

PARP Inhibitors in Metastatic Prostate Cancer: Evidence to Date

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Abstract: Poly (ADP-ribose) polymerase inhibitors (PARPi) are a unique class of antineoplastic agents that function by inducing synthetic lethality. Synthetic lethality occurs when PARPi and either another agent or an underlying genetic alteration together lead to overwhelming DNA damage and ultimately cell death. PARPi first showed promise as a cancer therapy in patients with *BRCA1/2* mutations and have become part of standard treatment for breast and ovarian cancer. In prostate cancer, two PARPi, rucaparib and olaparib, have been FDA approved for the treatment of metastatic castration-resistant prostate cancer (mCRPC). While both agents are approved for tumors with *BRCA1/2* alterations, for olaparib the indication is also expanded to patients with 12 other homologous recombination deficiency (HRD) gene alterations including *ATM* and *PALB2*. PARPi differ in their pharmacokinetics and pharmacodynamics, and additional studies are being conducted with niraparib, veliparib, and talazoparib in prostate cancer. While PARPi are fairly well tolerated, common toxicities include hematologic (anemia/thrombocytopenia) and gastrointestinal effects (nausea/vomiting). Ongoing studies are being conducted combining PARPi with other agents in patients with and without HRD alterations. Early data are promising for the combination of PARPi with second-generation antiandrogens and with immunotherapy. As additional trials are developed and reported, the hope is that the patient population who may benefit from PARPi will continue to expand.

Keywords: PARP inhibitor, prostate cancer, homologous recombination

Introduction

Poly (ADP-ribose) polymerase inhibitors (PARPi) are a class of anticancer drugs that utilize the mechanism of “synthetic lethality” to induce cell death.^{1,2} Synthetic lethality refers to the concept that cell death occurs when there is an underlying feature of the cancer which is exploited and becomes toxic when used in combination with another agent or genetic lesion.³ The two predominant PARP enzymes (PARP1 and PARP2) are integral to the DNA damage response mechanism, which is critical to maintaining intact DNA integrity.¹ PARP1 binds to DNA at sites of single-stranded DNA breaks in order to induce the post-translational modification of protein poly ADP-ribosylation (PARylation).⁴ The binding of DNA and post-translational modification recruits DNA repair proteins for single-stranded break repair and non-homologous end joining (NHEJ).⁵ Multiple mechanisms have been proposed for how PARPi lead to increased DNA damage. One idea is that single-stranded breaks are not corrected, and consequently, during DNA replication the replication fork is stalled with the creation of double-stranded breaks. Additionally, it has been recognized that PARPi trap the PARP enzymes on the DNA strand by inhibiting normal auto-PARylation.⁶ By trapping the PARP complex on DNA, replication is stalled and DNA breaks are formed.¹ The cytotoxic

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effect of PARPi is hypothesized to be mediated through the creation of an intolerable amount of DNA damage when combined with an additional cytotoxic agent or underlying genetic deficiency in DNA damage repair. It was recognized in 2005 by Farmer et al, and separately by Bryant et al, that homologous recombination deficient cells with *BRCA1/2* mutations are specifically susceptible to PARPi-induced apoptosis.^{7,8}

The *BRCA1/2* proteins are crucial to double-stranded DNA break repair through homologous recombination. Homologous recombination is a conserved system of DNA damage repair which is comparatively error free.⁹ With genetic defects in homologous recombination proteins, the cell becomes dependent on methods of DNA repair that are more prone to error such as NHEJ. *BRCA1/2* interact with a complex of proteins and are part of a greater pathway that regulates homologous recombination.¹⁰ While robust literature exists elucidating the role of *BRCA1/2* in homologous recombination and cancer predisposition, an increasing array of proteins which lead to a homologous recombination-deficient phenotype when they are impaired are being identified.¹¹ This includes proteins such as *PALB2*, *FANCA*, *ATM*, *CHEK1*, *CHEK2*, *RAD51* and others.¹²

The current PARPi that have been FDA approved or are under investigation for the treatment of prostate cancer are olaparib, rucaparib, niraparib, talazoparib and veliparib. Differences exist in the metabolism of the different PARPi, with niraparib being metabolized by carboxylesterase-catalysed amide hydrolysis, while rucaparib, talazoparib, veliparib, and olaparib are metabolized by cytochrome P450 enzymes.¹³ The ability to trap PARP on chromatin varies between the different PARPi as well, with talazoparib having the most potent effect on trapping PARP.^{14,15} Pamiparib is a new PARPi that has not yet been approved for any cancer type, but investigation studies have begun using this agent in prostate cancer.¹⁶ The most significant toxicity noted for PARP inhibitors as a class are hematological dyscrasias including anemia, thrombocytopenia, and neutropenia.¹³ Anemia is seen in ~50% of patients. Additional noted toxicities include gastrointestinal effects, with nausea and anorexia being the most frequently observed. Additional important toxicities to note are creatinine elevations and fatigue.

