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Liposomal Irinotecan + 5-FU/LV in Metastatic Pancreatic Cancer

Subgroup Analyses of Patient, Tumor, and Previous Treatment Characteristics in the Pivotal NAPOLI-1 Trial

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Objectives: The NAnoliPOsomaL Irinotecan (NAPOLI-1) study (NCT01494506) was the largest global phase 3 study in a post-gemcitabine metastatic pancreatic adenocarcinoma (mPAC) population (N = 417). The subanalyses reported here investigated the prognostic effect of tumor characteristics and disease stage, prior treatment characteristics, baseline patient characteristics on survival outcomes in NAPOLI-1, and whether liposomal irinotecan (nal-IRI) + 5-fluorouracil/leucovorin (5-FU/LV) benefited patients with mPAC across subgroups.

Methods: Post hoc analyses were performed in the NAPOLI-1 population (4 across tumor characteristics and disease stage, 6 across prior treatment characteristics, and 4 across patient baseline characteristics). Survival outcomes were estimated by Kaplan-Meier analysis and patient safety data were evaluated.

Results: Mortality and morbidity risk was lower on nal-IRI+5-FU/LV treatment across subgroups. Exceptions were patients who had received prior nonliposomal irinotecan and those who had undergone prior Whipple procedure (overall survival hazard ratio = 1.25 and 1.23, respectively). Decreased appetite, liver metastases, and number of measurable metastatic lesions seemed to be prognostic of survival in this population. Subgroup safety data were generally comparable with those in the overall NAPOLI-1 safety population.

Conclusions: A diverse population of patients with mPAC that progressed on gemcitabine-based therapy benefited from nal-IRI+5-FU/LV versus 5-FU/LV, potentially helping guide treatment decisions for challenging cases.

Key Words: irinotecan liposomal injection, mPAC, pancreatic cancer, phase 3 clinical trial, subanalysis, post hoc

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Pancreatic cancer is relatively rare and is estimated to be responsible for 2.5% of cancer cases (458,918 cases) in a global analysis.[1] A recent population-based prospective cohort study of patients from the Netherlands suggests that pancreatic cancer prevalence may be generally underreported; of 113 cases identified in the study, only 67.3% of cases in the Dutch Cancer registry were initially reported as pancreatic cancer, with other cases registered as unknown primary tumors or different cancers.[2] The

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Where patient data can be anonymized, Servier and Ipsen will share all individual participant data that underlie the results reported in this article with qualified researchers who provide a valid research question. Study documents, such as the study protocol and clinical study report, are not always available. Proposals should be submitted to Servier via https://clinicaltrials.servier.com/data-request-portal/ or to Ipsen via 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 will be available.

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disease has a relatively poor prognosis versus other tumors, for which survival rates seem to be improving.[3] Globally, the disease is predicted to be the second most common cause of cancer-related death by 2030, with median overall survival (mOS) without treatment estimated as 4.6 months in Europe.[4–6]

First-line treatment options for patients with metastatic pancreatic adenocarcinoma (mPAC) and a good performance status (PS) of Eastern Cooperative Oncology Group (ECOG) 0 to 1 include 5-fluorouracil + folinic acid [5-FU/LV] + nonliposomal irinotecan + oxaliplatin (FOLFIRINOX) and gemcitabine + nab-paclitaxel regimens.[7–9] For patients with a poor PS (ECOG 2), gemcitabine monotherapy is generally more appropriate, although some patients may also be able to receive gemcitabine + nab-paclitaxel.[9] The phase 3 NAPOLI-1 trial (NAnoliPOsomaL Irinotecan-1; NCT01494506) evaluated liposomal irinotecan (nal-IRI) + 5-FU/LV every 2 weeks versus 5-FU/LV weekly in patients with mPAC that had progressed after gemcitabine-based therapy.[10] This study demonstrated that nal-IRI+5-FU/LV significantly increased mOS in the intention-to-treat (ITT) population compared with 5-FU/LV alone (6.1 months vs 4.2 months, unstratified hazard ratio [HR], 0.67; $P = 0.012$), whereas nal-IRI monotherapy every 3 weeks did not show a significant benefit. Notable toxicities with nal-IRI+5-FU/LV included neutropenia, diarrhea, vomiting, and fatigue.[10] Despite this, quality of life was maintained versus 5-FU/LV alone.[11] These results led to approval of nal-IRI+5-FU/LV for treatment of mPAC after gemcitabine-based therapy in numerous countries, and inclusion in National Comprehensive Cancer Network, American Society of Clinical Oncology, and European Society for Medical Oncology clinical guidelines for patients with disease that has progressed on gemcitabine-based therapy and ECOG PS 0–2.[9,12,13]

There is a relative paucity of suitable biomarkers and prognostic indicators for pancreatic cancer survival outcomes, mostly because of the complexity of disease biology.[14] Potential prognostic factors include number and location of metastases, weight loss, and PS.[15] In terms of serum biomarkers, carcinoembryonic antigen levels of 5 ng/mL or less are prognostic of longer survival in patients with metastatic pancreatic cancer.[16] Carbohydrate antigen 19-9 (CA 19-9) has been associated with prognosis and recurrence in multiple studies; however, its utility is somewhat limited because of its nonspecificity.[17]

Regarding treatment, tumor carboxylesterase 2 expression levels were shown to be associated with longer mOS and progression-free survival (PFS) in a study of predictive biomarkers for FOLFIRINOX treatment in pancreatic ductal adenocarcinoma (PDAC).[18] In addition, expression of *hENT1* has been suggested to predict benefit of gemcitabine-based therapies in PDAC, although this has not been confirmed in other studies or the metastatic setting.[15]

The NAnoliPOsomaL Irinotecan (NAPOLI-1) trial was the largest global phase 3 study (N = 417) in the post-gemcitabine mPAC population and thus provides an opportunity to identify prognostic factors for survival in mPAC as well as further investigating patient groups that may benefit nal-IRI+5-FU/LV treatment. Recent studies of the prognostic value of 3 key biomarkers in the NAPOLI-1 population suggest that lower CA 19-9, neutrophil-to-lymphocyte ratio, and modified Glasgow prognostic score after the start of treatment are all prognostic of improved survival outcomes.[19–21] In addition, neutrophil-to-lymphocyte ratio was predictive of benefit with nal-IRI+5-FU/LV treatment.[19]

The post hoc subanalyses of the NAPOLI-1 population presented here investigate the impact on outcomes of tumor and disease stage characteristics, prior treatment history, and baseline patient characteristics. The aims of these analyses are to identify whether the analyzed parameters are prognostic of outcomes in the NAPOLI-1 and to evaluate the benefit of nal-IRI+5-FU/LV versus 5-FU/LV alone in different patient subgroups.

MATERIALS AND METHODS

Study Design

NAPOLI-1 study design, treatment regimens, and methods were previously published in detail.[10] The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guidance on Good Clinical Practice, the requirements of the US Food and Drug Administration, and local regulatory authorities. All patients provided written informed consent. Adult patients with mPAC that had progressed on gemcitabine-based therapy were included (Fig. 1).

The ITT population included 417 patients. Patients were assigned to nal-IRI+5-FU/LV (n = 117) after a protocol amendment and were compared with those assigned to 5-FU/LV control after the amendment (n = 119). The nal-IRI+5-FU/LV arm was included after availability of safety data on the combination.[22] Patients assigned nal-IRI monotherapy (n = 151) were compared with those allocated 5-FU/LV control under either version of the protocol (n = 149) (Fig. 1).

