Pancreatic Adenocarcinoma, Version 2.2021

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ABSTRACT

Pancreatic cancer is the fourth leading cause of cancer-related death among men and women in the United States. A major challenge in treatment remains patients' advanced disease at diagnosis. The NCCN Guidelines for Pancreatic Adenocarcinoma provides recommendations for the diagnosis, evaluation, treatment, and follow-up for patients with pancreatic cancer. Although survival rates remain relatively unchanged, newer modalities of treatment, including targeted therapies, provide hope for improving patient outcomes. Sections of the manuscript have been updated to be concordant with the most recent update to the guidelines. This manuscript focuses on the available systemic therapy approaches, specifically the treatment options for locally advanced and metastatic disease.

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Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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The complete NCCN Guidelines for Pancreatic Adenocarcinoma are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

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Individual disclosures for the NCCN Pancreatic Adenocarcinoma Panel members can be found on page 457. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.

PRINCIPLES OF SYSTEMIC THERAPY

Locally Advanced Disease (First-Line Therapy)

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Good PS	<ul style="list-style-type: none"> • FOLFIRINOX or modified FOLFIRINOX^{d,e,f,6} • Gemcitabine + albumin-bound paclitaxel^{d,f,7} <p>Only for known BRCA1/2 or PALB2 mutations:</p> <ul style="list-style-type: none"> • FOLFIRINOX or modified FOLFIRINOX^{d,e,f,6} • Gemcitabine + cisplatin¹⁰ 	<ul style="list-style-type: none"> • Gemcitabine + erlotinib^{9,8} • Gemcitabine + capecitabine⁹ • Gemcitabine • Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B) • Fixed-dose-rate gemcitabine, docetaxel, capecitabine (GTX regimen)¹¹ (category 2B) • Fluoropyrimidine + oxaliplatin (5-FU + leucovorin + oxaliplatin [OFF]¹² or CapeOx¹³) (category 2B) 	<ul style="list-style-type: none"> • Induction chemotherapy with any of the preferred/other regimens (≥4–6 cycles) followed by chemoradiation^{b,h} or SBRT¹⁴ (in selected patients, locally advanced disease without systemic metastases)¹⁵ • Chemoradiation^{b,i} or SBRTⁱ (in select patients who are not candidates for combination therapy)
Poor PS	<ul style="list-style-type: none"> • Gemcitabine <ul style="list-style-type: none"> ▶ 1000 mg/m² over 30 minutes, weekly for 3 weeks every 28 days (category 1) ▶ Fixed-dose-rate gemcitabine (10 mg/m²/min) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B) • Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B) 	• None	• None

See Subsequent Therapy on PANC-F (6 of 8)

^b See Chemoradiation (PANC-F, 7 of 8*).^d The recommendations for FOLFIRINOX or modified FOLFIRINOX and gemcitabine + albumin-bound paclitaxel in patients with locally advanced disease are based on extrapolations from randomized trials in patients with metastatic disease.^e Due to the high toxicity of this regimen, bolus 5-FU is often omitted.^f FOLFIRINOX or modified FOLFIRINOX should be limited to those with ECOG 0-1. Gemcitabine + albumin-bound paclitaxel is reasonable for patients with ECOG 0-2. 5-FU + leucovorin + liposomal irinotecan is a reasonable subsequent therapy option for patients with ECOG 0-2.⁹ Although this combination significantly improved survival, the actual benefit was small, suggesting that only a small subset of patients benefit.^h Based on LAP-07 trial data, there is no clear survival benefit with the addition of conventional chemoradiation following gemcitabine monotherapy. Chemoradiation may improve local control and delay the need for resumption therapy.¹⁶ⁱ If patients present with poorly controlled pain or local obstructive symptoms, it may be preferable to start with upfront chemoradiation or SBRT. See Principles of Radiation Therapy (PANC-G*).

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Overview

During the year 2021 in the United States, an estimated 60,430 people will be diagnosed with pancreatic cancer, and approximately 48,220 people are expected to die of the disease.¹ Pancreatic cancer is the fourth most common cause of cancer-related death among US men (after lung, prostate, and colorectal cancer) and women (after lung, breast, and colorectal cancer).¹ Although the incidence is roughly equal in both sexes, African Americans have a higher incidence of pancreatic cancer than white Americans.^{2,3} The incidence of pancreatic cancer in the United States increased from 1999 to 2008, possibly because of the increasing prevalence of obesity, an aging population, and other unknown factors.³⁻⁵ Mortality rates have remained largely unchanged.^{6,7}

In the NCCN Guidelines for Pancreatic Adenocarcinoma, the diagnosis and management of adenocarcinomas of the exocrine pancreas are discussed; neuroendocrine tumors are not included (see the NCCN Guidelines for Neuroendocrine Tumors, available at NCCN.org). These NCCN Guidelines are intended to assist with clinical decision-making, but they cannot

incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the panel members during the process of developing and updating these guidelines. A 5% rule (omitting clinical scenarios that comprise less than 5% of all cases) was used to eliminate uncommon clinical occurrences or conditions from these guidelines. A study of 3,706 patients treated for pancreatic cancer in large California hospitals showed that compliance with these NCCN Guidelines for Pancreatic Adenocarcinoma, defined very permissively, improves survival.⁸

As an overall guiding principle of these guidelines, the panel believes that decisions about diagnostic management and resectability of pancreatic cancer should involve multidisciplinary consultation at high-volume centers with use of appropriate imaging studies. In addition, the panel believes that increasing participation in clinical trials (only 4.6% of patients enroll in a pancreatic cancer trial⁹) is critical to making progress in this disease. Thus, the panel unanimously endorses participation in a clinical trial over standard or accepted therapy.

PRINCIPLES OF SYSTEMIC THERAPY

Metastatic Disease (First-Line Therapy)

• Patients who progress with metastatic disease are not candidates for radiation unless required for palliative purposes.

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Good PS	<ul style="list-style-type: none"> • FOLFIRINOX (category 1) or modified FOLFIRINOX^{e,f,6} • Gemcitabine + albumin-bound paclitaxel^{f,7} (category 1) Only for known BRCA1/2 or PALB2 mutations: <ul style="list-style-type: none"> • FOLFIRINOX (category 1) or modified FOLFIRINOX^{e,f,6} • Gemcitabine + cisplatin¹⁰ 	<ul style="list-style-type: none"> • Gemcitabine + erlotinib^{9,8} (category 1) • Gemcitabine (category 1) • Gemcitabine + capecitabine⁹ • Fixed-dose-rate gemcitabine, docetaxel, capecitabine (GTX regimen)¹¹ (category 2B) • Fluoropyrimidine + oxaliplatin (eg, 5-FU + leucovorin + oxaliplatin [OFF]¹² or CapeOx¹³) (category 2B) 	<ul style="list-style-type: none"> • None
Poor PS	<ul style="list-style-type: none"> • Gemcitabine <ul style="list-style-type: none"> ▶ 1000 mg/m² over 30 minutes, weekly for 3 weeks every 28 days (category 1) ▶ Fixed-dose-rate gemcitabine (10 mg/m²/min) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B) • Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B) 	<ul style="list-style-type: none"> • None 	<ul style="list-style-type: none"> • Pembrolizumab^{j,16} (only for MSI-H or dMMR tumors) • Larotrectinib (if NTRK gene fusion positive) • Entrectinib (if NTRK gene fusion positive) (category 2B)

See Maintenance Therapy for Metastatic Disease on PANC-F (5 of 8)

See Subsequent Therapy on PANC-F (6 of 8)

^e Due to the high toxicity of this regimen, bolus 5-FU is often omitted.

