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Original Research

NAPOLI-1 phase 3 study of liposomal irinotecan in metastatic pancreatic cancer: Final overall survival analysis and characteristics of long-term survivors

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Abstract ***Background:*** Liposomal irinotecan (nal-IRI) plus 5-fluorouracil and leucovorin (5-FU/LV) is approved for patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) previously treated with gemcitabine-based therapy. This approval was based on significantly improved median overall survival compared with 5-FU/LV alone (6.1 vs 4.2 months; hazard ratio [HR], 0.67) in the global phase 3 NAPOLI-1 trial. Here, we report the final survival analysis and baseline characteristics associated with long-term survivors (survival of ≥1 year) in the NAPOLI-1 trial.

Patients and methods: Patients with mPDAC were randomised to receive nal-IRI + 5-FU/LV (n = 117), nal-IRI (n = 151), or 5-FU/LV (n = 149) for the first 4 weeks of 6-week cycles. Baseline characteristics and efficacy in the overall population were compared with those in patients who survived ≥1 year. Through 16th November 2015, 382 overall survival events had occurred.

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Results: The overall survival advantage for nal-IRI+5-FU/LV vs 5-FU/LV was maintained from the original nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1) analysis (6.2 vs 4.2 months, respectively; HR, 0.75; 95% confidence interval: 0.57–0.99). Median progression-free survival, objective response rate and disease control rate also favoured nal-IRI+5-FU/LV therapy. Estimated one-year overall survival rates were 26% with nal-IRI+5-FU/LV and 16% with 5-FU/LV. Baseline characteristics associated with long-term survival in the nal-IRI+5-FU/LV arm were Karnofsky performance status ≥90, age ≤65 years, lower CA19-9 levels, neutrophil-to-lymphocyte ratio ≤5 and no liver metastases. No new safety concerns were detected.
Conclusions: The survival benefits of nal-IRI+5-FU/LV versus 5-FU/LV were maintained over an extended follow-up, and prognostic markers of survival ≥1 year were identified.
Clinical trial registration number: NCT01494506.

1. Introduction

Patients with pancreatic cancer have a poor prognosis [1,2]. A systematic review of 91 European observational studies, including all stages of disease and various interventions, reported median survival durations ranging from 1.0 to 6.1 months (median: 4.6 months, based on 12 studies reporting data), with one-year survival rates of 10%–23% [3]. One-year survival rates ranging from 23% to 35% have been reported with first-line gemcitabine-based regimens in patients with advanced or metastatic disease [4–6]. A recent meta-analysis of 10 phase 2 studies evaluating the combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin in patients with metastatic pancreatic cancer (N = 332) reported a pooled overall survival (OS) of 10.6 months [7]. Traditionally, second and subsequent lines of therapy have failed to consistently provide a survival benefit, highlighting an unmet need in this population of patients [8,9].

Liposomal irinotecan (nal-IRI; Onivyde®; Ipsen Biopharmaceuticals, Inc., Basking Ridge, NJ, USA) is an intravenous liposomal formulation of irinotecan, which is a topoisomerase I inhibitor [10,11]. Preclinical studies comparing nal-IRI versus conventional irinotecan found that similar tumour exposure to the active metabolite of irinotecan, SN-38, was achieved with lower doses of nal-IRI than with those of conventional irinotecan, as measured by area under the curve [12]. In addition, nal-IRI administration prolonged tumour exposure (ie, tumour SN-38 concentrations above 120 nmol/L) and provided greater tumour growth inhibition compared with conventional irinotecan. Clinically, data from a pilot study in patients with various types of cancer showed higher levels of SN-38 in tumour biopsy samples than in plasma at 72 h after dosing, which supports local metabolic activation of irinotecan to SN-38 [10].

The global phase 3 NAPOLI-1 trial (NCT01494506) demonstrated improved outcomes (OS, progression-free survival [PFS], objective response rate [ORR] and CA19-9 response [defined as ≥50% decrease from the baseline]) in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with nal-IRI in combination with 5-fluorouracil and leucovorin (5-FU/LV) vs 5-FU/LV alone after disease progression following gemcitabine-based therapy [13]. Median OS duration was 6.1 months in patients who received nal-IRI+5-FU/LV versus 4.2 months in patients who received 5-FU/LV (unstratified hazard ratio [HR], 0.67; $P = 0.012$). Overall response rates were 16% with nal-IRI+5-FU/LV versus 1% with 5-FU/LV ($P < 0.0001$), and CA19-9 response rates were 29% (28/97) with nal-IRI+5-FU/LV versus 9% (7/81) with 5-FU/LV ($P = 0.0006$). The results of this study led to the approval of nal-IRI with 5-FU/LV for the treatment of mPDAC in patients who previously received gemcitabine-based therapy. This report provides an updated OS analysis from a longer follow-up and the results of a post hoc analysis evaluating the characteristics of long-term survivors in NAPOLI-1. Updated safety and tolerability data are also presented.