Post hoc analyses were performed on the NAPOLI-1 ITT population under the categories of tumor characteristics and disease stage, treatment history, and baseline patient characteristics (Fig. 1). Tumor characteristics evaluated subgroups based on the number and location of baseline metastatic lesions (presence of any liver, lung, or peritoneal metastases; presence of liver metastases only), disease stage at initial diagnosis (IIA, IIB, III, or IV), and primary tumor location (head only, body only, tail only, multiple locations including head [H_{incl}], or multiple locations excluding head [H_{excl}]). Prior treatment characteristics included subgroups based on prior irinotecan-based therapy, prior gemcitabine-based therapy, prior surgery, prior Whipple procedure, number of prior lines of anticancer therapy in the metastatic setting (0–1 or ≥2), and presence of a biliary stent at baseline. Baseline patient characteristics investigated the impact of best response to prior anticancer therapy (prior complete response/partial response [CR/PR] versus no prior CR/PR, prior CR/PR/stable disease [SD] versus no prior CR/PR/SD), presence or absence of metabolism and nutrition disorders, baseline weight parameters (body surface area [BSA], body mass index [BMI], and weight), baseline pain intensity (rated during the 7 days preceding treatment using the visual analog scale [range, 0–100] with a minimum 3 days of data required), and baseline analgesic use (milligram per day morphine equivalent). Patients were divided into subgroups based on presence or absence of baseline pain intensity/analgesic use and whether baseline pain intensity/analgesic use was greater or less than or equal to median values. Additional details regarding subgroups are provided in Figure 1.

Objective response rate (ORR) is defined as percentage of CR and PR in the subgroups; responses are defined by Response Evaluation Criteria in Solid Tumors v1.1. A CA 19-9 response is defined as 50% reduction in baseline CA 19-9 levels, in patients with baseline levels of greater than 30 U/mL and at least one postbaseline CA 19-9 measurement.

Safety, Dose Modifications, and Treatment Exposure Analysis

Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0, in patients who received one or more dose (including a partial dose) of study treatment. Hematological parameters were assessed based on laboratory evaluations. Changes from baseline to end of treatment or highest postdose Common Terminology Criteria for Adverse Events grade were summarized

by treatment group. Duration of exposure in weeks was calculated as: time from date of last administration of study drug + projected days to next dose of study drug administration − date of first study drug administration/7.

Statistical Analysis

Median OS, PFS (mOS, mPFS), and time to treatment failure were estimated for subgroups using Kaplan-Meier analysis. All survival outcomes are reported as time after trial inclusion. For evaluation of prognostic effects, all treatment groups were included in the analyses, except where prognositic effects in the nal-IRI+5-FU/LV arm alone were analyzed, and treatment group was not taken into account in these analyses. Treatment effect analyses compared patients receiving nal-IRI+5-FU/LV with those receiving 5-FU/LV after the protocol amendment discussed previously (Fig. 1). Relevant HRs and corresponding 95% confidence intervals (CI) were estimated for each pair of subgroups using unstratified Cox proportional hazards regression. These analyses were not powered, and *P* values are descriptive and obtained using the log-rank method. For ORR and tumor marker responses, *P* values were calculated using a pairwise Fisher exact test.

RESULTS

Baseline Characteristics

Baseline patient characteristics and demographic data for subgroups were generally consistent with those reported for the whole ITT population (Supplemental Table 1, http://links.lww.com/MPA/A756). Sex, ethnicity, and Karnofsky PS tended to

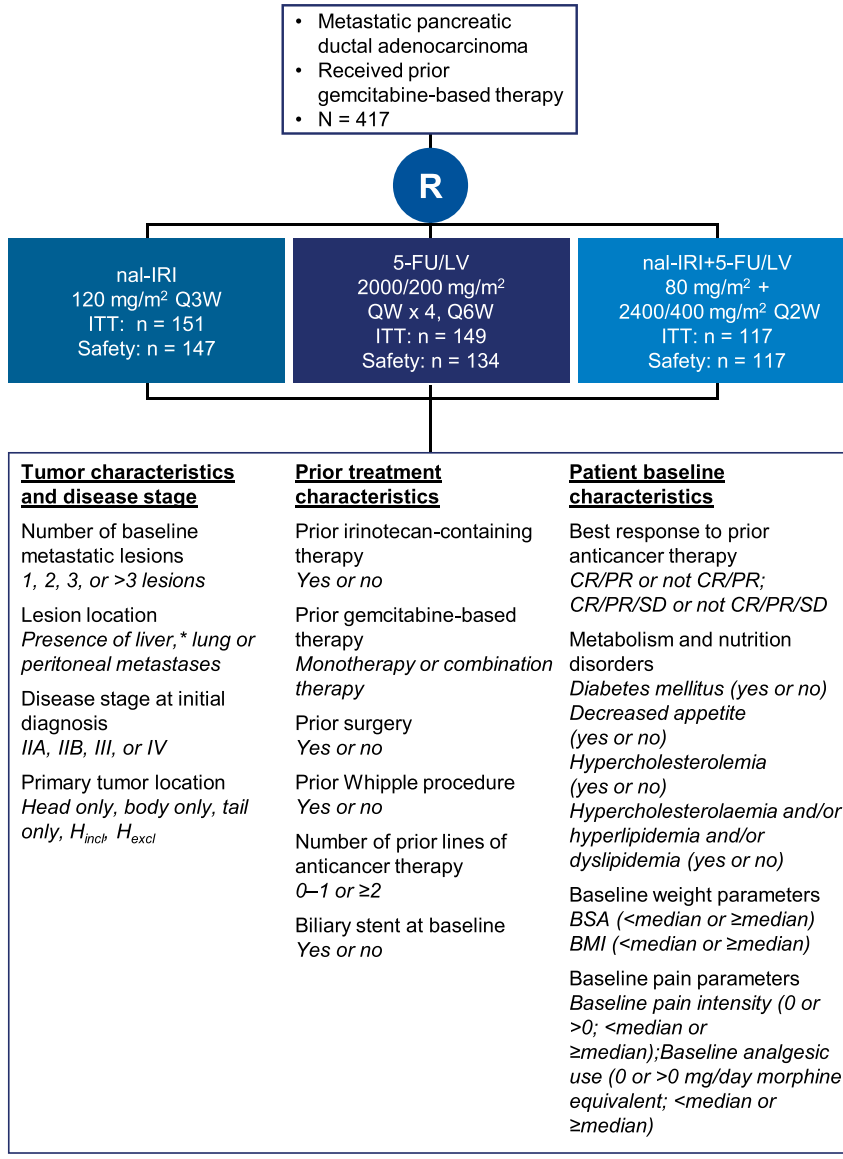

FIGURE 1. NAPOLI-1 trial design and subgroup analyses. *The study was amended to add the nal-IRI+5-FU/LV arm once safety data on the combination became available. Only those patients enrolled in the 5-FU/LV arm after the amendment (n = 119) were used as the control for the combination arm (trial registered at ClinicalTrials.gov, NCT01494506). Abbreviation Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; SD, stable disease.

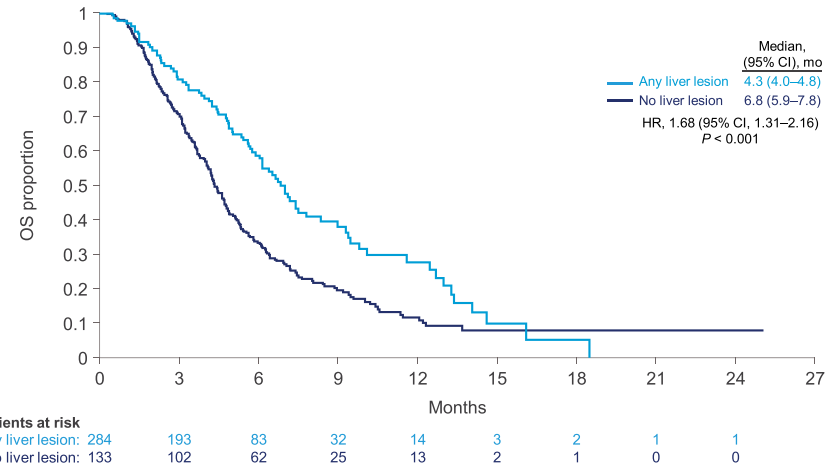

FIGURE 2. Overall survival in NAPOLI-1 by baseline liver lesions (ITT population). Patients with baseline liver lesion data available were included in this analysis.

differ from the ITT population in lesion number, lesion location, baseline pain intensity, baseline analgesic use, weight parameter, and metabolism and nutrition disorder subgroups (data not shown). In addition, patients with biliary stents at baseline had primary tumors in the head of the pancreas more frequently than those without (89% vs 59%).

