Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

September 2018 Volume 16, Issue 9, Supplement 17

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Therapeutic Advances in Metastatic Pancreatic Adenocarcinoma and Related Cancers: Focus on Evidence-Based and Sequenced Approaches to Survival Extension in Metastatic Pancreatic Adenocarcinoma

Proceedings From a Live Symposium

June 2, 2018 • Chicago, Illinois

Jointly provided by Postgraduate Institute for Medicine and Millennium Medical Publishing

PIM Postgraduate Institute for Medicine

A CME Activity
Approved for 1.25
AMA PRA
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Release date: September 1, 2018
Expiration date: September 30, 2019
Estimated time to complete activity: 1.25 hours
Project ID: 13438

ON THE WEB:
hematologyandoncology.net

Supported through an educational grant from Ipsen Biopharmaceuticals, Inc.

Indexed through the National Library of Medicine (PubMed/MEDLINE), PubMed Central (PMC), and EMBASE

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This activity has been designed to meet the educational needs of oncologists and nurses involved in the management of patients with pancreatic cancer.

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- Apply the most recent guidelines from the National Comprehensive Cancer Network to the management of patients with metastatic pancreatic adenocarcinoma
- Determine which patients with metastatic pancreatic adenocarcinoma are candidates for the use of surgical interventions (resection), medical therapy, and/or systemic chemotherapy, based on presentation, symptoms, tumor type and stage, clinical profile, extent of disease, biomarkers, and other factors
- Differentiate among approved therapies for pancreatic cancer based on mechanistic differences, delivery systems, formulations, metabolism, and local and systemic antitumor properties
- Describe recent clinical trial data supporting the use of new and emerging treatment regimens in metastatic pancreatic carcinoma

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This monograph was authored by an independent medical writer, Megan Garlapow, PhD, based on presentations given at "Therapeutic Advances in Metastatic Pancreatic Adenocarcinoma and Related Cancers: Focus on Evidence-Based and Sequenced Approaches to Survival Extension in Metastatic Pancreatic Adenocarcinoma," a live symposium held on June 2, 2018.

Translating Landmark Trial-Based Evidence to the Front Lines of Care for Pancreatic Cancer: The Evolving Trial-Based and Guideline-Supported Role for Nanoliposomal Topoisomerase Inhibitors in Metastatic Pancreatic Adenocarcinoma

Caio Max S. Rocha Lima, MD

Frontline Options in Pancreatic Cancer

The prognosis for patients with pancreatic cancer remains poor, and advances in therapeutic approaches have been incremental and gradual. In 1997, a small, randomized phase 3 trial of treatment-naive patients with unresectable, locally advanced, or metastatic pancreatic cancer showed an improvement in clinical benefit and overall survival with gemcitabine compared with 5-fluorouracil (5-FU).[1] Clinical benefit response was defined as a composite measurement of pain (analgesic use and pain intensity), performance status, and weight.[1] More patients in the gemcitabine arm experienced clinical benefit vs the 5-FU arm (23.8% vs 4.8%; *P*=.0022).[1] The median overall survival was also improved in the gemcitabine arm (5.7 vs 4.4 months; *P*=.0025).[1] These results established gemcitabine as the therapeutic backbone for frontline treatment of pancreatic adenocarcinoma.

In a randomized phase 3 trial of 569 patients with advanced pancreatic cancer, the addition of erlotinib to gemcitabine was associated with a modest but significant improvement in median overall survival vs gemcitabine alone (6.24 vs 5.91 months; *P*=.038).[2] The 1-year survival and the median progression-free survival (PFS) were also longer in the erlotinib group, but the overall response rate (ORR) was not significantly different.[2] The US Food and Drug Administration (FDA) approved erlotinib in combination with gemcitabine. The clinical use of erlotinib remains low, however, based on the modest improvement in overall survival.

In a randomized phase 2 trial in patients with metastatic pancreatic cancer, a regimen of folinic acid, 5-FU, irinotecan, and oxaliplatin (FOLFIRINOX) improved median overall survival vs single-agent gemcitabine (11.1 vs 6.8 months; *P*<.001).[3] In a phase 3 trial, the addition of nab-paclitaxel to gemcitabine improved median overall survival vs gemcitabine alone (8.5 vs 6.7 months; *P*<.001).[4] These results established 2 frontline standards of care: FOLFIRINOX and nab-paclitaxel plus gemcitabine.

Second-Line Options in Advanced Pancreatic Cancer

The phase 3 CONKO-003 trial (A Phase 3 Second Line Trial in Advanced Pancreatic Cancer) was a randomized, open-label trial enrolling gemcitabine-refractory patients.[5] The primary analysis included 160 patients. At a median follow-up of 54.1 months, the addition of oxaliplatin to folinic acid and 5-FU improved median overall survival vs folinic acid plus 5-FU alone (5.9 vs 3.3 months; *P*=.010).[5] Time to progression was significantly longer in the oxaliplatin group. Rates of adverse events were similar. However, in a randomized phase 3 trial of patients previously treated with gemcitabine, the addition of oxaliplatin to 5-FU plus leucovorin was associated with an inferior median overall survival (6.1 vs 9.9 months; *P*=.024).[6] A toxicity profile resulting in frequent discontinuations of therapy in the oxaliplatin group could explain the inferior results.

Several trials have assessed irinotecan in the second-line setting for pancreatic cancer.[7-11] The median overall survival was approximately 6 to 7 months, suggesting some benefit to the incorporation of irinotecan in the second-line setting.

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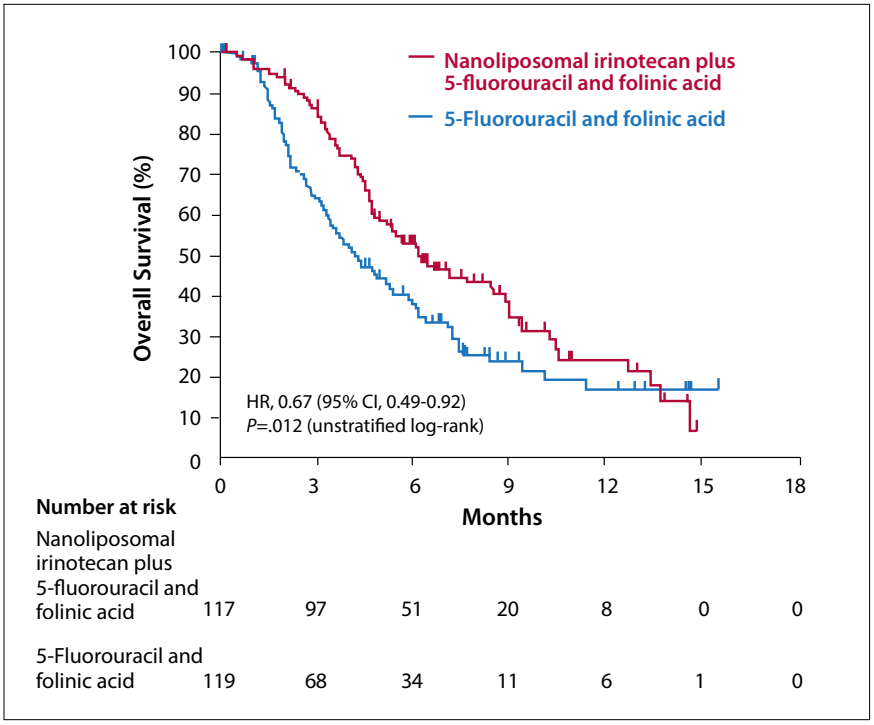