2. Patients and methods

2.1. Study design

The study design and patient population of NAPOLI-1 have been previously described [13]. Briefly, NAPOLI-1 was a global, phase 3, open-label, randomised trial. Patients received nal-IRI monotherapy 120 mg/m^2 (equivalent to 100 mg/m^2 of the irinotecan free base) every 3 weeks or 5-FU 2000 mg/m^2 plus LV 200 mg/m^2 every week for the first 4 weeks of 6-week cycles; the protocol was amended to add a third study arm of nal-IRI 80 mg/m^2 (equivalent to 70 mg/m^2 of the irinotecan free base) every 2 weeks plus 5-FU 2400 mg/m^2 and LV 400 mg/m^2 every 2 weeks based on safety data from a concurrent study in metastatic colorectal cancer, as well as a 5-FU/LV control group for the combination arm [14]. Key inclusion criteria, a description of study end-

points and ethics considerations are provided in the Supplementary Appendix.

2.2. Study end-points and assessments

The primary end-point was OS, assessed in the intent-to-treat (ITT) population [13]. Secondary end-points included PFS, ORR and serum CA19-9 response (ie, ≥50% decrease in amount of CA19-9 from the baseline at least once during the treatment period). Key assessments are described in the Supplementary Appendix.

For the post hoc long-term survivor analysis, baseline characteristics and efficacy among patients assigned to treatment with nal-IRI monotherapy, patients assigned to treatment with nal-IRI+5-FU/LV and patients assigned to the combination control arm (5-FU/LV) in the ITT population were compared with those among the subgroup of patients who survived for ≥1 year. Efficacy end-points, including ORR, OS, PFS and disease control rate (DCR, defined as best response of complete or partial response, stable disease or non-complete response/non-progressive disease), were reported for the ITT population and safety/tolerability end-points were reported for the safety population, in which patients were categorised as treated. Information regarding post-study therapy also was collected.

2.3. Statistical analyses

The two analyses were conducted using data through the cutoff date of 16 th November 2015, at which time all patients were no longer receiving study treatment. The updated survival analysis compared the primary end-point of OS in each treatment arm with its corresponding 5-FU/LV control (ie, monotherapy and combination therapy) using unstratified log-rank test and descriptive *P*-values. Confidence intervals (CIs) were based on the exact method. For time-to-event variables (OS, PFS), Kaplan–Meier analyses were performed on each treatment to obtain non-parametric estimates of median OS and PFS. For response variables (ORR, DCR), proportions of responders were computed. HRs were derived using the Cox proportional hazards model, with treatment as the independent variable. In addition, a supportive stratified analysis of OS was performed, accounting for randomisation strata (baseline albumin levels [≥40 g/L vs < 40 g/L], Karnofsky performance status [KPS; 70 and 80 vs ≥90] and ethnic origin [white vs East Asian vs all others]). For the post hoc evaluation of long-term survivors, defined as those who survived ≥1 year, no statistical comparisons were performed owing to the small sample sizes.

3. Results

3.1. Updated survival analysis

A total of 76 sites in 14 countries enrolled 417 patients between January 2012 and September 2013 [13]; 117 patients assigned to nal-IRI+5-FU/LV, 151 assigned to nal-IRI monotherapy and 149 assigned to 5-FU/LV. The original survival analysis was performed after 313 OS events, at a cutoff date of 14th February 2014. As of the updated cutoff date (16th November 2015), 382 OS events had occurred in the ITT population. Patient demographic and baseline clinical characteristics were well balanced across treatment arms. nal-IRI+5-FU/LV was found to retain an OS advantage compared with 5-FU/LV (6.2 vs 4.2 months, respectively), with an unstratified HR of 0.75 (95% CI: 0.57–0.99; $P = 0.039$; stratified HR 0.63; 95% CI: 0.47–0.85; $P = 0.002$; Table 1, Fig. 1A). No OS advantage was observed with nal-IRI monotherapy versus 5-FU/LV (4.9 vs 4.2 months; Fig. 1B). With OS events in nearly all patients, the Kaplan–Meier OS curves converged at approximately 20 months, with 23 (9.8%) patients surviving beyond 20 months. Kaplan–Meier estimated one-year survival rates were 26% in the nal-IRI+5-FU/LV arm versus 16% in the 5-FU/LV combination control arm.

Median PFS was 3.1 months in patients receiving nal-IRI+5-FU/LV and 1.5 months in those receiving 5-FU/LV combination control (HR: 0.57; 95% CI: 0.43–0.76; $P < 0.0001$; Table 1, Fig. 1C) and was 2.7 months for nal-IRI monotherapy compared with 1.6 months for 5-FU/LV monotherapy control (Fig. 1D). The ORR was significantly higher with nal-IRI+5-FU/LV (17%) than with 5-FU/LV combination control (1%), with a difference of 16.3% (95% CI: 9.2%–23.3%; $P < 0.0001$; Table 1), and the DCR was also higher with nal-IRI+5-FU/LV (52%) than with 5-FU/LV combination control (24%; Table 1).