Subgroup Analyses of Potential Prognostic Signals

Tumor and Disease Characteristics

Location of Metastases

The presence of liver metastases at study entry as measured by RECIST v1.1 was prognostic of lower mOS and mPFS in the NAPOLI-1 ITT population. Patients with any liver metastases (n = 284) had a significantly shorter mOS and mPFS versus those with no liver metastases (n = 133) (mOS: 4.3 months vs 6.8 months; HR, 1.68; $P < 0.001$; mPFS: 1.6 months vs 4.2 months; HR, 1.93; $P < 0.001$) (Fig. 2, Table 1). In the nal-IRI+5-FU/LV arm (n = 117), patients with any liver metastases (n = 75) seemed to have worse survival outcomes than those with no liver metastases (n = 42) (mOS: 5.2 months vs 9.3 months; HR, 1.88; $P = 0.015$; mPFS: 2.8 months vs 5.6 months; HR, 1.87; $P = 0.010$), although there was no obvious difference in ORR (Table 1). The OS in patients with any lung metastases versus no lung metastases in the ITT population was 5.6 versus 4.8 months, respectively (HR, 0.80; $P = 0.070$) (Table 1). The presence of only liver metastases or any peritoneal metastases did not seem to influence survival outcomes.

Number of Metastatic Lesions

Poorer survival outcomes were associated with a greater number of measurable metastatic lesions in the NAPOLI-1 ITT population. Patients with 1 measurable lesion had better survival outcomes versus those with 2, 3, or 3 or more measurable lesions (mOS: 6.1 months vs 4.6, 4.8, or 2.7 months; HR, 1.59, 1.38, and 2.51, respectively, $P = 0.003$, 0.110, and <0.001, respectively). This effect was not seen in the nal-IRI+5-FU/LV treatment arm (mOS: 6.1 months vs 6.0, 4.7, and 4.4 months; HR, 1.31, 1.42, and 1.36, respectively, $P = 0.380$–0.598) (Supplemental Table 2, http://links.lww.com/MPA/A756). There was no effect of number of metastatic lesions on ORR, either in the ITT population or the nal-IRI+5-FU/LV treatment arm. There were no clear changes in survival outcomes when other groups were cross-compared.

Primary Tumor Location

Primary tumor location in the head of the pancreas at initial diagnosis did not impact postinclusion survival outcomes in the NAPOLI-1 ITT population (H_{incl} versus H_{excl}: mOS, 5.1 months vs 4.4 months; HR, 0.87; $P = 0.240$). The same seemed to be true of PFS outcomes (H_{incl} versus H_{excl}: mPFS, 2.7 months versus 1.7 months; HR, 0.82; $P = 0.084$) (Supplemental Fig. 1, http://links.lww.com/MPA/A756).

Disease Stage at Diagnosis

Locally advance (stage III) disease at initial diagnosis was also associated with improved postinclusion survival outcomes versus metastatic (stage IV) disease in the NAPOLI-1 ITT population and the nal-IRI+5-FU/LV treatment arm. In the overall ITT population, patients with locally advanced disease at diagnosis had significantly improved mOS after trial inclusion compared with those with metastatic disease in both the ITT population (6.3 months vs 4.2 months; HR, 0.57; $P < 0.001$) and the nal-IRI+5-FU/LV arm (9.0 months vs 4.7 months; HR, 0.43; $P = 0.021$) (Supplemental Table 3, http://links.lww.com/MPA/A756). The ORR was generally similar between patients with locally advanced and metastatic disease (Supplemental Table 3, http://links.lww.com/MPA/A756).

Prior Treatment Characteristics

Prior Surgery

Patients in the ITT population who underwent resection with curative intent before trial inclusion exhibited improved mOS during the trial compared with those who had not (6.8 months vs 4.4 months; HR, 0.62; $P < 0.001$). There did not seem to be a reduced risk of disease progression in these patients (mPFS 2.7 months versus 2.2 months; HR, 0.84; $P = 0.129$) (Supplemental Table 4, http://links.lww.com/MPA/A756). There were no clear effects of prior surgery on ORR or tumor marker CA 19-9 responses (Supplemental Table 5, http://links.lww.com/MPA/A756).

Prior Whipple Procedure

A Whipple procedure, or pancreatoduodenectomy, seemed to be associated with better survival outcomes for patients in the NAPOLI-1 trial versus no Whipple procedure (mOS: 6.1 months vs 4.6 months; HR, 0.74; $P = 0.020$). As with prior surgery, prior Whipple procedure was not clearly associated with changes in disease progression (mPFS 2.6 months vs 2.3 months; HR, 0.96;

TABLE 1. Outcomes in Selected Baseline Lesion Location Subgroups

	Overall							
	Liver Only (n = 104)	**No Liver Only (n = 313)**	**Any Liver (n = 284)**	**No Liver (n = 133)**	**Any Lung (n = 129)**	**No Lung (n = 288)**	**Any Peri (n = 115)**	**No Peri (n = 302)**
OS, median (95% CI), mo	4.4 (4.0–6.0)	5.0 (4.7–5.6)	4.3 (4.0–4.8)	6.8 (5.9–7.8)	5.6 (4.7–6.5)	4.8 (4.2–5.2)	4.8 (4.0–5.2)	5.2 (4.4–5.9)
HR (95% CI)	1.15 (0.90–1.48)		1.68 (1.31–2.16)		0.80 (0.62–1.02)		1.16 (0.91–1.48)	
*P**	0.260		<0.001		0.070		0.235	
PFS, median (95% CI), mo	2.0 (1.5–2.7)	2.6 (1.8–2.8)	1.6 (1.4–2.2)	4.2 (2.9–5.4)	2.6 (1.7–3.3)	2.4 (1.6–2.8)	2.4 (1.5–2.8)	2.6 (1.8–2.8)
HR (95% CI)	1.21 (0.94–1.55)		1.93 (1.50–2.47)		0.86 (0.68–1.09)		1.09 (0.86–1.40)	
*P**	0.144		<0.001		0.225		0.473	
ORR, %	8	7	7	7	9	6	3	8
P†	0.824		1.000		0.216		0.129	
	nal-IRI+5-FU/LV							
	Liver Only (n = 27)	**No Liver Only (n = 90)**	**Any Liver (n = 75)**	**No Liver (n = 42)**	**Any Lung (n = 36)**	**No Lung (n = 81)**	**Any Peri (n = 28)**	**No Peri (n = 89)**
OS, median (95% CI), mo	6.1 (3.4–8.9)	6.1 (4.8–9.4)	5.2 (4.4–6.7)	9.3 (6.0–13.4)	6.0 (4.6–12.7)	6.2 (4.6–8.9)	9.0 (4.4–14.6)	6.1 (4.7–8.4)
HR (95% CI)	1.53 (0.93–2.50)		1.88 (1.12–3.14)		0.87 (0.52–1.46)		0.72 (0.41–1.26)	
*P**	0.091		0.015		0.604		0.246	
PFS, median (95% CI), mo	2.7 (1.4–4.0)	4.0 (2.8–4.4)	2.8 (1.5–3.4)	5.6 (3.3–8.0)	4.1 (2.0–7.1)	3.0 (2.4–4.2)	2.8 (1.4–7.0)	3.3 (2.3–4.2)
HR (95% CI)	1.53 (0.93–2.52)		1.87 (1.15–3.03)		0.79 (0.48–1.30)		0.89 (0.53–1.49)	
*P**	0.095		0.010		0.350		0.643	
ORR%	19	16	17	14	17	16	11	18
P†	0.768		0.796		1.000		0.558	

Subgroup analyses of "lung only versus no lung only" and "peri only versus no peri only" were not included because of very small patient numbers in these groups.

**P* from log-rank test.

†*P* from pairwise Fisher exact test.

Peri indicates peritoneal.

$P = 0.725$) (Supplemental Table 5, http://links.lww.com/MPA/A756). There was no effect on ORR or CA 19-9 responses (Supplemental Table 5, http://links.lww.com/MPA/A756).

Biliary Stent at Baseline

In the ITT population, 37 patients had a biliary stent at baseline, including 15 in the nal-IRI+5-FU/LV arm (Supplemental Table 6, http://links.lww.com/MPA/A756). Association of biliary stents at baseline with overall survival outcomes was not apparent in the ITT population (mOS: 5.3 months vs 4.8 months; HR, 0.97; $P = 0.895$) or the nal-IRI+5-FU/LV arm (6.2 months vs 6.1 months; HR, 0.91; $P = 0.785$). Biliary stenting was associated with numerically improved ORR and CA 19-9 responses in both the ITT population and the nal-IRI+5-FU/LV arm of the study (Supplemental Table 6, http://links.lww.com/MPA/A756).

