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ORIGINAL ARTICLE

Second-line 5-FU plus nanoliposomal irinotecan versus FOLFOX/XELOX in metastatic pancreatic cancer after gemcitabine—nab-paclitaxel failure: a propensity score-matched analysis

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Background: There is limited evidence comparing second-line therapies following gemcitabine plus nab-paclitaxel (GemNab) in metastatic pancreatic ductal adenocarcinoma (PDAC). This study aimed to compare the effectiveness and safety of 5-fluorouracil plus nanoliposomal irinotecan (5-FU + Nal-IRI) versus oxaliplatin-based regimens (FOLFOX/XELOX) in this setting.

Patients and methods: We retrospectively analyzed 445 patients with metastatic PDAC progressing after first-line GemNab, treated across 12 centers in Italy and Asia (2014-2024). Patients received either 5-FU + Nal-IRI ($n = 180$) or FOLFOX/XELOX ($n = 265$) as second-line therapy. The primary endpoint was overall survival (OS); secondary endpoints included progression-free survival (PFS), overall response rate (ORR), and safety. Exact propensity score matching was carried out to reduce baseline imbalances.

Results: In the matched cohort, median OS was 7.2 months [95% confidence interval (CI) 5.8-8.4 months] for 5-FU + Nal-IRI and 5.8 months (95% CI 4.1-6.8 months) for FOLFOX/XELOX [hazard ratio (HR) 0.74, 95% CI 0.58-0.95, $P = 0.015$], and median PFS was 3.0 months (95% CI 2.5-3.6 months) versus 2.5 months (95% CI 2.2-2.9 months), respectively (HR 0.75, 95% CI 0.61-0.91, $P = 0.0048$). ORR was similar (9% versus 10%, $P = 0.79$). Grade 3-4 adverse events were more frequent with 5-FU + Nal-IRI (31.1% versus 9.4%), particularly anemia (13.9% versus 1.7%) and diarrhea (5.6% versus 1.2%). FOLFOX/XELOX was associated with higher rates of any-grade thrombocytopenia and peripheral neuropathy.

Conclusions: 5-FU + Nal-IRI showed a modest yet statistically significant survival advantage compared with FOLFOX/XELOX in patients with metastatic PDAC previously treated with GemNab, despite being associated with a higher incidence of adverse events. None the less, the selection of second-line therapy should be guided by a balanced evaluation of both efficacy and toxicity profiles.

Key words: pancreatic cancer, second-line therapy, nanoliposomal irinotecan, oxaliplatin

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a major cause of cancer-related mortality in Europe, with ∼140 000 new cases and 132 000 deaths reported in 2020.[1,2]

Its incidence is progressively increasing, particularly in countries with a high Human Development Index,

with an annual rise of 0.5% since 2010 in the United States.[3,4]

Approximately 80% of PDAC cases are diagnosed at a locally advanced or metastatic stage, and chemotherapy is the only treatment that has demonstrated a survival benefit.[5-7] The most commonly used first-line treatments for advanced PDAC patients include fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX), as well as the combination of gemcitabine and nab-paclitaxel (GemNab), both of which have shown superior overall survival (OS) compared with gemcitabine monotherapy in randomized clinical trials.[8,9]

More recently, the NAPOLI-3 trial[10] demonstrated that the combination of liposomal irinotecan, fluorouracil, leucovorin, and oxaliplatin (NALIRIFOX) provides superior OS compared with GemNab, leading to its approval by the United States Food and Drug Administration and the European Medicines Agency.

However, despite the availability of more effective regimens, GemNab remains one of the most widely used first-line treatments worldwide due to its more manageable toxicity profile and reduced spectrum of adverse events.[11,12]

Following disease progression after a gemcitabine-based first-line treatment, two therapeutic options have emerged: the phase III NAPOLI-1 trial showed that the combination of liposomal irinotecan, fluorouracil, and leucovorin was superior in terms of OS compared with fluorouracil and leucovorin alone.[13] Similarly, the CONKO-003 trial demonstrated that the combination of oxaliplatin, fluorouracil, and leucovorin (OFF regimen) improved OS compared with fluorouracil and leucovorin alone.[14] However, this benefit was not confirmed in the PANCREOX trial, another phase III randomized study comparing oxaliplatin and fluorouracil (as the FOLFOX regimen) with fluorouracil monotherapy.[15]

In these trials, most enrolled patients had received gemcitabine monotherapy as their first-line treatment, and only limited retrospective data are available regarding the efficacy of these regimens following first-line GemNab.[16-18]

To date, no randomized prospective trials have directly compared oxaliplatin-based and liposomal irinotecan-based therapies in this setting. In the absence of prospective comparative studies, we conducted a propensity score-matched analysis to compare these two treatment strategies following progression on GemNab.

