

# Metastatic Pancreatic Cancer: ASCO Guideline Update

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Sohal et al.

# Introduction

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- The first ASCO guideline for patients with metastatic pancreatic cancer was published in 2016 and addressed initial assessment after diagnosis, first- and second-line treatment options, palliative and supportive care, and follow-up after treatment.
- In 2018, new evidence triggered a focused update of the second-line therapy recommendations for patients who had experienced progression or intolerable toxicity with first-line therapy, including the addition of pembrolizumab as an option for mismatch repair deficient (dMMR) or microsatellite instability (MSI)-high tumors, as well as associated testing recommendations.
- This 2020 update was prompted by new evidence for PARP inhibitor olaparib as an option for maintenance therapy after first-line treatment, and new studies of tissue agnostic agents that target fusions of the neurotrophin tyrosine receptor kinase 1/2/3 genes. In addition, the Expert Panel considered that these newer agents have been approved by the FDA for use in the target population.
- As there was not any new information relevant to the other topics included in this guideline identified, the Expert Panel continues to endorse previous ASCO recommendations on first-line therapy, palliative and supportive care, and follow-up.

# ASCO Guideline Development Methodology

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The ASCO Clinical Practice Guidelines Committee guideline process includes:

- a systematic literature review by ASCO guidelines staff
- an expert panel provides critical review and evidence interpretation to inform guideline recommendations
- final guideline approval by ASCO CPGC

The full ASCO Guideline methodology manual can be found at:

[www.asco.org/guideline-methodology](http://www.asco.org/guideline-methodology)

# Clinical Questions

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This clinical practice guideline addresses six overarching clinical questions:

1. After a histopathologic confirmation of pancreatic adenocarcinoma diagnosis, what initial assessment is recommended before initiating any therapy for metastatic pancreatic cancer?
2. What is the appropriate first-line treatment of patients with metastatic pancreatic cancer?
3. 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?
4. When should the concept of palliative care be introduced?
5. For patients with metastatic pancreatic cancer, what are the recommended strategies for relief of pain and symptoms?
6. What is the recommended frequency of follow-up care/surveillance for patients with metastatic pancreatic cancer?

The purpose of this focused update is to incorporate new evidence that is relevant to Clinical Question 3. For this guideline update, the Expert Panel also included studies of maintenance treatment after first-line therapy.

# Target Population and Audience

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## Target Population

Patients with metastatic pancreatic adenocarcinoma

## Target Audience

Medical oncologists, radiation oncologists, surgeons, gastroenterologists, pathologists

# Summary of Recommendations

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## 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).

# Summary of Recommendations

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## ***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).

# Summary of Recommendations

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## ***Recommendation 1.5***

Early testing for actionable genomic alterations is recommended for patients who are likely to be potential candidates for additional treatment following first-line therapy. Both germline and tumor (somatic) testing are recommended. This includes testing for microsatellite instability/mismatch repair deficiency, BRCA mutations (excluding variants of unknown significance), and NTRK gene fusions. Results of testing can lead to therapies such as PARP inhibitors, PD-1 checkpoint inhibitor therapy, TRK fusion inhibitors, and clinical trials of targeted therapies. Genomic testing is recommended as part of initial assessment to ensure that the results of testing are available at the time of treatment decision-making where applicable after first-line therapy (see Section 3; Treatment Options Following First-line Therapy). (Type: informal consensus; Strength of Recommendation: strong).

***Qualifying Statement.*** *The decision to test for actionable genomic alterations should involve a discussion between the patient and physician regarding frequency of actionable findings, treatment implications of testing results, and genetic counseling related to germline testing. ASCO has previously developed a provisional clinical opinion (PCO) on Evaluating Susceptibility to Pancreatic Cancer that contains recommendations for germline genetic testing.<sup>1</sup>*



# Summary of Recommendations

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## ***Recommendation 1.6***

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).

# Summary of Recommendations

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## 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).

### ***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).

# Summary of Recommendations

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## ***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 nab-paclitaxel or capecitabine or erlotinib to gemcitabine may be offered in this setting, with proactive dose and schedule adjustments to minimize toxicities (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

## ***Recommendation 2.4***

Patients with an ECOG PS 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).

# Summary of Recommendations

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## Treatment Options Following First-line Therapy

### ***Recommendation 3.1***

In patients with tumors harboring NTRK fusions, treatment with larotrectinib or entrectinib is recommended (Type: evidence based; 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: high; Strength of Recommendation: strong).

# Summary of Recommendations

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## **Recommendation 3.3.**

In patients who have a germline BRCA1 or BRCA2 mutation and have received first-line platinum-based chemotherapy without disease progression for at least 16 weeks, options for continued treatment include chemotherapy or PARP inhibitor olaparib (Type: evidence-based; benefits outweigh harms; Evidence quality: low; Strength of Recommendation: moderate).