Best Response to Prior Therapy

There was no obvious influence of CR/PR as best response to prior therapy on survival outcomes in the overall ITT population (mOS: 5.6 months vs 4.8 months; HR, 0.73) (Supplemental Fig. 2A, http://links.lww.com/MPA/A756). There was also no clear effect of prior CR/PR/SD versus no prior CR/PR/SD on survival outcomes (mOS: 4.9 months vs 4.9 months; HR, 0.95) (Supplemental Fig. 2A, http://links.lww.com/MPA/A756). However, patients with prior CR/PR seemed to have a numerically longer time to disease progression than those without (mPFS: 3.8 months vs 2.4 months; HR, 0.73; $P = 0.065$) (Supplemental Fig. 2B, http://links.lww.com/MPA/A756).

Baseline Patient Characteristics

Baseline Pain Intensity and Analgesic Use

In the ITT population, patients were separated into subgroups greater than or equal to or less than the median baseline pain intensity of 25, as well as having any (>0) or no (0) baseline pain intensity. Patients with higher baseline pain intensity seemed to have an increased mortality risk (baseline pain intensity >25 vs ≤25: mOS: 4.0 months vs 6.3 months; HR, 1.95; $P < 0.001$; baseline pain intensity 0 versus >0: mOS: 4.7 months vs 8.9 months; HR, 2.01; $P < 0.001$) (Fig. 3A).

Patients were also divided into subgroups based on the median value of 8.1 mg/d morphine equivalent and presence or absence of

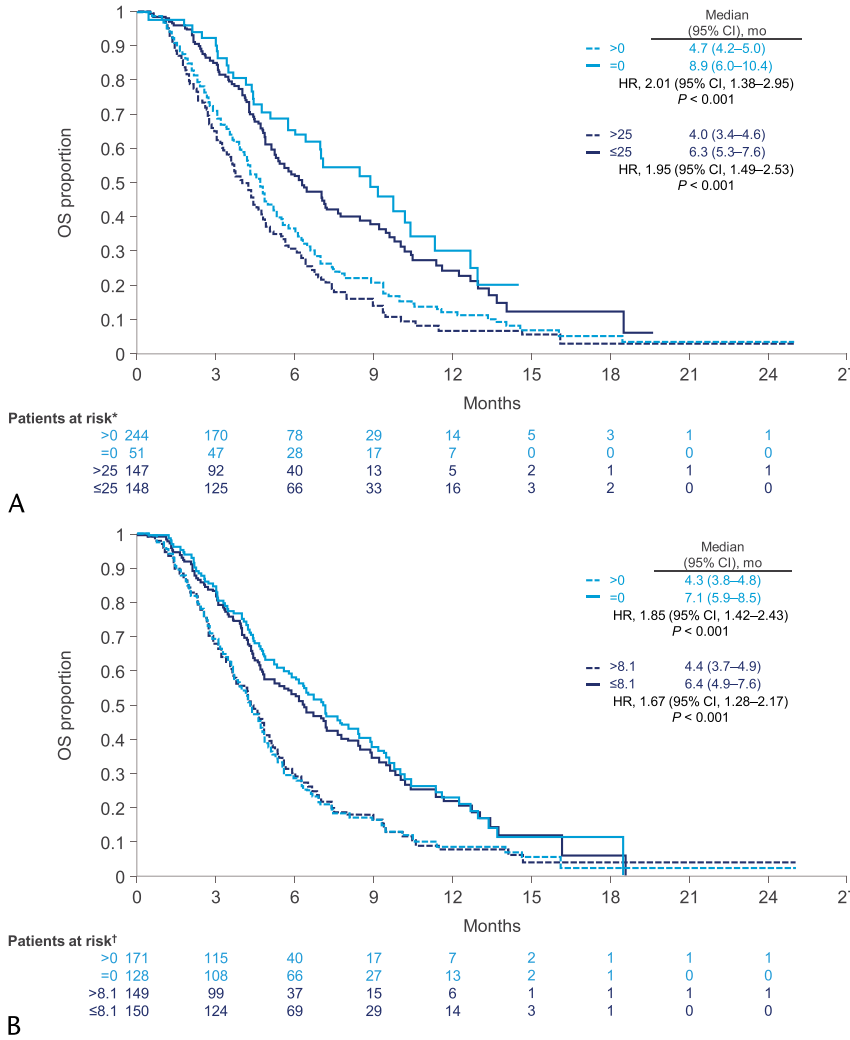

FIGURE 3. Mortality in patients with increased baseline pain and analgesic use. A, Overall survival based on baseline pain subgroups; mean value for baseline pain is 25. B, Overall survival based on baseline analgesic use subgroups; median baseline analgesic use is 8.1 mg/d. *Patients with baseline pain intensity data available (includes all treatment arms). †Patients with baseline analgesic use data available (includes all treatment arms).

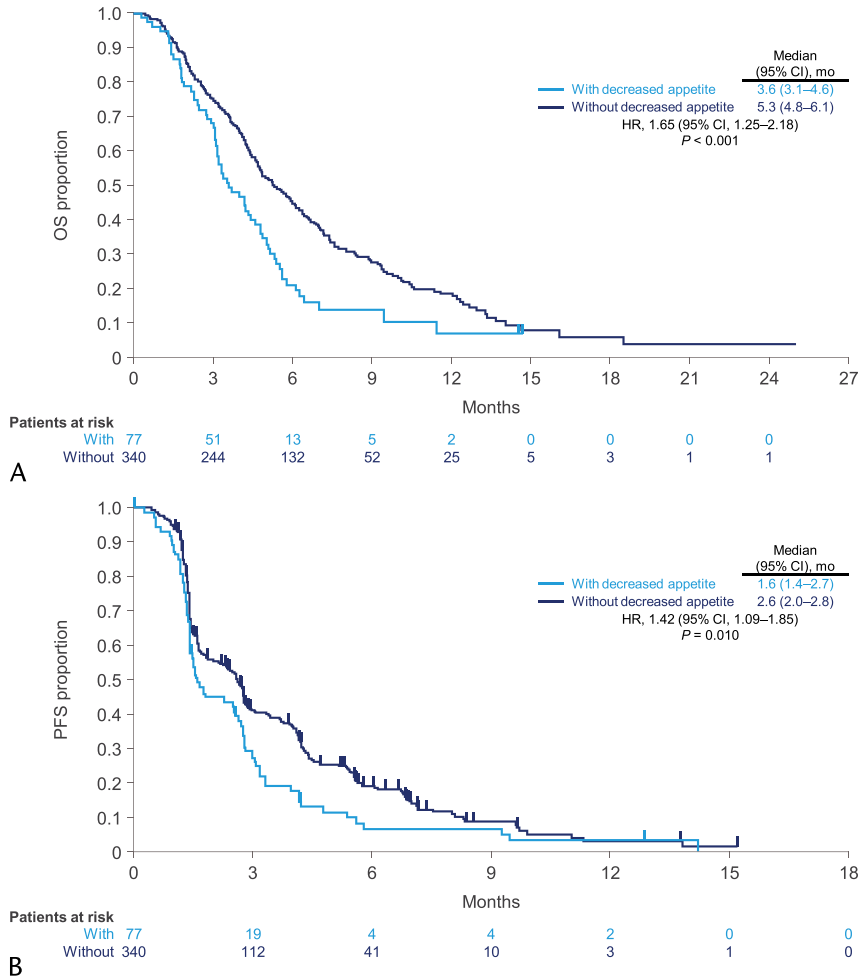

FIGURE 4. Survival outcomes in patients with decreased appetite at baseline in the NAPOLI-1 ITT population. A, Overall survival in patients with or without decreased appetite at baseline. B, Progression-free survival in patients with or without decreased appetite at baseline.

baseline analgesic use. Similar to that seen with baseline pain intensity, patients with higher baseline analgesic use were also at an increased risk of mortality (mOS: 4.4 months [baseline analgesic use >8.1 mg/d] vs 6.4 [≤8.1 mg/d] months; HR, 1.67; $P < 0.001$; mOS: 4.3 months [baseline analgesic use 0 mg/d] vs 7.1 [baseline analgesic use >0 mg/d] months; HR, 1.85; $P < 0.001$) (Fig. 3B).