The safety profiles of nal-IRI+5-FU/LV and nal-IRI monotherapy described in the current updated analysis did not change appreciably from those reported in the primary analysis [13]. The most frequently reported grade ≥3 treatment-emergent adverse events (TEAEs) in the nal-IRI–containing arms were neutropenia, diarrhoea, vomiting and fatigue (Supplemental Table 1). TEAEs led to dose delay, reduction and/or discontinuation in 73% of patients in the nal-IRI+5-FU/LV arm, 56% of patients in the nal-IRI monotherapy arm and 37% of patients in the 5-FU/LV control arm (Table 2). TEAEs led to treatment discontinuation in 13% of patients in the nal-IRI+5-FU/LV arm, 14% of patients in the nal-IRI monotherapy arm and 8% of patients in the 5-FU/LV control arm. In the original analysis [13], 47 patients died during the study or within 30 days from the last dose of study drug; of these, 30 deaths were attributed to pancreatic cancer, 16 were due to an adverse event (AE; five related to treatment [one in nal-IRI+5-FU/LV arm and four in nal-IRI monotherapy arm], according to the investigator), and one was due to unknown causes later identified as gastric outlet obstruction, which was considered disease related. In the updated analysis, two additional deaths occurred within the 30-day window, both of which were attributed to

Table 1
Summary of updated efficacy.[a]

End-point	nal-IRI+5-FU/LV (n = 117)[b]	5-FU/LV combination control (n = 119)[b]	Treatment effect[c]	nal-IRI monotherapy (n = 151)	5-FU/LV monotherapy control (n = 149)	Treatment effect[a]
OS, mo, median (95% CI)	6.2 (4.8−8.4)	4.2 (3.3−5.3)	HR: 0.75 P = 0.039	4.9 (4.2−5.6)	4.2 (3.6−4.9)	HR, 1.07 P = 0.568
OS rate at 6 mo, % (95% CI)[d]	53 (44−62)	38 (29−47)	–	39 (31−46)	35 (27−43)	–
OS rate at 12 mo, % (95% CI)[d]	26 (18−35)	16 (10−24)	–	11 (6−16)	15 (9−21)	–
PFS, mo, median (95% CI)	3.1 (2.7−4.2)	1.5 (1.4−1.8)	HR: 0.57 P = 0.0001	2.7 (2.1−2.9)	1.6 (1.4−1.8)	HR, 0.81 P = 0.105
ORR, % (95% CI)[e]	17 (10−24)	1 (0−2)	P < 0.0001	6 (3−11)	1 (0−4)	P = 0.020
Disease control rate (CR + PR + SD), % (95% CI)	52 (43−61)	24 (17−33)	–	44 (36−52)	26 (19−33)	–
Best overall response, n (%)[e]						
PR	20 (17)	1 (1)	–	9 (6)	1 (1)	–
SD[f]	38 (32)	26 (22)	–	54 (36)	35 (23)	–
PD	34 (29)	56 (47)	–	51 (34)	71 (48)	–
Other[g]	3 (3)	2 (2)	–	3 (2)	2 (1)	–
Not evaluable	22 (19)	34 (29)	–	34 (23)	40 (27)	–
CA19-9						
20% reduction from baseline, n/N[g] (%)	38/95 (40)	11/82 (13)		41/124 (33)	16/106 (15)	
50% reduction from baseline, n/N[h] (%)	27/95 (28)	8/82 (10)	–	29/124 (23)	13/106 (12)	–

5-FU, 5-fluorouracil; CA 19-9, carbohydrate antigen 19-9; CI, confidence interval; CR, complete response; HR, hazard ratio; LV, leucovorin; nal-IRI, liposomal irinotecan; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; SD, stable disease.

[a] Confidence intervals are based on the exact method.

[b] In nal-IRI+5-FU/LV and 5-FU/LV combination control arms, 36% and 42%, respectively, received any post-study drug; corresponding percentages among long-term survivor subgroups were 59% and 76%, respectively.

[c] HRs derived using Cox proportional hazards model with treatment as the independent variable; P values based on unstratified log-rank test.

[d] Survival function estimate and 95% CI at each time point are from Kaplan−Meier analysis.

[e] Designation of response did not require confirmation and was based solely on the investigator's assessment using RECIST v1.1.

[f] Minimum duration for stable disease from the baseline is 6 weeks from date of randomisation.

[g] Patients without measurable (target) disease at baseline may have a best overall response of non-CR/non-PR.

[h] N = patients with baseline CA19-9 >30 IU/mL.