PARPi in Metastatic Prostate Cancer

Initially, patients with germline *BRCA1/2* mutations were the focus of studies with PARPi, which enrolled multiple

types of cancer including prostate cancer.¹⁷ Olaparib was the first PARPi to be investigated in 2009 in a Phase I clinical trial enriched for germline *BRCA1/2*-deficient solid tumor patients.¹⁸ In that study, among patients with *BRCA1/2*-deficient tumors, 63% were reported to have a clinical benefit to olaparib, defined as radiographic or tumor marker response or disease stabilization. A patient with metastatic castration-resistant prostate cancer (mCRPC) was noted to have a significant response with a decline in PSA and improvement of bone metastasis. After this study, multiple Phase III studies have been conducted in patients with *BRCA1/2* deficient tumors leading the approval of PARPi in breast and ovarian cancer. Specifically in ovarian cancer, PARPi have been shown to be effective in patients with unknown or wild-type *BRCA1/2* status who previously responded to platinum therapy.¹⁹ Additional studies have been conducted to evaluate surrogates to *BRCA1/2* mutations that may determine tumor response. With the impressive response to PARPi in breast and ovarian cancer, there has been a recognition that PARPi may also be a therapeutic option in other cancers including pancreatic and prostate cancer. PARPi monotherapy for mCRPC is summarized in Table 1.

Olaparib

Recently, PARPi have been recognized as an important cytotoxic agent in prostate cancer. The somatic and germline mutational landscape of mCRPC shows that ~15-25% have HRD gene alterations.²⁰⁻²³ In 2015, olaparib was studied in a Phase II clinical trial (TOPARP-A) of patients with mCRPC enriched for germline and somatic HRD gene mutations.²⁴ In this study, the primary endpoint of response rate (composite of 50% PSA decline, objective tumor response by RECIST, or CTC reduction) of 33% was observed, with a median duration of response of 40 weeks. One-third of the patients analyzed were determined to have germline or somatic bi-allelic defects in HRD genes. *BRCA2* was the most commonly mutated gene, but additional defects were noted in *ATM*, *BRCA1*, *FANCA*, *CHEK2* and *PALB2*. Importantly, patients with HRD alterations had an 88% composite response rate to olaparib, while patients without an HRD defect had a response rate of 6%. This study was followed by the TOPARP-B trial, which accrued patients based on having a HRD gene alteration.²⁵ Overall, two dose-levels of olaparib (300 mg and 400 mg, each given twice daily) were evaluated in patients with mCRPC who progressed on previous treatment. The primary endpoint was again

Table I Summary of Ongoing or Completed Trials of PARP Inhibitor Monotherapy in mCRPC

| PARPi | Study | Study Population | Selected Outcomes | Study Result |
|-------------|---|--|--|--|
| Olaparib | TOPARP-A Phase II, ²⁴ single arm, start date 7/2012, enrollment 50 patients | mCRPC, unselected for HRD mutations, previously received taxane therapy | Composite RR (PSA decline by \geq 50%, objective tumor response, CTC reduction) | - Composite RR 33% entire population - Composite RR 88% HRD mutations - Composite RR 6% no HRD mutation |
| | TOPARP-B Phase II, ²⁵ single arm, start date 4/1/2015, enrollment 98 patients | mCRPC, HRD selected, previously received taxane therapy | Composite RR (PSA decline by \geq 50%, objective tumor response, CTC reduction) | - Composite RR 54% at 400 mg dose level - Composite RR 39% for 300 mg dose level |
| | PROfound Phase III, ²⁶ compared to enzalutamide or abiraterone, start date 2/6/2017, enrollment 387 patients | mCRPC, HRD selected (cohort A: BRCA1, BRCA2, ATM mut, cohort B: 12 other pre-specific HRD genes), received second-generation hormonal agent and up to one taxane (or taxane-unfit) | Primary outcome rPFS in cohort A, secondary pre-specified outcome rPFS in cohort A+B, OS cohort A | - rPFS cohort A vs control 7.4 vs 3.6 mo - rPFS cohort A+B vs control 5.8 vs 3.5 mo - OS cohort A vs control 18.5 mo vs 15.1 mo |
| Rucaparib | TRITON2 Phase II, ^{27,28} single arm, start date 2/15/2017, estimated enrollment 360 patients | mCRPC, HRD selected, received second-generation hormone agent and a taxane | ORR per RECIST/PCWG3 Secondary: PSA decline by \geq 50% | - ORR for BRCA1/2 mut 43.5-50.8% - PSA response for BRCA1/2 mut 53.8% - ORR for ATM mut 10.5% - ORR for CDK2 mut 0% - ORR for CHEK2 mut 11.1% - ORR for other HRD mut 28.6% |
| Niraparib | GALAHAD Phase II, ²⁹ single arm, start date 8/31/2016, enrollment 291 patients | mCRPC, HRD selected bi-allelic, received second-generation hormone agent and a taxane | ORR by RECIST Composite RR (PSA decline by \geq 50%, objective tumor response, CTC reduction) | - ORR for BRCA/2 mut 41% - Composite RR for BRCA1/2 mut 63% - ORR non-BRCA1/2 HRD mut 9% - Composite RR non-BRCA1/2 HRD mut 17% |
| Talazoparib | TALAPRO-I Phase II, ^{30,31} single arm, start date 7/4/2017, estimated enrollment 100 patients | mCRPC, HRD selected, received second-generation hormone agent and a taxane | ORR per RECIST | - ORR of 25.6% |

