The Role of PARP Inhibitors in Germline BRCA-Associated Pancreatic Ductal Adenocarcinoma

Gordon T. Moffat, MD, and Eileen M. O’Reilly, MD

Abstract: Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy that remains a challenge to treat. In pursuit of personalized medicine, researchers continue active exploration of the genetic and molecular framework of PDAC to apply novel therapeutics and enhance outcomes. In patients who have PDAC, germline mutations—such as those in the BRCA1/2 and PALB2 genes—are predominantly associated with the DNA damage response pathway. On the basis of studies completed in patients with BRCA-mutated advanced breast and ovarian cancer, the poly(ADP-ribose) polymerase (PARP) inhibitors have been evaluated for safety, tolerability, and efficacy in patients with advanced PDAC who are carrying germline BRCA gene mutations. Results have demonstrated meaningful activity and identified BRCA as a predictive and targetable biomarker in PDAC, and have also identified the role of olaparib as a maintenance therapy in PDAC. On the basis of the principle of synthetic lethality, and to avert resistance to PARP inhibitors, clinical trials of combination therapy with PARP inhibitors and platinum-based chemotherapy have been conducted with an early signal. As we continue to explore the role of PARP inhibitors in the management of PDAC, recent clinical trials are studying the effectiveness of PARP inhibitors in combination with immunotherapy, targeted inhibitors, and angiogenesis inhibitors. The next steps are to understand the role of PARP inhibitors beyond germline BRCA in other homologous recombination repair gene mutations and in other subgroups of patients with PDAC.

Introduction

The current landscape in medical oncology is increasingly focused on individualizing therapy. Novel therapeutics are being developed to target mutations or actionable molecular subgroups that often go beyond the anatomical origin or tissue type of the malignancy. Although the applications of this approach were once limited, it is becoming increasingly important in the management of lethal malignancies such as pancreatic ductal adenocarcinoma (PDAC). Aligned with this trend is the use of a group of pharmacologic inhibitors...
of poly(ADP-ribose) polymerase (PARP) enzymes in BRCA1 (breast cancer gene)–mutated solid tumors. The effectiveness of PARP inhibition was first identified in the treatment of breast and ovarian BRCA-mutated tumors, and a recent flagship study has identified its efficacy in the management of advanced PDAC. This review article explores the background of PARP inhibitors, reviews significant clinical trials involving PARP inhibitors for the treatment of BRCA-mutated tumors, and describes recent advances in the use of PARP inhibitors for the management of advanced PDAC. In addition, the article comments on strategies currently in development to enhance the efficacy of BRCA-targeted therapies.

**Background**

PDAC is an aggressive malignancy that exhibits immune privilege and harbors complex somatic genetic alterations in key driver oncopgenes (including KRAS, TP53, SMAD4, and CDKN2A) in a majority of patients. PDAC is challenging to treat, with a 1-year mortality rate of 80%.

1-4 It has one of the lowest 5-year overall survival (OS) rates of all malignancies and is expected to become a larger burden in the United States by 2030.5 A total of 57,600 new cases of the second-leading cause of cancer-related death in the United States in 2020.6 Globally, these numbers are 458,918 and 432,242, respectively, in 2018.7 At the time of presentation, approximately 50% of patients have stage IV disease, with systemic therapies achieving a real but relatively modest effect on outcome.3,8,9 Given the poor prognosis, research into new systemic therapies is needed. The key to these discoveries could come from further understanding the genomic and molecular profile of PDAC and its high-penetrance inheritable mutations, which cause selective pressure for biallelic tumor suppressor gene inactivation.10

The prevalence of BRCA2 sporadic mutations in PDAC is not precisely known and has been reported as 3.6% to 7%. BRCA1 and PALB2 (partner and localizer of BRCA2 gene) sporadic mutations are more limited, with an estimated frequency of less than 3%.11-13

Genomic analysis of PDAC has identified pathogenic germline alterations in BRCA1/2, PALB2, and other genes associated with the DNA damage response (DDR) pathway, including BLM, CHEK2, BARD1, ATM, RAD51D, and RAD50.12,14-16 In a study of 159 patients with PDAC, a pathogenic germline alteration was discovered in 15%, with BRCA1 and BRCA2 mutations the most predominant, at rates of 2.5% and 8.2%, respectively.16 In 2018, a similar study of 615 patients with PDAC from Memorial Sloan Kettering Cancer Center (MSKCC), in which a larger gene panel was used, reported a cumulative 19.8% rate of germline mutations, with BRCA1 mutations in 2.4%, BRCA2 mutations in 5.7%, and PALB2 mutations in 0.2%.15 BRCA2 gene alterations account for the highest proportion of cases of inherited PDAC and have been identified in 5% to 17% of families with familial pancreatic cancer.16-21 Since the recognition in 2009 of PALB2 as an integral linker protein for BRCA1/2, PALB2 has emerged as a tumor suppressor protein associated with susceptibility to hereditary PDAC, with frequencies of approximately 4% in European, Australian, and Japanese populations, and less than 1% in Dutch, Italian, and North American populations.22 The relative risks for the development of PDAC in patients with an inherited BRCA1 or BRCA2 mutation are estimated to be 2.26 and 3.5, respectively.23,24 Therefore, the National Comprehensive Cancer Network (NCCN) recommends germline testing for all patients with PDAC who are candidates for anti-cancer therapy, and tumor profiling for all those with locally advanced/metastatic PDAC, to identify uncommon, potentially actionable mutations.25 It is noteworthy that in a study of 854 patients with PDAC, up to 40% of those with germline homologous recombination DNA damage repair (HR-DDR)–mutated PDAC did not have a significant family history of cancer, and germline testing helped to identify those patients who might benefit from platinum-based chemotherapy and other actionable molecular targeted therapy in the HR-DDR pathway.25,26 Table 1 summarizes some of the key recent studies of germline testing in PDAC.

