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ASCO SPECIAL ARTICLE

Metastatic Pancreatic Cancer: ASCO Clinical Practice Guideline Update

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Editor's note: This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/gastrointestinal-cancer-guidelines.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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A B S T R A C T

Purpose

In 2016, ASCO published a guideline to assist in clinical decision making in metastatic pancreatic cancer for initial assessment after diagnosis, first- and second-line treatment options, palliative and supportive care, and follow-up. The purpose of this update is to incorporate new evidence related to second-line therapy for patients who have experienced disease progression or intolerable toxicity during first-line therapy.

Methods

ASCO convened an Expert Panel to conduct a systematic review of the literature on second-line therapy published between June 2015 and January 2018. Recommendations on other topics covered in the 2016 Metastatic Pancreatic Cancer Guideline were endorsed by the Expert Panel.

Results

Two new studies were found that met the inclusion criteria.

Recommendations

For second-line therapy, gemcitabine plus nanoparticle albumin-bound paclitaxel should be offered to patients with first-line treatment with FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin), an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1, and a favorable comorbidity profile; fluorouracil plus nanoliposomal irinotecan can be offered to patients with first-line treatment with gemcitabine plus NAB-paclitaxel, an ECOG PS of 0 to 1, and a favorable comorbidity profile; fluorouracil plus irinotecan or fluorouracil plus oxaliplatin may be offered when there is a lack of availability of fluorouracil plus nanoliposomal irinotecan; gemcitabine or fluorouracil should be offered to patients with either an ECOG PS of 2 or a comorbidity profile that precludes other regimens. Testing select patients for mismatch repair deficiency or microsatellite instability is recommended, and pembrolizumab is recommended for patients with mismatch repair deficiency or high microsatellite instability tumors. Endorsed recommendations from the 2016 version of this guideline for computed tomography, baseline performance status and comorbidity profile, defining goals of care, first-line therapy, and palliative care are also contained within the full guideline text. Additional information is available at www.asco.org/gastrointestinal-cancer-guidelines.

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INTRODUCTION

There were an estimated 55,440 new cases and 44,330 deaths as a result of pancreatic cancer in the United States in 2017, and an estimated 338,000 deaths worldwide in 2012.[1] A diagnosis of pancreatic ductal carcinoma is associated with poor prognosis due to early micrometastatic spread, and the 5-year survival rate for metastatic pancreatic cancer is approximately 2%.[2]

In 2016, ASCO published a guideline to assist in clinical decision making in metastatic pancreatic cancer. The guideline provided recommendations for initial assessment after diagnosis, first- and second-line treatment options, palliative and supportive care, and follow-up after treatment.[3]

ASCO guidelines are periodically assessed for currency using the signals approach,[4] which is designed to identify new, potentially practice-changing data that might translate into revised practice recommendations. This approach relies on targeted routine literature monitoring and regular review and assessment of the recommendations by ASCO Expert Panel members. Using this approach, new evidence was identified

ASSOCIATED CONTENT

Appendix
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Data Supplement
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THE BOTTOM LINE

Metastatic Pancreatic Cancer: ASCO Clinical Practice Guideline Update

Guideline Question

The purpose of this focused update is to incorporate new evidence that is relevant to Clinical Question 3 from the previous version of this guideline[3]: What is the appropriate therapy for patients with metastatic pancreatic cancer who experience either disease progression or intolerable toxicity with prior regimens?

Target Population

Patients with metastatic pancreatic cancer

Target Audience

Medical oncologists, radiation oncologists, surgeons, gastroenterologists

Methods

An Expert Panel was convened to develop updated clinical practice guideline recommendations based on a focused systematic review of the medical literature related to second-line therapy. This review resulted in additions or clarifications to recommendations 3.1, 3.2, 3.4, and 3.5. All other recommendations from the previous (2016) version of this guideline are endorsed for this 2018 update.

New recommendations or changes to the 2016 recommendations are denoted by ***bold, italicized text***. A comparison of the original 2016 recommendations and the updated 2018 recommendations can be found in the Data Supplement. See the full guideline text for definitions of favorable and relatively favorable comorbidity profiles.

RECOMMENDATIONS

1. Initial Assessment

Recommendation 1.1. A multiphase computed tomography scan of the chest, abdomen, and pelvis should be performed to assess extent of disease. Other staging studies should be performed only as dictated by symptoms (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.2. The baseline PS, symptom burden, and comorbidity profile of a patient with metastatic pancreatic cancer should be evaluated carefully (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.3. The goals of care (to include a discussion of an advance directive), patient preferences, as well as support systems should be discussed with every patient with metastatic pancreatic cancer and his or her caregivers (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.4. Multidisciplinary collaboration to formulate treatment and care plans and disease management for patients with metastatic pancreatic cancer should be the standard of care (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.5. Every patient with pancreatic cancer should be offered information about clinical trials, which include therapeutic trials in all lines of treatment as well as palliative care, biorepository/biomarker, and observational studies (Type: informal consensus, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