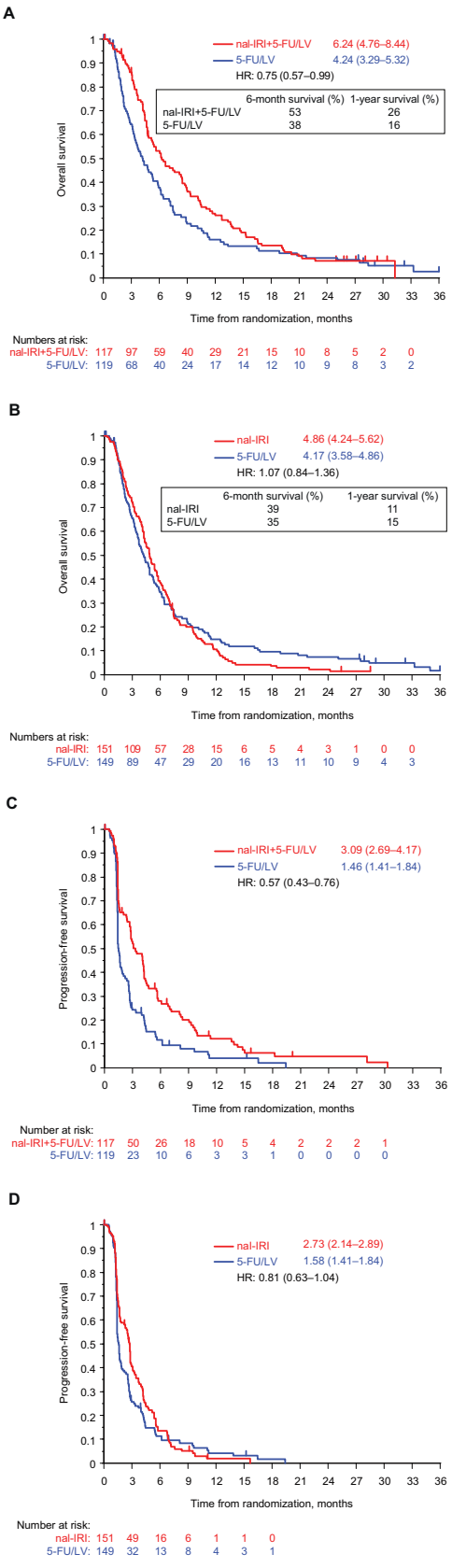

Fig. 1. Overall survival (A, B) and progression-free survival (C, D) in patients receiving nal-IRI+5-FU/LV compared with those in the 5-FU/LV combination control arm and in patients receiving nal-IRI monotherapy versus 5-FU/LV monotherapy control.

pancreatic cancer. Additional safety data are reported in the Supplementary Appendix.

3.2. Long-term survivor analysis

A total of 15 (10%) patients in the nal-IRI monotherapy arm, 29 (25%) in the nal-IRI+5-FU/LV arm and 20 (13%) in the 5-FU/LV control arms were alive (and not censored) ≥1 year. Among long-term responders, median OS was 19.1 (95% CI: 15.3–21.3), 23.4 (95% CI: 16.1–33.3) and 13.7 (95% CI: 12.3–18.5) months in the nal-IRI+5-FU/LV, 5-FU/LV and nal-IRI monotherapy arms, respectively; median PFS was 9.9 (95% CI: 7.0–14.2), 8.1 (95% CI: 2.7–13.8) and 7.2 (95% CI: 3.7–11.0) months in the nal-IRI+5-FU/LV, 5-FU/LV and nal-IRI monotherapy arms, respectively. Overall response rates among long-term responders were 31% (95% CI: 15.3–50.8), 0% (95% CI: 0–17) and 7% (95% CI: 0–32) in the nal-IRI+5-FU/LV, 5-FU/LV and nal-IRI monotherapy arms, respectively. DCRs among long-term responders were 86% (95% CI: 68–96), 70% (95% CI: 46–88) and 73% (95% CI: 45–92) in the nal-IRI+5-FU/LV, 5-FU/LV and nal-IRI monotherapy arms, respectively. Baseline characteristics of these long-term survivors and those of the overall study arms are summarised in Table 3. Patients in the nal-IRI+5-FU/LV arm who survived ≥1 year were more likely to be aged ≤65 years; have KPS ≥90, neutrophil-to-lymphocyte ratio ≤5 and CA19-9 level <59 × the upper limit of normal and be less likely to have liver metastases than all patients in the nal-IRI+5-FU/LV arm. Overall, these trends were similar when comparing long-term survivors in the nal-IRI monotherapy and 5-FU/LV arms with all patients, except a greater percentage of long-term survivors who received nal-IRI monotherapy were aged >65 years (60%).

4. Discussion

This updated analysis of the NAPOLI-1 trial at 382 survival events confirmed the OS advantage observed in the primary analysis of approximately 2 months in favour of nal-IRI+5-FU/LV versus 5-FU/LV alone (median OS: 6.2 vs 4.2 months, respectively). The OS data observed with the combination of nal-IRI+5-FU/LV as second-line therapy in mPDAC compares favourably with that observed with other regimens in the second-line setting. In a systematic review of 71 studies in patients with unresectable locally advanced or mPDAC who received various second-line therapies, the pooled median OS among all treatments by class ranged

Hazard ratios were derived using the Cox proportional hazards model, with treatment as the independent variable. 5-FU, 5-fluorouracil; HR, hazard ratio; LV, leucovorin; nal-IRI, liposomal irinotecan.

