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Clinical News From the American Society of Clinical Oncology

First-Line Treatment of Metastatic Pancreatic Ductal Adenocarcinoma: Did 2024 Offer New Insights?

January 22, 2025

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Key Points:

- The NAPOLI-3 trial established superiority of NALIRIFOX over gemcitabine/nab-paclitaxel (GnP) for first-line treatment of unselected patients with metastatic pancreatic ductal adenocarcinoma (mPDAC).
- NALIRIFOX treatment is more costly than FOLFIRINOX and the relative efficacy of NALIRIFOX versus FOLFIRINOX or modified FOLFIRINOX (mFFX) has yet to be explored head-to-head in a prospective randomized trial.
- Superiority of NALIRIFOX in NAPOLI-3 could be driven by molecular differences in the study population, as compared with the PASS-01 and GENERATE trials; the field awaits publication of outcome data for the DNA damage repair (DDR) wild-type subgroup.

FOLFIRINOX and GnP chemotherapy have both been demonstrated to improve median overall survival (mOS) compared with single-agent gemcitabine in fit patients with mPDAC when given in the first-line setting.^{1,2} However, in the decade since their initial approvals, no prospective randomized, head-to-head

comparisons between the 2 regimens have been conducted. This has left oncologists struggling to choose between them based on toxicity profile alone, given the absence of high-level data on superiority.

For patients with PDAC with tumors containing mutations in DDR-related genes, such as *BRCA1/2* and *PALB2*, excellent data exist that demonstrate that the use of platinum-containing regimens such as FOLFIRINOX in the first-line setting result in improved OS.³⁻⁶ Last year, data from 3 new studies shed light on comparative activity of first-line combination chemotherapy regimens in the remaining mPDAC population.



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NAPOLI-3 Sets the Stage

Definitive evidence for a superior first-line combination chemotherapy regimen for fit patients with mPDAC is and remains an important milestone in the field. NAPOLI-3, the first prospective randomized phase 3 study to address this issue, compared NALIRIFOX to GnP in the first-line setting in unselected patients with mPDAC and established the superiority of NALIRIFOX.⁷ Although some patients and oncologists might still favor GnP for its lower gastrointestinal toxicities, such as diarrhea, nausea, and vomiting, NALIRIFOX offered approximately 2 months' improvement in mOS, decreased hematologic toxicity, and half the rate of peripheral neuropathy as GnP. The U.S. Food and Drug Administration approved NALIRIFOX for first-line mPDAC treatment in February 2024 based on these data, putting GnP in the backseat in the first-line setting.⁸

However, NAPOLI-3 did not address whether NALIRIFOX represents an improvement over FOLFIRINOX or is simply an equivalent derivative. NALIRIFOX contains the same chemotherapy agents as FOLFIRINOX, except that standard irinotecan is replaced by the more costly nanoliposomal irinotecan (nal-IRI). Although studies exist to support that nal-IRI has a prolonged half-life and achieves improved intratumoral drug concentration compared with standard irinotecan, the efficacy of nal-IRI versus irinotecan has not been directly compared in a prospective randomized clinical trial either alone or in parallel combinations such as NALIRIFOX versus FOLFIRINOX. Although cross-trial comparisons are fraught with issues, NAPOLI-3 and the 2011 PRODIGE-4 study that established FOLFIRINOX as a standard of care had identical 11.1 months mOS, and the 2 studies enrolled a similar patient population.^{1,7} Currently, we lack clear evidence to assess whether the higher cost of NALIRIFOX is compensated by increased efficacy.

Less attention has been paid to 2 other differences between FOLFIRINOX and NALIRIFOX. First, NALIRIFOX eliminates the 5-fluorouracil bolus, mimicking the mFFX adjuvant regimen that improves survival in patients with resectable

disease.⁹ This significantly lessens regimen toxicity. Second, NALIRIFOX uses a reduced dose of oxaliplatin as compared with FOLFIRINOX and mFFX, which certainly contributed to the reduction in peripheral neuropathy (3% vs 9%) reported for NALIRIFOX-treated patients in NAPOLI-3 versus FOLFIRINOX-treated patients in PRODIGE-4. These regimen modifications have made NALIRIFOX more tolerable for patients.

