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Original Research

Survival with nal-IRI (liposomal irinotecan) plus 5-fluorouracil and leucovorin versus 5-fluorouracil and leucovorin in per-protocol and non-per-protocol populations of NAPOLI-1: Expanded analysis of a global phase 3 trial

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Abstract ***Background:*** In the phase 3 randomised NAPOLI-1 clinical study, a 45% increase in median overall survival (OS) was shown with liposomal irinotecan, 5-fluorouracil and leucovorin (nal-IRI+5-FU/LV) versus 5-FU/LV in patients with metastatic pancreatic cancer progressing after gemcitabine-based therapy. Here, we report data from a pre-specified, expanded analysis of outcomes in the per-protocol (PP) population.
Materials and methods: The PP population comprised patients receiving ≥80% of planned treatment during the first 6 weeks, with no major protocol violations. A *post-hoc* analysis of the non-PP population was also performed.
Results: For PP patients, median OS was 8.9 (95% confidence interval: 6.4–10.5) months with nal-IRI+5-FU/LV (n = 66) *vs* 5.1 (4.0–7.2) months with 5-FU/LV (n = 71; unstratified hazard ratio [HR] 0.57, p = 0.011). For non-PP patients, it was 4.4 (3.3–5.3) months with nal-IRI+5-FU/LV (n = 51) *vs* 2.8 (1.7–3.2) months with 5-FU/LV (n = 48; unstratified HR 0.64, p = 0.0648).
Conclusion: A statistically significant survival advantage was observed with nal-IRI+5-FU/LV *vs* 5-FU/LV in the PP patient population.

1. Introduction

Pancreatic cancer has a poor prognosis, with recently reported estimated median overall survival (OS) of 4.6 months [1]. Gemcitabine plus nab-paclitaxel and the FOLFIRINOX (5-fluorouracil/leucovorin [5-FU/LV]+ irinotecan + oxaliplatin) regimen are recommended for the first-line treatment of metastatic pancreatic ductal adenocarcinoma in patients with good performance status, whereas gemcitabine monotherapy and other gemcitabine-based combinations may be used in less fit patients [2–5]. Combination therapy with liposomal irinotecan (nal-IRI) and 5-FU/LV is the first regimen approved in the United States, the European Union, Australia and Taiwan for the treatment of patients progressing after gemcitabine-based therapy, based on the positive findings of the phase 3 NAPOLI-1 study (NCT01494506) [6]. Liposomal irinotecan comprises irinotecan sucrosofate salt encapsulated in pegylated liposomes that protect the drug from premature conversion in the liver into its 1000 times more active metabolite, SN-38. This leads to extended circulation in plasma in patients and prolonged tumour exposure in pre-clinical tumour models compared with non-liposomal irinotecan [7–9]. It is proposed that locally enhanced permeability of tissues at tumour sites promotes retention of circulating liposomes and subsequent uptake and activation by tumour-associated macrophages, resulting in sustained high local concentrations of SN-38 [8,10–12].

In NAPOLI-1, median OS was significantly extended in patients receiving nal-IRI+5-FU/LV (median 6.1 months; 95% confidence interval [CI]: 4.8–8.9) compared with controls receiving 5-FU/LV only (4.2 months; 95% CI: 3.3–5.3) (unstratified hazard ratio [HR] 0.67; 95% CI: 0.49–0.92; p = 0.012), and this benefit was confirmed in an updated survival analysis [13]. A recently published analysis of the NAPOLI-1 data suggested that nal-IRI+5-FU/LV increased quality-adjusted survival *vs* 5-FU/LV, with patients receiving this regimen having a 1.3-months longer mean quality-adjusted time without symptoms of disease progression or grade ≥3 toxicity (5.1 months; 95% CI: 4.5–5.8) compared with the 5-FU/LV group (3.9 months; 95% CI: 3.3–4.5) [14].