PATIENTS AND METHODS

Patients with metastatic pancreatic adenocarcinoma who had progressed after a first-line combination of GemNab were enrolled across 12 centers both in Italy and in Asia (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105874). The patients could have received one of two second-line treatments: the combination of leucovorin, 5-fluorouracil and nanoliposomal irinotecan (5-FU + Nal-IRI) or the combination of 5-FU or capecitabine and oxaliplatin (FOLFOX/XELOX). The study was conducted in accordance with the Declaration of Helsinki. It received approval from the ethics committees of the following institutions: Fondazione Policlinico Gemelli (No. 6723-2024), Chang Gung Memorial Hospital (No. 202100783B0), China Medical University Hospital (No. CMUH109-REC2-176), National Cheng Kung University Hospital (No. A-ER-112-215), Kaohsiung Medical University Hospital (No. KMUHIRB-E(I)-20210150), and Taipei Veterans General Hospital (No. 2021-08-001AC).

The primary endpoint of the study was OS, defined as the time from the date of second line's start to the date of death from any cause (living patients were censored at last follow-up when the patient was known to be alive). Secondary endpoints included progression-free survival (PFS), defined as the time from the start of the second-line treatment to first evidence of disease progression or death from any cause, whichever occurred first, investigator-assessed overall response rate (ORR) according to RECIST criteria v1.1,[19] and toxicity. Safety data were obtained from patients' electronic medical records and routinely documented during follow-up visits according to each institution's standard clinical practice. Adverse events were classified and graded using the Common Terminology Criteria for Adverse Events, version 5.0.[20]

Qualitative variables were evaluated using the χ^2 test or Fisher's exact test and continuous variables using the Mann—Whitney test when appropriate to compare clinical and molecular baseline characteristics among treatment groups. Survival curves were estimated using the Kaplan—Meier method and compared with the log-rank test. Hazard ratio (HRs) with 95% confidence intervals (CIs) were estimated with the Cox proportional hazards model.

To reduce confounding in the estimation of treatment effects on OS and PFS, we used a propensity score analysis. Exact matching was carried out pairing patients 1 : 1 based on seven key clinical and demographic covariates such as age, number of metastatic sites, gender, site of primary tumor, metachronous disease, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and duration of first-line treatment. Covariate balance was assessed through standardized mean differences (<0.1 for all variables) and density plots (Supplementary Figures S1 and S2, available at https://doi.org/10.1016/j.esmoop.2025.105874). Survival analysis was conducted using a weighted Cox proportional hazards model, estimating the marginal HR between treatment groups. Robust standard errors were calculated to account for weighting and the matched data structure. Median survival times were estimated using the weighted Kaplan—Meier method, and corresponding 95% CIs were obtained through bootstrapping (1000 replicates). All tests were two-sided; P values <0.05 were considered statistically significant. All analyses were carried out in R (version 4.5.0), utilizing the WeightIt, MatchIT, survival, boot, and survminer packages, and SAS 9.4.

RESULTS

Patients' characteristics

Patients fulfilling the inclusion criteria were enrolled from 12 centers across Italy and Asia between June 2014 and

June 2024. A total of 445 patients were included in the analysis: 180 received 5-FU + Nal-IRI and 265 received FOLFOX or XELOX as second-line treatment following first-line GemNab (Figure 1).

Baseline characteristics were generally well balanced between treatment arms. However, patients in the 5-FU + Nal-IRI group were significantly younger, with a median age of 63.0 years (range 36-81 years) compared with 68.0 years (range 32-85 years) in the FOLFOX/XELOX group ($P < 0.0001$). Consistently, a higher proportion of patients were younger than 70 years of age in the 5-FU + Nal-IRI group (72.8%) compared with the FOLFOX/XELOX group (54.3%) ($P < 0.0001$). Most patients presented with synchronous (<6 months) metastases at diagnosis (78.9% in the 5-FU + Nal-IRI group versus 84.5% in the FOLFOX/XELOX group; $P = 0.1265$), and the majority had not undergone primary tumor resection (78.3% and 81.5%, respectively; $P = 0.4090$).

