

# The Role of Nanoliposomal Irinotecan Plus Fluorouracil and Folinic Acid as Second-Line Treatment Option in Patients With Metastatic Pancreatic Ductal Adenocarcinoma

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## Research Article

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# Abstract

## Background

According to the NAPOLI-1 trial, nanoliposomal irinotecan (nal-IRI) plus 5-fluorouracil/leucovorin (5-FU/LV) showed improved overall survival compared to fluorouracil alone for patients with metastatic pancreatic cancer who previously treated gemcitabine-based therapy. In that trial, Asian patients had frequent dose modification due to hematological toxicity. There has been limited information on the clinical benefit and toxicity of this regimen in a real-world setting. Herein, we assessed real-world experience of nal-IRI plus 5-FU/LV in patients with advanced pancreatic cancer after gemcitabine failure.

## Methods

We conducted a single institution retrospective analysis of response, survival and safety in patients who had been treated with nal-IRI with 5-FU/LV. Patients with metastatic pancreatic ductal adenocarcinoma previously treated with gemcitabine-based therapy received nal-IRI (80mg/m<sup>2</sup>) with 5-FU/LV every 2 weeks.

## Results

Fifty-one patients received nal-IRI plus 5-FU/LV between January 2015 and December 2020. The median age was 67 years, and males were 58.8%. A total of 40 (78.4%) and 11 (21.6%) patients had received one and two lines of prior chemotherapy before enrollment, respectively. Median progression-free survival was 2.8 months (95% confidence interval [CI] 1.8-3.7) and median overall survival was 7.0 months (95% CI 6.0-7.9). Chemotherapy doses were reduced or delayed in 33 (64.7%) patients during the first 6 weeks and median relative dose intensity was 0.87. Thirty-six (70.6%) patients experienced any grade 3 or 4 adverse events. Most common grade 3 or 4 adverse event was neutropenia (58.8%) and most non-hematologic adverse events were under grade 2. Since the start of first-line chemotherapy, median overall survival was 16.3 months (95% CI 14.1-18.4).

## Conclusions

Nal-IRI plus 5-FU/LV seems to be effective, with manageable toxicities, after gemcitabine-based treatment in patients with metastatic pancreatic ductal adenocarcinoma.

## Trial registration

Retrospectively registered

## Background

Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer-related deaths worldwide, more than 80% of patients present with either unresectable locally advanced or metastatic

disease upon diagnosis [1, 2]. When curative resection is not possible, the prognosis is poor, with an overall 5-year survival rate of < 5% [3].

Since the development of the new combination regimens including FOLFIRINOX (a combination of oxaliplatin, irinotecan, folinic acid and fluorouracil) and albumin-bound paclitaxel (nab-paclitaxel) with gemcitabine has improved the survival of patients with metastatic PDAC (mPDAC) [4, 5]. In clinical practice, for elderly patients or patients with relatively poor performance status (PS), nab-paclitaxel with gemcitabine is more preferred than FOLFIRINOX due to toxicity concerns [6]. Although, fluoropyrimidine-based combination regimens are recommended after gemcitabine-based treatment failure [7], more than half of patients who previously treated with gemcitabine-based therapy are not suitable for FOLFIRINOX due to poor general condition [6, 8].

Nanoliposomal irinotecan (nal-IRI) consists of irinotecan free base encapsulated in liposome nanoparticles, which maintain higher intra-tumoral levels of both irinotecan and SN-38 (the active metabolite of irinotecan) compared with conventional irinotecan [9]. In a phase III study (NAPOLI-1), in patients with mPDAC previously treated with gemcitabine-based therapy, nal-IRI combination with fluorouracil and folinic acid (5-FU/LV) showed superior survival compared with 5-FU/LV (6.1 months vs. 4.2 months; hazard ratio [HR], 0.67,  $p = 0.012$ ) and manageable toxicity profile [10]. According to this results, nal-IRI combined with 5-FU/LV was approved by the FDA to be used as a subsequent therapy following gemcitabine-based treatment in patients with mPDAC.

Patients in NAPOLI-1 trial had heterogeneity of clinical feature such as previous anticancer therapy, and only half of patients were treated with gemcitabine combination regimens. Real-world clinical data about efficacy, safety, and dose reduction of nal-IRI plus 5-FU/LV in patients with mPDAC who previously treated with nab-paclitaxel with gemcitabine as first-line regimen are scarce [11, 12]. Therefore, clinical data are needed for nal-IRI plus 5-FU/LV in a changed clinical environment.

In this study, we retrospectively evaluated the efficacy and safety of nal-IRI plus 5-FU/LV in patients with mPDAC who failed to nab-paclitaxel with gemcitabine and assessed the association between nal-IRI dose intensity and clinical outcomes. Furthermore, we investigated whether the use of nal-IRI with 5-FU/LV as the second-line treatment is reasonable option as a continuum of care treatment algorithm in patients with mPDAC.