2. First-Line Treatment

Recommendation 2.1. FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin) is recommended for patients who meet all of the following criteria: an ECOG PS of 0 to 1, favorable comorbidity profile, patient preference and a support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

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THE BOTTOM LINE (CONTINUED)

Recommendation 2.2. Gemcitabine plus NAB-paclitaxel is recommended for patients who meet all of the following criteria: an ECOG PS of 0 to 1, a relatively favorable comorbidity profile, and patient preference and a support system for relatively aggressive medical therapy (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 2.3. Gemcitabine alone is recommended for patients who have either an ECOG PS of 2 or a comorbidity profile that precludes more aggressive regimens and who wish to pursue cancer-directed therapy. The addition of either capecitabine or erlotinib to gemcitabine may be offered in this setting (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 2.4. Patients with an ECOG PS $\geq$ 3 or with poorly controlled comorbid conditions despite ongoing active medical care should be offered cancer-directed therapy only on a case-by-case basis. The major emphasis should be on optimizing supportive care measures (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

3. Second-Line Treatment

Recommendation 3.1. ***Routine testing for dMMR or MSI-H is recommended, using IHC, PCR, or NGS for patients who are considered to be candidates for checkpoint inhibitor therapy*** (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 3.2. ***PD-1 immune checkpoint inhibitor pembrolizumab is recommended as second-line therapy for patients who have tested positive for dMMR or MSI-H*** (Type: evidence-based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.3. Gemcitabine plus NAB-paclitaxel can be offered as second-line therapy to patients who meet all of the following criteria: first-line treatment with FOLFIRINOX, an ECOG PS of 0 to 1, a relatively favorable comorbidity profile, and patient preference and a support system for aggressive medical therapy (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 3.4. ***Fluorouracil plus nanoliposomal irinotecan, or fluorouracil plus irinotecan where the former combination is unavailable,*** is preferred as second-line therapy for patients who meet all of the following criteria: first-line treatment with gemcitabine plus NAB-paclitaxel, an ECOG PS of 0 to 1, a relatively favorable comorbidity profile, patient preference and a support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 3.5. ***Fluorouracil plus oxaliplatin may be considered*** as second-line therapy for patients who meet all of the following criteria: first-line treatment with gemcitabine plus NAB-paclitaxel, an ECOG PS of 0 to 1, a relatively favorable comorbidity profile, patient preference and a support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Qualifying statement for recommendations 3.4 and 3.5. A recent phase III trial comparing mFOLFOX6 with FU + LV demonstrated a higher rate of grade 3 or 4 adverse events and significantly reduced OS within the mFOLFOX6 arm of the trial.[7] However, previous phase III data have demonstrated a benefit with the OFF regimen compared with FU + LV.[10] Considering the inconsistency of these results, although fluorouracil plus nanoliposomal irinotecan is preferred, the Expert Panel continues to support the use of fluorouracil plus oxaliplatin as an option where the availability of fluorouracil plus nanoliposomal irinotecan is limited or where residual toxicity from first-line therapy or comorbidities preclude the use of fluorouracil plus nanoliposomal irinotecan.

Recommendation 3.6. Gemcitabine or fluorouracil can be considered as second-line therapy for patients who have either an ECOG PS of 2 or a comorbidity profile that precludes more aggressive regimens and who wish to pursue cancer-directed therapy (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

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THE BOTTOM LINE (CONTINUED)

Recommendation 3.7. No data are available to recommend third-line (or greater) therapy with a cytotoxic agent. Clinical trial participation is encouraged (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

4. Palliative Care

Recommendation 4.1. Patients with metastatic pancreatic cancer should have a full assessment of symptom burden, psychological status, and social supports as early as possible, preferably at the first visit. In most cases, this assessment will indicate a need for a formal palliative care consult and services (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

5. Treatment of Pain and Symptoms

Recommendation 5.1. Patients with metastatic pancreatic cancer should be offered aggressive treatment of the pain and symptoms of the cancer and/or the cancer-directed therapy (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

6. Follow-Up/Surveillance

Recommendation 6.1. For patients on active cancer-directed therapy outside a clinical trial, imaging to assess first response should be offered at 2 to 3 months from the initiation of therapy. Computed tomography scans with contrast are the preferred modality. Thereafter, clinical assessment, conducted frequently during visits for cancer-directed therapy, should supplant imaging assessment. The routine use of positron emission tomography scans for the management of patients with pancreatic cancer is not recommended. CA19-9 is not considered an optimal substitute for imaging for the assessment of treatment response (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).

Recommendation 6.2. No data exist on the duration of cancer-directed therapy. An ongoing discussion of goals of care and assessment of treatment response and tolerability should guide decisions to continue or to hold or terminate cancer-directed therapy (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).

Additional Resources

More information, including a Data Supplement, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/gastrointestinal-cancer-guidelines. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

in 2017 that could affect the Metastatic Pancreatic Cancer guidelines for second-line therapy for patients who had experienced disease progression or intolerable toxicity with first-line therapy.

