

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

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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 and repair 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

Keywords

BRCA, germline, olaparib, pancreatic cancer, platinum, poly(ADP-ribose) polymerase inhibitors

of poly(ADP-ribose) polymerase (PARP) enzymes in *BRCA* (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 oncogenes (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 the second-leading cause of cancer-related death in the United States by 2030.⁵ A total of 57,600 new cases of PDAC and 47,050 deaths due to PDAC are anticipated in the United States in 2020.⁶ Globally, these numbers were 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.^{5,8,9} 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.

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

Study	First Author	Year	Cancer Type	Participants, No.	Genes Tested, No.	Germline Mutations, Total No. (%)	<i>BRCA1</i> , %	<i>BRCA2</i> , %	<i>PALB2</i> , %
Identification of Germline Genetic Mutations in Patients With Pancreatic Cancer	Salo-Mullen ¹⁶	2015	PDAC	159	8	24 (15.1)	2.52	8.18	0.63
Germline <i>BRCA</i> Mutations in a Large Clinic-Based Cohort of Patients with PDAC	Holter ¹²	2015	PDAC	306	2	14 (4.58)	0.98	3.59	N/A
Mutation Detection in Advanced Cancer by Universal Sequencing of Cancer-Related Genes in Tumor and Normal DNA vs Guideline-Based Germline Testing	Mandelker ²⁸	2017	Advanced cancer types	176	76	44 (25)	3.4	6.25	0.56
Real-time Genomic Characterization of Advanced Pancreatic Cancer to Enable Precision Medicine	Aguirre ⁹⁸	2018	PDAC	71	81	13 (18.3)	2.82	4.23	1.41
Prospective Study of Germline Genetic Testing in Incident Cases of Pancreatic Adenocarcinoma	Brand ⁹⁹	2018	PDAC	298	32	29 (9.7)	13.8	13.8	3.4
Prospective Evaluation of Germline Alterations in Patients With Exocrine Pancreatic Neoplasms	Lowery ¹⁵	2018	PDAC	615	76	122 (19.8)	2.4	5.7	0.16
Germline Cancer Susceptibility Gene Variants, Somatic Second Hits, and Survival Outcomes in Patients With Resected Pancreatic Cancer	Yurgelun ¹⁰⁰	2019	PDAC	289	24	28 (9.7)	1.04	1.38	0.35
Hereditary Cancer Genetic Testing Among Patients With Pancreatic Cancer	Taherian ¹⁰¹	2019	PDAC	1676	29	207 (12.3)	N/A	3.8	1.2

BRCA, breast cancer gene; *PALB2*, partner and localizer of *BRCA2* gene; PDAC, pancreatic ductal adenocarcinoma.

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, as opposed to non-platinum 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,

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-naïve 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).³⁹ 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.³⁹ No apparent positive prognostic value was associated with mutations in the HR-DDR pathway in platinum-naïve 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.³⁹

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.⁴⁶ 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-ribosyl)ation of PARP-1 and neighboring histones and signals the recruitment of other components of the DNA repair pathway.⁴⁷ 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.⁴⁷ 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.⁴⁷ A study by Farmer and colleagues illustrated that *BRCA1/2* dysfunction profoundly sensitizes cells to the inhibition of PARP enzyme activity.⁴⁸ 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.^{47,49-53}

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).^{54,55} 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.⁵⁶

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.⁴⁴ 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.⁴⁴ 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*-

mutated advanced PDAC demonstrated a response rate (RR) of 21.7% and stable disease (SD) in 34.8% of patients at 8 or more weeks of therapy, and a 1-year survival rate of 41%. Included in this study was 1 patient with a CR and 4 patients with PRs (Table 2).⁴⁹ All of these responses occurred in patients whose disease had not progressed on platinum-based therapy. In 2018, Lowery and colleagues evaluated veliparib monotherapy in patients with previously treated germline *BRCA1/2*- or *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 the lack of objective responses.³⁸ In a prospective phase 2 trial of rucaparib monotherapy in previously treated patients with germline *BRCA*-mutated PDAC, Shroff and colleagues observed an RR of 15.8% 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.⁵⁷ These studies strengthened the argument for the value of PARP inhibitors in the treatment of *BRCA*-associated PDAC.

