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Real-world outcomes of FOLFIRINOX versus gemcitabine plus nab-paclitaxel and prognostic factors in advanced pancreatic cancer: a retrospective cohort study

Ther Adv Med Oncol

2026, Vol. 18: 1–13

DOI: 10.1177/17588359261456797

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Carlos Escriva-Aranda, Eduardo Giner-Moreno, Emilio Soria Hernández, Josep Esteve Gallego, Elisa Gómez Roch, Patricia Capdevila, Cristobal Carrasco Picazo, Alba Ortiz Gracia, Daniel Vidal Jiménez, Jorge Aparicio and Robert Díaz Beveridge

Abstract

Background: FOLFIRINOX (FFX) and gemcitabine plus nab-paclitaxel (GnP) are the main first-line regimens for advanced pancreatic adenocarcinoma. No randomized clinical trials have directly compared their efficacy, and real-world data remain limited.

Objectives: The primary endpoint of this study was to compare overall survival (OS) and progression-free survival (PFS) between the two regimens. Secondary endpoints included the objective response rate (ORR) and the identification of prognostic factors.

Design: Retrospective, single-center cohort study.

Methods: Patients with locally advanced or metastatic pancreatic adenocarcinoma treated with first-line FFX or GnP at a tertiary referral center in Spain between 2011 and 2024 were included. OS and PFS were estimated using the Kaplan–Meier method and compared with the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazard models. Propensity score matching was performed as a sensitivity analysis.

Results: A total of 200 patients were analyzed (FFX, $n = 42$; GnP, $n = 158$). Median OS was 10.6 months (95% CI 8.0–14.3) for FFX and 9.6 months (95% CI 8.4–11.6) for GnP (HR 1.05, 95% CI 0.74–1.50; $p = 0.78$). Median PFS was 5.19 months (95% CI 3.12–8.64) and 4.63 months (95% CI 3.61–5.72), respectively (HR 1.09, 95% CI 0.77–1.54; $p = 0.64$). ORR was 44.2% for FFX and 29.1% for GnP ($p = 0.063$). Independent prognostic factors for OS included Eastern Cooperative Oncology Group performance status ⩾2, elevated neutrophil-to-lymphocyte ratio, lactate dehydrogenase, and CA 19-9 levels. Propensity score-matched analysis confirmed comparable OS and PFS between groups.

Conclusion: In this real-world cohort, FFX and GnP were associated with similar OS and PFS outcomes. The retrospective design and baseline imbalances between groups limit causal inference due to potential residual confounding and selection bias.

Keywords: adenocarcinoma, FOLFIRINOX, gemcitabine, nab-paclitaxel, pancreatic cancer, survival

Received: 15 December 2025; revised manuscript accepted: 11 May 2026.

Correspondence to:
Carlos Escriva-Aranda
Robert Díaz Beveridge
Medical Oncology Department, Hospital Universitario y Politécnico La Fe, Avenida Fernando Abril Martorell Nº 106, Valencia 46026, Spain
escriva.c95@gmail.com
robertdiazbeveridge@gmail.com

Eduardo Giner-Moreno
Pathology Department, Hospital Universitario y Politécnico La Fe, Valencia, Spain

Emilio Soria Hernández
Josep Esteve Gallego
Elisa Gómez Roch
Patricia Capdevila
Cristobal Carrasco Picazo
Alba Ortiz Gracia
Daniel Vidal Jiménez
Jorge Aparicio
Medical Oncology Department, Hospital Universitario y Politécnico La Fe, Valencia, Spain

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Introduction

Pancreatic cancer (PC) ranks as the twelfth most common cancer worldwide and is the sixth leading cause of cancer-related deaths, predominantly affecting high-income regions.[1] In Europe, PC is the fourth leading cause of cancer mortality in both men and women and ranks third in North America.[2] The 5-year survival rate remains low, at approximately 8%–10%, largely because 80% of cases are diagnosed at locally advanced or metastatic stages.[3] Despite advances in chemotherapy and supportive care, the prognosis for advanced PC remains poor, with a median overall survival (OS) of approximately 11 months.[4]

Historically, gemcitabine was the standard first-line treatment for metastatic pancreatic cancer (mPC).[5] In 2011, a phase III randomized clinical trial demonstrated the superiority of FOLFIRINOX (FFX; a combination of oxaliplatin, irinotecan, leucovorin (LV), and fluorouracil) over gemcitabine monotherapy, with a median OS of 11.1 versus 6.8 months, respectively.[6] Subsequently, another phase III trial showed that gemcitabine plus nab-paclitaxel (GnP) improved median OS compared with gemcitabine alone (8.7 vs 6.6 months).[7]

Over the past decade, both FFX and GnP have become widely accepted first-line therapies for mPC. Although FFX appears to be associated with longer OS in clinical trials, no head-to-head randomized study has directly compared its efficacy with GnP. Current clinical guidelines recommend FFX for younger patients (age <65 years) with Eastern Cooperative Oncology Group performance status (ECOG PS) 0–1, normal liver function, and limited comorbidities.[8] In contrast, GnP is often used in patients with poorer performance status or greater symptom burden.[4]

Differences in OS observed between these regimens may reflect variations in patient selection rather than intrinsic treatment efficacy. Notably, the GnP trial included patients with Karnofsky performance status ≥ 70, representing a potentially less fit population, whereas the FFX trial enrolled only patients with ECOG PS 0–1. This raises the question of whether the reported survival differences are attributable to treatment effects or baseline patient characteristics.

