THERAPEUTIC ADVANCES in
Medical Oncology

Original Research

A real-world analysis on the efficacy and tolerability of liposomal irinotecan plus 5-fluorouracil and folinic acid in metastatic pancreatic ductal adenocarcinoma in Belgium

Lise Verbruggen*, Lisa Verheggen*, Greetje Vanhoutte, Catherine Loly, Willem Lybaert, Ivan Borbath, Philippe Vergauwe, Koen Hendrickx, Celine Debeuckelaere, Amy de Haar-Holleman, Jean-Luc Van Laethem and Marc Peeters

Abstract

Background: Currently, nanoliposomal irinotecan (nal-IRI) + 5-fluorouracil/folinic acid (5-FU/LV) is the only approved second-line treatment for patients suffering from metastatic pancreatic ductal adenocarcinoma (mPDAC). However, also other chemotherapeutic regimens are used in this setting and due to the lack of clear real-world data on the efficacy of the different regimens, there is no consensus on the optimal treatment sequence for mPDAC patients.

Objectives: To provide information on the safe and efficacious use of nal-IRI + 5-FU/LV in clinical practice in Belgium, which is needed for healthcare professionals to estimate the risk–benefit ratio of the intervention.

Methods: Medical data of adult patients with mPDAC who were treated with nal-IRI + 5-FU/LV in one of the participating Belgian hospitals were retrospectively collected. Kaplan–Meier analysis was performed to obtain survival curves to estimate the median overall survival (OS) and progression-free survival (PFS). All other results were presented descriptively.

Results: A total of 56 patients [median age at diagnosis: 69 years (range 43 years), 57.1% male] were included. Patients received a median of 5 (range 49 cycles) nal-IRI + 5-FU/LV cycles, extended over 10 weeks (range 130.8 weeks). The median start dose for nal-IRI was 70 mg/m² (range 49.24 mg/m²) and chemotherapy dose reduction and delay occurred in, respectively, 42.8% and 37.5% of the patients. The median OS was 6.8 months (95% CI: 5.6–8.4 months) with a 6-month survival rate of 57.4% and a 1-year survival rate of 27.8% in the overall study population. The median OS for patients treated with nal-IRI as second-line therapy or as later-line treatment was, respectively, 6.8 months (95% CI: 5.9–7.0 months) and 5.6 months (95% CI: 4.2–*no upper limit*). In the overall study population, a median PFS of 3.1 months (95% CI: 2.4–4.6 months) and a disease control rate of 48.3%, comprising 30.4% stable disease, 16.1% partial and 1.8% complete response, was observed. The median PFS for patients treated with nal-IRI as second-line therapy was 3.9 months (95% CI: 2.8–4.8 months) while this was 2.4 months (95% CI: 1.9–9.1 months) for those that received nal-IRI in a later-line treatment. In terms of safety, gastrointestinal problems occurred most (64.3% of the patients) and from all reported treatment emergent adverse events, 39.2% were grade 3 or 4.

Conclusion: Nal-IRI + 5-FU/LV is a valuable, effective, and safe sequential treatment option following gemcitabine-based therapy in patients with mPDAC.

Trial details: Retrospective study on the efficacy and tolerability of liposomal irinotecan (NALIRI); ClinicalTrials.gov Identifier: NCT0509506 (https://clinicaltrials.gov/ct2/show/NCT05095064?term=naliri&draw=2&rank=2).

Ther Adv Med Oncol

2023, Vol. 15: 1–13

DOI: 10.1177/17588359231181500

Correspondence to:
Lise Verbruggen
Multidisciplinary Oncological Center Antwerp, Antwerp University Hospital (UZA), Drie Eikenstraat 655, Edegem 2650, Belgium.
lise.verbruggen@uza.be

Lisa Verheggen
Greetje Vanhoutte
Marc Peeters
Multidisciplinary Oncological Center Antwerp, Antwerp University Hospital (UZA), Edegem, Belgium

Catherine Loly
Department of Gastroenterology, University Hospital CHU de Liège, Domaine Universitaire, Liège, Belgium

Willem Lybaert
Department of Medical Oncology, VITAZ, Sint-Niklaas, Belgium

Ivan Borbath
Department of Hepato-gastroenterology, Cliniques Universitaires Saint Luc, Brussels, Belgium

Philippe Vergauwe
Department of Gastroenterology, General Hospital Groeninge, Kortrijk, Belgium

Koen Hendrickx
Department of Gastroenterology, OLV Hospital, Aalst, Belgium

Celine Debeuckelaere
Department of Digestive Oncology and Gastroenterology, ASZ Aalst, Belgium

Amy de Haar-Holleman
Department of Medical Oncology, University Hospital Brussels, Jette, Belgium

Jean-Luc Van Laethem
Department of Gastroenterology and Digestive Oncology, Erasme Hospital, Lenniks, Brussels, Belgium

*These authors contributed equally.

Keywords: efficacy, mPDAC, nanoliposomal irinotecan, nal-IRI, pancreatic cancer, safety

Received: 22 November 2022; revised manuscript accepted: 24 May 2023.

Introduction

Metastatic pancreatic ductal adenocarcinoma (mPDAC) is a highly aggressive and lethal malignancy. Patients with mPDAC have a poor prognosis with a 5-year survival of less than 5%. Surgery combined with chemotherapy is still the only potentially curative treatment. However, due to the absence of early warning symptoms, late diagnosis, and rapid metastatic spreading, curative resection is only possible for 10–20% of patients.[1] As such, there is a high need for the development of new therapeutic options, especially for patients with metastatic disease. A lot of effort has already been made to improve the first-line treatment, gemcitabine, with the addition of a second cytotoxic agent or targeted therapy.[2,3] The addition of nab-paclitaxel to gemcitabine in a first-line setting significantly improved clinical outcomes, whereas the addition of erlotinib seemed to have a rather modest effect on the survival of the patients.[4,5] Recent advances in chemotherapeutics and a better understanding of the molecular biology of mPDAC have established the potential of a combination of oxaliplatin, irinotecan, folinic acid, and fluorouracil (FOLFIRINOX) as first-line therapy for mPDAC patients,[1] but this is only recommended when the patients' performance status is optimal.[6] Hence, most patients are still treated with gemcitabine-based therapy in first line, but many patients progress under this regimen. Recently, the combination of nanoliposomal irinotecan (nal-IRI) with 5-fluorouracil and folinic acid (5-FU/LV) has been shown to be superior to the use of 5-FU/LV alone in patients that progressed after gemcitabine-based therapy.[7,8] A 2-month advantage in median overall survival (OS) was observed. Likewise, the median progression-free survival (PFS), objective response rate and disease control rate were all in favor of nal-IRI + 5-FU/LV.[7,8] This led to the approval of nal-IRI + 5-FU/LV for use in adult patients with mPDAC who have progressed following gemcitabine-based therapy by both the European Medicines Agency (EMA) and Food and Drug Administration.[9,10]

