

A real-world analysis of nanoliposomal-irinotecan with 5-fluorouracil and folinic acid as third- or later-line therapy in patients with metastatic pancreatic adenocarcinoma

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Abstract

Background: Nanoliposomal encapsulation of irinotecan (nal-IRI) with 5-fluorouracil and leucovorin (5-FU/LV) has shown a survival benefit for gemcitabine-pretreated patients with metastatic pancreatic adenocarcinoma (mPAC). The aim of this study was to evaluate the effectiveness and safety of nal-IRI with 5-FU/LV for use beyond second-line treatment after standard frontline therapy for mPAC.

Method: This multicenter, retrospective, non-comparative observational study included mPAC patients who received nal-IRI plus 5-FU/LV as third- or later-line therapy after disease progression on first-line FOLFIRINOX (FFX) or gemcitabine plus nab-paclitaxel.

Results: In all, 128 patients who received nal-IRI plus 5-FU/LV beyond second-line treatment between October 2017 and July 2021 were analyzed. Most patients (82%) received nal-IRI plus 5-FU/LV as a third-line treatment. The median overall survival (OS) was 4.9 months and the median progression-free survival (PFS) was 2.4 months. Patients with better Eastern Cooperative Oncology Group (ECOG) performance status experienced significantly longer OS (ECOG 0, 8.7 months; ECOG 1, 4.8 months; ECOG 2, 2.9 months; $p < 0.001$) and PFS (3.9 months; 2.1 months; 1.5 months; $p = 0.019$). Patients who had not been previously treated with FFX or had a time to progression of 7 months or more on FFX experienced longer OS and PFS than those who did not (6.1 months and 5.6 *versus* 4.1 months, $p = 0.053$; 3.6 months and 2.4 *versus* 2.1 months, $p = 0.002$). The most common adverse events were neutropenia (56%) and anemia (51%).

Conclusion: Our real-world data indicated that nal-IRI plus 5-FU/LV can be effective not only as second-line therapy, but also as third-line or later-line treatment in selected patients. Nal-IRI plus 5-FU/LV may be particularly beneficial for the survival of patients that maintain good general condition or those with favorable prior experience to irinotecan.

Keywords: antineoplastic agents, carcinoma, irinotecan, liposomes, pancreatic ductal, survival

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Introduction

Pancreatic cancer is the seventh leading cause of cancer deaths worldwide. It is predicted to be the

second leading cause of cancer deaths in the United States by 2030.¹ Patients with pancreatic adenocarcinoma (PAC), the most common

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histological type of pancreatic cancer, have a poor prognosis with a 5-year survival rate of 9%.² Only less than 20% of patients have resectable PAC at initial diagnosis, and the majority of patients present with unresectable advanced stage pancreatic cancer. Systemic chemotherapy is the mainstay treatment strategy for unresectable PAC. However, options of chemotherapeutic regimens were limited until the emergence of FOLFIRINOX [FFX; combination of 5-fluorouracil (5-FU), leucovorin (LV), irinotecan, and oxaliplatin] and the gemcitabine plus nab-paclitaxel (GnP). Both regimens significantly improved response rates and survival benefits compared to sole gemcitabine treatment in their pivotal phase III studies, and have currently been considered as standard first-line treatments for patients with unresectable PAC.³⁻⁶

As approximately half of patients receive second-line treatment, PAC therapy should now be considered as a continuum care for patients who are fit, with second-line and even third-line treatments.⁷ Patients who have undergone gemcitabine-based therapy may consider receiving fluoropyrimidine-based combination therapies as a subsequent therapy, and *vice versa*.⁶ A combination of 5-FU, LV, and oxaliplatin (FOLFOX) or 5-FU, LV, and irinotecan (FOLFIRI) was used for rescue after gemcitabine-based therapy in the past decade.⁸ Subsequent FFX or GnP can be considered as a second-line therapy for selected PAC patients in good general condition, resulting in favorable survival outcomes.⁹ However, the number of high-quality data to establish a standard therapeutic regimen in the second-line setting is limited.

