THERAPEUTIC ADVANCES in
Medical Oncology

Case Series

Real-world effectiveness and safety of second- or third-line pegylated liposomal irinotecan plus 5-fluorouracil and folinic acid in pancreatic ductal adenocarcinoma in Spain

Rafael Álvarez-Gallego, Roberto Pazo-Cid, Borja López de San Vicente, Teresa Macarulla, Eva Martinez, Fernando Garicano, Irene Hernández, Monica Granja, Ismael Ghanem, Joaquina Martinez, Paula Ribera, Roberto Diaz, Jose Ignacio Martin Valadés, Maria Cristina Angeles and Antonio Cubillo

***Abstract*:** Treatment with pegylated nanoliposomal irinotecan (nal-IRI) plus 5-fluorouracil/leucovorin (folinic acid; 5-FU/LV) has demonstrated remarkable efficacy for metastatic pancreatic ductal adenocarcinoma (PDAC) in clinical trials. However, real-world data on the effectiveness of nal-IRI+5-FU/LV is heterogeneous and is lacking in Spain. To assess the effectiveness and safety of nal-IRI+5-FU/LV in real-life PDAC patients in Spain. A multicenter retrospective study was conducted. Patients aged ⩾18 years who had received at least one cycle of nal-IRI+5-FU/LV as second- or third-line therapy for PDAC were included. The primary endpoint was overall survival (OS) from nal-IRI+5-FU/LV treatment initiation and OS from the diagnosis of metastatic disease (metOS). Overall, 200 evaluable patients were included (⩾3 metastatic sites: 22%; liver/lung metastases: 71.5%/36.9%; and Eastern Cooperative Oncology Group 0–1: 87% at nal-IRI+5FU/LV treatment initiation). Patients received a median of four cycles of nal-IRI+5FU/LV for 2.8 months (range 1.4–7.2), and the treatment was received in the second line by 80% of the patients. The median OS was 7.2 months (6- and 12-month OS rates: 58.1% and 28.9%, respectively), with 27.2% of the patients achieving OS ⩾12 months. The median metOS was 17.5 months, with 30.2% of the patients experiencing metOS ⩾ 24 months. The median progression-free survival (PFS) was 3.7 months (6- and 12-month PFS rate: 37.6% and 15.3%, respectively). The disease control rate was 35.5%. The median CA 19-9 levels decreased by at least 50% in 28.2% of the cases during treatment. Overall, 36% of the patients experienced at least one grade 3–4 adverse event during treatment, the most common being diarrhea (42.6%) and asthenia (30.9%). This real-world study shows that treatment with nal-IRI+5-FU/LV for advanced or metastatic PDAC affords benefit in terms of survival, radiological and CA 19-9 response, and PFS comparable to that reported in the clinical trial setting with a manageable safety profile.

Keywords: 5-fluorouracil/folinic acid (5-FU/LV), metastases, pancreatic cancer, pegylated nanoliposomal irinotecan (nal-IRI), real world

Received: 14 April 2024; revised manuscript accepted: 10 December 2024.

Ther Adv Med Oncol

2025, Vol. 17: 1–12

DOI: 10.1177/17588359241309828

Correspondence to:
Rafael Álvarez-Gallego
Centro Integral Oncológico Clara Campal HM CIOCC, Hospital Universitario HM Sanchinarro, C\ Oña Nº10, Madrid 28050, Spain

Facultad HM Hospitales de Ciencias de la Salud, Universidad Camilo José Cela (UCJC), Madrid, Spain
ralvarezgallego@hmhospitales.com

Roberto Pazo-Cid
Hospital Universitario Miguel Servet, Zaragoza, Spain

Borja López de San Vicente
Hospital Universitario de Basurto, Bilbao, Spain

Teresa Macarulla
Vall d'Hebrón Institute of Oncology (VHIO), Hospital Universitario Vall d'Hebrón, Barcelona, Spain

Eva Martinez
Hospital Universitario Marques de Valdecilla, Santander, Spain

Fernando Garicano
Hospital de Galdakao-Usansolo, Galdakao, Spain

Irene Hernández
Complejo Hospitalario de Navarra, Pamplona, Spain

Monica Granja
Hospital Clínico San Carlos, Madrid, Spain

Ismael Ghanem
Hospital La Paz, Madrid, Spain

Joaquina Martinez
Instituto de Investigación Biosanitaria de Granada (ibs.GRANADA), Hospital Universitario Virgen de las Nieves, Granada, Spain

Paula Ribera
Hospital Universitario Parc Tauli, Sabadell, Barcelona, Spain

Roberto Diaz
Hospital Universitario y Politécnico La Fe, Valencia, Spain

Jose Ignacio Martin Valadés
Hospital MD Anderson Cancer Center Madrid, Madrid, Spain

Maria Cristina Angeles
Hospital Universitario San Juan de Alicante, Sant Joan d'Alacant, Alicante, Spain

Antonio Cubillo
Centro Integral Oncológico Clara Campal HM CIOCC, Hospital Universitario HM Sanchinarro, Madrid, Spain

Facultad HM Hospitales de Ciencias de la Salud, Universidad Camilo José Cela (UCJC), Madrid, Spain