The majority of germline mutations identified in patients with PDAC pertain to the DDR and HR repair pathways. Up to 25% of patients with PDAC have a mutation in the HR repair pathway.27,28

Alterations in BRCA1 result in deficient DNA damage signaling and cell cycle checkpoint activation, whereas alterations in BRCA2 result in functionally impaired proteins in the process of HR and the repair of double-stranded DNA breaks.29-32 HR is the primary and preferred repair mechanism because of its accuracy and ability to remove DNA cross-links.29,33,34

Impairment of HR results in the accumulation of mutations and chromosomal breaks, in turn causing genomic instability and consequential carcinogenesis.34,35

Cells with mutations in HR are particularly sensitive to cross-linking agents such as platinum-based chemotherapeutic drugs.36-39 In studies that examined platinum-based chemotherapy in BRCA-mutated PDAC, superior OS was demonstrated in nonrandomized cohorts.37,40-44 When alterations occur in BRCA1/2 or the HR pathway, alternative, error-prone DNA repair mechanisms are engaged.45 One such alternative mechanism is a group of nuclear PARP enzymes, which may be the precise molecular target required to improve OS in patients with BRCA-associated PDAC.
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Platinum Therapy and BRCA Mutations in PDAC

In 2014, Golan and colleagues identified the importance of a BRCA association in patients with PDAC as a prognostic and predictive biomarker. In this retrospective study, patients with BRCA-associated PDAC had favorable outcomes and significantly improved OS in stage III/IV disease if they were treated with platinum-based chemotherapy regimens (22 vs 9 months).42 In 2018, Blair and colleagues conducted a retrospective analysis that showed improved OS in patients with BRCA-related PDAC who received platinum-based adjuvant chemotherapy vs alternative therapy or no adjuvant therapy (31 vs 17.8 vs 9.3 months).41

In 2019, a retrospective study from the Know Your Tumor program of the Pancreatic Cancer Action Network (PanCAN) revealed that up to 16.5% of 820 patients with resectable or advanced PDAC had somatic or germline mutations of genes involved in the HR-DDR pathway,

### Table 1. Studies of the Frequency of Germline Mutations of BRCA1/2 and PALB2 in PDAC

<table>
<thead>
<tr>
<th>Study</th>
<th>First Author</th>
<th>Year</th>
<th>Cancer Type</th>
<th>Participants, No.</th>
<th>Genes Tested, No.</th>
<th>Germline Mutations, Total No. (%)</th>
<th>BRCA1, %</th>
<th>BRCA2, %</th>
<th>PALB2, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification of Germline Genetic Mutations in Patients With Pancreatic Cancer</td>
<td>Salo-Mullen16</td>
<td>2015</td>
<td>PDAC</td>
<td>159</td>
<td>8</td>
<td>24 (15.1)</td>
<td>2.52</td>
<td>8.18</td>
<td>0.63</td>
</tr>
<tr>
<td>Germline BRCA Mutations in a Large Clinic-Based Cohort of Patients with PDAC</td>
<td>Holter12</td>
<td>2015</td>
<td>PDAC</td>
<td>306</td>
<td>2</td>
<td>14 (4.58)</td>
<td>0.98</td>
<td>3.59</td>
<td>N/A</td>
</tr>
<tr>
<td>Mutation Detection in Advanced Cancer by Universal Sequencing of Cancer-Related Genes in Tumor and Normal DNA vs Guideline-Based Germline Testing</td>
<td>Mandelker28</td>
<td>2017</td>
<td>Advanced cancer types</td>
<td>176</td>
<td>76</td>
<td>44 (25)</td>
<td>3.4</td>
<td>6.25</td>
<td>0.56</td>
</tr>
<tr>
<td>Real-time Genomic Characterization of Advanced Pancreatic Cancer to Enable Precision Medicine</td>
<td>Aguirre98</td>
<td>2018</td>
<td>PDAC</td>
<td>71</td>
<td>81</td>
<td>13 (18.3)</td>
<td>2.82</td>
<td>4.23</td>
<td>1.41</td>
</tr>
<tr>
<td>Prospective Study of Germline Genetic Testing in Incident Cases of Pancreatic Adenocarcinoma</td>
<td>Brand99</td>
<td>2018</td>
<td>PDAC</td>
<td>298</td>
<td>32</td>
<td>29 (9.7)</td>
<td>13.8</td>
<td>13.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Prospective Evaluation of Germline Alterations in Patients With Exocrine Pancreatic Neoplasms</td>
<td>Lowery15</td>
<td>2018</td>
<td>PDAC</td>
<td>615</td>
<td>76</td>
<td>122 (19.8)</td>
<td>2.4</td>
<td>5.7</td>
<td>0.16</td>
</tr>
<tr>
<td>Germine Cancer Susceptibility Gene Variants, Somatic Second Hits, and Survival Outcomes in Patients With Resected Pancreatic Cancer</td>
<td>Yurgelun100</td>
<td>2019</td>
<td>PDAC</td>
<td>289</td>
<td>24</td>
<td>28 (9.7)</td>
<td>1.04</td>
<td>1.38</td>
<td>0.35</td>
</tr>
<tr>
<td>Hereditary Cancer Genetic Testing Among Patients With Pancreatic Cancer</td>
<td>Taherian101</td>
<td>2019</td>
<td>PDAC</td>
<td>1676</td>
<td>29</td>
<td>207 (12.3)</td>
<td>N/A</td>
<td>3.8</td>
<td>1.2</td>
</tr>
</tbody>
</table>

BRCA, breast cancer gene; PALB2, partner and localizer of BRCA2 gene; PDAC, pancreatic ductal adenocarcinoma.
and the study demonstrated that these mutations have a role in predicting response to platinum-based chemotherapy. OS was 3-fold greater in patients with advanced PDAC and HR-DDR mutations who were treated with platinum-based chemotherapy compared with platinum-naive patients. In the 311 patients with advanced PDAC who received platinum-based chemotherapy, OS was significantly better in the patients with mutated HR-DDR than it was in those with proficient HR-DDR (2.37 vs 1.45 years). In the same patient group, improvement in the median progression-free survival (PFS) was observed in both the first-line setting (13.7 vs 8.1 months) and the second-line setting (8.6 vs 4.1 months), a finding further underpinning the predictive value of HR-DDR mutations in decisions regarding platinum-based therapy. No apparent positive prognostic value was associated with mutations in the HR-DDR pathway in platinum-naive patients who had PDAC. In fact, HR-DDR mutations may have contributed to a worse outcome in these patients compared with those who had HR-DDR proficiency; however, this finding is not validated, and further research is needed.

At the 2019 American Society of Clinical Oncology annual meeting, Park and colleagues further contributed to the evidence of HR deficiencies as a biomarker predictive of response to first-line platinum-based chemotherapy in patients with advanced PDAC. In this preliminary report of a retrospective study of 461 patients with advanced PDAC, OS in the patients with a germline HR deficiency (HRD) who received platinum-based chemotherapy was superior to OS in the patients with non-germline HRD who received similar chemotherapy (median not reached vs 17.9 months). The patients with either germline or somatic HRD who received first-line platinum-based chemotherapy showed improved OS (50 vs 47 months) and PFS (27.7 vs 17 months) compared with the patients who did not have HRD and received similar chemotherapy. Final data are awaited.