While this is currently the only approved second-line treatment for mPDAC patients, other chemotherapy regimens, such as FOLFIRINOX, 5-FU + oxaliplatin, 5-FU-based monotherapy, oxaliplatin + capecitabine, or capecitabine monotherapy, are also used after progression under gemcitabine-based therapy.[11] Due to the lack of predictive molecular markers favoring one chemotherapy regimen over another, no clear recommendations regarding the optimal sequence of treatment for mPDAC are currently available. Hence, the therapeutic choice is mostly defined by the patients' performance status, age, the residual toxicity profile of the previous treatment, and the preference of the physician. Another reason for the lack of consensus in this field is the unavailability of head-to-head comparison between different treatment approaches. Indeed, apart from the NAPOLI-1 trial, no prospective studies were performed to compare nal-IRI + 5-FU/LV with other recommended chemotherapy regimens. However, a recent retrospective analysis compared nal-IRI + 5-FU/LV with modified FOLFIRINOX on one hand and FOLFIRI (irinotcan + 5-FU/LV) on the other hand as second-line therapy for unresectable pancreatic cancer and confirmed the favorable risk–benefit balance of nal-IRI + 5-FU/LV.[12]

Although randomized clinical trials, like the NAPOLI-1 trial, are considered the reference standard for comparing the efficacy and safety of treatments, these studies do not always reflect everyday clinical practice.[7,8,13–15] Postmarketing surveillance has a big impact on the decision of a physician to choose one approach over the other as it provides updates to healthcare professionals with regard to the safe and efficacious use of medicines to estimate the risk–benefit ratio of the intervention.[16] Hence, the objective of this study is to investigate whether the efficacy and safety profile of nal-IRI + 5-FU/LV as described in the prospective phase III NAPOLI-1 trial is similar when it is used in real-life clinical practice in Belgium.

Patients and methods

This national, retrospective data collection study included patients with histologically confirmed mPDAC. Patients who received at least one cycle of nal-IRI + 5-FU/LV in the context of post-gemcitabine-based therapy between 14 October 2016

(EMA marketing authorization) and 01 April 2021 were included. Patients of whom only limited clinical data were available or who were previously treated with irinotecan-based therapy in metastatic setting were excluded, in line with the Belgian reimbursement criteria for nal-IRI.

The regulatory sponsor was the Antwerp University Hospital and this work was financially supported by Servier. The study was approved by the local ethics committees of the participating institutions (Supplemental Table 1) and was executed in accordance with Good Clinical Practice and the Declaration of Helsinki (ICH GCP E6(R2)). Informed consent was not required due to the retrospective nature of the study.

Relevant clinical data of the patients recorded in the patients' medical files till database lock (01/02/2022) were entered into an electronic case report form (eCRF). Baseline data were used to map patients' demographics. Dosing of nal-IRI + 5-FU/LV was assessed using the duration of the treatment in combination with both the starting doses and the dose intensity of all chemotherapeutic agents. The latter is defined as the mean dose used over the entire treatment period of a patient. Also, data on dose reductions, therapy delays, and treatment discontinuations were recorded.

Efficacy was assessed using the OS from the start of treatment with nal-IRI + 5-FU/LV (primary outcome), the survival rate at 6 months and 1 year, the PFS, disease control rate, and OS from the date of diagnosis of metastatic disease (secondary outcomes). OS is defined as the time from the start of nal-IRI + 5-FU/LV treatment (primary outcome) or the date of diagnosis of metastatic disease (secondary outcome) until death of any cause or until the day of database lock for the patients who were alive at that point. PFS is defined as the time from the start of nal-IRI + 5-FU/LV treatment until disease progression or patient death, whatever comes first or until the day of database lock for the patients who were still alive and did not show signs of progression at that point. Patients were assessed every 8–12 weeks by computed tomography. The overall response rate is defined as the percentage of patients in whom the best response was complete response or partial response. In addition, disease control rate was calculated based on the percentage of patients in whom the best response was a complete response, partial response, or stable disease.[17,18]

The safety of the nal-IRI + 5-FU/LV treatment was assessed by the occurrence of treatment-emergent adverse events (TEAEs). These are defined as any adverse event with an onset date on or after the first dose of nal-IRI + 5-FU/LV or any adverse event that worsened after the first dose nal-IRI + 5-FU/LV. Adverse events were recorded using the Standardized Medical Dictionary for Regulatory Activities (MedDRA) coding system (SMQs) and graded for severity according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.[19] In this context also, the percentage of patients with dose reductions, treatment cycle delays, and discontinuations due to treatment toxicity was calculated and the number of hospital admissions and emergency department visits that were linked to the toxicity of the treatment were monitored.

Most results of this observational and exploratory study were summarized in a descriptive way. Survival curves were used to estimate the median OS, survival rates, and median PFS by means of the Kaplan–Meier method. For these analyses, patients for which the second event (i.e. death or disease progression) did not occur before the date of database lock were censored. Statistical analyses (chi-squared test for categorical data, Mann–Whitney test for numerical data and Log-rank test for survival data) were performed using GraphPad Prism 8 software (www.graphpad.com) and R software (www.r-project.org). A (two-sided) p value of <0.05 was considered statistically significant. Results and two-sided 95% CIs are presented in the corresponding figures.

Results

Patient characteristics

Clinical data of 56 mPDAC patients from 9 participating institutions in Belgium were retrospectively assessed (Supplemental Figure 1). All patients received gemcitabine-based therapy as the first-line treatment of metastatic disease. Baseline patient demographics and disease characteristics are presented in Supplemental Table 2. The median age at diagnosis was 69 years (range 43 years). With 32 (57.1%) male and 24 (42.9%) female patients, a good balance between both genders was present in the study population. After progression under first-line therapy, 38 patients (67.9%) received nal-IRI + 5-FU/LV as second-line treatment and 18 (33.1%) patients received nal-IRI + 5-FU/LV as a

third-line treatment or later. Subsequent third-line or fourth-line therapy after nal-IRI + 5-FU/LV was given to 20 patients (35.7%).