The previous 2016 version of this guideline[3] included the following consensus-based, moderate-strength recommendations for second-line therapy, based on low-quality evidence:

- Gemcitabine plus nanoparticle albumin-bound paclitaxel (NAB-paclitaxel) can be offered as second-line therapy to patients who meet all of the following criteria: first-line treatment with FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin), an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1, a relatively favorable comorbidity profile, and patient preference and a support system for aggressive medical therapy.
- Fluorouracil plus oxaliplatin, irinotecan, or nanoliposomal irinotecan can be offered as second-line therapy to patients who meet all of the following criteria: first-line treatment with gemcitabine plus NAB-paclitaxel, an ECOG PS of 0 to 1, a relatively favorable comorbidity profile, patient preference and a support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services.
- Gemcitabine or fluorouracil can be considered as second-line therapy to patients who have either an ECOG PS of 2 or a comorbidity profile that precludes more aggressive regimens and who wish to pursue cancer-directed therapy.
- No data are available to recommend third-line (or greater) therapy with a cytotoxic agent. Clinical trial participation is encouraged.

Based on the identification of two new studies related to these recommendations during the routine signals-based assessment, the Expert Panel for this guideline (Table A1, online only) chose to undertake a focused update of this guideline, including a systematic review for evidence related to the recommendations listed above for second- (or greater-) line therapy. Using the signals-based approach, no new studies were identified that were relevant to the remaining clinical questions; therefore, the Expert Panel continues to endorse the 2016 recommendations on those topics. A summary of the current recommendations is contained in the Bottom Line.

GUIDELINE QUESTION

This clinical practice guideline update addresses the following clinical question: What is the appropriate therapy for patients with metastatic pancreatic cancer who experience either disease progression or intolerable toxicity with prior regimens for metastatic pancreatic cancer?

METHODS

Guideline Update Process

This systematic review-based guideline product was developed by a multidisciplinary Expert Panel, which included a patient representative and a member of the ASCO guidelines staff with health research methodology expertise. The Expert Panel met via teleconference and/or webinar and corresponded through e-mail. Based on the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then submitted to *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guideline Committee prior to publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed by using a systematic review of PubMed for studies published between June 2015 and January 2018. Articles were selected for inclusion in the systematic review of the evidence based on the following criteria:

- The population included patients with metastatic pancreatic cancer who experience either disease progression or intolerable toxicity with prior regimens
- Studies of the efficacy of systematic treatment options for this patient population were considered for inclusion. Included systemic therapy options were chemotherapy or programmed cell death-1 (PD-1) immune checkpoint blockade.
- Study design was limited to phase III randomized controlled trials (RCTs) for studies of chemotherapy. There was no limitation placed on study design for studies of PD-1 immune checkpoint blockade.

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, narrative reviews; or (3) published in a non-English language. The guideline recommendations were crafted, in part, using the Guidelines Into Decision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software.[5] In addition, a guideline implementability review was conducted. Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation (Methodology Supplement).

Detailed information about the methods used to develop this guideline update, including an overview (eg, panel composition, development process, and revision dates), literature search and data extraction, the recommendation development process (Guidelines Into Decision Support and BRIDGE-Wiz), and quality assessment, is available in the Methodology Supplement at www.asco.org/gastrointestinal-cancer-guidelines.

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. Based on a formal review of the emerging literature, ASCO will continue to determine the need to update these guideline recommendations.

This is the most recent information as of the publication date; to submit new evidence, visit www.asco.org/gastrointestinal-cancer-guidelines.

Definitions

A favorable comorbidity profile is loosely defined as hemoglobin $\geq$ 10 g/dL and platelet count $\geq$ 100,000/μL without transfusion support; absolute neutrophil count $\geq$ 1,500/μL; bilirubin and international normalized ratio $\leq$ 1.5 times the upper limit of normal; albumin $\geq$ 3 g/dL; creatinine clearance $\geq$ 60 mL/min/1.73 m^2; and absence of comorbid conditions that require ongoing active medical care, such as congestive heart failure, chronic obstructive pulmonary disease, uncontrolled diabetes mellitus, and neurologic disorders.

A relatively favorable comorbidity profile is loosely defined as hemoglobin $\geq$ 9 g/dL and platelet count $\geq$ 75,000/μL without transfusion support; absolute neutrophil count $\geq$ 1,500/μL; bilirubin and international normalized ratio $\leq$ 1.5 times the upper limit of normal; albumin $\geq$ 3 g/dL; creatinine clearance $\geq$ 60 mL/min/1.73 m^2; and absence of poorly controlled comorbid conditions, such as congestive heart failure, chronic obstructive pulmonary disease, uncontrolled diabetes mellitus, and neurologic disorders.

