

Starting at the Front Line in Metastatic Pancreatic Cancer As New Options Emerge, How Do You Select and Sequence?

FACULTY



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LEARNING OBJECTIVES

Upon successful completion of this activity, you should be better prepared to:

- Select appropriate first-line therapy for locally advanced or metastatic pancreatic cancer based on relevant biomarkers, clinical, and logistical factors.
- Develop an evidence-based strategy for the treatment of metastatic pancreatic cancer in patients who experience disease progression on front-line chemotherapy, exploring the importance of age, performance status, and prior therapy exposure
- Explain the biologic rationale and clinical data for investigational agents currently being evaluated in pancreatic cancer
- Identify a plan to recognize and manage adverse effects associated with approved systemic regimens commonly employed in the management of pancreatic cancer to support quality of life and continuation of therapy

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Pancreatic cancers have the dubious distinction of having the lowest survival rates of any major cancer, with an overall 5-year relative survival of only 13%.¹ The majority of pancreatic cancers are detected after they have already spread, with 29% of cases involving regional lymph nodes and 51% of patients receiving a diagnosis of metastatic cancer. Pancreatic ductal adenocarcinoma (PDAC) accounts for 90% of pancreatic cancers.² PDAC is particularly resistant to chemotherapy owing to the broad heterogeneity of mutations and dense stromal environment found in these tumors.

Head-to-Head Trials of First-Line Chemotherapy

Both modified FOLFIRINOX (mFFX) and gemcitabine plus nab-paclitaxel (GnP) are preferred first-line regimens for PDAC, according to National Comprehensive Cancer Network (NCCN) guidelines.³ The randomized phase 2 PASS-01 trial (NCT04469556) compared these regimens head-to-head in 140 patients with de novo metastatic PDAC (mPDAC).⁴ Patients given GnP experienced a numerically but not statistically longer progression-free survival (PFS) than did those given FOLFIRINOX (5.5 vs 4.0 months, respectively; $P=.14$). Median overall survival (OS) was 9.7 months with GnP and 8.4 months with mFFX ($P=.04$). Partial response (PR) was achieved in 29% of patients receiving GnP and 24% of patients receiving mFFX. Serious adverse events (AEs) were reported in 3% of patients receiving GnP and 13% of patients receiving mFFX.

The phase 3 NAPOLI 3 trial (NCT04083235) compared NALIRIFOX vs GnP in 770 patients with metastatic PDAC.⁵ Median OS with NALIRIFOX therapy was 11.1 months (95% CI, 10.0-12.1 months) vs 9.2 months (95% CI, 8.3-10.6 months) with GnP (HR, 0.83; 95% CI, 0.70-0.99; $P=.036$). The 12-month OS was 45.6% (95% CI, 40.5%-50.5%) in the NALIRIFOX arm and 39.5% (95% CI, 34.6%-44.4%) in the GnP arm. The 18-month OS was 26.2% (95% CI, 20.9%-31.7%) with NALIRIFOX and 19.3% (95% CI, 14.8%-24.2%) with GnP. Median PFS with NALIRIFOX was 7.4 months vs 5.6 months with GnP (HR, 0.69; 95% CI, 0.58-0.83; $P=.0001$). Treatment-emergent AEs (TEAEs) were reported in 369 (99.7%) of 370 patients who received NALIRIFOX and 376 (99.2%) of 379 patients who received GnP. The most common TEAEs of grade 3 or 4 with NALIRIFOX and GnP, respectively, were diarrhea (20.3% vs 4.5%), nausea (11.9% vs 2.6%), hypokalemia (15.1% vs 4.0%), anemia (10.5% vs 17.4%), and neutropenia (14.1% vs 24.5%). Treatment-related AEs (TRAEs) leading to death occurred in 2% of patients in the NALIRIFOX group and 2% of patients in the GnP group.

Targeted Therapies in Early-Phase Trials

The phase 1b/2 OPTIMIZE-1 trial (NCT04888312) evaluated whether adding the anti-CD40 antibody mitazalimab to mFFX would improve outcomes for 70 patients with newly diagnosed PDAC.⁶ Objective responses were confirmed in 23 of 57 patients (40.4%) evaluated for efficacy (1-sided 90% CI; ≥ 32 of 57 patients),

including 1 complete response. Median OS was 14.3 months, median PFS was 7.4 months, and median duration of response (DOR) was 12.5 months.⁷ The most commonly reported AEs of grade 3 or greater were consistent with the mFFX safety profile: neutropenia (25.7%), anemia (11.4%), hypokalemia (15.7%), and thrombocytopenia (11.4%). The most common serious AEs reported were vomiting (5%), decreased appetite (6%), diarrhea (4%), and cholangitis (4%).⁶ None were considered related to mitazalimab.