## Methods

### Patients

This is a single-institution, retrospective, observational analysis including patients diagnosed with mPDAC at the Catholic University of Korea, Seoul St. Mary's Hospital from January 2015 to December 2020. We included patients aged 19 years or older with histologically confirmed either recurrent or metastatic PDAC, who have failed to gemcitabine-based treatment as first-line palliative therapy. Other key inclusion criteria were a Eastern Cooperative Oncology Group (ECOG) PS 0–2 and measurable or

evaluable lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria and adequate hematological (hemoglobin > 9.0 g/dL, white blood cell count > 4000/mm<sup>3</sup>, absolute neutrophil count > 1000/mm<sup>3</sup>, platelet count > 100 000/mm<sup>3</sup>), renal (creatinine < 1.5-fold higher than the upper normal limit) and hepatic functions (total bilirubin < 1.5-fold higher than the upper normal limit, serum transaminase < 3-fold higher than the upper normal limit).

## Treatment

Patients received intravenous infusion of nal-IRI at a dose of 80mg/m<sup>2</sup> (equivalent to 70mg/m<sup>2</sup> of irinotecan free base) over 90 min followed by folinic acid 400mg/m<sup>2</sup> over 30 min, then fluorouracil 2400mg/m<sup>2</sup> over 46h, every 2 weeks. This treatment course was repeated until disease progression, unacceptable toxicities, or patient's refusal to continue.

Chemotherapy dose and schedule adjustments were allowed. Dose reduction was defined as a decrease of 15% in the chemotherapy dose relative to the standard regimen in first three scheduled treatment cycle. Dose delays were defined as a delay of  $\geq 7$  days from the target date in first three scheduled treatment cycle. Chemotherapy relative dose intensity (RDI) was defined as the ratio of the delivered dose intensity to the planned dose intensity expressed as percentage. Reduced RDI was defined as a RDI < 85% from standard dosing, because RDI < 85% has worse survival outcomes in various solid tumors [13].

We did serial computed tomography scans and measured carbohydrate antigen 19 – 9 (CA 19 – 9) at baseline and every 6–8 weeks until disease progression. Radiographic tumor response assessment was analyzed according to RECIST version 1.1. We assessed safety by grading adverse events according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.

## Statistical analysis

The objective response rate (ORR) represented the percentage of patients with a complete response (CR) or partial response (PR) and disease control rate (DCR) represented the percentage of patients with a CR or PR or stable disease (SD) among patients with measurable lesions. Progression-free survival (PFS) was defined as the time from the first dose of nal-IRI plus 5-FU/LV to the date of disease progression or death. Overall survival (OS) was estimated from the date of nal-IRI plus 5-FU/LV initiation to the date of death or last follow-up visit.

To assess the efficacy of the entire first-line and second-line treatment strategy as accurately as possible, we evaluated the PFS 2 and OS 2 in patients who received gemcitabine with nab-paclitaxel as first-line treatment followed by nal-IRI plus 5-FU/LV as second line therapy. PFS 2 was defined as the time from the initiation of gemcitabine with nab-paclitaxel to the date of disease progression on nal-IRI plus 5-FU/LV given after first disease progression, or death. OS 2 was defined as the time from the beginning of gemcitabine with nab-paclitaxel to the date of death from any cause.

Kaplan-Meier analysis was performed to obtain median OS and median PFS. The HR and 95% confidence intervals (CIs) for OS and PFS were estimated using a stratified Cox regression model. A multivariate Cox

proportional hazards regression model was used to identify the effects of clinical factors on PFS and OS. All tests were two-sided and p-values < 0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS for Window version 24.0 (IBM SPSS Inc., Armonk, New York, USA) and GraphPad Prism version 8.0 (GraphPad Software Inc., San Diego, CA, USA).

## Results

### Patient characteristics

From January 1, 2015 to December 31, 2020, a total of 51 patients were found to be eligible for this study. The baseline demographics and clinical characteristics are listed in Table 1. Median age was 67 years (range, 50–78) and 30 patients (58.8%) were male. Majority of the patients presented with metastatic disease at the diagnosis and only nine patients (17.6%) had recurrent disease after curative surgery. Serum CA 19 – 9 levels were elevated in 42 (82.4%) of 51 patients with available data at initiation of nal-IRI with 5-FU/LV treatment. Liver (80.4%), lung (31.4%), distant lymph node (31.4%) and peritoneum (29.4%) were most frequent metastatic sites and 8 (15.7%) of total patients had more than three metastases.

