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New Frontiers and Therapeutic Advances for Metastatic Adenocarcinoma and Pancreatic Neuroendocrine Tumors: Focus on Evidence-Based Approaches to Optimizing PFS in Pancreatic NET and Survival Extension in Pancreatic Adenocarcinoma

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Target Audience

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

Statement of Need/Program Overview

Although pancreatic cancer accounts for only 3% of all cancer diagnoses in the United States, it is the fourth deadliest cancer for both men and women. Appropriate staging is key to treatment planning for pancreatic cancer. Multiple clinical guidelines are available to help inform the treatment selection process. Treatment recommendations vary based on multiple factors, including disease stage, performance status, symptoms, and treatment history. Newer treatment regimens for pancreatic adenocarcinoma and gastroenteropancreatic neuroendocrine tumors have expanded options for these patients. Ongoing clinical challenges include the optimal sequencing of systemic therapies. Research is investigating the role of molecular biology to inform treatment decisions, as well as the efficacy and safety of new therapies.

Educational Objectives

After completing this activity, the participant should be better able to:

- Detail the epidemiology, burden, and clinical challenges associated with detecting, diagnosing, and classifying metastatic pancreatic adenocarcinoma and pancreatic neuroendocrine tumors
- Outline recommendations from the most recent clinical practice guidelines for metastatic pancreatic adenocarcinoma and pancreatic neuroendocrine tumors
- Describe data from the latest clinical trials of therapies in pancreatic adenocarcinoma and pancreatic neuroendocrine tumors
- Differentiate among approved therapies for pancreatic cancer based on mechanistic differences, delivery systems, formulations, metabolism, and local and systemic antitumor properties
- Devise treatment plans based on disease characteristics and patient factors

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This monograph was authored by an independent medical writer, Mindy Tanzola, PhD, based on presentations given at "New Frontiers and Therapeutic Advances for Metastatic Adenocarcinoma and Pancreatic Neuroendocrine Tumors: Focus on Evidence-Based Approaches to Optimizing PFS in Pancreatic NET and Survival Extension in Pancreatic Adenocarcinoma," a live symposium held on October 14, 2017.

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New Strategies, Guidelines, and Therapeutic Advances for the Comprehensive Continuum of Metastatic Pancreatic Cancers: Focus on Chemotherapeutic and Surgical Approaches to Pancreatic Adenocarcinoma and Pancreatic Neuroendocrine Tumors

George P. Kim, MD

Pancreatic cancer is a relatively rare but highly lethal malignancy. Although pancreatic cancer accounts for only 3% of all cancer diagnoses in the United States, it is the fourth deadliest cancer for both men and women, behind only lung cancer, colorectal cancer, prostate cancer, and breast cancer.[1] In contrast to other cancer types, in which relative survival has improved dramatically in recent decades, the prognosis for patients with pancreatic cancer remains poor, with a 5-year survival rate of 8%. This rate drops to 2.7% for the 52% of patients with metastatic disease at diagnosis.[2]

Epidemiology of Pancreatic Cancer

The incidence of pancreatic cancer varies geographically, with the highest rates reported in more-developed areas and lower rates in less-developed areas.[3] Pancreatic cancer is primarily a disease of older adults, with a median age at diagnosis of 70 years.[2] As the population ages, the incidence of pancreatic cancer is expected to increase. By 2030, pancreatic cancer is predicted to become the second-leading cause of cancer death, surpassing breast, prostate, and colorectal cancers (Figure 1).[4]

Rates of pancreatic cancer are higher in men than women (14.2 vs 11.1 per 100,000 persons) and in African Americans vs whites among both men (17.0 vs 14.2 per 100,000 persons) and women (14.3 vs 11.1 per 100,000 persons).[2] Among lifestyle factors, tobacco smoking is associated with a significant increase in the risk of pancreatic cancer.[5]

Anatomy of the Pancreas and Overview of Pancreatic Cancer

The structure of the pancreas can be divided into 4 sections. The rightmost section, the head, is surrounded by the duodenum and delivers pancreatic enzymes directly to the intestines. To the left is the pancreatic neck, followed by the body and the tail. The pancreas interacts closely with surrounding blood vessels, delivering insulin and other hormones involved in digestion and energy usage. These interactions affect the treatment approach for pancreatic cancer.

Surgical treatment of pancreatic cancer is feasible in some cases, and is the only curative treatment modality. More than 80% of patients with pancreatic cancer have locally advanced or metastatic disease at the time of diagnosis and are therefore ineligible for surgical resection.[6,7]

The location of a tumor within the pancreas affects both the pattern of symptoms and the likelihood of resectability.[6] Approximately 60% to 70% of pancreatic tumors arise in the head, and these tumors are more often associated with jaundice owing to pressure on the bile duct.[8] Approximately 20% to 25% of tumors arise in the body and tail of the pancreas. These tumors are often associated with the development of epigastric pain.[7] Across the pancreas, tumors that develop near major veins and arteries are difficult to remove surgically.

One challenge in the timely diagnosis of pancreatic cancer is a lack of distinctive signs and symptoms at the early stage. The lack of early characteristic symptoms results in late detection of pancreatic cancer, often after metastasis has occurred. This contributes to the high mortality rate.[9] Most patients remain asymptomatic until the disease reaches an advanced stage. However, symptoms of early pancreatic cancer can occur, particularly in the 6 months preceding diagnosis, and include back pain, shoulder pain, dysphagia, changes in bowel habits, lethargy, and depression.[9,10] The most common symptoms of advanced pancreatic cancer include obstructive jaundice, abdominal or back pain, weight loss, and anorexia.[11]

Treatment of Pancreatic Cancer

Appropriate staging is key to treatment planning for pancreatic cancer. Stage I and II pancreatic cancer does not involve major blood vessels and is generally resectable.[10] Potentially curative resection may be followed by adjuvant chemotherapy or chemoradiotherapy. A subset

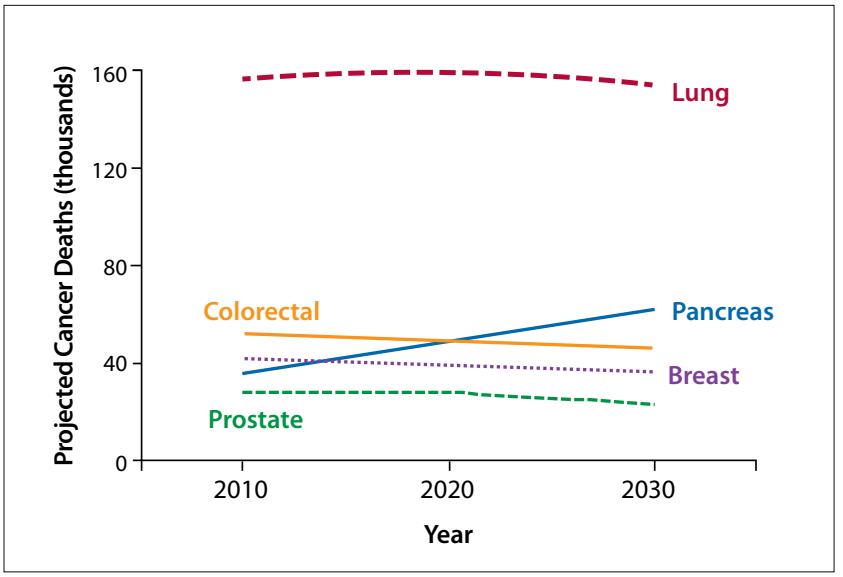

Figure 1. Pancreatic cancer is expected to become the second-leading cause of cancer-related death by 2030. Adapted from Rahib L et al. *Cancer Res*. 2014;74(11):2913-2921.[4]

of patients with stage III pancreatic cancer are considered to have "borderline resectable" disease and may benefit from neoadjuvant chemotherapy or chemoradiotherapy prior to potentially curative resection, followed by adjuvant therapy.[6,9] Unresectable stage III pancreatic cancer involves major blood vessels,[12] whereas stage IV disease is associated with distant metastases. These patients are treated with systemic therapy as well as pain management and end-of-life care, as appropriate.

Multiple clinical guidelines are available to help inform the treatment selection process. The European Society for Medical Oncology (ESMO) recommendations were last updated in 2015,[7] and the US National Comprehensive Cancer Network (NCCN) guidelines were updated in September 2017.[13] Treatment recommendations vary based on multiple factors, including disease stage, performance status, symptoms, and treatment history.

Overview of Neuroendocrine Tumors

Neuroendocrine tumors (NETs) can arise from cells throughout the endocrine system, including in the pancreas. The incidence and prevalence of NETs has been rising in recent decades, possibly owing to increased detection of early-stage disease. Age-adjusted incidence rates for NETs increased more than 6-fold from 1973 to 2012, with the reported incidence rate rising from 1.09 to 6.98 cases per 100,000 individuals.[14] NETs arise most frequently in gastroenteropancreatic (GEP) sites (3.56 cases per 100,000), followed by the lung (1.49 cases per 100,000). GEP-NETs have often metastasized by the time of diagnosis, and most patients die within 5 years of diagnosis.

In general, outcomes are better for patients with NETs compared with pancreatic adenocarcinoma. Prognosis for NETs varies significantly based on the stage, grade, age at diagnosis, and primary site.[14] Some patients survive for years after the diagnosis. Conventional chemotherapy has limited efficacy in patients with GEP-NETs, and there remains a significant unmet need for effective, safe therapies for these patients.