Recently, nanoliposomal encapsulation of irinotecan (nal-IRI) plus 5-FU/LV has shown an improvement of survival outcomes in the intent-to-treat population over 5-FU/LV in a global NAPOLI-1 phase III trial of patients with metastatic PAC following treatment with gemcitabine. The trial showed a median overall survival (OS) of 6.1 months and progression-free survival (PFS) of 3.1 months in the nal-IRI plus 5-FU/LV group compared to 4.2 months and 1.5 months in the 5-FU/LV group.¹⁰

In third-line setting, the only randomized evidence is identified in the NAPOLI-1 trial. Approximately 30% of the patients had received at least two prior lines of chemotherapy in the

study. Although some retrospective studies reported real-world data of nal-IRI plus 5-FU/LV as second-line therapy in gemcitabine-refractory advanced PAC, data reporting efficacy beyond second-line therapy are scarce.¹¹⁻¹³ To the best of our knowledge, there is no real-world data solely comprised of patients with third- or later-line nal-IRI plus 5-FU/LV treatment. Therefore, the present multicenter, retrospective study is aimed to evaluate the effectiveness and safety of nal-IRI plus 5-FU/LV for use beyond second-line treatment after standard frontline therapy in patients with metastatic PAC (mPAC).

Methods

Patients

This multicenter, retrospective, non-comparative observational study included patients that received nal-IRI plus 5-FU/LV as third- or later-line therapy after disease progression on first-line FFX or GnP for unresectable PAC at two tertiary referral hospitals in Korea, between October 2017 and July 2021. In cases with tumor recurrence after previous pancreatectomy, the treatment line was counted after the start of palliative chemotherapy.

Demographic and clinicopathological data including performance status [Eastern Cooperative Oncology Group (ECOG)], tumor location, tumor size, site of metastatic lesions, date of diagnosis, date of disease progression, baseline laboratory findings, and detailed information of treatment were retrospectively collected and analyzed from the electronic medical records system. The cutoff date for data analysis was 11 November 2021. Survival data were obtained from the Ministry of the Interior and Safety of Korea. The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the institutional review boards of participating institutions (National Cancer Center, approval number NCC2021-0324; Seoul National University Hospital, approval number H-2110-173-1266).

Drugs were administered as described in the NAPOLI-1 trial (nal-IRI 70 mg/m² as the irinotecan-free base, followed by LV 400 mg/m², and 5-FU 2400 mg/m² over 46 h, every 2 weeks).¹⁰ Dose modification and schedule adjustment were determined according to the general condition of

the individual patient and toxicities at the discretion of the treating physician. Tumor assessment was conducted prior to treatment and every 6–8 weeks by contrast enhanced computed tomography or magnetic resonance imaging. Tumor response was assessed by the clinician according to the Response Evaluation Criteria in Solid Tumors version 1.1. Adverse events were evaluated and graded in accordance with the Common Terminology Criteria for Adverse Events, version 4.0.

Objectives and statistical analysis

OS was defined as the period between the initiation of nal-IRI plus 5-FU/LV and death or last follow-up. PFS defined as the time from the date of initiating nal-IRI plus 5-FU/LV treatment to the date of disease progression, death of any cause, or loss to follow-up. Survival outcomes from the initiation of first-line therapy (the starting date of palliative FFX or GnP treatment) were also evaluated. The objective response rate (ORR) was defined as the percentage of patients with complete response or partial response. The disease control rate (DCR) was defined as ORR plus the rate of stable disease.

Descriptive statistics were expressed as median (range), number (percentage, %) as appropriate. Survival analysis was performed using the Kaplan–Meier method and compared by log-rank test. We performed subgroup analyses according to performance status, irinotecan exposure and time to progression (TTP), line of therapy, presence of dose reduction, first-line chemotherapy regimen, and sequential chemotherapy regimens. Patients previously treated with FFX were divided by TTP of 7 months, and this cutoff level was determined based on our previously reported median PFS of patients who were treated with FFX as first-line therapy.⁹ Univariable analyses for survival outcomes were performed by the Cox proportional hazard regression model test. We fitted the multivariable model using pre-selected variables with univariable p value < 0.2 . The final model was determined by performing backward selection with an elimination criterion of p value > 0.1 . A p value < 0.05 was considered to be statistically significant. All statistical analyses were performed using SAS systems version 9.2 (SAS Institute, Inc, Cary, NC, USA) and SPSS 24.0 statistical software (SPSS Inc., Chicago, IL, USA).

Results

Overall characteristics of patients treated with nal-IRI plus 5-FU/LV

Among a total of 165 patients who received nal-IRI plus 5-FU/LV, 128 patients who received nal-IRI plus 5-FU/LV beyond second-line treatment were analyzed (Figure 1). Baseline demographics and clinicopathological characteristics are summarized in Table 1. Median age was 64 years (range, 37–79) and 81 patients (63%) were male. The majority of patients had ECOG performance status of 0 (23%) or 1 (71%). Liver was the most common metastatic site (68%) followed by peritoneum (31%). Curative-intent surgical resection and radiotherapy were previously performed in 51 (40%) and 37 (29%) patients, respectively.