^f FOLFIRINOX or modified FOLFIRINOX should be limited to those with ECOG 0-1. Gemcitabine + albumin-bound paclitaxel is reasonable for patients with ECOG 0-2. 5-FU + leucovorin + liposomal irinotecan is a reasonable subsequent therapy option for patients with ECOG 0-2.

⁹ Although this combination significantly improved survival, the actual benefit was small, suggesting that only a small subset of patients benefit.

^j See NCCN Guidelines for Management of Immunotherapy-Related Toxicities¹.

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Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Pancreatic Adenocarcinoma, an electronic search of the PubMed database was performed to obtain key literature in the field of pancreatic cancer using the following search terms: (pancreatic cancer) OR (pancreatic adenocarcinoma) OR (pancreas adenocarcinoma) OR (pancreas cancer). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.¹⁰

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Practice Guideline; Guidelines; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The potential relevance of the PubMed search citations over the past year was examined. The data from key PubMed articles and articles from additional sources deemed as relevant to these Guidelines and discussed by

the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on NCCN.org.

Risk Factors and Genetic Predisposition

Although the increase in risk is small, pancreatic cancer is firmly linked to cigarette smoking.^{11–16} Exposure to chemicals and heavy metals such as beta-naphthylamine, benzidine, pesticides, asbestos, benzene, and chlorinated hydrocarbons is associated with increased risk for pancreatic cancer,^{17,18} as is heavy alcohol consumption.^{11,13,19–21} Periodontal disease is associated with pancreatic cancer, even when controlling for other risk factors such as gender, smoking, body mass index (BMI), diabetes, and alcohol consumption.²²

An increased BMI is associated with an increased risk for pancreatic cancer,^{19,23–25} with BMI during early adulthood being associated with increased pancreatic cancer

PRINCIPLES OF SYSTEMIC THERAPY

Metastatic Disease (Maintenance Therapy)

- Patients who have response or stable disease after 4–6 months of chemotherapy may undergo maintenance therapy.

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
<ul style="list-style-type: none"> • If previous platinum-based chemotherapy: <ul style="list-style-type: none"> ▸ Olaparib (only for germline <i>BRCA1/2</i> mutations) 	<ul style="list-style-type: none"> • Clinical trial or • If previous first-line FOLFIRINOX: <ul style="list-style-type: none"> ▸ Capecitabine or • If previous first-line gemcitabine + nab-paclitaxel: <ul style="list-style-type: none"> ▸ Gemcitabine + nab-paclitaxel modified schedule (category 2B) ▸ Gemcitabine single agent (category 2B) 	<ul style="list-style-type: none"> • If previous first-line FOLFIRINOX: <ul style="list-style-type: none"> ▸ 5-FU ± irinotecan^k ▸ FOLFOX^l (category 2B)

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^k 5-FU ± irinotecan may be considered for maintenance therapy in the case of oxaliplatin-related progressive neuropathy or allergy to oxaliplatin.

^l While FOLFOX is not commonly used in the maintenance setting, it may be considered as an alternative to irinotecan-based therapy when GI toxicity is a concern.

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mortality.²⁶ A meta-analysis including 22 cohort studies with 8,091 patients with pancreatic cancer showed that those who engage in low levels of physical activity have an increased risk for pancreatic cancer, relative to those who engage in high levels of physical activity (relative risk [RR], 0.93; 95% CI, 0.88–0.98).²⁷ Regarding diet, there is some evidence that increased consumption of red/processed meat and dairy products is associated with an elevation in pancreatic cancer risk,^{28,29} although other studies have failed to identify dietary risk factors for the disease.^{15,30,31} The association between tea consumption and pancreatic cancer risk has been examined, with mostly null associations being found.

Studies examining the association between vitamin D and risk for pancreatic cancer have shown contradictory results. Some data suggest that low plasma 25-hydroxyvitamin D levels may increase the risk for pancreatic cancer.³² A pooled analysis of 9 case-control studies, including 2,963 patients with pancreatic cancer and 8,527 control subjects, showed a positive association between vitamin D intake and pancreatic cancer risk (odds ratio [OR], 1.13; 95% CI, 1.07–1.19; $P < .001$).³³ This

association may be stronger in those with low retinol/vitamin A intake.

Chronic pancreatitis has been identified as a risk factor for pancreatic cancer,^{34–37} with one study demonstrating a 7.2-fold increased risk for pancreatic cancer for patients with a history of pancreatitis.³⁸ A meta-analysis including 2 case-control studies and one cohort study (1,636 patients with pancreatic cancer) showed that hepatitis B infection is associated with pancreatic cancer (OR, 1.50; 95% CI, 1.21–1.87).³⁹ Patients with systemic lupus erythematosus are also suggested to be at an increased risk for pancreatic cancer. In a meta-analysis of 11 cohort studies, patients with systemic lupus erythematosus were found to be an increased risk for developing pancreatic cancer (CI 1.32–1.53, hazard ratio [HR], 1.43).⁴⁰ However, further epidemiologic studies involving careful evaluation of these possible risk factors with adjustments for potential confounders are needed to clarify their impact on pancreatic cancer risk.

Diabetes and Pancreatic Cancer

The association between diabetes mellitus and pancreatic cancer is particularly complicated. A population-based

PRINCIPLES OF SYSTEMIC THERAPY

Subsequent Therapy for Locally Advanced/Metastatic Disease and Therapy for Recurrent Disease

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Good PS	<ul style="list-style-type: none"> • None 	<p>(If prior gemcitabine-based therapy)</p> <ul style="list-style-type: none"> • 5-FU + leucovorin + liposomal irinotecan^{f,17} (category 1 for metastatic disease) • 5-FU + leucovorin + irinotecan (FOLFIRI)¹⁸⁻²⁰ • FOLFIRINOX or modified FOLFIRINOX^f • Oxaliplatin + 5-FU + leucovorin (OFF) • FOLFOX • Capecitabine + oxaliplatin • Capecitabine • Continuous infusion 5-FU <p>(If prior fluoropyrimidine-based therapy)</p> <ul style="list-style-type: none"> • Gemcitabine • Gemcitabine + albumin-bound paclitaxel^f • Gemcitabine + cisplatin (only for known BRCA1/2 or PALB2 mutations) • Gemcitabine + erlotinib • 5-FU + leucovorin + liposomal irinotecan^f (if no prior irinotecan) 	<ul style="list-style-type: none"> • Pembrolizumab^j (only for MSI-H or dMMR tumors) • Larotrectinib (if NTRK gene fusion positive) • Entrectinib (if NTRK gene fusion positive) • Chemoradiation,^{b,c} if not previously given, only an option for: <ul style="list-style-type: none"> ▶ Locally advanced disease if primary site is the sole site of progression ▶ Select patients with recurrent disease in combination with systemic therapy
Poor PS	<ul style="list-style-type: none"> • None 	<ul style="list-style-type: none"> • Gemcitabine <ul style="list-style-type: none"> ▶ 1000 mg/m² over 30 minutes, weekly for 3 weeks every 28 days (category 1) ▶ Fixed-dose-rate gemcitabine (10 mg/m²/min) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B) • Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B) 	<ul style="list-style-type: none"> • Pembrolizumab^j (only for MSI-H or dMMR tumors) • Larotrectinib (if NTRK gene fusion positive) • Entrectinib (if NTRK gene fusion positive) (category 2B)

^b See Chemoradiation (PANC-F, 7 of 8*).

^c If considering chemoradiation due to positive margins, chemotherapy should be given prior to the administration of chemoradiation.