Introduction

Pancreatic cancer (PC) is the fourth leading cause of cancer-related death in Europe[1] and the third in Spain in 2022.[2] Pancreatic ductal adenocarcinoma (PDAC), the most frequent type of PC, is associated with a poor prognosis and high mortality mainly due to the advanced stage of the disease at diagnosis—with most patients presenting either locally advanced or metastatic disease (about half of all cases)[2,3]—and because of the limited therapeutic options for advanced PC especially after progression to first-line treatment. The median overall survival (OS) in metastatic PC is around 6 months, and the 5-year survival rate ranges from 0.5% to 9%.[4] Additionally, disease relapses after surgical resection are observed in 75%–80% of all PC patients.[5,6]

Chemotherapy with gemcitabine monotherapy has been the standard of care in advanced PC for many years,[7–9] although its benefits have been mainly related to quality of life and symptom relief.[9,10] The treatment scenario for advanced/metastatic PDAC has changed notably in the last decade. Two active combination chemotherapy regimens, FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin) and gemcitabine in combination with paclitaxel in albumin-stabilized nanoparticle formulation (nab-P/Gem) were introduced in the first-line setting after demonstrating superior efficacy outcomes, including progression-free survival (PFS) and OS benefits, compared to gemcitabine.[11,12] Although these two combination regimens are currently considered the standard first-line treatment for patients with metastatic disease,[13] their use is limited to patients with a good performance status (PS).[7,13] Limited treatment options are available after disease progression to first-line therapy, which highlights the urgent need for effective treatment approaches to improve the outcomes of PC patients after therapy failure.

The multicenter randomized phase III NAPOLI-1 trial demonstrated the efficacy of treatment with nanoliposomal irinotecan (nal-IRI) in combination with 5-fluorouracil and leucovorin (folinic acid) (5-FU/LV) compared to 5-FU/LV alone, in patients with metastatic PDAC (mPDAC) who had experienced unresectable disease progression on gemcitabine-based treatment.[14] Treatment with nal-IRI plus 5-FU/LV showed improvement in multiple key efficacy outcomes, including OS, PFS, time to treatment failure, overall response rate (ORR), and CA 19-9 tumor marker response. The nal-IRI plus 5-FU/LV combination showed a substantial prolongation of OS by 1.9 months compared to the 5-FU/LV arm. These results led to FDA and EMA approval of nal-IRI plus 5-FU/LV, and it is currently recommended as second-line treatment for mPDAC patients previously treated with gemcitabine-based therapy in both the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines.[7,13]

The benefit demonstrated with nal-IRI plus 5FU/LV combination therapy in clinical trials has also been observed in the real-world setting.[15–24] However, most real-world evidence came from single-site experiences involving less than 60 patients,[16,21,23] and the clinical outcomes in these studies are moreover heterogeneous. On the other hand, real-world data on this combination therapy in the second- and third-line setting is lacking in Spain.

The present real-world study aimed to explore and assess the effectiveness of nal-IRI plus 5FU/LV combination therapy in terms of survival in patients with advanced or metastatic PDAC in Spain. We also assessed the results with this combination in terms of multiple effectiveness outcomes, including radiographic and CA 19-9 response, and its safety and tolerability profile when used under routine clinical practice conditions.

Methods

Study design and patients

The NALIRI trial was a multicenter retrospective study conducted in medical oncology departments from 14 hospitals throughout Spain.

The study included consecutive patients aged ⩾18 years and diagnosed with PDAC who had received at least one cycle of nal-IRI plus 5-FU/LV as second- or third-line therapy for PDAC between January 2017 and January 2020. All patients were treated with 60 mg/m^2 nal-IRI and 2400 mg/m^2 of 5FU in 46 h infusion continued every 14-days cycle. Antiemetic prophylaxis and neutropenia prophylaxis were used according to the therapeutic guidelines of each center. The requirement for informed consent from eligible patients was waived for the retrospective collection of data from medical charts.

Independent ethics committees (HM Hospitales CEIm number 226-21.02.1776-GHM) approved the study, which was carried out in accordance with the Declaration of Helsinki guidelines and the applicable national regulatory requirements. The reporting of this study conforms to the ESMO-Grow statement.[25]

The primary endpoint was OS from the initiation of treatment with nal-IRI plus 5-FU/LV, and OS from the diagnosis of metastatic disease (metOS). Secondary endpoints included the survival rates at 2, 6, and 12 months from treatment initiation, PFS and PFS rates at 2, 6, and 12 months, the disease control rate (DCR), characterization of exposure to treatment with nal-IRI plus 5-FU/LV (cycles, treatment modification, and discontinuation), and the incidence of treatment-related adverse events (AEs).

Statistical analysis

A descriptive statistical analysis was performed to describe the demographic and clinical characteristics of the patients at PDAC diagnosis and at nal-IRI plus 5FU/LV treatment initiation; prior treatment for PDAC; and data related to nal-IRI plus 5FU/LV treatment management, modification (dose reduction or delay) and discontinuation. Measures of central tendency and dispersion (mean ± standard deviation, median, and interquartile range (IQR)) were used to report quantitative variables, while counts and percentages were applied to describe qualitative variables.