Most patients (82%) received nal-IRI plus 5-FU/LV as third-line treatment. FFX (73%) was most commonly given as the first-line therapy prior to nal-IRI plus 5-FU/LV treatment. Prior administration of irinotecan was observed in 99 patients (77%), all of whom had been treated with FFX as first- or second-line therapy. Among patients with previous FFX treatments, 81 patients experienced controlled disease (partial response, 29; stable disease, 52 patients) and 18 patients had progressive disease on FFX treatment.

Treatment overview of nal-IRI plus 5-FU/LV

The dose delivery of nal-IRI plus 5-FU/LV beyond second-line therapy is presented in Table 2. The median number of cycles of chemotherapy was three (range, 1–26). In all, 36 patients (28%) received only one or two cycles of nal-IRI plus 5-FU/LV due to rapid disease progression, deterioration of general condition, or loss to follow-up. In total, 56 patients (44%) received a reduced dose of nal-IRI at the beginning or during treatment: the most common reduced dose amount was 56 mg/m². One patient started nal-IRI plus 5-FU/LV treatment with 56 mg/m² of nal-IRI and received a subsequent dose reduction to 47 mg/m² due to adverse events.

The effectiveness of treatment with nal-IRI plus 5-FU/LV is summarized in Table 3. Only five patients (4%) had a partial response and 56 patients (44%) a stable disease at the time of analysis, indicating a DCR of 48%. In all, 53 patients (41%) received subsequent chemotherapy after disease progression on nal-IRI plus 5-FU/LV treatment.

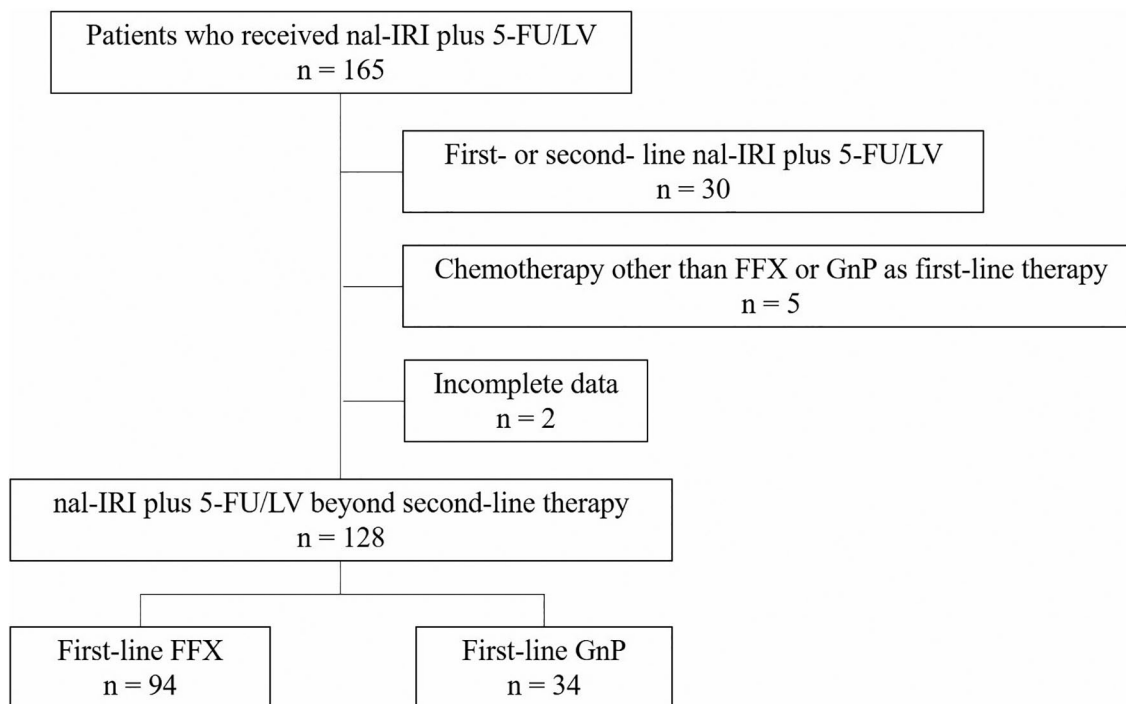


Figure 1. Flow chart of patients.

The survival analysis was performed based on 121 (95%) deaths and 108 (84%) disease progressions (Figure 2). The median OS was 4.9 months [95% confidence interval (CI): 4.2–5.6 months], and median PFS was 2.4 months (95% CI: 1.9–2.9 months). The 6-month OS and PFS rate was 41% (95% CI: 33–49%) and 20% (95% CI: 12–28%), respectively. The median OS and PFS from the start of the first-line therapy were 17.6 months (95% CI: 14.9–20.3 months) and 15.2 months (95% CI: 13.9–16.5 months).

