

# Metastatic Pancreatic Cancer: ASCO Guideline Update

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## abstract

**PURPOSE** The aim of this work was to provide an update to the ASCO guideline on metastatic pancreatic cancer pertaining to recommendations for therapy options after first-line treatment.

**METHODS** ASCO convened an Expert Panel and conducted a systematic review to update guideline recommendations for second-line therapy for metastatic pancreatic cancer.

**RESULTS** One randomized controlled trial of olaparib versus placebo, one report on phase I and II studies of larotrectinib, and one report on phase I and II studies of entrectinib met the inclusion criteria and inform the guideline update.

**RECOMMENDATIONS** New or updated recommendations for germline and somatic testing for microsatellite instability high/mismatch repair deficiency, *BRCA* mutations, and *TRK* alterations are provided for all treatment-eligible patients to select patients for recommended therapies, including pembrolizumab, olaparib, larotrectinib, or entrectinib, or potential clinical trials. The Expert Panel continues to endorse the remaining recommendations for second-line chemotherapy, as well as other recommendations related to treatment, follow-up, and palliative care from the 2018 version of this guideline. Additional information is available at [www.asco.org/gastrointestinal-cancer-guidelines](http://www.asco.org/gastrointestinal-cancer-guidelines).

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## ASSOCIATED CONTENT

### Appendix

### Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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## INTRODUCTION

There were an estimated 57,600 new cases and 47,050 deaths as a result of pancreatic cancer in the United States in 2020,<sup>1</sup> and an estimated 460,000 new cases worldwide in 2018.<sup>2</sup> A diagnosis of pancreatic ductal adenocarcinoma is associated with poor prognosis as a result of early micrometastatic spread, and the 5-year survival rate for metastatic pancreatic cancer is approximately 2.9%.<sup>3</sup>

The first ASCO guideline for clinical decision making for patients with metastatic pancreatic cancer was published in 2016 and included recommendations for initial assessment after diagnosis, first- and second-line treatment options, palliative and supportive care, and follow-up after treatment.<sup>4</sup> ASCO guidelines are assessed annually for potential updating, or an update can be triggered whenever new potentially practice-changing evidence is published. In 2018, new evidence triggered a focused update of the recommendations for second-line therapy 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 or microsatellite instability-high tumors, as well as associated testing recommendations.<sup>5</sup>

The previous version of this ASCO guideline, published in 2018, included 7 moderate-strength recommendations for second-line therapy that were based on lower-quality evidence.<sup>5</sup> This 2020 update of the 2018 recommendations was triggered by new evidence for poly (ADP-ribose) polymerase (PARP) inhibitor olaparib as an option for maintenance therapy after first-line treatment, as well as new studies of tissue agnostic agents that target fusions of the neurotrophin tyrosine receptor kinase (*NTRK*) 1/2/3 genes. In addition, the Expert Panel considered that these newer agents have been approved by the US Food and Drug Administration (FDA) for use in the target population.<sup>6-8</sup> It is duly noted that overall evidence was limited in terms of the number of studies and patients with pancreatic cancer in these studies,

## THE BOTTOM LINE

### Metastatic Pancreatic Cancer: ASCO Guideline Update

#### Guideline Question

The purpose of this focused update is to incorporate new evidence that is relevant to Clinical Question 3 from previous versions of this guideline<sup>4,5</sup>: What is the appropriate therapy for patients with metastatic pancreatic cancer who experience either disease progression or intolerable toxicity with prior regimens? For this guideline update, the Expert Panel also included studies of maintenance treatment after first-line therapy.

#### Target Population

Patients with metastatic pancreatic adenocarcinoma

#### Target Audience

Medical oncologists, radiation oncologists, surgeons, gastroenterologists, and pathologists

#### 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- or greater-line therapy. On the basis of a systematic evidence review, recommendations 1.5, 3.1, and 3.3 were added. Minor modifications were made to recommendations 2.3, 3.5, and 3.7 based on Expert Panel consensus. All other recommendations from the previous version (2018)<sup>5</sup> of this guideline are endorsed for this 2020 update. New recommendations or changes to the 2018 recommendations are denoted by bold, italicized text. The full guideline text contains 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 the 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 performance status (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, and 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. Early testing for actionable genomic alterations is recommended for patients who are likely to be potential candidates for additional treatment after 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 poly (ADP-ribose) polymerase inhibitors, programmed death-1 checkpoint inhibitor therapy, TRK fusion inhibitors, and clinical trials of targeted therapies. Genomic testing is recommended as part of an initial assessment to ensure that the results of testing are available at the time of treatment decision where applicable after first-line therapy (see 3. Treatment Options After 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 the frequency of actionable findings, treatment implications of testing results, and genetic counseling related to germline testing. ASCO has previously developed a provisional clinical opinion on Evaluating Susceptibility to Pancreatic Cancer that contains recommendations for germline genetic testing.<sup>10</sup>**

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).