The NAPOLI-1 data are encouraging as they demonstrate efficacy in patients with advanced pancreatic cancer who have progressed following gemcitabine-based

therapy, although it is difficult to place these findings in context due to significant differences in prior treatment, patient characteristics, and outcome measures among recent studies in this setting [15]. The NAPOLI-1 trial results have been included by recent treatment guidelines, such that the nal-IRI+5-FU/LV combination is now recommended for these patients [3,5,16–18].

Here, we report the findings of a pre-specified expanded analysis on the survival outcomes in the NAPOLI-1 per-protocol (PP) population as a sensitivity analysis to confirm that the efficacy of the nal-IRI+5-FU/LV regimen seen in the ITT population was also seen in PP patients receiving optimal or near-optimal scheduled treatment. We additionally discuss data from an unplanned analysis of the non-PP population (including patients not receiving planned treatment, e.g. due to toxicity or clinical deterioration).

2. Methods

The study design and methodology for NAPOLI-1 have been published previously [6]. This three-arm study assessed efficacy and tolerability of nal-IRI monotherapy (120 mg/m^2 Q3 weeks [Q3W]), 5-FU/LV (200 mg/m^2 LV then 2000 mg/m^2 5-FU, 24 h infusion QW for the first 4 weeks of each 6-week cycle) and, after safety data becoming available on this combination, nal-IRI+5-FU/LV (80 mg/m^2 nal-IRI [irinotecan hydrochloride trihydrate salt; equivalent to 70 mg/m^2 irinotecan free base], subsequently 400 mg/m^2 LV, then 2400 mg/m^2 5-FU, 46 h infusion Q2W) in adults with metastatic pancreatic ductal adenocarcinoma who had progressed after gemcitabine-based therapy. Patients had a Karnofsky Performance Status (KPS) score $\geq$70 and adequate haematologic, hepatic and renal function.

This PP analysis used the same cut-off date as the pivotal analysis; the analysis of non-PP population data was not pre-planned. Data for nal-IRI monotherapy are not included here as, although the survival data suggested clinical activity in NAPOLI-1, OS was not significantly increased *vs* 5-FU/LV.

The PP population was defined as patients who met inclusion criteria, were treated as randomised, received $\geq$80% of protocol-defined treatment during the first 6 weeks with no more than one dose reduction in the nal-IRI containing arms and did not receive any prohibited treatments.

Treatment groups were compared for OS using an unstratified log-rank test. Only patients enrolled in the 5-FU/LV arm after a study protocol amendment to include a nal-IRI+5-FU/LV arm were included in this analysis. Hazard ratios were estimated by Cox regression. Progression-free survival (PFS) and time to treatment failure (TTF) were compared using the log-rank method, and objective response rate (ORR) by Fisher's exact test. p-values for statistical significance (defined at a level of $p < 0.05$) are presented for descriptive purposes.

3. Results

Of 117 patients in the nal-IRI+5-FU/LV group and 119 patients in the 5-FU/LV group who were randomised to treatment, 66 and 71 patients in these groups (56.4% and 59.7%), respectively, met the criteria for PP analysis (see Fig. S1 for additional details on study population composition). The non-PP populations for the nal-IRI+5-FU/LV and 5-FU/LV groups thus comprised 51 (43.6%) and 48 (40.3%) patients, respectively. Among the non-PP population, 35 (68.6%) patients in the nal-IRI+5-FU/LV group and 17 (35.4%) patients in the 5-FU/LV group were treated for the first 6 weeks but received <80% dose. Early progression, clinical deterioration or death led to exclusion of 8 patients in each treatment group (15.6% and 16.6%, respectively) from the PP population. Other reasons for not meeting PP population criteria included not receiving any study drug (2 and 13 patients, respectively) and consent withdrawal or other reasons (4 and 6 patients, respectively). For 11 of the 13 patients in the 5-FU/LV group who did not receive any study drug, 'subject decision' was the reason recorded for treatment termination.