Treatment of NETs

Treatment of patients with GEP-NETs is multidisciplinary and involves medical oncology, surgery, endocrinology, nuclear medicine, diagnostic and interventional radiology, gastroenterology, cardiology, radiation oncology, and pathology. The therapies used vary according to the location and spread of the tumor. They involve surgery, radiolabeled treatments, chemotherapy, and embolization of the liver for metastases. GEP-NETs tend to be hypervascular and express vascular endothelial growth factor (VEGF) and other proangiogenic growth factors. These proteins, along with their downstream effectors—such as c-KIT, epidermal growth factor receptor, IGF-1R, phosphoinositide-3 kinase, AKT, mammalian target of rapamycin (mTOR), and platelet-derived growth factor—are among the potential therapeutic targets for GEP-NETs.[15]

Symptoms of NETs can be vague and nondescript, and there can be a substantial delay between the onset of symptoms and diagnosis. In a survey that included 758 patients with a NET in the United States, 34% of patients required more than 5 years to obtain an accurate diagnosis (Table 1).[16] Patients saw an average of 5.7 healthcare providers across an average of 12.7 visits before obtaining

Table 1. Time Between the First Reported Symptom and Diagnosis of a NET

NET Diagnosis in the Following Time Period	Did Not Know/NA	<6 Months	6 Months to 5 Years	≥5 Years	Mean (months)
Total US sample (n=758)	8%	18%	36%	34%	59.0
GI NETs	8%	15%	37%	36%	61.4
pNETs	6%	21%	40%	29%	53.4
Lung NETs	8%	24%	33%	31%	58.2

FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin; GI, gastrointestinal; NA, not available; NET, neuroendocrine tumor; pNET, pancreatic neuroendocrine tumor.

Data from Wolin E et al. DDW abstract 668. *Gastroenterology*. 2015;148(suppl 1).[16]

the correct diagnosis.[16] Conditions initially diagnosed in patients with NETs (regardless of site) included irritable bowel syndrome (in 49% of respondents), gastritis or other digestive disorders (46%), anxiety or a psychosomatic-type condition (26%), and inflammatory bowel disease (23%).

Systemic therapies approved for the treatment of GEP-NETs include the antiproliferative agents streptozocin, everolimus, sunitinib, and lanreotide depot/autogel. Short-acting octreotide and octreotide long-acting release (LAR) are used for the relief of carcinoid syndrome. Many clinical challenges remain in the treatment of patients with NETs, including the optimal sequencing of systemic therapies, the integration of locoregional therapies, timing in the use of lanreotide depot/autogel, and incorporation of peptide receptor radiotherapy. Ongoing research is investigating the role of molecular biology to inform treatment decisions, as well as the efficacy and safety of new therapies.

Disclosure

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Real World Decision-Making for Metastatic Pancreatic Adenocarcinoma: Navigating the Complex Roadmap of NCCN Guidelines and Selecting Among Evidence-Based Treatment Regimens to Optimize Survival Extension—A Year 2017 Update

George P. Kim, MD

Clinical guidelines are available for the treatment of pancreatic adenocarcinoma, which accounts for 90% of pancreatic cancer cases.[1] Guidelines from the NCCN recommend that a patient with clinical suspicion of pancreatic cancer, or evidence of a dilated pancreatic and/or bile duct, should undergo a pancreatic protocol computed tomography (CT) scan.[2] Results will inform next steps in terms of the diagnostic workup and treatment.

If a mass was detected on imaging, but CT scans showed no metastatic disease, a multidisciplinary review is indicated, and endoscopic ultrasonography should be considered.[2] This type of patient may be a candidate for surgery. If a pancreatic CT does not show a mass, then endoscopic ultrasonography is used to further assess the area. Magnetic resonance imaging/magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography may be indicated. If results from these studies suggest a diagnosis of pancreatic cancer, the patient should undergo surgical consultation.

Surgical Treatment

Surgical resection is a cornerstone of treatment for pancreatic cancer. For patients with nonmetastatic disease, a key determination is whether a tumor is resectable. A new category known as borderline resectable refers to tumors that have a limited amount of contact with nearby major arteries.[2] Patients who have symptomatic jaundice (cholangitis or fever) should undergo stent placement prior to surgery. Baseline measurement of the cancer antigen (CA) 19-9 level should also be obtained, as it can provide useful information later in the treatment course.

Patients with borderline resectable disease may benefit from neoadjuvant therapy, which would be followed by posttreatment imaging and measurement of CA 19-9. Staging laparoscopy should be considered if not previously performed.[2] Eligible patients would then proceed to surgical resection. After completion of surgical resection, adjuvant treatment in a clinical trial is recommended. Alternatives include chemotherapy alone or followed by chemoradiation, with or without subsequent chemotherapy.[2]

Treatment of Locally Advanced/Metastatic Disease

For patients with locally advanced, unresectable or metastatic disease, placement of a self-expanding metal stent is appropriate to relieve symptoms.[2] Systemic treatment options are selected based on the patient's performance status. Clinical trials or combination chemotherapy regimens are recommended for patients with a good performance status, whereas single-agent chemotherapy, palliative radiotherapy, and other palliative approaches are more appropriate for patients with a poor performance status.

Currently, the 2 main approaches used for the first-line treatment of patients with a good performance status are the 4-drug regimen of 5-fluorouracil (5-FU), leucovorin (LV), irinotecan, and oxaliplatin (FOLFIRINOX) and gemcitabine-based regimens (gemcitabine plus albumin-bound paclitaxel, erlotinib, capecitabine, or cisplatin).[2] Options for patients with a poor performance status include single-agent gemcitabine, capecitabine, and continuous-infusion 5-FU.

In the second-line setting, recommended options for patients who have previously received gemcitabine-based therapy include nanoliposomal irinotecan plus 5-FU/LV (a category 1 option for metastatic disease), FOLFIRINOX, oxaliplatin/5-FU/LV, and capecitabine/oxaliplatin, as well as various single-agent approaches (Table 2).[2] Patients previously treated with fluoropyrimidine-based therapy can receive gemcitabine plus albumin-bound paclitaxel or another gemcitabine-based regimen. The checkpoint inhibitor pembrolizumab is approved by the US Food and Drug Administration (FDA) for use in patients with previously treated microsatellite instability–high or mismatch repair–deficient solid tumors. Some patients with pancreatic cancer may meet these criteria.

Table 2. Options for the Second-Line Treatment of Patients With Metastatic Pancreatic Cancer

If the patient was previously treated with gemcitabine-based therapy, options include:
• 5-FU + leucovorin + nanoliposomal irinotecan (category 1 for metastatic disease)
• FOLFIRINOX
• Oxaliplatin/5-FU/leucovorin
• FOLFOX
• Capecitabine/oxaliplatin
• Capecitabine
• Continuous 5-FU
• Chemoradiation[a]
If the patient was previously treated with fluoropyrimidine-based therapy, options include:
• Gemcitabine + albumin-bound paclitaxel
• Gemcitabine
• Gemcitabine + cisplatin
• Gemcitabine + erlotinib
• 5-FU + leucovorin + nanoliposomal irinotecan (if no prior irinotecan)
• Chemoradiation[a]

[a]Chemoradiation is an option for patients with locally advanced disease, who had not received chemoradiation previously, and if the primary site is the sole site of progression.

FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin; FOLFOX, leucovorin, 5-fluorouracil, oxaliplatin; 5-FU, 5-fluorouracil.

Data from the NCCN Clinical Practice Guidelines in Oncology. Pancreatic adenocarcinoma. Version 3.2017.[2]

ESMO publishes clinical guidelines for the treatment of patients with pancreatic cancer.[3] Similar to the NCCN guidelines, the ESMO guidelines recommend systemic therapies based on the extent of disease and the patient's performance status. For patients with metastatic pancreatic cancer and a good performance status, recommended first-line options are FOLFIRINOX or gemcitabine plus nab-paclitaxel. For patients with an intermediate performance status and/or elevated bilirubin, single-agent gemcitabine is recommended.[3] Whether patients receive FOLFIRINOX, gemcitabine plus nab-paclitaxel, or gemcitabine alone in the first-line setting, for second-line treatment, European guidelines propose that nanoliposomal irinotecan plus 5-FU/LV is potentially the best option.[3]

Future Directions

Ongoing trials are evaluating new uses for existing regimens. An open-label, phase 2 study is comparing the efficacy and safety of 2 liposomal irinotecan–containing regimens—nanoliposomal irinotecan plus 5-FU/LV with or without oxaliplatin—vs nab-paclitaxel plus gemcitabine in 168 patients with previously untreated metastatic pancreatic adenocarcinoma.[4]

Other lines of research are working to further elucidate the molecular mechanisms of pancreatic cancer. *KRAS* mutations occur in more than 90% of patients with pancreatic cancers and are considered to be a signature.[5] *BRAF* mutations are observed in approximately 30% of pancreatic cancers with wild-type *KRAS*.[6] Amplifications in *AKT1, AKT2,* and *MYB* are also observed in a subset of pancreatic cancers.[7-9] Inactivation of tumor suppressor genes has been observed in patients with pancreatic cancer, including *p16* (in up to 95% of sporadic pancreatic cancers), *p53* (in 55%-75% of cases), *p21*, *SMAD4*, and *BRCA1/2*.[7,10-12] *BRCA1/2* mutations appear to be prognostic in pancreatic cancer and may help guide therapy, particularly with the availability of poly(ADP-ribose) polymerase (PARP) inhibitors.[13]

Disclosure

Dr Kim is a consultant for and on the speakers bureaus of Celgene and Ipsen.