Dosing details

Details on the dosing of nal-IRI + 5-FU/LV in the study population are given in Table 1. The median number of nal-IRI + 5-FU/LV cycles was 5 (range 49 cycles) and the median duration of the therapy was 10 weeks (range 130.8 weeks). The median starting dose for nal-IRI was 70 mg/m² (range 49.24 mg/m²) and the median dose intensity was 63.77 mg/m² (range 64.18 mg/m²). Of all included patients, 40 (71.4%) patients started treatment with at least 90% of the recommended dose of nal-IRI, specified in the Summary of Product Characteristics (70 mg/m²). These patients will be referred to as patients who started with an optimal dose of nal-IRI in further analyses described in this article.

Dose reductions of any of the components of the nal-IRI + 5-FU/LV treatment occurred in 24 (42.8%) patients, 22 of which included a reduction in nal-IRI. Of these 22 patients, 18 had started therapy with an optimal dose of nal-IRI and for 16 patients the dose reduction of nal-IRI was due to treatment-related toxicity. Other reasons for dose reductions included patient deterioration and medical decision. Treatment delay was reported in 21 (37.5%) patients of which 15 patients started with an optimal dose of nal-IRI. For 11 patients, treatment delay was induced by the occurrence of a TEAE (Supplemental Table 3). Other reasons for a delay in the treatment scheme were therapy pause, a medical decision, and patient deterioration.

The most reported reason for discontinuation of the treatment with nal-IRI + 5-FU/LV was the occurrence of disease progression (35 patients; 62.5%), but for 5 (8.9%) patients treatment discontinuation was linked to treatment-related toxicity. Other reasons for treatment discontinuation included the patient's wish, patient deterioration, and death (Supplemental Table 4).

Efficacy

In the overall study population, a median OS from the start of treatment with nal-IRI + 5-FU/LV of 6.8 months [95% CI: 5.6–8.4 months, Figure 1(a)] and a median OS from the diagnosis of metastatic disease of 15.2 months (95% CI: 13.2–19.2 months) was observed [Figure 1(b)]. Kaplan–Meier estimated a 6-month survival rate of 57.4% (95% CI: 43.2–69.3%) and a 1-year survival rate of 27.8% (95% CI: 16.7–40.0%) with four (7.1%) patients surviving beyond 20 months after the start of nal-IRI + 5-FU/LV. Another three (5.4%) patients were still alive at the moment of database lock and had an OS of, respectively, 16.5, 18.5, and 18.8 months from the start of treatment with nal-IRI + 5-FU/LV.

Patients being treated with nal-IRI + 5-FU/LV as second-line therapy for metastatic disease had a median OS from the start of treatment with nal-IRI + 5FU/LV for 6.8 months [95% CI: 5.9–7.0 months, Figure 1(c)], and an estimated 6-month survival rate of 62.2% (95% CI: 44.6–75.6%) and a 1-year survival rate of 24.3% (95% CI: 12.2–38.8%). Patients that received nal-IRI + 5-FU/LV in later-line treatment had a median OS from the start of treatment with nal-IRI + 5FU/LV for 5.6 months [95% CI: 4.2 months – *no upper limit of the 95% CI could be calculated due to skewedness of the data*, Figure 1(d)], an estimated 6-month survival rate of 47.1% (95% CI: 23.0–68.0%) and a 1-year survival rate of 35.3% (95% CI: 14.5–57.0%).

In total, this study counted 15 long-term survivors (patients with an OS > 12 months from the start of treatment with nal-IRI + 5-FU/LV). In Table 2, the patients' characteristics of these long-term survivors are compared to the patients' characteristics of patients who did not survive longer than 12 months after initiation of treatment with nal-IRI + 5FU/LV. The group of long-term survivors had a median age of 71 (range 35 years), and 10 (66.7%) of the patients were male. Among the 15 long-term survivors, 9 (60.0%) patients started therapy with an optimal dose of nal-IRI and 7 of these patients underwent dose reductions for nal-IRI. Nal-IRI was given as a second-line treatment to nine (60.0%) of these patients. Statistical analysis did not show any significant differences between the baseline patients' characteristics of both groups.

The median PFS for the whole study population was estimated to be 3.1 months [95% CI: 2.3–4.6 months, Figure 2(a)]. Patients being treated with nal-IRI + 5-FU/LV as second-line therapy for metastatic disease had a median PFS of 3.9 months [95% CI: 2.8–4.8 months, Figure 2(b)], while this was 2.4 months [95% CI: 1.9–9.1 months, Figure 2(c)] for those who received nal-IRI +

Table 1. Dosing details of nal-IRI + 5-FU/LV treatment of included patients.

Therapy duration (*n* = 56)		
Median number of cycles (range)	5 (49)	
Median treatment duration (weeks; range)	10 (130.8)	9.5 (129)*
Patients with therapy delay	4 (7.1%)	
Median duration (weeks; range)	2.4 (5.1)	
Starting dose (*n* = 56)		
Nal-IRI		
Median (mg/m²; range)	70.00 (49.24)	
<50**	3 (5.4%)	
50–60**	9 (16.1%)	
60–70**	16 (28.6%)	
70–80**	20 (35.7%)	
>80**	5 (8.9%)	
Missing	3 (5.4%)	
5-FU		
Median (mg/m²; range)	2400 (1291)	
LV		
Median (mg/m²; range)	240.2 (272.7)	
Dose intensity		
Nal-IRI		
Median (mg/m²; range)	63.77 (64.18)	
5-FU		
Median (mg/m²; range)	2266 (2151)	
LV		
Median (mg/m²; range)	282.2 (367.4)	

5-FU, 5-fluorouracil; LV, folinic acid; nal-IRI, nanoliposomal irinotecan.
*Without patients that had therapy delay.
**Limits of dosing ranges are set at whole numbers, if the upper limit is exceeded by 0.01 and the dose belongs to the next range.

5-FU/LV in later-line treatment. The overall response rate was 17.9% and the disease control rate was 48.3%, with 1 patient (1.8%) showing a complete response, 9 (16.1%) showing a partial response, and 17 patients (30.4%) showing stable disease. Immediate disease progression during nal-IRI + 5-FU/LV treatment was observed for 29 patients (51.8%).