PARP Inhibition

The PARP enzymes are primarily involved in the major short-patch base excision repair mechanism for DNA single-strand breaks (SSBs). When an SSB occurs, PARP-1 binds at the site and activates catalytic activity, which causes the poly(ADP-ribose)lation of PARP-1 and neighboring histones and signals the recruitment of other components of the DNA repair pathway. Inhibition of PARP enzymes arrests SSB repair, and persistent DNA SSBs encountered by a replication fork will result in increased DNA lesions, replication fork collapse, and the formation of double-stranded breaks. In a patient with a BRCA1/2 mutation and impairment of HR, these double-stranded breaks eventually result in cell cycle arrest and subsequent apoptosis. A study by Farmer and colleagues illustrated that BRCA1/2 dysfunction profoundly sensitizes cells to the inhibition of PARP enzyme activity. This synergistic activity, termed synthetic lethality, could allow the increased use of PARP inhibitors in BRCA-mutated tumors; PARP inhibitors are theoretically less toxic and more specific than some other forms of systemic therapy. The use of DNA-damaging chemotherapy regimens (eg, platinum-containing regimens) along with PARP inhibition could be an effective strategy for BRCA-associated PDAC, exploiting the synthetic lethality vulnerability of these cancers.

PARP Inhibitors and BRCA-Mutated Breast and Ovarian Cancer

Olaparib (Lynparza, AstraZeneca), rucaparib (Rubraca, Clovis Oncology), and niraparib (Zejula, Tesaro) are approved as treatment for patients with germline BRCA-mutated advanced ovarian, fallopian, or primary peritoneal cancer who have received at least 3 prior lines of chemotherapy; they are also approved as maintenance therapy for patients with recurrent, platinum-sensitive ovarian, fallopian, or primary peritoneal cancer. Olaparib is the only medication that is approved as first-line maintenance therapy in patients with germline or somatic BRCA-mutated advanced ovarian, fallopian, or primary peritoneal cancer and a partial response (PR) or complete response (CR) to first-line platinum-based chemotherapy. Similar results have been shown in studies of olaparib in patients with germline BRCA-mutated, HER2-negative metastatic breast cancer who have received chemotherapy in the neoadjuvant, adjuvant, or metastatic setting, with consequent drug approval (see the eTable at www.hematologyandoncology.net). Talazoparib (Talzenna, Pfizer) demonstrated efficacious antitumor activity in the management of germline BRCA-mutated, HER2-negative breast cancer and is approved for the treatment of locally advanced or metastatic disease.

PARP Inhibitors and PDAC

In a 2011 study from our group at MSKCC, BRCA-mutated PDAC was identified as a clinically important subgroup. The study also illustrated the relevant therapeutic rationale for the development of PARP inhibitors to treat PDAC. In a retrospective cohort of 15 patients with BRCA1/2-mutated PDAC, 2 of the 3 patients treated with the combination of a PARP inhibitor and gemcitabine had a clinical and radiographic response, as did 1 patient treated with PARP inhibitor monotherapy. Table 2 summarizes key trials of PARP inhibitors in PDAC. A phase 2 study of olaparib monotherapy by Kaufman and colleagues in patients with recurrent germline BRCA-
advanced or metastatic disease. These studies strength-

The DCR was 44.4% in patients who had previously

rate (DCR) of 31.6%, with 2 CRs and 2 PRs, in patients

leagues observed an RR of 15.8% and a disease control

with germline \textit{-mutated} PDAC, Shroff and col-

in patients with \textit{BRCA1/2-} or \textit{PALB2-mutated} PDAC; their results revealed that 25% of

patients had SD for at least 4 months. All but one of these

patients, however, were exposed or resistant to platinum, a fact that likely was at least partially responsible for

lack of objective responses. In a prospective phase 2 trial

drug and a disease control rate (DCR) of 31.6%, with 2 CRs and 2 PRs, in patients

whose cancer had not progressed on platinum therapy.

The DCR was 44.4% in patients who had previously

received only 1 prior chemotherapy regimen for locally advanced or metastatic disease. These studies strength-

ened the argument for the value of PARP inhibitors in the treatment of \textit{BRCA1-associated} PDAC.

In a second-line treatment setting, Chiorean and col-

leagues used leucovorin, 5-fluorouracil (5-FU), and iri-

notecan (FOLFIRI) with or without veliparib to evaluate the effect of combination therapy in a randomized phase

2 North American cooperative group trial in unselected

patients. This trial had a preplanned retrospective analysis of HRD genes and outcome. The results of the study

showed that in unselected patients, the addition of veli-

parib to FOLFIRI did not improve OS and increased toxicity. However, improvements in OS (11.9 vs 5.7

months) and PFS were observed in patients with either germline or somatic \textit{BRCA4-mutated} or with non-\textit{BRCA}-

mutated HRD in comparison with the no-HRD group.

Similarly, Pishvaian and colleagues reported that therapy

combining leucovorin, 5-FU, and oxaliplatin (FOLFOX) with veliparib had an RR of 58%, a DCR of 79%, and

relatively longer OS and PFS in platinum-naive patients

with metastatic PDAC who had a positive family history and a DDR mutation in \textit{BRCA1/2, PALB2, or ATM}. In an effort to overcome resistance to a single-agent targeted strategy, O’Reilly and colleagues conducted a phase 1 trial evaluating the combination of gemcitabine, cisplatin, and veliparib in platinum-naive patients with locally advanced or metastatic \textit{BRCA1/2-} or \textit{PALB2-mutated} PDAC. The study reported an RR of 77.8% and improved OS in patients with a \textit{BRCA} mutation vs those without a \textit{BRCA} mutation (23.3 vs 11.0 months). No objective responses were seen in the \textit{BRCA} wild-type subgroup. Since these observations, a randomized study comparing patients with germline \textit{BRCA1/PALB2-mutated} PDAC who were treated with gemcitabine and cisplatin with or without veliparib has been reported. O’Reilly and colleagues reported very high response rates in both study arms (74% for the triplet; 65% for the doublet) and encouraging median OS rates of 15.5 and 16.4 months, respectively. Significantly more myelosuppression was observed with the triplet than with the doublet. The authors believe that cisplatin plus gemcitabine represents a standard regimen in germ-

line \textit{BRCA1/PALB2-mutated} PDAC, and is an alternative to modified leucovorin, 5-FU, irinotecan, and oxaliplatin (mFOLFIRINOX). In patients with unresetable, locally advanced PDAC, Tuli and colleagues explored the combi-

nation of gemcitabine, veliparib, and intensity-modulated radiation therapy and reported a longer OS (18 vs 14 months) in the patients with DDR pathway mutations.