The ORR was defined as the percentage of patients achieving complete response (CR), and partial response (PR), and DCR was defined as the percentage of patients reaching CR, PR, or stable disease (SD) according to the assessment of the treating oncologist, based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. OS was calculated from nal-IRI plus 5FU/LV treatment initiation to death from any cause, and metOS was calculated from the diagnosis of mPDAC. PFS was calculated from nal-IRI plus 5FU/LV treatment initiation to disease progression or death from any cause. Time-to-event variables were estimated using the Kaplan–Meier method. Patients without disease progression or death were censored at the last follow-up date.

Univariate and multivariate Cox regression analyses of potential factors associated with PFS and metOS were performed. Variables with statistical significance $p < 0.2$ in the univariate analysis were included in a multivariate model using a stepwise selection method. Hazard ratios (HRs) and 95% confidence intervals (CI) were calculated. The covariates assessed as potential independent factors for PFS and metOS in the univariate analysis included the number of metastatic sites, the presence of liver metastases, and the blood neutrophil-to-lymphocyte ratio (NLR) at the start of treatment with nal-IRI plus 5FU/LV, and primary tumor resection.

All AEs occurring while the patients were treated with the nal-IRI plus 5-FU/LV combination were recorded, and the patients experienced grade 2 and grade 3–4 AEs according to the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) version 4.0 during treatment were documented. Statistical analyses were performed using the statistical package for the social sciences (SPSS) version 29 (SPSS Inc., Chicago, IL, USA). This article follows ESMO's recommendations regarding real-world evidence communications (ESMO-GROW).[26]

Results

Study design and patients

From January 2017 to January 2020, a total of 210 patients were enrolled in the study. Ten patients were excluded due to non-compliance with eligibility criteria. Thus, a total of 200 patients were evaluable for effectiveness and safety analysis. The demographic and clinical characteristics of the evaluable patients are described in Table 1. Briefly, most patients (70.5%) were in stage IV at diagnosis of PDAC. The median number of metastatic sites at nal-IRI plus 5FU/LV treatment initiation was 2 (1–2), with 22% of the patients having ⩾3 metastatic sites. The most common metastatic sites were the liver (71.5%), lymph nodes (43.8%) and lung (36.9%). The Eastern Cooperative Oncology Group (ECOG) PS score was 0–1 in 87% of the patients at the time of nal-IRI plus 5FU/LV treatment initiation. The median albumin level at treatment initiation was 38 g/L (IQR 35–41), and the median NLR was 2.6×10^9/L (1.8–5.0). The median CA 19-9 levels were seen to be elevated (>50 U/mL) in nearly 70% of the patients, with a median concentration of 636.9 U/mL (40.8–5257.8) at nal-IRI plus 5FU/LV treatment initiation.

Table 1. Patient demographic and clinical characteristics ($n = 200$).

Characteristic	Value
Sex, *n* (%)	
Men	111 (55.5)
Women	89 (54.5)
TNM disease stage at diagnosis, *n* (%)[a]	
Data not reported	10 (5)
IA/IB	3 (1.5)/3 (1.5)
IIA/IIB	10 (5)/13 (6.5)
III	26 (13)
IV	135 (67.5)
Time since PC diagnosis to metastatic disease, median (IQR)[b] ($n = 67$)	7.19
Clinical and laboratory data at nal-IRI + 5-FU/LV treatment initiation	
ECOG performance status, *n* (%)	
Data not reported	54 (27)
0	7 (3.5)
1	120 (60)
2	17 (8.5)
3[c]	2 (1)
Neutrophil-to-lymphocyte ratio, *n* (%)	121 (60.8)
Neutrophils, median (IQR) (10^9/L)	4.2 (3.2–6.3)
Lymphocytes, median (IQR) (10^9/L)	1.6 (1.0–2.2)
NLR	2.6 (1.8–5.0)
Albumin, *n* (%)	149 (75.3)
Albumin levels, median (IQR) (g/L)	38 (35–41)
CA 19.9, *n* (%) (U/mL)	181 (91.0)
CA 19.9 levels, median (IQR)	636.9 (40.8–5257)
CA 19.9 levels >50 U/mL	128 (69.9)
Histological grade	
G1 or 2	41 (20.5)
G3 or indifference	37 (18.5)
Metastatic sites ($n = 200$)	
0	30 (15.0)
1	62 (31.0)
2	64 (32.0)
3	28 (14.0)
>3	16 (8.0)
Metastases location, *n* (%)	
No metastatic	30 (15)
Liver	123 (61.5)
Lung	62 (31)
Lymph node	74 (37)
Peritoneum	53 (26.5)
Bone	10 (5)

[a]Percentages calculated over 170 patients with at least one metastatic site at the time of nal-IRI + 5-FU/LV treatment initiation in whom data was available.
[b]Median calculated exclusively on the 67 patients with no metastatic disease at baseline.
[c]Patients with ECOG3 candidates for treatment indicated by their oncologist.
ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

Prior treatment

About one-quarter of the patients (47) had received neoadjuvant treatment, with gemcitabine plus nab-paclitaxel (GEM-NabP) being administered in 40 patients (20%) and FOLFIRINOX in 6 patients (3%). Eleven patients (5.5%) received chemotherapy plus radiotherapy in the neoadjuvant setting. Forty-four (22%) patients had undergone pancreatectomy.