Table 1  
Baseline clinical characteristics

<b>Variable</b>	<b>nal-IRI plus 5-FU/LV (n = 51)</b>
<b>Age</b>	67 (50–78)
Median (Range)	
<b>Gender</b>	30 (58.8%)
Male	21 (41.2%)
Female	
<b>Pancreatic tumor location</b>	19 (37.3%)
Head	18 (35.3%)
Body	14 (27.4%)
Tail	
<b>Disease status at start of nal-IRI</b>	9 (17.6%)
Recurrent	42 (82.4%)
Initially Metastatic	
<b>Baseline CA 19 – 9 level</b>	9 (17.6%)
Within normal range (< 40U/mL)	42 (82.4%)
Above normal range (≥ 40U/mL)	
<b>Site of metastatic lesions</b>	41 (80.4%)
Liver	16 (31.4%)
Lung	16 (31.4%)
Lymph node, Distant	15 (29.4%)
Peritoneum	7 (13.7%)
Bone	
<b>Measurable metastatic sites</b>	19 (37.3%)
1	24 (47.0%)
2	8 (15.7%)
≥ 3	

*Nal-IRI*/nanoliposomal irinotecan, *5-FU/LV* 5-fluorouracil/leucovorin, *CA 19 – 9* carbohydrate antigen 19 – 9.

Variable	nal-IRI plus 5-FU/LV (n = 51)
Previous radiotherapy	8 (15.7%)
Previous surgery	12 (23.5%)
Previous lines of palliative chemotherapy	40 (78.4%)
1	11 (21.6%)
2	
Previous first-line palliative chemotherapy	48 (94.1%)
Gemcitabine plus nab-paclitaxel	3 (5.9%)
Gemcitabine monotherapy	
Previous irinotecan containing chemotherapy	1 (2.0%)
Previous 5-FU/LV containing chemotherapy	13 (25.5%)
<i>Nal-IRI</i> nanoliposomal irinotecan, <i>5-FU/LV</i> 5-fluorouracil/leucovorin, <i>CA 19 - 9</i> carbohydrate antigen 19 - 9.	

Forty patients (78.4%) had received one previous line of metastatic treatment, and 11 (21.6%) patients had previously received two lines of palliative chemotherapy. As first-line chemotherapy, gemcitabine plus nab-paclitaxel was given to most patients (94.1%), and only three patients (5.9%) had received gemcitabine monotherapy. Irinotecan and 5-FU/LV were previously administered in 1 (2.0%) and 13 (25.5%) patients, respectively.

## Treatment outcomes

A summary of treatment dose modification is listed in Table 2. The median duration of exposure to nal-IRI plus 5-FU/LV was 1.9 months (range, 0.5-7.0) and median number of cycles was four (range, 2–12). At the time of this analysis, 7 patients (13.7%) were undergoing nal-IRI plus 5-FU/LV treatment. Median RDI was 0.87 (range, 0.54-1.00) and 15 patients (29.4%) treated with less than 85% RDI. Thirty patients (58.8%) had dose reduction and 13 patients (25.5%) had dose delay in first 6 weeks of treatment.

Table 2  
Relative dose intensity, dose reduction and delay of the nal-IRI plus 5-FU/LV

	<b>nal-IRI plus 5-FU/LV (n = 51)</b>
<b>Median duration of treatment, months (range)</b>	1.9 (0.5-7.0)
<b>Median cycles of treatment, n (range)</b>	4 (2–12)
<b>Median relative dose intensity, n (range)</b>	0.87 (0.54-1.00)
<b>RDI ≥ 85%, n (%)</b>	36 (70.6)
<b>RDI &lt; 85%, n (%)</b>	15 (29.4)
<b>Dose reduction in first 3 cycles, n (%)</b>	30 (58.8)
<b>Dose delay in first 3 cycles, n (%)</b>	13 (25.5)
<i>Nal-IRI</i> nanoliposomal irinotecan, <i>5-FU/LV</i> 5-fluorouracil/leucovorin, <i>RDI</i> relative dose intensity.	

Effectiveness outcomes are summarized in Table 3. At the time of analysis, 44 patients (86.3%) had progressive disease. The response evaluation showed a partial response in three patients (5.9%), stable disease in 28 patients (54.9%), and progressive disease in 20 patients (39.2%). The ORR and DCR was 5.9% and 60.8%, respectively. The survival analysis was based on 39 (76.4%) deaths of 51 patients with a cutoff date of March 31, 2021. Median PFS was 2.8 months (95% CI 1.8–3.7) and median OS was 7.0 months (95% CI 6.0-7.9) (Table 3 and Fig. 1). The six-months PFS and OS rate was 27.2% (95% CI 15.3–40.6) and 62.2% (95% CI 46.3–78.0), respectively.

Table 3  
Efficacy of treatment with nal-IRI plus 5-FU/LV

	<b>nal-IRI plus 5-FU/LV (n = 51)</b>
<b>Best response</b>	
<b>Complete response</b>	0
<b>Partial response</b>	3 (5.9%)
<b>Stable disease</b>	28 (54.9%)
<b>Progressive disease</b>	20 (39.2%)
<b>Objective response rate</b>	3 (5.9%)
<b>Disease control rate</b>	31 (60.8%)
<b>Median PFS, months [95% CI]</b>	2.8 [1.8–3.7]
<b>6-month PFS, % [95% CI]</b>	27.2 [15.3–40.6]
<b>Median OS, months [95% CI]</b>	7.0 [6.0–7.9]
<b>6-month OS, % [95% CI]</b>	62.2 [46.3–78.0]
<i>Nal-IRI</i> nanoliposomal irinotecan, <i>5-FU/LV</i> 5-fluorouracil/leucovorin, <i>PFS</i> progression-free survival, <i>OS</i> overall survival.	