The phase 1/1b ARC-8 clinical trial (NCT04104672) investigated the benefit of the CD73 inhibitor quemliclustat.⁸ CD73 is overexpressed in 40% to 60% of PDAC and is associated with poor outcomes. ARC-8 combined quemliclustat with GnP with and without the anti-PD-1 antibody zimberelimab in 122 patients with untreated mPDAC. Outcomes were better in the arm without zimberelimab. In the quemliclustat plus GnP arm, the

objective response rate (ORR) was 41% (95% CI, 24%-61%), the median PFS was 8.8 months (95% CI, 6.4-12.6 months), and the median OS was 19.4 months (95% CI, 12.1-23.0 months). AEs of grade 3 or greater were reported in 85% of trial participants, with the most common being decreased neutrophil count (31%) and anemia (25%). A total of 23% of patients discontinued the study due to AEs.

For patients with core homologous repair deficiency (HRD) such as germline *BRCA1/2* mutations, maintenance olaparib therapy has been shown to improve PFS.⁹ The phase 2 POLAR study (NCT04666740) investigated whether the benefit of this PARP inhibitor combined with pembrolizumab as maintenance therapy could be extended to 30 patients with non-core HRD mutations (cohort B) and exceptional platinum responders (cohort C).¹⁰ The ORR was 0% in cohort B and 13.5% in cohort C. The disease control rate (DCR) was 60% in cohort B and 46.5% in cohort C. The median PFS was 4 months (95% CI, 4-not reached [NR]) in cohort B and 3.3 months (95% CI, 1.9-5.4) in cohort C. Median OS was not reached (95% CI, 12-NR) in cohort B and 11 months (95% CI, 9.1-NR) in cohort C. TRAEs grade 3 and higher were diarrhea (7%), hyperglycemia (7%), anemia (14%), and increased lipase (7%).

Breaking the *KRAS* Barrier

KRAS mutations occur in approximately 90% of pancreatic cancers, including *KRAS* G12C mutations in approximately 2%.¹¹ Adagrasib is an irreversible inhibitor of *KRAS* G12C that was evaluated for



efficacy as monotherapy in patients with unresectable or metastatic solid tumors harboring this mutation in the phase 1/2 KRYSTAL-1 trial (NCT03785249). In the 21-patient PDAC cohort, ORR was 33.3%, DCR was 81.0%, median PFS was 5.4 months (95% CI, 3.9-8.2 months), and median OS was 8.0 months (95% CI, 5.2-11.8 months). In all 63 patients in this basket trial, the most common TRAEs were nausea (49.2%), diarrhea (47.6%), fatigue (41.3%), and vomiting (39.7%). Grade 3 TRAEs were reported in 25.4% of patients; grade 4 TRAEs were reported in 1.6%. In the phase 1/2 LOXO-RAS-20001 study (NCT04956640) in patients with solid tumors harboring *KRAS* G12C mutations, LY3537982 yielded an ORR of 42% in the 12-patient pancreatic cancer cohort.¹²

The ORR was also 42% in 7 patients with pancreatic cancer, including 3 PRs in a phase 1 basket trial of divarasib monotherapy in advanced or metastatic solid tumors harboring a *KRAS* G12C muta-

tion.¹³ In the overall population of 137 patients, grade 3 TRAEs were reported in 11% of patients, most commonly diarrhea, increased alanine aminotransferase (ALT) level, and increased aspartate aminotransferase (AST) level. One grade 4 event of anaphylaxis was reported.

Glecirasib produced a confirmed ORR of 46.4%, including 13 PRs and a DCR of 96.4% in 28 patients with PDAC harboring a *KRAS* G12C mutation in a phase 1/2 clinical trial (NCT05002270).¹⁴ Median DOR was 4.1 months, and median PFS was 5.5 months (95% CI, 1.2-13.1 months). The most common TRAEs were anemia (52.1%), increased blood bilirubin (39.6%), decreased white blood cell count (18.8%), increased AST (18.8%), diarrhea (16.7%), increased ALT (14.6%), asthenia (14.6%), hypertriglyceridemia (10.4%), and nausea (10.4%). Grade 3 or 4 TRAEs were reported in 25% of patients.

According to NCCN guidelines, germline testing, as well as somatic tumor profiling to look for actionable molecular findings, should be considered for all patients with pancreatic cancer.³ With the advent and advancement of next-generation sequencing technology, molecularly informed treatment selection and sequencing is at the forefront of the field. ■



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