Figure 1. In the phase 3 NAPOLI-1 trial, the addition of nanoliposomal irinotecan improved median overall survival. HR, hazard ratio; NAPOLI-1, Nanoliposomal Irinotecan. Adapted from Wang-Gillam A et al. *Lancet*. 2016;387(10018): 545-557.[14]

Nanoliposomal Irinotecan

A formulation in which irinotecan is encased within a nanoliposome was designed to improve drug delivery to the tumor. Nanoliposomal irinotecan is taken up by tumor-associated macrophages.[12] After macrophage uptake, the nanoliposome dissolves, and irinotecan is metabolized to its active form, SN-38, by carboxylesterase.[12] SN-38 is delivered to the tumor, creating a large deposit of irinotecan within it.[12] This nanoliposomal formulation of irinotecan allows longer drug exposure to plasma and the tumor at lower doses.[12,13]

Clinical Trials of Nanoliposomal Irinotecan

The randomized, phase 3 NAPOLI-1 trial (Nanoliposomal Irinotecan) compared the safety and efficacy of 3 treatment regimens: nanoliposomal irinotecan plus 5-FU/leucovorin, nanoliposomal irinotecan alone, and 5-FU/leucovorin alone.[14] Patients had progressive disease after frontline gemcitabine-based treatment. The combination of nanoliposomal irinotecan plus 5-FU/leucovorin improved median overall survival compared with 5-FU/leucovorin alone (6.1 vs 4.2 months; *P*=.012; Figure 1).[14] The addition of nanoliposomal irinotecan also improved median PFS (3.1 vs 1.5 months; *P*=.0001) and the ORR (16% vs 1%; *P*<.0001) compared with 5-FU/leucovorin alone. Single-agent nanoliposomal irinotecan was not superior to 5-FU/leucovorin, suggesting that this agent does not have a role as monotherapy.

Subgroup analyses suggested that most patients benefited from the addition of nanoliposomal irinotecan to 5-FU/leucovorin.[14] In an expanded per-protocol analysis, median overall survival was 8.9 months with the addition of nanoliposomal irinotecan to 5-FU/leucovorin vs 5.1 months with 5-FU/leucovorin alone (*P*=.0018).[15] In comparison, the median overall survival was 6.1 months with nanoliposomal irinotecan in the intention-to-treat population, suggesting that patients who follow the protocol could experience a greater clinical benefit.

The safety profile was generally manageable. In the nanoliposomal irinotecan arms, the most frequent grade 3/4 adverse events were neutropenia (27%), fatigue (14%), diarrhea (13%), and vomiting (11%).[14] The protocol for NAPOLI-1 did not mandate the use of antiemetics, which can decrease the rate of grade 3/4 vomiting, or loperamide, which could reduce diarrhea. Similarly, growth factor support was not routinely used in the trial to treat neutropenia (which manifested predominantly as myelosuppression), another approach that could be applied in clinical practice to better manage toxicities.

NAPOLI-1 was not a second-line trial; patients could have received 2 or more prior lines of therapy. Approximately one-third of patients received treatment as third-line or even fourth-line therapy.[14] Additionally, although nab-paclitaxel plus gemcitabine is the standard of care in the United States, in this international trial, only approximately 20% of patients had received this regimen as a prior therapy.[14] Nanoliposomal irinotecan with 5-FU/leucovorin is now recommended by the National Comprehensive Cancer Network (NCCN) for second-line treatment of pancreatic cancer.[16]

Disclosure

Dr Rocha Lima is on the speakers bureaus of Celgene and Ipsen.

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A Treatment Landscape in Evolution: New Strategies, Guidelines, and Therapeutic Advances for Metastatic Pancreatic Adenocarcinoma

Tanios Bekaii-Saab, MD

Pancreatic cancer is the third-leading cause of cancer-related death in the United States.[1] Within the next decade, it is expected to become the leading cause (Figure 2).[1] The prognosis for pancreatic cancer remains poor, with the lowest survival of any malignancy, stage for stage.[2] Additionally, 80% to 85% of patients have advanced-stage disease at the time of diagnosis, and patients diagnosed with early-stage disease have a 70% to 80% chance of relapsing following curative surgery.[2-4] The cure rate for metastatic disease remains at 1% to 2%, and the 5-year relative survival rate across stages is 8.5% (95% CI, 8.0-9.0).[5] The incidence of pancreatic cancer varies geographically, with a high exceeding 6.3 new cases per 100,000 people per year in developed countries.[6]

Patients with resectable disease have improved outcomes, likely based on the negative margins achieved during surgery plus the neoadjuvant and adjuvant therapy used after the procedure. Patients with borderline resectable disease are likely to have positive tumors after surgery, and therefore should receive neoadjuvant therapy postsurgery. Patients with unresectable disease should never undergo tumor resection. Some palliative surgical procedures, such as combined biliary and duodenal bypass, are possible options for patients with locally advanced disease and unresectable tumors,[7] although these approaches have not been assessed in randomized clinical trials.

Anatomy of the Pancreas and Development of Pancreatic Cancer

The pancreas is located in close proximity to blood vessels and nerve bundles, and therefore surgery is limited to less than 20% of cases.[8,9] At diagnosis, surgery is not an option for more than 80% of patients, who will present with disease that advanced locally or became metastatic during the asymptomatic phase.[8,9] Structurally, the pancreas consists of 4 sections. The head is the rightmost section of the pancreas; it is surrounded by the duodenum and delivers pancreatic enzymes directly to the intestines. To the left of the pancreatic head is the neck, then the body,

