

NALIRIFOX Compared With FOLFIRINOX for Treatment-Naive Metastatic Pancreatic Ductal Adenocarcinoma: An Overall Survival External Control Arm Study

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Abstract

The pivotal NAPOLI 3 trial reported superior overall survival (OS) for NALIRIFOX (liposomal irinotecan+oxaliplatin + 5-fluorouracil/leucovorin) vs gemcitabine + nab-paclitaxel (GnP) in patients with treatment-naive metastatic pancreatic ductal adenocarcinoma (mPDAC) ($P = .036$). No prospective studies have compared first-line NALIRIFOX vs FOLFIRINOX (irinotecan + oxaliplatin + 5-fluorouracil/leucovorin) for mPDAC. Using patient-level data from NAPOLI 3 and the Flatiron Health electronic health record database, we compared OS for first-line NALIRIFOX in NAPOLI 3 to external control arms treated with FOLFIRINOX or modified FOLFIRINOX (mFOLFIRINOX). The mFOLFIRINOX cohorts were aligned to NAPOLI 3 eligibility criteria and statistically matched (inverse probability of treatment weighting [IPTW]) on key baseline characteristics. The NALIRIFOX cohort included 383 patients; the FOLFIRINOX and mFOLFIRINOX cohorts included 219 and 154 patients, respectively. Measurable baseline characteristics for the comparator cohorts were generally well balanced following IPTW adjustments. IPTW-adjusted OS (HR; 95% CI) favored NALIRIFOX vs FOLFIRINOX (0.79; 0.64-0.96; $P = .02$) and mFOLFIRINOX (0.80; 0.64-0.99; $P = .04$). Pending evidence from clinical trials or real-world prospective studies, this analysis provides preliminary insights into the comparative survival benefit of NALIRIFOX vs mFOLFIRINOX in patients with untreated mPDAC.

Introduction

Pancreatic cancer is the third leading cause of cancer-related death in the US.¹ Pancreatic ductal adenocarcinoma (PDAC) accounts for more than 90% of pancreatic cancer cases² and has a poor prognosis owing to its aggressive nature, nonspecific early symptoms, and limited treatment options; 5-year survival for patients with an advanced disease diagnosis is approximately 3%.^{1,3,4}

Historically, FOLFIRINOX (irinotecan + oxaliplatin + 5-fluorouracil/leucovorin [5-FU/LV]) and gemcitabine in combination with nab-paclitaxel (GnP) were considered first-line (1L) standard-of-care treatment options for patients with metastatic PDAC (mPDAC). Regulatory approval of GnP was based on significant overall survival (OS) benefits in patients with mPDAC treated with GnP compared with gemcitabine monotherapy in the international phase 3 MPACT trial (hazard ratio [HR] for OS, 0.72; 95% CI, 0.62-0.83; $P < .001$).⁵⁻⁷

Conversely, FOLFIRINOX does not have regulatory approval for use as a 1L regimen for mPDAC; its widespread adoption in clinical practice followed demonstration of significant OS benefit compared with gemcitabine monotherapy in the French phase 3 PRODIGE trial in patients with newly diagnosed mPDAC (HR for OS, 0.57; 95% CI, 0.45-0.73; $P < .001$).⁸ Comparative clinical trial data for FOLFIRINOX and GnP are limited, and optimal treatment selection has been complicated by frequent tolerability-related modifications to the FOLFIRINOX dosing regimen (mFOLFIRINOX), the absence of a standard mFOLFIRINOX regimen, and inconsistent results from real-world studies comparing FOLFIRINOX and GnP.⁹⁻¹⁵ The phase 2 PASS-01 study, conducted to inform biomarker-driven treatment selection in treatment-naïve patients without germline pathogenic variants *BRCA* or *PALB2*, reported numerically longer progression-free survival with GnP compared with mFOLFIRINOX (5.3 vs 4.0 months, respectively; HR, 1.37; 95% CI, 0.97-1.92; $P = .069$). However, median OS for both treatment arms suggested limited survival benefit with either regimen for patients with advanced disease.¹⁶

In 2024, liposomal irinotecan was added to 1L mPDAC treatment armamentarium for use in combination with 5-FU/LV + oxaliplatin (NALIRIFOX) in adult patients. Regulatory approval of 1L NALIRIFOX was based on the phase 3 NAPOLI 3 trial, which reported clinically meaningful and statistically significant improvements in OS and progression-free survival with NALIRIFOX vs GnP (HR for OS, 0.83; 95% CI, 0.70-0.99; $P = .036$).¹⁷

However, clinically informed treatment selection remains limited by the lack of direct head-to-head trials of the comparative efficacy–safety profiles of these quadruplet, triplet, and doublet regimens.

The comparator arm for the NAPOLI 3 trial was decided based on regulatory approval for 1L mPDAC treatments; while FOLFIRINOX and mFOLFIRINOX are widely used based on clinical trial data,^{8,19} GnP has been the only regimen approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).^{6,7} Pending the availability of prospective real-world comparative data, we utilized a robust US electronic health record (EHR) database to create a proxy control arm for the NAPOLI 3 NALIRIFOX treatment arm. This included patients treated with 1L FOLFIRINOX in real-world clinical practice who met the eligibility criteria for NAPOLI 3. Using this external control arm (ECA), an FDA-endorsed methodology in the absence of relevant trial evidence,²⁰ we aimed to provide preliminary insights into the comparative OS for 1L NALIRIFOX and FOLFIRINOX in patients matched on key baseline characteristics.