Several clinical and laboratory variables have been associated with poorer prognosis in mPC, including ECOG PS ≥ 2, liver metastases, higher metastatic burden, metastatic disease at diagnosis, elevated CA19-9 levels (≥ 59 times the upper limit of normal (ULN)), hypoalbuminemia (<3.5 g/dL), and increased neutrophil-to-lymphocyte ratio (NLR).[4] To date, no validated predictive biomarkers have been established.

Although several international real-world studies have compared outcomes between FFX and GnP, most data derive from North American cohorts and reflect treatment patterns prior to 2020.[9] Results remain heterogeneous and are strongly influenced by baseline patient characteristics, with limited evidence from Southern European countries, particularly Spain. Moreover, few real-world series have simultaneously examined comparative treatment outcomes and established prognostic factors within the same cohort.

Therefore, the present study aimed to retrospectively compare OS, progression-free survival (PFS), and objective response rate (ORR) between FFX and GnP in a real-world cohort of patients with advanced PC, while concurrently evaluating established clinical and laboratory prognostic factors. By integrating comparative effectiveness and prognostic assessment within a contemporary Spanish cohort, this study seeks to clarify whether previously reported survival differences may be related to treatment selection or baseline patient characteristics.

Materials and methods

Study design and patient population

This observational study analyzed real-world data from patients with de novo or recurrent advanced pancreatic adenocarcinoma, including unresectable locally advanced or metastatic disease, diagnosed by biopsy, and computed tomography.

Patients classified as having recurrent unresectable disease included those with recurrence after prior curative-intent surgery. In all cases, unresectability was determined prior to initiation of first-line chemotherapy based on radiological assessment and multidisciplinary team evaluation according to institutional criteria.

Retrospective data were collected from patients treated with GnP or FFX in the first-line setting between 2011 and 2024 at Hospital Universitario y Politécnico La Fe in Valencia, Spain. Clinical

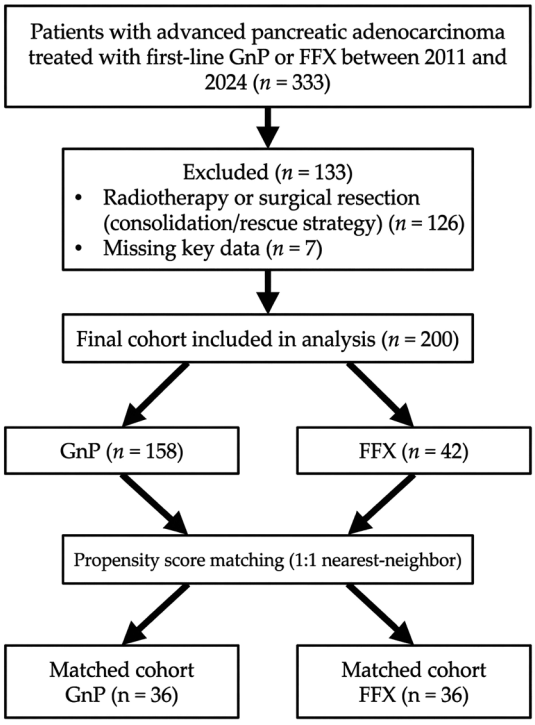

Figure 1. Flow diagram of patient selection and propensity score matching. A total of 333 patients with advanced pancreatic adenocarcinoma treated with first-line GnP or FFX between 2011 and 2024 were identified. After applying predefined exclusion criteria, 200 patients were included in the final analysis (GnP, *n* = 158; FFX, *n* = 42). Propensity score matching using 1:1 nearest-neighbor matching yielded a matched cohort of 36 patients per group. GnP, gemcitabine plus nab-paclitaxel; FFX, FOLFIRINOX.

and laboratory data were retrieved from electronic medical records. All consecutive patients meeting inclusion criteria were enrolled to minimize selection bias. No sample size calculation was performed, as all eligible patients during the study period were included. Patients with missing key baseline or outcome data were excluded from the study cohort.

Patients who received surgical resection or radiotherapy with curative or consolidative intent at any time were excluded to maintain a homogeneous population treated with palliative systemic therapy. The patient selection process is summarized in Figure 1.

This study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[10]

OS and PFS were the primary endpoints of the study. OS was defined as the time from initiation of first-line chemotherapy to death from any cause. PFS was defined as the time from treatment initiation to radiological or clinical disease progression or death, whichever occurred first.

Secondary endpoints included the ORR and the identification of clinical and laboratory prognostic factors associated with OS, both in the overall cohort and within each treatment group.

Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors, version 1.1, based on routine radiological evaluations performed during standard clinical practice. Imaging assessments were typically conducted every 8–12 weeks at the discretion of the treating physician, without an independent central radiological review. ORR was defined as the proportion of patients achieving a complete or partial response as their best overall response.

Safety outcomes were not predefined endpoints of this study. Given the retrospective nature of the analysis, toxicity data were not systematically collected and were, therefore, not included in the present analysis. Similarly, treatment exposure variables, including number of cycles, treatment duration, and reasons for discontinuation, were not systematically collected and were, therefore, not included in the analysis.

Treatment selection and eligibility criteria

Treatment selection was not protocolized and reflected routine clinical practice during the study period. The choice between FFX and GnP was made by the treating physician based on individual clinical judgment and supported by contemporary European and American clinical practice guidelines. Patient-related factors guiding treatment selection included age, ECOG PS, comorbidity burden, and liver function.

In general, FFX was preferentially offered to younger and fitter patients with preserved organ function and limited comorbidity burden, whereas GnP was more frequently selected for older patients, those with higher comorbidity burden, or less favorable performance status. No strict age cutoffs or institutional treatment protocols mandated regimen selection. Treatment decisions were not made prospectively for the purposes of this study and were based on routine

clinician discretion at the time of treatment initiation.