## Multivariate analysis of prognostic factors

Results of the multivariate analysis are shown in Table 4 with subgroups according to age (65 years older or younger), number of prior lines of chemotherapy, organ metastases (liver, lung, peritoneum and bone), metastatic burden (more or less than three metastases), RDI and pre-treatment neutrophil-to-lymphocyte ratio (NLR). Median PFS and OS did not differ significantly according to the number of prior lines of palliative chemotherapy (2 vs. 1) ( $p = 0.132$  and  $p = 0.213$ , respectively). Liver or lung metastases did not affect both PFS and OS. Bone metastases were not related to PFS (HR = 1.54; 95% CI, 0.58–4.10;  $p = 0.386$ ), but significantly associated with worse OS outcomes (HR = 3.06; 95% CI, 1.06–8.82;  $p = 0.038$ ) (Table 4. Figure 2A-B). Patients with high metastatic burden (metastases > 3) had worse PFS compared to patients with low metastatic burden (metastases 1–3) (HR = 2.17; 95% CI, 1.01–4.64;  $p = 0.046$ ) without association with OS (HR = 1.71; 95% CI, 0.74–3.93;  $p = 0.210$ , Table 4. Figure 2C-D). Patients with reduced RDI (RDI < 85%) showed better PFS than patients with RDI  $\geq$  85% (HR = 0.47; 95% CI, 0.23–0.99;  $p = 0.047$ , Table 4. Figure 2E). Median OS did not differ significantly according to the RDI (HR = 0.62; 95% CI, 0.30–1.28,  $p = 0.195$ , Table 4. Figure 2F). No significant differences were evident in subgroups with high vs. low pre-treatment NLR.

Table 4  
Multivariate analysis of the clinical factors for PFS or OS in patients with mPDAC who received nal-IRI plus 5-FU/LV

Variables	PFS		OS	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Age ( $\geq 65$ vs. $<65$ years)	0.80 (0.40–1.64)	0.554	1.09 (0.51–2.35)	0.824
Prior lines of chemotherapy (2 vs. 1)	1.82 (0.83–3.98)	0.132	1.78 (0.72–4.38)	0.213
Liver metastases	1.02 (0.40–2.58)	0.967	1.10 (0.49–2.52)	0.803
Peritoneum metastases	0.79 (0.36–1.72)	0.553	0.94 (0.42–2.08)	0.936
Bone metastases	1.54 (0.58–4.10)	0.386	<b>3.06 (1.06–8.82)</b>	<b>0.038</b>
Metastatic burden ( $> 3$ vs. 1–3)	<b>2.17 (1.01–4.64)</b>	<b>0.046</b>	1.71 (0.74–3.93)	0.210
RDI ( $< 85\%$ vs. $\geq 85\%$ )	<b>0.47 (0.23–0.99)</b>	<b>0.047</b>	0.62 (0.30–1.28)	0.195
NLR ( $> 5$ vs. $\leq 5$ )	0.82 (0.36–1.87)	0.635	1.47 (0.64–3.37)	0.364

*Nal-IRI* nanoliposomal irinotecan, *5-FU/LV* 5-fluorouracil/leucovorin, *PFS* progression-free survival, *OS* overall survival, *HR* hazard ratio, *RDI* relative dose intensity, *NLR* neutrophil-to-lymphocyte ratio.

## Safety

Table 5 summarizes the treatment-related toxicity profiles. There were no treatment-related adverse events that resulted in death. Any-grade adverse events were observed in the most of patients ( $n = 50$ , 98%), and grade 3 or 4 adverse events were observed in 36 patients (70.6%). The most common treatment-related adverse events in patients receiving nal-IRI plus 5-FU/LV were anemia ( $n = 43$ , 84.3%), neutropenia ( $n = 43$ , 84.3%), nausea ( $n = 22$ , 43.1%), diarrhea ( $n = 12$ , 23.5%) and fatigue ( $n = 11$ , 21.6%). Neutropenia was the most common grade 3 or 4 adverse event ( $n = 30$ , 58.8%). Febrile neutropenia was recorded in 4 patients (7.8%) and granulocyte colony stimulating factor was administered to 17 patients (33%).