Materials and Methods

Data Sources

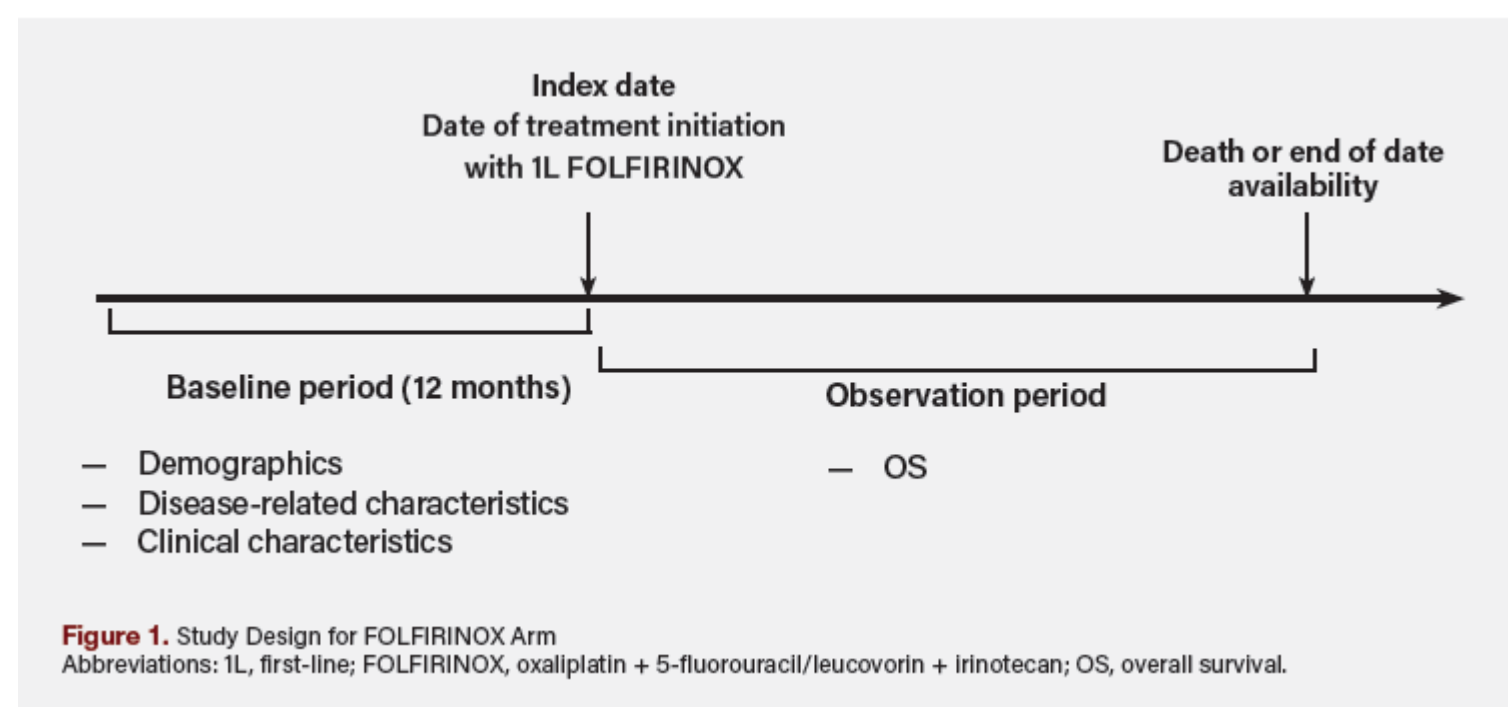
The NALIRIFOX cohort for the present analysis was the intention-to-treat (ITT) population of the NALIRIFOX cohort from the NAPOLI 3 trial. NAPOLI 3 was a phase 3, open-label, randomized trial in previously untreated adults with mPDAC. A total of 770 participants were randomized 1:1 to receive NALIRIFOX ($n = 383$) or GnP ($n = 387$) between February 19, 2020, and August 17, 2021. The ITT population included all patients who were randomized to receive the NALIRIFOX regimen of liposomal irinotecan plus oxaliplatin plus 5-FU/LV. Participants were followed every 2 months after the end of treatment until death or trial closure.

The FOLFIRINOX ECA for the present analysis was constructed from the Flatiron Health EHR database, which contains deidentified, patient-level, longitudinal, demographically and geographically diverse data, representing more than 2.5 million patients with active cancer who were treated at over 280 cancer clinics and academic centers across the US. The dataset was derived from structured (eg, items directly captured in the EHR) and unstructured (eg, physician notes and pathology reports) data elements.

Study Design

The index date for the NALIRIFOX cohort was defined as the date of randomization during the trial; participants' baseline characteristics and medical history were assessed during screening (ie, within 28 days prior to randomization). For the FOLFIRINOX cohort, the index date was defined as the initiation of 1L treatment with FOLFIRINOX for mPDAC. The baseline period was defined as the 12-month period prior to the index date.

The observation period was defined as the duration from index date to the earliest of patient death or date of last confirmed activity based on the available data (ie, the last record of patient vitals, medication administrations, reported laboratory tests/results from structured data, or clinician confirmed receipt of treatments from unstructured data). An overview of the study design for the FOLFIRINOX cohort is shown in **Figure 1**.



Study Population and Cohorts

To align the FOLFIRINOX cohort to the NALIRIFOX arm cohort, patients with mPDAC treated with 1L FOLFIRINOX were eligible if they initiated treatment between January 1, 2020, and July 31, 2022 (ie, during the NAPOLI 3 study period) and met key NAPOLI 3 eligibility criteria within the EHR data (**Table S1**).