BRCA1/2 mutation status was missing in 118/180 (65.6%) patients in the 5-FU + Nal-IRI group and in 112/265 (42.3%) in the FOLFOX/XELOX group; among those with available data, BRCA mutations were detected in 3.2% of patients treated with 5-FU + Nal-IRI and 6.5% of those treated with FOLFOX/XELOX ($P = 0.5156$). A response to first-line therapy was observed in 27.8% and 24.2% of patients in the 5-FU + Nal-IRI and FOLFOX/XELOX groups, respectively ($P = 0.3897$). Approximately half of the patients in both groups had received first-line treatment for more than 6 months (52.8% versus 54.3%, $P = 0.74$).

At the beginning of second-line therapy, 40.0% of patients in the 5-FU + Nal-IRI group and 35.1% in the FOLFOX/XELOX group had a single metastatic site ($P = 0.2930$). Liver-only disease was present in 24.4% and 20.0% of patients, respectively ($P = 0.2651$). Baseline characteristics are detailed in Table 1.

Second-line treatment activity and effectiveness

At data cut-off, objective responses were observed in 17 out of 180 patients (9%, 95% CI 5% to 14%) in the 5-FU + Nal-IRI group and in 27 out of 265 (10%, 95% CI 7% to 14%) in the FOLFOX/XELOX group (odds ratio 0.92, 95% CI 0.49-1.75, $P = 0.79$).

After a median follow-up of 19.6 months (95% CI 16.1-90.2 months), median PFS (mPFS) in the unmatched population was 3.0 months (95% CI 2.6-3.7 months) for 5-FU + Nal-IRI and 2.7 months (95% CI 2.5-2.9 months) for FOLFOX/XELOX (HR 0.85, 95% CI 0.70-1.04, $P = 0.109$). Median OS (mOS) was 7.5 months (95% CI 6.1-8.9 months) in the 5-FU + Nal-IRI group and 6.1 months (95% CI 5.3-7.0 months) in the FOLFOX/XELOX group (HR 0.84, 95% CI 0.67-1.05, $P = 0.116$) (Supplementary Figure S3A and B, available at https://doi.org/10.1016/j.esmoop.2025.105874). To minimize potential baseline imbalances, exact propensity score matching was carried out. Matching was based on age (<70 versus ≥70 years), sex, ECOG PS (0 versus 1-3), primary tumor location (head versus body/tail), timing of