Table 5  
Toxicity profile during treatment

Adverse event	Any grade, n (%)	Grade 3–4, n (%)
All	50 (98.0)	36 (70.6)
Nausea	22 (43.1)	4 (7.8)
Vomiting	9 (17.6)	0
Diarrhea	12 (23.5)	3 (5.9)
Fatigue	11 (21.6)	2 (3.9)
Neutropenia	43 (84.3)	30 (58.8)
Febrile neutropenia	4 (7.8)	4 (7.8)
Anemia	43 (84.3)	14 (27.5)

## Survival outcome from beginning of the first-line treatment

Of the total 51 patients, 37 patients (72.5%) were treated with gemcitabine with nab-paclitaxel as first-line chemotherapy followed by nal-IRI plus 5-FU/LV as second-line treatment. At a median follow-up of 13.3 months (95% CI 12.9–18.1), 31 patients (83.8%) had events of PFS 2 and 26 patients (70.3%) had events of OS 2. Median PFS 2 was 13.8 months (95% CI 8.9–18.7, Fig. 3A) and median OS 2 was 16.3 months (95% CI 14.1–18.4, Fig. 3B). The one-year PFS 2 and OS 2 rate was 50.3% (95% CI 32.6–65.6) and 72.7% (95% CI, 54.0-84.8), respectively.

## Discussion

Since the results of the phase III MPACT trial and the phase III PRODIGE trial, gemcitabine with nab-paclitaxel or FOLFIRINOX has been used as the first-line treatment for patients with mPDAC [4, 5]. As a second-line treatment, for patients who have received prior gemcitabine-based therapy, fluoropyrimidine-based chemotherapy regimens are acceptable option. On the other hand, gemcitabine-based treatment can be given to patients who previously treated with fluoropyrimidine-based therapy [7]. However, since there are debates about the optimal sequencing strategy for treatment of mPDAC, it is necessary to establish optimal strategy through real-world clinical outcomes. The aim of this study was to evaluate effectiveness and safety of nal-IRI plus 5-FU/LV in patients with mPDAC following gemcitabine-based treatment in a real-world clinical setting. Furthermore, this is the first analysis to evaluate the survival outcomes from the initiation of first-line treatment in patients with mPDAC who treated with nal-IRI plus 5-FU/LV as second-line therapy after failure of first-line gemcitabine with nab-paclitaxel.

The characteristics of the patients in this study were comparable to those of patients enrolled in the NAPOLI-1 trial [10]. With respect to prior treatment, only 55% of patients in the NAPOLI-1 trial received gemcitabine combination treatment, but in this study, most patients (94.1%) were treated with

gemcitabine with nab-paclitaxel as first-line treatment. In addition, in this study, only one patient previously treated with conventional irinotecan containing regimen. Patients who previously progressed on conventional irinotecan had poor survival outcome with nal-IRI plus 5-FU/LV in prior studies [10, 11]. Compared to several other real-world study of nal-IRI plus 5-FU/LV, the patients in this study were relatively homogenous in terms of their previous treatment history [11, 12].

Concerning the survival outcomes, results of our study demonstrate real world evidence of treatment benefit with nal-IRI plus 5-FU/LV with similar outcome results that reported in the NAPOLI-1 trial (median PFS 2.8 versus 3.1 months, median OS 7.0 versus 6.1 months). In this study, 6-months PFS and OS rate was 27.2% and 62.2%, respectively. These findings were consistent with the results of the NAPOLI-I trial and prior real-world analyses with Asian population [10, 14]. Based on these consistent clinical outcomes, despite difference in patient characteristics, nal-IRI plus 5-FU/LV showed real-world clinical benefit in patients with mPDAC who failed to gemcitabine-based therapy.

With respect to dose modification, 33 (64.7%) of 51 patients experienced dose modification (dose reduction, n = 30; dose delay, n = 13) during the first 6 weeks. These findings were consistent with the results that 50 (60%) of 93 patients treated with modified dose during the first 6 weeks in the NAPOLI-I study [15]. Reduced RDI was expected to be associated with poor survival outcomes<sup>13</sup>, but in the current study, reduced RDI was not significantly associated with clinical outcomes which is consistent with other previous studies [14, 15]. Rather, patients with reduced RDI showed longer PFS, probably because patients who had been treated for a long period of time received more frequent modified dose of chemotherapy. Many of patients with mPDAC has deteriorated after first-line treatment failure, frequent dose modification is necessary due to adverse events. Therefore, appropriate dose modification is considered because dose modification is not significantly associated with survival outcomes. Moreover, according to the post hoc analysis of the NAPOLI-I study, Asian patients had more frequent hematological toxicities than Caucasian patients [16], so active dose adjustment should be considered in Asian patients.

We observed that several baseline characteristics were associated with survival outcome through multivariate analysis. Patients with bone metastases had poor OS, which was consistent with the results of previous real-world study [14]. In prior real-world study, patients with liver metastases showed poor PFS [14]. Also, in analysis of NAPOLI-1 long-term survivals, patients who survived one year more were less likely to have liver metastases [17]. However, in the current study, no association between liver metastases and survival outcome was observed. The subgroup analysis on metastatic burden indicates a better prognosis for the patients with less than three metastases. NLR at the baseline was significantly associated with worse OS in the updated analysis of NAPOLI-1 trial [17], but not in this study. Because the prognosis for patients with mPDAC remains poor, there are critical needs to evaluate a biomarker related to the efficacy of nal-IRI plus 5-FU/LV and select patients for optimal treatment based on prognostic biomarkers.