Treatment regimens and supportive care

Patients received first-line chemotherapy with either GnP or FFX according to routine clinical practice. GnP was administered as nab-paclitaxel 125 mg/m^2 followed by gemcitabine 1000 mg/m^2 on days 1, 8, and 15 of a 28-day cycle.

FFX consisted of oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, and leucovorin (calcium folinate) 400 mg/m^2, followed by 5-fluorouracil (5-FU) 400 mg/m^2 administered as an intravenous bolus and 5-FU 2400 mg/m^2 given as a continuous infusion over 46 h, every 2 weeks.

Dose modifications, treatment delays, and supportive measures were implemented at the discretion of the treating physician according to patient tolerance, organ function, and institutional practice. Modified FFX regimens, including dose reductions or omission of the 5-FU bolus, were used in selected patients. Supportive care, including antiemetic prophylaxis and growth factor support, was provided according to standard clinical practice and contemporary guideline recommendations.

Statistical analysis

OS and PFS were analyzed using standard time-to-event methods. Patients without a documented event at the time of analysis were censored at their last available follow-up. Survival curves were estimated using the Kaplan–Meier method and compared between treatment groups using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using Cox proportional hazard regression models to evaluate the association between treatment regimen and survival outcomes. ORR was compared between treatment groups using Fisher's exact test.

Multivariable Cox regression models were performed to identify independent prognostic factors for OS. Covariates were selected a priori based on clinical relevance and evidence from previous studies in advanced PC. These included age and ECOG PS as measures of patient fitness; disease stage (locally advanced vs metastatic), presence of liver metastases, and number of metastatic sites as indicators of disease burden; and baseline laboratory parameters reflecting tumor activity, systemic inflammation, and nutritional status, including NLR, lactate dehydrogenase (LDH), serum albumin level, and CA 19-9. Continuous variables were categorized using clinically relevant cut-offs when available or cohort-based medians when appropriate to facilitate clinical interpretability and model stability.

LDH was categorized using a cohort-derived threshold identified through exploratory analyses. Given the absence of a universally accepted prognostic cutoff, findings related to LDH should be interpreted cautiously. Treatment regimen (FFX vs GnP) was included as a covariate in all multivariable Cox regression models. Formal comorbidity indices were not available due to the retrospective nature of the study. Although age and ECOG performance status were included as general measures of patient fitness, they do not fully capture comorbidity burden.

Patients with unresectable locally advanced and metastatic disease were analyzed together, as both groups were treated with palliative-intent systemic chemotherapy in routine practice. Disease stage (locally advanced vs metastatic) was included as a covariate in all multivariable and propensity score analyses to account for potential prognostic differences between stages.

Exploratory subgroup analyses were conducted within each treatment group using Cox proportional hazards models to evaluate the consistency of associations between selected clinical and laboratory variables and OS across patient subsets.

To further mitigate confounding by indication and address baseline imbalances between treatment groups, a propensity score-matched analysis was conducted as a sensitivity analysis. Propensity scores were estimated using a logistic regression model including age, ECOG PS, disease stage, number of metastatic sites, baseline albumin level, NLR, and CA 19-9. Patients treated with FFX were matched 1:1 to patients treated with GnP using nearest-neighbor matching without replacement. Balance between groups after matching was assessed using standardized mean differences (SMDs), with values <0.1 considered indicative of adequate covariate balance.

Table 1. Baseline characteristics across treatment groups.

Variable	Category	GnP ($n = 158$)	FFX ($n = 42$)	p-Value	SMD
ECOG PS	0–1	112 (71.1%)	40 (95%)	0.005	0.22
	⩾2	46 (29.1%)	2 (5%)		
Age (years)	<65	68 (40%)	38 (90.5%)	<0.001	1.07
	>65	90 (60%)	4 (9.5%)		
NLR	Over the median (3.83)	109 (69%)	29 (69%)	1.000	0.16
	Under the median	49 (31%)	13 (31%)		
CA 19-9 (U/mL)	⩽30 × ULN	82 (51.9%)	19 (46%)	0.491	0.06
	>30 × ULN	76 (48.1%)	23 (54%)		
Albumin <3.5 g/dL	No	111 (70.3%)	35 (83.3%)	0.113	0.19
	Yes	47 (29.7%)	7 (16.7%)		
Stage	Locally advanced	53 (32.9%)	12 (29.6%)	0.878	0.03
	Metastatic	106 (67.1%)	30 (71.4%)		
Hepatic metastasis	Yes	85 (53.8%)	25 (59.5%)	0.724	0.13
	No	73 (46.2%)	17 (40.5%)		
⩾2 metastatic sites	No	57 (29.8%)	10 (23.8%)	0.660	0.05
	Yes	111 (70.3%)	32 (76.2%)		
LDH (U/L)	<150	14 (8.9%)	0 (0%)	0.068	0.43
	⩾150	144 (91.1%)	42 (100%)		

ECOG PS, Eastern Cooperative Oncology Group Performance Status; FFX, FOLFIRINOX; GnP, gemcitabine plus nab-paclitaxel; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; SMD, standardized mean differences; ULN, upper limit of normal.

OS and PFS in the matched cohort were analyzed using Kaplan–Meier methods and Cox proportional hazard models, and HRs with 95% CIs were reported.