We performed a subgroup analysis on the patient group that started therapy with an optimal dose of nal-IRI [*n* = 40, Figure 3(a) and (b)]. Within

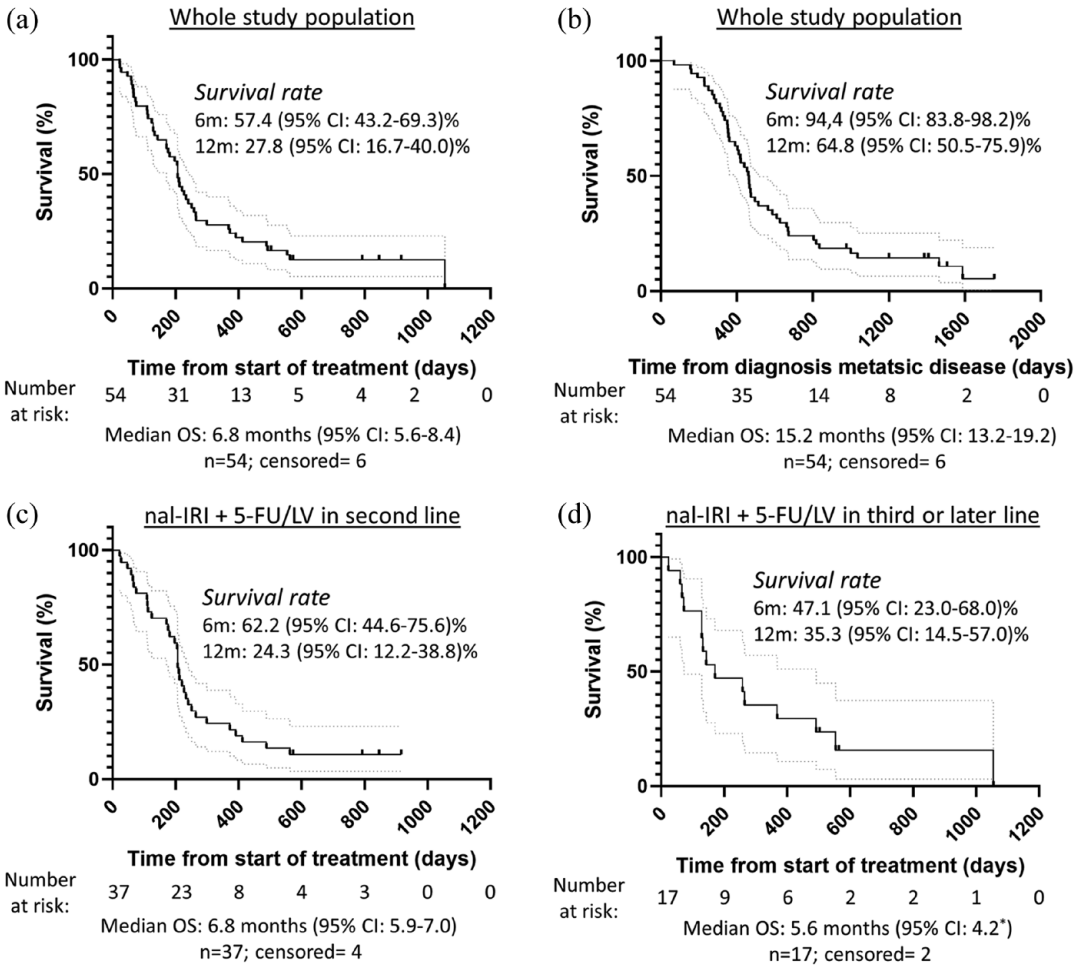

Figure 1. Kaplan–Meier curves showing median OS of the whole population ($n=56$) in this study since the start of treatment with nal-IRI + 5-FU/LV (a), the whole population ($n=56$) since the date of diagnosis of metastatic disease (b), and the subgroup that started nal-IRI + 5-FU/LV therapy in second line (c) and those that started this therapy in later lines (d). *No upper limit of the 95% CI could be calculated due to skewedness of the data.
5-FU/LV, 5-fluorouracil/folinic acid; nal-IRI, nanoliposomal irinotecan; OS, overall survival.

these subpopulation, we could show that patients, who underwent dose reductions ($n=18$) for nal-IRI during their treatment, had a better OS ($p=0.0051$) and PFS ($p=0.0296$) compared to the patients that did not have any dose reductions: median OS 7.6 months [95% CI: 6.7 months – *no upper limit of the 95% CI could be calculated due to skewedness of the data*, Figure 3(c)] and median PFS 3.9 months [95% CI: 2.8–15.7 months, Figure 3(d)] *versus* median OS 5.8 months [95% CI: 4.1–8.4 months, Figure 3(c)] and median PFS 2.2 months [95% CI: 1.8–4.6 months, Figure 3(d)], respectively. Kaplan–Meier estimated a 6-month survival rate of 70.6% (95% CI: 43.1–86.6%) and a 1-year survival rate of 41.2% (95% CI: 18.6–62.4%) for patients who underwent dose reductions, with four patients surviving beyond 20 months. For the patient group that had no dose reductions, an estimated 6-month survival rate of 48.0% (95% CI: 25.7–19.0%) and a 1-year survival rate of 9.6% (95% CI: 1.6–16.6%) was observed, with no patients surviving beyond 20 months.

Safety

A summary of all reported TEAEs is given in Table 3. In total, 74 TEAEs were reported, of which 25 (39.2%) were scored grade 3 and only one grade 4 TEAE (fatigue) was reported. The most common TEAEs of all grades included gastrointestinal problems such as noninfectious diarrhea as well as gastrointestinal nonspecific inflammation and dysfunctional conditions. In total, 36 patients

Table 2. Demographic and clinical patient characteristics of long-term survivors compared to non-long-term survivors.

Patient characteristic	Long-term survivors (*n* = 15)	Non-long-term survivors (*n* = 39*)
Gender		
Male	10 (66.7%)	22 (56.4%)
Female	5 (33.3%)	17 (43.6%)
Age		
Median (range)	71 (35)	68 (42)
⩽65 years (%)	7 (46.7%)	17 (43.6%)
>65 years (%)	8 (53.3%)	22 (56.4%)
ECOG		
0	1 (6.7%)	8 (19.5%)
1	7 (46.7%)	15 (36.6%)
2	1 (6.7%)	10 (24.4%)
3	0	4 (9.7%)
Missing	6 (40%)	4 (9.7%)
Optimal start dose nal-IRI		
Yes	9 (60.0%)	29 (74.4%)
With dose reduction	7 (46.7%)	10 (25.6%)
No	5 (33.3%)	9 (23.1%)
Unknown	1 (6.67%)	1 (2.6%)
Line of metastatic therapy		
2nd	9 (60.0%)	28 (71.8%)
3rd or more	6 (40.0%)	11 (28.2%)
Hepatic metastasis		
No	6 (40.0%)	8 (20.5%)
Yes	9 (60.0%)	31 (79.5%)
Subsequent therapy		
Yes	8 (53.3%)	12 (30.8%)
No	7 (46.7%)	27 (69.2%)
No. of metastatic site		
1	6 (40.0%)	17 (43.6%)
2	5 (33.3%)	11 (28.2%)
3	4 (26.7%)	8 (20.5%)
4	0 (0.0%)	3 (7.7%)

*For two patients, data on OS are missing.
ECOG, Eastern Cooperative Oncology Group; nal-IRI, nanoliposomal irinotecan.