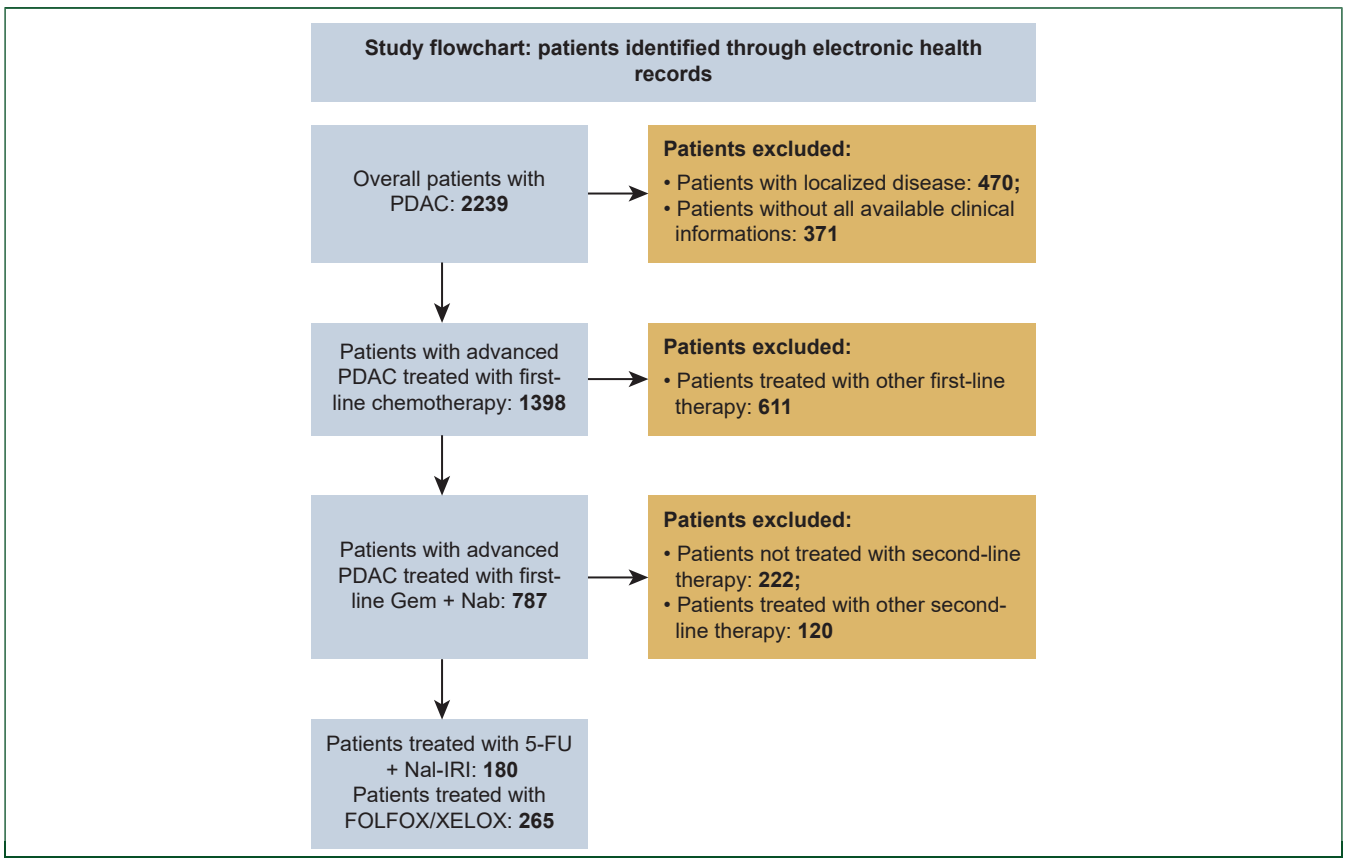

Figure 1. Study flow diagram indicating the number of patients initially screened, excluded, and included in the study.
5-FU, 5-fluorouracil; Gem, gemcitabine; Nab; nab-paclitaxel; Nal-IRI, nanoliposomal irinotecan; PDAC, pancreatic ductal adenocarcinoma.

Table 1. Characteristics of the two treatment groups

	Treatment 5-FU + Nal-IRI (*N* = 180)	FOLFOX/XELOX (*N* = 265)	*P* value
Age, years			<0.0001[a]
Median	63.0	68.0	
Range	36.0-81.0	32.0-85.0	
Age, groups, *n* (%)			<0.0001[b]
<70 years	131 (72.8)	144 (54.3)	
≥70 years	49 (27.2)	121 (45.7)	
Gender, *n* (%)			0.0839[b]
Female	74 (41.1)	131 (49.4)	
Male	106 (58.9)	134 (50.6)	
Primary tumor site, *n* (%)			0.0766[b]
Body_tail	77 (42.8)	136 (51.3)	
Head	103 (57.2)	129 (48.7)	
Primary resected, *n* (%)	39 (21.7)	49 (18.5)	0.4090[b]
Type of metastases, *n* (%)			0.1265[b]
Metachronous	38 (21.1)	41 (15.5)	
Synchronous	142 (78.9)	224 (84.5)	
BRCA mutation, *n* (%)			0.5156[c]
No	60 (96.8)	143 (93.5)	
Yes	2 (3.2)	10 (6.5)	
Missing	118	112	
Liver-only disease, *n* (%)	44 (24.4)	53 (20.0)	0.2651[b]
ECOG PS, *n* (%)			0.4730[b]
0	50 (27.8)	82 (30.9)	
1-2-3	130 (72.2)	183 (69.1)	
First-line regimen, *n* (%)			
Gemcitabine + nab-paclitaxel	180 (100.0)	265 (100.0)	
Best response to first line, *n* (%)			0.3897[b]
Response	50 (27.8)	64 (24.2)	
No response	130 (72.2)	201 (75.8)	
Duration of first line, *n* (%)			0.7457[b]
<6 months	85 (47.2)	121 (45.7)	
>6 months	95 (52.8)	144 (54.3)	
Metastatic sites at second line, *n* (%)			0.2930[b]
1	72 (40.0)	93 (35.1)	
>1	108 (60.0)	172 (64.9)	
CEA, *n* (%)			0.1867[b]
≤10 ng/ml	78 (60.9)	112 (53.6)	
>10 ng/ml	50 (39.1)	97 (46.4)	
Missing	52	56	
CA19.9, *n* (%)			0.0701[b]
<40 U/ml	37 (22.2)	35 (15.1)	
≥40 U/ml	130 (77.8)	197 (84.9)	
Missing	13	33	