Treatment groups were generally well balanced with regards to patients' baseline demographic and clinical characteristics (Table 1), except for a higher proportion of patients of Asian ethnicity and a lower proportion of Caucasian patients in the nal-IRI+5-FU/LV non-PP *vs* PP population groups and a lower incidence of pancreatic head tumours in the 5-FU/LV non-PP population. The number of PP patients whose prior anticancer therapy included a gemcitabine combination regimen was somewhat higher in the nal-IRI+5-FU/LV group (59.1%) compared with the 5-FU/LV group (50.7%) (Table 1). Conversely, prior anticancer therapy with gemcitabine alone was more common in the 5-FU/LV group (40.9% *vs* 49.3%). In non-PP patients, prior treatment with gemcitabine alone was more common in the nal-IRI+5-FU/LV arm (51.0%) compared with the 5-FU/LV arm (41.7%). This was reversed with a prior gemcitabine combination (49.0% *vs* 58.3%). A similar number of patients in the PP and non-PP populations treated with 5-FU/LV had previously received anticancer therapy containing irinotecan (10 [14.1%] and 7 [14.6%] patients, respectively) compared with those who received nal-IRI+5-FU/LV (6 [9.1%] and 6 [11.8%], respectively). Non-PP patients in the 5-FU/LV group more frequently received prior platinum-containing therapy compared with those in the nal-IRI+5-FULV group (43.8% *vs* 33.3%). The proportion of PP patients receiving post-study anticancer therapy was lower in those treated with nal-IRI+5-FU/LV (39.4%) compared with 5-FU/LV (49.3%) and comparable among non-PP

Table 1
Baseline demographics and clinical characteristics of the PP and non-PP populations for the nal-IRI+5-FU/LV and 5-FU/LV treatment groups.

	nal-IRI+5-FU/LV		5-FU/LV	
	PP (n = 66)	Non-PP (n = 51)	PP (n = 71)	Non-PP (n = 48)
Median age, years (y)	63	64	62	62
Age <65 y, n (%)	36 (54.5)	27 (52.9)	45 (63.4)	32 (66.7)
Age ≥65 y, n (%)	30 (45.5)	24 (47.1)	26 (36.6)	16 (33.3)
Ethnicity, n (%)				
Caucasian	47 (71)	28 (55)	45 (63)	30 (63)
East Asian	14 (21)	20 (39)	22 (31)	14 (29)
KPS, n (%)[a]				
70–80	25 (37.9)	26 (51.0)	28 (39.4)	24 (50.0)