(64.3%) suffered from one of these adverse events during the treatment. Other commonly reported TEAEs included peripheral neuropathy, fatigue, hematopoietic cytopenias, and hypokalemia. During the treatment period, 21 (37.5%) patients visited the emergency department at least once and 27 (48.2%) patients were hospitalized, but only 8.9% of the emergency department visits and 16.1% of the hospitalizations were caused by a TEAE.

Discussion

While in the past, the majority of mPDAC patients received one single line of chemotherapy, treatment options are expanding.[2,3] Yet, there are debates regarding the optimal sequence of these treatment options and it is necessary to establish an optimal strategy through real-world clinical outcomes.[20,21] The NAPOLI-1 trial showed evidence that nal-IRI + 5-FU/LV is an effective second-line treatment option with an extent in survival and a manageable safety profile in adults who progressed under gemcitabine-based therapy.[8] This retrospective real-world study showed similar survival rates and a similar tolerability profile of nal-IRI + 5-FU/LV when used in daily clinical practice. The TEAEs observed in this study corresponded with the adverse events reported in the NAPOLI-1 trial, but the incidence of each TEAE is lower in this study. The same applies to the incidence of treatment discontinuations due to TEAEs which is lower in this study (8.9%), compared to what was described in the NAPOLI-1 trial (13.0%).[8] This may be the result of a less vigorous collection of adverse events in a postmarketing studies compared to prospective clinical trials, indicating that safety-related results of postmarketing surveillance studies must be viewed with caution.

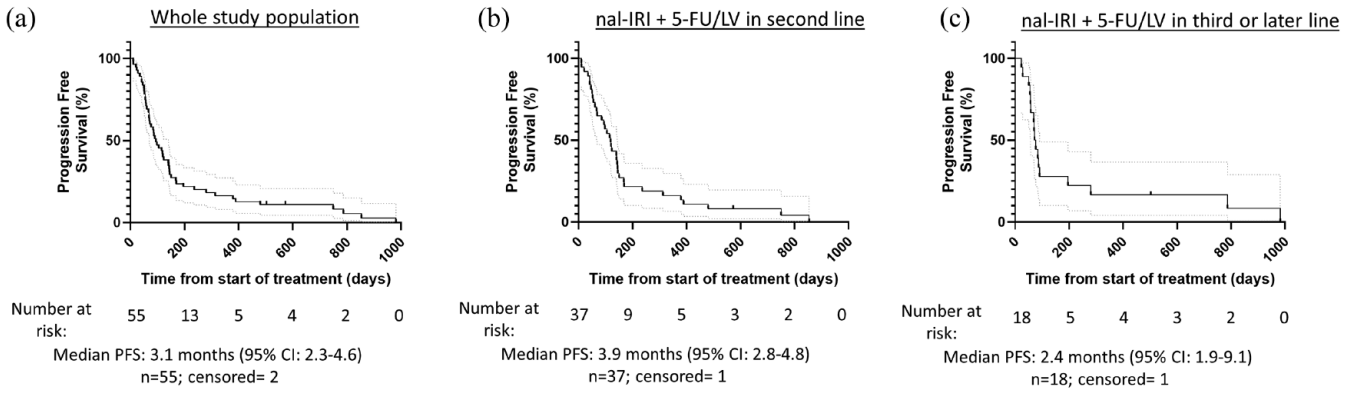

Figure 2. Kaplan–Meier curves showing median PFS of the whole population ($n = 56$) since the start of treatment with nal-IRI + 5-FU/LV (a), the subgroup that started nal-IRI + 5-FU/LV therapy in second line (b), and those that started this therapy in later lines (c).
Nal-IRI, nanoliposomal irinotecan; PFS, progression-free survival; 5-FU/LV, 5-fluorouracil/folinic acid.

In the study population of the NAPOLI-1 trial, a median OS of 6.1 months and median PFS of 3.1 months were observed for nal-IRI + 5-FU/LV after progression upon gemcitabine-based treatment. This was shown to be superior compared to the survival outcomes of patients receiving 5-FU/LV monotherapy (4.2 and 1.5 months, respectively).[7,8] The current study demonstrates comparable survival outcomes of nal-IRI + 5-FU/LV with a median OS of 6.8 months and a median PFS of 3.1 months in the overall study population. A significant association between dose reductions and clinical outcome in patients who started with an optimal dose of nal-IRI was observed. Patients who started with an optimal dose of nal-IRI and underwent dose reductions had a longer median OS and median PFS (7.6 and 3.9 months) compared to those without dose reduction (OS 5.8 months and PFS 2.2 months). While these findings are in contrast with the findings of Kieler and coworkers,[13] another retrospective study did show an association between dose reduction and longer survival, as shown in our study.[14,21] This might be explained by the fact that dose reductions were used to manage adverse effects, as such preventing treatment discontinuation and allowing patients to remain on the treatment longer.[22] Indeed, limiting treatment toxicities using dose modifications improved the efficacy of nab-paclitaxel + gemcitabine.[23–25] All this indicates that improving the tolerability of the chemotherapy with dose modifications might lead to a better quality of life, without compromising the efficacy and even results in increased time on treatment. This might also explain the reduced starting dose (<60 mg/m²) that was applied in 19.6% of the patients. A recent database study performed in the United States demonstrated that, in clinical practice, 44.5% of the patients received a dose of nal-IRI that was lower (30–65 mg/m²) than what is specified in the Summary of Product Characteristics (70 mg/m²).[26] It should be noted that our results might be confounded by patients with early disease progression or death, as reported in the post hoc analysis of the NAPOLI-1 study. Patients who only received one cycle of nal-IRI + 5-FU/LV before the occurrence of disease progression or death, are characterized as 'without dose reduction', hence skewing the results toward a better survival in the groups of patients with dose reduction.[25]