Missing data for key variables were infrequent and were handled using complete-case analysis. The proportional hazards assumption was assessed using Schoenfeld residuals and was not violated. Given the exploratory nature of subgroup and prognostic analyses, no formal adjustment for multiple comparisons was applied; therefore, all p values should be interpreted descriptively. A two-sided p value <0.05 was considered statistically significant. All statistical analyses were performed using R software (version 4.5.0; R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 200 patients were included, of whom 158 (79%) received GnP and 42 (21%) received FFX. Baseline characteristics are summarized in Table 1.

The median age of the overall cohort was 63.5 years (range 21–84). Patients treated with GnP were significantly older than those receiving FFX. Overall, 112 patients (56%) were male and 88 (44%) were female. At diagnosis, most patients presented with stage IV disease (67.5%), liver metastases, and more than two metastatic sites. Most patients had serum albumin levels >3.5 g/dL, elevated LDH (>150 U/L), and a median NLR of 3.83. Approximately half of the patients had CA 19-9 levels greater than 30 times the ULN.

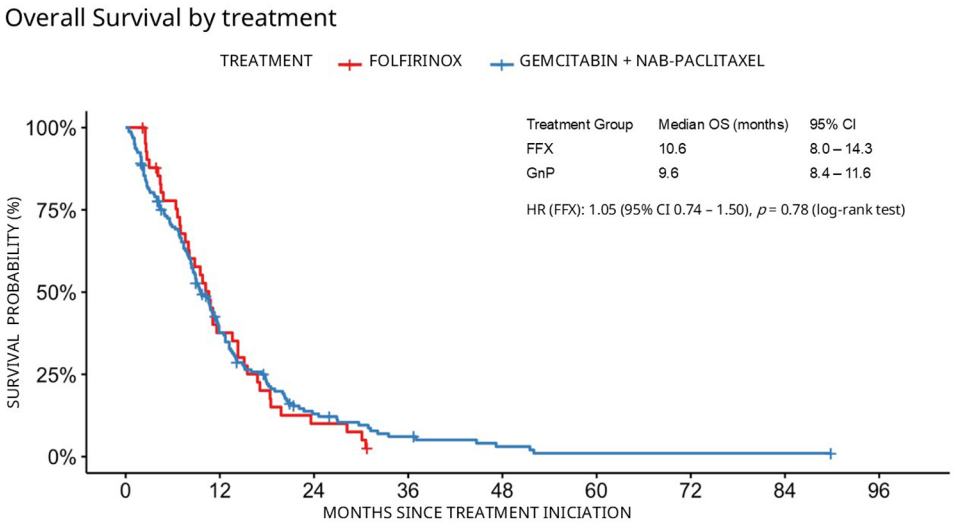

Figure 2. OS by treatment regimen. Kaplan–Meier curves for OS comparing FFX ($n = 42$) versus GnP ($n = 158$). Median OS was 10.6 months (95% CI 8.0–14.3) for FFX and 9.6 months (95% CI 8.4–11.6) for GnP. The HR for death (FFX vs GnP) was 1.05 (95% CI 0.74–1.50; $p = 0.78$, log-rank test).
CI, confidence interval; FFX, FOLFIRINOX; GnP, gemcitabine plus nab-paclitaxel; HR, hazard ratio; OS, overall survival.

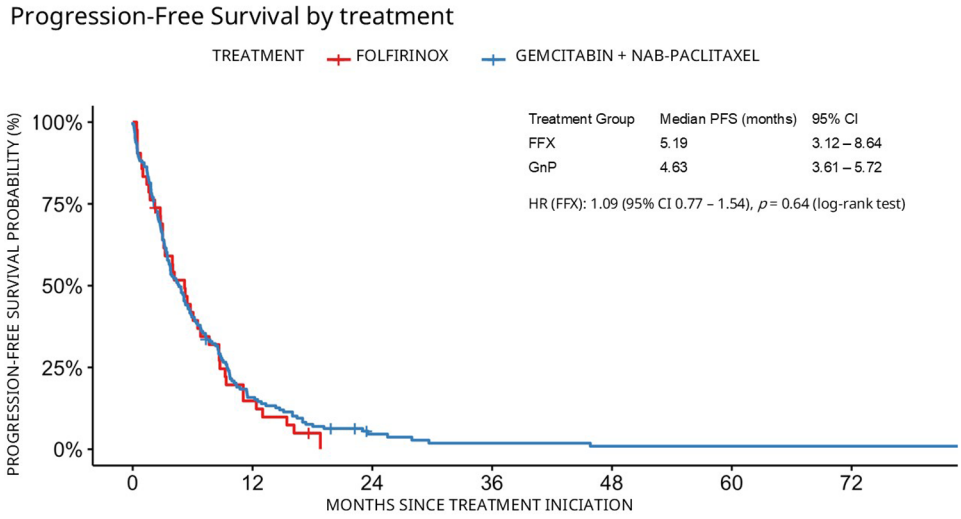

Figure 3. PFS by treatment regimen. Kaplan–Meier curves for PFS comparing FFX ($n = 42$) versus GnP ($n = 158$). Median PFS was 5.19 months (95% CI 3.12–8.64) for FFX and 4.63 months (95% CI 3.61–5.72) for GnP. The HR for progression or death (FFX vs GnP) was 1.09 (95% CI 0.77–1.54; $p = 0.64$, log-rank test).
CI, confidence interval; FFX, FOLFIRINOX; GnP, gemcitabine plus nab-paclitaxel; HR, hazard ratio; PFS, progression-free survival.

At baseline, 152 patients (76%) had an ECOG PS of 0–1, whereas 48 (24%) had an ECOG PS ⩾2. The distribution of ECOG PS and age differed significantly between treatment groups ($p = 0.005$ and $p < 0.001$, respectively), with patients in the FFX group being younger and fitter. SMDs for baseline variables are reported in Table 1.