Overall, 41 patients (20%) received adjuvant treatment, with 16% of the patients receiving adjuvant GEM-NabP and 8.5% gemcitabine monotherapy (Table 2).

Overall, more than 85% of the patients (174/200) had previously received treatment for metastatic

Table 2. Prior treatment for PDAC management.

Treatment approach	*N* (%)
Primary tumor resection	44 (22.2)
Neoadjuvant treatment	47 (24.5)
Chemotherapy	47 (23.5)
GEM-NabP	40 (20.0)
FOLFIRINOX	6 (3.0)
Other[a]	2(1.0)
Radiotherapy	11 (5.5)
Chemotherapy and radiotherapy[b]	11 (5.5)
Adjuvant treatment	41 (20.5)
GEM-NabP	16 (8.0)
Gemcitabine plus capecitabine	7 (3.5)
Gemcitabine only	17 (8.5)
FOLFIRINOX	1 (0.5)
Treatment for metastatic disease	
GEM-NabP	126 (63.0)
5-FU + oxaliplatin	32 (23.0)
Gemcitabine monotherapy	8 (4.0)
5-FU + irinotecan	8 (4.0)

[a]Therapies used in less than three patients each.
[b]Some patients were treated with chemotherapy followed by chemo-radiotherapy.
FOLFIRINOX, 5-FU/LV, irinotecan and oxaliplatin; GEM-NabP, gemcitabine plus nab-paclitaxel; PDAC, pancreatic ductal adenocarcinoma.

disease. Of these, 76% were administered gemcitabine-based combinations, with 63% of the patients receiving GEM-NabP (Table 2).

Treatment with nal-IRI plus 5FU/LV

The median time from diagnosis to nal-IRI plus 5FU/LV treatment initiation was 10.5 months (6.9–17.6), and the median time from metastatic disease to treatment initiation was 8.3 months (4.4–13.2). Overall, 80% of the patients had received nal-IRI plus 5FU/LV as second-line treatment (Table 3).

The patients had received a median of four cycles of nal-IRI plus 5FU/LV, and the median duration of treatment was 2.8 months (1.4–7.2). The main reason for treatment discontinuation was disease progression (68%). Discontinuation due to toxicity occurred in 13 patients (6.5%; Table 3).

Dose reduction was required in 60 patients (30%), and of these, 21.7% experienced a single dose reduction while 66.7% needed two dose reductions. The occurrence of AEs was the reason for dose reduction in most patients (82.4%). Dose delay occurred in 52 patients (26%), mainly due to AEs (82.7%).

Effectiveness outcomes

The DCR with nal-IRI plus 5FU/LV was 35.0% (95% CI: 28.4–42.1) and the ORR was 15.5%. Only one patient achieved CR (0.5%); 30 patients (15%) reached PR; and 39 patients (19.5%) had SD as the best response to treatment (Table 4). The DCR among patients who had previously received irinotecan for PDAC ($n=8$) was 34.8% (95% CI: 16.4–57.3).

The median OS was 7.2 months (95% CI: 6.2–8.2), and the estimated OS rate at 2, 6, and 12 months was 87.2%, 58.1%, and 28.9%, respectively (Figure 1(a) and Table 4). Overall, 53 patients (27.2%) achieved an OS of at least 12 months. With a median follow-up of 1.4 years (0.9–2.2) from the diagnosis of metastatic disease, the median metOS was 17.5 months (Figure 1(b) and Table 4), with patients 30.2% of patients experiencing a metOS $\geqslant$24 months. Overall, 97.9% of the patients (189/193) had died at the time of analysis. The median PFS was 3.7 months (95% CI: 2.6–4.8), and the estimated PFS rate at 2, 6, and 12 months was 71.7%, 37.6%, and 15.3%, respectively (Figure 1(c) and Table 4).

The median CA 19-9 levels, which were elevated (>50 U/mL) in nearly 70% of the patients at nal-IRI plus 5FU/LV treatment initiation, decreased by at least 50% in 28.2% of the patients during treatment. The median time from treatment initiation to the >50% decrease in CA 19-9 levels was 8 weeks (Table 4).

The univariate Cox regression analysis showed that of covariates assessed, the number of metastatic sites (HR: 1.15; 95% CI: 1.01–1.31; $p=0.037$) and primary tumor resection (HR: 1.69; 95% CI: 0.48–0.99; $p=0.04$) were

Table 3. Treatment with nal-IRI plus 5-FU/LV.

