# Treatment Options for Germline *BRCA*-Mutated Metastatic Pancreatic Adenocarcinoma

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Author's disclosure of conflicts of interest is found at the end of this article.

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https://doi.org/10.6004/jadpro.2021.12.5.4



**Abstract**

Pancreatic cancer is the fourth leading cause of death from cancer in both men and women. Pancreatic cancer is typically diagnosed at an advanced stage and has an overall 5-year survival of approximately 9.3%. The National Comprehensive Cancer Network recommends both germline testing (testing cells such as blood or skin that do not have cancer) as well as somatic testing (testing cells with cancer) for pathogenic variants that may increase the risk of pancreatic cancer. In December 2019, the U.S. Food & Drug Administration approved the poly(ADP-ribose) polymerase (PARP) inhibitor olaparib for maintenance treatment of germline *BRCA*-mutated metastatic pancreatic adenocarcinoma in individuals who have completed at least 16 weeks of progression-free treatment with first-line platinum-based chemotherapy. This new therapy option has implications not only for treatment but also for the role of the oncology advanced practitioner as genetic testing becomes more prevalent in the care of patients with cancer.

Pancreatic cancer currently accounts for 3.2% of all cancers. It is the fourth leading cause of death from cancer in both men and women. In 2020, it was estimated to affect more than 57,600 adults and lead to approximately 48,000 deaths (American Cancer Society, 2020). Approximately 10% of pancreatic cancers are diagnosed at a stage when the patient would benefit from resection, resulting in a 5-year survival of 34%. Currently, surgery is the only curative treatment. For those with stage 4 disease, the 5-year survival is 3% (Cancer.Net, 2020), with a median survival of 8.5 months (Rahib et al., 2014, pp. 2,920). The overall survival for those diagnosed between 2009 and 2015 was 9.3%. The lifetime risk of developing pancreatic cancer is 1.6% (Cancer.Net, 2020).

It is estimated that by 2030, pancreatic cancer will become the second leading cause of cancer death, surpassing breast, prostate, and colon cancer. There are several reasons for the increase in pancreatic cancer deaths when compared with other

J Adv Pract Oncol 2021;12(5):488–491

cancers. One reason is more effective screening methods for breast and prostate cancer, leading to more people being screened. In addition, individuals with breast and prostate cancer are living longer with their disease due to improved treatment modalities (Wallis, 2017).

Risk factors for pancreatic cancer include smoking, obesity (body mass index > 30), type 2 diabetes, history of pancreatitis, increased age, an inherited high-risk pathogenic variant (PV), family history with no PV, and possibly alcohol intake. Obesity is now a larger concern than smoking due to the obesity epidemic in the United States. Risk reduction methods for pancreatic cancer include cessation of smoking, exercise, and diet (Ilic & Ilic, 2016, pp. 9,694; Wallis, 2017).

## GENETIC TESTING RECOMMENDATIONS

In 2018, the National Comprehensive Cancer Network (NCCN) recommended *BRCA* germline testing (testing blood or skin of noncancer cells) for all individuals with pancreatic cancer, although 40% to 50% of pancreatic cancer patients have no family history that would indicate the need for genetic testing. In April 2019, NCCN recommended somatic testing (testing tumor cells) for all patients with advanced pancreatic cancers to evaluate for candidacy for other therapies that may be beneficial at the time of testing or in the future (Research to Practice, 2020). It is possible somatic testing will not identify a germline mutation that may be present due to testing methodology used by individual companies and their criteria for reporting possible germline PV (Forman & Sotelo, 2019). Tumor testing (if tissue is available) is recommended over liquid biopsies, as liquid biopsies are sensitive but not necessarily specific, leading to false negative results (Research to Practice, 2020).

There are several genes that are considered high risk for pancreatic cancer when a PV is present. These genes include *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, the Lynch syndrome genes (*MLH1*, *MSH2*, *MSH6*, and *EPCAM*), *PALB2*, *STK11*, and *TP53*. About 25% of pancreatic tumors have a PV, with 17% of these in DNA repair deficiency genes such as *BRCA* and *ATM*, which are detected in 3% to 5% and 6% of patients with pancreatic cancer, respectively. Microsatellite instability-high (MSI-H) tumors are rare in pancreatic cancer, occurring in about 0.5% to 0.7% of cases. It appears that MSI-H tumors respond to checkpoint inhibitors (NCCN, 2020a; Research to Practice, 2020). A microsatellite is an area of repeated DNA sequences in a noncoding area of the gene. MSI-H can result when there are errors in base pair matches or failure to identify and correct errors of insertions or deletions of base pairs. The Lynch syndrome genes previously mentioned act as mismatch repair (MMR) genes by correcting these errors (Griffiths et al., 2020, pp. 1–3). When there is a defect in the MMR genes (dMMR), there is increased MSI in tumor cells. Many MSI-H tumors respond to treatment with immune checkpoint inhibitors, such as the programmed cell death protein 1 (PD-1) inhibitor pembrolizumab (Keytruda). One of the functions of T cells in our immune system is production of the PD-1 protein that aids in cell death; however, some tumor cells produce ligands that bond with PD-1 protein, which blocks this process. The PD-1 inhibitors block this binding process, allowing the T cells to aid in tumor cell death (Flavell, 2020).

A germline *BRCA* PV is present in 17% of familial pancreatic cancer cases (Hasan et al., 2019), while overall, approximately 3.8% to 11.5% of patients with pancreatic cancer will have a germline PV. Of these, 2% will have a *BRCA2* PV and 1% or less have a *BRCA1* PV. In individuals with a family history (two or more first-degree relatives with pancreatic cancer), 5% to 10% will have a *BRCA2* PV and 1% have a *BRCA1* PV. Lifetime risk of pancreatic cancer for those with *BRCA2* PV is 5% to 10%, and for those with *BRCA1* PV, it is 2 to 4 times the baseline population risk of 1.6% (Pilarski, 2019, pp. 1–3).