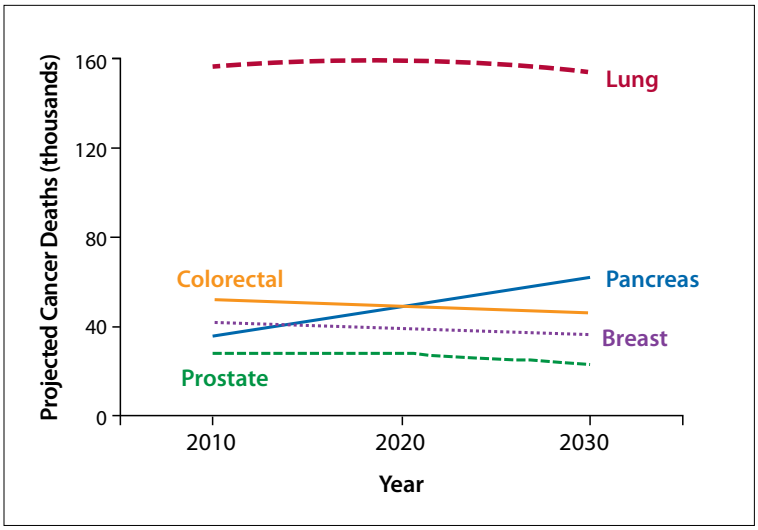

Figure 2. By 2030, pancreatic cancer is expected to become the second most-common cause of cancer-related death. Adapted from Rahib L et al. *Cancer Res*. 2014;74(11):2913-2921.[1]

and then the leftmost section of the tail. Disease-related symptoms are diverse and affected by the location of the tumors. The extent of symptoms does not necessarily correlate with the tumor burden.[10] Tumors that arise in the pancreatic head often wrap around the bile ducts, resulting in jaundice.[11] Tumors that develop in the pancreatic tail frequently drop into the abdominal cavity and cause symptoms of epigastric pain.[9]

Treatment of Pancreatic Cancer

In the frontline setting, chemotherapy usually consists of FOLFIRINOX or gemcitabine with nab-paclitaxel. After frontline FOLFIRINOX, second-line therapy will vary according to the patient's performance status, with gemcitabine plus nab-paclitaxel for those with a performance status of 0 to 1 and either gemcitabine monotherapy or best supportive care for patients with a performance status of 2 or worse. Guidelines do not indicate third-line therapy for patients who received frontline FOLFIRINOX.[9,12] For patients who received frontline gemcitabine-based therapy (gemcitabine alone or with nab-paclitaxel or erlotinib), second-line therapy consists of nanoliposomal irinotecan with 5-FU for those with a performance status of 0 or 1 and fluoropyrimidine monotherapy or best supportive care for those with a performance status of 2. For patients with a performance status of 0 or 1, third-line treatment consists of platinum-based chemotherapy if they had not received it earlier.[9,12]

The many types of treatment-emergent toxicities include deep vein thrombosis, anemia, sepsis, infusion-related reactions, and severe diarrhea.[9] Management of treatment-emergent toxicity, along with disease symptoms, presents a challenge.

Treatment of Subgroups in Pancreatic Cancer

Clinical trials have examined the role of inhibitors of poly-adenosine 5'-diphosphate (ADP)-ribose polymerase (PARP) in pancreatic cancer patients harboring mutations in the breast cancer 1 or 2 (*BRCA1/2*) gene. In a study of 23 patients with *BRCA*-mutated pancreatic cancer and a mean of 2 prior lines of therapy, the response rate to the PARP inhibitor olaparib was 22%, and the rate of stable disease was 35%.[13] In a study of 16 patients with *BRCA*-mutated pancreatic cancer and a mean of 2 prior lines of therapy, the PARP inhibitor veliparib was associated with a response rate of 0%, and a stable disease rate of 25%.[14] Among 19 patients with *BRCA*-mutated pancreatic cancer who had received a mean of 1 to 2 prior lines of therapy, the PARP inhibitor rucaparib was associated with an ORR of 15%, and a stable disease rate of 21%.[15]

Approximately 1% of patients with pancreatic cancer are mismatch repair deficient (MMR-D) or have high microsatellite instability (MSI-H). Under these conditions, tumors can be susceptible to treatment with an immune checkpoint inhibitor.[16] The immune checkpoint inhibitor pembrolizumab is now approved for MMR-D or MSI-H tumors, regardless of tumor type, and can be used to treat this small subset of patients with pancreatic cancer.[17]

Disclosure

Dr Bekaii-Saab is an advisor or consultant for Amgen, ARMO, Bristol-Myers Squibb, Celgene, Exelixis, Genentech, Glenmark, Ipsen, Merck & Co, Merrimack, Roche, and SillaJen.

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New Guideline-Sanctioned and Emerging Interventions for Pancreatic Cancer

Tanios Bekaii-Saab, MD

Pancreatic adenocarcinoma accounts for approximately 90% of all cases of pancreatic cancer, and more than half of these cases are metastatic.[1,2] Guidelines from the NCCN for the management of metastatic pancreatic cancer recommend placement of a self-expanding metal stent if jaundice is present, and suggest consideration of testing for microsatellite instability and mismatch repair deficiency.[3] Subsequent treatment depends on the patient's performance status.[3] Patients with a poor performance status should receive palliative radiotherapy or palliative best supportive care, with consideration of single-agent chemotherapy.[3] The NCCN guidelines recommend that patients with a good performance status enroll in a clinical trial or receive chemotherapy.[3]

First-Line Therapy in Pancreatic Cancer

Historically, gemcitabine has been the standard of care in the first-line setting, as it improved clinical benefit and overall survival compared with 5-FU in patients with advanced disease.[4] A randomized phase 3 trial compared gemcitabine vs 5-FU in 126 patients with advanced symptomatic pancreatic cancer.[4] Clinical benefit—a composite measurement of pain, performance status, and weight—was reported in 23.8% of patients in the gemcitabine arm vs 4.8% of patients in the 5-FU arm (P=.0022).[4] The median overall survival was 5.7 months vs 4.4 months, respectively (P=.0025). This trial established gemcitabine as the backbone of frontline therapy.[4]

Subsequent trials that combined other chemotherapeutic agents with gemcitabine established additional treatment options.[5] Phase 3 trials also evaluated gemcitabine in combination with a targeted therapy, but the results were generally not encouraging.[6] For example, an early-stage trial of a farnesyltransferase inhibitor plus gemcitabine showed clinical efficacy compared with gemcitabine alone, but no improvement was seen in a phase 3 trial.[6]

In a phase 2/3 trial, median overall survival was 11.1 months with FOLFIRINOX vs 6.8 months with gemcitabine (hazard ratio [HR] for death, 0.57; 95% CI, 0.45-0.73; P<.001).[7] A phase 3 trial comparing nab-paclitaxel with gemcitabine vs single-agent gemcitabine showed a median overall survival of 8.5 months vs 6.7 months, respectively (HR for death, 0.72; 95% CI, 0.62-0.83; P<.001).[8] The results from these trials cannot be compared because they occurred in different regions and enrolled different patient populations.[7,8] No clinical trials have directly compared FOLFIRINOX with the combination of nab-paclitaxel and gemcitabine.