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The Evolving Evidence-Based and Guideline-Supported Role for Nanoliposomal Topoisomerase Inhibitors in Metastatic Pancreatic Adenocarcinoma: The Mechanistic Basis, PK/PD Profiles, and Effects of Novel Formulations on Intratumoral Levels of Active Metabolites and Their Clinical Implications

Alok A. Khorana, MD

Outcomes for patients with pancreatic cancer remain poor. Most patients are ineligible for resection, and few have complete responses to available therapies. An analysis of recent clinical trial outcomes shows that survival is improving, albeit slowly. In the first-line metastatic setting, median survival improved from approximately 5 to 6 months in the late 1990s, with the introduction of single-agent gemcitabine,[1] to 10 to 11 months in the past few years, with FOLFIRINOX and gemcitabine-based combinations.[2-4]

For patients with progression after first-line therapy, the notion of even considering second-line therapies represents an advance in and of itself. Until the development of current first-line regimens, patients attained little benefit from first-line chemotherapy and were generally referred to hospice following progression on first-line therapy. With the recent advances in first-line therapy, patients are living longer and feeling better, allowing the consideration of second-line therapy upon disease progression.

A series of studies in the second-line setting have focused on oxaliplatin-based regimens, yielding mixed results. In the CONKO-003 trial (German Charité Onkologie), oxaliplatin plus 5-FU/LV was associated with a significant improvement in median overall survival (OS) compared with 5-FU/LV alone (5.9 vs 3.3 months; hazard ratio [HR], 0.66; *P*=.010).[5] In the PANCREOX trial (A Randomized Phase III Study of Fluorouracil/Leucovorin With or Without Oxaliplatin for Second-Line Advanced Pancreatic Cancer in Patients Who Have Received Gemcitabine-Based Chemotherapy), however, median OS was significantly shorter with modified FOLFOX6 (infusional 5-FU/LV and oxaliplatin) compared with 5-FU/LV alone (6.1 vs 9.9 months; HR, 1.78; *P*=.024).[6] Similarly, a phase 2 Japanese study did not yield a significant survival benefit with the addition of oxaliplatin to the oral 5-FU prodrug known as S-1 (median OS, 7.4 vs 6.9 months; *P*=.82).[7]

Another line of studies evaluated the use of irinotecan for the second-line treatment of pancreatic cancer, yielding median OS durations of 6 to 7 months.[8-12] Although these studies suggest some benefit, there is still a need for improvement over standard therapies.

Nanoliposomal Irinotecan

To improve upon drug delivery to the tumor, a formulation was developed in which irinotecan is contained within a stable nanoliposome. The nanoliposome protects the cargo delivery within the circulation, enabling tumor targeting and subsequent sustained drug exposure.[13] The leaky vasculature of tumors allows nanoliposomal irinotecan to penetrate the tumor microenvironment, permitting more targeted drug delivery. Nanoliposomes are then preferentially taken up by tumor-associated macrophages that degrade the liposomes, releasing irinotecan into the cell.[13] There, irinotecan is metabolized by carboxylesterases and converted into its active metabolite, SN-38, which is released from tumor-associated macrophages and delivered to tumor cells.

The encapsulation of irinotecan offers benefits over conventional irinotecan, including extended exposure both in the plasma (>50 hours vs 8 hours) and in tumors (168 hours vs >90% clearance within 24 hours), a lower dose required to attain similar exposure to the active drug (10 mg/kg vs 50 mg/kg), and enhanced inhibition of tumors in animal models (Table 3).[13]

Clinical Trials of Nanoliposomal Irinotecan

A phase 1 study from 2015 demonstrated acceptable safety with nanoliposomal irinotecan in patients with advanced solid tumors.[14] Phase 2 studies were then performed to further assess the activity and safety of this therapy. In a multinational phase 2 study in 40 patients with gemcitabine-refractory metastatic pancreatic cancer,

Table 3. Irinotecan Formulations

Advantage of Nanoliposomal Irinotecan Encapsulation	Conventional Irinotecan	Nanoliposomal Irinotecan
Prolonged exposure in plasma	Irinotecan and SN-38 plasma levels cleared from circulation within 8 hours	Irinotecan and SN-38 remained in circulation for >50 hours
Prolonged exposure in tumors	>90% irinotecan was cleared from tumors within 24 hours SN-38 exposure in tumors <48 hours	Irinotecan levels persisted >10,000 nmol/L for 168 hours in tumors Prolonged SN-38 exposure above activity threshold for up to 168 hours
Dose needed to achieve similar SN-38 exposure in plasma and tumors	50 mg/kg	10 mg/kg
Enhanced tumor growth inhibition in animal models	~40%	~110%

Data from Kalra AV et al. *Cancer Res.* 2014;74(23):7003-7013.[13]

Table 4. Overall Survival Among the Intent-to-Treat and Per Protocol Populations of NAPOLI-1

Population	Overall Survival, months (n)		Stratified HR (95% CI) *P* Value
	Combination Therapy: Nanoliposomal Irinotecan + 5-FU/LV	Combination Therapy Control: 5-FU/LV	
Intent-to-treat	6.1 (117)	4.2 (119)	0.57 (0.41-0.80); *P*=.0009
Per protocol	8.9 (66)	5.1 (71)	0.47 (0.29-0.77); *P*=.0018

5-FU/LV, 5-fluorouracil/leucovorin; HR, hazard ratio; NAPOLI, Nanoliposomal Irinotecan.

Adapted from Chen LT et al. ASCO GI abstract 234. *J Clin Oncol.* 2015;33(suppl 3).[17]

nanoliposomal irinotecan was associated with a 3-month OS rate of 75%, and tumor shrinkage was observed in 75% of patients (30 of 40).[15] Significant tumor shrinkage and a reduction in CA 19-9 responses were observed in 25% of evaluable patients (5 of 25). Moreover, 31% of evaluable patients (10 of 32) experienced sustained clinical benefit as measured by pain intensity and morphine consumption. The most frequent severe toxicities were neutropenia, abdominal pain, asthenia, and diarrhea.

Based on the results of this phase 2 study, the randomized, phase 3 NAPOLI-1 trial (Nanoliposomal Irinotecan) was performed to compare the efficacy and safety of nanoliposomal irinotecan vs 5-FU/LV in patients with metastatic pancreatic cancer that had progressed after previous gemcitabine-based treatment.[16] A third arm was later added evaluating nanoliposomal irinotecan plus 5-FU/LV. The trial enrolled 417 patients with metastatic pancreatic cancer that had progressed after previous gemcitabine-based treatment. Patients were stratified based on their serum albumin level, Karnofsky performance status, and ethnicity.

In the NAPOLI-1 trial, nanoliposomal irinotecan plus 5-FU/LV was significantly more effective than 5-FU/LV alone as assessed by median OS (6.1 vs 4.2 months; HR, 0.67; *P*=.012), median progression-free survival (PFS; 3.1 vs 1.5 months; HR, 0.56; *P*=.0001), overall response rate (ORR; 16% vs 1%; *P*<.0001), and CA 19-9 response rate (29% vs 9%; *P*=.0006; Figures 2 and 3).[16] The median OS reported with nanoliposomal irinotecan alone was 4.9 months vs 4.2 months with 5-FU/LV (HR, 0.99; 96% CI, 0.77-1.28; *P*=.94). Subset analyses suggested that most subgroups could benefit from the addition of nanoliposomal irinotecan to 5-FU/LV. The survival benefit was also consistent in an expanded per protocol analysis, in which the median OS was 8.9 months with nanoliposomal irinotecan plus 5-FU/LV vs 5.1 months with 5-FU/LV alone (stratified HR, 0.47; *P*=.0018; Table 4).[17]

Although the safety profile was generally manageable, the addition of nanoliposomal irinotecan to the regimen was associated with some increase in toxicity. The most frequent grade 3/4 adverse events (AEs) occurring in the nanoliposomal irinotecan arm were neutropenia (27%), fatigue (14%), diarrhea (13%), and vomiting (11%).[16] A subsequent analysis of safety outcomes in NAPOLI-1 found that the incidence of treatment-related AEs was higher in older vs younger patients, although the distribution of toxicities was similar regardless of age.[18]

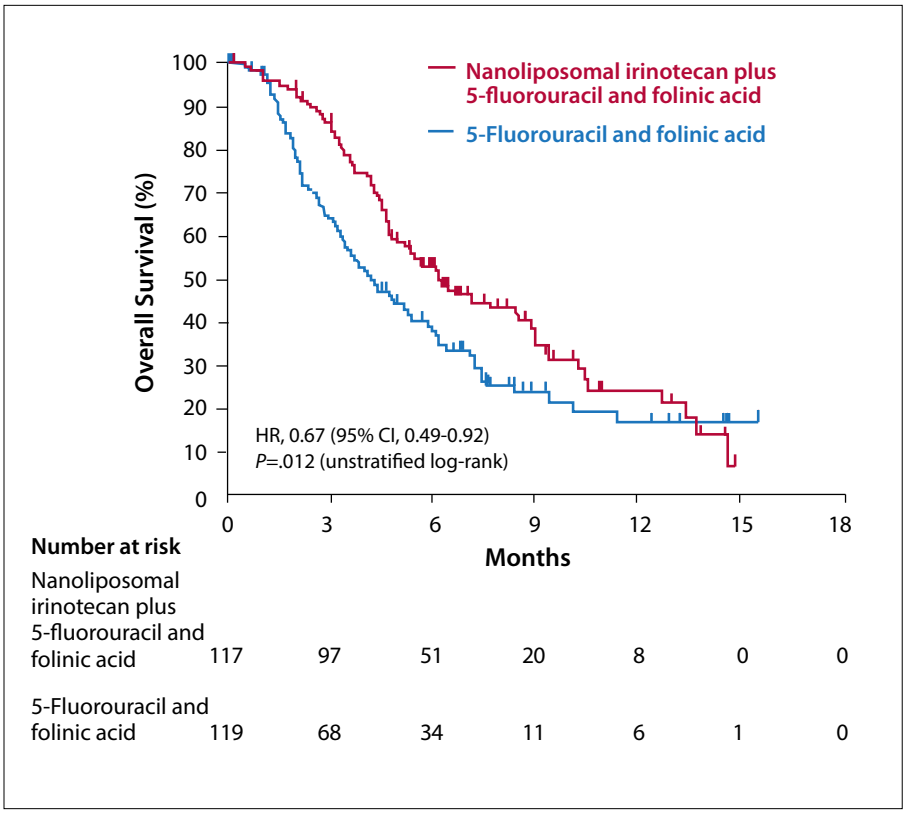

Figure 2. Median overall survival in the phase 3 NAPOLI-1 trial. HR, hazard ratio; NAPOLI-1, Nanoliposomal Irinotecan. Adapted from Wang-Gillam A et al. *Lancet*. 2016;387(10018):545-557.[16]