PASS-01 and GENERATE Throw a Curveball

Results from the randomized multicenter PASS-01 and GENERATE (JCOG1611) studies, which evaluated the efficacy of first-line mPDAC regimens, were reported at the 2024 ASCO Annual Meeting and 2024 European Society for Medical Oncology Congress. In PASS-01, the still-maturing data show that GnP is superior to mFFX; similarly, the GENERATE study, which was designed to establish the superiority of mFFX (and S-1, irinotecan, and oxaliplatin) over GnP, closed early for futility.^{10,11}

Most likely, differences in study population contributed to the disparate efficacy results of PASS-01 and GENERATE as compared with NAPOLI-3. GENERATE recruited an exclusively Japanese population, a group that has well-known differences in ability to metabolize mFFX components, whereas only 5% of patients in NAPOLI-3 were Asian. Importantly, PASS-01 excluded patients with DDR mutations. Case control studies have estimated a 37% increase in response rate and at least a 13-month increase in OS for patients with a *gBRCA1/2* mutation versus patients with wild-type advanced PDAC who receive platinum-containing regimens.^{5,12} Incidence of DDR mutations in the NAPOLI-3 population has not yet been reported, so it is not possible to determine whether the survival advantage seen with NALIRIFOX would remain significant in the subset of study participants lacking DDR mutations.

Notably, outcomes in the PASS-01 population were numerically poorer for both arms as compared with other studies. This potentially reflects the effect of removing patients with better prognosis and DDR-mutant tumors and replacing them with patients more likely to have poor-prognosis basal-subtype disease.¹³ In PASS-01, patients with basal subtype had inferior progression-free survival compared with those with classical subtype, as expected (2.7 vs 5.7 months; *P* = .03). New treatment paradigms are needed to address basal disease.

An alternative hypothesis that could explain the divergent results of PASS-01 and GENERATE, as compared with NAPOLI-3, is that we have wrongly assumed that NALIRIFOX is just an equivalent derivative regimen to mFFX. NALIRIFOX led to better outcomes than GnP, but mFFX failed to do so. Perhaps we should recalibrate and consider that NALIRIFOX may be superior to mFFX and endeavor to determine if this is true. A head-to-head study could address whether there is sufficient improvement in benefit to justify the cost difference.

Select randomized trials of first-line therapy in mPDAC are summarized in the Table.^{1,2,7,10,11}

Table. Randomized Trials of First-Line Therapy in mPDAC

Study	Intervention	Comparator	Date	Phase	Pts	ECOG PS	Age (U/C)	Liver mets (% of pop U/C)	mOS (months U/C; <i>P</i> value)	mPFS (months U/C; <i>P</i> value)	Comments
PRODIGE-4 ¹	FOLFIRINOX	Gem	2011	3	342	0-1	61/61	87.6/87.7	11.1/6.8 (< .001)	6.4/3.3 (< .001)	Independent radiologic review
MPACT ²	GnP	Gem	2013	3	861	0-2	62/63	85/84	8.5/6.7 (< .001)	5.5/3.7 (< .001)	—
NAPOLI-3 ⁷	NALIRIFOX	GnP	2023	3	770	0-1	62.8/64.0	80/80	11.1/9.2 (.026)	7.4/5.6 (< .0001)	Investigator review of images No DDR mutation data
JCOG-1611 (GENERATE) ¹⁰	A: S-1/ROX B: mFFX	GnP	2024	2/3	527	0-1	65/67/65	A: 70.5 B: 70.9/66.5	A: 13.2 B: 12.5/15.3a	A: 6.0 B: 5.9/6.5b	Exclusively Japanese population
PASS-01 ¹¹	mFFX	GnP	2024	2	160	0-1	62/66	87/80	8.4/9.7 (.014)c	4.0/5.5 (.08)	Germline BRCA1/2, PALB2 excluded

^aGnP versus S-IROX (HR 1.23, 95% CI [0.98, 1.56]) and GnP versus mFFX (HR 1.27, 95% CI [1.01, 1.61]).

^bGnP versus S-IROX (HR 0.96, 95% CI [0.77, 1.20]) and GnP versus mFFX (HR 1.06, 95% CI [0.86, 1.32]).

^cData are still maturing.

Abbreviations: C, comparator; DDR, DNA damage repair; Gem, gemcitabine; GnP, gemcitabine/nab-paclitaxel; I, intervention; mets, metastases; mFFX, modified FOLFIRINOX; mOS, median overall survival; mPDAC, metastatic pancreatic ductal adenocarcinoma; mPFS, median progression-free survival; pop, population; PS, performance status; S-IROX, S-1/irinotecan/oxaliplatin.