The median follow-up was 64.6 months (range 1.6–164.7). Median OS for the entire cohort was 10.1 months (range 0.23–72.3). Thirty-eight

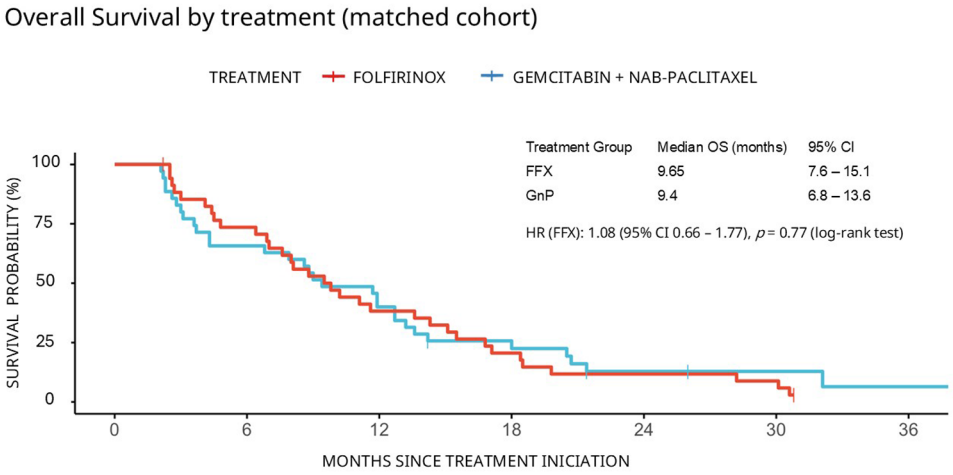

Figure 4. OS in the propensity score-matched cohort. Kaplan–Meier curves for OS comparing FFX ($n=36$) versus GnP ($n=36$). Median OS was 9.65 months (95% CI 7.6–15.1) for FFX and 9.4 months (95% CI 6.8–13.6) for GnP. The HR for death (FFX vs GnP) was 1.08 (95% CI 0.66–1.77; $p=0.77$, log-rank test).
CI, confidence interval; FFX, FOLFIRINOX; GnP, gemcitabine plus nab-paclitaxel; HR, hazard ratio; OS, overall survival.

patients (19%)—22 men and 16 women—achieved an OS longer than 18 months.

Multivariable prognostic model

A multivariable Cox regression model was used to identify independent prognostic factors for OS in the entire cohort. ECOG PS ⩾2 was significantly associated with worse OS (HR 2.16, 95% CI 1.52–3.06; $p<0.001$), as were NLR above the median (3.83; HR 1.52, 95% CI 1.06–2.17; $p=0.023$), elevated LDH >150 U/L (HR 2.00, 95% CI 1.10–3.65; $p=0.024$), and CA 19-9 levels >30 times the ULN (HR 1.51, 95% CI 1.08–2.12; $p=0.016$).

In contrast, liver metastases, disease stage (metastatic vs locally advanced), age, sex, and hypoalbuminemia were not independently associated with OS in this model.

OS according to treatment regimen

Median OS was 10.6 months (95% CI 8.0–14.3) in the FFX group and 9.6 months (95% CI 8.4–11.6) in the GnP group. A total of 39 deaths occurred among 42 patients in the FFX group, and 142 deaths among 158 patients in the GnP group. No statistically significant difference in OS was observed between groups (log-rank test, $p=0.78$). The HR for death with FFX versus GnP was 1.05 (95% CI 0.74–1.50). Kaplan–Meier survival curves are shown in Figure 2.

Progression-free survival

Median PFS was 5.19 months (95% CI 3.12–8.64) in the FFX group, whereas it was 4.63 months (95% CI 3.61–5.72) in the GnP group. Progression events occurred in 40 of 42 patients (95%) in the FFX group and 156 events among 158 patients (99%) in the GnP group. No statistically significant difference in PFS was observed between regimens (log-rank test, $p=0.64$). The HR for progression or death with FFX versus GnP was 1.09 (95% CI 0.77–1.54). Kaplan–Meier curves are shown in Figure 3.

Propensity score-matched sensitivity analysis

To address baseline imbalances and mitigate confounding by indication, a propensity score-matched sensitivity analysis was performed. Using 1:1 nearest-neighbor matching, 36 patients treated with FFX were matched to 36 treated with GnP. Baseline characteristics after matching demonstrated improved covariate balance across clinically relevant variables, with SMDs <0.1 for most covariates; minor residual imbalances persisted for selected laboratory parameters (Supplemental Table 1).

In the matched cohort, median OS was 9.65 months (95% CI 7.6–15.1) in the FFX group and 9.4 months (95% CI 6.8–13.6) in the GnP group. No significant difference in OS was observed (HR 1.08, 95% CI 0.66–1.77; $p=0.77$; Figure 4).