^f FOLFIRINOX or modified FOLFIRINOX should be limited to those with ECOG 0-1. Gemcitabine + albumin-bound paclitaxel is reasonable for patients with ECOG 0-2. 5-FU + leucovorin + liposomal irinotecan is a reasonable subsequent therapy option for patients with ECOG 0-2.

^j See NCCN Guidelines for Management of Immunotherapy-Related Toxicities[†].

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study of 2,122 patients with diabetes found that approximately 1% of patients diagnosed with diabetes who are aged 50 years or younger will be diagnosed with pancreatic cancer within 3 years.⁴¹ Prediabetes may also be associated with increased risk for pancreatic cancer.⁴² A systematic review and dose-response meta-analysis including 9 prospective studies (n=2,408) showed that every 0.56 mmol/L increase in fasting blood glucose is associated with a 14% increase in pancreatic cancer incidence.⁴³

Numerous studies have shown an association between new-onset non-insulin-dependent diabetes and the development of pancreatic cancer,^{41,44-47} especially in those who are elderly, have a lower BMI, experience weight loss, or do not have a family history of diabetes.⁴⁸ In these short-onset cases of diabetes diagnosed prior to pancreatic cancer diagnoses, diabetes is thought to be caused by the cancer, although the physiologic basis for this effect is not yet completely understood.⁴⁹

Long-term diabetes, conversely, appears to be a risk factor for pancreatic cancer, as some studies have shown an association of pancreatic cancer with diabetes of 2- to 8-year duration.⁵⁰ However, certain risk factors such as obesity, associated with both diabetes and

pancreatic cancer, may confound these analyses.⁵¹ A meta-analysis including 44 studies showed that the strength of the association between diabetes and pancreatic cancer risk decreases with duration of diabetes, potentially due to the effects of long-term treatment of diabetes.⁵²

The use of diabetic medications such as insulin and sulfonylureas has been found to be associated with an increased risk for pancreatic cancer.⁵³⁻⁵⁵ On the other hand, metformin may be associated with a reduced risk for pancreatic and other cancers,⁵³⁻⁵⁸ though a retrospective cohort study (n=980) showed that metformin did not significantly improve survival in diabetic patients diagnosed with pancreatic cancer.⁵⁹

In addition, diabetes and diabetic medication may affect outcomes in patients with pancreatic cancer. Metformin use has been reported to result in higher pancreatic cancer survival in patients with diabetes. A retrospective analysis of 302 patients with pancreatic cancer and diabetes treated at The University of Texas MD Anderson Cancer Center found that metformin use was associated with increased survival at 2 years (30.1% vs 15.4%; $P=.004$) and increased overall survival (OS; 15.2 vs 11.1 months; $P=.009$).⁶⁰ The OS difference was

significant only in patients without distant metastases and remained significant when insulin users were excluded. In contrast, data from a meta-analysis of more than 38,000 patients show that those with pancreatic cancer and diabetes have a significantly lower OS than those without diabetes (14.4 vs 21.7 months; $P < .001$).⁴⁶ A similar result was seen in a prospective cohort study, in which the survival of 504 patients with and without diabetes who developed pancreatic cancer in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial was compared.⁶¹ After multivariable adjustment, mortality was significantly higher in participants with diabetes compared with those without (HR, 1.52; 95% CI, 1.14–2.04; $P < .01$).

Genetic Predisposition

Pancreatic cancer is thought to have a familial component in approximately 10% of cases, and familial excess of pancreatic cancer is associated with high risk.^{15,62–65} A retrospective review of 175 families in which a family history of pancreatic cancer was present showed that a genetic mutation was present in 28% of families.⁶⁶ A prospective registry-based study of 5,179 individuals from 838 kindreds found that having just 1 first-degree relative with pancreatic cancer raises the risk for pancreatic cancer by 4.6-fold, whereas having 2 affected first-degree relatives raises the risk by about 6.4-fold.⁶⁷ An analysis of 9,040 family members of 1,718 kindreds with pancreatic cancer showed that a family history of early-onset pancreatic cancer (ie, <50 years) was associated with greater risk of pancreatic cancer (standardized incidence ratio, 9.31; 95% CI, 3.42–20.28; $P < .001$), and lifetime risk of pancreatic cancer increases as the age of onset decreases (HR, 1.55; 95% CI, 1.19–2.03 per year).⁶⁸ The genetic basis of this inherited predisposition is not known in most cases, and as many as 80% of patients with a family history of pancreatic cancer have no known genetic cause.⁶² The genes most commonly associated with pathogenic germline alterations are *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *CDKN2A*, and *TP53*.⁶⁹ Germline mutations in the *STK11* gene result in Peutz-Jeghers syndrome, in which individuals have gastrointestinal polyps and an increased risk for colorectal cancer.^{70–72} These individuals also have a highly elevated risk for developing pancreatic cancer, reported to be increased by as much as 132-fold.^{73,74} Furthermore, *STK11* undergoes somatic mutation in approximately 5% of pancreatic cancers.⁷⁵

As with nonhereditary forms of pancreatitis, familial pancreatitis is also associated with an increased risk for pancreatic cancer.⁷⁶ Several genes are associated with the familial form of pancreatitis, including *PRSS1*, *SPINK1*, and *CFTR*.⁷⁷ The increased risk for the development of pancreatic cancer in these individuals is estimated to be 26-fold to as high as 87-fold.^{35,78–80}

Familial malignant melanoma syndrome (also known as melanoma-pancreatic cancer syndrome or familial atypical multiple mole melanoma [FAMMM]) syndrome is caused by germline mutation of the *CDKN2A* (p16INK4a/p14ARF) gene.⁸¹ This syndrome is associated with a 20- to 47-fold increased risk for pancreatic cancer.^{82,83} In addition, patients with Melanoma-Pancreatic Cancer syndrome may experience an earlier onset of pancreatic cancer than the general population.⁸⁴

Lynch syndrome is the most common form of genetically determined colorectal cancer predisposition and is caused by germline mutations in DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*).^{85–90} Patients with Lynch syndrome also have an estimated 9- to 11-fold elevated risk for pancreatic cancer.^{91,92} In a sample of 96 patients with pancreatic cancer, 2 mutations were found in the *MSH6* MMR gene.⁹³

Microsatellite instability (MSI) is also a prognostic factor for survival in many cancers, notably for colon cancer although rare in pancreatic adenocarcinoma. Microsatellites are regions of coding and noncoding DNA where short sequences or single nucleotides of DNA are repeated. MSI is caused by a loss of DNA MMR activity. Mutations in germline MMR genes result in a lack of repair of any errors, such as destabilizing errors introduced during DNA replication that shorten or lengthen microsatellites, which then persist in somatic cells. Tumor samples can be assessed for the sizes of microsatellite markers and classified as MSI high (MSI-H), low (MSI-L), and stable (MSS).^{87,90} The NCCN Panel recommends MSI testing and/or MMR testing on available tumor tissue for patients with locally advanced or metastatic pancreatic adenocarcinoma.