Table 2
TEAEs resulting in dose delay or dose reduction in ≥5% of patients in any treatment arm or treatment discontinuation in ≥2% in any treatment arm.

Grade ≥3 TEAE, n (%)	nal-IRI+5-FU/LV (n = 117)	nal-IRI monotherapy (n = 147)	5-FU/LV (n = 134)
Dose delay	74 (63.2)	49 (33.3)	43 (32.1)
Neutropenia	18 (15.4)	6 (4.1)	3 (2.2)
Leukopenia	8 (6.8)	1 (0.7)	1 (0.7)
Diarrhoea	11 (9.4)	9 (6.1)	4 (3.0)
Fatigue	8 (6.8)	3 (2.0)	1 (0.7)
Vomiting	7 (6.0)	4 (2.7)	3 (2.2)
Decreased neutrophil count	11 (9.4)	6 (4.1)	2 (1.5)
Decreased platelet count	6 (5.1)	1 (0.7)	1 (0.7)
Decreased WBC count	14 (12.0)	1 (0.7)	1 (0.7)
Dose reduction	40 (34.2)	46 (31.3)	6 (4.5)
Neutropenia	10 (8.5)	3 (2.0)	0
Diarrhoea	7 (6.0)	17 (11.6)	0
Vomiting	2 (1.7)	9 (6.1)	0
Decreased neutrophil count	8 (6.8)	7 (4.8)	0
Decreased WBC count	6 (5.1)	3 (2.0)	0
Treatment discontinuation	15 (12.8)	20 (13.6)	11 (8.2)
Neutropenia	2 (1.7)	1 (0.7)	0
Ascites	2 (1.7)	0	0
Diarrhoea	2 (1.7)	3 (2.0)	0
Vomiting	2 (1.7)	3 (2.0)	1 (0.7)
Jaundice	0	0	2 (1.5)
Sepsis	2 (1.7)	1 (0.7)	1 (0.7)
Decreased WBC count	2 (1.7)	0	0

5-FU, 5-fluorouracil; LV, leucovorin; nal-IRI, liposomal irinotecan; TEAE, treatment-emergent adverse event; WBC, white blood cell.

from 4.0 to 5.4 months [15]. The NAPOLI-1 trial included >400 patients, whereas the studies in the systematic review were much smaller, with most including <50 patients. Convergence of the OS curves at 20 months in the NAPOLI-1 trial, with approximately 10% of patients surviving beyond 20 months, may explain the observed attenuation of the OS HR estimates and unstratified log-rank P values. The estimated probability of survival at 1 year was 26% in the nal-IRI+5-FU/LV arm and 16% in the 5-FU/LV arm; this compares favourably to the one-year survival rates of 10%–23% reported in a large European systematic review of observational studies that encompassed all disease stages and lines of therapy [3].

Oxaliplatin also has been investigated in the second-line setting for patients with mPDAC [16,17]. In a randomised, open-label, phase 3 study of fluorouracil/folinic acid (n = 84) versus oxaliplatin fluorouracil/folinic acid (n = 76) in patients with advanced pancreatic cancer who had progressed on first-line gemcitabine monotherapy (CONKO-3), median OS was 3.3 months and 5.9 months, respectively [16]. In the PANCREOX phase 3 study, patients previously treated with gemcitabine were randomised to biweekly infusional fluorouracil/leucovorin (FU/LV; n = 54) or biweekly-modified FOLFOX6 (infusional FU/LV plus oxaliplatin; n = 54) [17]. Median OS was 9.9 months in the FU/LV group and 6.1 months in the modified FOLFOX6 group. The difference in OS between treatment groups in this study was attributed to a shorter time from diagnosis and a greater frequency of post-progression therapy in the FU/LV group. A systematic review of data from randomised trials evaluating oxaliplatin- or irinotecan-containing regimens in patients with pancreatic cancer previously treated with gemcitabine showed that the dissimilarities in study settings, patient populations, treatment schedules and end-points prevented indirect treatment comparison [18]. Given the conflicting results with oxaliplatin-based therapies observed in the CONKO-3 and PANCREOX studies, the European Society for Medical Oncology guidelines suggest that nal-IRI–based therapy may be a better option for second-line treatment [19]. Current National Comprehensive Cancer Network guidelines for the treatment of pancreatic adenocarcinoma recommend nal-IRI+5-FU/LV as category 1 second-line therapy for metastatic disease [20]. In addition, the American Society of Clinical Oncology Clinical Practice Guidelines for the treatment of metastatic pancreatic cancer recommend nal-IRI+5-FU/LV as second-line therapy in patients previously treated with gemcitabine plus nab-paclitaxel [21].