≥90	41 (62.1)	25 (49.0)	43 (60.6)	24 (50.0)
Albumin, n (%)[a]				
<40 g/dl	34 (51.5)	30 (58.8)	37 (52.1)	28 (58.3)
≥40 g/dl	32 (48.5)	21 (41.2)	34 (47.9)	20 (41.7)
CA19–9, n (%)[b]				
>40 U/ml	54 (81.8)	38 (79.2)	53 (75.7)	38 (86.4)
Other	12 (18.2)	10 (20.8)	17 (24.3)	6 (13.6)
Stage at diagnosis, n (%)				
Stage 4	35 (53.0)	26 (51.0)	36 (50.7)	26 (54.2)
Other	31 (47.0)	25 (49.0)	35 (49.3)	22 (45.8)
Pancreatic tumour location, n (%)				
Head	40 (60.6)	36 (70.6)	48 (67.6[c])	21 (43.8[c])
Other	26 (39.4)	15 (29.4)	23 (32.4)	27 (56.2)
Liver metastases, n (%)				
Yes	42 (63.6)	33 (64.7)	53 (74.7)	31 (64.6)
No	24 (36.4)	18 (35.3)	18 (25.3)	17 (35.4)
Previous lines of metastatic therapy, n (%)				
0	9 (13.6)	6 (11.8)	9 (12.7)	6 (12.5)
1	35 (53.0)	27 (52.9)	42 (59.2)	25 (52.1)
≥2	22 (33.3)	18 (35.3)	20 (28.2)	17 (35.4)
Prior anticancer therapy, n (%)[d]				
Gemcitabine alone	27 (40.9)	26 (51.0)	35 (49.3)	20 (41.7)
Gemcitabine combination	39 (59.1)	25 (49.0)	36 (50.7)	28 (58.3)
Fluorouracil-containing	28 (42.4)	22 (43.1)	26 (36.6)	26 (54.2)
Irinotecan-containing	6 (9.1)	6 (11.8)	10 (14.1)	7 (14.6)
Platinum-containing	21 (31.8)	17 (33.3)	20 (28.2)	21 (43.8)
Post-study anticancer therapy, n (%)[d]	26 (39.4)	10 (19.6)	35 (49.3)	10 (20.8)
Gemcitabine combination	8 (12.1)	3 (5.9)	10 (14.1)	2 (4.2)
Fluorouracil-containing	18 (27.3)	4 (7.8)	25 (35.2)	5 (10.4)
Irinotecan-containing	5 (7.6)	3 (5.9)	7 (9.9)	2 (4.2)
Platinum-containing	15 (22.7)	4 (7.8)	17 (23.9)	5 (10.4)
Other non-investigational agents	8 (12.1)	5 (9.8)	9 (12.7)	0
Investigational agents	2 (3.0)	1 (2.0)	2 (2.8)	2 (4.2)
Not recorded	40 (60.6)	41 (80.4)	36 (50.7)	38 (79.2)
Median time since last therapy, months (1st and 3 rd quartiles)	1.4 (0.9, 2.1)	1.4 (1.0, 2.8)	1.2 (1.0, 2.3)	1.2 (1.0, 2.1)
Median time since diagnosis, months (1st and 3rd quartiles)	10.3 (5.2, 15.8)	10.8 (6.6, 19.1)	10.3 (6.5, 15.1)	10.5 (5.6, 16.2)
Median time from last study drug exposure to first post-study anticancer therapy, weeks (1st and 3rd quartiles)	3.14 (2.7, 5.9)	2.93 (2.4, 5.4)	3.14 (2.9, 4.9)	3.86 (1.4, 4.7)