An excess of pancreatic cancer is also seen in families harboring *BRCA1/2* (breast cancer susceptibility gene-1 and -2) mutations, although the link with *BRCA2* is better established.^{93–100} Studies of unselected patients with pancreatic cancer have detected *BRCA1/2* mutations at a frequency of 4%–7%.^{101,102} The risk for pancreatic cancer is elevated 2- to 6-fold in these patients, and the age of onset is younger than average in the general population.^{94,98,99} Patients with pancreatic cancer who have Ashkenazi Jewish ancestry may have a greater likelihood of testing positive for a *BRCA1/2* mutation, with prevalence of detected mutations in this group ranging from 5.5% to 19%, with mutations being more common for *BRCA2*.^{96,102–104}

BRCA1/2 is also involved in the Fanconi DNA anemia/*BRCA* pathway. This pathway is responsible for the repair of DNA interstrand cross-links, and particular mutations in other Fanconi anemia/*BRCA* pathway genes, including in *PALB2*, *FANCC*, and *FANCG*, have also been identified as increasing pancreatic cancer susceptibility.^{100,105–107}

Whole-genome sequencing allowed for the identification of germline mutations in *ATM*, a DNA damage response gene, in 2 kindreds with familial pancreatic cancer.¹⁰⁸ Further

analyses then revealed *ATM* mutations in 4 of 166 individuals with familial pancreatic cancer. In a sample of 96 patients with pancreatic cancer, 4% had a mutation in *ATM*.⁹³

Patients with pancreatic cancer for whom a hereditary cancer syndrome is suspect should be considered for genetic counseling.¹⁰⁹ The panel emphasizes the importance of taking a thorough family history when seeing a new patient with pancreatic cancer. In particular, a family history of pancreatitis, melanoma, and cancers of the pancreas, colorectum, breast, and ovaries should be noted. A free online pancreatic cancer risk prediction tool, called PancPRO, is available and may help determine risk.⁶⁵ Referral for genetic counseling may be considered for patients diagnosed with pancreatic cancer, especially those who have a family history of cancer or who are young, as well as those of Ashkenazi Jewish ancestry. The panel recommends germline testing in any patient with confirmed pancreatic cancer and in those in whom there is a clinical suspicion for inherited susceptibility (see the NCCN Guidelines for Genetic/Familial High-Risk Assessment, Breast, Ovarian, and Pancreatic, available at NCCN.org). The panel currently does not identify a specific age to define early-onset pancreatic cancer, though age 50 has been used in previous studies of familial pancreatic cancer.⁶⁸ If a cancer syndrome is identified, at-risk relatives should be offered genetic counseling. With or without a known syndrome, individuals with a suspicious family history should be advised on risk-reducing strategies including smoking cessation and weight loss. In addition, the possibility of screening for pancreatic (see subsequent section) and other cancers should be discussed. For patients with locally advanced or metastatic disease who are candidates for anticancer therapy, the NCCN Panel recommends testing for actionable somatic mutations, including but not limited to fusions (*ALK*, *NRG1*, *NTRK*, *ROS1*), mutations (*BRAF*, *BRCA 1/2*, *HER2*, *KRAS*, *PALB2*), and MMR deficiency.

Premalignant Tumors of the Pancreas

Mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are cystic lesions that can be small and asymptomatic and are often discovered incidentally; MCNs have an ovarian-like stroma.^{110–112} IPMNs can occur in the main duct and/or in the branch ducts. Lesions involving the main duct have a higher malignant potential than those in the branches, with the risk of malignancy at around 62%.¹¹³ The risk of malignancy in MCNs is <15%.¹¹³

An international group of experts has established guidelines for the management of pancreatic IPMNs and MCNs,¹¹⁴ as has a European group.¹¹⁵ The international group strongly recommends resection in fit patients with main duct IPMNs ≥ 10 mm.¹¹³ For branch-duct IPMNs, surveillance is considered an appropriate option in patients

who are older or unfit or for cysts lacking high-risk stigmata. Branch-duct IPMNs that have an enhancing mural nodule ≥ 5 mm, or are in the head of the pancreas causing obstructive jaundice should be considered for resection.¹¹³ Patients with resected IPMNs are followed with imaging studies to identify recurrences. For MCNs, the international group recommends resection for all fit patients, and recurrences are not observed.¹¹³ The European group gives similar recommendations.¹¹⁵

Systemic Therapy Approaches for Locally Advanced or Metastatic Disease

The data supporting the regimens used in pancreatic cancer are described in subsequent sections (also summarized in Table 2, available in these guidelines at NCCN.org).

FOLFIRINOX and Modified FOLFIRINOX

In 2003, a French group reported the results of an open phase I study to assess the feasibility of a combination therapy consisting of 5-FU/leucovorin plus oxaliplatin and irinotecan (FOLFIRINOX) for the treatment of patients with metastatic solid tumors.¹¹⁶ Their study included 2 patients with pancreatic cancer, and the regimen showed antitumor activity. A subsequent multicenter phase II trial specifically for patients with advanced pancreatic adenocarcinoma demonstrated promising response rates.¹¹⁷ A later randomized phase II trial showed a response rate of >30% to FOLFIRINOX in patients with metastatic pancreatic cancer.¹¹⁸

Results from the randomized phase III PRODIGE trial evaluating FOLFIRINOX versus gemcitabine in patients with metastatic pancreatic cancer and good performance status showed dramatic improvements in both median progression-free survival (PFS) (6.4 vs 3.3 months; $P<.001$) and median OS (11.1 vs 6.8 months; $P<.001$), in favor of the group receiving FOLFIRINOX.¹¹⁹ Eligibility criteria for this trial, however, were stringent, limiting real-world generalizability.¹²⁰ For example, patients with abnormal bilirubin levels were excluded from participating.

A systematic review including 11 studies and 315 patients with locally advanced pancreatic cancer showed a pooled median OS of 24.2 months (95% CI, 21.7–26.8).¹²¹ An observational study including 101 patients with locally advanced unresectable disease who were treated with FOLFIRINOX as induction therapy showed that 29% of the sample (20% without administration of chemoradiation) had a reduction in tumor size of greater than 30%, and half of the patients who experienced a reduction in tumor size underwent resection.¹²² Out of the patients who underwent resection, 55% achieved an R0 resection.

Because of the strong results from the PRODIGE trial, FOLFIRINOX is included as a preferred, category 1 recommendation for first-line treatment of patients with good performance status (ie, ECOG 0-1) with

metastatic pancreatic cancer. It is listed as a category 2A recommendation for patients with locally advanced disease by extrapolation. The panel also lists this regimen as an acceptable option in the neoadjuvant/borderline resectable setting.

There are some concerns about the toxicity of the FOLFIRINOX regimen. In the PRODIGE trial, some of the grade 3-4 toxicity rates that were significantly greater in the FOLFIRINOX group than in the gemcitabine group were 45.7% for neutropenia, 12.7% for diarrhea, 9.1% for thrombocytopenia, and 9.0% for sensory neuropathy.¹¹⁹ Despite the high levels of toxicity, no toxic deaths have been reported.¹¹⁷⁻¹¹⁹ Furthermore, the PRODIGE trial determined that, despite this toxicity, fewer patients in the FOLFIRINOX group than in the gemcitabine group experienced a degradation in their quality of life at 6 months (31% vs 66%, $P<.01$).¹¹⁹ A more detailed analysis of the quality of life of patients in this trial was published and showed that FOLFIRINOX maintained and even improved quality of life more so than gemcitabine.¹²³

The panel appreciates that the toxicity of FOLFIRINOX can be managed with a variety of approaches. For example, a group from Memorial Sloan Kettering Cancer Center reported good activity and acceptable toxicity of first-line FOLFIRINOX at 80% dose intensity with routine growth factor support in carefully selected patients with metastatic or locally advanced disease.¹²⁴ Median OS was 12.5 months in the metastatic setting and 13.7 months in patients with locally advanced disease.

The efficacy and toxicity of a modified FOLFIRINOX regimen in which the initial dosing of bolus 5-FU and irinotecan were each reduced by 25% were assessed in a phase II single-arm prospective trial ($n=75$).¹²⁵ In patients with metastatic disease, the efficacy of the modified regimen was comparable to that of the standard regimen (median OS, 10.2 months). In patients with locally advanced disease, the median OS was 26.6 months. Patients who received the modified regimen experienced significantly less neutropenia, fatigue, and vomiting, relative to patients who received the standard FOLFIRINOX regimen. Thus, to reduce the toxicity associated with FOLFIRINOX and improve its tolerability, the modified FOLFIRINOX regimen is also included as a preferred treatment option.