No new safety concerns were detected with nal-IRI monotherapy or nal-IRI+5-FU/LV with the extended follow-up. The most common grade 3 or worse TEAEs were neutropenia, diarrhoea, fatigue and vomiting. Treatment discontinuations due to AEs occurred at similar rates with nal-IRI+5-FU/LV and nal-IRI monotherapy; rates were higher than those observed with 5-FU/LV alone. Treatment exposure also was longer,

Table 3
Baseline characteristics of all patients and long-term survivors.[a]

Characteristic	All patients					Long-term survivors				
	nal-IRI (n = 151)	nal-IRI+ 5-FU/LV (n = 117)	5-FU/LV combination control (n = 119)	All 5-FU/LV monotherapy control (n = 149)	Total (N = 417)	nal-IRI (n = 15)	nal-IRI+5-FU/ LV (n = 29)	5-FU/LV combination control (n = 17)	All 5-FU/LV monotherapy control (n = 20)	Total (N = 64)
Age										
Mean (SD), y	64 (10)	63 (9)	61 (9)	62 (10)	63 (10)	63 (13)	60 (10)	56 (12)	58 (12)	60 (11)
Median (IQR, range), y	65 (58–70, 31–87)	63 (57–70, 41–81)	62 (55–69, 34–80)	63 (55–69, 34–83)	63 (57–70)	67 (58–71, 31–80)	59 (55–66, 41 –81)	57 (44–63, 34–76)	58.5 (47–67, 34–76)	59.5 (54–68)
≤65 y	82 (54)	65 (56)	81 (68)	94 (63)	241 (58)	6 (40)	21 (72)	14 (82)	14 (70)	40 (63)
>65 y	69 (46)	52 (44)	38 (32)	55 (37)	176 (42)	9 (60)	8 (28)	3 (18)	6 (30)	24 (38)
Sex										
Female	64 (42)	48 (41)	52 (44)	68 (46)	180 (43)	6 (40)	13 (45)	9 (53)	11 (55)	30 (47)
Race										
White	89 (59)	72 (62)	76 (64)	92 (62)	253 (61)	10 (67)	19 (66)	8 (47)	10 (50)	39 (61)
East Asian	52 (34)	34 (29)	36 (30)	50 (34)	136 (33)	4 (27)	10 (34)	7 (41)	8 (40)	22 (34)
Black	3 (2)	4 (3)	3 (3)	3 (2)	10 (2)	0	0	2 (12)	2 (10)	2 (3)
Other	7 (5)	7 (6)	4 (3)	4 (3)	18 (4)	1 (7)	0	0	0	1 (2)
Region										
Asia	50 (33)	34 (29)	35 (29)	48 (32)	132 (32)	3 (20)	10 (34)	6 (35)	7 (35)	20 (31)
Europe	54 (36)	47 (40)	49 (41)	55 (37)	156 (37)	8 (53)	13 (45)	5 (29)	5 (25)	26 (41)
North America	26 (17)	19 (16)	19 (16)	25 (17)	70 (17)	2 (13)	2 (7)	4 (24)	6 (30)	10 (16)
Other	21 (14)	17 (15)	16 (13)	21 (14)	59 (14)	2 (13)	4 (14)	2 (12)	2 (10)	8 (13)
KPS										
≥90	85 (56)	66 (56)	67 (56)	84 (56)	235 (56)	13 (87)	22 (76)	13 (76)	16 (80)	51 (80)
<90	66 (44)	51 (44)	52 (44)	65 (44)	182 (44)	2 (13)	7 (24)	4 (24)	4 (20)	13 (20)
Neutrophil-to-lymphocyte ratio										
≤5	107 (71)	83 (71)	81 (68)	102 (68)	292 (70)	12 (80)	25 (86)	10 (59)	13 (65)	50 (79)
>5	44 (29)	33 (28)	38 (32)	47 (32)	124 (30)	3 (20)	3 (10)	7 (41)	7 (35)	13 (21)
Albumin										
≥40 g/L	63 (42)	53 (45)	54 (45)	66 (44)	182 (44)	9 (60)	16 (55)	13 (76)	14 (70)	39 (61)
<40 g/L	88 (58)	64 (55)	65 (55)	83 (56)	235 (56)	6 (40)	13 (45)	4 (24)	6 (30)	25 (39)
CA19-9 level[b]										
Median (IQR), U/mL	2189 (195 –17,678)	1278 (120 –9001)	1292 (99–16,381)	1019 (80 –12,765)	1542 (120 –12,815)	478 (83 –4002)	334 (18–2264)	108 (16–475)	117 (22–1545)	344 (31 –2078)
≥40 U/mL, n/N (%)	125/146 (86)	92/114 (81)	91/114 (80)	116/144 (81)	333 (82)	13/15 (87)	19/27 (70)	10/16 (63)	13/19 (68)	45 (74)
<40 U/mL, n/N (%)	21/146 (14)	22/114 (19)	23/114 (20)	28/144 (19)	71 (18)	2/15 (13)	8/27 (30)	6/16 (38)	6/19 (32)	16 (26)
<59x ULN, n/N (%)	73/146 (50)	64/114 (56)	61/114 (54)	79/144 (55)	216/404 (53)	11/15 (73)	20/27 (74)	14/16 (88)	16/19 (84)	47/61 (77)
Pancreatic tumour location										
Head	99 (66)	76 (65)	69 (58)	81 (54)	256 (61)	11 (73)	20 (69)	12 (71)	13 (65)	44 (69)
Not head	52 (34)	41 (35)	50 (42)	68 (46)	161 (39)	4 (27)	9 (31)	5 (29)	7 (35)	20 (31)
Site of metastatic lesions										
Liver	101 (67)	75 (64)	84 (71)	109 (73)	285 (68)	8 (53)	12 (41)	8 (47)	9 (45)	29 (45)
Lung	49 (32)	36 (31)	36 (30)	44 (30)	129 (31)	7 (47)	9 (31)	8 (47)	10 (50)	26 (41)
Distant lymph nodes	44 (29)	32 (27)	31 (26)	40 (27)	116 (28)	3 (20)	10 (34)	5 (29)	6 (30)	19 (30)
Regional lymph nodes	19 (13)	13 (11)	14 (12)	20 (13)	52 (12)	4 (27)	6 (21)	2 (12)	3 (15)	13 (20)