The survival data in this retrospective study are in line with previously reported single institution real-world data from the United States and Korea[15,21] and our findings for disease control rate (48.3%), complete response (1.8%), partial response (16.1%), and stable disease (30.4%) are in line with data obtained in studies in Austria and Japan.[13,27] Other studies demonstrated better clinical outcomes when exclusively patients who received nal-IRI + 5-FU/LV as second-line therapy were assessed.[13,28] Kieler *et al.* reported a median OS of 6.79 months and a PFS of 3.84 months in the overall study population, but a subgroup analysis, including only patients who received nal-IRI + 5-FU/LV in second line after gemcitabine-based chemotherapy, revealed a median PFS of 4.49 months.[13] In addition, Park *et al.* described a median OS of 7.7 months and a PFS of 3.7 months with nal-IRI + 5-FU/LV in second-line setting.[28] These observations are supported by the data from our study population. We observed an increased median OS of

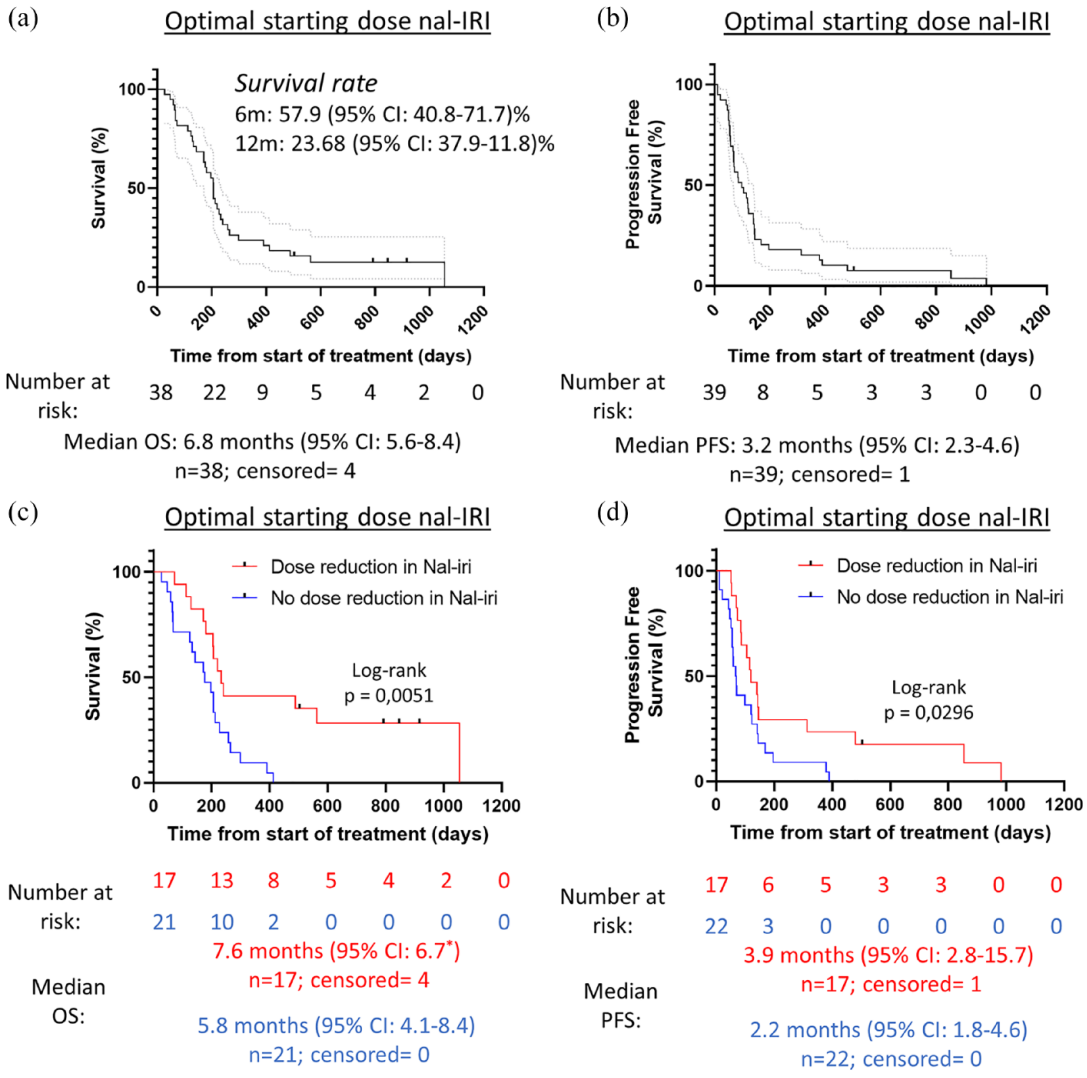

Figure 3. Subgroup analysis on the treatment efficacy. Kaplan–Meier curves showing the OS and PFS of the subgroup that started with an optimal dose of nal-IRI ($n = 40$; a + b) and comparing the effect of dose reduction *versus* no dose reduction in the population that started with an optimal dose of nal-IRI ($n = 40$; c + d). *No upper limit of the 95% CI could be calculated due to skewedness of the data.
Nal-IRI, nanoliposomal irinotecan; OS, overall survival; PFS, progression-free survival.

6.8 months and a median PFS of 3.9 months for patients that received nal-IRI + 5FU/LV as second-line treatment. Although this could be linked to the better performance status of patients under second-line treatment compared to patients who were already exposed to more lines of therapy, the data support the fact that nal-IRI + 5-FU/LV has been listed as the first choice second line-therapy for mPDAC patients previously treated with gemcitabine-based therapy in both the National Comprehensive Cancer Network and European Society for Medical Oncology guidelines.[3,29] Indeed, while the NAPOLI-1 phase III trial clearly shows a beneficial effect of nal-IRI + 5-FU/LV,[7,8] the results of phase III trials studying the efficacy of second-line oxaliplatin + 5-FU/LV treatment options revealed conflicting results.[30–32] In the NAPOLI-1 trial, 5-FU/LV was selected as a control, but prospective trials investigating the efficacy of nal-IRI + 5-FU/LV compared with other second-line treatment options such as FOLFIRI are lacking. Nevertheless, retrospectively collected data from mPDAC patients, who were treated with nal-IRI + 5-FU/LV or oxaliplatin + fluoropyrimidines therapy in second line after gemcitabine-based therapy from a center in Vienna (Austria), provided further evidence that nal-IRI + 5-FU/LV is a preferable choice as

Table 3. TEAEs recorded during the study period.