Gemcitabine Monotherapy

For patients with locally advanced or metastatic disease, gemcitabine has been established as providing clinical benefit and a modest survival advantage over treatment with bolus 5-FU.¹²⁶ The panel recommends gemcitabine monotherapy as one option for front-line therapy for patients with locally advanced or metastatic disease (category 1) disease and a good performance status. Because the approved indications for gemcitabine include

the relief of symptoms, the panel also recommends gemcitabine monotherapy as a reasonable first-line and second-line option for symptomatic patients with locally advanced or metastatic disease with poor performance status (category 1).

Gemcitabine monotherapy also has category 1 evidence supporting its use in the adjuvant setting. In the large phase III CONKO-001 trial, in which 368 patients without prior chemotherapy or radiation therapy were randomly assigned to adjuvant gemcitabine versus observation after macroscopically complete resection, an intention-to-treat analysis of the data showed that the primary endpoint of increased DFS was met (13.4 vs 6.9 months; $P<.001$, log rank).¹²⁷ Final results from this study showed median OS to be improved significantly for patients in the gemcitabine arm (22.8 vs 20.2 months; HR, 0.76; 95% CI, 0.61–0.95; $P=.01$).¹²⁸ An absolute survival difference of 10.3% was observed between the 2 groups at 5 years (20.7% vs 10.4%).¹²⁸

Gemcitabine Response: hENT1

Human equilibrative nucleoside transporter 1 (hENT1) is a nucleoside transporter that has been studied as a predictor for response to gemcitabine.¹²⁹ Preliminary clinical data showed that hENT1 expression may in fact predict response to gemcitabine.¹³⁰⁻¹³⁵

hENT1 was validated as a predictive biomarker for benefit from gemcitabine in the adjuvant setting. A meta-analysis including 7 studies with 770 patients with resected pancreatic cancer showed that hENT1 expression was associated with DFS (HR, 0.58; 95% CI, 0.42–0.79) and OS (HR, 0.52; 95% CI, 0.38–0.72) in patients who received adjuvant gemcitabine, but not in patients who received adjuvant fluoropyrimidine-based therapy.¹³⁶ Two retrospective analyses from ESPAC-3 and RTOG-9704 found the same results, although results from the adjuvant CONKO-001 trial and the AIO-PK0104 trial were unable to confirm these results using a different antibody for the immunohistochemical analysis (SP120).^{137,138}

Unfortunately, hENT1 could not be validated in the metastatic setting in the LEAP trial, which also used the SP120 assay to determine hENT1 expression.

Further studies based on hENT1 expression using the 10D7G2 assay are limited by the fact that no commercial source of the antibody and no CLIA-approved testing are available.

Fixed-Dose-Rate Gemcitabine

Studies have suggested that the infusion rate of gemcitabine may be important for its efficacy. Gemcitabine is a prodrug, which must be phosphorylated for antitumor activity. Clinical studies have shown that administering gemcitabine at a fixed dose rate (FDR) maximizes intracellular concentrations of the phosphorylated forms of

gemcitabine.¹³⁹ In a randomized phase II trial of patients with locally advanced or metastatic pancreatic cancer, the infusion of gemcitabine at an FDR led to better survival compared with gemcitabine delivered at a higher dose, over 30 minutes.¹⁴⁰ In the phase III randomized ECOG-6201 trial of patients with advanced pancreatic cancer, median survival was increased in the group receiving FDR gemcitabine versus standard gemcitabine (6.2 vs 4.9 months; $P=.04$), although this outcome did not satisfy the protocol-specified criteria for superiority.¹⁴¹ When gemcitabine is considered for the treatment of advanced pancreatic cancer, the NCCN Panel views FDR gemcitabine (10 mg/m²/min) as a reasonable alternative to the standard infusion of gemcitabine over 30 minutes (category 2B).

FDR gemcitabine is incorporated into some commonly used gemcitabine-based regimens (eg, GEMOX [gemcitabine and oxaliplatin]; GTX [gemcitabine, docetaxel, and capecitabine]). See Gemcitabine Combinations, next section.^{142,143} The combination of FDR gemcitabine and capecitabine has also been found to be active and well-tolerated.¹⁴⁴

Gemcitabine Combinations

The NCCN Panel acknowledges that, historically, combination chemotherapy did not appear to be superior to monotherapy in the era of 5-FU-based therapy. However, because gemcitabine is superior to bolus 5-FU in the advanced setting when efficacy endpoints of survival and relief from symptoms are used, it is now often combined with other chemotherapeutic agents for patients with good performance status. Gemcitabine has been investigated in combination with potentially synergistic agents (such as cisplatin, oxaliplatin, capecitabine, 5-FU, and irinotecan) or in a multidrug combination (eg, cisplatin, epirubicin, gemcitabine, 5-FU).^{141–143,145–155} Two meta-analyses of randomized controlled trials (RCTs) found that gemcitabine combinations give a marginal benefit in OS over gemcitabine monotherapy in the advanced setting, with a significant increase in toxicity.^{156,157}

Combinations recommended in the advanced setting are discussed subsequently. The panel does not consider the combination of gemcitabine plus docetaxel¹⁵⁸ or gemcitabine plus irinotecan^{155,158,159} to meet the criteria for inclusion in the guidelines. In addition, gemcitabine plus sorafenib is not recommended. The multicenter, double-blind, placebo-controlled, randomized phase III BAYPAN trial compared gemcitabine plus either sorafenib or placebo in chemotherapy-naïve patients with advanced or metastatic disease.¹⁶⁰ This trial did not meet its primary endpoint of PFS in its 104 patients (5.7 vs 3.8 months; $P=.90$). Gemcitabine combinations are currently being used and studied in the adjuvant setting.

Of note, results from several studies have indicated that the benefit of gemcitabine combination

chemotherapy is predominantly seen in patients with good performance status.^{149,150,152}

Gemcitabine Plus Albumin-Bound Paclitaxel

Albumin-bound paclitaxel is a nanoparticle form of paclitaxel. In a publication of a phase I–II trial, 67 patients with advanced pancreatic cancer received gemcitabine plus albumin-bound paclitaxel. At the maximum tolerated dose, the partial response rate was 48%, with an additional 20% of patients demonstrating stable disease for 16 or more weeks. The median OS at this dose was 12.2 months.¹⁶¹

Based on these results, the large, open-label, international, randomized, phase III MPACT trial was initiated in 861 patients with metastatic pancreatic cancer and no prior chemotherapy.¹⁶² Participants were randomized to receive gemcitabine plus albumin-bound paclitaxel or gemcitabine alone. The trial met its primary endpoint of OS (8.7 vs 6.6 months; $P<.0001$; HR, 0.72).¹⁶² The addition of albumin-bound paclitaxel also improved other endpoints, including 1-year survival, 2-year survival, response rate, and PFS. OS was associated with a decrease in CA 19-9 (HR, 0.53; 95% CI, 0.36–0.78; $P=.001$).¹⁶³ Tumor response was validated with PET imaging.¹⁶⁴ The most common grade 3 or higher adverse events attributable to albumin-bound paclitaxel were neutropenia, fatigue, and neuropathy. Development of peripheral neuropathy was associated with longer treatment duration and greater treatment efficacy.¹⁶⁵ Updated results of the MPACT trial show that long-term survival is possible with gemcitabine plus albumin-bound paclitaxel, as 3% of patients from that arm were alive at 42 months, whereas no patients were alive from the control arm at that time.¹⁶⁶ Factors associated with survival in this trial include Karnofsky performance status score and absence of liver metastases.¹⁶⁷

Gemcitabine plus albumin-bound paclitaxel is a category 1 recommendation for the treatment of patients with metastatic disease and good performance status based on these results, and is listed as a preferred option in this setting. Good performance status for this regimen is defined as ECOG 0–2, since the clinical trial used Karnofsky performance status ≥ 70 as an eligibility criterion.^{162,166} Therefore, some patients with an ECOG score of 2 may be eligible to receive this regimen.^{168,169} By extrapolation of the data, the panel recommends this combination in the locally advanced, good performance status setting as well (category 2A). The panel also notes that this combination is an acceptable option in the neoadjuvant/borderline resectable setting.