Our results concerning adverse events are also comparable with the results previously reported in the NAPOLI-1 study, except that grade 3 or 4 diarrhea was less observed (5.9% vs. 13%), and grade 3 or 4 neutropenia (58.8% vs. 27%) was more frequently occurred. The safety profile in our study was consistent with the results of the Asian subgroup analysis of NAPOLI-1 trial including grade 3 or 4 diarrhea (5.9% vs. 3.0%) and grade 3 or 4 neutropenia (58.8% vs. 54.5%) [16]. Most patients were tolerable to treatment, and 11% of patients discontinued treatment because of any adverse events. According to analysis of population pharmacokinetics of nal-IRI, the ethnic differences of adverse events could be associated with blood level of uncapsulated SN-38 [18]. Dose modification of nal-IRI should be considered for Asian population because dose modification did not affect survival outcomes and neutropenia occurred frequently at standard dose.

Although, gemcitabine with nab-paclitaxel or FOLFIRINOX recommended as first-line treatment in patients with mPDAC, according to several real-world analysis, first-line FOLFIRINOX could only be applied in 20–40% of advanced mPDAC patients due to higher incidence of hematological toxicity [19, 20]. Therefore, gemcitabine with nab-paclitaxel could be considered as first-line treatment for the rest of 50–60% patients with mPDAC. Current National Comprehensive Cancer Network guidelines for the treatment of patients with mPDAC, 5-FU-based combination regimens are recommended as second-line therapy after gemcitabine-based treatment failure [7]. However, there is no universally accepted standard regimen for patients with mPDAC after gemcitabine with nab-paclitaxel. Nal-IRI plus 5-FU/LV could be considered in patients with poor PS, due to relatively manageable toxicities. Additionally, unlike with the oxaliplatin plus 5-FU/LV regimen, nal-IRI plus 5-FU/LV is not associated peripheral neuropathy. Therefore, nal-IRI plus 5-FU/LV should be considered as a treatment option considering that patients who received gemcitabine with nab-paclitaxel, are more likely had peripheral neuropathy.

The two first-line treatment options, gemcitabine with nab-paclitaxel and FOLFIRINOX, have not been compared in the first-line setting. This means that currently the optimal first-line treatment and therapeutic sequence are unknown for patients with mPDAC. In the current study population, the median OS from the start of first-line chemotherapy with gemcitabine plus nab-paclitaxel was 16.3 months. Excluding patients ongoing of nal-IRI plus 5-FU/LV, 20 (45.5%) of 44 patients received best supportive care and 24 (54.5%) patients received a third line of chemotherapy after disease progression on nal-IRI plus 5-FU/LV. According to previous prospective studies, for patients who treated with gemcitabine with nab-paclitaxel following FOLFIRINOX, the median OS from the initiation of first-line chemotherapy was 14.2–18.0 months [21, 22]. Compared to these studies, sequential treatment of nal-IRI plus 5-FU/LV after gemcitabine with nab-paclitaxel is a reasonable sequential treatment strategy. A comparative prospective randomized trial is needed to confirm optimal sequential treatment strategy for patients with mPDAC.

There are some limitations in our study. First this is retrospective analysis conducted in a single center. Second, relatively small sample size limits the interpretation of subgroup analysis. Third, dose modification and treatment discontinuation were left to the discretion of the physicians, not according to the specified protocol. In addition, variability in response assessment intervals can have effect on the results for PFS.

## Conclusions

Our study showed that nal-IRI plus 5-FU/LV was an effective and well-tolerated treatment after gemcitabine-based therapy in a real-world clinical setting. Strategy based on gemcitabine with nab-paclitaxel followed by nal-IRI plus 5-FU/LV was a feasible sequential treatment option. Prospective trials are needed to validate the preliminary results of our study.

## Abbreviations

nal-IRI: Nanoliposomal irinotecan; 5-FU/LV: 5-fluorouracil/leucovorin; PDAC: Pancreatic ductal adenocarcinoma; mPDAC: Metastatic pancreatic ductal adenocarcinoma; PS: Performance status; ECOG: Eastern Cooperative Oncology Group; RDI: Relative dose intensity; CA 19-9: Carbohydrate antigen 19-9; ORR: Objective response rate; CR: Complete response; PR: Partial response; SD: Stable disease; DCR: Disease control rate; PFS: Progression-free survival; OS: Overall survival; NLR: Neutrophil-to-lymphocyte ratio

## Declarations

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### Availability of data and materials

The datasets used in the current study are available from the corresponding author on request.