PARP inhibitors have been studied in patients with \textit{BRCA1/2-associated} PDAC. Initially, the concept of \textit{BRCA1/2} (known DDR deficiency mutation and/or family history of \textit{BRCA1/2-associated} cancers in ≥2 first-degree relatives without DDR genetic aberrations) described a constellation of traits or susceptibility to sporadic muta-
tions in the genes coding for proteins involved in the DNA-repair process, likely related to \textit{BRCA1/2}. More recently, this term has evolved to refer to any defect in the HR repair pathway, likely related to the replication fork, that mimics the deletion or loss of function of \textit{BRCA1/2} in the absence of a germline alteration in \textit{BRCA1/2} and increases the risk for carcinogenesis. A phase 2 study by Golan and colleagues explored the use of olaparib in patients with PDAC and a \textit{BRCA1/2-associated} phenotype. Patients included in this study were negative for a germline \textit{BRCA} mutation, were known to have a previously identified DDR deficiency, and had a family history of \textit{BRCA1/2-associated} cancers in 2 or more first-degree relatives without a DDR deficiency. The objective response rate was 40.6%, with 2 patients having a PR and 11 patients having SD at longer than 16 weeks. The PFS was 14 weeks in the Israel trial group and 24.7 weeks in the US trial group. Overall, olaparib was well tolerated and presented encouraging initial antitumor activity in patients with platinum-sensitive, germline \textit{BRCA1/2-negative} PDAC with a known DDR deficiency mutation and a known family history of \textit{BRCA1/2-associated} cancers.

In 2019, 2 important clinical trials demonstrated that PARP inhibitors are effective as maintenance therapy in patients with advanced PDAC and SD following platinum-based chemotherapy. In patients with germline or somatic \textit{BRCA1/2-} or \textit{PALB2-mutated} PDAC, Reiss and colleagues reported an early analysis of an ongoing phase 2 trial and noted an RR of 36.8%, a DCR of 89.5% at 8 weeks, and a median PFS of 9.1 months with rucaparib monotherapy. Most recently, the POLO (Pancreas Olaparib Ongoing) trial significantly demonstrated the benefit of the PARP inhibitor olaparib as maintenance
### Table 2. Completed Clinical Trials of PARP Inhibitors in the Treatment of PDAC

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Year</th>
<th>Cancer Type</th>
<th>PARP Inhibitor</th>
<th>Study Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaufman et al&lt;sup&gt;49&lt;/sup&gt;</td>
<td>2</td>
<td>2015</td>
<td><em>BRCA</em>-mutated advanced solid tumors</td>
<td>Olaparib</td>
<td>Olaparib 400 mg twice daily</td>
<td>• In patients with PDAC, RR of 21.7% with SD at ≥8 wk in 34.8% and 1-y survival rate of 41%, N=28</td>
</tr>
<tr>
<td>Lowery et al&lt;sup&gt;38&lt;/sup&gt;</td>
<td>2</td>
<td>2018</td>
<td><em>BRCA1/2</em>- or <em>PALB2</em>-mutated PDAC and 1-2 prior treatment regimens</td>
<td>Veliparib</td>
<td>Veliparib 400 mg twice daily</td>
<td>• 25% of patients with SD for ≥4 mo</td>
</tr>
<tr>
<td>O’Reilly et al&lt;sup&gt;60&lt;/sup&gt;</td>
<td>1</td>
<td>2018</td>
<td>Locally advanced or metastatic <em>BRCA1/2</em> or <em>PALB2</em>-mutated PDAC, and wild-type <em>BRCA</em>-negative</td>
<td>Veliparib</td>
<td>Gemcitabine and cisplatin with 4 dose levels of veliparib evaluated: 20, 40, and 80 mg twice daily for efficacy and safety in 2 cohorts  • Cohort 1: germline <em>BRCA1/2</em>-mutated  • Cohort 2: wild-type <em>BRCA</em>-negative</td>
<td>• In <em>BRCA</em>-mutated patients, 77.8% with a complete or partial response  • Median survival of 23.3 mo in <em>BRCA</em>-mutated patients vs 11 mo in patients with wild-type <em>BRCA</em></td>
</tr>
<tr>
<td>Golan et al&lt;sup&gt;65&lt;/sup&gt;</td>
<td>2</td>
<td>2018</td>
<td>Platinum-sensitive, <em>gBRCA</em> mutation negative, metastatic PDAC with <em>BRCA</em>ness and ≥1 previous systemic chemotherapy</td>
<td>Olaparib</td>
<td>Olaparib twice daily as monotherapy</td>
<td>• Olaparib well tolerated with encouraging initial antitumor activity</td>
</tr>
<tr>
<td>Shroff et al&lt;sup&gt;57&lt;/sup&gt;</td>
<td>2</td>
<td>2018</td>
<td><em>BRCA</em>-mutated locally advanced or metastatic PDAC</td>
<td>Rucaparib</td>
<td>Rucaparib twice daily</td>
<td>• RR of 15.8%; DCR of 31.6% in all patients and in 44.4% in those with prior chemotherapy</td>
</tr>
<tr>
<td>Pishvaian et al&lt;sup&gt;19&lt;/sup&gt;</td>
<td>1/2</td>
<td>2019</td>
<td>Germline or somatic DDR mutation in patients with metastatic PDAC</td>
<td>Veliparib</td>
<td>• Phase 1: veliparib  • Phase 2: veliparib and mFOLFOX</td>
<td>• Veliparib + mFOLFOX safe and well tolerated, with RR of 58%, DCR of 79%, and longer PFS and OS in platinum chemotherapy–naïve patients with metastatic PDAC plus a positive family history and a DDR mutation</td>
</tr>
<tr>
<td>Tuli et al&lt;sup&gt;62&lt;/sup&gt;</td>
<td>1</td>
<td>2019</td>
<td>Unresectable locally advanced PDAC</td>
<td>Veliparib</td>
<td>Veliparib, gemcitabine, and IMRT</td>
<td>• This combination of therapy safe and well tolerated  • Median OS for those with DDR pathway gene alterations of 19 mo, vs 14 mo for those with intact genes  • DDR genes <em>PARP3</em> and <em>RBX1</em> associated with OS</td>
</tr>
<tr>
<td>Reiss et al&lt;sup&gt;66&lt;/sup&gt;</td>
<td>2</td>
<td>2019</td>
<td>Germline or somatic <em>BRCA1/2</em>- and <em>PALB2</em>-mutated PDAC with SD after platinum-based chemotherapy</td>
<td>Rucaparib</td>
<td>Rucaparib 600 mg twice daily as maintenance therapy</td>
<td>• Median PFS of 9.1 mo, overall RR of 37%, and DCR of 90% at 8 wk</td>
</tr>
<tr>
<td>Chiorean et al&lt;sup&gt;29&lt;/sup&gt;</td>
<td>2</td>
<td>2019</td>
<td>Metastatic PDAC</td>
<td>Veliparib</td>
<td>mFOLFIRI and veliparib as a second line of therapy vs FOLFIRI alone</td>
<td>• Increased toxicity and no improvement in OS when veliparib added to mFOLFIRI in unselected patients  • Better OS and PFS with FOLFIRI +/- veliparib in HRD group than in no-HRD group  • Irinotecan of value in the treatment of HRD-associated PDAC</td>
</tr>
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</table>