Treatment administration	Value
Line of treatment, *n* (%) (*n* = 200)	
First line after disease progression following neoadjuvant treatment[a]	2 (1.0)
First line after disease progression following adjuvant treatment[a]	12 (6.0)
Second line	160 (80.0)
Third-line	26 (13.0)
Treatment initiation, median (IQR) (months)	
Time since PDAC diagnosis to treatment initiation (*n* = 200)	10.5 (6.9–17.6)
Time since diagnosis of metastatic disease to treatment initiation (*n* = 169)	8.3 (4.4–13.2)
Time since last treatment based on irinotecan to treatment inhiation (*n* = 6)	7 (1.8–11.3)
Treatment exposure	
Number of cycles administered, median (IQR)	4.0 (1.0-8.0)
Treatment duration, median (IQR) (months)	2.8 (1.4-7.2)
Treatment modification, *n* (%) (*n* = 200)	76 (38)
Dose reduction, *n* (%)	
Patients requiring dose reduction	60 (30.0)
Total number of dose reductions	125
Number of dose reductions per patient (*n* = 60)	
1	13 (21.7)
2	40 (66.7)
⩾3	7 (11.7)
Reason for dose reduction (*n* = 125)	
Toxicity	103 (82.4)
Patient health status deterioration	9 (7.2)
Physician decision	7 (5.6)
Other	6 (4.8)
Dose delay	
Patients requiring dose delay, *n* (%)	52 (26.0)
Time of dose delay, median (IQR) (*n* = 51)	2.0 (1.0–2.0)
Reason for dose delay, *n* (%) (*n* = 52)	
Toxicity	43 (82.7)
Patient health status deterioration	3 (5.8)
Physician decision	1 (1.9)
Other	5 (9.6)
Treatment discontinuation	
Reason, *n* (%)	
Disease progression	136 (68.0)
Patient health status deterioration	23 (11.5)
Death	17 (8.5)
Toxicity	13 (6.5)
Other	8 (4.0)

[a]Patients with progression under neoadjuvant or adjuvant treatment.
IQR, interquartile range; PDAC, pancreatic ductal adenocarcinoma.

significantly associated with OS. However, these factors were not found to be significantly associated with OS in any multivariate model. Primary tumor resection was also significantly associated with PFS in the univariate Cox regression analysis, though an optimal multivariate model was likewise not obtained for PFS (Supplemental Table 1).

Overall, 78.5% of the patients (62/79) maintained their ECOG PS score from baseline to cycle 2 of nal-IRI plus 5FU/LV treatment and 80% had an ECOG PS score of 0–1 at cycle 6 (Supplemental Table 2).

Table 4. Effectiveness outcomes.

Endpoint	Value
Best response, *n* (%)	
Complete response	1 (0.5)
Partial response	30 (15.0)
Stable disease	40 (20)
Progressive disease	98 (49.0)
Not evaluable	32 (16.0)
Number of cycles to best response achievement, median (IQR)	5.0 (3.0–6.0)
ORR, *n* (%) (95% CI)	15.5 (28.4–42.1)
DCR, *n* (%) (95% CI)	3 35.0 (28.4–42.1)
CA 19.19 response	
>50% reduction, *n* (%) (*n* = 156)	44 (28.2)
Time to 50% reduction, *n* (%) (weeks) (*n* = 40)	8.0 (4.5–16.0)
Progression-free survival	
Median (95% CI) (months)	3.7 (2.6–4.8)
At 2 months, *n* (%) (95% CI)	71.7 (65.4–78.0)
At 6 months, *n* (%) (95% CI)	37.6 (30.9–44.4)
At 12 months, *n* (%) (95% CI)	15.3 (10.2–20.3)
OS	
Median (95% CI) (months)	7.2 (6.2–8.2)
At 2 months, *n* (%) (95% CI)	87.2 (82.5–91.9)
At 6 months, *n* (%) (95% CI)	58.1 (51.1–65.0)
At 12 months, *n* (%) (95% CI)	28.9 (22.5–35.4)
⩾12 months, *n* (%) (*n* = 195)	53 (27.2)
OS since metastatic disease	
Median (95% CI) (months)	17.5 (15.2–19.7)
⩾24 months, *n* (%) (*n* = 192)	58 (30.2)

CI, confidence interval; DCR, disease control rate; IQR, interquartile range; ORR, overall response rate; OS, overall survival.

Safety

A total of 226 grade 2 AEs occurred in 61.4% of the patients (116/189) during treatment with nal-IRI plus 5FU/LV, with 44% of them experiencing only one AE. The most common treatment-related grade 2 AEs (reported in >15% of the patients) were asthenia (50%), diarrhea (42.2%) and nausea (18.1%). Overall, 36% of the patients (68/189) experienced at least one grade 3–4 AE related to nal-IRI plus 5FU/LV treatment. A total of 97 treatment-related grade 3–4 AEs were reported in 68 patients, with 69.1% of these patients experiencing only one AE. The most common treatment-related grade 3–4 AEs (reported in >10% of the patients) were diarrhea (42.6%), asthenia (30.9%), emesis (11.8%), and neutropenia (13.2%; Table 5).

Discussion

In this real-world study, we evaluated the effectiveness and safety of treatment with nal-IRI plus 5FU/LV as second- or third-line therapy for locally advanced or metastatic PDAC. Our study population is heterogeneous and reflects the reality of patients treated in the usual clinic setting (worse PS, not patient selection) but still, our findings confirm the efficacy results obtained with nal-IRI plus 5FU/LV in the clinical trial setting and support the survival benefit of this combination in real-life patients. This heterogeneous population includes two patients with ECOG3 in relation to pain due to tumor involvement who would have been unable to participate in a clinical trial but were considered by their oncologist as an exceptional case for treatment. Additionally, treatment with nal-IRI plus 5FU/LV showed an acceptable and generally manageable safety profile in the real-world setting.