5-FU, 5-fluorouracil; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; Nal-IRI, nanoliposomal irinotecan; PS, performance status.
[a]Wilcoxon rank sum *P* value.
[b]Chi-square *P* value.
[c]Fisher exact *P* value.

metastasis (synchronous versus metachronous), number of metastatic sites (1 versus >1), and first-line therapy PFS (<6 versus ≥6 months). This process excluded 97 patients but achieved optimal covariate balance across groups (Figure 2).

In the matched cohort, mPFS was 3.0 months (95% CI 2.5-3.6 months) in the 5-FU + Nal-IRI group and 2.5 months (95% CI 2.2-2.9 months) in the FOLFOX/XELOX group (HR 0.75, 95% CI 0.61-0.91, $P = 0.0048$); the 6-month PFS rate was 27.5% (95% CI 20.5% to 34.9%) versus 16.1% (95% CI 10.3% to 23.2%), respectively. The mOS was 7.2 months (95% CI 5.8-8.4 months) for 5-FU + Nal-IRI versus 5.8 months (95% CI 4.1-6.8 months) for FOLFOX/XELOX (HR 0.74, 95% CI 0.58-0.95, $P = 0.015$); the 6-month OS rate was 57.1% (95% CI 47.9% to 65.2%) versus 47% (95% CI 37.7% to 55.7%) in the 5-FU + Nal-IRI versus FOLFOX/XELOX groups, respectively (Figure 3A and B).

Safety

Adverse events of any grade occurred in 158 patients (88.3%) in the 5-FU + Nal-IRI group and in 216 (84.4%) in the FOLFOX/XELOX group. Grade 3-4 events occurred in 56 patients (31.1%) in the 5-FU + Nal-IRI and in 25 patients (9.4%) in the FOLFOX/XELOX groups.

Dose reductions due to adverse events were required in 99 patients (55%) in the 5-FU + Nal-IRI group and in 71 patients (26.8%) receiving FOLFOX/XELOX. Treatment discontinuation due to toxicity occurred in 14 (7.8%) and 4 (1.5%) patients, respectively.

Specific toxicities differed between regimens. FOLFOX/XELOX was associated with higher rates of any-grade thrombocytopenia (27.8% versus 16.0%, $P = 0.0049$), peripheral neuropathy (47.7% versus 9.5%, $P < 0.0001$), and fatigue (55.5% versus 44.1%, $P = 0.02$). Conversely, patients in the 5-FU + Nal-IRI group experienced more frequent any-grade liver enzyme elevations (27.4% versus 11.3%, $P < 0.0001$), diarrhea (35.8% versus 21.5%, $P = 0.0010$), and alopecia (15.6% versus 4.3%, $P < 0.001$). G3-4 anemia (13.9% versus 1.7%, $P < 0.001$) and diarrhea (5.6% versus 1.2%, $P = 0.0098$) were more common in the 5-FU + Nal-IRI group (Table 2).

DISCUSSION

This is a multicenter retrospective study, and it represents one of the largest real-world comparative analyses of second-line treatment strategies in patients with metastatic PDAC previously treated with first-line GemNab. Our findings provide new insights into the relative efficacy and safety of 5-FU + Nal-IRI versus oxaliplatin-based regimens (FOLFOX/XELOX) in this population.

In the unmatched cohort, both PFS and OS were numerically longer with 5-FU + Nal-IRI, although the differences did not reach statistical significance. However, after applying exact propensity score matching to reduce confounding due to imbalances in baseline characteristics, 5-FU + Nal-IRI was associated with a statistically significant improvement in both PFS and OS. Specifically, matched patients treated with 5-FU + Nal-IRI achieved a median OS of 7.2 months versus 5.8 months for the FOLFOX/XELOX group (HR 0.74, $P = 0.015$). These results suggest that 5-FU + Nal-IRI may offer a modest but clinically relevant survival advantage over oxaliplatin-based therapy in this setting.