Peritoneum	48 (32)	28 (24)	32 (27)	39 (26)	115 (28)	3 (20)	11 (38)	3 (18)	4 (20)	18 (28)
Pancreas	99 (66)	75 (64)	72 (61)	97 (65)	271 (65)	10 (67)	18 (62)	7 (41)	9 (45)	37 (58)
Other	38 (25)	27 (23)	39 (33)	48 (32)	113 (27)	2 (13)	7 (24)	5 (29)	7 (35)	16 (25)
Measurable metastatic lesions										
1	36 (24)	19 (16)	22 (18)	26 (17)	81 (19)	7 (47)	7 (24)	8 (47)	8 (40)	22 (34)
2	63 (42)	49 (42)	58 (49)	72 (48)	184 (44)	3 (20)	10 (34)	3 (18)	4 (20)	17 (27)
3	22 (15)	22 (19)	15 (13)	21 (14)	65 (16)	2 (13)	4 (14)	2 (12)	3 (15)	9 (14)
>3	7 (5)	7 (6)	8 (7)	10 (7)	24 (6)	0	1 (3)	0	0	1 (2)
Prior therapy										
Gemcitabine monotherapy only	67 (44)	53 (45)	55 (46)	66 (44)	186 (45)	8 (53)	13 (45)	9 (53)	10 (50)	31 (48)
Gemcitabine in combination	84 (56)	64 (55)	64 (54)	83 (56)	231 (55)	7 (47)	16 (55)	8 (47)	10 (50)	33 (52)
5-FU	70 (46)	50 (43)	52 (44)	63 (42)	183 (44)	5 (33)	14 (48)	6 (35)	6 (30)	25 (39)
Platinum	54 (36)	38 (32)	41 (34)	45 (30)	137 (33)	5 (33)	10 (34)	5 (29)	5 (25)	20 (31)
Irinotecan	17 (11)	12 (10)	17 (14)	17 (11.4)	46 (11)	1 (7)	0	2 (12)	2 (10)	3 (5)
Radiotherapy	40 (26)	24 (21)	27 (23)	33 (22)	97 (23)	5 (33)	9 (31)	7 (41)	8 (40)	22 (34)
Whipple procedure	47 (31)	30 (26)	33 (28)	36 (24)	113 (27)	5 (33)	8 (28)	9 (53)	9 (45)	22 (34)
Biliary stent	13 (9)	15 (13)	8 (7)	9 (6)	37 (9)	0	3 (10)	1 (6)	1 (5)	4 (6)
Prior lines of metastatic therapy										
0[c]	17 (11)	15 (13)	15 (13)	19 (13)	51 (12)	1 (7)	1 (3)	3 (18)	4 (20)	6 (9)
1	86 (57)	62 (53)	67 (56)	86 (58)	234 (56)	10 (67)	18 (62)	9 (53)	10 (50)	38 (59)
>1	48 (32)	40 (34)	37 (31)	44 (30)	132 (32)	4 (27)	10 (34)	5 (29)	6 (30)	20 (31)

5-FU, 5-fluorouracil; CA19-9, carbohydrate antigen 19-9; IQR, interquartile range; KPS, Karnofsky performance status; LV, leucovorin; nal-IRI, liposomal irinotecan; SD, standard deviation; ULN, upper limit of normal (37 U/mL for CA19-9).

[a] Data are n (%) unless otherwise specified.

[b] Includes only patients who had a measured CA19-9 value before treatment, with denominators as shown.