The NAPOLI-1 trial demonstrated that the combination nal-IRI plus 5-FU/LV is an effective second-line treatment option affording a significant extension of survival in patients with mPDAC who progress on gemcitabine-based therapy,[14] showing a median survival of 6.1 months in patients receiving nal-IRI plus 5FU/LV compared to 4.2 months in those treated with 5-FU/LV alone. We found the median OS of 7.2 months observed in this real-world study to be consistent or even slightly longer than that reported in the NAPOLI-1 trial.[14] The high 12-month survival rate of 28.9% achieved in our real-world analysis is also in line with that reported in the NAPOLI-1 trial (26%). The median PFS observed in our

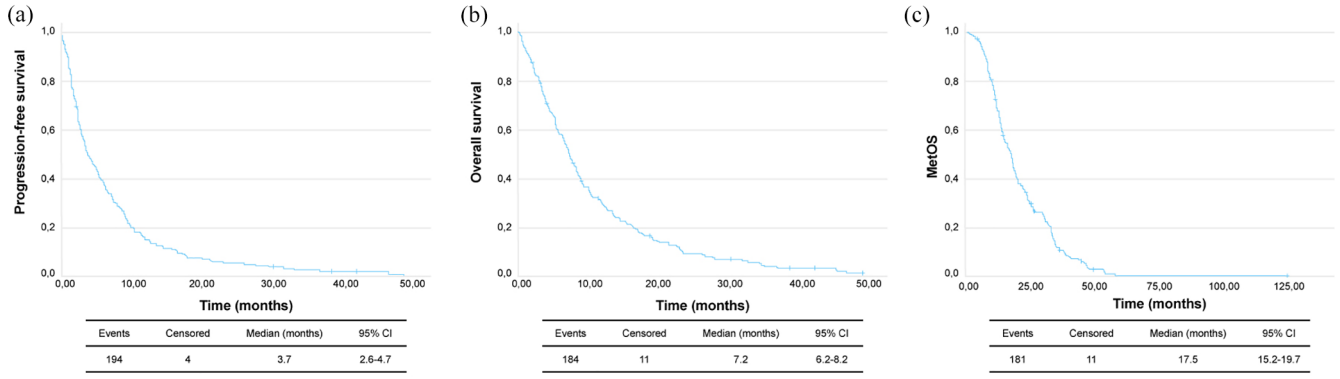

Figure 1. Kaplan–Meier curves for progression-free survival (a), overall survival from the initiation of treatment with nal-IRI plus 5-FU/LV (b), and overall survival from the diagnosis of metastatic disease (metOS).

Table 5. Adverse events during treatment with nal-IRI plus 5-FU/LV.

Adverse events	Grade 2, *N* (%)	Grade 3–4, *N* (%)
Non-hematological		
Asthenia	58 (50.0)	21 (30.9)
Diarrhea	49 (42.2)	29 (42.6)
Anorexia	23 (19.8)	3 (4.4)
Nausea	21 (18.1)	0 (0.0)
Neuropathy	14 (12.1)	4 (5.9)
Mucositis	12 (10.3)	1 (1.5)
Emesis	11 (9.5)	8 (11.8)
Vomiting	9 (7.8)	0 (0.0)
Fever	1 (0.9)	2 (2.9)
Hepatotoxicity	1 (0.9)	2 (2.9)
Hematological		
Neutropenia	8 (6.9)	9 (13.2)
Febrile neutropenia	0 (0.0)	2 (2.9)
Anemia	3 (2.6)	3 (4.4)
Plateletopenia	3 (2.6)	4 (5.9)
Leukopenia	1 (0.9)	0 (0.0)
Bleeding	0 (0.0)	1 (1.5)

5-FU/LV, 5-fluorouracil/folinic acid.

series (3.7 months) was likewise similar to that obtained in the NAPOLI-1 trial (3.1 months). This real-world analysis also showed the nal-IRI plus 5-FU/LV combination to afford notable effectiveness in terms of radiographic response (15.5%), in line with the findings from the

NAPOLI-1 study (17%). However, comparison with the NAPOLI-1 trial is purely descriptive and limited, due to differences in patient and disease characteristics, including disease stage and line of therapy. Although the line of therapy in which nal-IRI plus 5-FU/LV was received was not selected in our study, we found that 80% of the patients received this combination as second-line therapy according to European guideline recommendations.[13] Prior real-world studies have shown an increased survival benefit when treatment with nal-IRI plus 5-FU/LV was administered in the second-line setting.[16,20,23] However, compared to the NAPOLI-1 trial, we observed similar effectiveness of this combination in our study where only 13% of the patients received this combination as third-line treatment.

