# NCCN Guidelines Updates: Pancreatic Cancer

Presented by Margaret A. Tempero, MD

## ABSTRACT

Outcomes for pancreatic cancer are becoming less discouraging with the refinement of molecular profiling, both germline and somatic, and beneficial effects seen with adjuvant chemotherapy. The NCCN Guidelines for Pancreatic Adenocarcinoma reflect these advances, and recommend that clinicians consider germline testing for all patients with pancreatic cancer and consider a molecular analysis for those with metastatic disease. The guidelines further recommend that clinicians consider adjuvant therapy with modified FOLFIRINOX (leucovorin/5-FU/irinotecan/oxaliplatin) for patients who are able to tolerate it.

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## Panel Adds to Pancreatic Cancer Recommendations

For the first time in decades, advances in diagnostics and adjuvant therapies appear to be improving outcomes in pancreatic cancer. These advances are reflected in additions to the NCCN Clinical Practice Guidelines for Oncology (NCCN Guidelines) for Pancreatic Adenocarcinoma. The new recommendations are that clinicians consider (1) germline testing for all patients with pancreatic cancer, (2) molecular tumor analysis in patients with metastatic disease, and (3) adjuvant therapy with modified FOLFIRINOX (leucovorin/5-FU/irinotecan/oxaliplatin) for patients who are able to tolerate it.

Presenting these updates was Margaret A. Tempero, MD, Professor of Medicine, and Director of the UCSF Pancreas Center, UCSF Helen Diller Family Comprehensive Cancer Center. Dr. Tempero has served as Chair of the NCCN Pancreatic Adenocarcinoma Panel for 20 years.

## Pancreatic Cancer Deaths Increasing

These recent treatment advances are long overdue. Although deaths from most malignancies are declining, pancreatic cancer moved from the fourth leading cause of cancer death to the third in 2016, surpassing breast cancer. The population is growing older and living longer, and innovative new therapies have largely passed this tumor by, Dr. Tempero said. The vast majority of patients with pancreatic cancer are diagnosed with advanced unresectable disease; most patients experience relapse after treatment. Furthermore, the "cure rate" for this disease is only 9%, and without treatment, the median survival of patients with metastatic disease is only 3 months.

"This is a very tough disease," Dr. Tempero noted. "There are no early symptoms, the tumor invades and metastasizes early, it is somewhat chemotherapy-resistant, and patients suffer from debilitating cytokine-mediated symptoms."

## Current Treatment of Metastatic Disease Remains Challenging

First-line treatment regimens remain FOLFIRINOX and gemcitabine/albumin-bound nab-paclitaxel, and for patients with *BRCA1/2* and *PALB2* mutations, gemcitabine/cisplatin. Compared with nab-paclitaxel/gemcitabine, FOLFIRINOX may be associated with a somewhat better response rate and progression-free and overall survival (OS), but it is a difficult regimen that is best reserved for fit patients. Nab-paclitaxel/gemcitabine is "a bit easier to manage than FOLFIRINOX," she said, "but it is also not a walk in the park." Selection of treatment depends on patient preference, comorbidities, goals of treatment, compatibility with investigational agents, and predictive biomarkers.

"Moving forward, we want to build on both FOLFIRINOX and gemcitabine/nab-bound paclitaxel," she said.

## Recent Advances and Changes to the NCCN Guidelines

Based on better understanding of the molecular basis of pancreatic cancer and on encouraging outcomes from clinical trials, the NCCN Guidelines recommend that clinicians consider germline testing in any patient diagnosed with pancreatic cancer and consider a molecular analysis of tumors in those with metastatic disease. With FOLFIRINOX recently shown to improve both

disease-free survival and OS when given as adjuvant therapy, this regimen should be considered for fit patients, the guidelines note.

Germline testing is important because pancreatic cancer is associated with numerous hereditary syndromes. There is also the phenomenon of familial pancreatic cancer, where the disease occurs in multiple generations but the typical genetic mutations are not found. "That's because each of these families probably has its own pathogenic mutation," Dr. Tempero explained. "It would be labor-intensive to look for it and would not help the patient."