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## THE BOTTOM LINE (CONTINUED)

## 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 Eastern Cooperative Oncology Group (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).

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 of 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. Major emphasis should be on optimizing supportive care measures (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

## 3. Treatment Options After 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. Programmed death-1 immune checkpoint inhibitor pembrolizumab is recommended as second-line therapy for patients who have tested positive for mismatch repair deficiency or microsatellite instability high (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 3.3. **In patients who have a germline BRCA1 or BRCA2 mutation and who 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, the 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>11</sup>**

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 a 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).

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).

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## THE BOTTOM LINE (CONTINUED)

**Qualifying statement.** A phase III trial comparing mFOLFOX6 (infusional fluorouracil, leucovorin, and oxaliplatin) with fluorouracil plus leucovorin demonstrated a higher rate of grade 3 or 4 adverse events and significantly reduced overall survival within the mFOLFOX6 arm of the trial<sup>12</sup>; however, previous phase III data have demonstrated a benefit with the OFF (oxaliplatin, folinic acid, and fluorouracil) regimen compared with fluorouracil plus leucovorin.<sup>5,13</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 when availability of fluorouracil plus nanoliposomal irinotecan is limited or when residual toxicity from first-line therapy or comorbidities preclude the use of fluorouracil plus nanoliposomal irinotecan.

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 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).

### 4. Palliative Care

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

### 6. Follow-Up and Surveillance

Recommendation 6.1. For patients on active cancer-directed therapy outside of 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. 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 the 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 supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at [www.asco.org/gastrointestinal-cancer-guidelines](http://www.asco.org/gastrointestinal-cancer-guidelines). The Methodology Manual (available at [www.asco.org/guideline-methodology](http://www.asco.org/guideline-methodology)) provides additional information about the methods used to develop this guideline.

**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.**

along with the fact that 2 of the 3 included studies were nonrandomized trials. As the signals approach<sup>9</sup> did not identify any new information relevant to the other topics included in this guideline, the Expert Panel continues to

endorse previous ASCO recommendations on first-line therapy, palliative and supportive care, and follow-up. A summary of all current recommendations is contained in the Bottom Line Box.

## GUIDELINE QUESTIONS

This clinical practice guideline update addresses the following clinical question: After first-line therapy, what is the appropriate maintenance therapy or second-line therapy for patients with metastatic pancreatic cancer? Specific populations of interest for this focused guideline update include patients who have a germline *BRCA* mutation or somatic *NTRK* mutation.

## METHODS

### Guideline Development Process

This systematic review-based guideline product was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1, online only). The Expert Panel met in person and via teleconference and/or webinar and corresponded through e-mail. Based on a consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. Guideline recommendations were sent for an open comment period of 2 weeks, allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review and 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 Guidelines Committee before publication. All funding for the administration of the project was provided by ASCO.

A search of PubMed was conducted to capture studies of systemic therapy published after the last guideline update (January 2018) to December 31, 2019. For agents that were not included in the 2018 update search, the search was conducted from July 2015 (final search date of the original guideline) to December 31, 2019—these agents include PARP inhibitor olaparib and the *NTRK* inhibitors larotrectinib and entrectinib. Eligible study designs included phase III randomized controlled trials (RCTs) for studies of systemic therapy and olaparib, and phase I to III trials for studies of larotrectinib and entrectinib. Studies for which the sole purpose was determination of optimal therapeutic dose were excluded. The Expert Panel also planned to examine the testing methods used in the included studies to inform a potential update of informal consensus-based Recommendation 3.1 for biomarker testing.

In summary, the PICO (population, interventions, comparisons, outcomes) elements that informed the search strategy were as follows:

- Population: adult patients with metastatic pancreatic cancer, or patients with cancer of any site who have tested positive for actionable genetic mutations, including *BRCA1*, *BRCA2*, *NTRK 1/2/3*, or mismatch repair deficiency or microsatellite instability high, and who have undergone first-line therapy. Studies with a combination of adult and pediatric patients were considered eligible for inclusion.
- Interventions: systemic therapy, including chemotherapy, PARP inhibitor olaparib, pembrolizumab, or TRK inhibitors larotrectinib and entrectinib.
- Comparisons: other systemic therapy and placebo; no comparison group.
- Outcomes: rates of overall survival (OS), progression-free survival (PFS), objective response, adverse events, discontinuation of trial agent, dose reductions, and dose modifications.

Articles were excluded from the systematic review if they were meeting abstracts not subsequently published in peer-reviewed journals; editorials, commentaries, letters, news articles, case reports, and narrative reviews; and/or published in a non-English language. The complete search strategy is provided in the Data Supplement.