Our results are consistent with prior randomized trials, including the NAPOLI-1 study, and the results of a recently published meta-analysis,[21] which established 5-FU + Nal-

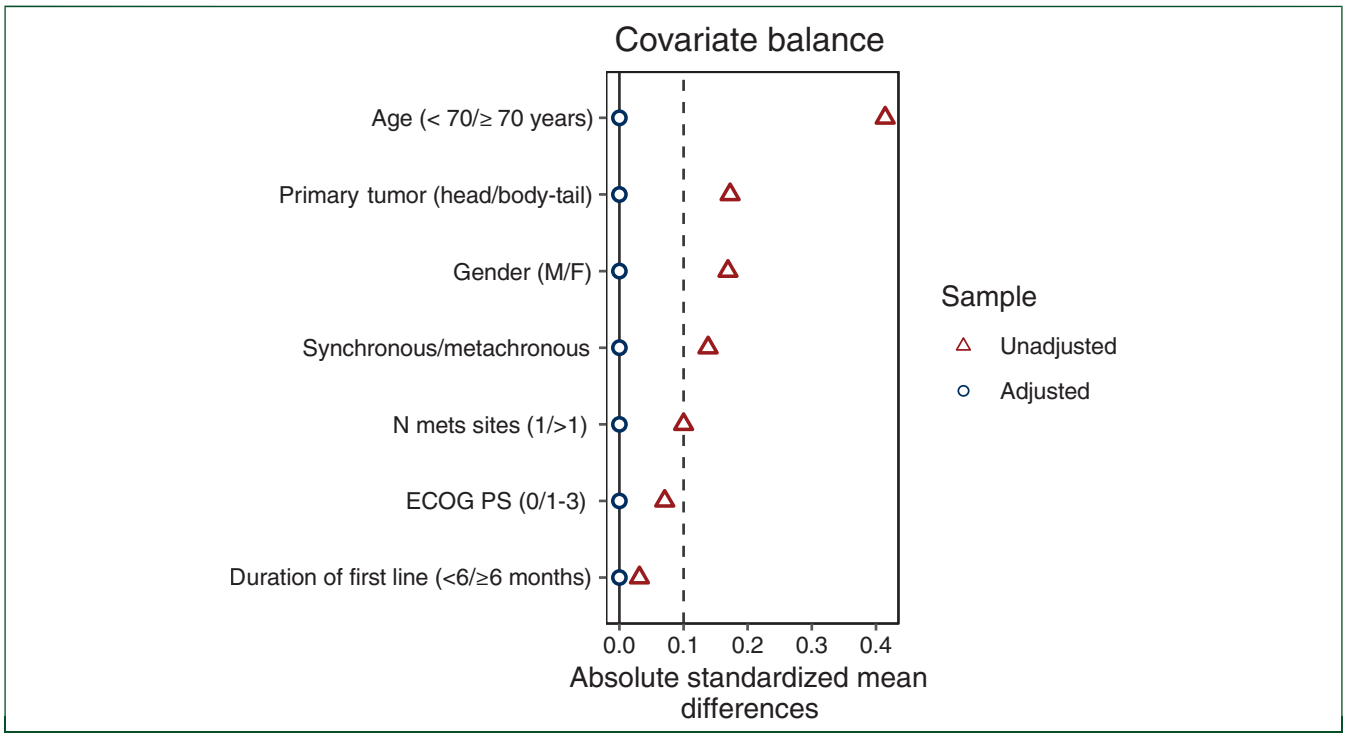

Figure 2. Love plot depicting absolute standardized mean differences before (red triangles) and after (blue circles) weighting.
ECOG, Eastern Cooperative Oncology Group; F, female; M, male; PS, performance status.

IRI as the preferred second-line option after gemcitabine failure. However, most of the evidences for both 5-FU + Nal-IRI and oxaliplatin-based regimens are derived from populations that received first-line gemcitabine monotherapy, limiting their generalizability to current clinical practice. Our study addresses this gap and offers evidence supporting the use of 5-FU + Nal-IRI in this updated treatment landscape.