Metabolism and Nutrition Disorders

The connection between metabolism and nutrition disorders and survival in the NAPOLI-1 ITT population was also investigated. Decreased appetite at baseline seemed to be associated with worse survival outcomes compared with no decreased appetite at baseline (mOS with vs without decreased appetite: 3.6 months vs 5.3 months; HR, 1.65; $P < 0.001$; mPFS with vs without decreased appetite: 1.6 months vs 2.6 months; HR, 1.42; $P = 0.010$) (Fig. 4, Table 2). There was also a slight numerical decrease in mOS with versus without hypercholesterolemia, which was not statistically significant (4.4 months vs 5.1 months; HR, 1.37; $P = 0.063$) (Table 2). Diabetes mellitus and dyslipidemia (including hyperlipidemia and hypercholesterolemia) were not clearly associated with survival outcomes in the NAPOLI-1 trial (Table 2). Metabolism and nutrition disorders were not associated with changes in ORR or CA 19-9 responses (Table 2).

Baseline Weight Parameters

Higher or lower baseline weight parameters (BSA or BMI) did not influence mOS in the ITT population (BSA <1.71 m^2 vs ≥1.71 m^2: 4.8 months vs 4.9 months; HR, 1.04; $P = 0.704$; BMI <22.9 kg/m^2 vs ≥22.9 kg/m^2: 4.7 months vs 5.2 months; HR, 1.17; $P = 0.175$). A similar effect was seen in the nal-IRI+5-FU/LV arm (Supplemental Fig. 3, http://links.lww.com/MPA/A756).

Effect of nal-IRI+5-FU/LV Treatment on Outcomes Versus 5-FU/LV in Selected Subgroups

Tumor Characteristics and Disease Stage

Improved survival outcomes were observed with nal-IRI+5-FU/LV versus 5-FU/LV in patients without tumors located in the head of the pancreas. This effect was observed for both mOS (5.2 months vs 3.2 months; HR, 0.52; $P = 0.015$) and mPFS (3.1 months vs 1.4 months; HR, 0.42; $P = 0.001$). For patients with tumors located in the head of the pancreas, treatment with nal-IRI +5-FU/LV was associated with improved PFS outcomes (H_{incl}: 3.4 months vs 1.6 months; HR, 0.61; $P = 0.010$). A numerical increase was also observed in these patients in terms of OS in patients treated with nal-IRI+5-FU/LV versus 5-FU/LV (Supplemental Fig. 4, http://links.lww.com/MPA/A756).

Prior Treatment Characteristics

Prior Irinotecan-Containing Therapy

Tumors can develop resistance to conventional irinotecan.[23] nal-IRI therapy has been shown to overcome irinotecan resistance in models of small cell lung cancer.[24] We therefore investigated whether patients who had received nonliposomal irinotecan before entry into the NAPOLI-1 trial benefited from treatment with nal-IRI+5-FU/LV. A similar proportion of patients were irinotecan-naive in the nal-IRI+5-FU/LV arm (90%, n = 105/117) and the 5-FU/LV arm (86%, n = 102/119). A treatment benefit was seen with nal-IRI+5-FU/LV for irinotecan-naive patients versus 5-FU/LV alone (mOS: 6.7 months vs 4.2 months; HR, 0.62; P = 0.005; mPFS: 3.4 months vs 1.5 months; HR, 0.52; $P < 0.001$) (Figs. 5A, C, Table 3). Conversely, this treatment benefit was not observed in patients who had previously received nonliposomal irinotecan receiving nal-IRI +5-FU/LV (n = 12) versus 5-FU/LV (n = 17) (mOS: 4.6 months vs 4.8 months; HR, 1.25; P = 0.639; mPFS: 1.5 months vs 1.4 months; HR, 0.83; P = 0.660) (Figs. 5B, D, Table 3). Treatment with nal-IRI +5-FU/LV was only associated with improvements in ORR and CA 19-9 responses in patients who had not previously received irinotecan-containing therapy (Table 3).

Prior Gemcitabine-Based Therapy

Patients treated with prior gemcitabine monotherapy had improved survival outcomes when treated with nal-IRI+5-FU/LV (n = 53) versus 5-FU/LV (n = 55) (mOS: 7.1 months vs 4.3 months; HR, 0.81; mPFS: 4.1 months vs 2.2 months; HR, 0.63). Patients treated with prior gemcitabine combinations also benefited from treatment with nal-IRI+5-FU/LV (n = 64) versus 5-FU/LV (n = 64) (mOS: 6.1 months vs 4.2 months; HR, 0.70; mPFS: 3.1 months vs 1.4 months; HR, 0.54) (Supplemental Fig. 5, http://links.lww.com/MPA/A756).

Prior Lines of Therapy

In terms of previous lines of metastatic therapy, improved survival outcomes were observed in patients treated with nal-IRI+5-FU/LV versus 5-FU/LV as first- or second-line metastatic treatment (Supplemental Fig. 6 and Supplemental Table 7, http://links.lww.com/MPA/A756). The response was less prominent in patients treated with nal-IRI+5-FU/LV versus 5-FU/LV at third line or beyond (mOS: 0–1 prior lines 6.2 months vs 4.2 months; HR, 0.66; P = 0.030; ≥2 lines: 5.4 months vs 4.3 months; HR, 0.68; P = 0.178) (Supplemental Fig. 6 and Supplemental Table 7, http://links.lww.com/MPA/A756). Treatment with nal-IRI+5-FU/LV was associated with improved ORR versus 5-FU/LV in patients with 0 to 1 and 2 or more prior lines of therapy (Supplemental Table 7, http://links.lww.com/MPA/A756).

Prior Surgery

Prior resection with curative intent did not impact the benefit of nal-IRI+5-FU/LV versus 5-FU/LV alone (prior resection: 8.4 months vs 6.1 months; HR, 0.84; P = 0.547; no prior resection: 5.3 months vs 3.4 months; HR, 0.56; P = 0.003) (Supplemental Table 8, http://links.lww.com/MPA/A756). Improvements in ORR and CA 19-9 responses were also observed in patients who received nal-IRI+5-FU/LV versus those receiving 5-FU/LV alone who had or

TABLE 2. Efficacy in Patients With or Without Metabolism and Nutrition Disorders

	Metabolism and Nutrition Disorders		Diabetes Mellitus and/or Type 2 Diabetes Mellitus		Decreased Appetite		Hypercholesterolemia		Hypercholesterolemia and/or Hyperlipidemia and/or Dyslipidemia	
	With (n = 267)	Without (n = 150)	With (n = 159)	Without (n = 258)	With (n = 77)	Without (n = 340)	With (n = 47)	Without (n = 370)	With (n = 87)	Without (n = 330)
OS										
OS, median (95% CI), mo	4.8 (4.2–5.4)	5.3 (4.4–6.1)	5.6 (4.5–6.3)	4.8 (4.3–5.3)	3.6 (3.1–4.6)	5.3 (4.8–6.1)	4.4 (3.3–5.0)	5.1 (4.6–5.6)	4.7 (3.7–5.8)	5.1 (4.5–5.6)
HR (95% CI)	1.10 (0.87–1.39)		0.88 (0.70–1.11)		1.65 (1.25–2.18)		1.37 (0.98–1.91)		1.13 (0.86–1.48)	
P*	0.412		0.279		<0.001		0.063		0.375	
PFS										
PFS, median (95% CI), mo	2.5 (1.7–2.8)	2.6 (1.6–3.1)	2.8 (2.0–3.1)	2.3 (1.6–2.7)	1.6 (1.4–2.7)	2.6 (2.0–2.8)	2.3 (1.6–2.8)	2.6 (1.8–2.8)	2.2 (1.6–2.8)	2.6 (1.8–2.8)
HR (95% CI)	1.11 (0.88–1.39)		0.86 (0.69–1.08)		1.42 (1.09–1.85)		1.15 (0.83–1.60)		1.19 (0.91–1.54)	
P*	0.358		0.191		0.010		0.390		0.196	
ORR, %	7	7	8	6	10	6	4	7	6	7
P†	1.000		0.436		0.213		0.759		0.813	
CA 19-9 response rate, n/N (%)‡	46/213 (22)	23/112 (21)	30/128 (23)	39/197 (20)	13/62 (21)	56/263 (21)	6/37 (16)	63/288 (22)	13/69 (19)	56/256 (22)
P†	0.887		0.488		1.000		0.526		0.740	

Disorders are defined by MedDRA v14.1.