On considering CA 19-9 treatment response, a reduction of the baseline levels by ⩾50% was observed in 28% of the patients during treatment with nal-IRI plus 5FU/LV, which is in line with the NAPOLI-1 trial (29%).[14]

Real-world outcome data on PFS and OS with nal-IRI plus 5FU/LV are heterogeneous, mainly due to differences in PS, disease stage, lines of therapy for PDAC management, and prior therapies (i.e., gemcitabine-based combinations) found in unselected, real-world patients. The outcome data in this retrospective study are in line with previously reported real-world survival data[16,18,21,23] which are mainly derived from single-site retrospective studies including approximately 50 patients,[16,21,23] with a similar proportion of patients receiving nal-IRI + 5-FU/LV as second-line treatment.[16,18,21] A single-site retrospective experience in Germany has recently reported an OS of 9.33 months in patients with advanced or metastatic disease who received second- or third-line treatment with nal-IRI + 5-FU/LV,[21] although this study was carried out in 29 patients with heterogeneous baseline characteristics. A noteworthy observation is that our effectiveness outcome data referred to PFS and OS are in line with those previously recorded in a large Italian real-world analysis of 296 patients treated with nal-IRI + 5-FU/LV, mainly in second line (72%), from June 2016 and November 2018, reporting an OS and PFS of 7.1 and 3.2 months, respectively.[18]

The high 12-month survival rate of 28.9% achieved in our real-world analysis is also in line with that reported in the NAPOLI-1 trial (26%). These findings suggest that there is a subpopulation of patients that obtain a superior survival advantage from treatment with nal-IRI plus 5-FU/LV. It is therefore important to identify factors associated with long-term survival that will enable the identification of the subpopulation of patients who may benefit most from treatment with nal-IRI plus 5-FU/LV, considering the poor prognosis of patients with mPDAC. A post hoc analysis of the NAPOLI-1 trial[25] showed younger age, more fit patients without liver metastases, and lower CA19-9 levels as characteristics associated with long-term survival, defined as survival ⩾1 year. In our study, we found a greater metastatic burden to be significantly associated with poorer OS from nal-IRI plus 5-FU/LV treatment initiation in the bivariate analyses. Additionally, the presence of liver metastases showed a trend toward shorter OS according to the bivariate analysis. However, primary tumor surgical resection showed a significant association with longer OS. A well-known prognostic marker such as NLR was not associated with OS in our analysis. However, we were unable to obtain an optimal multivariate analysis to identify characteristics independently associated with OS possibly due to the limited patients with primary tumor surgery or the need to include more patients in the analysis. Further research will be required to confirm the characteristics of long-term survivors with nal-IRI plus 5-FU/LV. Of note is the fact that our results showed that approximately 30% of the patients achieved a metOS of at least 24 months. However, we were not able to assess the characteristics associated with such long survival, due to the limited sample size available for analysis.

The NAPOLI-1 trial showed nal-IRI plus 5-FU/LV to be an effective second-line treatment option with a manageable safety profile in patients who progressed on gemcitabine-based therapy.[14] This real-world study showed a similar tolerability profile of this combination when used under clinical practice conditions. No new safety concerns were detected. In the NAPOLI-1 trial, the most common grade 3 or 4 AEs in the group receiving triplet chemotherapy were neutropenia (27%), diarrhea (13%), vomiting (11%), and fatigue (14%). Our real-world study revealed an incidence of gastrointestinal toxicities comparable to that reported in the NAPOLI-1 trial, though the incidence of each AE was lower in our series, with none of the patients experiencing vomiting. However, we observed a lower rate of neutropenia (13%). The difference in the incidence of

each AE may be due to the retrospective nature of our study, with safety data, therefore, coming from routine clinical practice, where less strict collection of AEs is performed compared to clinical trials. Furthermore, we observed a lower incidence of treatment discontinuation due to AEs (6.5%) compared to that reported in the NAPOLI-1 trial (13%).[14]

Some limitations must be acknowledged when interpreting the findings of this real-world study. In effect, this was a retrospective study where data were entirely obtained from the patient medical charts, in which clinical information is recorded for non-research purposes in the context of routine clinical practice. Missing clinical and safety data may therefore occur. Nevertheless, to our knowledge, with a study population of 200 patients, this is one of the most extensive and updated series providing real-world evidence and valuable insights on the effectiveness and tolerability of nal-IRI plus 5-FU/LV in terms of treatment response and clinical outcomes in patients with locally advanced or metastatic PDAC receiving this approach as second- or third-line treatment. This is therefore particularly interesting considering the urgent need for effective treatment approaches to improve the outcomes of patients with PC.

Conclusion

This real-world study supports the survival benefit of treatment with nal-IRI plus 5-FU/LV for advanced or metastatic PDAC previously demonstrated in the NAPOLI-1 trial. This combination also affords radiological and CA 19-9 responses and PFS figures similar to those observed in the randomized clinical trial setting. Additionally, the present analysis suggests that nal-IRI plus 5-FU/LV has a manageable safety profile when administered under routine clinical practice conditions.

Declarations

Ethics approval and consent to participate

Independent ethics committees approved the study (HM Hospitales CEIm number 226-21.02.1776-GHM) approved the study which was carried out in accordance with the Declaration of Helsinki guidelines and the applicable national regulatory requirements. The requirement for informed consent from eligible patients was waived for the retrospective collection of data from medical charts.

Consent for publication

Not applicable.

Author contributions

Rafael Álvarez-Gallego: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Validation; Writing – original draft; Writing – review & editing.

Roberto Pazo-Cid: Conceptualization; Investigation; Supervision; Writing – review & editing.

Borja López de San Vicente: Conceptualization; Investigation; Supervision; Writing – review & editing.

Teresa Macarulla: Conceptualization; Investigation; Supervision; Writing – review & editing.