Once constructed, a subgroup of the FOLFIRINOX cohort was identified that comprised patients who received a modified FOLFIRINOX (mFOLFIRINOX) regimen, defined as an initial dose of irinotecan of 150 mg/m² or less or initial cumulative dose (bolus + infusion) of 5-FU of 2720 mg/m² or less during the first cycle (within 30 days of the index date; **Table S2, Figure S1**). Sensitivity analyses were conducted to determine the impact on OS of application of NAPOLI 3 eligibility criteria to patients treated in real-world practice, and of aligning the real-world treatment window to that of the NAPOLI 3 study period: the first sensitivity analysis (the “all-comer cohort”) comprised all adults in the Flatiron Health EHR database with mPDAC who were treated with 1L FOLFIRINOX on or after January 1, 2014 (ie, start of data availability); the second sensitivity analysis (the “all-comer contemporary cohort”) comprised the subset of the all-comer cohort who were treated between January 1, 2020, and July 31, 2022.

Outcomes

Overall survival during the study period was assessed for all study cohorts and defined as the time from index date to death from any cause. Patients who did not experience an event during the study period were censored at the last known time that they were alive (for the NALIRIFOX cohort) or at their last confirmed activity date (for the mFOLFIRINOX cohorts).

No safety outcome evaluations were planned because of anticipated inconsistent documentation of adverse events in real-world practice, which would prevent meaningful comparison with per-protocol safety data collected during the NAPOLI 3 trial.

Statistical Analysis

Summary statistics were reported for baseline patient demographic, clinical, and disease-related characteristics, including frequencies and percentages for categorical variables and means, standard deviations, medians, and interquartile ranges for continuous variables. Differences between cohorts were calculated using standardized differences. Inverse probability of treatment weighting (IPTW) was used to control for potential confounding and reduce non-comparability between the 2 cohorts. IPTW is an established method used in observational studies where randomization is not feasible.²¹ The IPTW approach aims to “simulate” a randomized controlled trial where the distribution of measured baseline covariates is similar between treatment cohorts. Causal analysis methods, including IPTW, are recommended in FDA guidance as a means of addressing confounding and improving the rigor of non-randomized comparative analyses.²¹ Through IPTW, stabilized weights were calculated based on the estimated propensity scores. Propensity scores were derived using a logistic regression with NALIRIFOX treatment as the dependent variable and a set of measured baseline covariants that were clinically or statistically relevant (ie, variables showing imbalance between cohorts based on a standardized difference ≥10%) as independent variables: age category at index, sex, race, metastatic status at initial diagnosis of PDAC, European Cooperative Oncology Group (ECOG) performance status, surgery history, chemotherapy history, site of primary disease, time from metastatic diagnosis to index date, comorbidities (hypertension, thrombosis, ascites), and laboratory measures (alanine transaminase, creatinine clearance, platelet count, serum albumin, serum total bilirubin).

Median OS and corresponding 95% CI were calculated by Kaplan-Meier analysis for the unweighted and weighted NALIRIFOX and FOLFIRINOX cohorts, separately. Hazard ratios and 95% CI were estimated by Cox proportional hazards modeling with a robust variance estimator (level was set at 0.05).

Ethics

For the NAPOLI 3 trial data, anonymization and assessment of the risk of reidentification of trial participants was performed by a third party to protect clinical datasets against adversary attacks in compliance with EMA Policy 0070. The Flatiron Health EHR data were deidentified and complied with the Health Insurance Portability and Accountability Act (HIPAA). Therefore, ethical approval was not required.

Results

Patient Characteristics

In total, the NALIRIFOX cohort included the 383 patients from the NAPOLI 3 ITT arm, and the FOLFIRINOX cohort included 219 patients treated in real-world practice who met the key NAPOLI 3 eligibility criteria for the present analysis. Of the 219 patients in the overall FOLFIRINOX cohort, 70.3% (n = 154) received a regimen that met the study definition of mFOLFIRINOX and were included in the mFOLFIRINOX cohort (**Figure S1**). For the OS sensitivity analyses, the all-comer cohort included 3271 patients, and the contemporary all-comer cohort included 1000 patients.

The characteristics of patients in the NALIRIFOX and FOLFIRINOX cohorts, before and after weighting, are detailed in **Table 1**. Prior to weighting, a higher proportion of patients in the NALIRIFOX cohort than the FOLFIRINOX cohort had ECOG performance status of 1 at baseline (58.2% vs 47.0%; standardized difference, 22.6%). Most patients in both cohorts had metastatic disease at diagnosis. The mean ($\pm$ SD) time from metastatic diagnosis to index date was 3.6 ± 1.8 months in the NALIRIFOX cohort, and 4.6 ± 8.3 months in the FOLFIRINOX cohort (standardized difference, 16.7%). A greater proportion of patients in the NALIRIFOX cohort than the FOLFIRINOX cohort had primary disease in the body of the pancreas (30.3% vs 25.6%; standardized difference, 10.5%). Regarding prior treatments, approximately 5% of patients in the NALIRIFOX cohort and 8% in the FOLFIRINOX cohort had undergone surgery; 4% and 11%, respectively, had received prior chemotherapy for PDAC. Imbalances between the cohorts were also observed for various laboratory measures. After applying IPTW, key characteristics were generally well balanced between the NALIRIFOX cohort and the comparator FOLFIRINOX (**Table 1**), mFOLFIRINOX (**Table S3**), all-comer sensitivity (**Table S4**), and contemporary all-comer sensitivity (**Table S5**) cohorts.