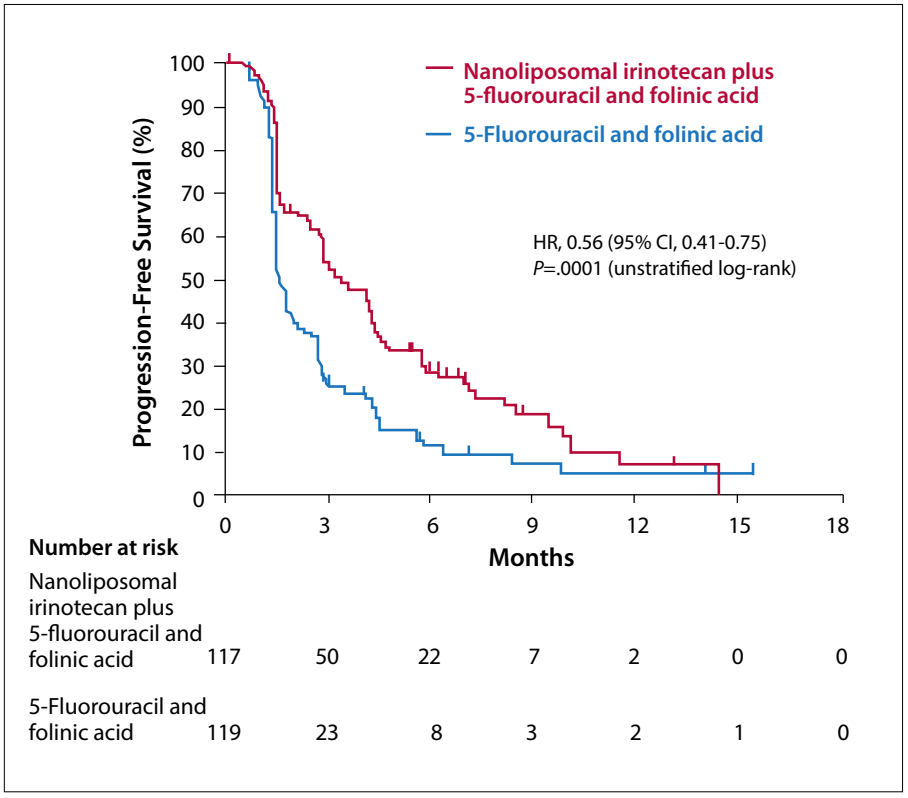

Figure 3. Progression-free survival in the phase 3 NAPOLI-1 trial. HR, hazard ratio; NAPOLI-1, Nanoliposomal Irinotecan. Adapted from Wang-Gillam A et al. *Lancet*. 2016;387(10018):545-557.[16]

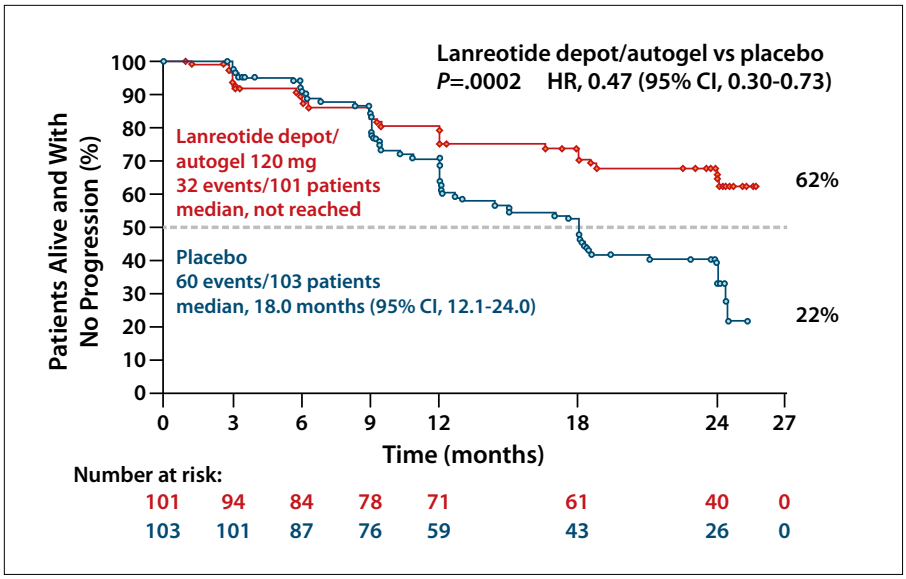

Figure 4. Progression-free survival among the intent-to-treat population in the CLARINET trial. CLARINET, Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors; HR, hazard ratio. Adapted from Caplin ME et al. *N Engl J Med.* 2014;371(3):224-233.[25]

Investigators found no appreciable deterioration in quality of life over 12 weeks, despite the addition of a second active agent.[19] An analysis of time spent with toxicities or relapse found that patients treated with nanoliposomal irinotecan plus 5-FU/LV had 1.3 additional months of quality-adjusted survival compared with patients treated with 5-FU/LV alone (P<.05).[20]

Incorporation of Nanoliposomal Irinotecan Into Practice

In October 2015, nanoliposomal irinotecan was approved by the FDA for use in combination with 5-FU/LV in patients with advanced pancreatic cancer previously treated with gemcitabine-based therapy.[21] Irinotecan plus 5-FU/LV is now a recommended second-line regimen in the ESMO guidelines[22] and the NCCN guidelines.[23] It is also recommended in the second-line setting for the treatment of metastatic pancreatic cancer. An ongoing phase 3 trial is evaluating nanoliposomal irinotecan–containing therapy in the first-line setting.[24]

Treatment of GEP-NETs

GEP-NETs arise within the gastrointestinal tract. Patients may not require immediate treatment. If patients have unresectable or advanced disease that is symptomatic (ie, carcinoid syndrome) or have clinically significant tumor burden or progressive disease, then symptoms should be managed as appropriate with a somatostatin analogue.

Lanreotide Depot/Autogel

In 2014, the randomized, double-blind, placebo-controlled phase 3 CLARINET trial (Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors) established the efficacy and safety of the somatostatin analogue lanreotide depot/autogel in patients with metastatic GEP-NETs. The trial enrolled 204 patients with progressive GEP-NETs that were advanced, well-differentiated or moderately differentiated, nonfunctioning, somatostatin receptor–positive, and grade 1 to 2.[25] Patients were randomly assigned to extended-release lanreotide depot/autogel at 120 mg or placebo administered once every 28 days for 96 weeks. Lanreotide depot/autogel was associated with a significant PFS benefit compared with placebo, with the median PFS not reached in the lanreotide depot/autogel arm vs 18.0 months with placebo (HR, 0.47; P<.001; Figure 4).

Outcomes were generally similar across patient subgroups, including those divided by extent of differentiation, disease stage (locally advanced vs metastatic), and degree of liver tumor burden.[25] The benefit of lanreotide depot/autogel was not statistically significant in small subgroups, including patients with pancreatic NETs. There was no significant difference in OS or quality of life between the arms. However, significantly more patients in the lanreotide depot/autogel arm had at least a 50% reduction in chromogranin A from baseline to the last postbaseline test available (42% vs 5%; P<.001).[25] The most common treatment-related AEs were diarrhea (reported in 26% of patients receiving lanreotide depot/autogel and 9% receiving placebo), abdominal pain (14% vs 2%), and cholelithiasis (10% vs 3%).

Octreotide

The other main drug used in the treatment of patients with GEP-NETs is octreotide. The safety and efficacy of octreotide were demonstrated in the double-blind,

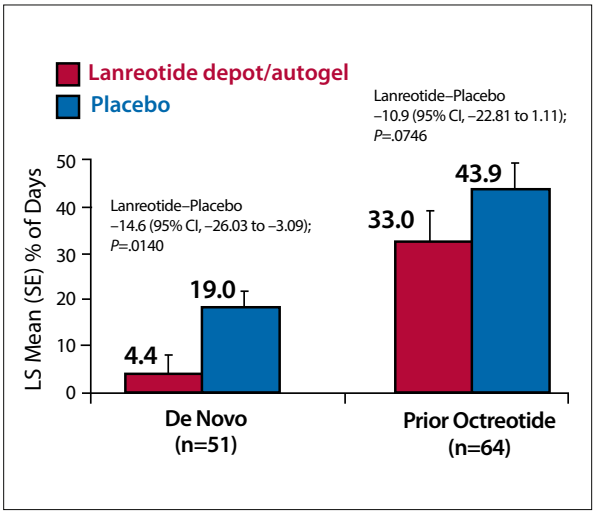

Figure 5. Moderate/severe diarrhea and/or flushing in the intent-to-treat population of the ELECT trial. ELECT, Evaluating Lanreotide Efficacy and Safety as a Carcinoid-Syndrome Treatment; LS, least square; SE, standard error. Adapted from Pommier RF et al. ASCO GI abstract 378. *J Clin Oncol*. 2017;35(suppl 4S).[28]

placebo-controlled, phase 3 PROMID trial (Placebo Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors), which enrolled 85 patients with well-differentiated metastatic midgut NETs.[26] Octreotide was associated with a significant improvement in the time to tumor progression compared with placebo. Confirmed survival outcomes were not reported owing to a low number of deaths during the trial.