Gemcitabine Plus Cisplatin

Data regarding the survival impact of combining gemcitabine with a platinum agent are conflicting, and results of RCTs have not provided support for use of gemcitabine plus cisplatin in the treatment of patients with advanced

pancreatic cancer. Three phase III trials evaluating the combination of gemcitabine with cisplatin versus gemcitabine alone in patients with advanced pancreatic cancer failed to show a significant survival benefit for the combination over the single agent.^{146,147,150}

Nevertheless, selected patients may benefit from this regimen because patients with breast and ovarian cancers who are carriers of a *BRCA* mutation^{170–172} and selected patients with inherited forms of pancreatic cancer⁹⁶ may have disease that is particularly sensitive to a platinum agent. A retrospective study from Johns Hopkins University School of Medicine of patients with metastatic pancreatic cancer and a family history of breast, ovarian, or pancreatic cancers suggested that response to gemcitabine and cisplatin was superior even with one affected relative.¹⁷³ Patients with a family history of pancreatic cancer alone demonstrated a large survival advantage when treated with platinum-based chemotherapy (6.3 vs 22.9 months; HR, 0.34; 95% CI, 0.15–0.74; $P < .01$).¹⁷³ Furthermore, a report of 5 of 6 patients with known *BRCA* mutations and metastatic pancreatic adenocarcinoma treated with a platinum-based regimen at Memorial Sloan Kettering Cancer Center showed a radiographic partial response.¹⁷⁴ Thus, gemcitabine plus cisplatin may be a good choice in selected patients with disease characterized by hereditary risk factors (eg, *BRCA* or *PALB2* mutations). The panel recommends gemcitabine plus cisplatin for patients with metastatic or locally advanced disease, only for known *BRCA1/2* or *PALB2* mutations. FOLFIRINOX and modified FOLFIRINOX are also possible treatment options for patients with *BRCA 1/2* and *PALB2* mutations.

Gemcitabine Plus Erlotinib and Other Targeted Therapeutics

Results of phase III studies of combinations of gemcitabine with a biologic agent have indicated that only the combination of gemcitabine plus erlotinib is associated with a statistically significant increase in survival when compared with gemcitabine alone.^{175–179} In the phase III, double-blind, placebo-controlled NCIC CTG PA.3 trial of 569 patients with advanced or metastatic pancreatic cancer randomly assigned to receive erlotinib (which is an inhibitor of epidermal growth factor receptor tyrosine kinase) plus gemcitabine versus gemcitabine alone, patients in the erlotinib arm showed statistically significant improvements in OS (HR, 0.82; $P = .038$) and PFS (HR, 0.77; $P = .004$) when compared with patients receiving gemcitabine alone.¹⁷⁵ Median survival was 6.24 months and 1-year survival was 23%, compared with 5.91 months and 17% in the control arm. Adverse events, such as rash and diarrhea, were increased in the group receiving erlotinib, but most were grade 1 or 2.¹⁷⁵ This trial, other trials, and community experience show that occurrence of grade 2 or higher skin

rash is associated with better response and OS of patients receiving erlotinib.^{175,180,181}

The NCCN Panel recommends the gemcitabine-erlotinib combination therapy as a treatment option, under other recommended regimens, for patients with locally advanced or metastatic disease and good performance status, with this combination being a category 1 recommendation for patients with metastatic disease. However, the panel notes that although this combination significantly improved survival, the actual benefit was small, suggesting that only a small subset of patients benefit.

Gemcitabine Plus Capecitabine

A number of randomized trials have investigated the combination of gemcitabine with capecitabine, a fluoropyrimidine, in patients with advanced pancreatic cancer. A randomized study in 533 patients with advanced disease found that PFS and objective response rates were significantly improved in patients receiving gemcitabine plus capecitabine when compared with gemcitabine alone, although a trend toward an improvement in OS for the combination arm did not reach statistical significance.¹⁴⁸ Similarly, results from another smaller phase III trial evaluating this combination did not demonstrate an OS advantage for overall study population receiving the combination of gemcitabine with capecitabine, although a posthoc analysis showed OS to be significantly increased in the subgroup of patients with good performance status.¹⁵² Results from a third randomized phase III trial also showed that gemcitabine with capecitabine did not significantly improve OS, compared with gemcitabine alone, though patients who received gemcitabine with capecitabine had a greater overall response rate (ORR), compared with patients who received gemcitabine only (43.7% vs 17.6%, respectively; $P = .001$).¹⁸² In a meta-analysis of 8 RCTs, OS was better in patients receiving gemcitabine plus capecitabine than in patients receiving gemcitabine alone (HR, 0.87; $P = .03$).¹⁸³ Although there are concerns about dosing and toxicity of capecitabine in a US population, a biweekly regimen of fixed-dose gemcitabine in combination with capecitabine may be both effective and well-tolerated in patients with advanced disease.¹⁴⁴

The panel includes the combination of gemcitabine, docetaxel, and capecitabine (GTX regimen) as a category 2B recommendation for the treatment of patients with metastatic or locally advanced disease and good performance status. In a report of 35 patients with metastatic pancreatic cancer treated with this regimen, the authors reported an ORR of 29% (all had partial responses), with an additional 31% of patients exhibiting a minor response or stable disease.¹⁴³ The median survival was 11.2 months for all patients and 13.5 months for patients exhibiting a partial response. This regimen demonstrated significant toxicities, however, with 14% of patients having grade 3–4 leukopenia,

14% having grade 3-4 thrombocytopenia, and 9% having grade 3/4 anemia. A retrospective case-review study at The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins found similar results, with a median OS of 11.6 months and grade 3 or greater hematologic and nonhematologic toxicity rates of 41% and 9%, respectively.¹⁸⁴

Gemcitabine combined with capecitabine and oxaliplatin (GEMOXEL) was recently assessed in a randomized phase II trial (n=67) for the metastatic setting.¹⁸⁵ Disease control rate ($P=.004$), PFS ($P<.001$), and OS ($P<.001$) were all superior in patients randomized to receive the GEMOXEL regimen, compared with patients randomized to receive gemcitabine alone.

The NCCN Panel considers gemcitabine-based combination therapy with capecitabine to be a reasonable option (category 2A) for patients with locally advanced or metastatic disease and a good performance status who are interested in pursuing more aggressive therapy outside a clinical trial.