Table 1. Baseline Characteristics for the NAPOLI 3 Trial NALIRIFOX Cohort vs the Trial-Aligned FOLFIRINOX Cohort, Before and After Weighting

	Unweighted			Weighted		
	NAPOLI 3 Trial NALIRIFOX Cohort (N = 383)	Trial-Aligned FOLFIRINOX Cohort (N = 219)	Std. Diff (%)	NAPOLI 3 Trial NALIRIFOX Cohort (N = 365)	Trial-Aligned FOLFIRINOX Cohort (N = 215)	Std. Diff (%)
Age at index $\geq$ 65 years, n (%)	190 (49.6)	111 (50.7)	2.2	179 (49.1)	102 (47.4)	3.5
Female, n (%)	179 (46.7)	100 (45.7)	2.2	170 (46.7)	102 (47.5)	1.6
Race, n (%)						
White	315 (82.2)	146 (66.7)	36.3*	293 (80.3)	164 (76.3)	9.9
Non-White	68 (17.8)	49 (22.4)	11.6*	72 (19.7)	42 (19.7)	0.0
Unknown	0 (0.0)	24 (11.0)	49.6*	0 (0.0)	9 (4.1)	29.1*
Year of mPDAC diagnosis date, n (%)						
2019	107 (27.9)	5 (2.3)	76.7*	110 (30.1)	7 (3.2)	77.4*
2020	276 (72.1)	70 (32.0)	87.6*	255 (69.9)	68 (31.6)	82.8*
2021	0 (0.0)	89 (40.6)	117.0*	0 (0.0)	78 (36.2)	107.0*
2022	0 (0.0)	55 (25.1)	81.9*	0 (0.0)	62 (29.0)	90.3**
Year of index, n (%)						
2020	383 (100.0)	71 (32.4)	204.2*	365 (100.0)	73 (34.0)	197.1*
2021	0 (0.0)	83 (37.9)	110.0*	0 (0.0)	74 (34.5)	103.0*
2022	0 (0.0)	65 (29.7)	91.9*	0 (0.0)	68 (31.5)	95.9*
ECOG performance status, ^b n (%)						
0	160 (41.8)	116 (53.0)	22.6*	166 (45.6)	102 (47.6)	4.0
1	223 (58.2)	103 (47.0)	22.6*	199 (54.4)	113 (52.4)	4.0
Stage at initial diagnosis of PDAC, n (%)						
Patients with known cancer stage	383 (100.0)	213 (97.3)	23.7*	365 (100.0)	211 (98.2)	19.3*
Resectable	19 (5.0)	14 (6.4)	6.2	23 (6.4)	11 (5.3)	4.5
Borderline resectable	3 (0.8)	11 (5.0)	25.5*	3 (0.8)	8 (3.8)	20.1*
Locally advanced	17 (4.4)	2 (0.9)	22.0*	16 (4.3)	1 (0.4)	25.9*
Metastatic	344 (89.8)	186 (84.9)	14.8*	323 (88.5)	190 (88.7)	0.4
Unknown	0 (0.0)	6 (2.7)	23.7*	0 (0.0)	4 (1.8)	19.3*
Site of primary disease, n (%)						
Head	147 (38.4)	90 (41.1)	5.6	146 (40.0)	82 (38.0)	4.0
Body	116 (30.3)	56 (25.6)	10.5*	103 (28.2)	59 (27.5)	1.5
Other sites (ie, tail, overlapping sites, pancreas NOS)	120 (31.3)	73 (33.3)	4.3	116 (31.9)	74 (34.5)	5.5
Time from metastatic diagnosis to index date, weeks						
mean $\pm$ SD	3.6 $\pm$ 1.8	4.6 $\pm$ 8.3	16.7*	3.7 $\pm$ 1.8	4.0 $\pm$ 5.7	8.1
median (IQR)	3.0 (2.1, 4.7)	3.0 (2.0, 4.6)		3.3 (2.3, 5.0)	3.1 (2.1, 4.1)	
Prior surgery for PDAC, n (%)	18 (4.7)	17 (7.8)	12.7*	21 (5.7)	13 (5.8)	0.4
Time from surgery to metastatic disease diagnosis, months						
mean $\pm$ SD	29.1 $\pm$ 33.5	14.6 $\pm$ 13.1	57.0*	31.0 $\pm$ 31.8	12.0 $\pm$ 10.5	80.2*
median (IQR)	23.6 (12.5, 36.9)	11.0 (3.5, 21.4)		24.6 (18.7, 36.9)	9.2 (2.2, 18.3)	
Prior chemotherapy for PDAC, n (%)	14 (3.7)	23 (10.5)	26.9*	21 (5.8)	13 (6.1)	1.1
Time from last chemotherapy to index, months						
mean $\pm$ SD	32.0 $\pm$ 34.4	11.5 $\pm$ 12.0	79.4*	30.4 $\pm$ 34.8	11.1 $\pm$ 8.5	76.4*
median (IQR)	20.6 (13.2, 35.7)	7.3 (2.7, 15.9)		20.7 (13.2, 44.6)	7.3 (3.4, 15.4)	