Certainty of the evidence (ie, evidence quality) for each outcome was assessed using the Cochrane Risk of Bias tool<sup>14</sup> and elements of the GRADE quality assessment and recommendations development process.<sup>15</sup> To facilitate quality assessment ratings, MAGICApp guideline development software was used. Within this framework, outcomes from observational—nonrandomized—studies are rated low quality and can subsequently be downgraded or upgraded if factors that affect quality (ie, certainty) are identified.<sup>15</sup> GRADE quality assessment labels (ie, high, moderate, low, very low) were assigned for each outcome by the project methodologist in collaboration with the Expert Panel co-chairs, and reviewed by the full Expert Panel.

Guideline recommendations are crafted, in part, using the Guidelines into Decision Support methodology and accompanying BRIDGE-Wiz software.<sup>16</sup> In addition, a guideline implementability review is 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.

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need for subsequent updates. The ASCO Guidelines Methodology Manual (available at [www.asco.org/guideline-methodology](http://www.asco.org/guideline-methodology)) provides additional information about the guideline update process. This is the most recent information as of the publication date.



## Definitions

A favorable comorbidity profile is loosely defined as hemoglobin  $\geq 10$  g/dL and platelet count  $\geq 100,000/\mu\text{L}$  without transfusion support; absolute neutrophil count  $\geq 1,500/\mu\text{L}$ ; 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<sup>2</sup>; 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  $\geq 75,000/\mu\text{L}$  without transfusion support; absolute neutrophil count  $\geq 1,500/\mu\text{L}$ ; 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<sup>2</sup>; 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.

## RESULTS

### Characteristics of Included Studies

Three studies met eligibility criteria and form the evidentiary basis for this focused guideline update. Nonrandomized studies include Drilon et al,<sup>17</sup> which is a basket trial of 55 patients with TRK fusion-positive cancers from 3 phase I or phase II single-arm studies of larotrectinib across multiple disease sites, and a report by Doebele et al<sup>18</sup> of 55 patients from the ALKA-372-001 and STARTRK-1 phase I and STARTRK-2 phase II trials of entrectinib. These 2 studies included 1 and 3 patients with pancreatic cancer, respectively. The POLO phase III RCT of olaparib compared with placebo<sup>11</sup> was conducted in 154 patients with metastatic pancreatic adenocarcinoma who had undergone at least 16 weeks of platinum-based chemotherapy and who had tested positive for a germline *BRCA1* or *BRCA2* mutation. Key characteristics of these studies are included in Table 1, and additional description is included in the Recommendations section.

### Assessment of Data Quality

Outcomes from the included RCTs were initially rated as high quality and downgraded as quality issues were identified. Phase I or II trials, as a result of the non-randomized study design, were initially rated as low quality, and quality was downgraded for such issues as small study size and industry funding. Where appropriate, evidence quality was upgraded because of a large magnitude of effect. More details regarding the reasons for quality (ie, certainty) ratings for the evidence are included in the footnotes to Tables 2 to 4.

TABLE 1. Characteristics of Included Studies

Study	Study Population	No. of Patients	Intervention	Comparator	Primary Study End Point(s)	Biomarker Testing Method(s)
Drilon et al <sup>17</sup> (phase I/II study)	Locally advanced or metastatic <i>NTRK</i> fusion-positive tumors (age 4 months to 76 years) previously treated with therapy other than kinase inhibitors (where available); ECOG PS 0-2 (ECOG PS 0-3 were eligible)	55 (8 adults and 12 pediatric patients from the phase I trial; 35 adults and adolescents from the phase II trial); 1 patient with pancreatic cancer	Larotrectinib (orally, 100 mg twice daily for adults or children with a BSA $\geq$ 1 m <sup>2</sup> )	No comparator	Overall (complete and partial) response rate	TRK fusions were identified using NGS (50 patients) or FISH (5 patients) as routinely obtained by each participating site
Doebele et al <sup>18</sup> ALKA-372-001 (phase I), STARTRK-1 (phase I), STARTRK-2 (phase II global basket study)	Locally advanced or metastatic <i>NTRK</i> fusion-positive solid tumors; ECOG PS 0-2; minimum life expectancy of 3 months (ALKA or STARTRK-1) or 4 weeks (STARTRK-2) and adequate organ function	54 patients with advanced or metastatic <i>NTRK</i> fusion-positive solid tumors (6%; 3 patients with pancreatic cancer); 51 patients from STARTRK-2; 2 patients from STARTRK-1; 1 patient from ALKA-372-001	Entrectinib (orally, at least 600 mg once per day in capsule form)	No comparator	Objective response rate and median duration of response	Patients enrolled on the basis of local testing, including FISH, quantitative PCR, or DNA-based or RNA-based NGS; STARTRK-2 phase II study patients required to provide tumor tissue for NGS
Golan et al <sup>11</sup> (phase III POLO trial, 119 sites, 12 countries)	Patients with platinum-sensitive metastatic pancreatic cancer and germline <i>BRCA1</i> or <i>BRCA2</i> mutations who received at least 16 weeks of platinum-based chemotherapy (therapy continued as long as there was no evidence of disease progression)	154 patients	Maintenance therapy with olaparib tablets (300 mg twice daily)	Placebo	Progression-free survival	"[D]etection of a germline <i>BRCA</i> mutation by central testing with the use of the BRACAnalysis CDx test (Myriad Genetic Laboratories) or by local testing with subsequent confirmation with the use of BRACAnalysis CDx test after randomization"

Abbreviations: BSA, body surface area; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; NGS, next-generation sequencing; PCR, polymerase chain reaction.