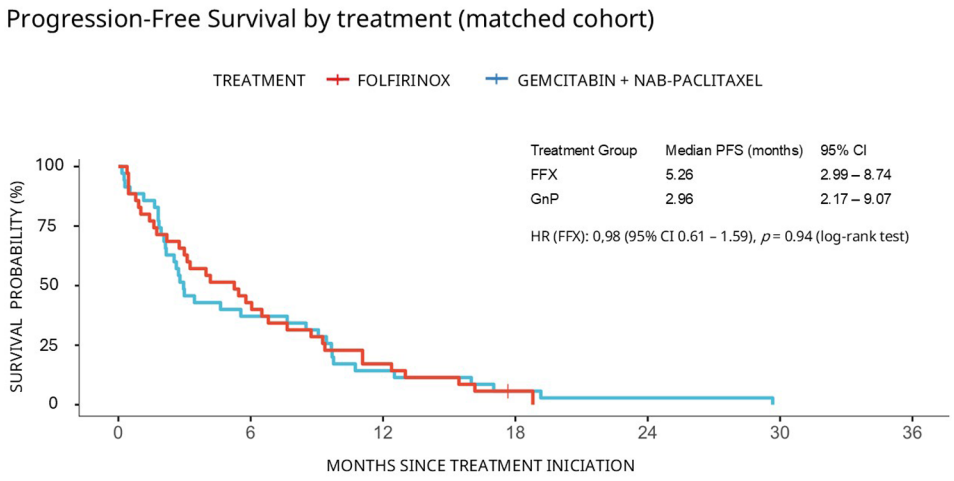

Figure 5. PFS in the propensity score-matched cohort. Kaplan–Meier curves for PFS comparing FFX ($n = 36$) versus GnP ($n = 36$). Median PFS was 5.26 months (95% CI 2.99–8.74) for FFX and 2.96 months (95% CI 2.17–9.07) for GnP. The HR for progression or death (FFX vs GnP) was 0.98 (95% CI 0.61–1.59; $p = 0.94$, log-rank test).
CI, confidence interval; FFX, FOLFIRINOX; GnP, gemcitabine plus nab-paclitaxel; HR, hazard ratio; PFS, progression-free survival.

Table 2. Distribution of best overall treatment responses by treatment group.

Treatment	PD	SD	PR	CR	Total *N*
FFX	15 (34.9%)	8 (18.6%)	19 (44.2%)	0 (0%)	42
GnP	74 (45.7%)	38 (23.2%)	44 (27.4%)	2 (1.2%)	158

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Median PFS was 5.26 months (95% CI 2.99–8.74) in the FFX group and 2.96 months (95% CI 2.17–9.07) in the GnP group. No significant difference in PFS was observed (HR 0.98, 95% CI 0.61–1.59; $p = 0.94$; Figure 5).

Objective response rate

The ORR was 44.2% in the FFX group and 29.1% in the GnP group. This difference did not reach statistical significance (Fisher's exact test, $p = 0.063$). Progressive disease as best overall response occurred in 34.9% of patients treated with FFX and in 45.7% of those receiving GnP. Complete responses were observed in two patients, both in the GnP group. Response distributions are summarized in Table 2.

Subgroup analysis by treatment

In exploratory subgroup analyses, hypoalbuminemia and a high NLR were associated with poorer OS in patients treated with FFX; however, these estimates were based on a limited sample size and were characterized by wide CIs. In the GnP group, ECOG PS ≥ 2 (HR 2.20; $p < 0.001$) and elevated LDH (HR 2.07; $p = 0.023$) were significantly associated with worse survival. These variables were underrepresented in the FFX cohort due to its smaller sample size.

Other factors, including age, sex, presence of liver metastases, number of metastatic sites, and disease stage at diagnosis, were not significantly associated with survival in either treatment group. Subgroup analysis of OS by treatment is presented in Table 3.

Discussion

This retrospective study describes the management of locally advanced and metastatic pancreatic adenocarcinoma over the past 14 years in a tertiary care center. We compared the two main first-line regimens used in this setting: FFX and GnP. Baseline demographic and disease characteristics

Table 3. Subgroup analysis of OS by treatment group.

Variable	HR (95% CI), FFX	HR (95% CI), GnP
Age >65 years	0.97 (0.25–3.75); $p = 0.970$	0.56 (0.31–1.01); $p = 0.056$
Sex (female)	1.23 (0.51–2.96); $p = 0.645$	0.87 (0.58–1.29); $p = 0.484$
ECOG PS ⩾2	1.65 (0.35–7.81); $p = 0.527$	2.20 (1.44–3.37); $p < 0.001$
No hepatic metastasis	1.65 (0.51–5.29); $p = 0.401$	0.91 (0.61–1.38); $p = 0.668$
Metastatic stage	2.07 (0.54–7.98); $p = 0.290$	1.33 (0.88–2.01); $p = 0.172$
>2 metastatic sites	0.84 (0.29–2.45); $p = 0.749$	1.15 (0.76–1.74); $p = 0.514$
LDH >150 U/L	NA	2.07 (1.11–3.85); $p = 0.023$
High NLR	6.11 (1.98–18.83); $p = 0.002$	1.34 (0.88–2.04); $p = 0.175$
Albumin <3.5 g/dL	9.16 (1.33–63.31); $p = 0.025$	1.00 (0.66–1.51); $p = 0.990$
High CA 19-9	1.63 (0.69–3.83); $p = 0.266$	1.42 (0.96–2.09); $p = 0.077$

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FFX, FOLFIRINOX; GnP, gemcitabine plus nab-paclitaxel; HR, hazard ratio; LDH, lactate dehydrogenase; NA, not applicable; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival.

were generally comparable, although ECOG PS and age differed significantly between groups.

No statistically significant differences in OS were observed between FFX (median 10.6 months) and GnP (median 9.6 months; HR 1.05, 95% CI 0.74–1.50; $p = 0.78$). Similarly, PFS did not differ significantly between regimens (median 5.19 vs 4.63 months; HR 1.09, 95% CI 0.77–1.54; $p = 0.64$). The ORR was 44.2% in the FFX group and 29.1% in the GnP group, without a statistically significant difference between regimens ($p = 0.063$).