Comorbidities, ^c n (%)						
Hypertension	187 (48.8)	50 (22.8)	56.3*	147 (40.2)	85 (39.7)	1.2
Thrombosis	19 (5.0)	5 (2.3)	14.4*	15 (4.1)	8 (4.0)	0.9
Ascites	3 (0.8)	5 (2.3)	12.2*	4 (1.0)	3 (1.2)	1.6
Laboratory measures ^d						
Absolute neutrophil count, 10 ⁹ /L						
mean ± SD	6.5 ± 3.3	6.3 ± 2.9	7.7	6.3 ± 3.1	6.5 ± 2.8	7.5
median (IQR)	5.6 (4.5, 7.9)	5.4 (4.3, 7.6)		5.5 (4.5, 7.6)	5.5 (4.5, 8.3)	
ALT, IU/L						
mean ± SD	38.2 ± 40.1	31.2 ± 23.3	21.3*	35.5 ± 35.1	34.2 ± 27.0	4.2
median (IQR)	25.0 (16.0, 46.0)	25.0 (15.0, 38.0)		24.0 (16.0, 42.0)	25.0 (16.0, 42.0)	
AST, IU/L						
mean ± SD	31.9 ± 34.2	29.9 ± 18.0	7.6	30.1 ± 30.3	31.5 ± 19.4	5.6
median (IQR)	24.0 (16.0, 36.0)	24.0 (18.0, 36.0)		23.0 (15.0, 35.0)	25.0 (18.0, 40.0)	
Creatinine clearance, ^e mL/min						
mean ± SD	100.9 ± 32.9	93.2 ± 28.6	24.7*	98.5 ± 31.3	98.0 ± 28.5	1.7
median (IQR)	96.8 (78.8, 120.8)	90.2 (71.3, 109.1)		95.8 (77.8, 118.8)	95.6 (75.6, 115.2)	
Hemoglobin, g/L						
mean ± SD	126.4 ± 16.5	125.1 ± 15.5	8.0	127.4 ± 15.7	125.6 ± 15.7	11.3a
median (IQR)	128.0 (116.0, 138.0)	126.0 (115.0, 134.0)		130.0 (118.0, 139.0)	127.0 (116.0, 135.0)	
Platelet count, 10 ⁹ /L						
mean ± SD	261.3 ± 91.6	245.7 ± 81.1	18.0*	255.4 ± 85.4	255.0 ± 80.2	0.5
median (IQR)	249.0 (198.0, 305.0)	229.0 (184.0, 289.0)		243.0 (193.0, 298.0)	238.0 (195.0, 301.0)	
Serum albumin, g/L						
mean ± SD	38.0 ± 4.1	39.2 ± 3.8	29.3*	38.5 ± 4.0	38.7 ± 3.9	4.5
median (IQR)	38.0 (36.0, 41.0)	40.0 (36.0, 42.0)		39.0 (36.0, 41.0)	39.0 (36.0, 42.0)	
Serum total bilirubin, μmol/L						
mean ± SD	11.6 ± 7.5	10.7 ± 5.2	14.4*	11.4 ± 7.1	11.1 ± 5.5	4.3
median (IQR)	9.4 (6.8, 14.0)	10.3 (6.8, 12.0)		9.2 (6.8, 13.5)	10.3 (6.8, 13.7)	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECOG, Eastern Cooperative Oncology Group; FOLFIRINOX, oxaliplatin + 5-fluorouracil/leucovorin + irinotecan; IQR, interquartile range; mPDAC, metastatic pancreatic ductal adenocarcinoma; NALIRIFOX, irinotecan liposome injection + oxaliplatin + 5-fluorouracil/leucovorin; NOS, not otherwise specified; PDAC, pancreatic ductal adenocarcinoma; SD, standard deviation; std. diff, standardized difference.

*Standardized difference ≥ 10%.

^aFor the NALIRIFOX cohort, ECOG performance status on Cycle 1 Day 1 (C1D1) was reported; if the assessment on C1D1 was unavailable, the closest assessment within 7 days prior to randomization was reported. For the trial-aligned FOLFIRINOX cohort, the most recent ECOG performance status score within 7 days on or prior to the index date was reported.

^cCategories are not mutually exclusive and therefore may not sum to 100%.

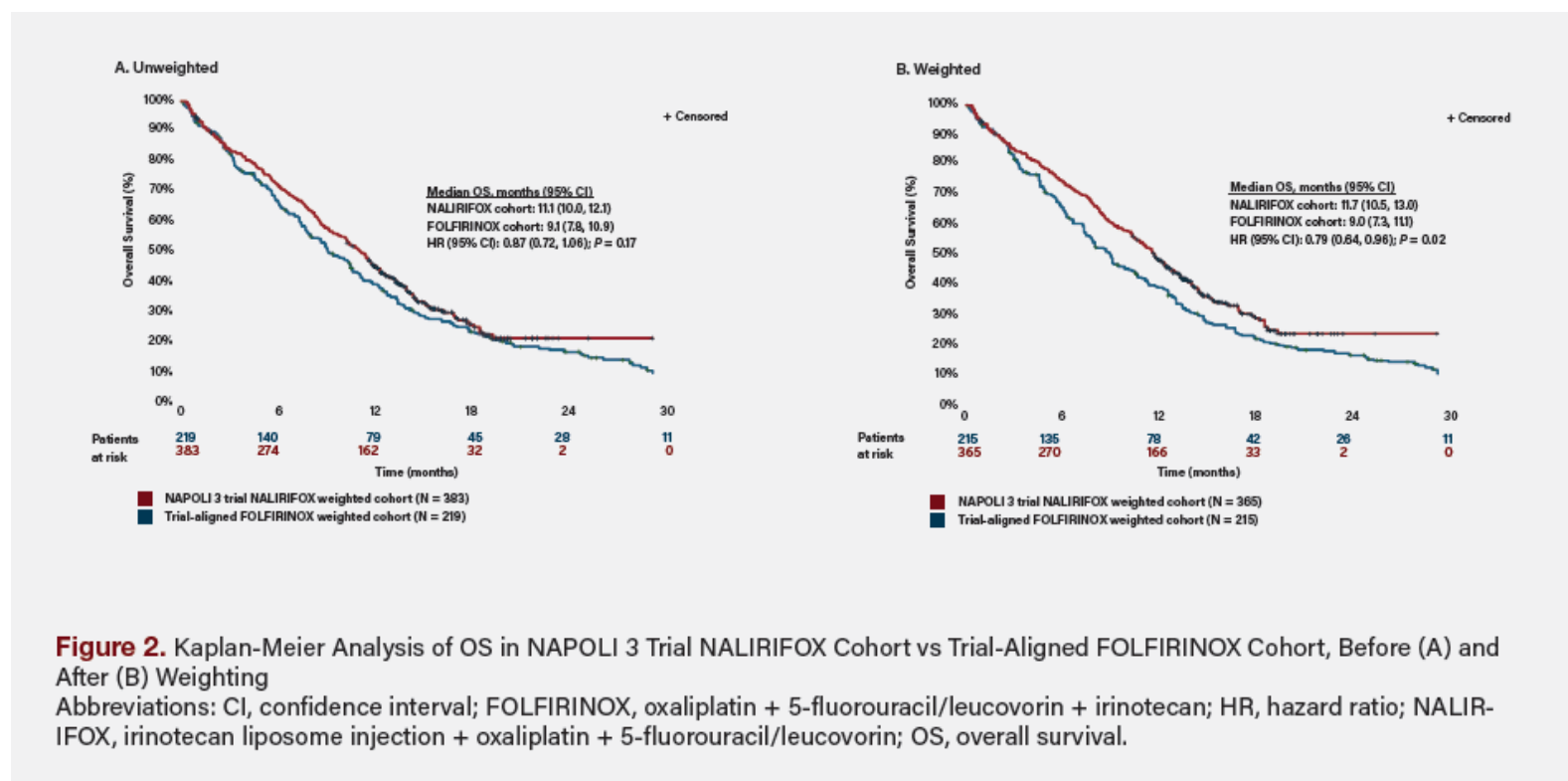
^dFor the trial-aligned FOLFIRINOX cohort, laboratory measures on the index date were reported; if assessment on the index date was unavailable, the assessment closest to the index date during the baseline period was reported. If multiple test results were available on the same date, the average value was used.