*P from log-rank test.

†P from pairwise Fisher exact test.

‡Response defined as ≥50% reduction in baseline CA 19-9 levels, in patients with baseline levels >30 U/mL, and at least one postbaseline CA 19-9 measurement.

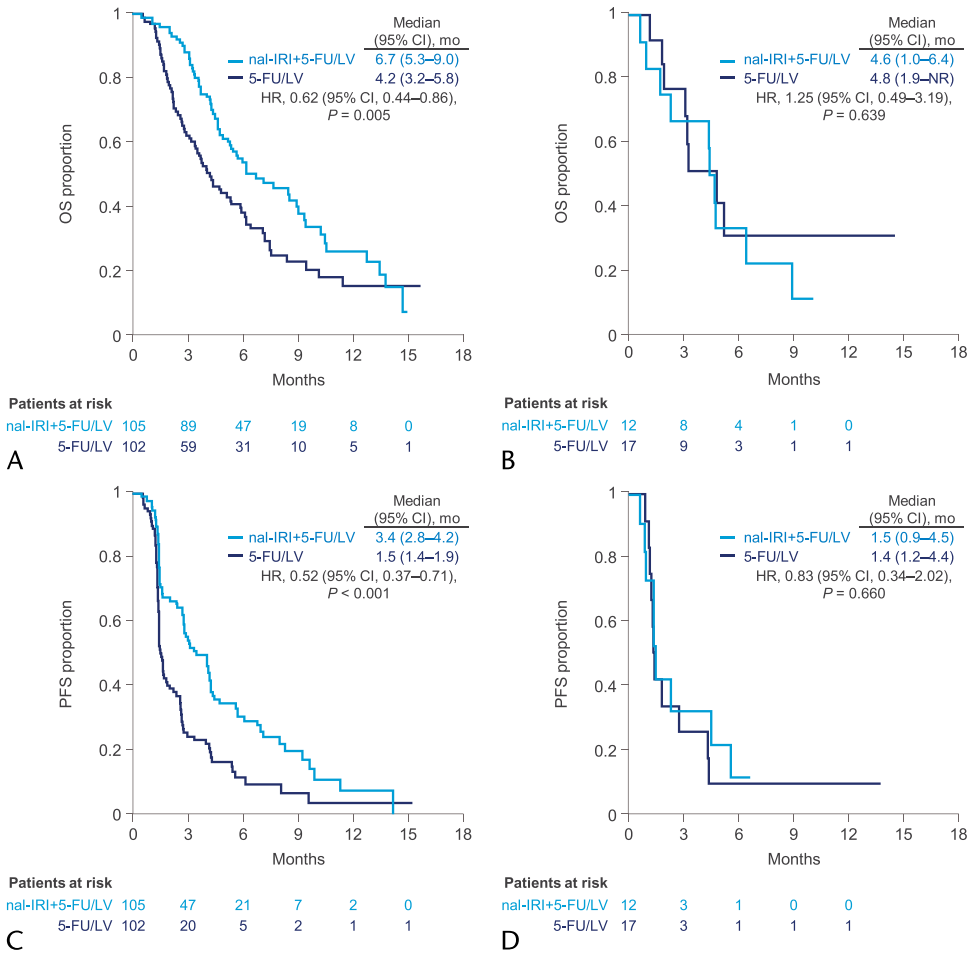

FIGURE 5. Survival outcomes in patients with or without prior irinotecan-based therapy treated with nal-IRI+5-FU/LV or 5-FU/LV. A, Overall survival, no prior irinotecan. B, Overall survival, prior irinotecan. C, Progression-free survival, no prior irinotecan. D, Progression-free survival, prior irinotecan. NR, not reached.

had not undergone prior surgery (Supplemental Table 8, http://links.lww.com/MPA/A756).

Prior Whipple Procedure

In the subanalysis of patients with prior Whipple procedure, nal-IRI+5-FU/LV (n = 30) treatment benefit did not improve mOS versus 5-FU/LV (7.1 months vs 7.4 months; HR, 1.23; $P = 0.533$) (Supplemental Table 9, http://links.lww.com/MPA/A756). There was a numerical effect of nal-IRI+5-FU/LV on ORR in patients who had undergone a prior Whipple procedure, although there was no effect on CA 19-9 responses in this group. Objective response rate and CA 19-9 responses were improved in patients who had not undergone a prior Whipple procedure on treatment with nal-IRI+5-FU/LV versus 5-FU/LV alone (Supplemental Table 9, http://links.lww.com/MPA/A756).

Biliary Stent at Baseline

In patients with or without a biliary stent at baseline, patients receiving nal-IRI+5-FU/LV exhibited numerically increased mOS versus 5-FU/LV alone with (6.2 months vs 5.2 months; HR, 0.44; $P = 0.156$) or without (6.1 months vs 4.2 months; HR, 0.68; $P = 0.022$) stent. Similar trends were also observed for PFS (Supplemental Table 10, http://links.lww.com/MPA/A756). There was no clear effect of nal-IRI+5-FU/LV treatment versus 5-FU/LV on CA 19-9 and ORR responses in patients with a biliary stent at baseline; however, nal-IRI+5-FU/LV did seem to improve outcomes versus 5-FU/LV in patients without stents (Supplemental Table 10, http://links.lww.com/MPA/A756).

Baseline Patient Characteristics

Best Response to Prior Anticancer Therapy

Patients in all prior therapy response groups benefited from treatment with nal-IRI+5-FU/LV versus 5-FU/LV (prior CR/PR: OS, 9.3 months vs 5.1 months; HR, 0.46; $P = 0.137$; no prior CR/PR: OS, 6.1 months vs 4.0 months; HR, 0.69; $P = 0.028$; prior CR/PR/SD: OS, 6.2 months vs 4.8 months; HR, 0.68; $P = 0.091$; no prior CR/PR/SD: OS, 6.1 months vs 3.6 months; HR, 0.63; $P = 0.045$) (Supplemental Fig. 7, http://links.lww.com/MPA/A756).

Metabolism and Nutrition Disorders

Survival outcomes were generally improved with nal-IRI + 5-FU/LV versus 5-FU/LV alone regardless of whether metabolism and nutrition disorders were present at baseline. For example, a nonsignificant reduction in HR was observed for patients with (HR, 0.51; $P = 0.151$), with a significant reduction for those without hypercholesterolemia (HR, 0.67; $P = 0.019$) upon

TABLE 3. Efficacy of nal-IRI+5-FU/LV Versus 5-FU/LV in Prior Irinotecan-Containing Therapy Subgroups

	All Patients		No Prior Irinotecan		Prior Irinotecan	
	nal-IRI+5-FU/LV (n = 117)	5-FU/LV (n = 119)	nal-IRI+5-FU/LV (n = 105 [90%])	5-FU/LV (n = 102 [86%])	nal-IRI+5-FU/LV (n = 12 [10%])	5-FU/LV (n = 17 [14%])
OS, median (95% CI), mo	6.1 (4.8–8.9)	4.2 (3.3–5.3)	6.7 (5.3–9.0)	4.2 (3.2–5.8)	4.6 (1.0–6.4)	4.8 (1.9–NR)
HR (95% CI)	0.67 (0.5–0.9)		0.62 (0.44–0.86)		1.25 (0.49–3.19)	
*P**	0.012		0.005		0.639	
PFS, median (95% CI), mo	3.1 (2.7–4.2)	1.5 (1.4–1.8)	3.4 (2.8–4.2)	1.5 (1.4–1.9)	1.5 (0.9–4.5)	1.4 (1.2–4.4)
HR (95% CI)	0.56 (0.4–0.8)		0.52 (0.37–0.71)		0.83 (0.34–2.02)	
*P**	<0.001		<0.001		0.660	
TTF, median (95% CI), mo	2.3 (1.6–2.8)	1.4 (1.3–1.4)	2.4 (1.6–2.9)	1.4 (1.3–1.4)	1.5 (0.9–4.5)	1.3 (0.6–1.5)
HR (95% CI)	0.60 (0.5–0.8)		0.57 (0.43–0.76)		0.73 (0.34–1.56)	
*P**	0.002		<0.001		0.407	
ORR, %	16	1	18	1	0	0
P†	<0.001		<0.001		N/A	
CA 19-9 response rate,* n/N (%)‡	28/97 (29)	7/81 (9)	28/87 (32)	7/71 (10)	0/10 (0)	0/10 (0)
P†	<0.001		<0.001		N/A	

**P* value from log-rank test.

†*P* value from pairwise Fisher exact test.