Survival outcomes in subgroups

Patients with better ECOG performance status experienced significantly longer OS and PFS (log-rank $p < 0.001$ and log-rank $p = 0.019$, respectively) (Figure 3(a) and (b)). Patients who maintained a very good general condition (ECOG 0) had an excellent median OS of 8.7 months compared to 4.6 months in patients with ECOG 1–2 ($p < 0.001$). The median PFS was 3.9 months and 2.1 months, respectively ($p = 0.018$). Patients with ECOG 1 had longer OS of 4.8 months and PFS of 2.1 months than those with ECOG 2, OS 2.9 months ($p = 0.019$) and 1.5 months ($p = 0.190$).

Prior irinotecan exposure and durability of chemotherapy were associated with survival outcomes. Patients with TTP less than 7 months on FFX treatment had worse OS and PFS compared to patients without prior irinotecan or with TTP greater than or equal to 7 months ($p = 0.053$ and $p = 0.002$, respectively) (Figure 3(c) and (d)). There were no significant differences in OS ($p = 0.544$) and PFS ($p = 0.360$) between patients without irinotecan exposure and those with a TTP of 7 months or more. Patients who experienced partial response on previous FFX treatment compared with patients with stable disease or disease progression had a median PFS of 3.5 *versus* 2.1 months ($p = 0.021$). The median OS was 5.0 *versus* 4.8 months ($p = 0.417$).

Prior lines of chemotherapy (third-line *versus* later-line therapy), chemotherapy dose reduction, and first-line palliative chemotherapy regimen (FFX *versus* GnP) were not associated with survival outcomes (Supplemental Figure 1A–F and Supplemental Figure 2A). According to the treatment sequence, the subsequent regimen of chemotherapy was not associated with survival outcomes (Supplemental Figure 1G–H). Such

Table 1. Baseline characteristics of patients.

	N = 128 (%)
Age	64 (37–79)
<65	68 (53.1%)
≥65	60 (46.9%)
Gender	
Male	81 (63.3%)
Female	47 (36.7%)
ECOG performance status	
0	29 (22.7%)
1	91 (71.1%)
2	8 (6.3%)
Primary tumor location	
Head	34 (26.6%)
Body	43 (33.6%)
Tail	51 (39.8%)
Site of metastatic lesions	
Liver	87 (68.0%)
Lung	29 (22.7%)
Peritoneum	39 (30.5%)
Lymph node	29 (22.7%)
Other	8 (6.3%)
Median CA 19-9 (IU/mL)	939 [2–13,160]
Previous surgery	51 (39.8%)
Previous radiotherapy	37 (28.9%)
Prior lines of palliative chemotherapy, median (range)	2 (2–4)
2	105 (82.0%)
3	19 (14.8%)
4	4 (3.1%)
Prior first-line palliative chemotherapy regimen	
FOLFIRINOX	94 (73.4%)
Gemcitabine plus nab-paclitaxel	34 (26.6%)

*(Continued)***Table 1.** (Continued)

	N = 128 (%)
Prior exposure to irinotecan (FOLFIRINOX)	99 (77.3%)
Controlled disease on FOLFIRINOX	68 (53.1%)
TTP on FOLFIRINOX ≥7 months	47 (36.7%)
ECOG, Eastern Cooperative Oncology Group; TTP, time to progression	

trends were maintained in analyses from the beginning of first-line therapy (Supplemental Figure 2B).

Prognostic factors for survival outcomes

The Cox proportional hazards regression analysis was performed to identify the factors affecting survival outcomes (Table 4). Absence of liver metastases and previous radiotherapy were significantly associated with better OS and PFS. In patients with prior irinotecan exposure, a trend of better prognosis as the irinotecan-free interval increased was observed in OS (HR: 0.97, 95% CI: 0.93–1.00; $p=0.071$) and PFS (HR: 0.97, 95% CI: 0.93–1.00; $p=0.051$). However, patients without irinotecan exposure were treated as missing because the irinotecan-free interval does not exist. Therefore, we analyzed the ‘prior exposure to irinotecan’ variable according to three categories. Patients with a TTP less than 7 months showed poor survival outcomes in the uni- and multivariable analyses. However, there were no statistical differences of OS and PFS between patients who were not previously exposed to irinotecan and those with a TTP greater than or equal to 7 months (HR: 1.16, 95% CI: 0.72–1.87; $p=0.547$ and HR: 1.27, 95% CI: 0.75–2.15; $p=0.360$, respectively).