**TABLE 2.** Study Outcomes: Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children

Outcome	Study Results	Certainty of the Evidence (quality of evidence)	Plain Text Summary
Overall response rate (primary outcome) <sup>a</sup>	ORR: 75% <sup>a</sup> (95% CI, 61% to 85%; pre-established lower boundary of 30% ruled out); 13% complete response (95% CI, 6% to 25%); 62% partial response (95% CI, 49% to 75%); 13% stable disease (95% CI, 6% to 25%); 9% progressive disease (95% CI, 3% to 20%); 4% early withdrawal because of clinical deterioration (95% CI, 0.5% to 13.5%)	Low (1, 2)	Larotrectinib may improve overall response for patients with TRK fusion-positive tumors
Progression-free survival	55% progression-free at 1 year (95% CI, 42% to 67%)	Low (1, 2)	Larotrectinib may improve progression-free survival for patients with TRK fusion-positive tumors
Most common grade 3-4 adverse events	1,038 events occurred among 55 patients (93% grade 1 or 2; 7% grade 3 or 4): Anemia (11%) Increased level of ALT or AST (7%) Weight increase (7%) Decreased neutrophil count (7%)	Very low (1)	Larotrectinib may result in adverse events for patients with TRK fusion-positive tumors
Drug reductions or discontinuations	15% had dose reductions related to adverse events; no discontinuations as a result of drug-related adverse events were recorded	Very low (1)	Larotrectinib may result in dose reductions for patients with TRK fusion-positive tumors

NOTE. Results from Drilon et al.<sup>17</sup> (1) Downgrade: commercially funded; indirectness: locally advanced included. (2) Upgrade: large magnitude of effect. Population: Fifty-five patients with TRK fusion-positive locally advanced or metastatic tumors, including 1 patient with pancreatic cancer. Intervention: Larotrectinib (20 patients treated in dose-escalation study and 35 treated at a therapeutic dose of 100 mg orally twice daily). Comparator: no comparator arm. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

<sup>a</sup>Independently assessed according to the RECIST version 1.1.<sup>19</sup> Overall response rate: sum of complete and partial responses.<sup>19</sup>

## 2020 NEW OR UPDATED RECOMMENDATIONS

The following section contains a summary of new or substantially updated recommendations, incorporating the results of the literature that met the inclusion criteria of the systematic review.

### Recommendation 1.5

Early testing for actionable genomic alterations is recommended for patients who are likely to be potential candidates for additional treatment after first-line therapy. Both germline testing 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, programmed death-1 checkpoint inhibitor therapy, TRK fusion inhibitors, and clinical trials of targeted therapies. Genomic testing is recommended as part of an initial assessment to ensure that the results of testing are available at the time of treatment decision where applicable after first-line therapy (see 3. Treatment Options After 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 the 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), Evaluating Susceptibility to Pancreatic Cancer, which contains recommendations for germline genetic testing.<sup>10</sup>

**Literature review update and analysis.** This recommendation is based on informal consensus of the Expert Panel. Because a proportion of patients, albeit small, with metastatic pancreatic cancer have targetable genomic alterations, the Expert Panel recognizes the need for biomarker testing to identify appropriate candidates for targeted therapies included in Recommendations 3.1 to 3.3. Additional guidance for evaluating susceptibility to pancreatic cancer with germline genetic testing is available in a separate ASCO PCO.<sup>10</sup>

### 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).

**Literature review and analysis. Larotrectinib in TRK fusion-positive cancers.** Drilon et al<sup>17</sup> studied TRK fusion inhibitor larotrectinib in 55 patients age 4 months to 76 years with TRK fusion-positive locally advanced or metastatic tumors who had received treatment with therapy other than kinase inhibitors (where available). Twelve different tumor disease sites were represented, including 1



**TABLE 3.** Study Outcomes: Entrectinib in Patients With Advanced or Metastatic *NTRK* Fusion-Positive Solid Tumors: Integrated Analysis of Three Phase I-II Trials