KPS, Karnofsky Performance Status.
[a] KPS and albumin summaries are based on classification per randomisation.
[b] Includes only patients with a measured CA19-9 level prior to treatment.
[c] Significant ($p < 0.01$) difference between the PP and non-PP populations.
[d] Columns add up to ≥100% as some patients received more than one prior line of therapy or more than one post-study treatment anticancer therapy and may therefore be included in more than one category.

treatment groups (19.6% *vs* 20.8%) (Table 1). Few patients (<10% per arm) treated with nal-IRI+5-FU/LV or 5-FU/LV in the PP and non-PP populations received post-study anticancer therapy containing non-liposomal irinotecan.

Among the PP population, median OS was 8.9 (95% CI: 6.4–10.5) months with nal-IRI+5-FU/LV *vs* 5.1 (4.0–7.2) months for the 5-FU/LV control (unstratified HR 0.57, p = 0.011) (Fig. 1A). For non-PP patients, median OS was 4.4 (3.3–5.3) months with nal-IRI+5-

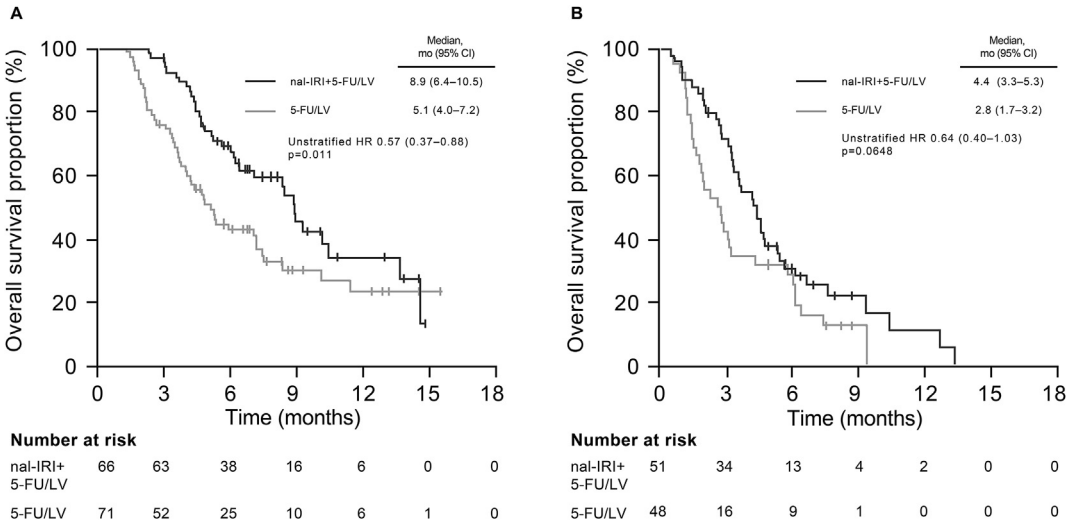

Fig. 1. Overall survival for the PP* (A) and non-PP (B) patient populations. *Per-protocol (PP) population: eligible patients who met inclusion criteria, were treated as randomised, received ≥80% of protocol-defined treatment during the first 6 weeks with no more than one dose reduction in the nal-IRI containing arms and did not receive any prohibited treatments. Vertical bars indicate censoring points. CI, confidence interval; HR, hazard ratio; mo, months.

FU/LV *vs* 2.8 (1.7–3.2) months with 5-FU/LV (unstratified HR 0.64, p = 0.0648) (Fig. 1B). The Kaplan–Meier survival function estimates for the proportion of PP population patients alive at 6 and 12 months, respectively, were 0.69 (95% CI: 0.56–0.79) and 0.34 (0.19–0.50) with nal-IRI+5-FU/LV *vs* 0.43 (0.31–0.54) and 0.24 (0.12–0.37) with 5-FU/LV.

Median PFS (4.3 [95% CI: 3.1–5.7] *vs* 1.6 [1.4–2.6] months, p < 0.0001), TTF (4.1 [2.8–5.4] *vs* 1.4 [1.4–2.4] months, p = 0.0001) and ORR (22.7% *vs* 1.4%, p < 0.0001) were statistically significantly improved among nal-IRI+5-FU/LV- *vs* 5-FU/LV-treated PP patients. Among non-PP patients, the median PFS with nal-IRI+5-FU/LV *vs* 5-FU/LV treatment was 1.6 (95% CI: 1.4–2.8) *vs* 1.4 (1.2–1.7) months (not significant [NS]), median TTF was 1.3 (1.1–1.5) *vs* 0.8 (0.6–1.2) months (p = 0.0221) and the ORR was 7.8% *vs* 0.0% (NS).

In the PP population, patients in the nal-IRI+5-FU/LV arm received a median of 7 cycles of randomised treatment, compared with 2 cycles in the non-PP population (Table 2). In the 5-FU/LV arm, the median number of cycles in the PP and non-PP populations was 1. PP patients receiving nal-IRI+5-FU/LV had increased time on treatment for ≥6 (98.5%), ≥12 (62.1%) and ≥18 (54.5%) weeks compared with those receiving 5-FU/LV (93.0%, 35.2% and 19.7%, respectively), in line with the observed increased efficacy of nal-IRI+5-FU/LV *vs* 5-FU/LV (Table 2). The difference in time on treatment was less pronounced in the non-PP population.

Table 2 shows grade ≥3 adverse events (AEs) with an incidence ≥5% in either population (PP or non-PP) of the nal-IRI+5-FU/LV group that had a ≥2% greater incidence *vs* either population of the 5-FU/LV group, whereas Table S1 shows all AEs with incidence ≥5% in either treatment group. The most common grade ≥3 side-effects with nal-IRI+5-FU/LV were neutropenia, fatigue and GI disturbances, in line with the primary analysis [6].