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert

Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

2018 UPDATED OR NEW RECOMMENDATIONS

Recommendation 3.1

Routine testing for deficiency in mismatch repair (dMMR) or high microsatellite instability (MSI-H) is recommended, using immunohistochemistry (IHC), polymerase chain reaction (PCR), or next-generation sequencing (NGS), for patients who are considered to be candidates for checkpoint inhibitor therapy (Type: informal-consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 3.2

PD-1 immune checkpoint inhibitor pembrolizumab is recommended as second-line therapy for patients who have tested positive for dMMR or MSI-H (Type: evidence-based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and analysis. **Study characteristics and quality assessment.** In Le et al,[6] dMMR was assessed using PCR or IHC. This study included 86 patients with 12 different cancer types (ampulla of vater, cholangiocarcinoma, colorectal, endometrial, gastroesophageal, neuroendocrine, osteosarcoma, pancreas (n = 8), prostate, small intestine, thyroid, and unknown primary), who had received at least one prior therapy and had evidence of progressive disease (Table 1). Median progression-free survival (PFS) and overall survival (OS) have not been reached yet in this study. A small, nonrandomized study such as that of Le at al[6] would generally be considered low quality due to the risk of bias associated with nonrandomized study designs and the indirectness resulting from the small number of patients with pancreatic cancer included in the study (n = 8). Nonetheless, the magnitude of the effect across disease sites in the population of patients with dMMR tumors is strong, and on this basis, the Expert Panel rated the study quality as intermediate.

Study outcomes. In the overall study population, Le et al[6] found a 21% rate of complete radiographic response, an objective response rate of 53% (46 of 86 patients; 95% CI, 42% to 64%), and a disease control rate (partial plus complete response or stable disease) of 77% (66 of 86 patients; 95% CI, 66% to 85%). Adverse events (AEs), which were mostly low grade, occurred in 74% of the study population. Twenty-one percent experienced endocrine-related AEs (mostly hypothyroidism) that could be controlled. Autoimmune phenomena were noted as a concern. Among the eight patients with pancreatic cancer included in this study, two (25%) experienced complete radiographic response, and the disease control rate was 75% (n = 6; Table 2).

Clinical interpretation. Immunotherapy has emerged as an option for metastatic pancreatic cancer since the previous version of this guideline was published in 2016. Le et al[6] have studied the effects of PD-1 blockade with pembrolizumab. dMMR cancers are predicted to have a large number of mutation-associated antigens that could potentially be recognized by the immune system. This study tests the hypothesis, established previously in a small study of patients with colorectal cancer, that PD-1 blockade is effective in dMMR tumors, regardless of their tissue of origin. In 2017, the US Food and Drug Administration (FDA) approved pembrolizumab for dMMR that can lead to high levels of MSI-H in the tumors, regardless of disease site.[8] In pancreatic cancer, a recent study found that only approximately 0.8% of tumors had dMMR.[9]

Recommendation 3.4

Fluorouracil plus nanoliposomal irinotecan, or fluorouracil plus irinotecan where the former combination is unavailable, is preferred as second-line therapy, for patients who meet all of the following criteria: first-line treatment with gemcitabine plus NAB-paclitaxel, an ECOG PS of 0 to 1, a relatively favorable comorbidity profile, patient preference and a support system for aggressive medical therapy, and

Table 1. Study Characteristics

First Author	Intervention or Comparison	No. of Patients Randomly Assigned	Median Age (years)	ECOG PS (%)	Median Follow-Up (months)	Disease Characteristics		
						Previous Treatment?	Eligibility Based on Timing of Disease Progression	Metastatic Disease (%)
Gill[7]	Biweekly mFOLFOX6 *v* FU + LV	108	mFOLFOX6: 65 (38-82) <70: 63% ≥ 70: 37% Infusional FU + LV: 67 (48-78) < 70: 67% ≥ 70: 33%	mFOLFOX6: 0: 13.0 1: 75.9 2: 11.1 Infusional FU + LV: 0: 18.9 1: 75.5 2: 5.7	8.8	Gemcitabine: Monotherapy: mFOLFOX6: 74.1% Infusional FU + LV: 77.8% Combination: mFOLFOX6: 25.9% Infusional FU + LV: 22.2%	Disease progression within 4 weeks of random assignment either during or after gemcitabine therapy	mFOLFOX6: 93 FU + LV: 94
Le[6]	PD-1 blockade (pembrolizumab)	86 (8 pancreatic)				Yes	Yes	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; mFOLFOX6, infusional fluorouracil, leucovorin, and oxaliplatin; FU + LV, infusional fluorouracil and leucovorin; PD-1, programmed cell death-1.