‡Response defined as ≥50% reduction in baseline CA 19-9 levels, in patients with baseline levels >30 U/mL, and at least one postbaseline CA 19-9 measurement.

N/A indicates not applicable; NR, not reached; PD, progressive disease; SD, stable disease; TTF, time to treatment failure.

treatment with nal-IRI+5-FU/LV versus 5-FU/LV (Supplemental Table 11, http://links.lww.com/MPA/A756). Patients treated with nal-IRI+5-FU/LV exhibited numerically improved ORR and tumor marker responses versus patients treated with 5-FU/LV alone across all metabolism and nutrition disorder subgroups (Supplemental Table 11, http://links.lww.com/MPA/A756).

TABLE 4. Efficacy of nal-IRI+5-FU/LV Versus 5-FU/LV in Baseline Weight Parameter Subgroups

	BSA				BMI			
	<1.71 m^2		≥1.71 m^2		<22.9 kg/m^2		≥22.9 kg/m^2	
	nal-IRI+5-FU/LV (n = 55)	5-FU/LV (n = 57)	nal-IRI+5-FU/LV (n = 62)	5-FU/LV (n = 62)	nal-IRI+5-FU/LV (n = 59)	5-FU/LV (n = 61)	nal-IRI+5-FU/LV (n = 58)	5-FU/LV (n = 58)
OS, median (95% CI), mo	6.1 (4.6–10.2)	4.0 (3.1–5.9)	6.2 (4.6–8.5)	4.2 (2.6–6.1)	6.0 (4.4–10.2)	4.2 (2.8–6.1)	6.2 (4.9–8.9)	4.2 (3.2–6.4)
HR (95% CI)	0.57 (0.35–0.90)		0.71 (0.45–1.10)		0.60 (0.38–0.95)		0.68 (0.43–1.07)	
*P**	0.015		0.123		0.028		0.091	
PFS, median (95% CI), mo	4.0 (2.4–4.2)	1.5 (1.4–2.4)	3.1 (1.5–4.3)	1.4 (1.3–2.2)	4.0 (1.5–5.6)	1.5 (1.4–2.6)	3.1 (2.4–4.2)	1.5 (1.3–1.8)
HR (95% CI)	0.49 (0.31–0.76)		0.59 (0.39–0.90)		0.47 (0.30–0.75)		0.58 (0.38–0.88)	
*P**	0.001		0.013		0.001		0.010	
ORR, %	13	0	19	2	14	2	19	0
P†	0.006		0.002		0.016		0.001	
CA 19-9 response, n/N (%)‡	12/46 (26)	4/45 (9)	16/51 (31)	3/36 (8)	15/49 (31)	1/46 (2)	13/48 (27)	6/35 (17)
P†	0.052		0.016		<0.001		0.428	

*Log-rank *P* value.

†*P* value from pairwise Fisher's exact test.

‡Response defined as ≥50% reduction in baseline CA 19-9 levels, in patients with baseline levels >30 U/ml and at least one post-baseline CA 19-9 measurement.

BL indicates baseline; BMI, body mass index; BSA, body surface area; CI, confidence interval; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

TABLE 5. Efficacy of nal-IRI+5-FU/LV Versus 5-FU/LV Alone in Baseline Pain Intensity and Baseline Analgesic Use Subgroups

	Baseline Pain Intensity									
	Overall			0		>0		≤25.0		>25.0	
	Total (n = 295)	nal-IRI+5-FU/LV (n = 88)	5-FU/LV (n = 76)	nal-IRI+5-FU/LV (n = 18)	5-FU/LV (n = 12)	nal-IRI+5-FU/LV (n = 70)	5-FU/LV (n = 64)	nal-IRI+5-FU/LV (n = 45)	5-FU/LV (n = 35)	nal-IRI+5-FU/LV (n = 43)	5-FU/LV (n = 41)
OS, median (95% CI), mo	4.9 (4.5–5.6)	6.1 (4.8–8.9)	3.7 (2.8–5.1)	8.9 (6.4–12.7)	11.4 (4.8–NR)	5.4 (4.6–8.9)	3.2 (2.4–4.0)	8.9 (6.4–12.7)	5.9 (3.5–NR)	4.7 (4.2–6.1)	2.8 (1.9–3.7)
HR (95% CI)	—	0.63 (0.43–0.91)		1.48 (0.51–4.24)		0.54 (0.36–0.80)		0.77 (0.43–1.38)		0.50 (0.31–0.83)	
*P**	—	0.013		0.477		0.002		0.381		0.006	
PFS, median (95% CI), mo	2.6 (1.8–2.8)	4.0 (2.7–4.2)	1.4 (1.3–1.8)	4.3 (1.5–14.2)	4.2 (1.2–9.6)	3.0 (2.4–4.2)	1.4 (1.3–1.6)	4.2 (2.8–6.1)	1.6 (1.3–2.8)	2.7 (1.4–4.2)	1.4 (1.3–1.6)
HR (95% CI)	—	0.55 (0.39–0.79)		0.68 (0.27–1.68)		0.50 (0.33–0.73)		0.66 (0.40–1.09)		0.45 (0.27–0.76)	
*P**	—	<0.001		0.399		<0.001		0.105		0.002	
ORR, %	8	18	1	17	0	19	2	24	0	12	2
P†	—	<0.001		0.255		0.001		0.002		0.202	
CA 19-9 response, n/N (%)‡	50/248 (20)	23/76 (30)	5/61 (8)	6/11 (55)	3/9 (33)	17/65 (26)	2/52 (4)	13/35 (37)	4/26 (15)	10/41 (24)	1/35 (3)
P†	—	0.001		0.406		0.001		0.085		0.009	
	Baseline Analgesic Use, mg/d										
	Overall			0		>0		≤8.1		>8.1	
	Total (n = 299)	nal-IRI+5-FU/LV (n = 89)	5-FU/LV (n = 77)	nal-IRI+5-FU/LV (n = 38)	5-FU/LV (n = 33)	nal-IRI+5-FU/LV (n = 51)	5-FU/LV (n = 44)	nal-IRI+5-FU/LV (n = 46)	5-FU/LV (n = 37)	nal-IRI+5-FU/LV (n = 43)	5-FU/LV (n = 40)
OS, median (95% CI), mo	4.9 (4.6–5.6)	7.6 (5.2–9.0)	4.0 (3.2–5.2)	8.9 (8.4–12.7)	7.2 (4.0–NR)	4.7 (4.3–6.0)	3.2 (2.6–4.2)	8.9 (7.1–12.7)	6.1 (4.0–NR)	4.8 (4.2–6.0)	3.1 (2.3–4.2)
HR (95% CI)	—	0.61 (0.42–0.89)		0.77 (0.40–1.47)		0.48 (0.30–0.76)		0.82 (0.45–1.47)		0.47 (0.28–0.77)	
*P**	—	0.009		0.424		0.002		0.501		0.002	
PFS, median (95% CI), mo	2.6 (1.8–2.8)	4.0 (2.8–4.3)	1.4 (1.3–1.8)	4.5 (2.8–7.1)	2.2 (1.3–4.4)	2.9 (1.5–4.2)	1.4 (1.3–1.6)	4.3 (2.8–6.8)	2.2 (1.3–4.2)	3.0 (1.5–4.2)	1.4 (1.3–1.5)
HR (95% CI)	—	0.54 (0.38–0.77)		0.64 (0.36–1.11)		0.39 (0.24–0.63)		0.67 (0.40–1.11)		0.37 (0.22–0.64)	
*P**	—	<0.001		0.112		<0.001		0.119		<0.001	
ORR, %	8	19	1	24	3	16	0	22	3	16	0
P†	—	<0.001		0.016		0.007		0.019		0.012	
CA 19-9 response, n/N (%)‡	50/250 (20)	24/75 (32)	6/61 (10)	11/28 (39)	5/24 (21)	13/47 (28)	1/37 (3)	12/36 (33)	5/28 (18)	12/39 (31)	1/33 (3)
P†	—	0.002		0.229		0.002		0.254		0.002	

*Log-rank *P* value.