## SCREENING

Screening for pancreatic cancer is evolving. In December 2019, NCCN recommended consideration of annual screening with contrast-enhanced MRI, magnetic resonance cholangiopancreatography (MRCP), and/or endoscopic ultrasound (EUS) for those at high risk for pancreatic cancer due to family history or a germline PV in a pancreatic cancer susceptibility gene. Age to begin screening depends on the gene with the PV and family history but is typically between ages 30 to 50. Screening is recommended to start at earlier ages for those with an *STK11* or *CDKN2A* variant, as they incur

a higher risk than other genes (Pilarski, 2019, pp. 1–3; NCCN, 2020b). Additionally, there are several research studies evaluating screening methods for high-risk individuals based on known genetic predisposition and family history.

## TREATMENT RECOMMENDATIONS FOR METASTATIC PANCREATIC CANCER

Systemic treatment is the current recommendation for all stages of pancreatic cancer. For those at earlier stages whose tumors are resectable, neoadjuvant chemotherapy is advised. Recommended regimens include FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) or modified FOLFIRINOX; gemcitabine plus albumin-bound paclitaxel; or for those with a known *BRCA* or *PALB2* PV, FOLFIRINOX, modified FOLFIRINOX, or gemcitabine with cisplatin. These regimens are also recommended as first-line treatment for those with metastatic disease (NCCN, 2020a).

The *BRCA* genes are tumor suppressor genes that produce a protein that aids in repair of double-strand breaks in the DNA by a method called homologous recombination. (Gorodetska et al., 2019, pp. 2,121). There is also evidence that this protein regulates the activity of other genes and proteins. An individual has two alleles of each gene, one from the paternal side and one from the maternal side. Germline mutations in the *BRCA* genes are autosomal dominant, meaning an individual needs only one defective allele from either the maternal or paternal side for increased risk of cancer. A mutation in one allele results in less production of protein, leading to changes in cells that can cause uncontrolled growth and division, resulting in cancerous tumors (MedlinePlus Genetics, 2020).

Poly(ADP-ribose) polymerase (PARP) enzymes aid in repair of DNA damage through various repair pathways. The constant DNA replication that occurs in rapidly dividing cells, such as cancer cells, requires increased need for DNA repair. When a *BRCA* mutation is present, there is a decrease in the DNA repair mechanisms, causing the cell to rely on other repair pathways such as single-strand repair, a less complex system than homologous recombination. Single-strand repair is one repair method used by PARP. By inhibiting the PARP pathway, in addition to the defective *BRCA* repair pathway, a condition known as "synthetic lethal effect" occurs, preventing the replication of cancer cells, which leads to cell death (Dziadkowiec et al., 2016; Yi et al., 2019, pp. 1).

On December 27, 2019, the U.S. Food & Drug Administration (FDA) approved olaparib (Lynparza), a PARP inhibitor, for germline *BRCA*-mutated metastatic pancreatic cancer in individuals who had not had disease progression for at least 16 weeks while on a first-line platinum-based chemotherapy regimen. This was the first new treatment for pancreatic cancer since 2015 and the first therapy approved for maintenance treatment of pancreatic cancer (Kennedy, 2020).

Olaparib was approved based on findings from the phase III POLO study. This study looked at 154 patients with germline *BRCA*-mutated metastatic pancreatic cancer. It compared olaparib maintenance with placebo in patients who had received a platinum-based maintenance treatment. Patients were randomized in a 3:2 fashion with a primary endpoint of progression-free survival (PFS). Results noted a 7.4-month PFS in the olaparib group compared with 3.8 months in the placebo group (Golan et al., 2019, pp. 325).

The recommended dose of olaparib is 300 mg orally twice a day. It may be taken with or without food. CYP3A inhibitors should be avoided if possible, but if they cannot be avoided, the olaparib dose should be reduced to 100 mg twice a day. For those with moderate renal impairment, the recommended dose is 200 mg twice daily (Stenger, 2020).

Common side effects include fatigue, nausea, abdominal pain, diarrhea, anemia, decreased appetite, constipation, and vomiting. Anemia and fatigue were the most common grade 3 to 4 adverse events (AEs). The most common AEs leading to dose reductions or interruptions were anemia, vomiting, abdominal pain, asthenia, and fatigue. Pneumonitis occurred in up to 1% of patients; individuals receiving olaparib should be monitored closely, with interruption of treatment if pneumonitis is suspected (Stenger, 2020).

Based on findings from the use of olaparib in breast and ovarian cancers, nausea is more frequent in the first few months of treatment but may improve over time. If nausea does occur, it can usually be controlled with prophylactic use of an oral antiemetic such as prochlorperazine or metoclopramide taken before each dose. Methods to coun-

ter fatigue include recommending energy-conserving strategies, ensuring adequate nutrition, and encouraging moderate exercise. Hematologic side effects should be monitored and may require dose interruption or dose reduction (Friedlander, 2016).

## IMPLICATIONS FOR THE ADVANCED PRACTITIONER

Ideally, individuals undergoing germline testing will have counseling by a genetic counselor or provider with experience in genetic assessment. Expanding criteria for cancer genetic testing will require more genetic counseling providers. In 2019, there were 4,600 genetic counselors in the United States, with 700 of those specializing in adult cancer genetics. It is estimated that there will be increased demand of 30% by 2026. To meet this demand, other care delivery models may be necessary (McNamara, 2017; Milliron & Griggs, 2019, pp. 445). The advanced practitioner with experience in oncology and additional education in genetics is ideally suited to help fill this need.

### Disclosure

The author has no conflict of interest to disclose.

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