^eFor the trial-aligned FOLFIRINOX cohort, if creatinine clearance value was not directly available in patients' lab data, it was calculated based on serum creatinine using the Cockcroft-Gault Formula: CLCR (mL/min) = (140 – age [years]) × weight (kg) / (72 × serum creatinine [mg/dL]) × 0.85 if female; (140 – age [years]) × weight (kg) / (72 × serum creatinine [mg/dL]) if male. For patients with a body mass index > 30 kg/m, adjusted body weight was used instead.

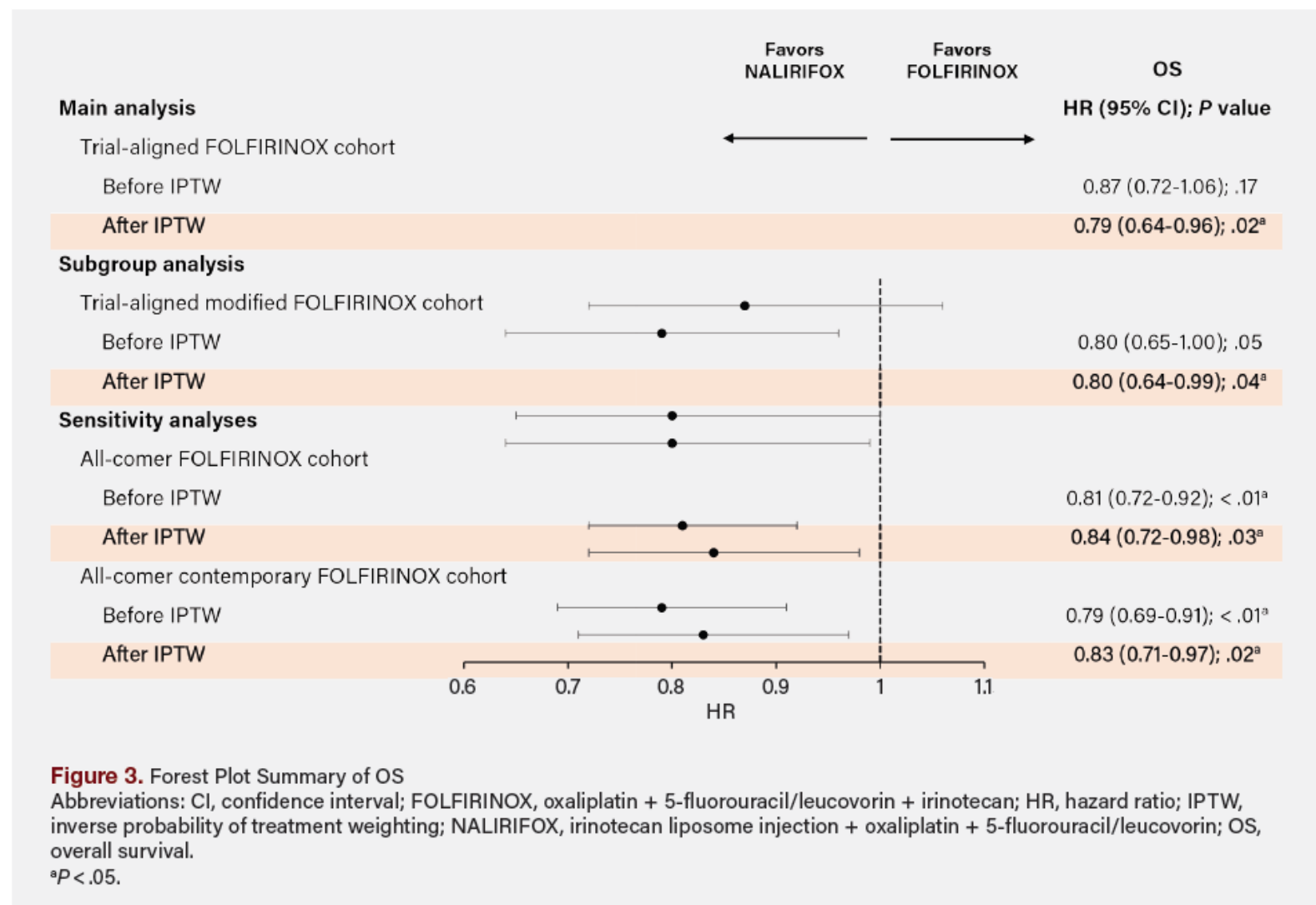
Comparison of OS

The median duration of follow-up was 10.9 months for the NALIRIFOX cohort and 8.9 months for the FOLFIRINOX cohort. Following IPTW, median (95% CI) OS was longer for the NALIRIFOX cohort compared with the FOLFIRINOX cohort (11.7; 10.5-13.0) months vs 9.0 (7.3-11.1) months, respectively). The analysis demonstrated a statistically significant OS benefit favoring NALIRIFOX compared with FOLFIRINOX (HR, 0.79; 95% CI, 0.64-0.96; *P* = .02) (**Table 2**, **Figure 2**).

Table 2. Comparative Analysis of OS for the NAPOLI 3 Trial NALIRIFOX Cohort vs the Trial-Aligned FOLFIRINOX Cohort, Before and After Weighting				
	Unweighted		Weighted	
	NAPOLI 3 Trial NALIRIFOX Cohort (N = 383)	Trial-Aligned FOLFIRINOX Cohort (N = 219)	NAPOLI 3 Trial NALIRIFOX Cohort (N = 365)	Trial-Aligned FOLFIRINOX Cohort (N = 215)
Death, n (%)	259 (67.6)	184 (84.0)	235 (64.5)	177 (82.6)
Censored, n (%)	124 (32.4)	35 (16.0)	130 (35.5)	37 (17.4)
Median OS, months (95% CI)	11.1 (10.0-12.1)	9.1 (7.8-10.9)	11.7 (10.5-13.0)	9.0 (7.3-11.1)
HR (95% CI); <i>P</i>	0.87 (0.72-1.06); <i>P</i> = .17	Reference	0.79 (0.64-0.96); <i>P</i> = .02	Reference
Probability of OS, n, % (95% CI)				
3 months	319, 84.2 (80.2-87.5)	178, 82.9 (77.2-87.3)	309, 85.4 (81.3-88.8)	174, 83.2 (76.1-88.4)
6 months	274, 72.4 (67.6-76.6)	140, 66.9 (60.1-72.7)	270, 74.6 (69.6-78.9)	135, 66.2 (57.8-73.3)
9 months	220, 58.1 (53.0-62.9)	106, 51.4 (44.5-58.0)	220, 61.0 (55.5-66.0)	98, 49.4 (41.1-57.2)
12 months	162, 45.6 (40.5-50.5)	79, 39.6 (32.9-46.2)	166, 48.9 (43.4-54.2)	78, 39.9 (31.8-47.8)
18 months	32, 26.2 (20.9-31.7)	45, 23.8 (18.1-29.8)	33, 29.7 (23.8-35.8)	42, 22.7 (16.2-29.9)
Follow-up duration, months				