Incorporating Current GEP-NET Therapies Into Practice

Recent trials have evaluated strategies for incorporating current therapies into practice. The multinational, double-blind, phase 3 ELECT trial (A Double-Blind, Randomized Placebo-Controlled Clinical Trial Investigating the Efficacy and Safety of Somatuline Depot [Lanreotide] Injection in the Treatment of Carcinoid Syndrome) evaluated the efficacy and safety of lanreotide depot/autogel in 115 patients with GEP-NETs or NETs of unknown origin, who had liver metastases and carcinoid syndrome (Figure 5).[27,28] Nearly half of patients (44%) were somatostatin analogue–naive, and the remaining 56% had previously responded to conventional doses of octreotide (short-acting or LAR). The primary objective of the trial—the proportion of days patients required rescue octreotide during the double-blind phase—was lower with lanreotide depot/autogel vs placebo (34% vs 49%; *P*=.02). However, the predefined absolute treatment difference was not met. In a subsequent subset analysis of patients previously responsive to octreotide, lanreotide depot/autogel was associated with significant improvement in symptoms of carcinoid syndrome.[29] In September 2017, the FDA expanded the indication of lanreotide depot/autogel to include treatment of carcinoid syndrome.[30]

The international, observational SYMNET study (A Study to Assess Neuroendocrine Tumour [NET] Patients Currently Treated by Somatuline Autogel for History of Carcinoid Syndrome Associated With Episodes of Diarrhea) evaluated patient-reported outcomes to assess the effect of lanreotide depot/autogel on carcinoid syndrome.[31] Among 273 patients treated with lanreotide depot/autogel for more than 3 months, 76% reported feeling "completely" or "rather" satisfied with diarrhea control, and 75% were unconcerned about the impact of diarrhea on their daily lives. Among patients with significant flushing, 73% were satisfied with flushing control.

In addition to somatostatin analogues, several biologic agents are used in the treatment of patients with GEP-NETs. The randomized, placebo-controlled phase 3 RADIANT-4 trial (RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial) evaluated the mTOR inhibitor everolimus among 302 patients with advanced nonfunctional NETs originating in the lung or the gastrointestinal tract. The median PFS was 11.0 months with everolimus vs 3.9 months with placebo (HR, 0.48; *P*<.00001; Figure 6).[32] Everolimus is FDA-approved for the treatment of patients with progressive, well-differentiated, nonfunctional NETs of gastrointestinal or lung origin that are unresectable, locally advanced, or metastatic.

Currently, the general treatment approach of NETs involves the sequential use of somatostatin analogues (eg, octreotide, lanreotide depot/autogel), biologic agents (eg, everolimus, sunitinib), and cytotoxic chemotherapy (eg, 5-FU, capecitabine, dacarbazine, oxaliplatin, streptozocin, temozolomide).[33] Recent trials have investigated whether combination approaches could be more effective. Some combinations have yielded improved outcomes, whereas others have not. In the COOPERATE-2 trial (Efficacy of Everolimus Alone or in Combination With Pasireotide LAR in Advanced PNET), the addition of the second-generation somatostatin analogue pasireotide to everolimus did not provide a PFS benefit in patients with advanced pancreatic NETs.[34] In a single-arm study, the combination of temsirolimus and the VEGF inhibitor bevacizumab had substantial activity, with a confirmed ORR of 41% and a 6-month PFS rate of 79%.[35] In the randomized, phase 2 80701 study from

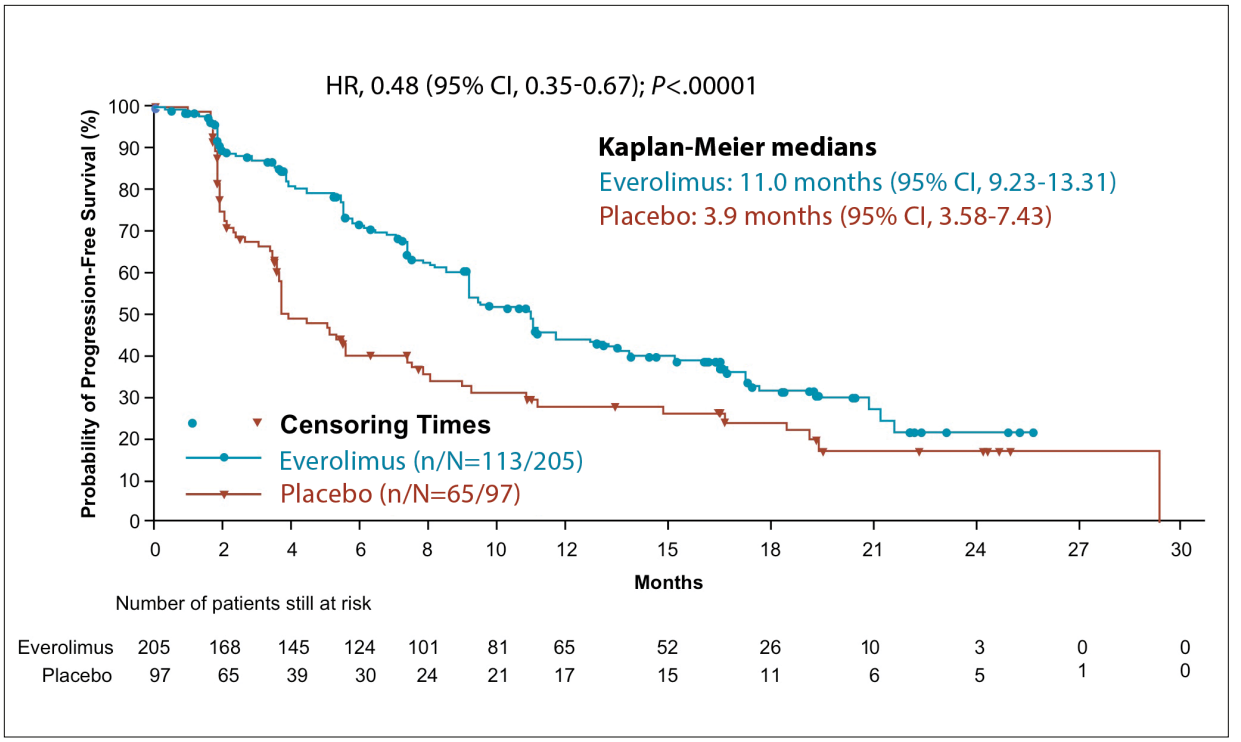

Figure 6. Progression-free survival according to central review in the RADIANT-4 trial. HR, hazard ratio; RADIANT-4, Everolimus Plus Best Supportive Care vs Placebo Plus Best Supportive Care in the Treatment of Patients With Advanced Neuroendocrine Tumors (GI or Lung Origin). Adapted from Yao J et al. *Lancet.* 2016;387(10022):968-977.[32]

the Cancer and Leukemia Group B, the combination of 3 agents—everolimus, bevacizumab, and octreotide—was associated with a significant improvement in ORR vs everolimus and octreotide alone (31% vs 12%; *P*=.005).[36] An improvement in median PFS did not reach statistical significance (16.7 vs 14.0 months; *P*=.12).

Combination approaches are likely to increase toxicity, which could negatively impact quality of life. However, if a combination strategy offers a significant survival benefit, it may be considered. Other approaches under evaluation for potential use in NETs include receptor tyrosine kinase inhibitors, cell cycle inhibitors, other targeted agents, and immunotherapy.[37]

Disclosure

Dr Khorana is a consultant for Janssen, Bayer, Pfizer, Sanofi, Halozyme, and AngioDynamics.

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Advancing the Treatment Frontiers for Metastatic Pancreatic Adenocarcinoma and panNETs

Tanios Bekaii-Saab, MD

The current era in the treatment of advanced pancreatic adenocarcinoma began with the approval of single-agent gemcitabine in 1996.[1] In 2005, erlotinib was approved in combination with gemcitabine.[2] Results of a positive phase 3 trial evaluating the regimen of FOLFIRINOX were published in 2011.[3] In 2013, nab-paclitaxel was approved in combination with gemcitabine.[4] Nanoliposomal irinotecan was approved for use in combination with 5-FU/LV in 2015.[5] Despite these advances, progress in the treatment of advanced pancreatic cancer has been slow.

Selecting a First-Line Treatment

Currently, the main options for the initial treatment of patients with advanced pancreatic cancer are FOLFIRINOX and gemcitabine plus albumin-bound paclitaxel.[6] Both regimens demonstrated significant improvements over single-agent gemcitabine in phase 3 trials. OS was 11.1 months in the FOLFIRINOX trial[3] and 8.5 months in the gemcitabine/nab-paclitaxel trial.[7] However, differences between the designs of the trials prevent a direct comparison of these outcomes. The FOLFIRINOX trial was smaller and enrolled a more narrow population of patients.[3] The trial evaluating gemcitabine plus nab-paclitaxel was larger and international.[7] It enrolled patients with less access to active salvage regimens and patients with a slightly worse performance status.