Importantly, these findings were consistent in the propensity score-matched analysis, in which survival outcomes remained comparable after balancing baseline characteristics. This suggests that the absence of significant survival differences was not solely attributable to measured baseline imbalances.

Multivariable analysis identified ECOG PS ⩾2, elevated NLR, elevated LDH, and elevated CA 19-9 as independent prognostic factors for OS, with ECOG PS showing the strongest association.

The pivotal PRODIGE 4/ACCORD 11 trial established FFX as a standard first-line regimen for fit patients (ECOG PS 0–1, normal bilirubin), demonstrating a significant OS benefit over gemcitabine monotherapy.[6] Similarly, the MPACT trial showed improved OS with GnP compared to gemcitabine alone, and GnP has since been preferentially used in patients with poorer performance status or relevant comorbidities.[7]

Although FFX and GnP have not been directly compared in randomized trials, the longer OS reported with FFX in PRODIGE 4 has often been interpreted as evidence of superiority. However, the PRODIGE 4 population was highly selected, whereas MPACT included patients with lower performance status, limiting cross-trial comparisons. This distinction has influenced treatment allocation in real-world practice, including at our institution, where FFX has generally been offered to younger and fitter patients and GnP to older or frailer individuals.

Our findings suggest broadly comparable effectiveness of the two regimens in routine clinical practice, without statistically significant differences in OS. This contrasts with some retrospective series that reported improved survival with FFX, including one study in which median OS was 9.6 months with FFX and 6.1 months with GnP.[11] In that analysis, patients treated with FFX were younger and had better ECOG PS,

which may have contributed to the observed differences.

The small, non-significant difference in OS observed between regimens in our cohort may partly reflect the preferential use of FFX in patients with better baseline performance status. However, FFX has been associated with a higher incidence of grade 3–4 toxicities in pivotal trials, including hematologic and gastrointestinal adverse events, as well as increased use of growth factor support.[6] Therefore, in patients receiving palliative-intent treatment without a realistic prospect of conversion to surgery or consolidative radiotherapy, the balance between potential tumor shrinkage and treatment-related toxicity should be carefully considered.

Our results can be compared with those reported by Klein-Brill et al.[9] in a large real-world cohort study published in *JAMA Network Open* (2022), which included 1102 patients with metastatic pancreatic ductal adenocarcinoma treated between 2016 and 2019. In that analysis, FFX was associated with longer median OS compared with GnP (9.27 vs 6.87 months; $p < 0.001$), even after multivariable adjustment. However, patients treated with FFX were generally younger and fitter, which may partly explain the observed survival advantage. More recent real-world data further support the role of patient selection in shaping treatment outcomes. In a large registry-based analysis, Marschner et al.[12] developed a prognostic score to inform treatment decision-making and reported comparable outcomes between regimens after accounting for baseline characteristics. Similarly, updated data from the prospective German TPK cohort highlighted the importance of treatment sequencing and clinical context in interpreting survival outcomes in advanced PC.[13]

The availability of liposomal irinotecan in the second-line setting after gemcitabine-based therapy may also have contributed to improved survival outcomes among patients initially treated with GnP. The NAPOLI-1 trial demonstrated a survival benefit with liposomal irinotecan plus 5-FU and leucovorin compared with 5-FU/LV alone.[14] Thus, evolving treatment sequencing strategies over time may partially explain the narrowing survival differences between regimens observed in contemporary real-world studies.

Current ASCO guidelines recommend FFX for patients with ECOG PS 0–1, favorable comorbidity profiles, and adequate support for intensive therapy. GnP is recommended as an alternative for patients with preserved performance status who are not candidates for FFX, whereas gemcitabine monotherapy is reserved for those with ECOG PS 2 or significant comorbidities.[15] Neither PRODIGE 4 nor MPACT included patients with unresectable locally advanced pancreatic cancer (uLAPC), as both trials were restricted to metastatic disease. Consequently, guideline recommendations for uLAPC are largely extrapolated from metastatic data and do not clearly favor one regimen over the other.[16] In our cohort, no differences between FFX and GnP were observed in patients with uLAPC, consistent with current guideline positions.

More recently, the phase III NAPOLI-3 trial demonstrated improved efficacy of NALIRIFOX (liposomal irinotecan, oxaliplatin, 5-FU, and leucovorin) compared with GnP in the first-line setting, with a median OS of 11.1 months (95% CI 10.0–12.1) versus 9.2 months (95% CI 8.3–10.6), respectively (HR 0.83, 95% CI 0.70–0.99; $p = 0.036$).[17] While this regimen represents a new therapeutic alternative to established treatments, the magnitude of the survival benefit was modest, and the HR was close to unity.[18] In addition, no detailed information regarding subsequent lines of therapy was reported, which may influence interpretation of OS outcomes. The broader clinical and economic implications of incorporating liposomal irinotecan into first-line therapy warrant further evaluation.

In our series, ORR was numerically higher in the FFX group, although this difference did not reach statistical significance. This finding is consistent with the greater tumor shrinkage reported in previous studies and may render FFX particularly suitable in the neoadjuvant setting, as investigated in the PANACHE01 (PRODIGE 48) trial,[19] or for patients who might subsequently benefit from consolidative radiotherapy.

However, this higher response rate did not translate into a statistically significant survival advantage. This discrepancy likely reflects multiple factors. FFX is generally administered as a more intensive multi-agent regimen in younger and fitter patients, potentially increasing radiological response rates without necessarily improving long-term survival. In addition, response assessment was performed according to routine clinical practice without independent central review,

which may introduce variability. Finally, OS in advanced PC is influenced by several factors beyond radiological response, including tumor biology, treatment tolerability, and subsequent lines of therapy.