(Table continued on next page)
therapies in patients with germline BRCA-mutated metastatic PDAC who had a response to or SD on platinum-based chemotherapy. In this international double-blind, controlled study, 154 patients with deleterious germline BRCA1/2-mutated metastatic PDAC were randomly assigned in a 3:2 ratio to olaparib or placebo maintenance therapy. The intervention was continued until progression of disease was identified on the basis of objective radiologic evidence. The primary endpoint was PFS by blinded central independent review, and secondary endpoints were OS, second PFS, and death. Median PFS was significantly longer in the patients randomly assigned to the olaparib arm than in the placebo group (7.4 vs 3.8 months; \( P = .04 \)). In addition, the patients who received olaparib had a higher RR (20% vs 10%), and among the responders, the median duration of response was longer compared with the placebo group (24.9 vs 3.7 months). Of note, the early survival data, somewhat suprisingly, did not show a difference between the 2 study arms, and further data maturity is awaited. Of additional note, the POLO trial did not have a comparative arm of cytotoxic therapy, and therefore the value of a comparison to standard therapy is uncertain. Nonetheless, the results of this study led to US Food and Drug Administration approval of olaparib in late 2019 for use in the maintenance setting in patients with platinum-sensitive disease and a germline BRCA1/2 mutation.

The role of PARP inhibitors in the treatment of PDAC has evolved significantly over the last few years. The POLO trial data provide a proof-of-principle and validation study demonstrating the effectiveness of PARP inhibitors as maintenance therapy in patients with platinum-sensitive germline BRCA-mutated metastatic PDAC. This is a pivotal study supporting the use of oral monotherapy as maintenance treatment in patients with advanced PDAC and a response to first-line platinum-based chemotherapy to control disease and improve PFS. Additionally, POLO reaffirms the safety and tolerability of PARP inhibitors, as well as the possibility of increased patient satisfaction with maintained quality of life scores vs placebo, and adherence given that olaparib is an oral medication and is dosed twice daily.

### Resistance to PARP Inhibitors

A critical issue for targeted therapies in general, and for PARP inhibitors specifically, in the management of PDAC is the emergence of de novo or acquired resistance. Mechanism-based resistance to targeted therapy and personalized medicine, especially in the HR-DDR pathway, can frequently develop in patients previously treated with platinum-based chemotherapy. Drug resistance can develop through distinct mutations in the molecular target, HR pathway, tumor microenvironment, or parallel alternative repair pathways, resulting in hyperactivity. In the case of PARP inhibitors, resistance might be due to a genetic reversion of BRCA1/2 mutations, stabilization of mutant proteins, or a succeeding mutation that restores the HR pathway. The proposed mechanisms of resistance indicate the possibility of the development of resistance to platinum-based chemotherapy; however, no definite results have been shown.

As previously explored by O’Reilly and colleagues, combination therapy may be a strategy to delay or prevent resistance to PARP inhibitors. In a study by Haynes and colleagues, olaparib-resistant cancer cells were re-sensitized by combination therapy with WEE1 and ATR kinase inhibitors. Per Pilié and colleagues, combination therapies with additional DDR pathway inhibition of ATM, CHK1/2, or DNA-PK could also be valuable strategies to manage PARP inhibitor resistance. Favorable response rates for

Table 2. (Continued) Completed Clinical Trials of PARP Inhibitors in the Treatment of PDAC

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Year</th>
<th>Cancer Type</th>
<th>PARP Inhibitor</th>
<th>Study Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Golan et al&lt;sup&gt;67&lt;/sup&gt;</td>
<td>3</td>
<td>2019</td>
<td>Germline BRCA-mutated metastatic PDAC and first-line platinum-based chemotherapy</td>
<td>Olaparib</td>
<td>Olaparib 300 mg twice daily vs placebo twice daily for maintenance therapy</td>
<td>• Median PFS longer in olaparib group (7.4 mo) than in placebo group (3.8 mo)</td>
</tr>
</tbody>
</table>
combination therapy with other targeted therapies—such as phosphoinositide 3-kinase (PI3K) alpha and androgen receptor inhibitors—have been shown in ovarian cancer and castration-resistant prostate cancer. Further, in the MEDIOLA study (A Phase I/II Study of MEDI4736 in Combination With Olaparib in Patients With Advanced Solid Tumors), the combination of olaparib and the immune checkpoint inhibitor durvalumab (Imfinzi, AstraZeneca) achieved DCRs of 80% and 81% at 12 weeks in patients with germline BRCA1/2-mutated, HER2-negative breast cancer or germline BRCA1/2-mutated, platinum-sensitive ovarian cancer, respectively.

Combinations of PARP inhibitors and angiogenesis inhibitors, such as vascular endothelial growth factor (VEGF) inhibitors, have been studied because of their ability to downregulate HR repair proteins such as those encoded by BRCA1/2 and potentiate PARP inhibitor sensitivity. In a phase 2 study by Liu and colleagues of patients with recurrent platinum-sensitive, high-grade serous or endometrioid ovarian cancer, combination therapy with olaparib and cediranib increased median PFS vs olaparib alone (17.6 vs 9 months). A caveat to all the therapy options previously mentioned plus others is the increased risk for myelosuppression and hematologic malignancies associated with additional inhibition of the DDR pathway. Future studies will continue to explore combination therapy based on inhibition of DDR proteins, DNA damage signaling, and DNA metabolism.

To avert resistance to PARP inhibitors, a further understanding of genetic and molecular processes is needed. To this end, plasma-derived circulating tumor DNA (ctDNA) testing and tumor tissue biopsy at progression of disease may be informative. Longitudinal ctDNA analysis is a potential tool for the early identification of de novo mutations and monitoring for somatic genetic alterations that might result in resistance to PARP inhibitors. A study by Christie and colleagues in patients with high-grade serous ovarian cancer found that ctDNA monitoring to identify reversion of germline BRCA1/2 mutations was able to predict treatment responses. Another study used ctDNA to monitor for secondary somatic mutations in patients with germline BRCA1/2-mutated ovarian cancer and was able to predict resistance to platinum-based chemotherapy and PARP inhibitors.