In a second-line treatment setting, Chiorean and colleagues used leucovorin, 5-fluorouracil (5-FU), and irinotecan (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 veliparib 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 *BRCA*-mutated or with non-*BRCA*-mutated HRD in comparison with the no-HRD group.⁵⁸ 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-naïve patients with metastatic PDAC who had a positive family history and a DDR mutation in *BRCA1/2*, *PALB2*, or *ATM*.⁵⁹ 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-naïve patients with locally advanced or metastatic *BRCA1/2*- or *PALB2*-mutated PDAC. The study reported an RR of 77.8% and improved OS in patients with a *BRCA* mutation vs those without a *BRCA* mutation (23.3 vs 11.0 months). No objective responses were seen in the *BRCA* wild-type subgroup.⁶⁰ Since these observations, a randomized study comparing patients with germline *BRCA/PALB2*-mutated PDAC who were treated

with gemcitabine and cisplatin with or without veliparib has been reported.⁶¹ 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 germline *BRCA/PALB2*-mutated PDAC, and is an alternative to modified leucovorin, 5-FU, irinotecan, and oxaliplatin (mFOLFIRINOX). In patients with unresectable, locally advanced PDAC, Tuli and colleagues explored the combination of gemcitabine, veliparib, and intensity-modulated radiation therapy and reported a longer OS (18 vs 14 months) in the patients with DDR pathway mutations.⁶²

PARP inhibitors have been studied in patients with *BRCA*-associated PDAC. Initially, the concept of *BRCA*-ness (known DDR deficiency mutation and/or family history of *BRCA*-associated cancers in ≥ 2 first-degree relatives without DDR genetic aberrations) described a constellation of traits or susceptibility to sporadic mutations in the genes coding for proteins involved in the DNA-repair process, likely related to *BRCA1/2*.⁶³ 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 *BRCA1/2* in the absence of a germline alteration in *BRCA1/2* and increases the risk for carcinogenesis.⁶⁴ A phase 2 study by Golan and colleagues explored the use of olaparib in patients with PDAC and a *BRCA*-ness phenotype. Patients included in this study were negative for a germline *BRCA* mutation, were known to have a previously identified DDR deficiency, and had a family history of *BRCA*-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.⁶⁵ Overall, olaparib was well tolerated and presented encouraging initial antitumor activity in patients with platinum-sensitive, germline *BRCA*-negative PDAC with a known DDR deficiency mutation and a known family history of *BRCA*-associated cancers.⁶⁵

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 *BRCA1/2*- or *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.⁶⁶ 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

Study	Phase	Year	Cancer Type	PARP Inhibitor	Study Design	Outcome
Kaufman et al ⁴⁹	2	2015	BRCA-mutated advanced solid tumors	Olaparib	Olaparib 400 mg twice daily	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
Lowery et al ³⁸	2	2018	BRCA1/2- or PALB2-mutated PDAC and 1-2 prior treatment regimens	Veliparib	Veliparib 400 mg twice daily	25% of patients with SD for ≥4 mo
O'Reilly et al ⁶⁰	1	2018	Locally advanced or metastatic BRCA1/2 or PALB2-mutated PDAC, and wild-type BRCA-negative	Veliparib	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 BRCA1/2-mutated - Cohort 2: wild-type BRCA-negative	- In BRCA-mutated patients, 77.8% with a complete or partial response - Median survival of 23.3 mo in BRCA-mutated patients vs 11 mo in patients with wild-type BRCA
Golan et al ⁶⁵	2	2018	Platinum-sensitive, gBRCA mutation negative, metastatic PDAC with BRCAness and ≥1 previous systemic chemotherapy	Olaparib	Olaparib twice daily as monotherapy	Olaparib well tolerated with encouraging initial antitumor activity
Shroff et al ⁵⁷	2	2018	BRCA-mutated locally advanced or metastatic PDAC	Rucaparib	Rucaparib twice daily	RR of 15.8%; DCR of 31.6% in all patients and in 44.4% in those with prior chemotherapy
Pishvaian et al ⁵⁹	1/2	2019	Germline or somatic DDR mutation in patients with metastatic PDAC	Veliparib	- Phase 1: veliparib - Phase 2: veliparib and mFOLFOX	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
Tuli et al ⁶²	1	2019	Unresectable locally advanced PDAC	Veliparib	Veliparib, gemcitabine, and IMRT	- 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 <i>PARP3</i> and <i>RBX1</i> associated with OS
Reiss et al ⁶⁶	2	2019	Germline or somatic BRCA1/2- and PALB2-mutated PDAC with SD after platinum-based chemotherapy	Rucaparib	Rucaparib 600 mg twice daily as maintenance therapy	Median PFS of 9.1 mo, overall RR of 37%, and DCR of 90% at 8 wk
Chiorean et al ⁵⁸	2	2019	Metastatic PDAC	Veliparib	mFOLFIRI and veliparib as a second line of therapy vs FOLFIRI alone	- 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