4. Discussion

The survival advantage with the nal-IRI+5-FU/LV combination *vs* 5-FU/LV originally reported for the ITT population (median OS difference = 1.9 months) was more apparent in this pre-specified PP population analysis (difference = 3.8 months). Differences between PP and non-PP populations (e.g. a better KPS) and the requirement for PP patients to receive ≥80% of planned treatment in the first 6 weeks with no more than one reduction in the nal-IRI containing arms, which excluded most patients with rapid disease progression or early death, explain that PP patients had a better prognosis. In patients receiving nal-IRI+5-FU/LV, median OS was 8.9 and 4.4 months (difference = 4.5 months) for the PP and the non-PP population, respectively. In contrast, median OS was 5.1 and 2.8 months (difference = 2.3 months) in patients receiving 5-FU/LV for the respective PP and non-PP populations. This analysis confirms the original results, providing deeper understanding of the treatment effect size estimate of the nal-IRI+5-FU/LV combination *vs* 5-FU/LV alone.

Other secondary outcomes such as PFS, TTF and ORR also showed statistically significantly superior efficacy for the nal-IRI+5-FU/LV regimen *vs* 5-FU/LV among PP patients. In the PP population, a higher proportion of post-study anticancer therapy was seen in the 5-FU/LV group, despite an increased survival with nal-IRI+5-FU/LV *vs* 5-FU/LV in these patients. While median OS was numerically larger with nal-IRI+5-FU/LV

Table 2
Dose intensity and adverse events for the PP and non-PP populations of the nal-IRI+5-FU/LV and 5-FU/LV treatment groups.[a]

	nal-IRI+5-FU/LV		5-FU/LV	
	PP (n = 66)	Non-PP (n = 49)	PP (n = 71)	Non-PP (n = 35)
Number of cycles of randomised treatment received[b]				
n	66	49	71	34
Mean (SD)	9.1 (6.67)	2.7 (2.32)	2.1 (2.02)	0.8 (0.83)
Median (1st and 3rd quartiles)	7.0 (3, 12)	2.0 (1, 3)	1.0 (1, 2)	1.0 (0, 1)
Minimum time on treatment, n (%)				
≥6 weeks	65 (98.5)[c]	17 (33.3)	66 (93.0)[c]	11 (22.9)
≥12 weeks	41 (62.1)	6 (11.8)	25 (35.2)	6 (12.5)
≥18 weeks	36 (54.5)	4 (7.8)	14 (19.7)	3 (6.3)
Mean (SD) relative dose intensity, %[d]				
nal-IRI	85.4 (15.8)	80.6 (19.9)[e]	n/a	63.1 (n/a)[f]
5-FU/LV	86.4 (16.0)	81.2 (20.5)[e]	97.9 (6.0)	90.1 (17.5)[e]
Mean (SD) duration of exposure, weeks				
nal-IRI	20.8 (14.6)	7.2 (7.4)	n/a	26.1 (n/a)[f]
5-FU/LV	20.8 (14.6)	7.2 (7.4)	12.5 (11.9)	5.5 (6.1)
Patients with AEs resulting in, n (%)				
Dose reduction	22 (33.3)	16 (32.7)	2 (2.8)	3 (8.6)
Dose delays	40 (60.6)	30 (61.2)	15 (21.1)	19 (54.3)
Treatment discontinuation	3 (4.5)	10 (20.4)	2 (2.8)	5 (14.3)
Grade ≥3 non-haematologic TEAEs occurring in ≥5% of patients in either population (PP or non-PP) of the nal-IRI + 5-FU/LV group with an incidence ≥2% greater than in either population of the 5-FU/LV group, %[g]				
Abdominal pain	4.5	8.2	2.8	14.3
Asthenia	4.5	12.2	5.6	5.7
Biliary tract infection	0	6.1	1.4	0
Decreased appetite	1.5	8.2	1.4	2.9
Diarrhoea	12.1	12.2	7.0	5.7
Fatigue	13.6	14.3	5.6	0
Gastroenteritis	0	6.1	0	0
Nausea	9.1	6.1	1.4	2.9
Sepsis	0	8.2	0	2.9
Vomiting	7.6	16.3	2.8	2.9
Grade ≥3 haematologic TEAEs occurring in ≥5% of patients in either population (PP or non-PP) of the nal-IRI + 5-FU/LV group with an incidence ≥2% greater than in either population of the 5-FU/LV group, %[g]				
Anaemia	7.6	12.2	5.6	2.9
Neutropenia[h]	22.7	32.7	2.8	5.7
White blood cell count decreased	3.0	14.3	0	0
Grade 5 AEs, %[g]				
Patients with ≥1 AE leading to death (all causes)	0	2.0[1]	5.6[2]	14.3[3]