Table 2. Study Outcomes

First Author	Type of Study	No. of Patients	CRR	ORR	DC	Median PFS (months)	Median OS	Adverse Events
Gill[7]	Phase III multicenter trial	Biweekly mFOLFOX6 (54) *v* FU + LV (54); safety pop: 102; QOL pop: 83				3.1 *v* 2.9 (HR, 1.00; 95% CI, 0.66 to 1.53; log-rank *P* = .989)	6.1 *v* 9.9 (HR, 1.78; 95% CI, 1.08 to 2.93; log-rank *P* = .024)	Grade 3 or 4: mFOLFOX6: 63%, infusional FU + LV: 11% Treatment discontinuation: mFOLFOX6: 20%, infusional FU + LV: 2%
Le[6]	Prospective study of PD-1 blockade (pembrolizumab)	86 patients across 12 disease sites*	18 (21%; 95% CI not reported)	46 (53%; 95% CI, 42% to 64%)	66 (77%; 95% CI, 66% to 85%)	Not yet reached, study ongoing. PFS at 1 year: 64%; PFS at 2 years: 54%	Not yet reached, study ongoing	74%, mostly low grade; endocrine disorders (mostly hypothyroidism): 21%; autoimmune response is a concern.
Le[6]	Prospective study of PD-1 blockade (pembrolizumab)	Subset of 8 patients with pancreatic cancer	2 (25%)	62%	6 (75%)	Not yet reached, study ongoing	Not yet reached, study ongoing	Not reported

Abbreviations: CRR, complete radiographic response; DC, disease control rate: partial response plus complete response plus stable disease; FU + LV, fluorouracil and leucovorin; HR, hazard ratio; mFOLFOX6, infusional fluorouracil, leucovorin, and oxaliplatin; ORR, objective radiographic response (tumor size reduction according to RECIST criteria); OS, overall survival; PFS, progression-free survival; PD-1, programmed cell death-1; pop, population; QOL, quality of life.

*Ampulla of vater, cholangiocarcinoma, colorectal, endometrial, gastroesophageal, neuroendocrine, osteosarcoma, pancreas, prostate, small intestine, thyroid, unknown primary.

access to chemotherapy port and infusion pump management services (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 3.5

Fluorouracil plus oxaliplatin may be considered as second-line therapy for patients who meet all of the following criteria: first-line treatment with gemcitabine plus NAB-paclitaxel, an ECOG PS of 0 to 1, a relatively favorable comorbidity profile, patient preference and a support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Qualifying statement. A recent phase III trial comparing infusional fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) with fluorouracil and leucovorin (FU + LV) demonstrated a higher rate of grade 3 or 4 AEs and significantly reduced OS within the mFOLFOX6 arm of the trial. However, previous phase III data have demonstrated a benefit with the OFF (oxaliplatin, folinic acid, and fluorouracil) regimen compared with FU + LV. Considering the inconsistency of these results, although fluorouracil plus nanoliposomal irinotecan is preferred, the Expert Panel continues to support the use of fluorouracil plus oxaliplatin as an option where the availability of fluorouracil plus nanoliposomal irinotecan is limited or where residual toxicity from first-line therapy or comorbidities precludes the use of fluorouracil plus nanoliposomal irinotecan.

Literature review and analysis. **Study characteristics and quality assessment.** One phase III RCT, the PANCREOX study,[7] met the eligibility criteria for this focused guideline update. The PANCREOX study compared leucovorin 400 mg/m^2 administered as a 2-hour intravenous (IV) infusion on day 1 and fluorouracil administered as a bolus IV dose of 400 mg/m^2 on day 1 followed by a 2,400 mg/m^2 continuous infusion for 46 hours, administered every 14 days to the same regimen plus oxaliplatin 85 mg/m^2 given as a 2-hour IV infusion on day 1, administered every 14 days. Fifty-four patients with an ECOG PS of 0 to 2 were randomly assigned to each treatment arm. Approximately three quarters of the study population had been treated previously with gemcitabine monotherapy, and the remainder had received gemcitabine combination therapy. Metastatic disease was present in 93% of patients (Table 1).

Quality assessment was conducted for the important outcomes of OS, PFS, and incidence of grade 3 or 4 AEs. Quality assessment included risk of bias, indirectness, imprecision, and inconsistency for each outcome. Risk of bias may have been introduced with the open-label study design, and no information was provided on allocation concealment. Intention-to-treat analysis was used, and study characteristics were mostly well balanced, with the FU + LV group having more patients within ECOG PS 0. This study accrued only 108 of the planned 128 patients; however, the *P* value of .989 for the primary end point PFS would likely have not attained significance with the addition of 20 more patients to the study. Imprecision was not considered to be a major quality issue for the primary outcome of this study (PFS), or for other important outcomes. The majority of patients included in this study received first-line monotherapy with gemcitabine. Therefore, the results are less applicable to the population of patients who received previous treatment with first-line combination chemotherapy. In terms of inconsistency, the results of this study differ from the findings of the CONKO-003 study of fluorouracil and oxaliplatin compared with fluorouracil alone.[10] The authors of PANCREOX note that differences in dose intensities of oxaliplatin, eligibility criteria, and postprogression therapy could have contributed to this inconsistency; however, the comparison of the differences between the two studies is inconclusive.[7] Taking these factors into consideration, the quality of this study is rated as intermediate.