Safety

Adverse events during the nal-IRI plus 5-FU/LV treatment are listed in Table 5. The majority of patients ($n=97$, 76%) experienced any grade of treatment-related adverse events. The most common adverse events were neutropenia (56%) and anemia (51%). Grade 3–4 adverse events frequently occurred in hematologic events: neutropenia (25%) and anemia (13%).

Table 2. Treatment overview.

	N= 128 (%)
Number of cycles, median	3 (1–26)
<3	36 (28.1%)
≥3	92 (71.9%)
Starting dose of nal-IRI	
70 mg/m ²	83 (64.8%)
63 mg/m ²	1 (0.8%)
56 mg/m ²	33 (25.8%)
50 mg/m ²	11 (8.6%)
Dose reduction during treatment	12 (9.4%)
56 mg/m ²	4 (3.1%)
50 mg/m ²	7 (5.5%)
47 mg/m ²	1 (0.8%)
Subsequent chemotherapy after nal-IRI	
No	75 (58.6%)
Yes	53 (41.4%)
nal-IRI, nanoliposomal encapsulation of irinotecan.	

Discussion

In real-world experience, nal-IRI plus 5-FU/LV is administered beyond second-line treatment due to the predominant use of first-line FFX treatment followed by second-line GnP, or the inverse.^{9,14} Therefore, this multicenter retrospective study evaluated the efficacy of third-line or later-line nal-IRI plus 5-FU/LV treatment in patients that previously received two effective frontline chemotherapy regimens. The median OS was 4.9 months and the median OS from the beginning of first-line therapy was 17.6 months. Nal-IRI plus 5-FU/LV resulted in a median PFS of 2.4 months and DCR of 48%. Patients with good performance status showed longer survival outcomes. Although prior irinotecan exposure was associated with poor survival, patients who had experienced favorable disease control with FFX treatment showed comparable survival outcomes to those without prior irinotecan exposure.

Regarding the effectiveness of nal-IRI plus 5-FU/LV treatment, survival outcomes in our study tend to be slightly shorter compared to those in

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

	N= 128 (%)
Best response	
Partial response	5 (3.9%)
Stable disease	56 (43.8%)
Progressive disease	56 (43.8%)
Not evaluable	11 (8.6%)
Response rate	
Objective response rate	5 (3.9%)
DCR	61 (47.7%)
6-month survival rate, % (95% CI)	
OS rate	41 (33–49)
PFS rate	20 (12–28)
Median survival, months (95% CI)	
OS	4.9 (4.2–5.6)
PFS	2.4 (1.9–2.9)
Median survival from first-line therapy, months (95% CI)	
OS	21.0 (18.4–23.6)
PFS	18.3 (15.6–21.0)
CI, confidence interval; DCR, disease control rate; 5-FU/LV, 5-fluorouracil and leucovorin; nal-IRI, nanoliposomal encapsulation of irinotecan; OS, overall survival; PFS, progression-free survival.	

previously reported real-world analyses (median OS 4.9 *versus* 5.3–9.4 months, median PFS 2.4 *versus* 2.5–3.8 months).^{12,13,15,16} Such discrepancies may result from the different characteristics of the enrolled patients. Patients who received a third-line or later-line treatment have been reported to have a worse prognosis.¹² In other studies, less than half of patients (23–42%) received nal-IRI plus 5-FU/LV as third-line therapy, compared to the majority of patients (82%) in our study. However, beyond second-line treatment, no significant difference in OS and PFS was found between third-line nal-IRI plus 5-FU/LV and later lines in this study. This result is in accordance with Glassman *et al.* that found no significant difference in survival between patients with third-line treatment or beyond third-line