### Author's contributions

All authors helped to perform the research; Park SJ was involved with manuscript writing, drafting conception and design, acquisition of data, performing procedures and data analysis; Kim HH, Shin KS, Hong TH, JH Suh contributed to writing the manuscript; Lee MA contributed to writing the manuscript, drafting conception and design, performing procedures and data analysis. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

All methods were performed in accordance with Korean regulations and the Declaration of Helsinki. This study was approved by the Institutional Review Board (IRB) of The Catholic University of Korea, Seoul St. Mary's Hospital (approval ID: KC21RISI0198) with a waiver of informed consent due to the retrospective nature of the analysis.

## Consent for publication

Not applicable.

## Competing interests

The authors declare that they have no conflict of interest.

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## Figures

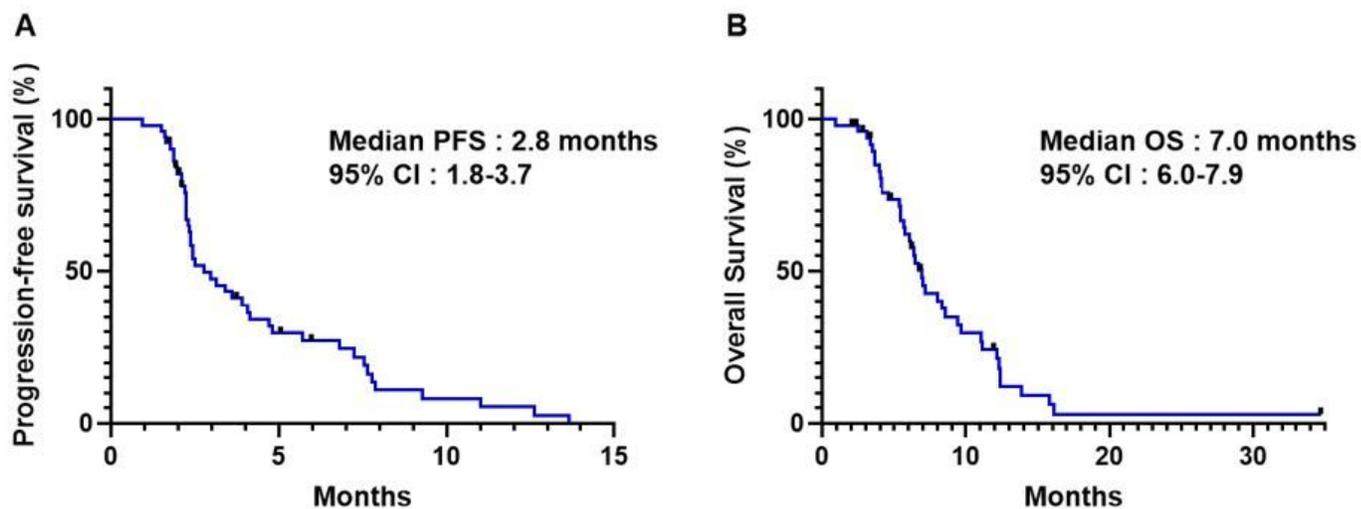
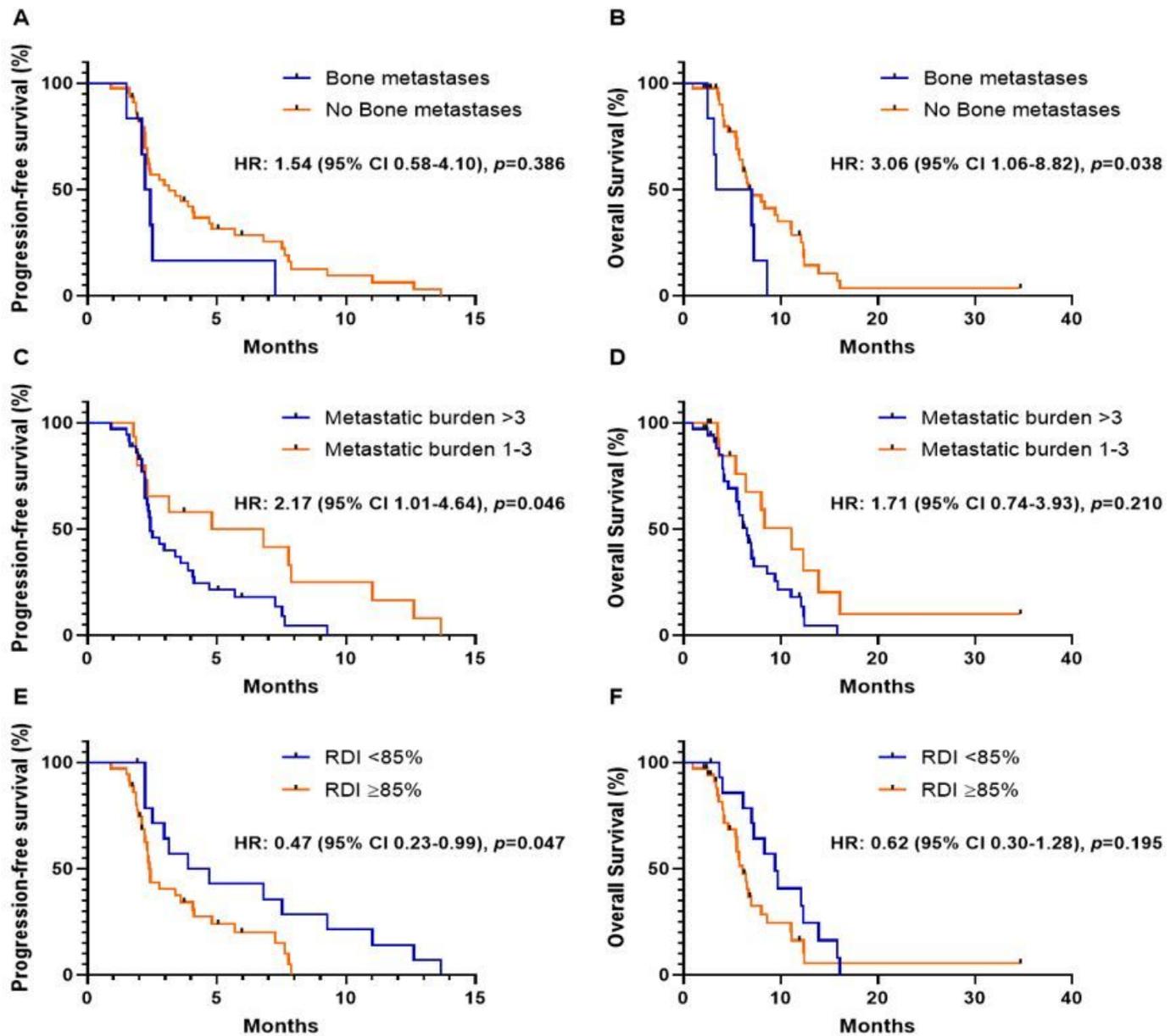