Retrospective real-world data from an electronic medical records database showed a similar effectiveness with FOLFIRINOX and nab-paclitaxel plus gemcitabine, with a median time to treatment discontinuation of 3.8 months and 3.4 months, respectively, and a median database persistence (a surrogate for survival) of 8.6 months with both therapies.[8] There was a nonsignificant trend toward a longer time to treatment discontinuation with gemcitabine plus nab-paclitaxel followed by 5-FU–based therapy vs the converse sequence (8.7 months vs 8.4 months; *P*=.52; Figure 7).

Another retrospective study demonstrated the feasibility of a modified regimen of biweekly gemcitabine and nab-paclitaxel in patients with metastatic pancreatic cancer.[9] Compared with a standard regimen, the modified regimen appeared to have similar efficacy and toxicity, but with lower costs. A prospective trial is needed to further evaluate the regimen.

In the absence of head-to-head studies, there is no clear choice in selecting FOLFIRINOX or gemcitabine/nab-paclitaxel for the first-line treatment of patients with metastatic pancreatic cancer. Clinicians tend to give FOLFIRINOX to the "best" patients and gemcitabine/nab-paclitaxel to "not quite as good" patients, although there is no evidence for this approach. Regardless of the treatment used, many patients ultimately require dose modifications, which do not appear to adversely impact outcome (and may even improve it).

Selecting Second-Line Therapy in Metastatic Pancreatic Cancer

There was little progress in the second-line treatment of advanced pancreatic cancer until the NAPOLI-1 trial, which established the efficacy and safety of adding nanoliposomal irinotecan to 5-FU/LV.[10] In NAPOLI-1, nanoliposomal irinotecan plus 5-FU/LV significantly improved OS and PFS compared with 5-FU/LV alone. The median OS was 6.1 months with nanoliposomal irinotecan plus 5-FU/LV vs 4.2 months for 5-FU/LV alone (HR, 0.57; *P*=.0009). The median PFS was 3.1 months vs 1.5 months, respectively (HR, 0.56; *P*=.0001).[10] The addition of nanoliposomal irinotecan was associated with an ORR of 16%, which is notable in a population that is unlikely to experience an objective response. Toxicities associated with the addition of nanoliposomal irinotecan are somewhat predictable and reflect those seen with standard irinotecan, although the nanoliposomal irinotecan formulation is associated with lower rates of alopecia.

Several other regimens have been evaluated in phase 3 trials. In the CONKO-003 trial, oxaliplatin plus 5-FU/LV improved median OS compared with 5-FU/LV alone (5.9 vs 3.3 months; HR, 0.66; *P*=.010).[11] In the PANCREOX trial, however, the addition of oxaliplatin to 5-FU/LV did not improve OS when compared with 5-FU/LV alone (6.1 vs 9.9 months; HR, 1.78; *P*=.024).[12] The inconsistency of the reported benefit with oxaliplatin-based therapies raises questions about the role of these regimens in the second-line treatment of advanced pancreatic cancer. A recent meta-analysis of various second-line treatment approaches found that both oxaliplatin-based and irinotecan-based regimens were associated with an improvement in PFS compared with fluoropyrimidine

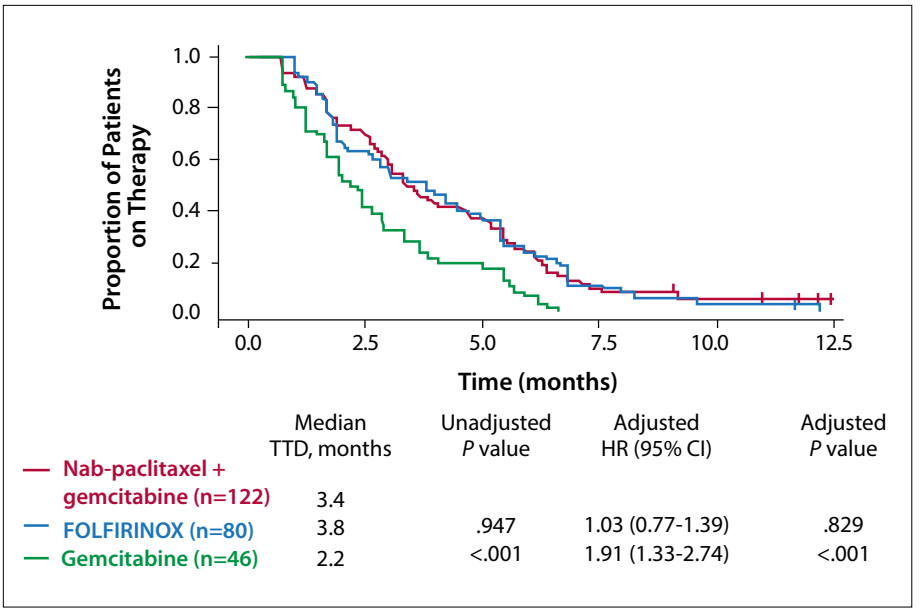

Figure 7. The proportions of patients who remained on treatment for metastatic pancreatic cancer in a real-world analysis. HR, hazard ratio; TTD, time to treatment discontinuation; FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin. Adapted from Braiteh F et al. *Cancer Manag Res.* 2017;9:141-148.[8]

alone (Figure 8).[13] However, only irinotecan-based combinations conferred a benefit in OS.

Based on the evidence, one preferred approach is to use gemcitabine plus nab-paclitaxel in the first-line setting, followed in the second-line setting by nanoliposomal irinotecan plus 5-FU for patients with a good performance status (Figure 9). Single-agent therapy or best supportive care can be used for patients with a poor performance status. In the third-line setting, patients with a good performance status could be considered for a platinum-based regimen, if they had not been treated with one previously.

An alternative approach is to start with FOLFIRINOX in the first-line setting, potentially switching to gemcitabine/nab-paclitaxel in the second-line setting. This sequence is supported primarily by retrospective or small, prospective studies. For patients with a poor performance status after first-line therapy, single-agent gemcitabine or best supportive care would be considered in the second-line setting. Limitations to this approach include the significant toxicities associated with FOLFIRINOX, which may preclude active second-line therapies, and a lack of reliable data in the second-line setting after FOLFIRINOX. One exception is patients with a *BRCA* mutation. These patients are especially sensitive to platinum agents and/or topoisomerase inhibitors. They may therefore benefit from a regimen such as FOLFIRINOX or gemcitabine/cisplatin earlier in the disease course.[14]

Emerging Therapies for Pancreatic Cancer

Several investigational agents are currently in phase 3 trials in pancreatic cancer. PEGPH20 targets hyaluronan, which has been shown to accumulate in the tumor microenvironment, increasing pressure and vascular compression and reducing drug delivery. PEGPH20 is a novel compound that degrades hyaluronan. In a phase 2 study, the addition of PEGPH20 to gemcitabine/nab-paclitaxel was associated with a significant improvement in median PFS (6.0 vs 5.3 months; HR, 0.77; *P*=.045).[15] In an exploratory subset analysis, the improvement in median PFS with PEGPH20 plus gemcitabine/nab-paclitaxel vs gemcitabine/nab-paclitaxel was enhanced in patients with high hyaluronan levels (11.5 vs 8.5 months; HR, 0.51; *P*=.048). The ongoing HALO-301 trial is evaluating the addition of PEGPH20 to gemcitabine/nab-paclitaxel in approximately 420 patients with previously untreated pancreatic ductal adenocarcinoma. Analysis of the primary outcome is expected in October 2018.[16]

Another line of research involves the novel cancer stemness inhibitor napabucasin, which appears to inhibit hypermalignant cancer cells. In a phase 1b/2 study of patients with metastatic pancreatic ductal adenocarcinoma, gemcitabine/nab-paclitaxel plus napabucasin was associated with an ORR of 55%, a median PFS exceeding 7 months, and a median OS exceeding 10.5 months.[17] The randomized, open-label, multicenter, phase 3 CanStem111P study is evaluating the efficacy and safety of adding napabucasin to gemcitabine/nab-paclitaxel in patients with metastatic pancreatic ductal adenocarcinoma.[18]

There are specific subsets of patients who may attain benefit from certain therapies. For the small percentage of patients with microsatellite instability–high or mismatch repair–deficient cancers, pembrolizumab can have significant activity with dramatic responses.[19] For this reason, at

