

# Pancreatic Adenocarcinoma: Emerging Systemic Therapy Options

Presented by Margaret A. Tempero, MD

## ABSTRACT

Although we are “winning the war against cancer,” pancreatic malignancies are expected to be the most common cause of cancer-related death by 2040. Several systemic therapies, such as oxaliplatin + irinotecan/fluorouracil/leucovorin (FOLFIRINOX) and gemcitabine + nab-paclitaxel, have shown activity in the adjuvant and neoadjuvant settings. The current NCCN Guidelines reflect the most up-to-date, evidence-based data relating to the evaluation and management of pancreatic adenocarcinoma. They were recently updated to recommend germline testing for any patient with pancreatic cancer and molecular analysis of any metastatic pancreatic tumor.

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**Although in many respects** we are “winning the war against cancer,” Margaret A. Tempero, MD, Director, UCSF Pancreas Center; Rombauer Family Distinguished Professor in Pancreas Cancer, Clinical and Translational Science; and Professor of Medicine, as well as Chair of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pancreatic Adenocarcinoma, noted that the rate of pancreatic cancer–related mortality is increasing. If this trend continues, pancreatic cancer is expected to be the most common cause of cancer-related death by 2040.<sup>1,2</sup> To address the unmet needs and clinical challenges faced by this patient population, Dr. Tempero presented an update on systemic therapy options and relevant changes to the NCCN Guidelines for Pancreatic Adenocarcinoma at the NCCN 2022 Annual Conference.

### Overview of Pancreatic Cancer

“We don’t really know why [pancreatic cancer] is so aggressive,” Dr. Tempero commented. She explained that it may be attributed to the lack of early symptoms, very early invasion and metastases, potential chemoresistance, and debilitating cytokine-mediated symptoms. On the other hand, the biologic development of pancreatic cancer is well understood. “Most of the pancreatic cancers develop through a pancreatic intraepithelial neoplasm mechanism, which is basically dysplasia that increases over time until you have a full-blown pancreatic ductal adenocarcinoma,” Dr. Tempero stated. “There is also an adenoma/adenocarcinoma sequence where benign tumors, such as intraductal papillary mucinous neoplasm and mucinous cystic neoplasm..., can transform into what looks exactly like the disease process of the other pathway.”<sup>3</sup>

### Emergence of Therapeutic Regimens

In the phase II/III PRODIGE 4/ACCORD 11 trial, patients with metastatic pancreatic cancer were randomly assigned to receive gemcitabine or a combination chemotherapy regimen consisting of oxaliplatin/irinotecan/fluorouracil/leucovorin (FOLFIRINOX).<sup>4</sup> To be enrolled, patients were required to have an ECOG performance status of 0 or 1. “We had never seen such dramatic benefit with any other treatment,” Dr. Tempero commented. “Although it is effective, FOLFIRINOX is a tough regimen, with dominating toxicities of myelosuppression, diarrhea, and neuropathy.” Omitting bolus fluorouracil, reducing doses, eliminating drugs that cause excessive toxicity, and using chemotherapy holidays have been found to increase the tolerability of this regimen.

Another frequently used regimen, nab-paclitaxel + gemcitabine, was evaluated in the global phase III MPACT trial. Patients with an ECOG performance status of 2 were randomly assigned to receive gemcitabine alone or in combination with nab-paclitaxel. The median duration of overall survival (OS) was 8.5 months with gemcitabine + nab-paclitaxel versus 6.7 months with gemcitabine alone (hazard ratio [HR], 0.72;  $P=.000015$ ).<sup>5,6</sup> “Although the HR was not as dramatic as that observed with FOLFIRINOX, we do have to remember that this is a different patient population, and the trial was conducted under different circumstances,” Dr. Tempero stated. “This is the trial that put gemcitabine and nab-paclitaxel into [the NCCN Guidelines].”

According to Dr. Tempero, compared with FOLFIRINOX, gemcitabine + nab-paclitaxel demonstrates an improved toxicity profile. She noted that this regimen is generally preferred by community oncologists, whereas

FOLFIRINOX is used more frequently in academic centers.

### Is a Chemotherapy Holiday Safe?

The question of whether a chemotherapy holiday is safe may be answered by the results of the phase II PANOPTIMOX-PRODIGE 35 trial. Patients with metastatic disease were randomly assigned to receive 12 cycles of FOLFIRINOX (arm A), 8 cycles of FOLFIRINOX followed by maintenance therapy with fluorouracil + leucovorin (arm B), or a sequential treatment alternating gemcitabine and fluorouracil/leucovorin/irinotecan every 2 months (arm C). According to Dr. Tempero, the median durations of OS did not seem to differ between arms A and B (10.1 vs 11.2 months).<sup>7</sup>

“This has given me reassurance that it is okay to give patients a chemotherapy holiday when they have reached maximum benefit from therapy,” she commented.