Exploratory subgroup analyses suggested an association between nutritional or inflammatory markers and outcomes in patients treated with FFX. However, given the limited sample size and wide CIs, no treatment-specific or mechanistic conclusions can be drawn. These findings should, therefore, be interpreted cautiously and considered hypothesis-generating.

Across the entire cohort, baseline ECOG PS, NLR, LDH, and CA 19-9 were independently associated with OS. The LDH cutoff was derived from exploratory cohort-based analyses rather than an externally validated threshold and should, therefore, be interpreted as hypothesis-generating. These findings differ partially from other prognostic studies in mPC, in which ECOG PS, serum albumin, and alkaline phosphatase have been identified as strong predictors.[20] A systematic review similarly highlighted age, performance status, and CA 19-9 as consistent prognostic variables across clinical trials of systemic therapy.[21]

Taken together, our findings suggest that FFX and GnP provide broadly comparable survival outcomes in routine clinical practice. Treatment selection should, therefore, be guided primarily by patient fitness, baseline inflammatory and nutritional status, therapeutic goals, and patient values and preferences, rather than by presumed regimen-specific differences in efficacy.

This study has several limitations. First, its retrospective, single-center design may introduce selection bias and limit generalizability. Treatment allocation was not randomized and was based on clinician discretion, which may have influenced outcomes. Second, the FFX cohort was relatively small compared with the GnP group, potentially limiting statistical power to detect differences between regimens.

Third, uLAPC and mPC represent biologically and clinically distinct entities but were analyzed together in this study. In addition, patients with recurrent disease after prior curative-intent treatment were included. Although this approach reflects real-world practice, it may increase population heterogeneity. To mitigate this, disease stage was included as a covariate in all multivariable and propensity score analyses. Formal stratified analyses according to disease stage or prior treatment status (de novo vs recurrent disease) were not performed due to limited sample size, and potential differences between these subgroups cannot be excluded. Exploratory stage-stratified analyses were, therefore, not feasible and warrant further investigation.

Additionally, patients who underwent radiotherapy or surgical rescue after initiation of first-line chemotherapy were not included to maintain a homogeneous population treated with palliative-intent systemic therapy. This may have introduced selection and immortal time bias and could have disproportionately affected the FFX group, given its more frequent use with conversion intent in fitter patients. The absence of formal comorbidity indices further limits the ability to fully account for underlying organ-specific comorbidities. Treatment exposure variables such as number of cycles, treatment duration, and reasons for discontinuation were not systematically available, limiting further interpretation of treatment tolerability and its potential impact on outcomes.

Despite these limitations, this study provides additional real-world evidence suggesting comparable effectiveness of both regimens in contemporary clinical practice.

The external validity of our findings should be interpreted within the context of routine clinical practice. As this study was conducted in a tertiary referral center, treatment strategies, patient selection, and supportive care may differ from other healthcare settings. However, the inclusion of consecutive patients treated over an extended period enhances the applicability of our results and reflects the heterogeneity and decision-making processes encountered in everyday clinical practice.

Conclusion

In this retrospective cohort of patients with advanced pancreatic adenocarcinoma, FFX and GnP were associated with comparable OS and PFS when used as first-line therapy. Although FFX achieved a numerically higher ORR, this did not translate into a survival advantage. Baseline patient characteristics and laboratory markers, including ECOG PS, NLR, LDH, and CA 19-9, were independently associated with OS. These findings suggest

that previously reported differences in treatment outcomes may reflect baseline patient characteristics rather than intrinsic differences in regimen efficacy, underscoring the value of real-world data in complementing clinical trial evidence.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee for Research with Medicinal Products (CEIm) of Hospital Universitario y Politécnico La Fe (Valencia, Spain), approved on July 9, 2025 (Act No. 594; protocol code: FPCP). Given the retrospective, observational nature of the study and the use of anonymized clinical data, the requirement for written informed consent was waived by the Ethics Committee in accordance with local regulations and institutional policies. The study was conducted in accordance with the Declaration of Helsinki and applicable national and institutional guidelines.

Consent for publication

Not applicable.

Author contributions

Carlos Escriva-Aranda: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Eduardo Giner-Moreno: Conceptualization; Formal analysis; Investigation; Supervision; Writing – review & editing.

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

Josep Esteve Gallego: Conceptualization; Investigation; Supervision; Writing – review & editing.

Elisa Gómez Roch: Conceptualization; Investigation; Supervision; Writing – review & editing.

Patricia Capdevila: Conceptualization; Investigation; Supervision; Writing – review & editing.

Cristobal Carrasco Picazo: Conceptualization; Investigation; Supervision; Writing – review & editing.

Alba Ortiz Gracia: Conceptualization; Investigation; Supervision; Writing – review & editing.

Daniel Vidal Jiménez: Conceptualization; Investigation; Validation; Writing – review & editing.

Jorge Aparicio: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing – review & editing.

Robert Díaz Beveridge: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Acknowledgements

The authors would like to thank the staff of the Department of Medical Oncology at Hospital Universitario y Politécnico La Fe for their assistance in data collection and patient management.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author* upon reasonable request. Due to the retrospective nature of the study and restrictions related to patient privacy and institutional regulations, the data are not publicly available.

ORCID iDs

Carlos Escriva-Aranda https://orcid.org/0009-0008-6851-8160

Elisa Gómez Roch https://orcid.org/0009-0007-0799-940X

Patricia Capdevila https://orcid.org/0009-0009-6803-8228

Supplemental material

Supplemental material for this article is available online.

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