†*P* from pairwise Fisher exact test.

‡Response defined as ≥50% reduction in baseline CA 19-9 levels, in patients with baseline levels >30 U/mL, and at least one postbaseline CA 19-9 measurement.

NR, not reached.

Baseline Weight Parameters

In all baseline weight parameter subgroups, treatment with nal-IRI+5-FU/LV resulted in improved survival outcomes in NAPOLI-1 (Table 4). There were also numerical improvements in ORR and tumor marker responses (Table 4).

Baseline Pain Parameters

A treatment benefit was also observed in all baseline pain intensity and baseline analgesic use subgroups with nal-IRI+5-FU/LV versus 5-FU/LV alone in terms of both OS and PFS (Table 5). This was true when subgroups were divided based on median values and when subgroups were divided based on the presence or absence of baseline analgesic use and baseline pain intensity. An improvement in ORR and CA 19-9 responses was observed in patients in all baseline pain intensity and analgesic use subgroups (Table 5).

Safety Across Subgroups

Safety data from all subanalyses were generally consistent with those reported for the whole ITT population (Supplemental Table 12, http://links.lww.com/MPA/A756). However, there were differences in grade 3 to 4 AEs in some subgroups. For example, patients with biliary stents at baseline (n = 34) tended to have a greater incidence of neutropenia (including agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutropenic sepsis, decreased neutrophil count, and pancytopenia) versus those without (n = 364) (21% vs 12%), although this did not translate into a greater incidence of febrile neutropenia (3% vs 2%) (additional data not shown). The small group of patients with prior nonliposomal irinotecan–containing therapy treated with nal-IRI+5-FU/LV (n = 12) underwent dose modifications less frequently than those without (n = 105) (50% vs 73%). However, patients with prior nonliposomal irinotecan–containing therapy had a shorter median duration of treatment exposure (10.1 weeks vs 15.5 weeks).

DISCUSSION

The subanalyses of the NAPOLI-1 population presented here have suggested several disease characteristics, prior treatment characteristics, and baseline patient characteristics that may influence survival outcomes. The subanalyses also indicated that nal-IRI+5-FU/LV consistently benefited patients in most NAPOLI-1 subgroups.

Tumor Characteristics and Disease Stage

The poor prognosis associated with any liver metastases aligns with previous studies showing that distant metastases are prognostic of worse outcomes in patients with mPAC and improved postinclusion survival outcomes in patients with no liver metastases.[25,26] In addition, a previously published analysis of the NAPOLI-1 study used the number of measurable liver metastases as a factor in developing a nomogram to predict 6- and 12-month mortality in patients with mPAC. Despite this, there was no obvious influence of existing liver metastases alone on postinclusion survival outcomes. Intriguingly, a small reduction in mortality risk was observed in patients with any lung metastases versus no lung metastases, although the reasons why this may be the case are unclear. The subanalysis of NAPOLI-1 presented here also indicates that an earlier disease stage at diagnosis is prognostic for improved survival in pancreatic cancer after trial inclusion.[27]

Prior Treatment Characteristics

A notable finding from our analysis of prior disease-directed and palliative treatments is that a greater treatment effect is observed in irinotecan-naive patients versus those who previously received nonliposomal irinotecan. This finding should, however, be interpreted cautiously, considering that few patients in the NAPOLI-1 trial had previously received therapy including nonliposomal irinotecan. Moreover, response, treatment duration, and lines of therapy may have differed in these patients, resulting in additional variation. These differences may also have influenced the different safety findings between these 2 subgroups. Liposomal irinotecan shows sustained efficacy in tumors resistant to nonliposomal irinotecan and topotecan in preclinical models of small cell lung cancer.[24] A recent retrospective observational study of patients with mPAC receiving nal-IRI+5-FU/LV indicated that of patients who received nonliposomal irinotecan, those whose disease did not progress on prior irinotecan-containing therapy had similar OS to those who had not received prior irinotecan, whereas those who had progressed had worse survival outcomes.[28] Thus, a better understanding of the interplay between nal-IRI and irinotecan resistance in mPAC is needed.

Prior mPAC tumor resection was associated with better outcomes in this subanalysis, perhaps as surgery is generally performed in patients who are fitter and had a diagnosis at an early stage.[9] Patients with or without prior surgery benefited from treatment with nal-IRI+5-FU/LV. Interestingly, patients who underwent prior Whipple procedure did not significantly benefit from treatment with nal-IRI+5-FU/LV versus 5-FU/LV alone. It should be noted that the relatively large CIs and patient numbers in the prior Whipple subgroup limit any further interpretation of these data.

In line with the use of nal-IRI+5-FU/LV after the failure of gemcitabine-based therapy,[10] patients in NAPOLI-1 benefited from receiving nal-IRI+5-FU/LV with gemcitabine monotherapy or combination therapy. This observation supports the timely use of nal-IRI+5-FU/LV in a patient's treatment journey, irrespective of prior gemcitabine based regimen. It may also be valuable to understand whether the duration of first-line treatment and time to progression on first-line treatment was prognostic of better postinclusion outcomes for patients with mPAC in the NAPOLI-1 trial, given the current indication of nal-IRI+5-FU/LV.[10]

The presence of a biliary stent at baseline was not prognostic of survival outcomes. There was no notable increase in infection-related complications, such as febrile neutropenia in this population, despite biliary stenting presenting a risk of infections.[29]

Baseline Patient Characteristics

This analysis indicates that higher baseline pain intensity and baseline analgesic use are associated with survival outcomes in the NAPOLI-1 population. This suggests that a lower symptom burden, represented by reduced pain, results in better outcomes. This finding is in line with a previous subanalysis of a phase 3 clinical trial in pancreatic cancer showing that higher patient-reported pain was prognostic of worse survival outcomes.[30]

The appetite of patients with pancreatic cancer can be affected by both the psychological burden of the disease and the production of tumor-related and inflammatory factors (eg, islet amyloid polypeptide and C-reactive protein).[31] It has also been reported that the reduced ability of patients with pancreatic cancer to digest food because of pancreatic enzyme insufficiency may result in an impaired nutritional status and thus a reduced ability to cope with their disease and associated treatments.[31,32] The finding here that decreased appetite may be associated with worse survival outcomes is in line with such previous results. Despite this and previous findings regarding the prognostic effect of weight loss in patients with pancreatic cancer,[15,30] we did not identify any prognostic effect of changes in baseline weight parameters on survival outcomes in the NAPOLI-1 population.

Limitations of These Analyses

Our analyses are limited because their descriptive, post hoc nature, a number of small subgroups relative to the ITT population,

lack of correction for multiple analyses or potential confounding factors, and the absence of multivariate analyses. No factors that definitively predict the efficacy of nal-IRI+5-FU/LV treatment over 5-FU/LV alone were identified. This may be due to the generally poor understanding of mPAC biology preventing focus on appropriate biological and clinical parameters and the wide variability of prior treatments in the NAPOLI-1 and mPAC populations in general.[9,10,14]

CONCLUSIONS

Our post hoc subanalyses of the NAPOLI-1 trial population identifies several characteristics that are potentially both positively and negatively prognostic of survival outcomes were identified, including decreased appetite at baseline, prior curative surgery, presence of liver metastases, a greater number of distant metastases, and higher baseline pain and analgesic use.

The findings from this analysis also suggest that nal-IRI + 5-FU/LV therapy versus 5-FU/LV alone consistently benefits a diverse population of patients with mPAC that progressed on gemcitabine-based therapy. The only exceptions to this treatment benefit that were identified were the potential lack of benefit in the small subgroup of patients who were previously treated with nonliposomal irinotecan, and the lack of significant treatment benefit in patients who had previously undergone a Whipple procedure. Taken together, these data on NAPOLI-1 treatment outcomes stratified by clinically relevant parameters may help guide treatment decisions, particularly for challenging cases.

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