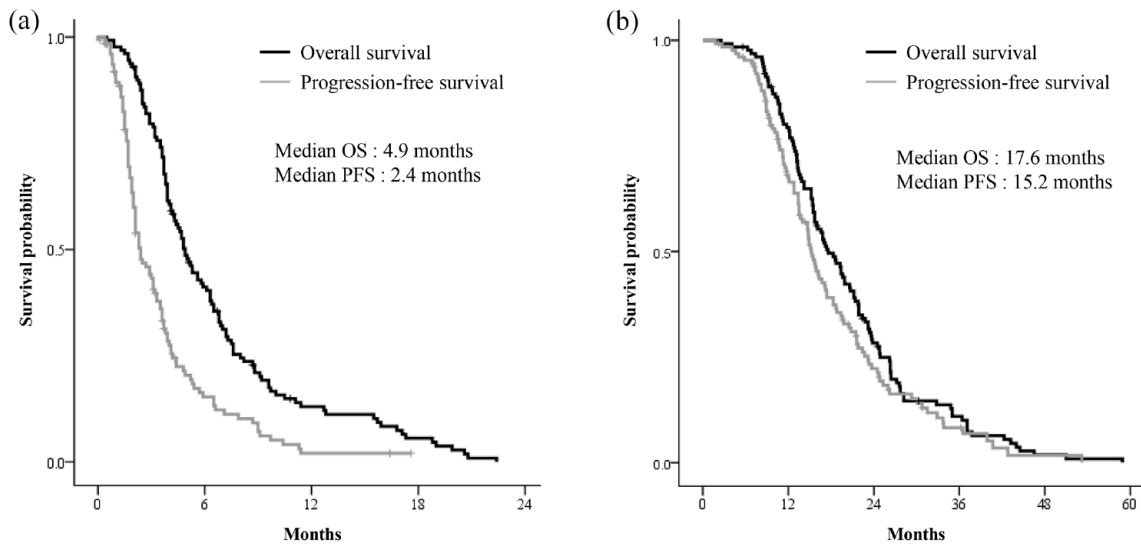


Figure 2. Kaplan–Meier survival analysis, patients who were treated with nal-IRI plus 5-FU/LV beyond second-line therapy: (a) from start of nal-IRI plus 5-FU/LV and (b) from start of first-line therapy. 5-FU/LV, 5-fluorouracil and leucovorin; nal-IRI, nanoliposomal encapsulation of irinotecan.

therapy.¹⁵ Furthermore, more than half of the patients in the current study did not receive subsequent chemotherapy following failure of nal-IRI plus 5-FU/LV. Patients who received subsequent chemotherapy after nal-IRI treatment failure had a median OS of 7.6 months, whereas those without further subsequent therapy had a median OS of 3.7 months (data not shown here).

We observed a significantly longer OS and PFS in patients with good performance status. This is consistent with the final analysis of the NAPOLI-1 study and also the real-world experience of an East Asian cohort which showed better performance status to be associated with long-term survival.^{13,17} Patients that maintain a good general condition despite previous chemotherapies might have a chance to receive effective chemotherapy for a longer period of time. Therefore, it seems preferable to consider nal-IRI plus 5-FU/LV as late-line treatment in patients with good performance status (ECOG 0–1) for optimal clinical benefits.

FFX and GnP were commonly used as second-line therapy after receiving their crossover regimen in our previous retrospective cohort study.⁹ Concerning the optimal treatment sequence, the results of our study demonstrate that the first-line chemotherapy regimen, FFX or GnP, was not associated with survival outcomes; this is consistent with other real-world data in Korea.¹⁶ And we

discovered that the sequential regimen of chemotherapy including second-line therapy (FFX followed by GnP or other; or GnP followed by FFX or other) prior to nal-IRI plus 5-FU/LV was not associated with survival. Therefore, nal-IRI and 5-FU/LV can be effectively utilized not only in second-line therapy, but also in later-line treatment regardless of the frontline chemotherapy regimen.

In this study, patients with prior irinotecan exposure experienced worse PFS in comparison to patients without previous exposure. The negative effect of prior irinotecan administration on survival outcomes with nal-IRI plus 5-FU/LV has already been reported, and the development of resistance to irinotecan was suggested as the potential cause.^{15,16} However, the number of patients who had previously received conventional irinotecan was small. Conversely, in this study, the vast majority of patients were previously treated with irinotecan-containing chemotherapy (i.e. FFX). Furthermore, we divided and classified patients who had been treated with FFX according to TTP. Although the cutoff level of 7 months is an arbitrary value based on our previous study, other studies including PRODIGE 4 trial have also reported median PFS as 6–7 months in patients with first-line FFX.^{3,18–20} Survival outcomes in patients that experienced favorable disease control on FFX treatment were comparable to those with no prior irinotecan