Study outcomes. There was no difference between arms in the PANCREOX study for the primary outcome, PFS (hazard ratio [HR], 1.00; 95% CI, 0.66 to 1.53; log-rank $P = .989$). Median OS was lower in the mFOLFOX6 group (6.1 *v* 9.9 months; HR, 1.78; 95% CI, 1.08 to 2.93; log-rank $P = .024$).[7] Grade 3 or 4 AEs were experienced by 63% of patients in the mFOLFOX6 group and by 11% of patients in the FU + LV group. Within these groups, 20% and 0% of patients discontinued treatment due to AEs, respectively. Dose reductions were more common in the mFOLFOX6 arm, most commonly due to hematologic toxicity (Table 2).[7]

Clinical interpretation. The authors of the previous version of this guideline noted that there is a lack of high-quality evidence to guide second-line therapy, and that previously, recommendations have been extrapolated from data for patients who have received gemcitabine monotherapy. The Expert Panel continues to recommend that the choice of therapy depend on performance status, comorbidities, organ function, residual toxicities from first-line therapy, and a support system for aggressive medical therapy.

The previous version of this guideline included a recommendation for the combination of fluorouracil and oxaliplatin, based on the results of CONKO-003, which compared folinic acid 200 mg/m^2 and fluorouracil 2,000 mg/m^2 over 24 hours on days 1, 8, 15, and 22 with oxaliplatin 85 mg/m^2 on days 8 and 22 (OFF regimen), with folinic acid and fluorouracil in patients with metastatic pancreatic cancer who had progressed on first-line gemcitabine.[10] This study demonstrated improved OS with the OFF regimen (5.9 *v* 3.3 months; HR, 0.66; 95% CI, 0.48 to 0.91; $P = .010$). New data from the PANCREOX trial, using the more commonly used mFOLFOX6 regimen, failed to find a benefit with the oxaliplatin combination.[7]

The Expert Panel continues to endorse the combination of fluorouracil and nanoliposomal irinotecan that was recommended in the previous version of this guideline for patients treated first line with gemcitabine plus NAB-paclitaxel, an ECOG PS of 0 to 1, a relatively favorable comorbidity profile, patient preference and a support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services. This recommendation is based on results from the NAPOLI-1 trial, which included a comparison of fluorouracil 2,400 mg/m^2 plus nanoliposomal irinotecan 80 mg/m^2 and leucovorin 400 mg/m^2 over 46 hours every 2 weeks, with fluorouracil in patients with metastatic pancreatic cancer who had progressed on first-line gemcitabine. This trial demonstrated improved OS with the combination (6.1 *v* 4.2 months; HR, 0.67; 95% CI, 0.49 to 0.92; $P = .01$).[11] Given the new data from the PANCREOX study, fluorouracil and nanoliposomal irinotecan are considered the preferred option for this patient population; however, fluorouracil and oxaliplatin may also be considered, as outlined in the qualifying statement to Recommendation 3.5.

DISCUSSION

The purpose of this focused update is to incorporate new data related to second-line treatment options for metastatic pancreatic cancer. For the previous version of this guideline, the evidence base included studies of patients who had been treated with first-line gemcitabine monotherapy, rather than the current standard combination chemotherapy. Despite this limitation, the Expert Panel concluded that OS could be improved with second-line cytotoxic therapy, with the choice of agents depending on performance status, comorbidities, organ function, and residual toxicities from prior treatment (p.2791).[3]

This guideline update incorporates new evidence related to second-line treatment options, including results from the PANCREOX study, which compared treatment with mFOLFOX6 with treatment with FU + LV,[7] and a study of pembrolizumab in patients whose tumors had a dMMR.[6]

The Update Expert Panel continues to support the following options from the previous version of the guideline, depending on patient characteristics (Bottom Line): gemcitabine plus NAB-paclitaxel, gemcitabine monotherapy or fluorouracil monotherapy, and a recommendation for clinical trial participation in the setting of third-line therapy.[3] Fluourouracil plus nanoliposomal irinotecan also continues to be recommended; however, data from the recent PANCREOX trial showing a higher rate of AEs and a reduced duration of OS for patients treated with mFOLFOX6 compared with those who received FU + LV have resulted in a modification to the recommendation related to the second-line option of fluorouracil plus oxaliplatin. For this version, fluorouracil plus oxaliplatin may be recommended where the availability of fluorouracil plus nanoliposomal irinotecan is limited or where the latter option is not preferred due to residual toxicities or comorbidities.

The Update Expert Panel noted that new results from the PANCREOX trial (2017)[7] differ from results of the CONKO-003 phase III RCT (2014),[10] which showed a benefit in the arm that included oxaliplatin. This may have been due to a difference in regimens; CONKO-003 used the OFF combination folinic acid 200 mg/m^2 and fluorouracil 2,000 mg/m^2 over 24 hours on days 1, 8, 15, and 22 with oxaliplatin 85 mg/m^2 on days 8 and 22) compared with folinic acid and fluorouracil, whereas the PANCREOX protocol called for the more common biweekly infusional FU + LV, and oxaliplatin (mFOLFOX6), with a higher dose intensity of oxaliplatin. In addition, all patients in CONKO-003 had first-line gemcitabine monotherapy, while in PANCREOX, approximately three quarters had first-line monotherapy. Eligibility criteria and rates of postprogression therapy also differed between the studies; however, it is difficult to determine a conclusive reason for the inconsistency in study results.