A real-world, retrospective analysis compared outcomes with first-line nab-paclitaxel plus gemcitabine, gemcitabine alone, or FOLFIRINOX in patients with metastatic pancreatic adenocarcinoma treated in the community setting in the United States. Time to treatment discontinuation and database persistence were lowest among patients treated with gemcitabine alone. There were no significant differences in surrogate endpoints between nab-paclitaxel plus gemcitabine vs FOLFIRINOX (Figure 3).[9] Results were not impacted by the patients' age.[9] Additionally, surrogate endpoints remained similar regardless of whether nab-paclitaxel

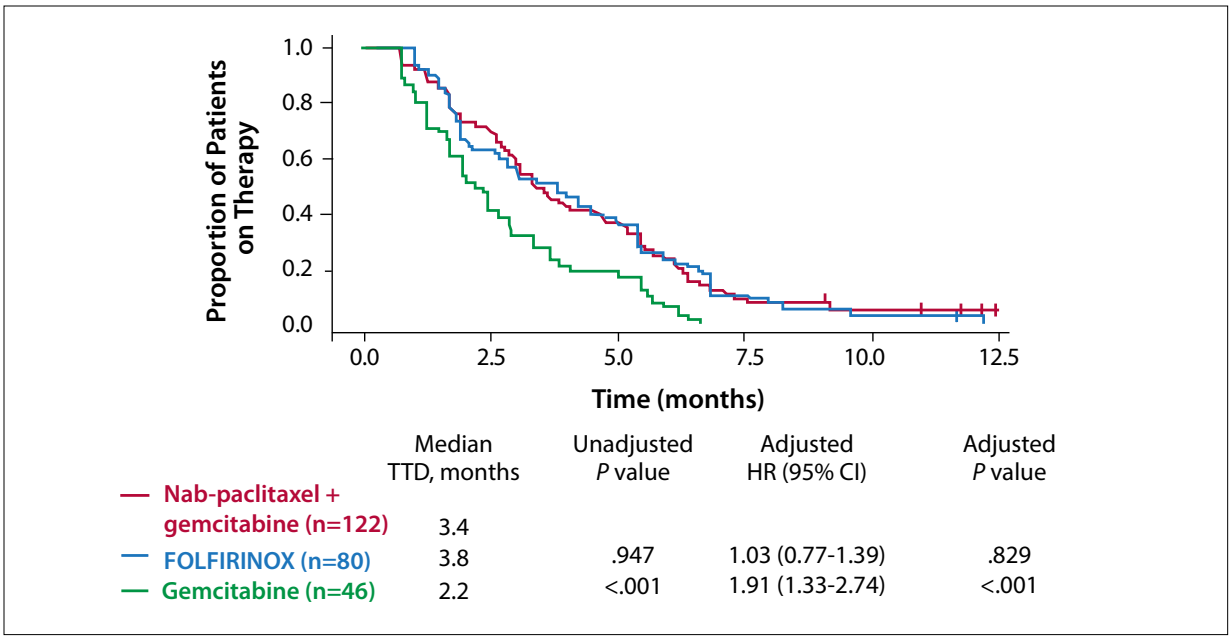

Figure 3. In a retrospective, real-world analysis, there were no significant differences in surrogate endpoints between nab-paclitaxel plus gemcitabine vs FOLFIRINOX alone. FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin; HR, hazard ratio; TTD, time to treatment discontinuation. Adapted from Braiteh F et al. *Cancer Manag Res*. 2017;9:141-148.[9]

plus gemcitabine or FOLFIRINOX was used first, and the other regimen initiated after disease progression.[9]

The phase 3 MPACT trial (Metastatic Pancreatic Adenocarcinoma Clinical Trial) compared gemcitabine alone or with the addition of nab-paclitaxel as frontline therapy in patients with metastatic pancreatic cancer.[10] Both drugs were administered in a dose-modified schedule.[10] In the nab-paclitaxel arm, dose reduction and delay improved median overall survival. In contrast, dose reduction, but not dose delay, improved median overall survival in the single-agent gemcitabine arm. The study indicates that dose reductions and delays can help manage toxicities and avoid discontinuation of therapy.

A retrospective analysis showed that gemcitabine and nab-paclitaxel administered biweekly instead of weekly improved clinical efficacy, decreased cost of treatment, and improved toxicity compared with the historical control.[11] Cost savings on this regimen reflected reductions in the costs of the treatment drugs and in the management of toxicities.[11]

Second-Line Therapy in Metastatic Pancreatic Cancer

The phase 3 NAPOLI-1 trial compared the addition of nanoliposomal irinotecan to 5-FU and leucovorin vs 5-FU/leucovorin in metastatic pancreatic cancer previously treated with a gemcitabine-based regimen.[12] The median overall survival was 6.1 months in the arm with nanoliposomal irinotecan vs 4.2 months in the arm without nanoliposomal irinotecan (HR, 0.67; 95% CI, 0.49-0.92; *P*=.012).[12] The median PFS was 3.1 months vs 1.5 months (HR, 0.56; 95% CI, 0.41-0.75; *P*=.0001).[12]

To elucidate the role of oxaliplatin in the second-line setting, a meta-analysis identified randomized controlled trials comparing single-agent fluoropyrimidine to combination therapy that included fluoropyrimidine and either oxaliplatin or different formulations of irinotecan.[13] The overall survival was not significantly different between fluoropyrimidine and regimens containing oxaliplatin (*P*=.9), but the overall survival was improved in regimens containing irinotecan compared with single-agent fluoropyrimidine (*P*=.004).[13] Compared with fluoropyrimidine, the PFS was improved in regimens containing oxaliplatin (*P*=.02) or irinotecan (*P*=.005).[13]

There is no clinically validated second-line option after frontline FOLFIRINOX. Frontline gemcitabine plus nab-paclitaxel allows for second-line irinotecan plus 5-FU in patients with good performance status.[3] In patients with poor performance status, options are 5-FU, capecitabine, or best supportive care.

Emerging Therapies in Pancreatic Cancer

The microenvironment of pancreatic cancer is hypovascular, hypoxic, and chemoresistant, in part because of the physical barrier formed by hyaluronan, a component of the extracellular matrix.[14,15] In a preclinical model, depletion of hyaluronan with PEGylated recombinant human hyaluronidase PH20 (PEGPH20) reversed chemoresistance of pancreatic tumors and permitted successful treatment with gemcitabine.[14,15] In a phase 2 trial that

evaluated the addition of PEGPH20 to nab-paclitaxel plus gemcitabine in patients with metastatic pancreatic cancer, there was no difference in median overall survival between the 2 arms.[16] There was, however, an improvement in median PFS in the PEGPH20 arm, for both the overall study population and the subset of patients with tumors that had high levels of hyaluronan. An ongoing phase 3 trial is investigating the same treatment regimen in patients with high levels of hyaluronan.[17]

Another emerging therapeutic approach uses cancer stemness inhibitors, such as napabucasin, to mitigate chemoresistance in pancreatic cancer. A phase 1b/2 trial assessed napabucasin with nab-paclitaxel and gemcitabine in metastatic pancreatic cancer.[18] The ORR was 55%, the median PFS exceeded 7 months, and the median overall survival was longer than 10.5 months.[18] A phase 3 trial is evaluating the addition of napabucasin to nab-paclitaxel plus gemcitabine in patients with metastatic disease.[19] The target enrollment is 1132 patients.

