Bridging the Gap between the NAPOLI 3 Trial and Real-World Practice: Real-World Overall Survival (OS) of First-Line (1L) FOLFIRINOX in Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC)

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Background

- NALIRIFOX (liposomal irinotecan + 5-fluorouracil/leucovorin [5-FU/LV] + oxaliplatin), approved by the US Food and Drug Administration (FDA) for the first line (1L) treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC), demonstrated significantly improved overall survival (OS) compared to 1L gemcitabine in combination with nab-paclitaxel (gem/NabP) in the phase 3 NAPOLI 3 trial (NCT04083235).[1]
  - The median OS (95% CI) among patients treated with NALIRIFOX was 11.1 (10.0, 12.1) months compared to 9.2 (8.3, 10.6) months for gem/NabP (hazard ratio [HR]: 0.83; 95% CI: 0.70, 0.99; p = 0.04).
- However, the relative efficacy of NALIRIFOX versus FOLFIRINOX (FFX) in the frontline setting is unknown. To further contextualize findings from NAPOLI 3 trial, the current study examined OS among patients treated with 1L FFX in the real-world setting.

Objective

- To describe OS for patients with mPDAC treated with 1L FFX in three cohorts: 1) all-comer patients, 2) patients who met the eligibility criteria of the NAPOLI 3 trial, and 3) a subgroup of cohort 2 who received the modified FFX (mFFX) regimen.

Methods

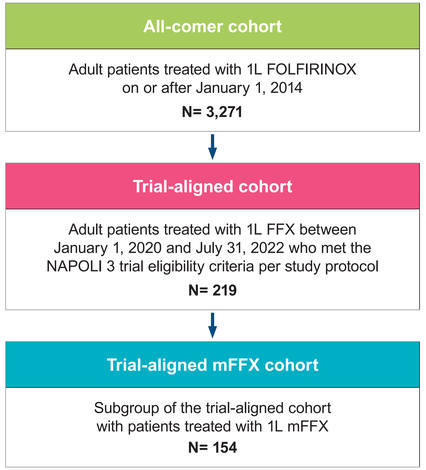
Database

- De-identified, patient-level, longitudinal data from Flatiron Health Electronic Health Record from January 1, 2014 to February 29, 2024 were used to construct the study cohorts for this study.

Study design

- A retrospective, longitudinal cohort design was used.
  - The *index date* was defined as the date of initiation of 1L treatment with FFX for mPDAC.
  - The *baseline period* was defined as the 12-month period prior to the index date, during which patients' demographics, disease-related characteristics, and clinical characteristics were assessed.
  - The *observation period* was defined as the duration from index date to the earlier of patient death or date of last confirmed activity based on the available data (i.e., end of data availability), during which the study outcome (i.e., OS) was assessed.
- Three cohorts of patients with mPDAC treated with 1L FFX were identified (**Figure 1**):
  - **All-comer cohort:** all adult patients with mPDAC treated with 1L FFX since January 2014.
  - **Trial-aligned cohort:** adult patients with mPDAC treated with 1L FFX between January 1, 2020 and July 31, 2022 (to align with the NAPOLI 3 trial) who met the inclusion/exclusion criteria of the NAPOLI 3 trial, to the extent possible.
  - **Trial-aligned mFFX cohort:** a subgroup of patients in the trial-aligned cohort who received modified FFX regimen, defined as receipt of initial dose of irinotecan ≤150 mg/m^2 or initial cumulative dose (bolus+infusion) of 5-FU of ≤2,720 mg/m^2 during the first cycle (within 30 days of the index date).

Figure 1. Patient disposition flowchart



Statistical methods

- Descriptive statistics were reported for baseline demographic, clinical, and mPDAC-related characteristics.
- OS was assessed using Kaplan-Meier (KM) methodology.

References

1. Wainberg ZA, Melisi D, Macarulla T, et al. NALIRIFOX versus nab-paclitaxel and gemcitabine in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma (NAPOLI 3): a randomised, open-label, phase 3 trial. *The Lancet* 2023; **402**(10409): 1272-81.

Abbreviations 1L, first-line; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FFX, FOLFIRINOX; IQR, interquartile range; mFFX, modified FOLFIRINOX; mPDAC, metastatic pancreatic ductal adenocarcinoma; PDAC, pancreatic ductal adenocarcinoma; SD, standard deviation.

Results

- The all-comer cohort consistent of 3,271 patients treated with 1L FFX. The trial-aligned cohort included 219 patients who met the inclusion/exclusion criteria of the NAPOLI 3 trial. The mFFX cohort included 154 patients.

Baseline characteristics (Table 1)

- The distribution of baseline characteristics was similar across cohorts. The mean (SD) age on the index date of the trial-aligned cohort was 64.6 (8.2) years; the majority of patients were male (54.3%) and White (66.7%); 47.0% of patients had a baseline ECOG of 1 (47.0%).

