 11)
Median, months [95% CI]	NE [NE, NE]	28.4 [3.52, NE]	NE [NE, 16.39]	NE [NE, NE]	9.4 [2.20, NE]	9.4 [3.52, NE]

Data are from the safety population and responses were determined using RECIST version 1.1.
Abbreviations: CI, confidence interval; CR, complete response; DCR, disease control rate; NE, not estimable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

[a] Dose of liposomal irinotecan (free-base equivalent)/dose of oxaliplatin expressed in mg/m^2 to be administered in combination with 5-fluorouracil 2400 mg/m^2 and leucovorin 400 mg/m^2 every on days 1 and 15 of each 28-day cycle.

[b] Comprises cohorts assigned to receive liposomal irinotecan 50 mg/m^2 and oxaliplatin 60 mg/m^2 during the dose-exploration or dose-expansion parts of the study.

[c] Best response recorded from the start of study treatment until disease progression or the start of new anti-cancer therapy.

[d] Patient received a diagnosis of locally advanced stage III disease.

[e] As per the protocol (version 1.0) at the time of their screening, one patient had a measurable lesion in a lymph node at screening that was too small to be considered a target lesion in accordance with RECIST version 1.1. Consequently, this patient was followed only for non-target lesions (included in the table above as 'non-PD/non-CR') but was included in the summary of overall response. The protocol was later amended to require the presence of target lesion(s).

[f] Proportion of patients with a CR or PR as the best overall response; 95% CIs were calculated using the Clopper–Pearson method.

[g] Proportion of patients with CR, PR or SD at the week-16 assessment; patients who died, whose tumours were no longer assessed, or who started new anti-cancer treatment before the week-16 assessment were not considered to have achieved disease control at week 16.

[h] Time from the first date of response (CR or PR) to the date of the first documented radiologically determined PD; duration of response was not calculated for patients who started a new anti-cancer treatment before the first response.

m^2), is already a recommended treatment option for patients with mPDAC following progression with gemcitabine-based therapy, based on the results of the NAPOLI-1 phase III trial [2,3,12]. Preclinically, the active metabolite, SN-38, persists longer in tumours after administration of liposomal irinotecan (up to 168 h) than after administration of non-liposomal irinotecan (<48 h) [13]. Furthermore, in patients with mPDAC receiving liposomal irinotecan + 5-FU/LV during NAPOLI-1 [12], longer exposures to unencapsulated SN-38 above a key threshold and higher average plasma concentrations of total irinotecan, total SN-38 and unencapsulated SN-38 were all associated with better overall survival (OS) and progression-free survival (PFS) [14]. Improved anti-tumour activity has also been observed with liposomal versus non-liposomal irinotecan, when administered with oxaliplatin + 5-FU, in a patient-derived xenograft model [15].

This open-label, phase I/II study used the NALIRIFOX regimen, in which liposomal irinotecan replaced the non-liposomal irinotecan component of FOLFIRINOX. It was designed to establish a recommended dose for further study, and to investigate safety/tolerability, efficacy and pharmacokinetics (PK) in patients with locally advanced or mPDAC who had not been treated previously in the advanced/metastatic setting.

2. Methods

2.1. Patients

The study comprised two parts: dose exploration followed by dose expansion. Eligible patients were ≥18 years of age, had histologically or cytologically confirmed pancreatic adenocarcinoma that was locally advanced or metastatic, and had not been treated previously in the advanced/metastatic setting. Patients also had measurable disease using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [16]; adequate haematological, hepatic and renal function; and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 [17] (dose-exploration part) or a Karnofsky Performance Status score of ≥70 [18] (dose-expansion part). Exclusion criteria included any second malignancy in the previous 3 years and use of strong CYP3A4 inhibitors or inducers, or strong UGT1A1 inhibitors.

2.2. Study design and treatment

This open-label, two-part, phase I/II study enrolled patients between 26 October 2015 and 29 October 2018. The study was conducted at 21 sites in Australia, Spain and the USA. The data cutoff for the long-term follow-up results presented here was 26 February 2020.