Disclosure

Dr Bekaii-Saab is an advisor or consultant for Amgen, ARMO, Bristol-Myers Squibb, Celgene, Exelixis, Genentech, Glenmark, Ipsen, Merck & Co, Merrimack, Roche, and SillaJen.

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Identifying Ideal Candidates for Nanoliposomal Topoisomerase Inhibitors in Metastatic Pancreatic Adenocarcinoma

Kenneth Yu, MD, MSc

Throughout the previous decade, treatment combinations and sequencing in pancreatic adenocarcinoma have become more complicated. Patients can now receive multiple lines of therapy, including combination chemotherapy. NCCN guidelines have recommendations for first- and second-line treatment.[1] FOLFIRINOX and nab-paclitaxel plus gemcitabine are the 2 first-line options.[1-4] Nanoliposomal irinotecan with 5-FU/leucovorin is recommended for second-line therapy.

Results from the phase 3 NAPOLI-1 trial of nanoliposomal irinotecan plus 5-FU/leucovorin vs 5-FU/leucovorin showed no significant difference in clinical

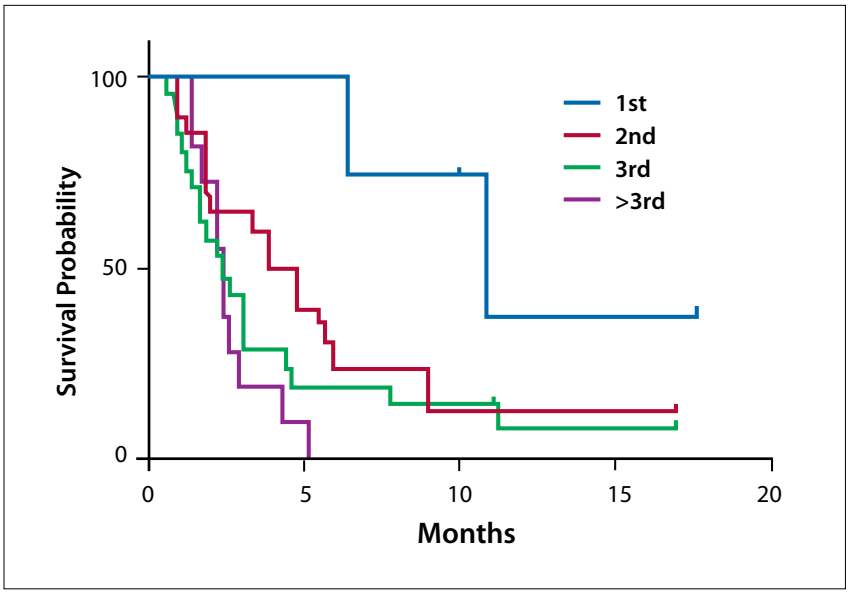

Figure 4. Median progression-free survival according to line of therapy in a retrospective real-world analysis of patients treated with nanoliposomal irinotecan plus 5-fluorouracil/leucovorin. Adapted from Glassman DC et al. ASCO GI abstract 471. *J Clin Oncol.* 2018;36(suppl 4S).[5]

outcomes based on performance status.[4] A retrospective real-world study from Memorial Sloan Kettering Cancer Center assessed patients with pancreatic cancer who started treatment with nanoliposomal irinotecan plus 5-FU/leucovorin between October 2015 and June 2017 at the cancer center and regional network sites.[5] A total of 56 patients were identified from pharmacy inquiries regarding prescriptions for nanoliposomal irinotecan, which is FDA-approved only for pancreatic adenocarcinoma. At the regional centers, some patients were treated by clinicians who were generalists rather than specialists. All patients had advanced pancreatic adenocarcinoma. The median PFS was 2.9 months, and the median overall survival was 5.3 months. A partial response was seen in 5% of patients, stable disease in 41%, and progressive disease in 41%.

Clinical outcomes were improved in patients receiving nanoliposomal irinotecan plus 5-FU/leucovorin in the frontline setting. The median PFS was 10.8 months in the frontline setting, 4.3 months in the second-line setting, 2.4 months in the third-line setting, and 2.5 months beyond the third-line setting (P=.0031; Figure 4). The median overall survival was not reached, 8.4 months, 3.9 months, and 4.5 months, respectively (P=.0002).

More than half of these patients (59%) had received prior irinotecan, which predicted a lack of efficacy for nanoliposomal irinotecan. The median overall survival across different therapy sequences was approximately 24 months. Additionally, there was no correlation between the starting dose of nanoliposomal irinotecan and the median PFS or overall survival. Patients who received 2 dose reductions had a higher probability for PFS, but these patients were also exposed to the drug for a longer time.

Compared with the NAPOLI-1 study, the patients in this analysis experienced fewer grade 3/4 adverse events, including nausea (4%) and vomiting (4%).[5] Notably, these patients were on lower doses of nanoliposomal irinotecan than patients in the NAPOLI-1 study.[4]

This real-world evidence supports the survival benefit of adding nanoliposomal irinotecan to 5-FU/leucovorin.[5] Survival was improved when nanoliposomal irinotecan was given earlier, and when the disease was not refractory to irinotecan. The treatment was safe and efficacious, even at lower doses and with dose reductions. Future studies should address whether multiple lines of active therapy affect disease biology.

Disclosure

Dr Yu is a consultant for Ipsen and Halozyme, and receives research support from Halozyme.

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Real-World Approaches for Extending Progression-Free Survival in Patients With Metastatic Pancreatic Neuroendocrine Tumors: Focus on Timing, Sequencing, Regimen Initiation, and Maintenance Strategies Using Somatostatin Analogs, Targeted Agents, and Peptide Receptor Radiotherapy

Edward M. Wolin, MD

Neuroendocrine tumors (NETs) arise from cells in the endocrine system, and they most commonly occur in gastroenteropancreatic (GEP) sites. The incidence of GEP-NETs has increased by more than 500% in the previous 3 decades, and NETs are the second most prevalent gastrointestinal malignancy (after colon cancer).[1] Early diagnosis of NETs enables initiation of therapy that can lead to long-term survival or even a cure.[2] However, a study showed that the correct diagnosis of NETs took longer than 2 years in 53% of patients and longer than 5 years in 34%.[2] The mean time to diagnosis of pancreatic NETs is 53.4 months. GEP-NETs often have metastasized by the time of diagnosis.