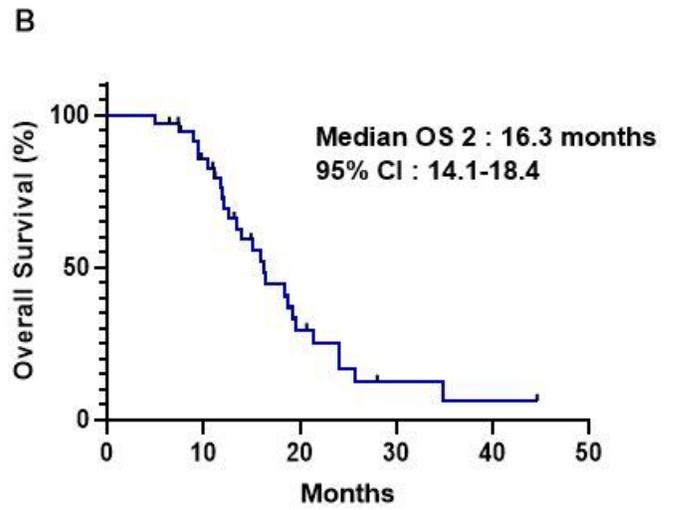
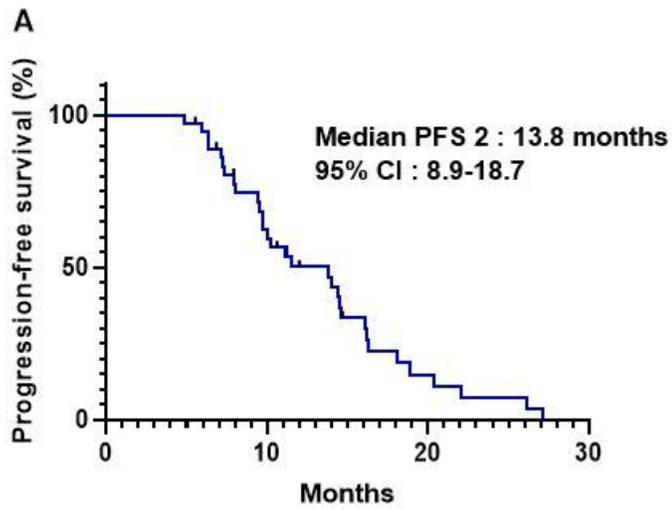
Figure 1

Kaplan-Meier analysis of (A) progression-free survival and (B) overall survival with nal-IRI plus 5-FU/LV.



**Figure 2**

Subgroup survival analysis with nal-IRI plus 5-FU/LV. Progression-free survival and overall survival according to bone metastases (A, B), metastatic burden (C, D), and relative dose intensity (E, F).



**Figure 3**

(A) Progression-free survival and (B) overall survival since the beginning of first-line chemotherapy.