Resistance to PARP inhibitors was also identified in post-progression tissue specimens by Pishvaian and colleagues in 2017. In this case, a 63-year-old woman with stage IV PDAC and a germline pathogenic BRCA2 mutation identified by next-generation sequencing (NGS) at diagnosis was treated in a phase 1/2 trial. After 31 cycles of 5-FU, oxaliplatin, and veliparib, she had a nearly complete response, with virtual radiographic disappearance of her pancreatic head mass and liver lesions. Several months after the cessation of treatment, radiographic progression of disease developed at the primary site. Given her previous response to treatment and minimal current disease, her recommended treatment was pancreatectoduodenectomy. Postsurgical specimens were evaluated by NGS, which revealed a new secondary somatic BRCA2 mutation that was a 26-base deletion located 13 bases upstream from the initial 4-base pair germline mutation on the same allele. This case report demonstrated a secondary reversion mutation that restored BRCA2 function in a patient with an initial loss-of-function germline BRCA1 mutation previously treated with a PARP inhibitor and platinum-based chemotherapy. The tumor cells were able to restore the defective DDR mechanism owing to the selective pressure of the patient’s combination therapy. This case highlights the potential utility of post-progression tissue biopsy with NGS to test for resistance and plan management. The presence of secondary BRCA1/2 mutations resulting in resistance to platinum-based therapies and PARP inhibitors has previously been reported in patients with BRCA1/2-mutated ovarian cancer as well.

PARP Inhibitors: Adverse Events, Tolerability

The PARP inhibitors as a class are generally well tolerated. In comprehensive trials studying olaparib, rucaparib, and niraparib, the most commonly reported adverse event was nausea, occurring in up to 75% of patients. Therefore, the NCCN has categorized olaparib, rucaparib, and niraparib as moderate emetic risks and recommends first-line antiemetic treatment with a serotonin receptor antagonist (5-HT₃ receptor antagonist). Niraparib increases the risk for thrombocytopenia and hypertension. The proposed mechanism for the hypertension is related to the drug’s relatively high central nervous system penetration and the inhibitory effect on dopamine, norepinephrine, and serotonin transporters. Pneumonitis has been reported in fewer than 1% of patients on olaparib, whereas rucaparib causes an increase in hepatic cholesterol biosynthesis through the upregulation and expression of sterol regulatory element-binding protein 1 (SREBP1). At the initiation of treatment, olaparib and rucaparib are associated with a mild increase in renal creatinine owing to their effect on renal transporter proteins OCT2 and MATE1; they also cause a mild elevation in liver transaminases because they are cytochrome P450 3A4 inhibitors. In each setting, the continuation of PARP inhibitor therapy is recommended with routine monitoring.

While patients are being treated with PARP inhibitors, it is key to be aware of hematologic toxicities and malignancies, especially in those with previous or concurrent cytotoxic chemotherapy. Myelosuppression, predominantly anemia and leukopenia, is a common
adverse event with all PARP inhibitors and DNA-damaging agents. The transfusion of packed red blood cells and the administration of iron, folic acid, and vitamin B₁₂ with erythropoiesis-stimulating agents may be required. Approximately 0.5% to 2% of patients treated with PARP inhibitors are at risk for myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).⁴⁹,⁸⁶,⁸⁷,⁸⁹,⁹⁵,⁹⁶ In a phase 1 trial of combination therapy with olaparib, irinotecan, cisplatin, and mitomycin C in patients with advanced PDAC, grade 3 or higher drug-related hematologic toxicities occurred in 89% of patients; these included neutropenia (89%), lymphopenia (72%), anemia (22%), and treatment-related MDS in 2 patients. In the first patient, who had BRCA2-mutated and treatment-naïve disease, MDS developed after 2 years of therapy that progressed to AML. The second patient, whose BRCA mutation status was unknown and who previously had been treated with multiple lines of therapy, progressed to MDS after 1 year in the trial.⁹⁷

In the POLO trial, the most common adverse events experienced by patients with PDAC in the olaparib group were fatigue and nausea, followed by anemia, abdominal pain, diarrhea, decreased appetite, and constipation. Serious adverse events occurred in 24% of the patients who received olaparib and in 15% of the patients who received placebo. Within the olaparib group, grade 3 or higher adverse events included anemia, fatigue, and decreased appetite, listed according to prevalence. No cases of MDS or AML were reported in the olaparib experimental arm, and no clinically meaningful change from baseline quality of life.⁶⁷

**Ongoing and Future Clinical Trials**

Similar in study design to the POLO trial, active clinical trials are examining the response rates and clinical effectiveness of veliparib, olaparib, niraparib, and rucaparib monotherapy in patients with BRCA1/2- and PALB2-mutated PARP. Table 3 outlines some of the key ongoing trials of PARP inhibitors in PDAC. Two phase 2 clinical trials involving niraparib, which are underway at the Dana-Farber Cancer Institute and the University of Kansas, are expanding the focus to include any germline or somatic mutations in genes involved in DNA repair, including CHEK2, ATM, and ATR (NCT03601923, NCT03553004). These studies will provide important insights into the role of PARP inhibitors in the management of a broader category of patients with HRD due to either germline or somatic biallelic inactivation of tumor suppressor genes.

Additional studies are investigating PARP inhibitor combinations with chemotherapy, immunotherapy, targeting agents, or antiangiogenic agents. Current trials are studying the combination of rucaparib and nanoliposomal irinotecan/5-FU in patients with metastatic PDAC, as well as veliparib and irinotecan in those with BRCA-mutated advanced solid tumors (NCT03337087, NCT00576654). These studies build on the known value of irinotecan as a DDR drug, as reported by Chiorean and colleagues.⁵⁸ A phase 1/2 two-arm trial of combination therapy with niraparib and nivolumab vs niraparib and ipilimumab, called Parpvax (Niraparib + Ipilimumab or Nivolumab in Progression Free Pancreatic Adenocarcinoma After Platinum-Based Chemotherapy; NCT03404960), is currently underway. A phase 2 study of olaparib and pembrolizumab (Keytruda, Merck) will open in early 2020 at MSKCC. And on the basis of success in patients with recurrent platinum-sensitive advanced ovarian cancer, a study of olaparib and cediranib in previously treated patients with a range of solid tumors, including PDAC, is underway (NCT02498613).