Importantly, our results by design apply only to patients who did not receive FOLFIRINOX or NALIRIFOX as first-line regimen. In routine practice this remains a sizeable group, as many patients are not candidates for triplet chemotherapy because of impaired PS, hyperbilirubinemia from biliary obstruction, or comorbidities/frailty. In Europe, several real-world series have shown that GemNab is still commonly used as first-line therapy: in a nine-country chart review in the period 2014-2016,[22] FOLFIRINOX and GemNab accounted for 35.6% and 25.7% of first-line regimens, respectively, while a more recent multicenter European cohort[23] found GemNab to be the most frequent first-line regimen (used in 62.6% of patients). In Asia, a nationwide Korean registry[24] reported first-line GemNab and FOLFIRINOX use in 34.5% and 13.1% of treated patients, respectively, with increasing adoption of combination therapy over time. Taken together, these data indicate that approximately one-third to two-thirds of patients with mPDAC across Europe and Asia are currently managed with first-line GemNab.

In terms of toxicity, the two regimens demonstrated distinct safety profiles. As expected, oxaliplatin-based regimens were associated with significantly higher rates of peripheral neuropathy and thrombocytopenia, consistent with the known toxicity spectrum of oxaliplatin. In contrast, 5-FU + Nal-IRI was more frequently associated with gastrointestinal side-effects (especially diarrhea) and liver enzyme elevations. Importantly, the overall rate of grade 3-4 adverse events was higher in the 5-FU + Nal-IRI group (31.1% versus 9.4%), which also led to more frequent dose reductions and treatment discontinuations. These findings emphasize the need to consider patient comorbidities, clinical conditions, and prior toxicities when selecting second-line therapy.

This study has several limitations. First of all, its retrospective design and non-randomized nature introduce potential selection biases, although we tried to mitigate these imbalances through propensity score matching. Secondly, the heterogeneous nature of the oxaliplatin-based regimens (FOLFOX and XELOX) may have introduced variability in efficacy and toxicity outcomes. Thirdly, data on BRCA1/2 mutation status were largely missing, precluding any analysis of potential predictive biomarkers.

In conclusion, our findings show a higher efficacy of 5-FU + Nal-IRI second-line treatment over oxaliplatin-based regimens but at the cost of a higher rate of adverse events. Prospective randomized trials directly comparing these and other treatments in this specific setting are