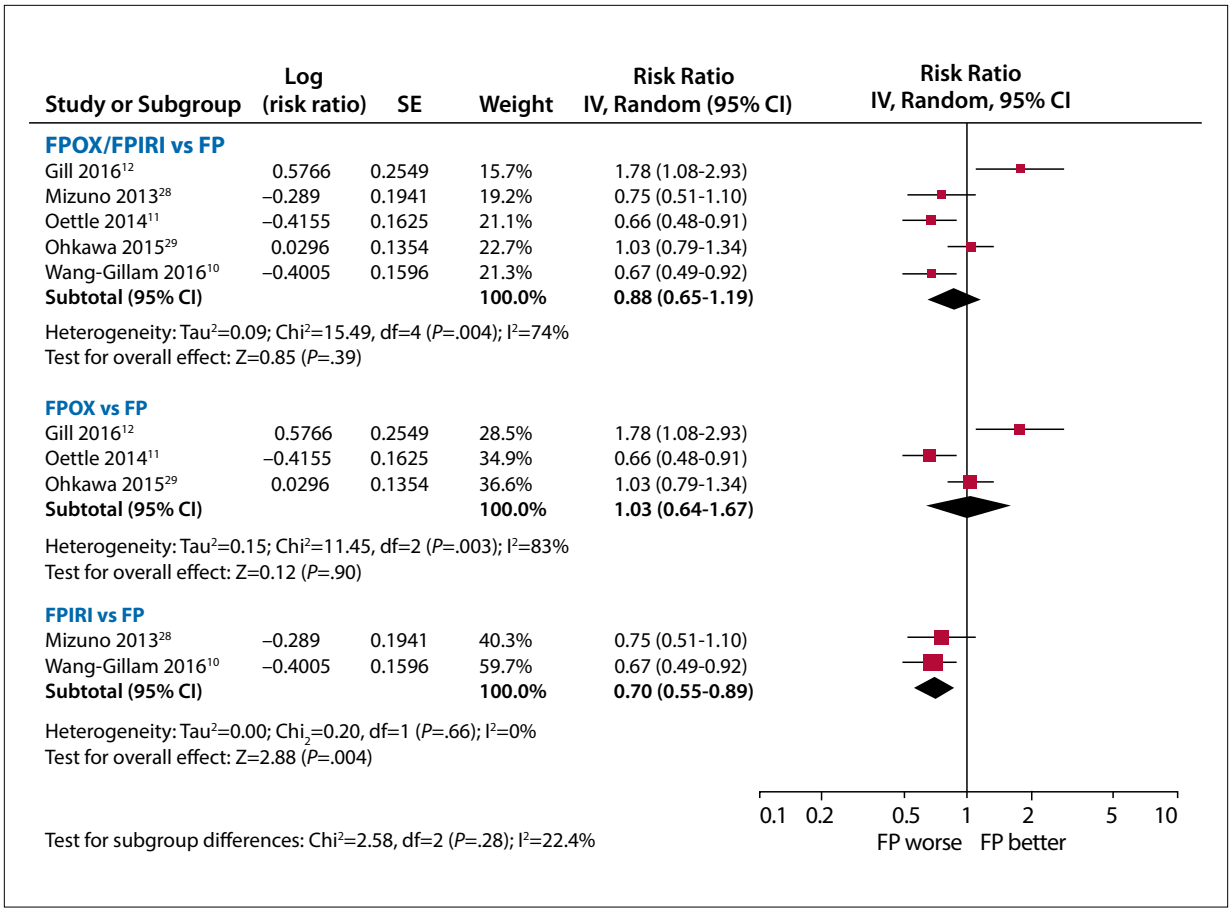

Figure 8. A meta-analysis of second-line treatment approaches found that both oxaliplatin-based and irinotecan-based regimens were associated with an improvement in progression-free survival compared with fluoropyrimidine alone. df, degrees of freedom; FP, fluoropyrimidine; FPIRI, fluoropyrimidine with irinotecan; FPOX, fluoropyrimidine with oxaliplatin; IV, inverse variance; SE, standard error. Adapted from Sonbol MB et al. Second-line treatment in patients with pancreatic ductal adenocarcinoma: a meta-analysis [published online August 17, 2017]. *Cancer*. doi:10.1002/cncr.30927.[13]

the Mayo Clinic, all patients who present with adenocarcinoma undergo testing of microsatellite instability.

Patients with *BRCA1/2* mutations have been shown to benefit from PARP inhibitors. Among patients with *BRCA1/2*-mutated pancreatic cancers, olaparib demonstrated an ORR of 22% (5 of 23 patients).[20] Veliparib was associated with no objective responses among 16 patients.[21] Rucaparib was associated with an ORR of 16% (3 of 19 patients).[22] Larger clinical trials are evaluating various PARP inhibitors for the treatment of patients with pancreatic ductal adenocarcinoma.

Treatment Approaches for Pancreatic NETs

A key treatment decision for patients diagnosed with pancreatic NETs is the resectability of the tumor.[23] A multidisciplinary evaluation is important for determining the optimal treatment approach. Surgical resection can be considered for some patients with metastatic disease, such as those with limited liver involvement. Alternatively, locoregional therapy may be appropriate, with the goal of making the primary tumor resectable.

If patients have a tumor that is clearly unresectable but has not metastasized, then locoregional therapies may be considered. For patients with metastatic or extensive disease that is not amenable to locoregional therapy, a variety of systemic approaches are used. Observation is also an option if patients are asymptomatic and doing fairly well.

mTOR inhibition has demonstrated a significant PFS benefit in phase 3 trials in patients with advanced pancreatic NETs.[24] The addition of the VEGF inhibitor bevacizumab to an mTOR inhibitor has demonstrated a minimal benefit in small trials.[25] Small-molecule tyrosine kinase inhibitors (eg, sunitinib, sorafenib, pazopanib) have demonstrated activity in patients with pancreatic

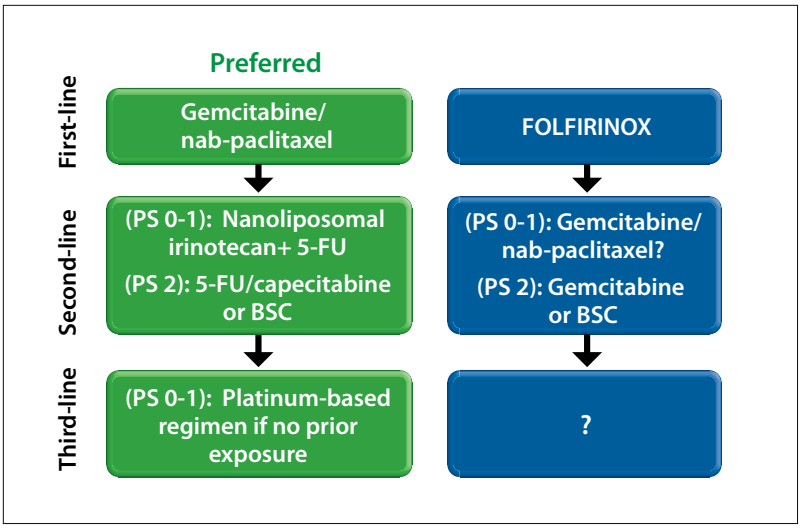

Figure 9. An approach to treatment sequencing for patients with metastatic pancreatic adenocarcinoma. BSC, best supportive care; FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin; 5-FU, fluorouracil; PS, performance status.

NETs.[25] A randomized, phase 3 trial of sunitinib was halted early after reaching an interim efficacy endpoint.[26]

The alkylating agent temozolomide may have a role in the treatment of selected patients with pancreatic NETs. Temozolomide targets *MGMT*, one of the most commonly hypermethylated genes in pancreatic NETs.[25] Clinical studies have suggested activity with temozolomide-based therapy in patients with pancreatic NETs. In a study that involved 30 patients with previously untreated metastatic pancreatic NETs, temozolomide plus capecitabine was associated with an ORR of 70% and a median PFS of 18 months.[27] Capecitabine and temozolomide might be considered for a patient with unresectable, highly symptomatic disease who is ineligible for localized therapy, or for a patient in whom a tumor could become resectable after systemic treatment.

Disclosure

Dr Bekaii-Saab has no real or apparent conflicts of interest to report.

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Case Study: Management of Metastatic Pancreatic Adenocarcinoma

Tanios Bekaii-Saab, MD

A 53-year-old white man presented to his primary care physician with epigastric pain radiating to the lower back that worsened with food intake. He had lost 15 pounds over 2 months and had poor appetite and fatigue. He was, however, still able to work full-time. Medical history included well-controlled hypertension. His mother, who had smoked, had died from lung cancer.

A CT scan of the abdomen, pelvis, and chest showed a 3-cm pancreas head mass with multiple liver lesions. His complete blood count was within normal limits. Alkaline phosphatase was elevated. Aspartate aminotransferase and alanine aminotransferase levels were normal. Total bilirubin was 0.6 mg/dL. CA 19-9 was 2356 U/mL. A CT-guided biopsy of the liver suggested pancreatic adenocarcinoma.

Options for initial therapy included a clinical trial, FOLFIRINOX, and gemcitabine plus nab-paclitaxel. The patient started treatment with weekly gemcitabine and nab-paclitaxel. On day 8, he skipped treatment owing to an absolute neutrophil count of 0.6. On day 15, his neutrophil count was 1.1, and he resumed treatment. His medical oncologist decided to continue the biweekly regimen. At week 8, a CT scan showed evidence of a reduction in the size of the liver lesions. The CA 19-9 level dropped to 150 U/mL. The patient's pain had resolved, and he had gained back 8 pounds.

Eight months after starting therapy, his pain worsened and he began to lose weight. A repeat CT scan showed evidence of progressive disease in the liver, with new evidence of peritoneal carcinomatosis. His CA 19-9 was 1900 U/mL, and his performance status was 1.

The patient began treatment with nanoliposomal irinotecan plus 5-FU/LV. He tolerated treatment well. He developed diarrhea (mostly grade 1) that was controlled with loperamide. After 2 months, a CT scan showed evidence of stable disease in the peritoneum, with shrinkage in the liver lesions. His CA 19-9 level dropped to 450 U/mL.

After 6 months of therapy, he started experiencing significant pain, appetite loss, and weight loss. His CA 19-9 was 10,000 U/mL. The bilirubin level was 3 times the upper limit of normal, and results from liver function tests were elevated. His performance status was 2. The patient was referred to hospice care.