Outcome/Timeframe	Study Results	Certainty of the Evidence (quality of the evidence)	Plain Text Summary
ORR (coprimary end point) median follow-up, 12.9 months	ORR: 31 of 54 (57%; 95% CI, 43.2% to 70.8%), 4 CR (7%), 27 PR (50%), 9 SD (17%); 2 of 3 patients with pancreatic cancer experienced PR by RECIST v1.1 (67%; 95% CI, 9% to 99%)	Moderate (1, 2)	Entrectinib may improve ORR (coprimary end point)
Median duration of response (coprimary end point)	By blinded independent review: 10.4 months (95% CI, 7.1 months to not estimable)	Low (1)	Entrectinib may improve duration of response (coprimary end point)
Median progression-free survival	Median PFS: 11.2 months (95% CI, 8.0 to 14.9 months)	Low (1)	Entrectinib may improve progression-free survival
Median overall survival	21 months (95% CI, 14.9 months to not estimable)	Low (1)	Entrectinib may improve overall survival
Most common grade 3-4 adverse events in <i>NTRK</i> fusion-positive safety population	Anemia (12%), increased weight (10%), fatigue (7%)	Very low (1)	Entrectinib may worsen adverse events
Dose modifications	Treatment discontinuations (4%), dose interruptions (31%), dose reductions as a result of treatment-related adverse events (40%); the latter were most commonly because of anemia (7%), increased blood creatinine levels (6%), and fatigue (6%)	Very low (1)	Entrectinib may result in dose modifications, interruptions, and reductions

NOTE. Results from Doebele et al.<sup>18</sup> (1) Downgrade: risk of bias, population dissimilarity (locally advanced included), low number of patients (3 of 54 patients with pancreatic cancer), commercially funded. (2) Upgrade: large magnitude of effect. Population: 54 patients with *NTRK* fusion-positive patients with solid tumors, including 3 patients with pancreatic cancer. Intervention: entrectinib (600 mg orally daily). Comparator: no comparator.

Abbreviations: CR, complete response; ORR, objective response rate; PR, partial response; SD, stable disease.

patient with pancreatic cancer, and 51% of patients had received at least 2 prior systemic chemotherapies. Genes included *NTRK1* (45%), *NTRK2* (2%), and *NTRK3* (53%). TRK fusions were identified using next-generation sequencing (50 patients) or fluorescence in situ hybridization (5 patients) as routinely obtained by each participating site. The primary study outcome was overall rate of response, which was 75% (95% CI, 61% to 85%) and exceeded a pre-established lower boundary of 30%. Thirteen percent of patients experienced complete response and 62% experienced partial response (Table 2). The patient with pancreatic cancer achieved a partial response. In addition, 73% of patients were progression free at 6 months and 55% were progression free at 1 year. Adverse events were most commonly grade 1 or 2. The most frequent grade 3 adverse event was anemia (15%).

**Entrectinib in patients with advanced or metastatic *NTRK* fusion-positive solid tumors.** Data from 3 patients in the STARTRK-1 and ALKA-1-372-011 trials who had solid tumors, *NTRK* molecular alterations, and were considered phase II eligible—that is, solid tumors, RECIST measurable disease, no prior tyrosine kinase inhibitor treatment targeting the fusion of interest, and treatment consistent with the established phase II dose of 600 mg/m<sup>2</sup> of entrectinib daily—were combined in an analysis with 51 patients from the STARTRK-2 phase II trial (Table 3). Objective response

rate, the primary end point, was 57% (95% CI, 43.2% to 70.8%), including 4 complete responses and 27 partial responses. Two of 3 patients with pancreatic cancer achieved a partial response. The outcome in the overall study population exceeded the prespecified lower clinically meaningful boundary of 30%. The second primary end point, median duration of response, was 10 months. Median PFS and OS were 11 months (95% CI, 8.0 months to 14.9 months) and 21 months (95% CI, 14.9 months to not estimable), respectively. Analyses were also conducted in a safety population that included 68 *NTRK* fusion-positive patients who had received at least 1 dose of entrectinib. Within this population, most treatment-related adverse events were grade 1 and 2 and reversible; 10% of patients reported serious adverse events. In addition, results were reported for a larger safety population that included patients with any gene rearrangement and tumor type and at least 1 dose of entrectinib. Overall, the results in this larger safety population were consistent with the safety profile of *NTRK* fusion-positive safety population.