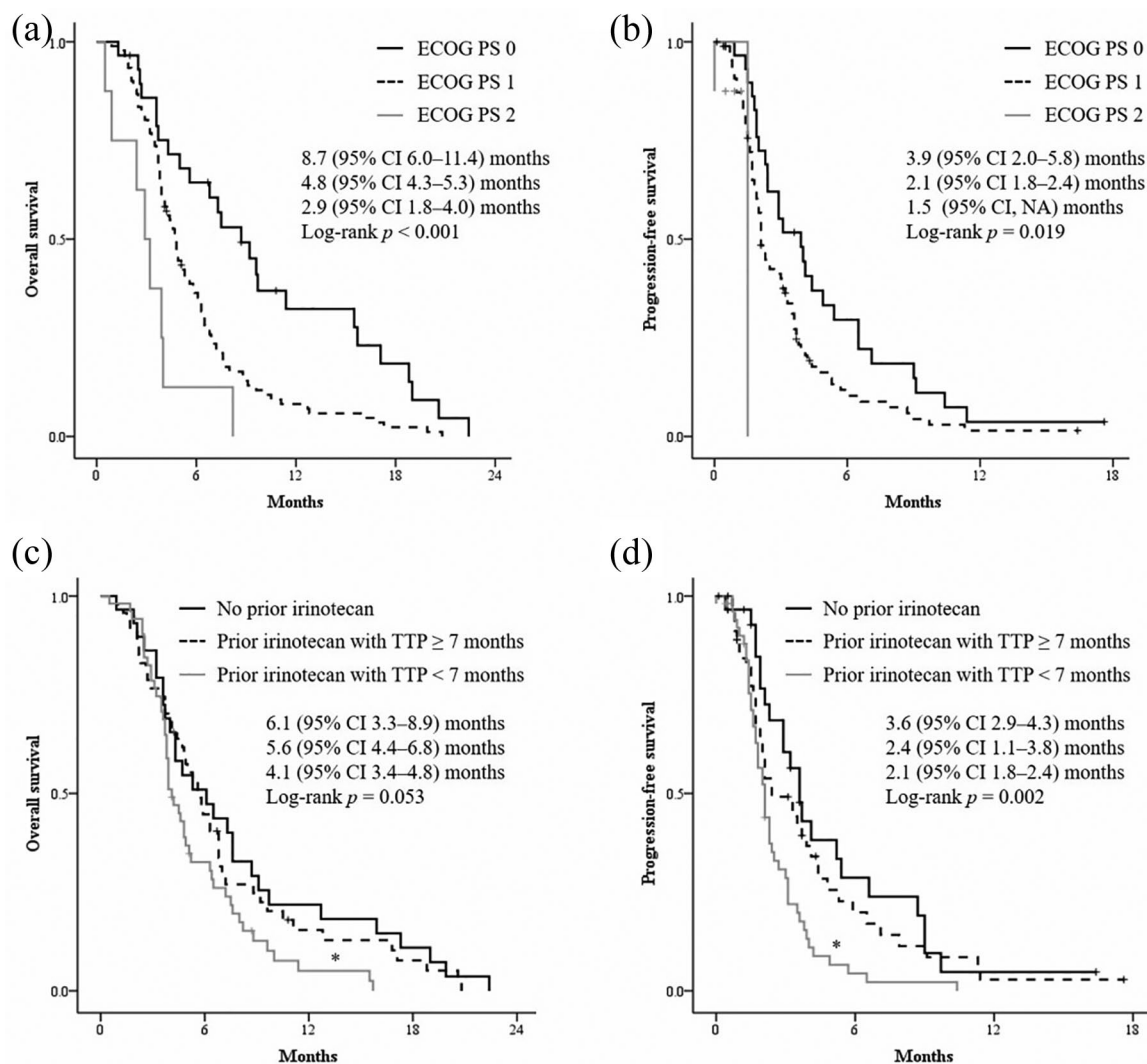


Figure 3. Kaplan–Meier survival analysis according to performance status: ECOG 0–2 (a, b), prior irinotecan exposure and response (c, d). ECOG, Eastern Cooperative Oncology Group.

exposure. This suggests that the response to prior conventional irinotecan-containing treatment could be a predictor factor for nal-IRI-based treatment. The irinotecan-free interval is also available potential predictive factors.^{21,22} And a correlation between irinotecan-free interval and survival outcomes was observed in the current study. Further investigation such as prospective, comparative cohort study is needed to clarify these prognostic factors.

This study has several limitations. First, its retrospective nature may result in a potential selection bias and lack of medical records including adverse events. We aimed to alleviate potential biases by collecting a relatively large number of patients

from multicenter tertiary hospitals. This study, to the best of our knowledge, included the largest number of patients who received nal-IRI plus 5-FU/LV beyond second-line treatment compared with previously reported real-world analyses.²³ Second, immortal time bias can also affect the survival outcomes. We calculated survival outcomes from the date of initiating nal-IRI plus 5-FU/LV treatment to avoid time bias.^{24,25} However, time-lead bias still exists in the analysis of total survival because patients who received chemotherapy beyond second-line therapy could not have died prior to third-line therapy. The effectiveness of nal-IRI + 5-FU/LV as a third- or later-line therapy can be further clarified through comparative study designs that include patients

Table 4. Univariable and multivariable analyses of survival outcomes.