**Qualifying Statement.** *For the group of platinum-sensitive patients included in recommendation 3.3, the decision to continue treatment with chemotherapy or proceed to maintenance therapy with olaparib should be based on a discussion between the patient and the oncologist, including consideration of whether a maximum response and plateau in response to chemotherapy have been achieved, level of cumulative toxicities associated with chemotherapy treatment, patient preference, convenience, toxicity, goals of care, cost, and clinical evidence, including a lack of overall survival benefit demonstrated in the POLO randomized controlled trial.<sup>2</sup>*

# Summary of Recommendations

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## ***Recommendation 3.4.***

Gemcitabine plus NAB-paclitaxel may 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 3.5.***

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 a gemcitabine-based regimen, 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).

# Summary of Recommendations

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## **Recommendation 3.6.**

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 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.<sup>3</sup> However, previous phase III data have demonstrated a benefit with the OFF regimen compared with FU + LV.<sup>4</sup> 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.*

# Summary of Recommendations

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## ***Recommendation 3.7.***

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 (the addition of nab-paclitaxel to gemcitabine or nanoliposomal irinotecan to 5-fluorouracil may be offered in this setting, with proactive dose and schedule adjustments to minimize toxicities) (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

## ***Recommendation 3.8.***

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).



# Summary of Recommendations

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## 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).(Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

## 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).

# Summary of Recommendations

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## 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).

# Summary of Recommendations

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## ***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).

# Discussion

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- Results for therapy options larotrectinib and entrectinib have been incorporated in this update.
- FDA approvals were based on evidence from “basket trials” where efficacy of treatment for a specific genomic alteration is evaluated regardless of tumor site.
- These trials did not include a comparator group, and recommendations for these interventions are based on the large magnitude of the objective response rate for larotrectinib (75%)<sup>5</sup> and entrectinib (57%),<sup>6</sup> which exceeded the predetermined minimum response rate of 30% that investigators agreed would indicate a clinically meaningful benefit.
- PARP inhibitor olaparib is a recommended treatment option as maintenance therapy, based on a statistically significant benefit in progression-free survival, compared to placebo.<sup>2</sup>
- This targeted update considered only new evidence for treatment after first-line therapy, the Expert Panel is aware of new evidence in the first-line setting, such as data from the FRAGRANCE trial of the efficacy and safety of nab-paclitaxel in combination with gemcitabine in patients with ECOG PS 2.<sup>7</sup> In response to this, minor modifications to recommendations 2.3, 3.7 and 3.9 were made.

# Biomarker Testing

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- In conjunction with these newer agents, this update includes a modification to the recommendation for molecular testing to include testing for biomarkers that are used to select patients for therapy.
- This recommendation was consensus-based; in the case of the recommendation for treatment of NTRK fusion positive cancers, the Expert Panel acknowledged the low prevalence of NTRK fusions,<sup>8,9</sup> but agreed that the high rate of response provided justification for testing all patients who are considered to be candidates for treatment.
- The Expert Panel recognized the challenges to implementing this recommendation, including accessibility and cost; many third-party payors in the U.S. and international markets may not reimburse adequately for such testing.
- There are various complexities associated with testing for NTRK fusions, and options for testing, including DNA- or RNA-level sequencing, or immunohistochemistry.<sup>8</sup> Each of these options has advantages under different circumstances and for different tumor types.
- Recommendations on germline genetic testing are contained in the ASCO provisional clinical opinion on Evaluating Susceptibility to Pancreatic Cancer.<sup>1</sup>

# Patient and Clinician Communication

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- Clear communication about diagnosis, treatment options, and goals of care is key for patient understanding.
- A conversation on the importance of both somatic and germline testing and the implications of testing on treatment options should be had soon after the patient's diagnosis is confirmed. The clinician must balance describing the importance of testing while providing realistic hope around the identification of actionable findings. Providers should describe the potential impact of genetic testing on the patient with pancreatic cancer and their family.
- Clinicians should clearly explain all potential treatment options, the testing needed to determine the appropriateness of those options, the potential outcomes of each, and possible adverse events 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.
- Clinicians should consider and proactively discuss quality-of-life issues, including dietary concerns, pain, and fatigue. The clinician is also responsible for offering ancillary support services, including a referral to palliative care consultation and services.

# Additional Resources

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More information, including a Data Supplement, slide sets, and clinical tools and resources, is available at

[www.asco.org/gastrointestinal-cancer-guidelines](http://www.asco.org/gastrointestinal-cancer-guidelines)

Patient information is available at [www.cancer.net](http://www.cancer.net)

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