**Clinical interpretation.** Several quality considerations were identified for the outcomes of studies of larotrectinib and entrectinib, which resulted in the downgrading of study quality. These included the small overall study sample sizes and even fewer patients with pancreatic cancer, inclusion of locally advanced patients, and risk of bias associated with

**TABLE 4.** Study Outcomes: Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer

Outcome/Timeframe	Study Results and Measurements	Absolute Effect Estimate		Certainty of the Evidence (quality of evidence)	Plain Text Summary
		Placebo	Olaparib		
Progression-free survival (primary outcome)	Hazard ratio, 0.53 (95% CI, 0.35 to 0.82)	904 per 1,000	711 per 1,000	Moderate (1, 4)	Olaparib probably improves progression-free survival (primary outcome)
	Based on data from 154 patients in 1 study; follow-up, 24 months	Difference: 193 fewer per 1,000 (95% CI, 344 fewer to 50 fewer)			
Overall survival	Hazard ratio, 0.91 (95% CI, 0.56 to 1.46)	640 per 1,000	605 per 1,000	Moderate (1, 2)	Olaparib may have little or no difference on overall survival
	Based on data from 154 patients in 1 study Follow-up 24 months	Difference: 35 fewer per 1,000 (95% CI, 204 fewer to 81 more)			
Response rate	Odds Ratio: 2.3 (95% CI, 0.89 to 6.76)	100 per 1000	204 per 1,000	Very low (1, 3)	Olaparib may have little or no difference on response rate
	Based on data from 154 patients in 1 study	Difference: 104 more per 1,000 (95% CI, 10 fewer to 329 more)			
Serious adverse events	Relative risk, 1.56 (95% CI, 0.76 to 3.16)	150 per 1,000	234 per 1,000	Low (1)	Olaparib may worsen serious adverse events
	Based on data from 151 patients in 1 study	Difference: 84 more per 1,000 (95% CI, 36 fewer to 324 more)			
Discontinuation of trial agent as a result of adverse events	Relative risk, 3.3 (95% CI, 0.39 to 27.5)	17 per 1,000	56 per 1,000	Very low (1, 3)	Olaparib may increase the risk of discontinuation of trial agent because of adverse events
	Based on data from 151 patients in 1 study	Difference: 39 more per 1,000 (95% CI, 10 fewer to 451 more)			

NOTE. Results from Golan et al.<sup>11</sup> (1) Downgrade: only one study, commercially funded. (2) Based on an interim analysis; however, Expert Panel members agreed that this result can be considered moderately certain to be corroborated by final study results. (3) Imprecision: wide confidence interval. (4) Upgrade: large magnitude of effect. Population: platinum-sensitive patients with metastatic pancreatic adenocarcinoma and a germline *BRCA1* or *BRCA2* mutation. Intervention: poly (ADP-ribose) polymerase inhibitor olaparib as maintenance therapy for disease that has not progressed during first-line platinum-based therapy. Comparator: placebo.

commercial sponsorship. Despite the limitations in quality and certainty of the evidence, the primary outcomes for both studies exceeded a prespecified clinically meaningful 30% threshold for objective response rate by a large margin (75% [95% CI, 61% to 85%] and 57% [95% CI, 43% to 71%] for larotrectinib and entrectinib, respectively). In addition, results for PFS and/or OS in these studies compared favorably with results published in previous trials, including a meta-analysis that demonstrated OS of 6 months with chemotherapy and 2.8 months with best supportive care.<sup>4,5,20</sup> The adverse events profiles associated with these agents were found to be manageable (Tables 2 and 3).

### Recommendation 3.3

In patients who have a germline *BRCA1* or *BRCA2* mutation and have received first-line platinum-based chemotherapy

without experiencing 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 to proceed to maintenance therapy with olaparib should be based on a discussion between the patient and 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 OS

benefit demonstrated in the POLO randomized controlled trial.<sup>11</sup>

**Literature review and analysis.** The phase III POLO RCT included patients with metastatic pancreatic cancer and a germline *BRCA1* or *BRCA2* mutation, which were identified via central testing with the use of the BRACAnalysis CDx test or by local testing and confirmation of positive results using BRACAnalysis. Maintenance olaparib was initiated 4 to 8 weeks after the completion of at least 16 weeks of continuous first-line platinum-based chemotherapy without evidence of disease progression or discontinuation because of toxicity (the platinum component of therapy could be discontinued as a result of toxicity after 16 weeks).<sup>11</sup> Nearly one half of patients (49.4%) achieved a complete or partial response to first-line platinum-based therapy. Radiologic disease progression was determined using modified RECIST version 1.1.<sup>19</sup> The primary outcome was PFS, and OS, response rates, and adverse events were also evaluated. PFS was significantly better for patients assigned to olaparib compared with placebo (hazard ratio, 0.53 [95% CI, 0.35 to 0.82]). There were no significant differences between groups for OS, response rate, rate of serious adverse events, or discontinuation of therapy as a result of adverse events; however, the quality of these outcomes was rated as low to very low (ie, high uncertainty; Table 1).

**Clinical interpretation.** The POLO phase III RCT demonstrated a statistically significant improvement in the primary study outcome of PFS. There was no difference in OS between groups in an analysis that was performed at data maturity of 46%. Patients receiving olaparib were more likely to experience serious adverse events and/or discontinue participation in the trial because of adverse events compared with placebo; however, these differences were not statistically significant. Based on the large magnitude of PFS benefit, the Expert Panel concluded that olaparib may be recommended as an option for maintenance therapy for patients with metastatic pancreatic cancer and an identified germline *BRCA* mutation. No head-to-head comparison of chemotherapy and PARP inhibitors was available to inform a recommendation for a preferred option; therefore, clinicians are advised to engage in shared decision making with patients, considering the factors outlined in the qualifying statement after Recommendation 3.3.