(Table continued on next page)

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

Study	Phase	Year	Cancer Type	PARP Inhibitor	Study Design	Outcome
Golan et al ⁶⁷	3	2019	Germline <i>BRCA</i> -mutated metastatic PDAC and first-line platinum-based chemotherapy	Olaparib	Olaparib 300 mg twice daily vs placebo twice daily for maintenance therapy	• Median PFS longer in olaparib group (7.4 mo) than in placebo group (3.8 mo)

BRCA, breast cancer gene; *BRCA*ness, known DNA damage repair deficiency mutation and/or family history of *BRCA*-associated cancers in ≥ 2 first-degree relatives without DNA damage repair genetic aberrations; DCR, disease control rate; DDR, DNA damage response; *gBRCA*, germline breast cancer gene; HRD, homologous recombination deficiency; IMRT, intensity-modulated radiation therapy; mFOLFIRI, modified leucovorin, and 5-fluorouracil, and irinotecan; mFOLFOX, modified leucovorin, 5-fluorouracil, and oxaliplatin; mo, month(s); OS, overall survival; *PALB2*, partner and localizer of *BRCA2* gene; PARP3, poly(ADP-ribose) polymerase 3 enzyme; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; RBX1, RING-box protein 1; RR, response rate; SD, stable disease; wk, week(s); y, year(s).

therapy in patients with germline *BRCA*-mutated metastatic PDAC who had a response to or SD on platinum-based chemotherapy. In this international double-blinded 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).⁶⁷ 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 continuation of cytotoxic therapy, and therefore the value of a comparison of olaparib maintenance therapy with cytotoxic therapy remains to be determined. 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.⁶⁷ 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.⁶⁷ The study justifies the continued exploration of PARP inhibitors as monotherapy or combination therapy in the treatment of *BRCA*-associated PDAC, as well as the continued exploration of actionable targets in the HR-DDR pathway.

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.⁴⁷ Drug resistance can develop through distinct mutations in the molecular target, HR pathway, tumor microenvironment, or parallel alternative repair pathways, resulting in hyperactivity.⁶⁸ 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.⁶⁹⁻⁷¹ The proposed mechanisms of resistance indicate the possibility of the development of resistance to platinum-based chemotherapy; however, no definite results have been shown.⁴⁹

As previously explored by O'Reilly and colleagues, combination therapy may be a strategy to delay or prevent resistance to PARP inhibitors.⁶⁰ In a study by Haynes and colleagues, olaparib-resistant cancer cells were re-sensitized by combination therapy with *WEE1* and *ATR* kinase inhibitors.⁷² 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.⁷³ Favorable response rates for

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.^{74,75} 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, Astra-Zeneca) 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.^{76,77} 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.⁷⁸ 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).⁷⁹ 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.⁸⁰

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.⁸¹ Another study used ctDNA to monitor for secondary somatic mutations in patients with germline *BRCA*-mutated ovarian cancer and was able to predict resistance to platinum-based chemotherapy and PARP inhibitors.⁸²

Resistance to PARP inhibitors was also identified in post-progression tissue specimens by Pishvaian and colleagues in 2017.⁸³ 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 pancreaticoduodenectomy. 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.⁸³ This case report demonstrated a secondary reversion mutation that restored *BRCA2* function in a patient with an initial loss-of-function germline *BRCA* 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.^{84,85}

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.⁸⁶⁻⁹⁰ 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).⁹¹ 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.⁸⁷ 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).⁹² 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.⁹³ In each setting, the continuation of PARP inhibitor therapy is recommended with routine monitoring.⁹⁴

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 PDAC. 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

Funding was partly supported by the National Institutes of Health/National Cancer Institute Cancer Center Support Grant P30CA008748. Dr Moffat has no conflicts of interest. Dr O'Reilly has received research funding to MSKCC from Genentech, Roche, Bristol-Myers Squibb, Halozyme, Celgene, MabVax Therapeutics, Acta Biologica, AstraZeneca, Silenseed, Pfizer, and Polaris, and has served as a consultant/advisor for CytomX Therapeutics, BioLineRx, Targovax, Celgene, Bayer, Polaris, and Sobi.