Patients received study treatment every 2 weeks (days 1 and 15 of each 28-day cycle). Intravenous treatment was administered sequentially beginning with liposomal irinotecan, then oxaliplatin, LV 400 mg/m^2 and 5-FU 2400 mg/m^2 (no bolus; continuous infusion over 46 h); see Appendix for further details. Patients were intended to receive study treatment until radiologically determined progressive disease (PD) or unacceptable toxicity related to study treatment. Patients could discontinue oxaliplatin alone at the investigator's discretion; otherwise, discontinuation was of all four study drugs. Granulocyte colony stimulating factors (G-CSF) were permitted at investigator discretion, to manage neutropenia or as prophylaxis if patients were considered high risk (see Appendix). Oxaliplatin dose reductions were permitted for sensory neuropathy (see protocol). Survival data and information about subsequent mPDAC therapies were obtained every 8 weeks after discontinuation until death or study completion.

Dose exploration used a traditional 3 + 3 design (see Appendix); with dosing based on that administered in the NAPOLI-1 (liposomal irinotecan 70 mg/m^2 free-base equivalent) and PRODIGE 4 (FOLFIRINOX; oxaliplatin 85 mg/m^2) pivotal studies [5,12]. Doses (in order of testing) were cohort A: liposomal irinotecan 70 mg/m^2 free-base equivalent + oxaliplatin 60 mg/m^2 (70/60); cohort B: 50/60; cohort C: 50/85 (all predetermined); and cohort D: 55/70 (introduced in a protocol amendment, see Appendix). Dose-limiting toxicities (DLTs, defined in Appendix) were measured during cycle 1 (28-day DLT period). Progression to the next cohort occurred after safety evaluation was complete for the last patient enrolled in a cohort.

During dose expansion, patients received the maximum tolerated dose (MTD); those withdrawing were not replaced.

2.3. Assessments and end-points

For dose exploration, the primary objectives were to characterise DLTs and determine the recommended dose. Overall, the primary study objectives were safety and tolerability, with secondary objectives of efficacy and PK.

Treatment-emergent adverse events (TEAEs) were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.1, and toxicity was graded using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Key TEAEs were defined in the clinical study report (CSR) using MedDRA terms, based on monitoring and the known safety profiles of liposomal irinotecan and oxaliplatin: diarrhoea (grade ≥3), febrile neutropenia (any grade), neutropenic sepsis (any grade), neutropenia (grade ≥3), thrombo-embolic events (any grade), peripheral neuropathy (grade ≥3).

Computerised tomography or magnetic resonance imaging was performed at screening (baseline), every 8 weeks thereafter until radiologically determined PD,

and at end of treatment. Disease was evaluated by investigators using RECIST version 1.1. Efficacy endpoints included PFS, OS, overall response rate (ORR), the disease control rate at 16 weeks (DCR_{16}) and the duration of response (DoR).

PK analyses and exploratory analyses of survival in *post hoc* subgroups are described in the Appendix.

2.4. Statistical analyses

The sample size for dose exploration was dependent on the number of patients enrolled into cohorts and the toxicity rate. The recommended dose was to be received by at least 30 patients; there was no efficacy hypothesis.

The median PFS and OS were calculated using the Kaplan–Meier method (with hazard ratios [HRs] determined using Cox regression for biomarker subgroups); 95% confidence intervals (CIs) were calculated using Brookmeyer–Crowley methods. For measures of clinical response, patients without a postbaseline tumour assessment were classified as not evaluable. DoR was analysed using the Kaplan–Meier method and 95% CIs were calculated using the Clopper–Pearson and Brookmeyer–Crowley methods for ORR and DCR_{16}, respectively.

Analyses were conducted for the safety and PK populations. Statistical analyses were performed with SAS® software version 9.3 or higher (SAS Institute, Inc., Cary, NC, USA). Censoring rules (Table A1) and population definitions are provided in the Appendix.

2.5. Study oversight

The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Consolidated Guideline on Good Clinical Practice. Study documentation was approved by an independent ethics committee and institutional review board. Patients provided written informed consent at screening. Protocol amendments made after the study started are described in the protocol.

3. Results

3.1. Dose exploration

Of the 31 patients enrolled for dose exploration, five experienced ≥1 DLT. The doses used in cohorts A and C were not considered tolerable because two patients in each cohort experienced ≥1 DLT. In cohort A (70/60, seven patients), neutropenic infection (grade 4) was reported in one patient and neutropenic sepsis (grade 4) in another patient. In cohort C (50/85, 10 patients), diarrhoea and vomiting were reported in one patient (both grade 4 and > 3 days in duration); and diarrhoea (grade 3, >3 days in duration), anal fissure, anal inflammation and proctalgia (all grade 2 and delayed the next scheduled dose by >14 days) were reported in another patient. Although no patients had DLTs in cohort D (55/70, seven patients), the dose was not considered tolerable following review of grade ≥3 TEAEs. Finally, one patient had a DLT of febrile neutropenia (grade 3) in cohort B (50/60, seven patients). Following review of cumulative safety in this cohort, 50/60 was the MTD recommended for expansion (Fig. 1).