## DISCUSSION

This focused update to the ASCO Metastatic Pancreatic Cancer guideline includes new evidence for targeted therapy options after first-line therapy for disease that has progressed, intolerable toxicity, or as maintenance therapy after a response. Since the time of previous update of this guideline in 2018, new evidence has been published for targeted agents that may provide clinical benefit to this patient population, and the FDA has approved new therapy options for the target patient population.

Results for therapy options larotrectinib and entrectinib have been incorporated in this update. Larotrectinib was approved in November 2018 by the FDA as a disease-site agnostic option for solid tumors with *NTRK* fusions.<sup>6</sup> Entrectinib was also approved by the FDA in August 2019 for this indication, as well as for *ROS1*-positive metastatic non-small-cell lung cancer when no other effective treatment options are available and for which first-line therapy has not been effective.<sup>7</sup> These approvals were based on evidence from basket trials in which efficacy of treatment of a specific genomic alteration is evaluated regardless of tumor site.<sup>21</sup> 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>17</sup> and entrectinib (57%),<sup>18</sup> which exceeded the predetermined minimum response rate of 30% that investigators agreed would indicate a clinically meaningful benefit. In addition, adverse events were largely grade 1 and 2 and manageable with dose modifications. Doebele et al<sup>18</sup> note that comparisons between trials of larotrectinib and entrectinib are difficult because of differences between patient populations and study design, and acknowledge that some tumor types are less responsive and that more of these were included in the entrectinib trials, which could account for the lower objective response rate.

PARP inhibitor olaparib is a recommended treatment option as maintenance therapy, based on a statistically significant benefit in PFS compared with placebo. Olaparib was approved by the FDA on December 27, 2019, for the maintenance treatment of adult patients with germline *BRCA* mutations and metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of first-line platinum-based chemotherapy.<sup>8</sup>

In addition, while this targeted update considered only new evidence for recommendations 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 Eastern Cooperative Oncology Group performance status of 2.<sup>22</sup> In response to this, minor modifications to Recommendations 2.3, 3.7, and 3.9 were also included, based on the consensus of the Expert Panel members.

## Biomarker Testing

In conjunction with the recommendation for these newer agents, this guideline update includes a modification to the recommendation for molecular testing to include testing for biomarkers used to select patients for therapy. This recommendation was consensus based. In the case of the recommendation for the treatment of *NTRK* fusion positive cancers, the Expert Panel acknowledged the low prevalence of *NTRK* fusions (ie, approximately 0.34% in patients with pancreatic cancer),<sup>23,24</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 of implementing this testing recommendation, including accessibility and cost—many third-party payors in the United States and international markets (eg, France) 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>23</sup> Each of these options has advantages under different circumstances and for different tumor types. These considerations and others are further addressed in Patient and Clinician Communication. A complete discussion of a molecular biomarker testing algorithm for metastatic pancreatic adenocarcinoma is outside the scope of this guideline. Recommendations for germline genetic testing are contained in the ASCO PCO, Evaluating Susceptibility to Pancreatic Cancer.<sup>10</sup>

### Ongoing Research

Patients can acquire resistance to first-generation TRK inhibitors. To overcome this, trials of newer agents, such as LOXO-195 and TPX-00005, are currently underway.<sup>21</sup> Research is also underway to determine the extent of cancer risk associated with *PALB2* (partner and localizer of *BRCA2*), which occurs in 3% to 4% of cases of familial pancreatic cancer.<sup>25</sup>

### PATIENT AND CLINICIAN COMMUNICATION

Patients with pancreatic cancer face difficult treatment decisions while presented with complex medical information, especially somatic and germline testing information, and a life-threatening diagnosis. Communication within the 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 somatic and germline testing, 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 importance of both somatic and germline testing and the implications of testing on treatment options is a conversation that should be had soon after the patient's diagnosis is confirmed. The clinician must also balance describing the importance of testing while providing realistic hope around the identification of actionable findings. Some actionable mutations are found in a small subset of patients but can have meaningful benefit for those patients. 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 the goals of care and treatment recommendations.