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The Bigger Picture

Choosing the most efficacious first-line regimen for each patient matters. A total of 44% of patients in PASS-01 were unable to receive second-line treatment, underscoring that second chances are frequently unavailable even for patients with good initial performance status. The data collectively emphasize the need for biomarker-driven approaches to choosing first-line therapy. We await new treatment breakthroughs in the field that might finally push mOS for patients with mPDAC beyond 1 year.

References:

1. Conroy T, Desseigne F, Ychou M, et al; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. [N Engl J Med](#) . 2011;364(19):1817-1825.
2. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. [N Engl J Med](#) . 2013;369(18):1691-1703.
3. O'Reilly EM, Lee JW, Zalupski M, et al. Randomized, multicenter, phase II trial of gemcitabine and cisplatin with or without veliparib in patients with pancreas adenocarcinoma and a germline *BRCA/PALB2* mutation. [J Clin Oncol](#) . 2020;38(13):1378-1388.
4. Fogelman D, Sugar EA, Oliver G, et al. Family history as a marker of platinum sensitivity in pancreatic adenocarcinoma. [Cancer Chemother Pharmacol](#) . 2015;76(3):489-498.
5. Reiss KA, Yu S, Judy R, Symecko H, Nathanson KL, Domchek SM. Retrospective survival analysis of patients with advanced pancreatic ductal adenocarcinoma and germline *BRCA* or *PALB2* mutations. [JCO Precis Oncol](#) . 2018;2(2):1-9.
6. Yu S, Agarwal P, Mamtani R, et al. Retrospective survival analysis of patients with resected pancreatic ductal adenocarcinoma and a germline *BRCA* or *PALB2* mutation. [JCO Precis Oncol](#) . 2019;3(3):1-11.
7. Wainberg ZA, Melisi D, Macarulla T, et al. NALIRIFOX versus nab-paclitaxel and gemcitabine in treatment-naïve patients with metastatic pancreatic ductal adenocarcinoma (NAPOLI 3): a randomised, open-label, phase 3 trial. [Lancet](#) . 2023;402(10409):1272-1281.
8. U.S. Food and Drug Administration. FDA approves irinotecan liposome for first-line treatment of metastatic pancreatic adenocarcinoma. Published February 13, 2024. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-irinotecan-liposome-first-line-treatment-metastatic-pancreatic-adenocarcinoma>
9. Conroy T, Hammel P, Hebbar M, et al; Canadian Cancer Trials Group and the Unicancer-GI-PRODIGE Group. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. [N Engl J Med](#) . 2018;379(25):2395-2406.
10. Kobayashi S, Ohba A, Ozaka M, et al. 1527P GnP vs mFOLFIRINOX or S-IROX in metastatic pancreatic cancer: 1-year follow-up updated data from the GENERATE (JCOG1611). [Ann Oncol](#) . 2024;35(suppl 2):S932.
11. Knox JJ, Jaffee EM, O'Kane GM, et al. Early results of the PASS-01 trial: pancreatic adenocarcinoma signature stratification for treatment-01. [J Clin Oncol](#) . 2024;42:17s (suppl; LBA4004).
12. Wattenberg MM, Asch D, Yu S, et al. Platinum response characteristics of patients with pancreatic ductal adenocarcinoma and a germline *BRCA1*, *BRCA2* or *PALB2* mutation. [Br J Cancer](#) . 2020;122(3):333-339.
13. Aung KL, Fischer SE, Denroche RE, et al. Genomics-driven precision medicine for advanced pancreatic cancer: early results from the COMPASS trial. [Clin Cancer Res](#) . 2018;24(6):1344-

1354.

Disclosures of Potential Conflicts of Interest

Dr. Nebojsa Skorupan: None disclosed.

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Research Funding (Inst.): HCW Biologics

Patents, Royalties, Other Intellectual Property: Receive royalties from a mouse model

Patents, Royalties, Other Intellectual Property (Inst.): Licensing fee from mouse model

Uncompensated Relationships (Inst.): Minneamrita Therapeutics, AstraZeneca, ProDa LLC

Drug Support: ProDa LLC, HCW Biologics, Minneamrita, and AstraZeneca for clinical studies

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