Table 3. Ongoing Studies With PARP Inhibitors and PDAC

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

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.

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Supporting Online Material

eTable. Previously Completed Clinical Trials and Outcomes of PARP inhibitors and *BRCA*-Associated Advanced Cancers

Trial and Author	Phase	Year	Cancer Type	PARP Inhibitor	Study Design	Outcome
Tutt et al ⁵³	2	2010	Recurrent, advanced <i>BRCA</i> -mutated breast cancer	Olaparib	• Cohort 1: olaparib 400 mg twice daily • Cohort 2: olaparib 100 mg twice daily	• PARP monotherapy in patients with <i>BRCA1/2</i> advanced breast cancer safe and effective • Cohort 1 with a 41% RR • Toxicities mainly low grade
Audeh et al ¹⁰²	2	2010	Recurrent, advanced <i>BRCA</i> -mutated ovarian cancer	Olaparib	• Cohort 1: olaparib 400 mg twice daily • Cohort 2: olaparib 100 mg twice daily	• PARP monotherapy in patients with <i>BRCA1/2</i> advanced ovarian cancer safe and effective • Cohort 1 with a 33% RR • Toxicities were mainly at low grade
Ledermann et al ⁹⁵	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 <i>BRCA</i>-mutated patients
Kaufman et al ⁴⁹	2	2015	Patients with confirmed germline loss-of-function <i>BRCA1/2</i> 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 <i>BRCA</i> -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 <i>BRCA</i> -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	<i>BRCA</i> -mutated or <i>BRCA</i> wild-type and LOH-high platinum-sensitive ovarian cancer	Rucaparib	Rucaparib 600 mg twice daily	• Median PFS longer with rucaparib therapy in <i>BRCA</i>-mutated subgroup (12.8 mo) than in LOH-high group (5.7 mo) and LOH-low group (5.2 mo)
Robson et al ⁵⁵	3	2017	<i>BRCA</i> -mutated and <i>HER2</i> -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	<i>BRCA</i> -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)

(Table continued on next page)

eTable. (Continued) Previously Completed Clinical Trials and Outcomes of PARP inhibitors and *BRCA*-Associated Advanced Cancers

Trial and Author	Phase	Year	Cancer Type	PARP Inhibitor	Study Design	Outcome
Coleman et al ⁸⁶	3	2017	<i>BRCA</i> -mutated or <i>BRCA</i> wild-type and LOH-high platinum-sensitive ovarian cancer maintenance therapy	Rucaparib	Rucaparib 600 mg twice daily vs placebo twice daily as maintenance therapy	• Median PFS longer in rucaparib group (16.6 mo) than in placebo group (5.4 mo)
Litton et al ⁵⁴	3	2018	<i>BRCA</i> -mutated and <i>HER2</i> -negative advanced breast cancer	Talazoparib	Talazoparib 1 mg daily vs standard chemotherapy with single agent (capecitabine, eribulin, gemcitabine, or vinorelbine) for safety and efficacy	• 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%)
Moore et al ⁸⁸	3	2018	<i>BRCA</i> -mutated high-grade ovarian cancer after completion of first-line platinum-based chemotherapy	Olaparib	Olaparib 300 mg twice daily vs placebo twice daily as maintenance therapy	• Risk for disease progression or death 70% lower with olaparib than with placebo
Turner et al ⁵⁶	2	2019	<i>BRCA</i> -mutated locally advanced or metastatic breast cancer	Talazoparib	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	• RRs of 21% in cohort 1 and 37% in cohort 2 • Median durations of response of 5.8 and 3.8 mo, respectively
Gonzalez-Martin et al ¹⁰⁴	3	2019	Advanced ovarian cancer with complete or partial response to frontline platinum-based chemotherapy	Niraparib	Niraparib daily vs placebo daily as maintenance therapy	• 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

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).