Providers should also describe the potential impact (both medical and emotional aspects) of genetic testing on both the patient with pancreatic cancer and their family. For the patient, germline testing can indicate potentially beneficial treatment options while also identifying a potential risk of pancreatic cancer and other cancers for their family. For additional recommendations and strategies to optimize patient-clinician communication regarding germline testing see ASCO's PCO, Evaluating Susceptibility to Pancreatic Cancer.<sup>10</sup>

Clinicians should clearly explain all potential treatment options, the specific somatic and germline testing needed to determine the appropriateness of those treatment 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. Patients should have the opportunity to participate in trials for their own treatment and 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 addressing of the many non-treatment-related issues patients face, and this referral should be offered to all patients with pancreatic cancer, regardless of the 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 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](http://www.cancer.net)) and the Pancreatic Cancer Action Network ([www.pancan.org](http://www.pancan.org)).

## EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from January 15, 2020, through January 29, 2020. Response categories of “Agree as written,” “Agree with suggested modifications,” and “Disagree. See comments,” were captured for every proposed recommendation with 6 written comments received. A total of 100% of the 6 respondents either agreed or agreed with slight modifications to the recommendations and none of the respondents disagreed. One comment asked “What initial assessment is necessary?” in the context of genetic testing, while emphasizing that the results of testing would not alter the choice of first-line therapy. The Expert Panel clarifies that the intention of conducting testing before treatment is to have this information available in a timely manner in the event that it is relevant for the selection of second-line therapy.

## GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO’s Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative on the guideline panel is to assess the

suitability of the recommendations to implementation in the community setting, but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

***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.***

## ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at <http://www.asco.org/gastrointestinal-cancer-guidelines>. Patient information is available at [www.cancer.net](http://www.cancer.net).

## RELATED ASCO GUIDELINES

- Integration of Palliative Care Into Standard Oncology Practice (<http://ascopubs.org/doi/10.1200/JCO.2016.70.1474>)<sup>26</sup>
- Locally Advanced, Unresectable Pancreatic Cancer (<http://ascopubs.org/doi/10.1200/JCO.2016.67.5561>)<sup>27</sup>
- Potentially Curable Pancreatic Adenocarcinoma (<https://ascopubs.org/doi/10.1200/JCO.19.00946>)<sup>28</sup>
- Evaluating Susceptibility to Pancreatic Cancer Provisional Clinical Opinion (<https://ascopubs.org/doi/10.1200/JCO.18.01489>)<sup>10</sup>
- Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer (<https://ascopubs.org/doi/10.1200/JCO.19.01461>)<sup>29</sup>

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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 supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at [www.cancer.net](http://www.cancer.net), is available at [www.asco.org/gastrointestinal-cancer-guidelines](http://www.asco.org/gastrointestinal-cancer-guidelines).

## AUTHOR CONTRIBUTIONS

**Manuscript writing:** All authors

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI <https://doi.org/10.1200/JCO.20.01364>.

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST****Metastatic Pancreatic Cancer: ASCO Guideline Update**

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## APPENDIX

**TABLE A1.** Metastatic Pancreatic Cancer Guideline Update Expert Panel Membership

Name	Affiliation/Institution	Role/Area of Expertise
Davendra P.S. Sohal, MD, MPH, co-chair	University of Cincinnati, Cincinnati, OH	Medical oncology
Daniel Laheru, MD, co-chair	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD	Medical oncology
Pelin Cinar, MD, MS	University of California, San Francisco, San Francisco, CA	Medical oncology
Thierry Conroy, MD	Université de Lorraine and Institut de Cancérologie de Lorraine, Lorraine, France	Medical oncology
Mehmet S. Copur, MD	Morrison Cancer Center, Hastings, NE	PGIN representative
Christopher H. Crane, MD	Memorial Sloan Kettering Cancer Center, New York, NY	Radiation oncology
Ignacio Garrido-Laguna, MD, PhD	Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT	Medical oncology
Tyler Johnson, MD	Stanford University, Palo Alto, CA	Medical oncology
Smitha Krishnamurthi, MD	Cleveland Clinic, Cleveland, OH	Medical oncology
Michelle W. Lau, MD	Phoenix VA Medical Center, Phoenix, AZ	PGIN representative
Cassadie Moravek	Pancreatic Cancer Action Network, Manhattan Beach, CA	Patient representative
Eileen M. O'Reilly, MD	Memorial Sloan Kettering Cancer Center, New York, NY	Medical oncology
Philip A. Philip, MD, PhD	Barbara Ann Karmanos Cancer Institute Farmington Hills, MI	Medical oncology
Shubham Pant, MD	MD Anderson Cancer Center, Houston, TX	Medical oncology
Vaibhav Sahai, MBBS, MS	University of Michigan, Ann Arbor, MI	Medical oncology
Manish A. Shah, MD	New York Presbyterian/Weill Cornell Medical Center, New York, NY	Medical oncology
Hope E. Uronis, MD, MHS	Duke University, Durham, NC	Medical oncology
Neeha Zaidi, MD	Johns Hopkins Medicine, Baltimore, MD	Medical oncology
Erin B. Kennedy, MHSc	American Society of Clinical Oncology, Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

Abbreviation: PGIN, Practice Guidelines Implementation Network.