Prognosis varies and depends on stage, grade, primary site, and age at diagnosis.[3] The 2010 classification from the World Health Organization divided NETs into 3 grades based on tumor differentiation.[4,5] Between 20% and 100% of NETs were classified as grade 3, the highest grade. A large heterogeneity of tumors and prognoses were seen within this grade. In 2017, the World Health Organization updated its classification of NETs, splitting grade 3 into 2 different grades.[6] The 2 new grades are grade 3 well-differentiated neuroendocrine tumors and grade 3 poorly differentiated neuroendocrine carcinomas.[6] Poorly differentiated neuroendocrine carcinoma refers to either a small-cell or large-cell type with more than 20 mitoses per high-power field.[6] Grade 3 well-differentiated neuroendocrine tumors are similar to grade 1 and grade 2 tumors.[6]

Genetics and Genomics of NETs

Pancreatic NETs can harbor mutations in *DAXX*, *ATRX*, and *MEN1*, which are genes involved in chromatin remodeling, and in genes in the mammalian target of rapamycin (mTOR) pathway, such as *PTEN* and *TSC2*.[7] Mutations in both the mTOR pathway and in *DAXX* or *ATRX* correlate with excellent survival, with a 10-year survival rate close to 100%.[8] Mutations in genes involved in DNA repair (eg, *BRCA2*, *CHEK2*, *MUTYH*) have been associated with poorly differentiated neuroendocrine carcinoma, as have mutations in *RB1* and *TP53*.[9,10] In contrast, small bowel NETs harbor a lower mutational burden, with only 14 mutations detected during a sequence of 48 tumors.[11] Mutated genes included those involved in the mTOR pathway, DNA repair, chromatin remodeling, and apoptosis.[11]

Assessing Grade and Functionality of NETs

The treatment plan begins with identification of the grade and functionality of NETs. Pancreatic NETs are usually subdivided into 2 groups.[12,13] Functional NETs cause clinical syndromes associated with excessive secretion of hormones.[12,13] Nonfunctional NETs do not cause syndromes associated with excessive secretion of hormones, and they are usually asymptomatic until the patient develops advanced disease.[12-14] Nonfunctional tumors are the most common, accounting for 40% to 90% of pancreatic NETs.[14] Functional pancreatic NETs secrete bioactive peptides or hormones, with the type of hormone secreted dependent on the type of cell of origin.[13] Syndromes caused by secreted peptides or hormones in functional NETs can be fatal, independent of the tumor proliferation.

Insulinomas account for approximately 70% of pancreatic functional NETs.[15] Less common types include glucagonomas, which account for approximately 15%, and gastrinomas and somatostatinomas, each accounting for approximately 5% to 10%.[15] VIPomas are more rare.

Approved Systemic Therapies for Pancreatic NETS

Treatment of NETs involves a multidisciplinary team from oncology, surgery, cardiology, radiation oncology, pathology, nuclear medicine, endocrinology, and other areas. Treatment regimens depend on the location of the NET, its grade and spread, and whether it is functional. The antiproliferative drugs streptozocin, everolimus, sunitinib, lanreotide depot/autogel, and Lu 177 dotatate are FDA-approved to treat pancreatic

NETs. Additionally, short-acting octreotide, octreotide long-acting release, lanreotide depot/autogel, and telotristat ethyl can provide relief of hormonal syndromes. Sequencing of treatment and the integration of locoregional therapies remain challenging.

Incorporating Current Therapies Into Clinical Practice

Targeting the Somatostatin Receptor in NETs

Somatostatin is a peptide hormone with activity that is mediated through somatostatin receptors. Approximately 80% to 90% of NETs express somatostatin receptors (of which there are 5 known subtypes). Somatostatin and somatostatin analogues send signals through somatostatin receptors to arrest the cell cycle at G1, resulting in apoptosis. These features make somatostatin receptors a target for the development of therapies for NETs. Somatostatin receptor type 2 is the most important subtype to target for the treatment of NETs.

Although human somatostatin has a relatively short half-life of 3 minutes, the somatostatin analogue octreotide has a half-life of 90 minutes.[16,17] Octreotide and lanreotide are both somatostatin analogues that bind to somatostatin receptor type 2 with a high affinity and are antineoplastic in their activity.[17,18] The long-term acting formulations of each allow for injections once every 4 weeks.[17,18] Somatostatin inhibitors have a manageable toxicity profile, and most adverse events are transient.[19] Diarrhea, steatorrhea, flatulence, and injection site pain are the most frequent adverse events (>20%).[19] Diarrhea and flatulence are related to the steatorrhea, and can be treated with the administration of pancreatic enzymes before meals.

The phase 3 CLARINET trial (Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors) established the efficacy and safety of lanreotide depot/autogel in patients with metastatic GEP-NETs.[20] CLARINET enrolled 204 patients with advanced, well- or moderately differentiated, nonfunctioning, somatostatin receptor–positive, grade 1 to 2, progressive GEP-NETs.[20] Patients were randomly assigned to receive either extended-release lanreotide depot/autogel or placebo once every 4 weeks for 96 weeks.[20]

The median PFS was not reached with lanreotide depot/autogel vs 18.0 months with placebo (HR, 0.47; *P*<.001; Figure 5).[20] The benefit of lanreotide depot/autogel was not significant in the subgroup of patients with pancreatic NETs, but this subgroup was small.[20] In general, lanreotide depot/autogel improved clinical outcomes across subgroups, including divisions based on liver tumor burden, disease stage, and extent of differentiation.[20] Neither overall survival nor quality of life were significantly different between the 2 treatment arms.[20] A decrease in chromogranin A of at least 50% from baseline was seen in 42% of the lanreotide depot/autogel arm vs 5% of the placebo arm (*P*<.001).[20] Based on results of the CLARINET trial, the FDA approved lanreotide depot/autogel for pancreatic NETs. Although octreotide is a similar somatostatin analogue, it does not have the same level 1 clinical evidence that CLARINET provided for lanreotide depot/autogel.

The phase 2/3 REMINET trial (A Study Evaluating Lanreotide as Maintenance Therapy in Patients With Non-Resectable Duodeno-Pancreatic Neuroendocrine Tumors) is currently recruiting patients with metastatic or locally advanced, nonresectable, grade 1 or 2 NETs.[21] At least 4 weeks before randomization, patients must have controlled disease after 1 line of chemotherapy. Results from REMINET should elucidate whether long-term maintenance with lanreotide after primary therapy should be part of an overall treatment approach.

Somatostatin analogues can also be linked to radioisotopes. This approach can enable delivery of highly accurate radiotherapy. The phase 3 NETTER-1 trial (A Study Comparing Treatment With 177Lu-DOTA0-Tyr3-Octreotate to Octreotide LAR [Control] in Patients With Inoperable, Progressive, Somatostatin Receptor Positive Midgut Carcinoid Tumors) compared the radioisotope-linked somatostatin analogue Lu 177 dotatate plus best supportive care vs long-acting octreotide.[22] A total of 229 patients with well-differentiated, metastatic, midgut NETs received either Lu 177 dotatate (n=116) at 7.4 GBq every 8 weeks plus best supportive care, including octreotide, or long-acting octreotide (n=113) at 60 mg once every 4 weeks.[22] At data cut-off for the primary analysis, the estimated PFS at 20 months was 65.2% in the Lu 177 dotatate arm (95% CI, 50.0%-76.8%) and 10.8% in the control arm (95% CI, 3.5%-23.0%).[22] The response rate was 18% in the Lu 177 dotatate arm and 3% in the control arm (*P*<.001).[22] In the planned interim analysis of overall survival, there were 14 deaths in the Lu 177 dotatate arm vs 26 deaths in the control arm (*P*=.004).[22] Grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia occurred in less than 10% of the Lu 177 dotatate arm and in no patients in the control arm.[22] Lu 177 dotatate is now FDA-approved for the treatment of pancreatic NETs in patients with progressive disease after primary therapy with a somatostatin analogue. Patients without somatostatin receptors are not candidates for this treatment.