For such families, screening of first- and second-degree relatives is recommended, using either annual endoscopic ultrasound or magnetic resonance cholangiopancreatography. "This has become very much a part of our practice in managing these folks," she said.

But screening will not detect all persons at risk, she said. The MSK-IMPACT study sought to determine the frequency of deleterious mutations in various tumor types.[1] Germline testing of 1,040 patients with cancer, looking at almost 100 predisposition genes, revealed a high incidence (17%) of mutations in the pancreatic cancer subset, including some unexpected ones. More than half the mutations were in genes involved in DNA repair, suggesting that those patients may benefit from platinum-containing regimens.

Strikingly, however, 42% of patients had no family history of the cancer and would not have met the current recommendation for screening, a finding that has been validated by other studies. "This led to the recommendation that we strongly consider germline testing in all patients with pancreatic cancer," she said. "This matters a lot, because it has implications for therapeutic directions and for other family members."

"At UCSF we have implemented the same program, and we are astounded at what we're seeing in terms of the number of germline mutations that we would not have recognized had we not started universal testing," she said.

## PARP Inhibitors in DNA Damage Repair Mutations

For patients with ovarian cancer and mutations in DNA damage repair genes (such as *BRCA1/2*), PARP inhibitors have demonstrated efficacy, and these drugs are expected to become approved in other tumors as well. Among studies evaluating PARP inhibitors in patients with pancreatic cancer and germline *BRCA* mutations are a phase II trial of veliparib with cisplatin and gemcitabine in the first-line metastatic setting and the phase III POLO trial of maintenance olaparib after platinum therapy.

Preliminary data from the veliparib trial have shown, interestingly, that with cisplatin/gemcitabine alone, approximately 80% of patients can show a response. "That's just amazing to me, that I can give a patient with a *BRCA* mutation a simple, tolerable regimen and not put the patient through FOLFIRINOX," Dr. Tempero commented. The addition of the PARP inhibitor could improve outcomes even more. "I'm hopeful that we will soon have another approved treatment option for our patients."

## Profiling of Mismatch Repair Deficiency

Molecular profiling also detects mismatch repair deficiency (dMMR) and microsatellite instability–high (MSI-H) status. Across tumor types, patients with this phenotype may respond to pembrolizumab, which is now approved for patients with metastatic cancer of any type and dMMR/MSI-H status. Although dMMR/MSI-H is present in only 1% of patients with pancreatic cancer, in the pivotal trial of pembrolizumab, 83% of patients with dMMR pancreatic cancer showed a response.[2,3] At UCSF, testing for dMMR/MSI-H status is part of the initial workup, Dr. Tempero said, describing one patient who benefited greatly from this assessment. After progressing on FOLFIRINOX, the patient has continued to respond to pembrolizumab for several years.

"This is the needle in the haystack you want to find," she said. "In our mind, it's worth it to test everybody for MSI-H status and to use pembrolizumab after first-line treatment."

## Molecular Subtyping Recommended

The NCCN panel has also strongly recommended somatic profiling of tumor tissue. Although the main driver mutation is *KRAS*, there are numerous other potentially actionable mutations that can be identified with molecular profiling.

Whole-exome sequencing has been shown to find genomic lesions that are theoretically actionable in almost 50% of tumors and to result in a change in clinical management in up to 30% of cases. For example, the identification of a *TRK* fusion means a patient is a candidate for larotrectinib, based on a pivotal trial reported last year.[4] Although a small subset in this study, patients with pancreatic cancer had very durable responses. Tumor profiling, therefore, can yield important information that affects treatment.

"How will you find those patients who are eligible for this if you don't profile them?" she said. "I think we are going to have more drugs 'agnostic' for tumor types, so this will become more important."

Dr. Tempero added that because of this additional molecular testing, it is increasingly important to obtain sufficient tissue in the diagnostic tumor sample. "We are going to have to start doing diagnostic biopsies differently. We're going to need to do multiple biopsies, fine-needle aspiration biopsies, and core biopsies in order to obtain enough material to make sure we get enough information to offer these treatments to our patients."