TEAEs	Any grade (%)	Grade 3/4 (%)
Noninfectious diarrhea	20 (35.7)	8 (14.3)
GI nonspecific inflammation and dysfunctional conditions	16 (28.6)	11 (19.6)
Peripheral neuropathy	6 (10.7)	0 (0)
Fatigue	4 (7.1)	1 (1.8)
Hematopoietic cytopenias	4 (7.1)	0 (0)
Hypokalemia	3 (5.4)	1 (1.8)
Sepsis	2 (3.6)	2 (3.6)
Hepatic disorders	2 (3.6)	1 (1.8)
Acute central respiratory depression	2 (3.6)	0 (0)
Dehydration	2 (3.6)	0 (0)
Embolic and thrombotic events	2 (3.6)	1 (1.8)
Opportunistic infections	2 (3.6)	0 (0)
CNS vascular disorders	1 (1.8)	1 (1.8)
Respiratory failure	1 (1.8)	1 (1.8)
Extravasation events	1 (1.8)	1 (1.8)
GI perforation, ulceration, hemorrhage, or obstruction	1 (1.8)	1 (1.8)
Angioedema	1 (1.8)	0 (0)
Hypersensitivity	1 (1.8)	0 (0)
Severe cutaneous adverse reactions	1 (1.8)	0 (0)
Taste and smell disorders	1 (1.8)	0 (0)
Palpitations GI (temporaire)	1 (1.8)	0 (0)
Emergency department visits (TEAE induced)	5 (8.9)	
Hospital admissions (TEAE induced)	9 (16.1)	

Number of cases of any grade and grade 3 or 4 for each TEAE. Percentages calculated on the total study population ($n = 56$).
CNS, central nervous system; GI, gastrointestinal; TEAEs, treatment-emergent adverse events.

second-line treatment after gemcitabine-based therapy.[13] Moreover, a recent retrospective study comparing the efficacy of nal-IRI + 5FU/LV *versus* modified FOLFORINOX and *versus* FOLFIRI, respectively, showed a risk–benefit balance in favor of nal-IRI + 5-FU/LV *versus* both FOLFIRI and mFOLFIRINOX as a second-line mPDAC treatment.[12] These results in combination with the results shown in our retrospective study support the use of nal-IRI + 5-FU/LV as second-line treatment for mPDAC patients who progressed after gemcitabine-based therapy.

In our study, median OS of 5.6 months and median PFS of 2.4 months were demonstrated for patients who received nal-IRI + 5-FU/LV in a later-line treatment. These results are in line with a real-world retrospective study from Korea demonstrating a median OS and PFS of 4.9 and

2.4 months, respectively[33] and indicate that nal-IRI + 5-FU/LV can be effective as third-line or later-line treatment.

In accordance with the NAPOLI-1 trial,[7] our study showed that more than 25% of the patients survived over 1 year from the start of treatment with nal-IRI + 5-FU/LV. This suggests that there is a subpopulation that responds exceptionally well to nal-IRI + 5-FU/LV treatment. However, we were unable to identify specific characteristics associated with long-term survival under nal-IRI + 5-FU/LV treatment. Hence, it is important that future research focuses on the identification of predictive characteristics of these long-term survivors to facilitate the treatment decision.

The retrospective nature of this study might result in a bias due to the lack of data in the medical records including safety data. By collecting data from different institutions, we tried to mitigate this bias. Moreover, using this multicentric approach, we are confident that the results of this study are more generalizable. To avoid a potential selection bias, all patients from all participating institutions who received at least one cycle of nal-IRI + 5-FU/LV confirm the reimbursement criteria for nal-IRI in Belgium and of whom data were available in the medical files were included. Disease assessment intervals might vary between the different institutions, which can impact PFS results, especially when we compare subgroups. Notwithstanding this potential bias in the efficacy data, the objective of this study was to map real-world clinical practice, in which assessment intervals are not completely standardized.

Conclusion

The results of this study not only confirm the safety and efficacy of nal-IRI + 5-FU/LV treatment in mPDAC patients who progressed under gemcitabine-based treatment, but it also points out that this strategy should be employed as the preferred second-line treatment, as recommended in the European Society for Medical Oncology guidelines.[3]

Declarations

Ethics approval and consent to participate

The regulatory sponsor was the Antwerp University Hospital. The study was approved by the local ethics committees of all participating institutions and was executed in accordance with Good Clinical Practice and the Declaration of Helsinki [ICH GCP E6(R2)]. Informed consent was not required due to the retrospective nature of the study.

Consent for publication

Not applicable.

Author contributions

Lise Verbruggen: Conceptualization; Data curation; Formal analysis; Investigation; Project administration; Visualization; Writing – original draft; Writing – review & editing.

Lisa Verheggen: Data curation; Formal analysis; Visualization; Writing – original draft; Writing – review & editing.

Greetje Vanhoutte: Conceptualization; Formal analysis; Writing – review & editing.

Catherine Loly: Investigation; Supervision; Writing – review & editing.

Willem Lybaert: Investigation; Supervision; Writing – review & editing.

Ivan Borbath: Investigation; Supervision; Writing – review & editing.

Philippe Vergauwe: Investigation; Supervision; Writing – review & editing.

Koen Hendrickx: Investigation; Supervision; Writing – review & editing.

Celine Debeuckelaere: Investigation; Supervision; Writing – review & editing.

Amy de Haar-Holleman: Investigation; Supervision; Writing – review & editing.

Jean-Luc Van Laethem: Investigation; Supervision; Writing – review & editing.

Marc Peeters: Conceptualization; Investigation; Methodology; Supervision; Writing – review & editing.

Acknowledgements

We kindly thank the NALIRI study teams from all different participating institutions for data collection. We are thankful for Ritu Dogra for support with the data analysis.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was financially supported by Servier.

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and material

Data are available upon reasonable request.

ORCID iDs

Lise Verbruggen https://orcid.org/0000-0002-1358-6405

Koen Hendrickx https://orcid.org/0000-0002-1551-0930

Supplemental Material

Supplemental material for this article is available online.