### Maintenance of Response: A New Window of Opportunity?

Maintenance of response has become a new window of opportunity for clinical trials, according to Dr. Tempero. In the POLO trial, patients with *BRCA*-mutated disease who received first-line platinum-based chemotherapy underwent maintenance therapy with olaparib or placebo. Treatment with olaparib seemed to prolong the median duration of progression-free survival (7.4 vs 3.8 months; HR, 0.53;  $P=.0038$ ).<sup>8,9</sup> “The tail on the curve suggests that some of the patients who received olaparib received not just maintenance but an additional therapeutic benefit that was frankly transformative,” Dr. Tempero commented. “Some of the [durations of progression-free] survival are out past 3 years.”<sup>9</sup>

### Systemic Therapy in the Adjuvant and Neoadjuvant Settings

“For many years we struggled with adjuvant therapy in the setting of resected pancreatic adenocarcinoma. Although there was an effort to try to improve median OS, it wasn't until we got to...gemcitabine and capecitabine that we were beginning to see some improvement,” Dr. Tempero remarked.<sup>10</sup> “However, now that we have more active regimens, it was very important to try to understand the benefit of these agents in the adjuvant setting.”

Since the introduction of the FOLFIRINOX regimen, it has been modified for tolerability. In the PRODIGE 24/CCTG PA.6 trial, patients with R0 or R1 resected pancreatic cancer were randomly assigned to receive this modified regimen or gemcitabine.<sup>4</sup> Treatment with modified FOLFIRINOX prolonged median disease-free survival (21.6 vs 12.8 months; HR, 0.58;  $P<.0001$ ) and OS (54.4 vs. 35.0 months; HR, 0.64;  $P=.003$ ) compared with gemcitabine.

“We also wanted to find out if gemcitabine and nab-paclitaxel would do something similar,” Dr. Tempero stated. She led the global AFACT trial in which patients who underwent surgery were randomly assigned to receive gemcitabine either alone or in combination with nab-paclitaxel. Improvements in the median duration of investigator-assessed disease-free survival (16.6 vs 13.7 months; HR, 0.82) and interim OS (40.5 vs 36.2 months; HR, 0.82) were reported with gemcitabine + nab-paclitaxel.<sup>11</sup>

“We are still very puzzled by this [marginal improvement in OS],” Dr. Tempero commented. “We certainly thought this would be a much better outcome and provide another option for patients following surgery, but clearly this does not seem to be the case.” She speculated that gemcitabine + nab-paclitaxel may be more active in bulky disease than in micrometastases.

It is unclear whether modified FOLFIRINOX or gemcitabine + nab-paclitaxel should be used in the preoperative setting. The phase II SWOG 1505 trial addressed this by randomly assigning patients with resectable disease to one of the aforementioned regimens.<sup>12</sup> According to Dr. Tempero, the median duration of OS seemed to be similar between the treatment arms (23.2 for FOLFIRINOX vs 23.6 months for gemcitabine + nab-paclitaxel). “I think people are quite comfortable in the neoadjuvant setting giving either gemcitabine + nab-paclitaxel or FOLFIRINOX despite the disappointing results of the AFACT trial that was done in the adjuvant setting,” she stated.

### Recent Additions to the NCCN Guidelines

The NCCN Guidelines for Pancreatic Adenocarcinoma were updated to recommend germline testing for any patient with pancreatic cancer.<sup>13</sup> This change was implemented because 8% to 10% of patients with pancreatic cancer have germline mutations and only half have a family history that historically would have provoked testing. Additionally, based on these data, gemcitabine + cisplatin was incorporated into the NCCN Guidelines for the specialized treatment of this patient population.<sup>13</sup> This is based on data from a phase II trial, patients with pancreatic adenocarcinoma and a germline *BRCA/PALB2* mutation seemed to benefit from gemcitabine + cisplatin ± the PARP inhibitor veliparib.<sup>14</sup>

Regarding the addition of germline testing for any patient with pancreatic cancer, Dr. Tempero commented that “now we test everyone who can have a therapeutic benefit in terms of choosing therapy depending on the mutation,” Dr. Tempero commented. “It also has tremendous benefit for the family, in which we can identify the appropriate syndrome, the cancers that arise in that syndrome, and tailor a screening program.” Per the NCCN Guidelines, molecular analysis of metastatic pancreatic tumors is also recommended.<sup>13</sup> Categorization of the mutational landscape of pancreatic cancer has

revealed a rare subgroup of patients with *RAS* wild-type disease who have an “unusual plethora” of potentially targetable mutations.<sup>15</sup>

To further highlight the importance of molecular analysis, Dr. Tempero presented a case study of a 47-year-old man with locally advanced disease. The patient initially responded to treatment with FOLFIRINOX; however, after experiencing disease progression, he was administered pembrolizumab. A subsequent decrease in the level of the tumor marker CA 19-9 was reported. “This is the type of case that we are trying to help: very unusual patients for whom specific targeted therapies can have a really transformative benefit,” she stated. “We feel it is worth looking for the needle in the haystack to find these patients and offer them effective therapy.”

Updated activity and safety results of the KRYSTAL-1 trial, which were presented during the ASCO 2022 Gastrointestinal Cancers Symposium, also support the notion of looking for the “needle in the haystack” to

provide transformative therapy.<sup>16</sup> Based on the results of this study, 50% of patients with metastatic pancreatic cancer who harbored the rare *KRAS* G12C point mutation achieved a partial response with the small molecule inhibitor adagrasib.

“There are additional small molecules that are being developed for other *RAS* mutations,” Dr. Tempero commented. “We have every hope that we are going to have a new arsenal of anti-*RAS* drugs available for our patients in the near future.”

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