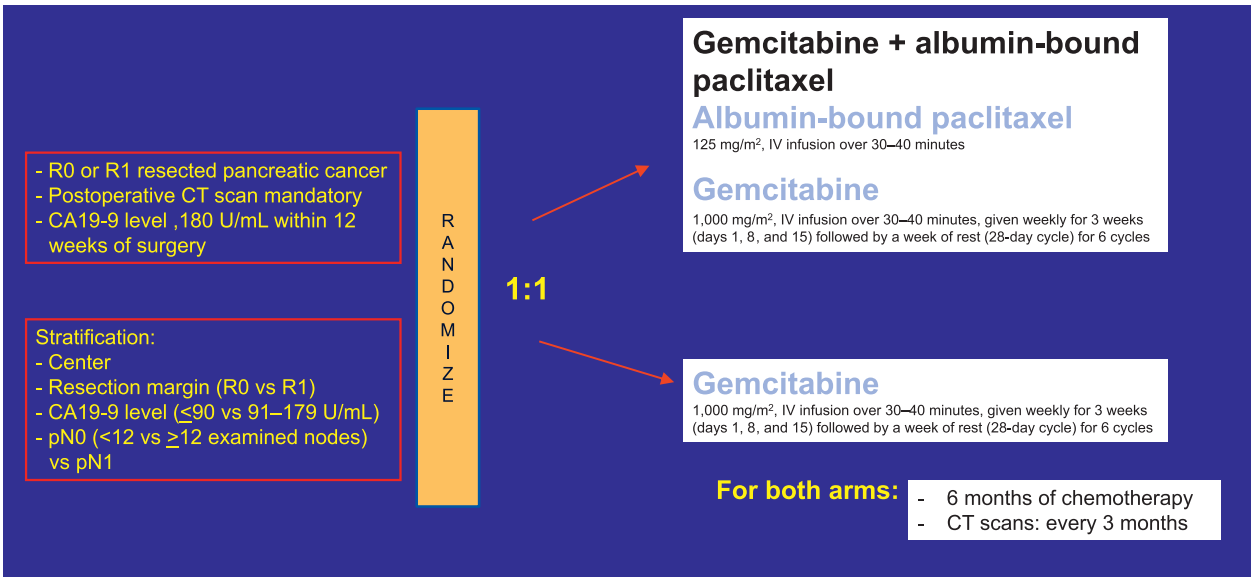


**Figure 1.** APACT trial study design (ClinicalTrials.gov identifier: NCT01964430).
Abbreviation: IV, intravenous.

## The Advent of Effective Adjuvant Therapy

Until last year, treatment in the adjuvant setting had not changed much in 30 years. "All we did was move the deck chairs around," Dr. Tempero said. In the most positive studies, median OS remained approximately 28 months. This changed with the results of the phase III Unicancer GI PRODIGE 24/CCTG PA.6 trial,[5] which compared adjuvant modified FOLFIRINOX with single-agent gemcitabine after tumor resection.

Treatment with modified FOLFIRINOX resulted in the longest OS reported yet for patients with pancreatic cancer after resection: 54.4 months compared with 35.0 months with gemcitabine (hazard ratio [HR], 0.64; $P$=.003). Median disease-free survival was 21.6 versus 12.8 months, respectively (HR, 0.58; $P$<.0001). Toxicity, however, was much higher with the modified regimen. Grade 3–4 adverse events occurred in 75.75% of this arm, versus 51.5% for the gemcitabine arm. The consensus is, therefore, that this adjuvant regimen should only be used in patients who are able to tolerate it.

"We saw quite an impressive difference in disease-free survival, with a hazard ratio of 0.58," she noted. "The OS data are still early, although it is looking quite good. This was enough for us to incorporate this adjuvant regimen in the NCCN Guidelines."

Another adjuvant therapy—gemcitabine/nab-paclitaxel versus gemcitabine alone—is being evaluated in the APACT trial, for which Dr. Tempero is the global principal investigator (Figure 1). Results are highly anticipated and will be presented at the 2019 ASCO Annual Meeting.

"I hope that, with these results, we will have another treatment option in the adjuvant setting, especially since not all patients can handle FOLFIRINOX postoperatively," Dr. Tempero commented.

**Disclosures:** Dr. Tempero has disclosed that she has no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors.

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