3.2. Population receiving the recommended dose

3.2.1. Patient disposition and baseline characteristics

In total, 32 of the 56 patients enrolled in the study received the recommended dose, seven during dose exploration and 25 during dose expansion (Fig. 1). These patients had a median age of 58.0 years; 87.5% had metastatic disease at diagnosis, 43.8% had liver metastases and 56.3% had an ECOG performance status score of 1 (Table 1).

3.2.2. Treatment

Treatment durations and cumulative doses are reported in Table 2. In total, 31 of 32 patients receiving the recommended dose discontinued study treatment, most commonly because of PD (14 patients) (Fig. 1, Table A2). Of those who discontinued treatment, 25 subsequently received second-line therapy, most commonly gemcitabine/nab-paclitaxel (15 patients) (Appendix).

3.2.3. Safety and tolerability

All 32 patients receiving the recommended dose experienced ≥1 TEAE considered related to treatment (Table 2). Key TEAEs defined in the CSR (using MedDRA v20.1) were experienced by 19 patients: grade ≥3 neutropenia (10 patients, all considered treatment-related); febrile neutropenia (four patients, all grade ≥3 and considered treatment-related); grade ≥3 diarrhoea (four patients, considered treatment-related in three); thrombo-embolic events (five patients); no patients experienced neutropenic sepsis or grade ≥3 peripheral neuropathy (which was present only in cohort C [50/85, one patient]; Table A3).

The most common grade ≥3 TEAEs apart from neutropenia, febrile neutropenia and diarrhoea (see above) were hypokalaemia (six patients), neutrophil count decreased and alanine aminotransferase increased (four patients each) (Table 2, Table A3).

Grade ≥3 treatment-related TEAEs occurred in 22 of 32 patients; the most common apart from neutropenia, febrile neutropenia and diarrhoea (see above) were hypokalaemia (four patients), nausea (three patients) and neutrophil count decreased (3 patients) (Table A4). The following grade ≥3 treatment-related liver function abnormalities were reported: increases in alanine aminotransferase (two patients), gamma-glutamyltransferase (two patients), aspartate

aminotransferase (one patient) and blood alkaline phosphatase (one patient); and hepatotoxicity (one patient).

Serious TEAEs were reported for 17 patients (Table 2, Table A5) and were considered treatment-related in 10 patients (Table A6). Three patients died from TEAEs considered unrelated to treatment (Table 2).

TEAEs led to discontinuation (of oxaliplatin alone or all four study treatments) in eight patients and dose adjustments of any study treatment in 26 (Table 2). Sixteen patients received G-CSF (Table A8).

Clinically significant laboratory test abnormalities were reported as TEAEs. Laboratory and other safety assessment results were in line with the expected safety profile of the study regimen.

3.2.4. Efficacy

The median PFS was 9.2 months (95% CI: 7.69–11.96; Fig. 2A) in patients receiving the recommended dose. Fifteen patients had censored data, of whom one was still receiving treatment. The median OS was 12.6 months (95% CI: 8.74–18.69; Fig. 2B), with 20 deaths reported. Best overall response, ORR, DCR_{16} and DoR are reported in Table 3.

3.2.5. Other end-points

Results of PK and exploratory analyses are reported in the Appendix.

4. Discussion

Improvements in survival rates remain elusive for patients with pancreatic cancer [6,19], underscoring the need for improved treatment options [1]. To date, only one phase III trial of targeted therapy added to chemotherapy has shown improvement in survival for patients newly diagnosed with mPDAC [1,11,20–22], highlighting the need for more durable combination chemotherapy regimens as the backbone for future first-line treatment. In this phase I/II study, patients with locally advanced or mPDAC received a new combination first line: liposomal irinotecan 50 mg/m^2 + oxaliplatin 60 mg/m^2 + 5-FU 2400 mg/m^2 + LV 400 mg/m^2 every 2 weeks (NALIRIFOX).