Radiotherapy-linked somatostatin analogues can also enable imaging of tumors just a few millimeters wide. Theranostics of NETs using molecular imaging with positron emission tomography/computed tomography (PET/CT) with (68)Ga-labeled somatostatin analogues can allow highly accurate detection of NETs

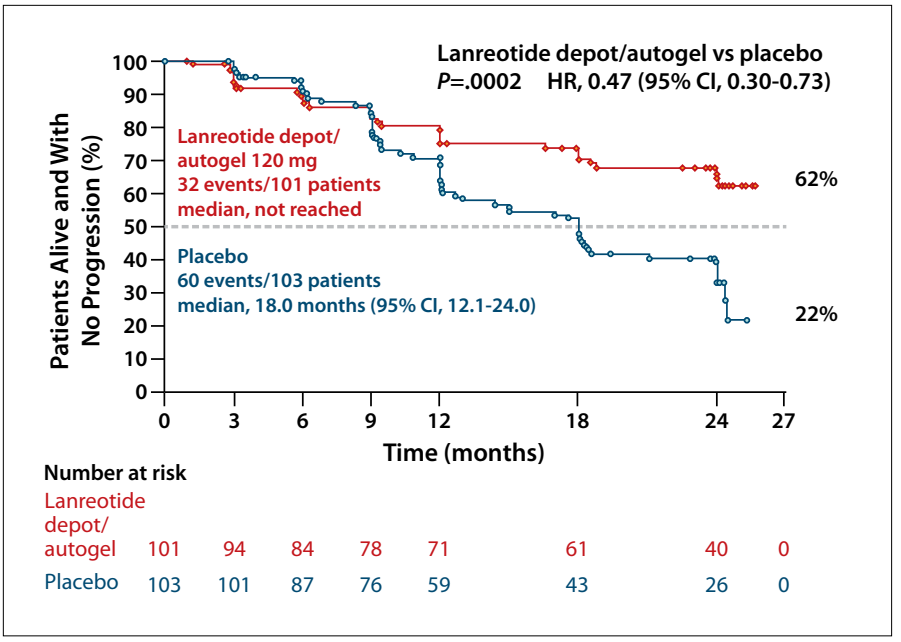

Figure 5. In the CLARINET trial, the median progression-free survival was not reached with lanreotide depot/autogel vs 18.0 months with placebo. CLARINET, Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors; HR, hazard ratio. Adapted from Caplin ME et al. *N Engl J Med.* 2014;371(3):224-233.[20]

and metastases with diagnostic specificity and sensitivity.[23] The reproducible and quantitative data can identify patients who are well-suited for treatment with agents such as Lu 177 dotatate.[23] Among the benefits are a fast imaging time (60-90 minutes), low radiation burden, flexibility in daily use, decreased cost compared with octreotide scintigraphy, and quick, routine quantification of tumors during PET/CT scans.[23]

Targeting the mTOR Pathway

The product of the *TSC2* gene inhibits mTOR activation. Patients with defective TSC2 develop pancreatic NETs.[24] Decreased expression of TSC2 and another mTOR inhibitor, PTEN, has been associated with shorter disease-free survival and overall survival.[25] NF1 also regulates mTOR, and patients with *NF1* gene loss develop pancreatic NETs characterized by neurofibromatosis.[26]

Everolimus is an inhibitor of mTOR. The phase 3 RADIANT-3 trial (Efficacy and Safety of Everolimus Compared to Placebo in Patients With Advanced Neuroendocrine Tumors) was a prospective, double-blind, randomized, placebo-controlled trial enrolling 410 patients with advanced pancreatic NETs who exhibited radiologically confirmed progression within 12 months.[27] Patients were randomly assigned to treatment with everolimus once daily (n=207) or placebo (n=203), until disease progression, unacceptable toxicity, or withdrawal.[27] Both treatment arms received best supportive care (that could include somatostatin analogues). Upon disease progression, treatment was unblinded, and patients in the control arm could cross over to receive everolimus.[27]

The median PFS was 11.0 months in the everolimus arm vs 4.6 months in the placebo arm (HR, 0.35; 95% CI, 0.27-0.45; *P*<.001), which represented a 65% reduction in the risk for death or progression.[27] The estimated proportion of patients alive and progression-free at 18 months was 34% (95% CI, 26%-43%) in the everolimus arm vs 9% (95% CI, 4%-16%) in the placebo arm.[27] Treatment-related adverse events were primarily grade 1 or 2.[27] The median exposure to everolimus was 38 weeks, and the median exposure to placebo was 16 weeks.[27]

Targeting Tumor Vascularity in NETs

Unlike pancreatic adenocarcinoma, GEP-NETs are usually hypervascular and express growth factors that promote angiogenesis, such as the vascular endothelial growth factor (VEGF).[28] Sunitinib inhibits multiple kinases, including VEGF and the epidermal growth factor receptor. In a phase 3, randomized, double-blind trial, 171 patients with advanced, well-differentiated pancreatic NETs and disease progression within the previous 12 months received sunitinib at 37.5 mg/day or placebo.[29] All patients also received best supportive care. The study was discontinued early, after the independent data and safety monitoring committee observed more serious adverse events and deaths in the placebo arm, as well as improved PFS with sunitinib.[29] The median PFS was 11.4 months in the sunitinib arm vs 5.5 months in the placebo arm (HR, 0.42; 95% CI, 0.26-0.66; *P*<.001). Analysis of PFS favored sunitinib across all subgroups. The ORR was 9.3% with sunitinib vs 0% with placebo. The most frequent adverse events in the sunitinib arm were diarrhea, nausea, vomiting, asthenia, and fatigue.

A randomized phase 2 study from the Cancer and Leukemia Group B, known as 80701, evaluated whether the VEGF inhibitor bevacizumab improved outcomes when added to everolimus and octreotide.[30] ORR was 31% among patients in the bevacizumab arm vs 12% among those treated with everolimus and octreotide alone (*P*=.005). No significant differences between the 2 arms were seen in median PFS (16.7 vs 14.0 months; *P*=.12) or median overall survival (36.7 vs 35.0 months; *P*=.16).[30] A single-arm phase 2 study of the mTOR inhibitor temsirolimus plus bevacizumab in patients with advanced, progressive pancreatic NETs showed an ORR of 41%, a 6-month PFS rate of 79%, and a median PFS of 11.7 months.[31] The potential of combination therapies to improve survival must be weighed against the possibility that they may have intolerable toxicity profiles.