**Conclusion**

The role of PARP inhibitors in the management of BRCA-associated advanced PDAC is established, especially with the recent approval of olaparib as maintenance monotherapy for patients with metastatic PDAC who respond to or have stable disease with platinum-based chemotherapy. As a class, PARP inhibitors are generally safe, well tolerated, and effective for a subset of genomically defined patients with PDAC. Current clinical trials are exploring the role of PARP inhibitors in combination with other DDR pathway inhibitors, targeted therapy, immunotherapy, and chemotherapy in an effort to understand their full therapeutic potential. Combination therapy may also be key to delaying or preventing resistance to PARP inhibitors or platinum-based chemotherapy in this patient population. Endorsement of the routine germline testing of patients with PDAC is essential to identify actionable targets, discover possible biomarkers for clinical use, select effective strategies to optimize therapy, and identify those patients in whom additional cascade family testing may be required. The next steps are to understand the value of PARP inhibitors beyond germline BRCA and PALB2, and to learn which somatic or germline pathogenic alterations are important for treatment decision making.

**Disclosures**

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### Table 3. Ongoing Studies With PARP Inhibitors and PDAC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Cancer Type</th>
<th>PARP Inhibitor</th>
<th>Study Design</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01585805</td>
<td>2</td>
<td>Locally advanced or metastatic <em>BRCA1</em>/<em>2</em>- or <em>PALB2</em>-mutated PDAC</td>
<td>Veliparib</td>
<td>• Part 1: first-line metastatic setting &lt;br&gt; • Arm A: gemcitabine, cisplatin, and veliparib &lt;br&gt; • Arm B: gemcitabine and cisplatin alone &lt;br&gt; • Part 2: single agent in previously treated disease &lt;br&gt; • Arm C: veliparib alone</td>
<td>• RR &lt;br&gt; • Results for part 2 pending</td>
</tr>
<tr>
<td>NCT03601923</td>
<td>2</td>
<td>Germline or somatic <em>BRCA1</em>/<em>2</em>, <em>PALB2</em>, <em>CHEK2</em>, or <em>ATM</em>-mutated locally advanced or metastatic PDAC</td>
<td>Niraparib</td>
<td>Niraparib once daily in combination with palliative radiation therapy</td>
<td>PFS</td>
</tr>
<tr>
<td>NCT03553004</td>
<td>2</td>
<td>Germline or somatic mutation in genes involved with DNA repair in patients with PDAC</td>
<td>Niraparib</td>
<td>Niraparib 300 mg daily</td>
<td>RR</td>
</tr>
<tr>
<td>NCT02677038</td>
<td>2</td>
<td>Germline <em>BRCA4</em>-negative metastatic PDAC treated previously with ≥1 previous chemotherapy regimen and <em>BRCA</em>ness</td>
<td>Olaparib</td>
<td>Olaparib twice daily on days 1-28; course repeated every 28 days in absence of disease progression.</td>
<td>Efficacy of olaparib monotherapy in stage IV PDAC</td>
</tr>
<tr>
<td>NCT03140670</td>
<td>2</td>
<td><em>BRCA1</em>/<em>2</em>- or <em>PALB2</em>-mutated PDAC, stable after platinum-based systemic therapy</td>
<td>Rucaparib</td>
<td>Rucaparib daily until progression of disease</td>
<td>Efficacy, safety, and antitumor activity of rucaparib</td>
</tr>
<tr>
<td>NCT02511223</td>
<td>2</td>
<td>Metastatic PDAC plus <em>BRCA</em>ness in patients treated previously with ≥1 chemotherapy regimen</td>
<td>Olaparib</td>
<td>Olaparib 300 mg twice daily until progression of disease</td>
<td>RR</td>
</tr>
<tr>
<td>NCT02498613</td>
<td>2</td>
<td>Advanced solid tumors treated previously with ≥1 chemotherapy regimen, <em>BRCA</em> mutation excluded</td>
<td>Olaparib</td>
<td>• Arm 1: cediranib orally daily on day 1, followed by olaparib twice daily on days 4-28 &lt;br&gt; • Arm 2: olaparib twice daily on days 4-28</td>
<td>RR</td>
</tr>
<tr>
<td>NCT03337087</td>
<td>1b / 2</td>
<td>Metastatic PDAC</td>
<td>Rucaparib</td>
<td>Rucaparib + liposomal irinotecan + 5-fluorouracil + leucovorin</td>
<td>ORR, best response rate</td>
</tr>
<tr>
<td>NCT03404960</td>
<td>1/2</td>
<td>Locally advanced or metastatic PDAC with minimum of 16 wk of platinum-based therapy and no progression of disease</td>
<td>Niraparib</td>
<td>• Arm A: niraparib + nivolumab &lt;br&gt; • Arm B: niraparib + ipilimumab</td>
<td>PFS</td>
</tr>
<tr>
<td>NCT00576654</td>
<td>1</td>
<td><em>BRCA</em>-mutated advanced solid tumors</td>
<td>Veliparib</td>
<td>Veliparib + irinotecan</td>
<td>OBD, MTD, RP2D</td>
</tr>
<tr>
<td>NCT01078662</td>
<td>2</td>
<td><em>BRCA</em>-mutated ovarian, breast, prostate, and pancreatic cancers, and advanced tumors</td>
<td>Olaparib</td>
<td>Olaparib 400 mg twice daily until progression of disease</td>
<td>RR</td>
</tr>
</tbody>
</table>

*ATM,* ataxia telangiectasia mutated kinase gene; *BRCA,* breast cancer gene; *BRCA*ness, breast cancer susceptibility gene negative +/- an additional DNA damage repair pathway aberration +/- a family history of *BRCA*-related tumors; *CHEK2,* checkpoint kinase 2 gene; *MTD,* maximum tolerated dose; *OBD,* optimum biologic dose; *ORR,* objective response rate; *PALB2,* partner and localizer of *BRCA2* gene; *PDAC,* pancreatic ductal adenocarcinoma; *PFS,* progression-free survival; *RP2D,* recommended phase 2 dose; *RR,* response rate.
THE ROLE OF PARP INHIBITORS IN GERMLINE BRCA-ASSOCIATED PDAC

72. Haynes B, Murai J, Lee JM. Restored replication fork stabilization, a mechanism of resistance'.
### eTable. Previously Completed Clinical Trials and Outcomes of PARP inhibitors and BRCA-Associated Advanced Cancers