Gemcitabine and Other Fluoropyrimidine-Based Therapies

Gemcitabine has been examined in combination with other fluoropyrimidine-based therapies. A recent meta-analysis of 8 RCTs, including more than 2,000 patients, found that OS was significantly improved when a fluoropyrimidine was added to gemcitabine.¹⁸³ In a phase II randomized trial, the effects of the FIRGEM regimen [irinotecan delivered before and after infusion of 5-FU/leucovorin (FOLFIRI.3), alternating with FDR gemcitabine] were assessed in 98 patients with metastatic pancreatic cancer.¹⁸⁶ Patients were randomized to receive the FIRGEM regimen or FDR gemcitabine monotherapy. The primary objective of a 45% PFS rate at 6 months was reached, and PFS was a median of 5.0 months in those randomized to receive the FIRGEM regimen, while those randomized to receive only gemcitabine had a median PFS of 3.4 months (HR, 0.59; 95% CI, 0.38–0.90). Rates of hematologic toxicity were higher in those who received the FIRGEM regimen, relative to those who received gemcitabine only. Study investigators deemed FIRGEM to be effective and feasible in the metastatic setting.

The ECOG E2297 trial compared gemcitabine monotherapy with gemcitabine and bolus 5-FU/leucovorin in patients with advanced pancreatic cancer; no statistically significant survival advantage was observed for patients receiving the combination regimen.¹⁴⁵

Recent randomized trials from Asia show that gemcitabine combined with the oral fluoropyrimidine S-1 may improve response and survival in patients with locally advanced pancreatic cancer, though trial results are inconsistent regarding whether outcomes are improved over gemcitabine monotherapy.^{187–189}

Capecitabine and Continuous Infusion 5-FU

The panel lists capecitabine monotherapy and continuous infusion 5-FU as first-line and second-line treatment options for patients with locally advanced disease (category 2B), and for patients with poor performance status and metastatic disease (category 2B). They are also recommended as options in the adjuvant settings (category 2A for continuous infusion 5-FU and category 2B for capecitabine). The capecitabine recommendation is supported by a randomized phase III trial from the Arbeitsgemeinschaft Internistische Onkologie (AIO) group in which OS was similar in patients with advanced pancreatic cancer receiving capecitabine plus erlotinib followed by gemcitabine monotherapy or gemcitabine plus erlotinib followed by capecitabine monotherapy.¹⁹⁰

Note that the capecitabine dose recommended by the panel (1,000 mg/m² by mouth twice daily) is less than the dose described by Cartwright et al, because the higher dose has been associated with increased toxicity (eg, diarrhea, hand and foot syndrome).¹⁹¹

Fluoropyrimidine Plus Oxaliplatin

The combination of a fluoropyrimidine (5-FU/leucovorin or capecitabine) with oxaliplatin is listed as a possible first-line treatment of metastatic or locally advanced disease (category 2B). The panel bases these recommendations on the randomized phase III CONKO-003 trial (5-FU/leucovorin/oxaliplatin [OFF] vs best supportive care) and on a phase II study (CapeOx).^{192,193} Both of these studies only enrolled patients who had received 1 prior chemotherapy regimen, but the panel feels the extrapolation to first-line therapy is appropriate (category 2B).

Maintenance Therapy in Advanced Disease

With the success of more effective regimens in patients with advanced disease, questions have been raised about how best to manage the treatment-free interval prior to disease progression. Options include continuing systemic therapy, stopping treatment, dropping the most toxic agents, and using different agents for maintenance therapy.

Based on the fact that the BRCA genes encode for proteins involved in homologous recombination repair and that cells with mutations are sensitive to poly (ADP ribose) polymerase (PARP) inhibitors, the efficacy of olaparib, a PARP inhibitor, was investigated. In a phase II trial assessing its efficacy and safety, the tumor response rate for patients with metastatic pancreatic cancer and a germline *BRCA1/2* mutation (n=23) was 21.7% (95% CI, 7.5–43.7).¹⁹⁴ Following this, in the randomized, double-blind, placebo-controlled phase 3 POLO trial, olaparib was found to be an effective maintenance therapy agent for patients with metastatic pancreatic cancer and germline *BRCA 1/2* mutations and no disease progression following at least 16 weeks of first-line platinum-based therapy. A total of 154

patients were randomized to receive either olaparib or placebo. In the olaparib arm, the median PFS was 7.4 months compared with 3.8 months in the placebo arm (95% CI 0.35-0.82, $P=.004$). At interim, however, there was found to be no difference in OS between the olaparib and placebo groups (18.9 vs 16.1 months, 95% CI 0.56-1.46, $P=.68$). Adverse events, such as those grade 3 or higher, were found to be higher in the olaparib arm than in the placebo arm (40% vs 23%).¹⁹⁵ Based on this data, olaparib is recommended by the NCCN Panel as a preferred targeted maintenance therapy for patients with germline *BRCA*-mutated metastatic disease and no disease progression after 4 to 6 months of first-line platinum-based therapy. Other maintenance therapy options for patients include clinical trial enrollment; gemcitabine-based therapy for patients who received previous first-line gemcitabine and nab-paclitaxel; or capecitabine, 5-FU with or without irinotecan, or FOLFOX for patients who received previous FOLFIRINOX. The NCCN Panel has included 5-FU with or without irinotecan for patients who exhibited oxaliplatin-related progressive neuropathy or allergy. Finally, if irinotecan-related gastrointestinal toxicity is of concern, then FOLFOX may be a suitable maintenance therapy.

Subsequent Therapy in the Advanced Setting

A systematic review of clinical trials that assessed the efficacy of subsequent therapy after gemcitabine in pancreatic cancer concluded that, while data are very limited, evidence suggests an advantage of additional chemotherapy over best supportive care.¹⁹⁶ For patients with advanced disease who have received prior gemcitabine-based therapy, fluoropyrimidine-based chemotherapy regimens are acceptable subsequent options.^{192,193,197,198} Gemcitabine-based therapy can be given to those previously treated with fluoropyrimidine-based therapy.

Results from the phase III CONKO-003 trial showed significant improvements in both median PFS (13 vs 9 weeks; $P=.012$) and median OS (20 vs 13 weeks; $P=.014$) when oxaliplatin was added to 5-FU/leucovorin,^{199,200} making this regimen the standard approach for subsequent therapy for patients without prior exposure to fluoropyrimidine-based therapy at that time. Final results of the trial were published in 2014.²⁰¹ The median OS in the OFF arm was 5.9 months (95% CI, 4.1–7.4), whereas it was 3.3 months (95% CI, 2.7–4.0) in the 5-FU/leucovorin arm, for a significant improvement in the HR (0.66; 95% CI, 0.48–0.91; $P=.01$).

However, results from the open-label phase III PANCREOX trial show that the addition of oxaliplatin to 5-FU/leucovorin (OFF) in subsequent treatment may be detrimental.²⁰² In this trial, 108 patients with advanced pancreatic cancer who progressed on gemcitabine-based treatment were randomized to receive second-line mFOLFOX6 or

infusional 5-FU/leucovorin. No difference was seen in median PFS (3.1 vs 2.9 months; $P=.99$), but median OS was worse in those in the FOLFOX arm (6.1 vs 9.9 months; $P=.02$). Furthermore, the addition of oxaliplatin resulted in increased toxicity, with rates of grade 3/4 adverse events of 63% in the FOLFOX arm and of 11% in the 5-FU/leucovorin arm. However, this trial was limited by imbalances in PS 2 proportion between the study arms and possible cross-over in treatment delivered following progression.²⁰³ The randomized phase II SWOG S1115 trial showed that patients with metastatic disease that failed to respond to gemcitabine-based therapy ($n=62$) who received mFOLFOX (fluorouracil and oxaliplatin) had a median OS of 6.7 months, which is comparable to the median OS rates found in the CONKO-003 and PANCREOX trials.²⁰⁴

In the NAPOLI-1 phase III randomized trial, the effects of nanoliposomal irinotecan were examined in patients with metastatic pancreatic cancer who previously received gemcitabine-based therapy.²⁰⁵ Patients were randomized to receive nanoliposomal irinotecan monotherapy, 5-FU/leucovorin, or both ($n=417$). Median PFS (3.1 vs 1.5 months; HR, 0.56; 95% CI, 0.41–0.75; $P<.001$) was significantly greater for patients who received nanoliposomal irinotecan with 5-FU/leucovorin, compared with patients who did not receive irinotecan. Updated analyses showed that median OS (6.2 vs 4.2 months; HR, 0.75; $P=.042$) was significantly greater for patients who received nanoliposomal irinotecan with 5-FU/leucovorin, compared with patients who received 5-FU/leucovorin without irinotecan.²⁰⁶ Grade 3 or 4 adverse events that occurred most frequently with this regimen were neutropenia (27%), fatigue (14%), diarrhea (13%), and vomiting (11%).²⁰⁵ Irinotecan liposomal injection, combined with 5-FU/leucovorin, was later approved by the FDA to be used as a subsequent treatment option after gemcitabine-based therapy in patients with metastatic disease. The panel recommends this regimen as a subsequent treatment option for patients with good performance status and disease progression.