	OS				PFS				
	Univariable		Multivariable		Univariable		Multivariable		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
Sex (female)	1.03	0.71–1.5	0.887	Ref			1.28	0.86–1.89	0.226
Age ≥65	1.09	0.76–1.56	0.656	Ref			1.06	0.73–1.55	0.769
ECOG									
0	Ref		(<0.001)	Ref		(<0.001)	Ref		(0.024)
1	2.13	1.34–3.39	0.001	2.29	1.43–3.66	0.001	1.67	1.07–2.60	0.024
2	5.03	2.21–11.5	<0.001	4.85	2.12–11.1	<0.001	4.63	1.02–20.9	0.047
Liver metastases	1.55	1.07–2.26	0.022	1.68	1.13–2.52	0.011	2.29	1.49–3.51	<0.001
Previous surgery	0.70	0.49–1.02	0.064				0.72	0.49–1.06	0.091
Previous radiotherapy	0.64	0.43–0.96	0.031				0.55	0.36–0.84	0.005
First-line regimen (GnP versus FFX)	0.96	0.64–1.44	0.84				0.83	0.53–1.30	0.409
Chemotherapy dose reduction	1.05	0.73–1.51	0.803				1.19	0.81–1.74	0.381
Irinotecan-free survival	0.97	0.93–1.00	0.075				0.97	0.93–1.00	0.051
Prior exposure to irinotecan									
No prior irinotecan	Ref		(0.059)	Ref		(0.084)	Ref		(0.003)
Prior irinotecan with TTP ≥7 months	1.17	0.73–1.89	0.516	1.22	0.75–1.98	0.416	1.27	0.75–2.14	0.376
Prior irinotecan with TTP <7 months	1.73	1.06–2.82	0.029	1.71	1.04–2.81	0.033	2.24	1.33–3.77	0.002
							2.81	1.63–4.86	<0.001

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FFX, FOLFIRINOX; GnP, gemcitabine plus nab-paclitaxel; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

Table 5. Adverse events of patients for any grade.

	Any grade (%)	Grade ≥ 3 (%)
Anemia	65 (50.7%)	16 (12.7%)
Neutropenia	71 (55.5%)	32 (25.4%)
Fatigue	31 (24.2%)	6 (4.7%)
Nausea	34 (26.6%)	2 (1.6%)
Vomit	22 (17.1%)	3 (2.3%)
Diarrhea	19 (14.8%)	1 (0.8%)
Abdominal pain	13 (10.2%)	-
Oral mucositis	10 (7.8%)	-

receiving other chemotherapy regimens or active symptom control. FFX and GnP regimens were considered as frontline treatment for unresectable pancreatic cancer, and each regimen was also considered as a subsequent line treatment. Median OS did not differ in patients with or without prior irinotecan (included in FFX) exposure in the current study. Therefore, nal-IRI plus 5-FU/LV may be notable, beyond second-line treatment option, and the data in this study can be meaningful in demonstrating the effectiveness of such lines of treatment. Patients that maintain good general condition or those with a favorable experience to prior irinotecan may particularly be beneficial for survival.

In conclusion, the effectiveness of nal-IRI plus 5-FU/LV beyond second-line treatment in real-world clinical practice was demonstrated in this multicenter retrospective study. The results presented here suggest that nal-IRI plus 5-FU/LV can be effective not only as second-line therapy, but also as a third-line or later line therapy in selected patients. Further investigations are necessary to identify patients that can benefit more from nal-IRI plus 5-FU/LV in various clinical settings.

Declarations

Ethics approval and consent to participate

Formal consent was waived because of the retrospective nature of this study, and which was approved by the Institutional Review Board (IRB). IRBs at Seoul National University Hospital

(H-2110-173-1266) and National Cancer Center (NCC 2021-0324) approved the study. All individual-level data were anonymized and only available to authorized researchers. IRB approved and monitored safety and adequacy of data management. This study was performed in accordance with the Declaration of Helsinki.

Consent for publication

All authors have read the manuscript and approve its submission to Therapeutic Advances in Medical Oncology.

Author contribution(s)

Jung Won Chun: Data curation; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

Sang Myung Woo: Data curation; Investigation; Writing – review & editing.

Sang Hyub Lee: Conceptualization; Investigation; Methodology; Supervision; Writing – review & editing.

Jin Ho Choi: Data curation; Investigation; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data sets used and/or analyzed during this study are available from the corresponding author on reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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