Disclosure

Dr Bekaii-Saab has no real or apparent conflicts of interest to report.

New Frontiers and Therapeutic Advances for Metastatic Adenocarcinoma and Pancreatic Neuroendocrine Tumors: Q&A

George P. Kim, MD, Alok A. Khorana, MD, and Tanios Bekaii-Saab, MD

Dr Kim How do you manage diabetes in patients with pancreatic cancer?

Dr Khorana Diabetes is a major comorbidity in this population, and we run the gamut of glucose control issues. We look to our palliative care partners to help address symptoms and medical issues, including diabetes. Having a second team to manage these issues allows us to focus more on treatment. In general, however, for diabetes management, we try to use oral glucose-lowering agents. We occasionally use insulin, if needed.

Dr Bekaii-Saab I allow the sugar level to reach a level, such as 200 mg/dL, that would be unacceptable in a different population. I do not try to aggressively manage it.

Dr Kim It is complex. Patients with diabetes are more prone to develop pancreatic cancer owing to the inflammatory state. Up to 30% of patients with pancreatic cancer have diabetes. However, the converse is also true: pancreatic cancer can result in the development of diabetes. Therefore, new-onset diabetes can be an indication of pancreatic cancer.

Dr Kim Are patients with comorbidities eligible for combination chemotherapy regimens?

Dr Khorana Most older patients with cancer have some degree of comorbidities. The key issue is performance status, which reflects how patients function in their daily lives. If patients have a decent performance status, we would recommend chemotherapy. If they are staying in bed all day, we would not want to put them through radiation or chemotherapy. Patients must have adequately functioning major organs in order to receive chemotherapy.

Dr Kim It is important to optimize performance status—addressing pain, nutritional treatments, diarrhea, and nausea—before making treatment decisions.

Dr Bekaii-Saab If patients are eligible for chemotherapy, then once they start therapy, they tend to start feeling better and can resume activities. They often eat well and can resume exercise. So it is important to treat the cancer first.

Dr Kim What are some of the other complications of pancreatic cancer, and how are they managed?

Dr Khorana Blood clots are common, affecting approximately 20% to 30% of patients. Randomized data have shown that planned prophylaxis with low-molecular-weight heparin can reduce the risk of blood clots in patients with pancreatic cancer.[1] The issue is that daily self-injections can be difficult for patients who are already sick. New oral anticoagulants have recently become available; ongoing trials are evaluating outpatient prophylaxis with these agents. Hopefully, data will become available by next year.

Obstructive jaundice is also an issue; it can occur at the time of presentation or later in the disease course. Our partners in gastroenterology help address it. Stenting can help. However, cholangitis can arise either at the time of stent placement or later.

Dr Kim How do you manage weight loss in patients with metastatic pancreatic cancer?

Dr Khorana At the Cleveland Clinic, patients start receiving care from palliative care medicine physicians at the time of diagnosis, through a program called the Early Palliative Care Partnership. This way, patients do not wait until they are transitioning to hospice to receive palliative care. Weight loss is one of the symptoms that palliative medicine helps to address. Effective treatment of the cancer will help address weight loss. However, in the short-term, patients can take steps to ensure adequate caloric intake, such as taking frequent meals throughout the day and using appetite stimulants if needed. Medical marijuana is not approved at the federal level, so prescribing it is not an option.

Dr Bekaii-Saab Ultimately, treating the cancer is what will address the symptoms; other measures are temporary. I find low-dose prednisone to be one of the most useful and low-cost ways to energize patients and improve their appetite, although there are issues with long-term use. I usually start with 5 mg and may increase to 10 mg. I may continue the prednisone until the patient has a response, which usually occurs within a few months. Some patients feel so good on prednisone that they refuse to stop it. I would add that it is critical to have a nutritionist see the patient.

Dr Kim How does muscle loss/wasting contribute to weight loss?

Dr Bekaii-Saab Muscle loss related to cachexia is the main driver of weight loss in patients with pancreatic cancer. The inflammatory nature of the cancer can essentially destroy muscle tissue. Significant weight loss typically translates into significant weakness and poor performance status. Malnutrition can add to the problem but is not a primary driver. Exercise can help rebuild muscle, but this intervention depends on the patient's capacity.

Dr Kim There are some nutritional supplement data. We recommend whey protein based on data from Mayo Clinic Rochester.

Dr Kim What is the role of pancreatic enzyme replacement in patients with pancreatic cancer?

Dr Bekaii-Saab I think all patients should receive pancreatic enzyme replacement. It improves digestive symptoms, facilitates absorption, reduces the risk of diarrhea, and can help with pain. Patients can develop small bouts of micropancreatitis because the pancreas is working so hard and barriers can be broken. The enzymes can end up digesting small parts of the pancreas, causing pain with eating. I recommend that patients take the enzymes 30 minutes before the meal. One challenge is that every patient needs a different dosage.

Dr Kim I tell patients to put the enzymes on a napkin, eat some food, and then take the enzymes with food to aid digestion.

Dr Kim What is the role of parenteral nutrition in patients with pancreatic cancer?

Dr Khorana If a patient is very sick and malnourished because the cancer is not responding to treatment and is progressing rapidly, I do not think that parenteral nutrition will change the long-term outlook. A discussion with hospice would be more appropriate.

Dr Bekaii-Saab Total parenteral nutrition has no role in this disease. Studies have shown that administering total parenteral nutrition to patients on chemotherapy often results in potentially fatal fungal infections. At the end of the day, if the treatment is working, the patient will feel better, eat, be active, and gain weight.

Dr Khorana There are other measures that might be appropriate. If a patient has pancreatic cancer that is invading the duodenum, local measures, such as a stent placement, could be considered.

Dr Kim What is your take-home message?

Dr Khorana Although there is a lot of nihilism around pancreatic cancer, we have made a lot of progress in the past few years, with the advent of combination regimens, targeted therapies, and immunotherapy. I see patients living longer. Hopefully, outcomes will continue to improve. Symptom management is key. Partnering with multiple other teams, such as palliative medicine and gastroenterology, is critical to deliver the best possible outcomes.

Dr Saab There is a lot of nihilism. Pancreatic cancer is often considered a disease where many agents fail. However, outcomes are improving, and patients are living longer. With more enrollment into clinical trials and introduction of new therapies, we will continue to improve outcomes in pancreatic cancer.

Disclosures

Dr Kim is a consultant for and on the speakers bureaus of Celgene and Ipsen. Dr Khorana is a consultant for Janssen, Bayer, Pfizer, Sanofi, Halozyme, and AngioDynamics. Dr Bekaii-Saab has no real or apparent conflicts of interest to report.

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New Frontiers and Therapeutic Advances for Metastatic Adenocarcinoma and Pancreatic Neuroendocrine Tumors

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

1. Pancreatic cancer is the ____ deadliest cancer in the United States.

   a. Second
   b. Third
   c. Fourth
   d. Fifth

2. In a survey of patients with a neuroendocrine tumor in the United States, what percentage required more than 5 years to obtain an accurate diagnosis?

   a. 26%
   b. 34%
   c. 44%
   d. 51%

3. Which treatment is an option for the first-line treatment of patients with pancreatic adenocarcinoma who have a good performance status?

   a. Capecitabine
   b. Continuous-infusion 5-fluorouracil
   c. Gemcitabine
   d. 5-Fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX)

4. Which mutation occurs in more than 90% of patients with pancreatic cancers?

   a. *AKT2*
   b. *BRAF*
   c. *KRAS*
   d. *MYB*

5. In the NAPOLI-1 trial of patients with metastatic pancreatic cancer, nanoliposomal irinotecan plus 5-FU/LV was associated with a median overall survival of:

   a. 3.9 months
   b. 4.2 months
   c. 5.8 months
   d. 6.1 months

6. In the CLARINET trial of patients with gastroenteropancreatic neuroendocrine tumors, PFS in the lanreotide depot/autogel arm was:

   a. 15.6 months
   b. 17.2 months
   c. 18.3 months
   d. Not reached

7. In the CALGB 80701 study of patients with neuroendocrine tumors, the combination of everolimus, bevacizumab, and octreotide was associated with an overall response rate of:

   a. 25%
   b. 31%
   c. 43%
   d. 55%

8. Which investigational agent targets hyaluronan?

   a. Napabucasin
   b. PEGPH20
   c. Rucaparib
   d. Veliparib

9. For patients with microsatellite instability–high or mismatch repair–deficient cancers, which therapy can have significant activity with dramatic responses?

   a. Bevacizumab
   b. Gemcitabine
   c. Pembrolizumab
   d. Sunitinib

10. In a study of patients with previously untreated metastatic pancreatic neuroendocrine tumors, temozolomide plus capecitabine was associated with an overall response rate of:

    a. 40%
    b. 50%
    c. 60%
    d. 70%

Evaluation Form: New Frontiers and Therapeutic Advances for Metastatic Adenocarcinoma and Pancreatic Neuroendocrine Tumors

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 13011**. 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:

Detail the epidemiology, burden, and clinical challenges associated with detecting, diagnosing, and classifying metastatic pancreatic adenocarcinoma and pancreatic neuroendocrine tumors

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

Outline recommendations from the most recent clinical practice guidelines for metastatic pancreatic adenocarcinoma and pancreatic neuroendocrine tumors

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

Describe data from the latest clinical trials of therapies in pancreatic adenocarcinoma and pancreatic neuroendocrine tumors

❒ 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

Devise treatment plans based on disease characteristics and patient factors

❒ 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

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:

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

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: **13011**