mean ± SD	10.1 ± 5.8	11.1 ± 9.2	10.4 ± 5.7	10.8 ± 9.0
median (IQR)	10.9 (5.2, 14.2)	8.9 (3.6, 15.3)	11.6 (5.7, 14.4)	8.0 (3.8, 15.0)
Abbreviations: CI, confidence interval; FOLFIRINOX, oxaliplatin + 5-fluorouracil/leucovorin + irinotecan; HR, hazard ratio; IQR, interquartile range; NALIRIFOX, irinotecan liposome injection + oxaliplatin + 5-fluorouracil/leucovorin; OS, overall survival; SD, standard deviation.				



Subgroup and sensitivity analyses results were consistent with the main analysis. Median (95% CI) OS was longer for the weighted NALIRIFOX cohort (11.5; 10.3-12.5 months) than for the IPTW-adjusted mFOLFIRINOX cohort (8.0; 6.7-11.2 months) (HR, 0.80; 95% CI, 0.64-0.99; $P = .04$).



Similarly, sensitivity analyses comparing OS for the NALIRIFOX cohort with that for the FOLFIRINOX all-comer and all-comer contemporary cohorts yielded similar results to those of the main analysis. Overall, treatment with NALIRIFOX was associated with a statistically significant reduction in the hazard of death compared with FOLFIRINOX (main analysis, 21% reduction; sensitivity analyses, 16%-17% reduction) and compared with mFOLFIRINOX (20% reduction) (**Figure 3**).

Discussion

The lack of direct comparative evidence for NALIRIFOX vs FOLFIRINOX from clinical trials or prospective real-world studies has created an important evidence gap for the management of previously untreated mPDAC. A meta-analysis of 7 clinical trials concluded that 1L NALIRIFOX and FOLFIRINOX may provide comparable efficacy and that both offer superior survival benefits over GnP.²²

In the absence of prospective comparative study data, we constructed an ECA of patients who received full or modified FOLFIRINOX treatment in real-world clinical practice and who met key eligibility criteria for NAPOLI 3. We further aligned the real-world mFOLFIRINOX cohorts to the NAPOLI 3 NALIRIFOX cohort using statistical weighting to adjust for residual differences in the distribution of key baseline characteristics. After weighting, NALIRIFOX was associated with a statistically significant reduction in the probability of death compared with FOLFIRINOX (21% reduction) and compared with mFOLFIRINOX (20% reduction).