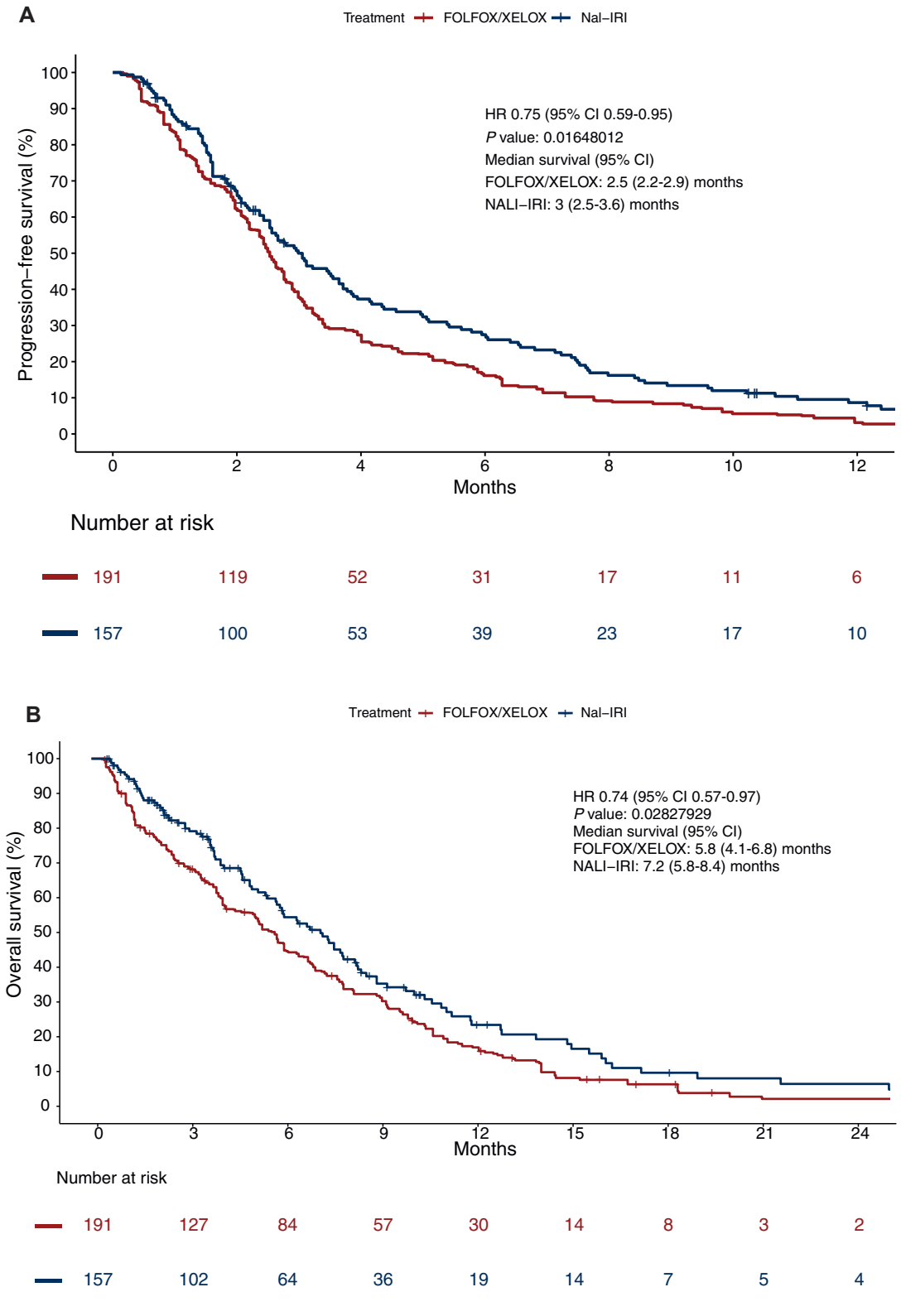

Figure 3. Efficacy outcomes in the matched population. (A) Progression-free survival and (B) overall survival according to chemotherapy regimen (5-FU + Nal-IRI versus FOLFOX/XELOX) in the matched population.
5-FU, 5-fluorouracil; CI, confidence interval; HR, hazard ratio; Nal-IRI, nanoliposomal irinotecan.

Table 2. Adverse events (both any grade and G3-G4) in the two treatment groups

Adverse events	5-FU + Nal-IRI (*N* = 180)	FOLFOX/XELOX (*n* = 265)
Anemia, *n* (%)		
Any grade	84 (48.6)	106 (45.1)
G3-4	24 (13.9)	4 (1.7)
Missing	7	30
Fatigue, *n* (%)		
Any grade	79 (44.1)	142 (55.5)
G3-4	8 (4.5)	3 (1.2)
Missing	1	9
Diarrhea, *n* (%)		
Any grade	64 (35.8)	55 (21.5)
G3-4	10 (5.6)	3 (1.2)
Missing	1	9
Nausea, *n* (%)		
Any grade	48 (32.7)	82 (32.0)
G3-4	4 (2.7)	2 (0.8)
Missing	33	9
Neutropenia, *n* (%)		
Any grade	53 (29.6)	74 (29.1)
G3-4	17 (9.5)	9 (3.5)
Missing	1	11
Elevated AST/ALT, *n* (%)		
Any grade	49 (27.4)	27 (11.3)
G3-4	4 (2.2)	2 (0.8)
Missing	1	27
Decreased appetite, *n* (%)		
Any grade	47 (26.4)	77 (30.3)
G3-4	4 (2.2)	1 (0.4)
Missing	2	11
Vomiting, *n* (%)		
Any grade	31 (17.3)	34 (13.4)
G3-4	3 (1.7)	0 (0.0)
Missing	1	11
Thrombocytopenia, *n* (%)		
Any grade	28 (16.0)	64 (27.8)
G3-4	5 (2.9)	3 (1.3)
Missing	5	35
Alopecia, *n* (%)		
Any grade	23 (15.6)	11 (4.3)
Missing	33	11
Neuropathy, *n* (%)		
Any grade	14 (9.5)	122 (47.7)
G3-4	2 (1.4)	1 (0.4)
Missing	33	9

5-FU, 5-fluorouracil; ALT, alanine aminotransferase; AST, aspartate aminotransferase G, grade; Nal-IRI, nanoliposomal irinotecan.

warranted to confirm our results and further refine therapeutic sequencing in PDAC.

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DISCLOSURE

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DATA SHARING

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

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