The safety of NALIRIFOX cannot be reliably compared with that of established therapies without head-to-head studies. However, no unexpected safety outcomes were apparent based on the known safety profiles of the drugs. Of the key TEAEs, grade ≥3 neutropenia was the most common among patients receiving the recommended dose (31.3%), followed by any grade of thrombo-embolic events (15.6%), then any grade of febrile neutropenia and grade ≥3 diarrhoea (12.5% for each). In addition, grade ≥3 neutrophil count decreased was reported in 12.5% of patients. G-CSF was administered to 50% of patients, to manage neutropenia or as prophylaxis in those considered high risk. G-CSF is permitted at the investigator's discretion in the ongoing NAPOLI-3 phase III study of NALIRIFOX (ClinicalTrials.gov NCT04083235; EudraCT 2018-003585-14). In the final long-term analysis of the NAPOLI-1 study, the most common grade ≥3 TEAEs (using MedDRA v14.1) [23] in patients receiving liposomal irinotecan + 5-FU/LV were neutropenia (32%; comprising neutropenia, neutrophil count decreased, neutropenic sepsis, febrile neutropenia and several other terms), fatigue (14%), diarrhoea (13%) and vomiting (12%) [24]. Similarly, in the PRODIGE 4 study, the most common grade 3–4 TEAEs (using CTCAE v3.0) in patients receiving FOLFIRINOX were neutropenia (45.7%), fatigue (23.6%), vomiting (14.5%) and diarrhoea (12.7%) [5].

Grade ≥3 sensory neuropathy is a particular concern with oxaliplatin-containing regimens [25]. For the recommended NALIRIFOX regimen, none was reported. By contrast, in PRODIGE 4, grade 3–4 sensory neuropathy was experienced by 9.0% of patients receiving FOLFIRINOX (for persistent grade 2 sensory neuropathy, an oxaliplatin dose reduction from 85 to 65 mg/m^2 was permitted) [5].

The efficacy of first-line NALIRIFOX warrants further investigation, given a median PFS of 9.2 months (95% CI: 7.69–11.96) and median OS of 12.6 months (8.74–18.69), although direct comparisons with other studies cannot be made. The outcomes of the PRODIGE 4 study are of interest, as these underpin the recommendations for the FOLFIRINOX regimen as first-line therapy in mPDAC [2,10,11,26]. FOLFIRINOX was associated with a median PFS of 6.4 months (95% CI: 5.5–7.2) and median OS of 11.1 months (9.0–13.1), using RECIST v1.0 [5]. However, important differences between the study populations include the proportions of patients with metastatic disease at study entry (recommended NALIRIFOX regimen: 90.6%; FOLFIRINOX in PRODIGE 4: 100%), the proportions with liver metastases (43.8% and 87.6%, respectively) and the median ages (58 and 61 years, respectively) [5].

Limitations inherent in the present study design include the small number of patients, which limits the precision of efficacy parameter estimates; the lack of an efficacy hypothesis; the non-randomised design; and the absence of a control group. Although only patients with adequate performance status were included, similar restrictions were used in PRODIGE 4 [5].

5. Conclusions

The present phase I/II study demonstrated that first-line NALIRIFOX had tolerability that was generally manageable for patients with locally advanced or mPDAC, with no unexpected safety outcomes. Ultimately, an important, as-yet-unanswered question is the

preferred treatment for patients newly diagnosed with mPDAC. NAPOLI-3, an ongoing, large randomised, controlled, phase III study, will compare the efficacy (primary endpoint, OS) and safety of first-line NALIRIFOX with gemcitabine/nab-paclitaxel in this population, using the doses established here.

Clinical trial information

ClinicalTrials.gov number, NCT02551991 (https://www.clinicaltrials.gov/); EudraCT 2015-003086-28 (https://www.clinicaltrialsregister.eu/).

Data sharing statement

If patient data can be anonymised, Ipsen will share all individual patient data that underlie the results reported in this article with qualified researchers who provide a valid research question. Study documents, such as the clinical study report, are not always available. Proposals should be submitted to DataSharing@Ipsen.com and will be assessed by a scientific review board. Data are available beginning 6 months, and ending 5 years, after publication; after this time, only raw data may be available.

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Author contributions

Conception and design: A. Wainberg, Bruce Belanger, Fiona Maxwell, Tiffany Wang, Bin Zhang and Andrew Dean.

All authors: acquisition, analysis or interpretation of data for the work.

All authors: drafting the work or revising it critically for important intellectual content.

All authors: final approval of the manuscript.

All authors are accountable for all aspects of the work.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Note**: relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution.

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Appendix A. Supplementary data

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