References

1. Lambert A, Schwarz L, Borbath I, *et al.* An update on treatment options for pancreatic adenocarcinoma. *Ther Adv Med Oncol* 2019; 11: 1758835919875568.
2. Thota R, Pauff JM and Berlin JD. Treatment of metastatic pancreatic adenocarcinoma: a review. *Oncology (Williston Park)* 2014; 28: 70–74.
3. Ducreux M, Cuhna ASa, Caramella C, *et al.* Cancer of the pancreas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up†. *Ann Oncol* 2015; 26: v56–v68.
4. Moore MJ, Goldstein D, Hamm J, *et al.* Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007; 25: 1960–1966.
5. Von Hoff DD, Ervin T, Arena FP, *et al.* Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; 369: 1691–1703.
6. Akhoundova Sanoyan D, Reiner CS, Papageorgiou P, *et al.* Sequential treatment of metastatic adenocarcinoma of the pancreatic duct with liver metastasis following the NAPOLI-1 study protocol with nal-irinotecan plus 5-FU in the second line. *Case Rep Oncol* 2020; 13: 79–84.
7. Wang-Gillam A, Hubner RA, Siveke JT, *et al.* NAPOLI-1 phase 3 study of liposomal irinotecan in metastatic pancreatic cancer: final overall survival analysis and characteristics of long-term survivors. *Eur J Cancer* 2019; 108: 78–87.
8. Wang-Gillam A, Li C-P, Bodoky G, *et al.* Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *Lancet* 2016; 387: 545–557.
9. European Medicines Agency. *Summary of product characteristics: onivyde pegylated liposomal (previously known as Onivyde)*. 2006.
10. US Food and Drug Administration. *Full prescribing information: ONIVYDE (irinotecan liposome injection)*. US Food and Drug Administration, 2015.
11. Tempero MA, Malafa MP, Al-Hawary M, *et al.* Pancreatic adenocarcinoma, version 2.2021, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2021; 19: 439–457.
12. Tezuka S, Ueno M, Kobayashi S, *et al.* Nal-IRI/5-FU/LV versus modified FOLFIRINOX and FOLFIRI as second-line chemotherapy for unresectable pancreatic cancer: a single center retrospective study. *Pancreatology* 2022; 22: 789–796.
13. Kieler M, Unseld M, Bianconi D, *et al.* A real-world analysis of second-line treatment options in pancreatic cancer: liposomal-irinotecan plus 5-fluorouracil and folinic acid. *Ther Adv Med Oncol* 2019; 11: 1758835919853196.
14. Kim GP, Surinach A, Corvino FA, *et al.* Real-world outcomes associated with liposomal irinotecan dose reductions in metastatic pancreatic ductal adenocarcinoma. *Future Oncol* 2021; 17: 675–688.
15. Park SJ, Kim H, Shin K, *et al.* Nanoliposomal irinotecan plus fluorouracil and folinic acid as a second-line treatment option in patients with metastatic pancreatic ductal adenocarcinoma: a retrospective cohort study. *BMC Cancer* 2021; 21: 1176.
16. Raj N, Fernandes S, Charyulu NR, *et al.* Postmarket surveillance: a review on key aspects and measures on the effective functioning in the context of the United Kingdom and Canada. *Ther Adv Drug Safety* 2019; 10: 2042098619865413.
17. Schwartz LH, Litière S, de Vries E, *et al.* RECIST 1.1—update and clarification: from the RECIST committee. *Eur J Cancer* 2016; 62: 132–137.
18. Eisenhauer EA, Therasse P, Bogaerts J, *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45: 228–247.

19. National Institutes of Health. *Common Terminology Criteria for Adverse Events (CTCAE)*. National Institutes of Health, U. S. Department of Health and Human Services, 2021.

20. Chiorean EG, Von Hoff DD, Tabernero J, *et al*. Second-line therapy after nab-paclitaxel plus gemcitabine or after gemcitabine for patients with metastatic pancreatic cancer. *Br J Cancer* 2016; 115: e13.

21. Glassman DC, Palmaira RL, Covington CM, *et al*. Nanoliposomal irinotecan with fluorouracil for the treatment of advanced pancreatic cancer, a single institution experience. *BMC Cancer* 2018; 18: 693.

22. Chiu TJ, Su YY, Yang SH, *et al*. Liposomal irinotecan pre-emptive dose reduction in patients with pancreatic ductal adenocarcinoma: 667 patients' experience within a population-based study. *Ther Adv Med Oncol* 2021; 13: 17588359211058255.

23. Scheithauer W, Ramanathan RK, Moore M, *et al*. Dose modification and efficacy of nab-paclitaxel plus gemcitabine vs. Gemcitabine for patients with metastatic pancreatic cancer: phase III MPACT trial. *J Gastrointest Oncol* 2016; 7: 469–478.

24. Ahn DH, Krishna K, Blazer M, *et al*. A modified regimen of biweekly gemcitabine and nab-paclitaxel in patients with metastatic pancreatic cancer is both tolerable and effective: a retrospective analysis. *Ther Adv Med Oncol* 2017; 9: 75–82.

25. Chen L-T, Macarulla T, Blanc J-F, *et al*. Early dose reduction/delay and the efficacy of liposomal irinotecan with fluorouracil and leucovorin in metastatic pancreatic ductal adenocarcinoma (mPDAC): a post hoc analysis of NAPOLI-1. *Pancreatology* 2021; 21: 192–199.

26. Barzi A, Miksad R, Surinach A, *et al*. Real-world dosing patterns and outcomes of patients with metastatic pancreatic cancer treated with a liposomal irinotecan regimen in the United States. *Pancreas* 2020; 49: 193–200.

27. Ueno M, Nakamori S, Sugimori K, *et al*. Nal-IRI+5-FU/LV versus 5-FU/LV in post-gemcitabine metastatic pancreatic cancer: randomized phase 2 trial in Japanese patients. *Cancer Med* 2020; 9: 9396–9408.

28. Park HS, Kang B, Chon HJ, *et al*. Liposomal irinotecan plus fluorouracil/leucovorin versus FOLFIRINOX as the second-line chemotherapy for patients with metastatic pancreatic cancer: a multicenter retrospective study of the Korean Cancer Study Group (KCSG). *ESMO Open* 2021; 6: 100049.

29. Network NCC. *NCCN guidelines version 2.2015 pancreatic adenocarcinoma*. National Comprehensive Cancer Network (NCCN), USA.

30. Pelzer U, Schwaner I, Stieler J, *et al*. Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. *Eur J Cancer* 2011; 47: 1676–1681.

31. Oettle H, Riess H, Stieler JM, *et al*. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. *J Clin Oncol* 2014; 32: 2423–2429.

32. Gill S, Ko Y-J, Cripps C, *et al*. PANCREOX: a randomized phase III study of fluorouracil/leucovorin with or without oxaliplatin for second-line advanced pancreatic cancer in patients who have received gemcitabine-based chemotherapy. *J Clin Oncol* 2016; 34: 3914–3920.

33. Chun JW, Woo SM, Lee SH, *et al*. 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. *Ther Adv Med Oncol* 2022; 14: 17588359221119539.