Another subsequent therapy option in patients with good performance status and locally advanced or metastatic disease is 5-FU + leucovorin + irinotecan (FOLFIRI). A phase II trial found comparable efficacy and safety in patients treated with mFOLFOX ($n=30$) and modified FOLFIRI-3 ($n=21$) regimens whose disease had failed previous gemcitabine treatment; OS was 14.9 and 16.6 weeks, respectively.²⁰⁷ Another phase II trial studied 63 patients with metastatic disease and failure in 1 to 3 lines of gemcitabine- and platinum-based chemotherapies, who received FOLFIRI (in 2 different schedules reported together; FOLFIRI-1 and -3).²⁰⁸ The median OS was 6.6 months (95% CI, 5.3–8.1 months). Patients who had grade 3-4 toxicities (23.8%) experienced mainly

hematologic or digestive toxicities. A GISCAD multicenter phase II study of locally advanced or metastatic disease evaluated the FOLFIRI-2 regimen in patients previously treated with gemcitabine with or without platinum-based therapies.²⁰⁹ The OS was 5 months and the toxicity was manageable; patients experienced grade 3–4 neutropenia (20%) and diarrhea (12%).

The AIO-PK0104 trial also assessed subsequent therapy in a randomized crossover trial and found capecitabine to be efficacious after progression on gemcitabine/erlotinib in patients with advanced disease.²¹⁰ In this trial, capecitabine/erlotinib followed by gemcitabine gave similar outcomes to the aforementioned sequence.

Advances in research have revealed that human immune-checkpoint-inhibitor antibodies that inhibit the interactions between immune cells and antigen-presenting cells may also do so in tumor cells.²¹¹ There is evidence that PD-1 blockade with pembrolizumab may be effective in tumors with MMR deficiency (dMMR).²¹² Pembrolizumab is an anti-PD-1 receptor antibody and blocks its interaction with PD-L1 and PD-L2, releasing the PD-1-mediated inhibition of the immune response, which improves antitumor immunity. The results of a phase II study in patients with 12 different dMMR advanced cancers, including pancreas, found that treatment with pembrolizumab resulted in durable responses (ORR in 53% of patients, with 21% complete response).²¹³ There were 6 patients with pancreatic cancer with an ORR in 62% of patients (2 had complete response and 3 had progressive disease). Adverse events were experienced by 74% of all patients receiving pembrolizumab; most were low grade (20% experienced grade 3 or 4 adverse events, such as diarrhea/colitis, pancreatitis/hyperamylasemia, fatigue, arthritis/arthralgias, or anemia).²¹³ Adverse events, however, for immune checkpoint inhibitors can be significant; see the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities, available at NCCN.org.

Based on these data, pembrolizumab was granted accelerated FDA approval in 2017 for patients with unresectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. Similar results were reported from the phase II KEYNOTE-158 study. Among 27 noncolorectal tumor types, including pancreatic cancer, with a median follow-up of 13.4 months, the ORR was reported to be 34.3% (95% CI 28.3%–40.8%), the median PFS was 4.1 months (95% CI 2.4–4.9 months), and the median OS was 23.5 months.²¹⁴ Pembrolizumab is recommended by the NCCN Panel for the advanced disease setting for first-line and subsequent treatment as appropriate.

Finally, neurotrophin receptor kinase (NTRK) gene fusions, although rare, have been implicated in the

oncogenesis of pancreatic cancer. In 3 multicenter, open-label, single-arm trials (a phase I study with adults, a phase I-II study with children, and a phase II study with adolescents and adults), the efficacy and safety of larotrectinib, an NTRK inhibitor, was investigated.^{215,216} The primary endpoint was set to be ORR and the secondary endpoints were determined to be PFS, duration of response, and safety. Among 17 tumor types, the ORR during independent review was 75% (95% CI, 61–85). After 9.4 months, 86% of participants had either underwent curative surgery or were continuing treatment. At 1 year, 55% of patients were progression-free and the toxicity profile of the agent was found to be minimal.²¹⁵ Based on this data, larotrectinib was approved by the FDA in 2018 for the treatment of NTRK gene fusion positive solid tumors in adult and pediatric patients with known acquired resistance and advanced or morbid disease that has progressed despite treatment.²¹⁶ Updated data published in 2020 reported that the percentage of patients with an objective response was 79% (95% CI 72–85) with 16% of patients showing a complete response.²¹⁷ Similarly, entrectinib is another NTRK inhibitor approved in 2019 by the FDA for adult and pediatric patients (ages 12 years and older) with advanced, morbid, or unresectable NTRK gene fusion positive solid tumors with acquired resistance to standard treatment.²¹⁸ Data from 3 phase I-II trials (ALKA-372-001, STARTRK-1, and STARTRK-2) revealed that entrectinib had an ORR of 57.4% and a median duration of response (DOR) of 10.4 months. Like its predecessor, it had a tolerable safety profile.^{219,220} Thus the NCCN Panel recommends larotrectinib and entrectinib as first-line and subsequent treatment options for patients with NTRK gene fusion positive locally advanced or metastatic pancreatic adenocarcinoma.

To summarize, subsequent treatment options for patients with good performance status and previously treated with gemcitabine-based therapy include: 5-FU/leucovorin/liposomal irinotecan (category 1 for metastatic disease), FOLFIRI, FOLFIRINOX or modified FOLFIRINOX, 5-FU/leucovorin/oxaliplatin (OFF), FOLFOX, CapeOx, capecitabine, or continuous infusion 5-FU. Options for patients with good performance status and previously treated with fluoropyrimidine-based therapy include: 5-FU/leucovorin/nanoliposomal irinotecan (if no prior irinotecan administered), gemcitabine/albumin-bound paclitaxel, gemcitabine/cisplatin, gemcitabine/erlotinib, or gemcitabine monotherapy. Chemoradiation may be a subsequent treatment option in select patients (see Management of Locally Advanced Disease, in these NCCN Guidelines at NCCN.org). For MSI-H or dMMR tumors, pembrolizumab is an option, whereas for NTRK gene fusion positive disease, larotrectinib or entrectinib may be considered.

Subsequent treatment options for patients with poor performance status include gemcitabine (standard infusion as a category 1 and fixed-dose-rate as a

category 2B recommendation), capecitabine (category 2B recommendation), and continuous infusion 5-FU (category 2B recommendation).

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Individual Disclosures for the NCCN Pancreatic Adenocarcinoma Panel

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The NCCN Guidelines Staff have no conflicts to disclose.

^aThe following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty:

Brian Czito, MD: UpToDate, Inc.

Timothy R. Donahue MD: Trethera Corporation

Robert A. Wolff, MD: McGraw-Hill