AE, adverse event; CTCAE, common terminology criteria for adverse events; GI, gastrointestinal; n/a, not applicable; TEAE, treatment-emergent adverse event.
Causes of death: [1] Septic shock, n = 1; [2] Hepatic failure, pathological fracture, pulmonary oedema, septic shock, all n = 1; [3] Hepatic failure, hyperbilirubinaemia, jaundice, pneumonia, respiratory failure, tumour haemorrhage, upper GI haemorrhage, all n = 1 with one patient having 3 events with fatal outcome. Only one death (a case of septic shock in a neutropenic patient in the nal-IRI+5-FU/LV treatment group) was considered to be possibly related to study treatment.

[a] Patients who did not receive any study drug are included in the non-PP population, but were neither included in the exposure summary nor in the safety summary.

[b] Cycle lengths: 2 weeks for nal-IRI+5-FU/LV and 6 weeks for 5-FU/LV.

[c] Values are <100% as patients who received their last scheduled dose earlier than the cut-off date of 6 weeks were categorised as <6 weeks on treatment despite having received all required doses.

[d] Time from (date of the last administration of study drug + projected days to the next dose − date of first administration)/7.

[e] Patients meeting the requirement to receive planned study treatment may have had other protocol violations requiring their classification into the non-PP group.

[f] 1 patient randomised to the 5-FU/LV treatment group erroneously received 26 weeks of nal-IRI treatment (i.e. the nal-IRI+5-FU/LV combination).

[g] Per CTCAE, version 4.

[h] Includes neutropenia, neutrophil count decreased, febrile neutropenia, granulocytopenia, neutropenic sepsis, agranulocytosis and pancytopenia. Patients with more than one of these events are only counted once in the proportion estimate.

vs 5-FU/LV in non-PP patients, this difference did not reach statistical significance. Although the data for the non-PP population do not demonstrate a statistically significant survival advantage for the nal-IRI+5-FU/LV regimen, the HR of 0.64 and p-value of 0.0648 signal that the regimen can also benefit patients who experience toxicities and require dose reductions.

Previous exploratory analyses of the NAPOLI-1 ITT population data set have led to the development of an OS nomogram for patients in this post-gemcitabine setting

[19]. The analysis, which also distinguished between risk groups, identified the following predictors for OS: treatment with nal-IRI+5-FU/LV, KPS, neutrophil-to-lymphocyte ratio, albumin level, baseline CA19-9, disease stage 4 at diagnosis, body mass index, and presence of liver metastasis. While prediction of PP or non-PP population assignment would be desirable in this treatment setting, the OS nomogram methodology could not be applied to the present analysis because of the limited number of patients in both populations.

AEs reported with nal-IRI+5-FU/LV treatment (Table 2) were in line with previous observations in patients receiving liposomal irinotecan [6,7,9,20]. The substantial proportion (56%) of ITT patients meeting the PP population analysis criteria, which excluded most of those with rapid disease progression and/or tolerability issues, highlights the efficacy and manageable toxicity of nal-IRI+5-FU/LV in this fragile patient population. The nal-IRI+5-FU/LV toxicity profile seen in NAPOLI-1 [6] and the present PP analysis, and the lack of treatment-associated neurotoxicity with this regimen, may make it more suitable for use after first-line gemcitabine plus nab-paclitaxel (a regimen associated with neurotoxicity [4]) than oxaliplatin-containing regimens, which are also known to be associated with neurotoxicity [21,22].