This update also incorporates new data from a study of PD-1 immune checkpoint inhibitor pembrolizumab. Recently, a unique FDA approval across disease sites was granted for pembrolizumab as a treatment option for patients with MSI-H status or dMMR solid tumors.[8] Although < 1% of patients in the target population for this guideline are expected to have tumors with this characteristic,[9] the potential for effectiveness is high. In formulating this recommendation, the Update Expert Panel considered the magnitude of the effect in the overall MSI-H population across pancreatic as well as other disease sites to be relevant. Although the key evidence for this recommendation included a nonrandomized study without a control group,[6] the evidence quality was graded as intermediate due to the magnitude of the effect and the opinion that future research would likely affirm the results of this study. To facilitate the implementation of the pembrolizumab recommendation, consensus-based recommendations have been included for testing for dMMR and MSI-H in this updated guideline. Other testing recommendations are considered outside the scope of this update, and a separate forthcoming ASCO guideline for germline testing in pancreatic cancer is currently under development.

Tumor mutation burden, as measured by NGS, has been hypothesized to indicate a potential for response to immunotherapy because it may be associated with a greater number of neoantigens. These, in turn, can be recognized by the immune system in response to checkpoint inhibition. Indeed, emerging data indicate that tumor mutation burden may be predictive of greater and more durable responses to immunotherapy in a variety of solid tumors.[12] It is possible that a high tumor mutation burden may also be a predictor of response to immunotherapy in metastatic pancreatic cancer, but until such data are available, the Panel felt it premature to recommend immunotherapy use for such tumors. Clear definitions of high tumor mutation burden and reduced variability among commercially available assays are also necessary for appropriate clinical implementation of this potential biomarker.

While developments in targeted therapy for this patient population are encouraging, there continues to be a need for more research and better therapy options. Poly (ADP-ribose) polymerase inhibitors are being studied in patients with advanced pancreatic cancer and a known BRCA mutation or a BRCAness genotype. Examples include the phase II open-label Rucaparib in Patients With Pancreatic Cancer and a Known Deleterious *BRCA* Mutation (RUCAPANC) study of rucaparib in 19 patients,[13] as well as the ongoing Olaparib in *gBRCA*-Mutated Pancreatic Cancer Whose Disease Has Not Progressed on First Line Platinum-Based Chemotherapy (POLO) phase III RCT.[14] Because the rate of BRCA positivity is approximately 4.6% in the advanced pancreatic cancer population,[15] these therapies are promising, and the Expert Panel will continue to monitor this literature for future guideline updates. Recent data published in an abstract from the Nab-paclitaxel in Combination With Gemcitabine in Fragile Patients With Advanced Pancreatic Cancer (FRAGRANCE) study showed that NAB-paclitaxel in combination with gemcitabine was well tolerated and showed acceptable survival outcomes and response rates in a patient population with ECOG PS 2 advanced pancreatic cancer.[16]

The Expert Panel is aware that additional data supporting the concept of referral to palliative care have been published since our original literature search. These new data support the previous recommendation for obtaining a palliative care consultation as early as possible.[17,18] The co-chairs and other members of the Expert Panel will also continue to monitor the literature on second-line therapy and on other aspects of the management of metastatic pancreatic cancer.

PATIENT AND CLINICIAN COMMUNICATION

Patients with pancreatic cancer face difficult treatment decisions while presented with complex medical information and a life-threatening diagnosis. Communication within a context of realistic hope and action between patients and clinicians can

improve patients' ability to make sound, informed decisions within their own personal value set. Patients should fully understand the goals of care before making decisions about treatment and care.

Clear communication with patients with pancreatic cancer and their caregivers about the diagnosis, treatment options, and goals of care is key for patient understanding. The clinician is also responsible for offering ancillary support services, which include a referral to palliative care consultation and services.

For patients to make informed decisions, providers should describe the potential impact of the diagnosis of pancreatic cancer on the patient and his or her family. It is important to provide realistic hope within honest, yet supportive, discussions. Providers should ask patients about their personal goals and preferences. What do they hope for? What is important to them in their personal lives? What do they value more, an extension of life or maintenance of the best possible quality of life? An understanding of a patient's specific goals should shape conversations about goals of care and treatment recommendations.

Clinicians should clearly explain all potential treatment options, the specific biomarker testing needed to determine the appropriateness of those treatment options, the potential outcomes of each, and possible AEs so that patients understand the benefits and drawbacks of each option and can make an informed decision. Treatment discussions should include relevant clinical trials at every stage of treatment. Patients should have the opportunity to participate in trials for their own treatment as well as be given the opportunity to contribute to research.

Clinicians should also consider and proactively discuss quality-of-life issues. In patients with pancreatic cancer, dietary concerns, pain, and fatigue are major concerns. Dietary issues tend to be overlooked and yet are real problems, with a significant impact on daily life. Referral to a registered dietitian and/or gastroenterologist with early intervention can be of great benefit. Clinicians should also consider the use of, and discuss the possible need for, pancreatic enzyme replacement therapy.