OS (Figure 2)

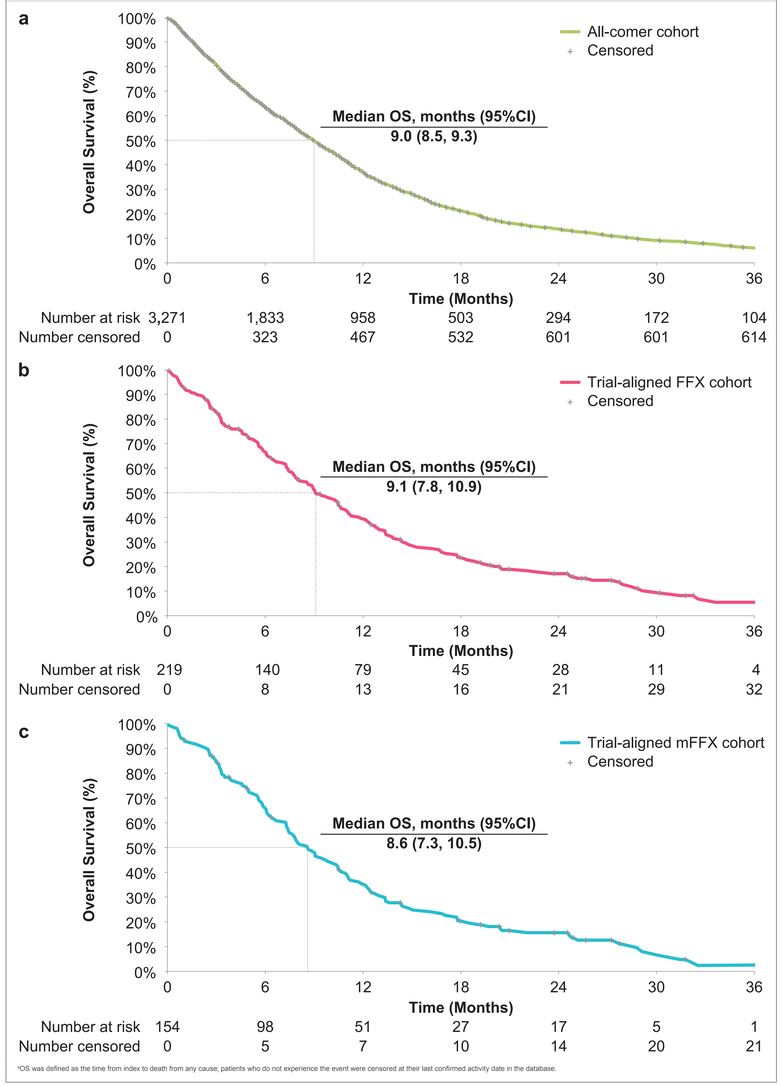
- For the trial-aligned cohort, median OS was 9.1 months (95% CI: 7.8, 10.9). Similar results were observed in the all-comer cohort (median OS: 9.0 months; 95% CI: 8.5, 9.3), while the mFFX had a median OS of 8.6 months (95% CI: 7.3, 10.5).

Table 1. Baseline demographic and clinical characteristics

	All-comer cohort N=3,271	Trial-aligned cohort N=219	Trial-aligned mFFX cohort N=154
Age at index, years			
Mean ± SD	63.5 (9.0)	64.6 (8.2)	65.1 (8.5)
Median [IQR]	64.0 [58.0, 70.0]	65.0 [59.0, 71.0]	65.5 [60.0, 72.0]
Male, n (%)	1,894 (57.9)	119 (54.3)	86 (55.8)
Race, n (%)			
Patients with known race	2,860 (87.4)	195 (89.0)	136 (88.3)
White	2,118 (64.8)	146 (66.7)	100 (64.9)
Black or African American	284 (8.7)	18 (8.2)	13 (8.4)
Asian	60 (1.8)	5 (2.3)	3 (1.9)
Other	398 (12.2)	26 (11.9)	20 (13.0)
Unknown	411 (12.6)	24 (11.0)	18 (11.7)
Time from metastatic diagnosis to index date, weeks			
Mean ± SD	4.5 ± 8.4	4.6 ± 8.3	4.8 ± 9.6
Median [IQR]	3.0 [1.9, 4.7]	3.0 [2.0, 4.6]	3.0 [2.0, 4.4]
Metastatic stage at initial diagnosis of PDAC, n (%)	2,628 (80.3)	186 (84.9)	127 (82.5)
ECOG performance status,[a,b] n (%)			
Patients with known ECOG	2,711 (82.9)	219 (100)	154 (100)
0	1,135 (34.7)	116 (53.0)	77 (50.0)
≥ 1	1,576 (48.2)	103 (47.0)	77 (50.0)
Unknown	560 (17.1)	0 (0)	0 (0)
Prior treatments for PDAC,[c] n (%)			
Surgery	371 (11.3)	17 (7.8)	15 (9.7)
Chemotherapy	452 (13.8)	23 (10.5)	19 (12.3)

Notes:
[a]ECOG performance status on the index date was reported. If the assessment on the index date was unavailable, the assessment closest to the index date within 7 days prior to index was reported. If multiple scores were available on the same date, the maximum value was used.
[b]Trial-aligned cohort and trial-aligned mFFX cohort only included patients with ECOG ≤1.
[c]Prior treatments were assessed between the date of first confirmed diagnosis of PDAC and the index date. Categories are not mutually exclusive.

Figure 2. KM analysis of OS[a]



[a]OS was defined as the time from index to death from any cause; patients who do not experience the event were censored at their last confirmed activity date in the database.

Conclusions

- The FFX regimen for mPDAC in the real-world setting demonstrated a median OS ranging from 8.6 to 9.1 months.
- Comparative analyses adjusting for differences in baseline characteristics between the NAPOLI 3 trial NALIRIFOX cohort and the real-world FFX cohorts are warranted to assess the relative efficacy of the two regimens.

Presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 2025 | Montreal, QC, Canada | May 13–16, 2025

This study was funded by Ipsen.