5. Conclusions

This analysis improves our understanding of the efficacy and safety of the nal-IRI+5-FU/LV regimen in patients with metastatic pancreatic cancer that progressed after gemcitabine-based therapy. The significant survival increase seen in PP patients who were treated with nal-IRI+5-FU/LV does not appear to be connected to particular patient baseline characteristics compared with the 5-FU/LV control group. The present data suggest that nal-IRI+5-FU/LV, used after failure of prior gemcitabine-based therapy, increases survival *vs* 5-FU/LV alone in metastatic pancreatic cancer patients of different therapeutic backgrounds and will help inform treatment decisions considering typically heterogenous prior therapy and varying degrees of AE-related treatment dose and schedule modification.

Conflict of interest statement

Fadi S. Braiteh reports honoraria and advisory board fees from Merrimack Pharmaceuticals and Ipsen. **Bruce Belanger** was employed by Merrimack Pharmaceuticals and is currently an employee at Ipsen Bioscience. **Jean-Frédéric Blanc** has received honoraria for lectures and consultancy and travel grants from Amgen, Bayer, Celgene, Merck, Roche and Sanofi-Aventis and has had a consultant or advisory role at Baxalta (now Shire), Merck, Amgen and Lilly. **György Bodoky** has served in a consulting or advisory role for Bayer, Ipsen, Janssen, Lilly, Novartis, Pfizer and Roche and has received support for travel, accommodation and expenses from Janssen, Lilly, Novartis, Pfizer and Roche. **Li-Tzong Chen** has received honoraria and/or has a consulting or advisory role at Eli Lilly, MSD, Ono Pharmaceutical, Baxalta (now Shire), PharmaEngine and Merrimack Pharmaceuticals, Syncore, TTY Biopharm, Novartis, Pfizer and Five Prime and reports research grants from Novartis, GSK, Celgene, Merck Serono, TTY Biopharm, OBI Pharma and Polaris to the institute, outside the submitted work. **Chang-Fang Chiu** reports no disclosures. **David Cunningham** is funded by the UK National Institute for Health Research Biomedical Research Centres (NIHR BRC) at the Royal Marsden Hospital, London, UK, and reports grants from AstraZeneca, Amgen, Celgene, Merck Serono, Sanofi, Merrimack Pharmaceuticals and Medimmune, outside the submitted work. **Andrew P. Dean** reports personal fees from AstraZeneca and Specialized Therapeutics, outside the submitted work; grants and personal fees from Roche, outside the submitted work, and grants from Boehringer Ingelheim, outside the submitted work. **Floris A. de Jong** is currently employed by Servier, was an employee of Shire at the time of study, and has stock or ownership interests in Shire. **Richard A. Hubner** has had a consultant or advisory role with Shire, BTG and Celgene. **Gayle S. Jameson** reports grants from Merrimack Pharmaceuticals during the conduct of the study and honoraria from Celgene and Ipsen. **Kyung-Hun Lee** reports no disclosures. **Chung-Pin Li** reports no disclosures. **Teresa Macarulla** has had a consultant or advisory role with Shire. **Khalid Mamlouk** was employed by Merrimack Pharmaceuticals and is currently an employee at Ipsen Bioscience. **Gilberto Schwartsmann** reports no disclosures. **Yan-Shen Shan** reports no disclosures. **Jens T. Siveke** has had a consultant or advisory role at Merrimack Pharmaceuticals, Lilly, Amcure, Baxalta (now Shire), Shire, Roche and Celgene and has received research funding from BMS, Novartis, Boehringer Ingelheim and Celgene, outside the submitted work. **Andrea Wang-Gillam** reports advisory boards for BMS, Ipsen, Jacobio, Merrimack Pharmaceuticals, NewLink, Pfizer and Rupugene.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.09.010.

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