<table>
<thead>
<tr>
<th>Trial and Author</th>
<th>Phase</th>
<th>Year</th>
<th>Cancer Type</th>
<th>PARP Inhibitor</th>
<th>Study Design</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Tutt et al\(^53\) | 2    | 2010 | Recurrent, advanced BRCA-mutated breast cancer | Olaparib | • Cohort 1: olaparib 400 mg twice daily  
• Cohort 2: olaparib 100 mg twice daily | • PARP monotherapy in patients with BRCA1/2 advanced breast cancer safe and effective  
• Cohort 1 with a 41% RR  
• Toxicities mainly low grade |
| Audeh et al\(^102\) | 2    | 2010 | Recurrent, advanced BRCA-mutated ovarian cancer | Olaparib | • Cohort 1: olaparib 400 mg twice daily  
• Cohort 2: olaparib 100 mg twice daily | • PARP monotherapy in patients with BRCA1/2 advanced ovarian cancer safe and effective  
• Cohort 1 with a 33% RR  
• Toxicities were mainly at low grade |
| Ledermann et al\(^35\) | 2    | 2014 | Platinum-sensitive recurrent high-grade serous ovarian cancer | Olaparib | Olaparib 400 mg twice daily vs placebo (as maintenance therapy after ≥2 platinum-based regimens with either a partial or complete response) | Median PFS longer in olaparib (11.2 mo) group than in placebo group (4.3 mo) in BRCA-mutated patients |
| Kaufman et al\(^49\) | 2    | 2015 | Patients with confirmed germline loss-of-function BRCA1/2 mutation and advanced solid tumor (platinum-resistant ovarian cancer, chemotherapy-refractory breast cancer, PDAC, or prostate cancer) | Olaparib | Olaparib 400 mg twice daily | Tumor RR of 26.2% overall and RRs of 31.1%, 12.9%, 21.7%, and 50.0% in ovarian, breast, pancreatic, and prostate cancers, respectively  
• SD for ≥8 wk observed in 42% overall, including in 40%, 47%, 35%, and 25% of ovarian, breast, pancreatic, and prostate cancers, respectively |
| Domchek et al\(^103\) | 2    | 2016 | Germline BRCA-mutated advanced ovarian cancer and ≥3 prior lines of chemotherapy | Olaparib | Olaparib 400 mg twice daily until progression of disease | RR of 34% in olaparib-treated patients with median duration of response of 7.4 mo |
| Mirza et al\(^87\) | 3    | 2016 | Platinum-sensitive germline BRCA-mutated recurrent ovarian cancer | Niraparib | Niraparib 300 mg daily vs placebo (as maintenance therapy after platinum-based chemotherapy) | Median PFS longer with niraparib (21 mo) vs placebo (5.5 mo) |
| Swisher et al\(^90\) | 2    | 2017 | BRCA-mutated or BRCA wild-type and LOH-high platinum-sensitive ovarian cancer | Rucaparib | Rucaparib 600 mg twice daily | Median PFS longer with rucaparib therapy in BRCA-mutated subgroup (12.8 mo) than in LOH-high group (5.7 mo) and LOH-low group (5.2 mo) |
| Robson et al\(^35\) | 3    | 2017 | BRCA-mutated and HER2-negative metastatic breast cancer | Olaparib | Olaparib 300 mg twice daily vs standard chemotherapy with single agent (capecitabine, eribulin, or vinorelbine) | Median PFS longer in olaparib group (7 mo) than in standard-therapy group (4.2 mo)  
• RR higher in olaparib group (59.9%) than in standard-therapy group (28.8%) |
| Pujade-Lauraine et al\(^89\) | 3    | 2017 | BRCA-mutated ovarian cancer with complete or partial response to platinum-based chemotherapy | Olaparib | Olaparib 300 mg twice daily vs placebo twice daily | Median PFS longer in olaparib group (19.1 mo) than in placebo group (5.5 mo) |
**cTable. (Continued) Previously Completed Clinical Trials and Outcomes of PARP inhibitors and BRCA-Associated Advanced Cancers**

<table>
<thead>
<tr>
<th>Trial and Author</th>
<th>Phase</th>
<th>Year</th>
<th>Cancer Type</th>
<th>PARP Inhibitor</th>
<th>Study Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coleman et al[86]</td>
<td>3</td>
<td>2017</td>
<td>BRCA-mutated or BRCA wild-type and LOH-high platinum-sensitive ovarian cancer maintenance therapy</td>
<td>Rucaparib</td>
<td>Rucaparib 600 mg twice daily vs placebo twice daily as maintenance therapy</td>
<td>• Median PFS longer in rucaparib group (16.6 mo) than in placebo group (5.4 mo)</td>
</tr>
<tr>
<td>Litton et al[54]</td>
<td>3</td>
<td>2018</td>
<td>BRCA-mutated and HER2-negative advanced breast cancer</td>
<td>Talazoparib</td>
<td>Talazoparib 1 mg daily vs standard chemotherapy with single agent (capecitabine, eribulin, gemcitabine, or vinorelbine) for safety and efficacy</td>
<td>• PFS longer in talazoparib group (8.6 mo) than in standard-therapy group (5.6 mo) • RR higher in talazoparib group (62.6%) than in standard-therapy group (27.2%)</td>
</tr>
<tr>
<td>Moore et al[87]</td>
<td>3</td>
<td>2018</td>
<td>BRCA-mutated high-grade ovarian cancer after completion of first-line platinum-based chemotherapy</td>
<td>Olaparib</td>
<td>Olaparib 300 mg twice daily vs placebo twice daily as maintenance therapy</td>
<td>• Risk for disease progression or death 70% lower with olaparib than with placebo</td>
</tr>
<tr>
<td>Turner et al[88]</td>
<td>2</td>
<td>2019</td>
<td>BRCA-mutated locally advanced or metastatic breast cancer</td>
<td>Talazoparib</td>
<td>Talazoparib 1 mg daily • Cohort 1: patients with partial or complete response to previous platinum-based chemotherapy • Cohort 2: patients with ≥3 previous cytotoxic chemotherapy regimens and no previous platinum-based chemotherapy</td>
<td>• RRs of 21% in cohort 1 and 37% in cohort 2 • Median durations of response of 5.8 and 3.8 mo, respectively</td>
</tr>
<tr>
<td>Gonzalez-Martin et al[89]</td>
<td>3</td>
<td>2019</td>
<td>Advanced ovarian cancer with complete or partial response to frontline platinum-based chemotherapy</td>
<td>Niraparib</td>
<td>Niraparib daily vs placebo daily as maintenance therapy</td>
<td>• Median PFS longer in niraparib group with HR deficiency (21.9 mo) than in placebo group (10.4 mo) • In all participants, PFS longer (13.8 mo) in niraparib group than in placebo group (8.2 mo) • OS of 84% in niraparib group vs 77% in placebo group</td>
</tr>
</tbody>
</table>

*BRCA,* breast cancer gene; *HER2,* human epidermal growth factor receptor 2 gene; *HR,* homologous recombination; *LOH,* loss of heterozygosity; *mo,* months; *OS,* overall survival; *PARP,* poly(ADP-ribose) polymerase 3 enzyme; *PDAC,* pancreatic ductal adenocarcinoma; *PFS,* progression-free survival; *RR,* response rate; *SD,* stable disease; *wk,* week(s).