In the present analysis, mFOLFIRINOX accounted for approximately 70% of patients in the FOLFIRINOX cohort, suggesting that modification of FOLFIRINOX is common in real-world clinical practice. This finding aligns with existing evidence that mFOLFIRINOX may be better tolerated and preferred over the traditional regimen.^{19,23} A 2018 meta-analysis of 11 studies evaluating the efficacy of mFOLFIRINOX indicated that it had similar survival benefits but lower toxicity than full FOLFIRINOX.²³ In the present analysis, NALIRIFOX consistently demonstrated improved OS compared with mFOLFIRINOX. However, it should be noted that the reasons for modifying FOLFIRINOX were not captured in this study and that, in the absence of a standardized definition of mFOLFIRINOX dosing, the definition used for the present analysis may not capture all modifications likely used in clinical practice.

The OS benefits observed for NALIRIFOX in the present analysis may, in part, reflect a key pharmacologic difference between the NALIRIFOX and mFOLFIRINOX regimens, specifically the inclusion of the liposomal vs non-liposomal irinotecan, respectively. Compared with the non-liposomal formulation, liposomal irinotecan has a longer half-life, and the liposomal encapsulation improves drug retention and tumor exposure, with potential benefits for enhanced efficacy.²⁴⁻²⁶

The results of this study should be interpreted while considering certain limitations. It is important to acknowledge that, although the baseline characteristics of the cohorts were aligned through application of key NAPOLI 3 eligibility criteria to all cohorts and subsequent statistical adjustments/weighting, some residual differences may have remained. In addition, it was not feasible to apply all NAPOLI 3 eligibility criteria to individuals in the mFOLFIRINOX cohorts owing to variability in data recorded in real-world practice. It is also relevant to note that heterogeneity in completeness of EHR data recording may have introduced selection bias owing to patients with insufficient data being unevaluable for inclusion in the mFOLFIRINOX study cohorts. Furthermore, comorbidities and concomitant medication use that existed prior to mPDAC diagnosis (or that are unrelated to the mPDAC treatment) may not be completely captured in the Flatiron Health EHR database, resulting in incomplete characterization (and potential under-representation) of the full comorbidity burden of the real-world mFOLFIRINOX cohorts. Further, the missingness or under-representation of certain variables that influence treatment selection or study endpoints may lead to potential residual or unmeasured confounding. However, key confounders were well balanced following IPTW adjustments, including ECOG performance score, which is recognized as an important prognostic factor in mPDAC populations.^{27,28}

Of additional note are the minor differences in the defined index dates for the cohorts: date of randomization for the NALIRIFOX; date of first FOLFIRINOX administration for the mFOLFIRINOX. Although the differences in index date definitions introduced potential for bias among the cohorts, the mean time between date randomization and the date of first NALIRIFOX administration in NAPOLI 3 was only 3 days, resulting in minimal potential impact that was likely insufficient to account for the observed difference in OS between the cohorts. Another factor to consider is that the NALIRIFOX cohort comprised all randomized patients in the NAPOLI 3 ITT population, including 13 patients (3.4%) who did not receive any dose of the NALIRIFOX regimen. In contrast, all patients in the mFOLFIRINOX cohorts received at least 1 treatment cycle. This difference may underestimate the clinical benefit of the NALIRIFOX regimen.

Another consideration is the regional difference between the 2 study cohorts; the Flatiron Health EHR includes data from US clinics; in contrast, NAPOLI 3 was a global trial. However, findings from NAPOLI 3 indicate that median OS was comparable across regional subgroups (North America, 11.2 months; rest of the world, 11.1 months), suggesting that regional differences are unlikely to bias the results meaningfully.¹⁷ Nonetheless, future analyses that include a balanced distribution of regions may help further evaluate this potential source of bias.

Lastly, because this study focused on a specific population of patients with mPDAC treated with 1L FOLFIRINOX who met the inclusion/exclusion criteria of NAPOLI 3, the findings of the main analysis may not be generalizable to the broader mPDAC population receiving 1L mFOLFIRINOX regimens. However, sensitivity analyses involving the all-comer and contemporary all-comer FOLFIRINOX cohorts were consistent with the main analysis, providing reassurance as to the robustness and generalizability of the results.

Conclusion

In the absence of head-to-head data from clinical trials, this ECA study demonstrated that patients with mPDAC who were statistically matched on baseline characteristics survived for significantly longer on 1L NALIRIFOX treatment than on 1L mFOLFIRINOX. Acknowledging inherent differences in ecology of care between clinical trials and real-world clinical practice, these results provide preliminary insights into the comparative efficacy/effectiveness of 1L NALIRIFOX and mFOLFIRINOX in patients with mPDAC, paving the way for more conclusive findings from prospective real-world studies.

Key Clinical Summary

- NALIRIFOX demonstrated significantly improved OS vs FOLFIRINOX and modified FOLFIRINOX in treatment-naïve metastatic PDAC using an external control arm with IPTW adjustment (HR ~0.79-0.80).
- Median OS was longer with NALIRIFOX (≈11.5-11.7 months) compared with FOLFIRINOX (≈9.0 months) and mFOLFIRINOX (≈8.0 months).
- Findings address the lack of head-to-head trials, supporting NALIRIFOX as a potentially more effective first-line option, though confirmation in prospective studies is needed.

Clinical Pathway Category: Treatment

This study informs the treatment domain of clinical pathways by providing comparative, evidence-based insights suggesting that first-line NALIRIFOX may offer superior overall survival vs FOLFIRINOX in metastatic PDAC, addressing a key gap where head-to-head trial data are lacking. By leveraging robust statistical adjustment of real-world and trial data, it aligns with evidence-based standards and supports pathway optimization toward more effective, data-driven regimen selection to improve oncology care delivery.

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