Referral to palliative care services can facilitate the addressing of many non–treatment-related issues patients face, and this referral should be offered to all patients with pancreatic cancer, regardless of stage of disease or expected prognosis. Patients should understand that referral to a consultation for palliative care services is not synonymous with a referral to hospice care. This discussion is important because palliative care provides important support and can be part of an active cancer treatment paradigm.

Patients must feel comfortable in the choices they make, and the knowledge that they have explored their options can bring comfort. As such, clinicians should support a patient's desire to get a second opinion. Clinicians should address the costs of care and offer referrals to specialists within the health care system who can discuss in more detail what a patient should expect as well as resources and information about managing the costs related to cancer care.

The provision of realistic hope to patients with pancreatic cancer, although the prognosis may be short, is important. Patients deserve to know that their medical team is working to help them reach their goals. Even if a cure is not possible, hope for an extension of life or a good quality of life is powerful.

The provision of resources to help patients communicate better with their health care team is also advisable. Patients should be offered decision-making tools and be urged to write down questions in between and in advance of appointments. Patients can be referred to resources that will extend the support and information clinicians are able to provide. For pancreatic cancer, two such resources are the ASCO patient-facing Web site (www.Cancer.net) and the Pancreatic Cancer Action Network (www.pancan.org).

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than are other Americans.[19-22] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform the treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

Because many patients for whom guideline recommendations apply present with MCC, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCC and highlight the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

In light of these considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCC, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended

care options are modified or not applied, as determined by best practice in consideration of any MCC.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[23,24] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[25,26]

Discussion of cost can be an important part of shared decision making.[27] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[27]

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even within the same insurance plan, the price may vary among different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[27]

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners, survivors of cancer, and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in *JCO* and *Journal of Oncology Practice*.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

Related ASCO Guidelines

- Integration of Palliative Care into Standard Oncology Practice[18] (http://ascopubs.org/doi/full/10.1200/JCO.2016.70.1474)
- Management of Immune-related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy (http://ascopubs.org/doi/10.1200/JCO.2017.77.6385)[28]
- Metastatic Pancreatic Cancer (http://ascopubs.org/doi/10.1200/JCO.2016.67.1412)[3]
- Locally Advanced, Unresectable Pancreatic Cancer (http://ascopubs.org/doi/10.1200/JCO.2016.67.5561)[29]
- Potentially Curable Pancreatic Cancer (http://ascopubs.org/doi/10.1200/JCO.2017.72.4948)[30]

ADDITIONAL RESOURCES

More information, including a Data Supplement, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/gastrointestinal-cancer-guidelines. Patient information is available at www.cancer.net.

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Metastatic Pancreatic Cancer: ASCO Clinical Practice Guideline Update

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Appendix

Table A1. Metastatic Pancreatic Cancer Update Expert Panel Membership

Name and Designation	Affiliation or Institution	Role or Area of Expertise
Daniel Laheru, MD (co-chair)	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD	Medical oncology
Davendra P.S. Sohal, MD, MPH (co-chair)	Cleveland Clinic, Cleveland, OH	Medical oncology
Mehmet S. Copur, MD	CHI Health St. Francis Cancer Treatment Center, Grand Island, NE	PGIN representative
Christopher H. Crane, MD	The University of Texas MD Anderson Cancer Center, Houston, TX	Radiation oncology
Ignacio Garrido-Laguna, MD, PhD	Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT	Medical oncology
Erin B. Kennedy, MHSc	ASCO, Alexandria, VA	Health research methodology
Alok Khorana, MD	Cleveland Clinic, Cleveland, OH	Medical oncology
Smitha Krishnamurthi, MD	Cleveland Clinic, Cleveland, OH	Hematology and medical oncology
Cassadie Moravek,	Pancreatic Cancer Action Network, Manhattan Beach, CA	Patient representative
Eileen M. O'Reilly, MD	Memorial Sloan Kettering Cancer Center, New York, NY	Internal medicine
Philip A. Philip, MD, PhD	Barbara Ann Karmanos Cancer Institute, Farmington Hills, MI	Medical oncology
Ramesh K. Ramanathan, MD	Mayo Clinic, Phoenix, AZ	Medical oncology
Joseph T. Ruggiero, MD	Weill Cornell Medicine, New York, NY	Hematology and medical oncology
Manish A. Shah, MD	Weill Cornell Medicine, New York, NY	Medical oncology
Susan Urba, MD	University of Michigan Health System Comprehensive Cancer Center, Ann Arbor, MI	Medical oncology
Hope E. Uronis, MD, MHS	Duke University, Durham, NC	Hematology and internal medicine
Michelle W. Lau, MD	Phoenix VA Medical Center, Phoenix, AZ	PGIN representative

Abbreviation: PGIN, Practice Guidelines Implementation Network.