Eva Martinez: Conceptualization; Investigation; Supervision; Writing – review & editing.

Fernando Garicano: Conceptualization; Investigation; Supervision; Writing – review & editing.

Irene Hernández: Conceptualization; Investigation; Supervision; Writing – review & editing.

Monica Granja: Conceptualization; Investigation; Supervision; Writing – review & editing.

Ismael Ghanem: Conceptualization; Investigation; Supervision; Writing – review & editing.

Joaquina Martinez: Conceptualization; Investigation; Supervision; Writing – review & editing.

Paula Ribera: Conceptualization; Investigation; Supervision; Writing – review & editing.

Roberto Diaz: Conceptualization; Investigation; Supervision; Writing – review & editing.

Jose Ignacio Martin Valadés: Conceptualization; Investigation; Supervision; Writing – review & editing.

Maria Cristina Angeles: Conceptualization; Investigation; Supervision; Writing – review & editing.

Antonio Cubillo: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project

administration; Supervision; Validation; Writing – review & editing.

Acknowledgements

The authors would like to acknowledge the NALIRI study investigators for their valuable contribution to the study. We also thank the Fundación HM for supporting the study. Medical writing and editorial support were provided by Evidenze Health España S.L (Scientific Advisory and Medical Writing Department; Clinical Research Unit), which was funded by Laboratorios Servier.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Fundación HM through a grant provided by Laboratorios Servier S.L.

Competing interests

This work received funding from Laboratorios Servier S.L. R.A.-G. has received consultancy and speaker honoraria from Servier and consultancy honoraria from AstraZeneca.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ORCID iDs

Rafael Álvarez-Gallego https://orcid.org/0000-0002-3167-8039

Jose Ignacio Martin Valadés https://orcid.org/0000-0001-7720-8713

Supplemental material

Supplemental material for this article is available online.

References

1. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer* 2018; 103: 356–387.
2. Las cifras del cáncer en España 2024, https://seom.org/images/publicaciones/informes-seom-de-evaluacion-de-farmacos/LAS_CIFRAS_2024.pdf
3. McGuigan A, Kelly P, Turkington RC, et al. Pancreatic cancer: a review of clinical diagnosis, epidemiology, treatment and outcomes. *World J Gastroenterol* 2018; 24: 4846–4861.
4. Carrato A, Falcone A, Ducreux M, et al. A systematic review of the burden of pancreatic cancer in Europe: real-world impact on survival, quality of life and costs. *J Gastrointest Cancer* 2015; 46: 201–211.
5. Conroy T, Castan F, Lopez A, et al. Five-year outcomes of FOLFIRINOX vs gemcitabine as adjuvant therapy for pancreatic cancer: a randomized clinical trial. *JAMA Oncol* 2022; 8: 1571–1578.
6. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. *CA Cancer J Clin* 2022; 72: 7–33.
7. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. *Pancreatic adenocarcinoma. Version 2*. 2023.
8. Sohal DPS, Kennedy EB, Cinar P, et al. Metastatic pancreatic cancer: ASCO Guideline Update. *J Clin Oncol* 2020; 38: 3217–3230.
9. Gómez-España MA, Montes AF, Garcia-Carbonero R, et al. SEOM clinical guidelines for pancreatic and biliary tract cancer (2020). *Clin Transl Oncol* 2021; 23: 988–1000.
10. Burris HA, III, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997; 15: 2403–2413.
11. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; 364: 1817–1825.
12. 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.
13. Conroy T, Pfeiffer P, Vilgrain V, et al. Pancreatic cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2023; 34: 987–1002.
14. Wang-Gillam A, Li CP, 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.
15. 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.

16. 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.
17. Yoo C, Im HS, Kim KP, et al. Real-world efficacy and safety of liposomal irinotecan plus fluorouracil/leucovorin in patients with metastatic pancreatic adenocarcinoma: a study by the Korean Cancer Study Group. *Ther Adv Med Oncol* 2019; 11: 1758835919871126.
18. Procaccio L, Merz V, Fasano M, et al. The role of nanoliposomal irinotecan plus fluorouracil/leucovorin in the continuum of care of patients with metastatic pancreatic ductal adenocarcinoma. *Cancer Med* 2023;12: 14337–14345.
19. Su YY, Chiang NJ, Tsai HJ, et al. The impact of liposomal irinotecan on the treatment of advanced pancreatic adenocarcinoma: real-world experience in a Taiwanese Cohort. *Sci Rep* 2020; 10: 7420.
20. 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.
21. 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.
22. 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.
23. Verbruggen L, Verheggen L, Vanhoutte G, et al. 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. *Ther Adv Med Oncol* 2023; 15: 17588359231181500.
24. Möhring C, Frontado Graffe FJ, Bartels A, et al. Second-line and third-line therapy with nanoliposomal irinotecan (nal-IRI) in pancreatic cancer: a single-center experience and review of literature. *J Gastrointest Oncol* 2023; 14: 352–365.
25. 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.
26. Castelo-Branco L, Pellat A, Martins-Branco D, et al. ESMO Guidance for Reporting Oncology real-World evidence (GROW). *Ann Oncol* 2023; 34: 1097–1112.