[c] Patients received neoadjuvant, adjuvant or locally advanced treatment but had no previous therapy for metastatic disease.

particularly for combination treatment. Neutropenia, diarrhoea and vomiting led to more treatment discontinuations in more patients receiving nal-IRI in combination or as monotherapy than in those receiving 5-FU/LV. Late-onset diarrhoea was more prevalent in the nal-IRI+5-FU/LV (44%) and nal-IRI monotherapy (65%) arms compared with the 5-FU/LV monotherapy arm (17%); as expected, prevalence was higher in the nal-IRI monotherapy group, likely because of the difference in dosing. However, discontinuations due to diarrhoea were ≤2% in all treatment arms.

More patients receiving nal-IRI+5-FU/LV (25%) were alive ≥1 year compared with those randomised to 5-FU/LV (13%), which is consistent with the Kaplan–Meier estimates of one-year survival. Several baseline characteristics were associated with long-term survival in the nal-IRI+5-FU/LV arm: younger age, better performance status, a lower neutrophil-to-lymphocyte ratio, lower CA19-9 level and absence of liver metastases. In the primary analysis of NAPOLI-1 data, stepwise regression analysis identified the following factors as associated with OS: treatment, baseline KPS, albumin level, time since most recent anticancer therapy, tumour stage at diagnosis, status of liver metastases and baseline CA19-9 level [13]. However, even after adjusting for prognostic factors, the treatment effect of nal-IRI+5-FU/LV on OS remained.

A 2016 review of prognostic markers in clinical trials of various therapeutic regimens for advanced or mPDAC identified age, performance status and CA19-9 level as primary prognostic factors affecting outcomes [22]. A phase 3 trial of gemcitabine and tipifarnib supported worse performance status and metastatic disease stage as negative predictors of survival [23]. An analysis from two international phase 3 trials of gemcitabine and marimastat took a multivariable approach to account for the functional relationship between continuous prognostic variables and survival, confirming albumin, CA19-9, alkaline phosphatase and lactate dehydrogenase levels and presence of metastases, as well as three additional factors: white blood cell count, aspartate aminotransferase levels and blood urea nitrogen levels [24]. In an updated analysis of the phase 3 MPACT trial of nab-paclitaxel + gemcitabine versus gemcitabine alone in 861 patients with metastatic pancreatic cancer, neutrophil-to-lymphocyte ratio (in both groups) and CA19-9 (in the gemcitabine group) at the baseline were significantly associated with worse OS [25]. The prognostic factors identified in these analyses are generally consistent with the characteristics of long-term survivors identified in the NAPOLI-1 trial, including younger, more fit patients without liver metastases and lower CA19-9 levels. Because the prognosis for patients with mPDAC remains poor, there is a critical need to identify high-risk patients and select patients for optimal treatment based on prognostic biomarkers. The identification of predictive and prognostic biomarkers in mPDAC is an area of active research and a number of potential markers have been investigated, including *BRCA* mutations, human equilibrative nucleoside transporter 1 and secreted protein acidic and rich in cysteine [22,26].

In the primary analysis, some patients had not yet had 12 months of follow-up. Although many survival events were included in the primary analysis, this updated survival analysis allowed evaluation of long-term survivors in the NAPOLI-1 trial. Our long-term survivor analyses are limited by small sample sizes that precluded statistical testing to compare the presence of prognostic factors among long-term survivors and all treated patients. The difference in OS for the long-term survivors may be explained by the small numbers of patients and/or administration of post-study therapy. Nevertheless, the clinical significance of the prognostic factors identified in NAPOLI-1 should be validated in future studies.

5. Conclusion

For patients with mPDAC, the nal-IRI+5-FU/LV treatment regimen represents a new standard of care following gemcitabine-based therapy. This combination regimen improves OS, PFS, CA19-9 response and DCR and has an acceptable safety profile and generally manageable AEs, while maintaining quality of life over time versus 5-FU/LV alone. In addition to better performance status and younger age, characteristics associated with longer survival in patients with mPDAC receiving nal-IRI+5-FU/LV may include the absence of liver metastases and lower CA19-9 level and neutrophil-to-lymphocyte ratio (≤5).

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Conflict of interest statement

A.W-.G. was a consultant or played an advisory role in BMS, Ipsen, Jacobio, Merrimack, Newlink, Pfizer and Rupugene; R.A.H. was a consultant or played an advisory role in Celgene, Ipsen and Shire; J.T.S. was a consultant or played an advisory role in Baxalta, Celgene, Eli Lilly and Shire and received research funding from 4SC, Bristol-Myers Squibb and Celgene; D.D.V.H. was a consultant or played an advisory role in AlphaMed Consulting and received research funding from Merrimack; B.B. is an employee of Ipsen; F.A.de.J. is an employee of Servier and has stock ownership in Shire; B.M. is an employee of Ipsen; L.-T.C. was a consultant or played an advisory role in Bristol-Myers Squibb, Ono Pharmaceutical, Eli Lilly, MSD, PharmaEngine, Merrimack, TTY Biopharm,

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Appendix A. Supplementary data

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