Disclosure

Dr Wolin is on the advisory boards of Novartis, Ipsen, and Lexicon.

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Therapeutic Advances in Metastatic Pancreatic Adenocarcinoma and Related Cancers

CME Post-Test: *Circle the correct answer for each question below.*

1. Approximately how many patients with pancreatic cancer have advanced-stage disease at the time of diagnosis?

   a. 45% to 50%
   b. 70% to 75%
   c. 80% to 85%
   d. 90% to 95%

2. What is the 5-year relative survival rate across stages for patients with pancreatic cancer?

   a. 6.5%
   b. 7.6%
   c. 8.5%
   d. 10.1%

3. Pancreatic adenocarcinoma accounts for approximately ___ of all cases of pancreatic cancer.

   a. 60%
   b. 70%
   c. 80%
   d. 90%

4. In the frontline management of pancreatic cancer, which is a typical chemotherapy regimen?

   a. Capecitabine or bevacizumab plus PEGylated human recombinant PH20 hyaluronidase
   b. Fluoropyrimidine plus oxaliplatin
   c. FOLFIRINOX or gemcitabine plus nab-paclitaxel
   d. Irinotecan plus 5-fluorouracil

5. In the phase 3 MPACT trial, which treatment approach improved median overall survival among patients treated with single-agent gemcitabine?

   a. Dose delay
   b. Dose reduction
   c. Both dose delay and dose reduction
   d. Neither dose delay nor dose reduction

6. In the NAPOLI-1 trial, the addition of ___ to 5-fluorouracil/leucovorin improved median overall survival compared with 5-fluorouracil/leucovorin alone.

   a. Erlotinib
   b. Gemcitabine
   c. Nanoliposomal irinotecan
   d. Oxaliplatin

7. In the phase 3 CLARINET trial, the median progression-free survival was ___ with lanreotide depot/autogel vs 18.0 months with placebo.

   a. 20.4 months
   b. 23.8 months
   c. 31.3 months
   d. Not reached

8. In the phase 3 NETTER-1 trial, the response rate was _____ in the Lu 177 dotatate arm vs 3% in the control arm.

   a. 18%
   b. 27%
   c. 33%
   d. 41%

9. In the phase 3 RADIANT-3 trial, which agent improved progression-free survival compared with placebo?

   a. Everolimus
   b. Lanreotide depot/autogel
   c. Octreotide
   d. Sunitinib

10. In the randomized phase 2 study from the Cancer and Leukemia Group B known as 80701, which agent improved outcomes when added to everolimus and octreotide?

    a. Bevacizumab
    b. Lu 177 dotatate
    c. Streptozocin
    d. Telotristat ethyl

Evaluation Form: Therapeutic Advances in Metastatic Pancreatic Adenocarcinoma and Related Cancers

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by **project ID 13438**. Upon successfully registering/logging in, completing the post-test and evaluation, your certificate will be made available immediately.

1. What degree best describes you?

❒ MD/DO ❒ PA/PA-C ❒ NP ❒ RN ❒ PharmD/RPh ❒ PhD
❒ Other, please specify:

2. What is your area of specialization?

❒ Oncology, Medical ❒ Oncology, Hematology/Oncology ❒ Oncology, Other

3. Which of the following best describes your *primary* practice setting?

❒ Solo Practice ❒ Group Practice ❒ Government
❒ University/teaching system ❒ Community Hospital
❒ HMO/managed care ❒ Non-profit/community ❒ I do not actively practice
❒ Other, please specify:

4. How long have you been practicing medicine?

❒ More than 20 years ❒ 11-20 years ❒ 5-10 years ❒ 1-5 years
❒ Less than 1 year ❒ I do not directly provide care

5. Approximately how many patients do you see each week?

❒ Less than 50 ❒ 50-99 ❒ 100-149 ❒ 150-199 ❒ 200+
❒ I do not directly provide care

6. How many patients do you currently see each week who have pancreatic cancer?

❒ Fewer than 5 ❒ 6-15 ❒ 16-25 ❒ 26-35 ❒ 36-45 ❒ 46-55
❒ 56 or more ❒ I do not directly provide care

7. Rate how well the activity supported your achievement of these learning objectives:

Apply the most recent guidelines from the National Comprehensive Cancer Network to the management of patients with metastatic pancreatic adenocarcinoma

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Determine which patients with metastatic pancreatic adenocarcinoma are candidates for the use of surgical interventions (resection), medical therapy, and/or systemic chemotherapy, based on presentation, symptoms, tumor type and stage, clinical profile, extent of disease, biomarkers, and other factors

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Differentiate among approved therapies for pancreatic cancer based on mechanistic differences, delivery systems, formulations, metabolism, and local and systemic antitumor properties

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Describe recent clinical trial data supporting the use of new and emerging treatment regimens in metastatic pancreatic carcinoma

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

8. Rate how well the activity achieved the following:

The faculty were effective in presenting the material

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The content was evidence-based

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The educational material provided useful information for my practice

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The activity enhanced my current knowledge base

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

The activity provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc.)

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The opportunities provided to assess my own learning were appropriate (e.g., questions before, during or after the activity)

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

9. Based upon your participation in this activity, do you intend to change your practice behavior? *(choose only one of the following options)*

❒ I do plan to implement changes in my practice based on the information presented

❒ My current practice has been reinforced by the information presented

❒ I need more information before I will change my practice

10. Thinking about how your participation in this activity will influence your patient care, how many of your patients are likely to benefit?

Please use a number (for example, 250):

11. If you plan to change your practice behavior, what type of changes do you plan to implement? *(check all that apply)*

❒ Apply latest guidelines ❒ Choice of treatment/management approach
❒ Change in pharmaceutical therapy ❒ Change in current practice for referral
❒ Change in nonpharmaceutical therapy ❒ Change in differential diagnosis
❒ Change in diagnostic testing ❒ Other, please specify:

12. How confident are you that you will be able to make your intended changes?

❒ Very confident ❒ Somewhat confident ❒ Unsure ❒ Not very confident

13. Which of the following do you anticipate will be the primary barrier to implementing these changes?

❒ Formulary restrictions ❒ Insurance/financial issues ❒ Time constraints
❒ Lack of multidisciplinary support ❒ System constraints
❒ Treatment-related adverse events ❒ Patient adherence/compliance
❒ Other, please specify:

14. Was the content of this activity fair, balanced, objective and free of bias?

❒ Yes ❒ No, please explain:

15. Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:

Request for Credit (*required fields)

Name* _____

Degree* _____

Organization _____

Specialty* _____

City, State, ZIP* _____

Telephone _____ Fax _____

E-mail* _____

Signature* _____ Date* _____

For Physicians Only:

I certify my actual time spent to complete this educational activity to be:

❒ I participated in the entire activity and claim 1.25 credits.
❒ I participated in only part of the activity and claim _____ credits.

Project ID: **13438**