Abbreviations: PARPi, poly (ADP-ribose) polymerase inhibitors; mCRPC, metastatic castration-resistant prostate cancer; RR, response rate; HRD, homologous recombination deficiency; CTC, circulating tumor cells; Mut, mutation; rPFS, radiographic progression-free survival; OS, overall survival; mo, months; ORR, objective response rate.

a composite of radiologic objection response, 50% decrease in PSA, or conversion of circulating tumor cells. An overall composite response of 54% was observed for the 400 mg dose level, and 39% for the 300 mg dose level. Of note, due to toxicity (mainly anemia), 37% of patients in the 400 mg dose level, and 12% of patients in the 300 mg dose level, required a dose reduction. The most commonly altered HRD genes in that study were *BRCA1/2* (33%), *ATM* (21%), *CDK12* (21%), *PALB2* (7%) and several others (21%). The overall composite response rate was 83% for men with alterations in *BRCA1/2*, and 20% in patients with unspecified other alterations. These

studies showed impressive efficacy in patients with mCRPC with an HRD gene alteration, which appeared to be driven primarily by mutations in *BRCA1/2*.

Recently, the pivotal phase III PROfound study compared olaparib to enzalutamide or abiraterone (physicians' choice) in patients with mCRPC who had previously received at least one second-generation hormonal agent and up to one taxane chemotherapy (permitted but not required).²⁶ For this study, patients all had an HRD gene alteration and were separated into two cohorts: cohort A patients with *BRCA1*, *BRCA2*, *ATM* mutations; and cohort B with alterations in one of the 12 other HRD

genes. The primary end-point for the study was radiographic progression-free survival (rPFS) in cohort A, which was significantly increased in the olaparib arm with an rPFS of 7.4 compared to 3.6 months in the physicians' choice arm (hazard ratio 0.34, $P < 0.001$). In a pre-specified secondary analysis, rPFS was then evaluated when combining all patients in both cohorts (cohort A + B); the rPFS was also substantially improved in this combined analysis in the olaparib group compared to the control group (5.8 months vs 3.5 months, hazard ratio 0.49, $P < 0.001$). Importantly, PROfound was the first study to show a statistical improvement in overall survival with PARPi in prostate cancer, with a median overall survival for cohort A of 19.1 months with olaparib versus 14.7 months with physicians' choice of second-generation hormonal therapy (hazard ratio 0.69, $P = 0.02$). Additional toxicities noted in this study included a 7% venous thromboembolism prevalence, and potential induction of myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML). The results of the PROfound study have led to the FDA approval (on May 19, 2020) of olaparib for men with metastatic castration-resistant prostate cancer harboring a germline or somatic HRD gene mutation (specifically: *BRCA1/2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*), who have previously received a second-generation hormonal agent.

Rucaparib

The results of the phase II TRITON2 study have led to accelerated FDA approval (on May 15, 2020) of rucaparib for men mCRPC harboring a germline or somatic *BRCA1/2* alteration, who have previously received a second-generation hormonal agent and a taxane chemotherapy.²⁷ The TRITON2 study showed an objective response rate (ORR) for patients with a *BRCA1/2* alterations of 43.5% (27/62 patients) when assessed by independent radiology review and 50.8% (33 of 65 patients) when assessed by the investigators, and a similar proportion achieved PSA responses as well.²⁸ When HRD alterations in non-*BRCA1/2* genes were analyzed (*ATM* 49 patients (pts), *CDK12* 15 pts, *CHEK2* 12 pts and other 14 pts), minimal response was observed.²⁷ Important toxicities that were reported include nausea (52%), anemia (43%), elevation in AST/ALT (33%) and additional gastrointestinal and hematological side effects. MDS/AML has been observed in small numbers of patients treated with rucaparib, but not specifically observed in the TRITON2 study. Full FDA

approval of this PARPi will be contingent upon positive results from the ongoing randomized phase III study, TRITON3, comparing rucaparib against physicians' choice of systemic therapy (chemotherapy or second-generation hormonal agent) in patients who have received one hormonal agent but not a taxane drug for mCRPC.

Niraparib

The phase II GALAHAD study using niraparib is being conducted in patients with mCRPC who have a biallelic HRD alteration and have progressed on a second-generation hormonal agent and a taxane chemotherapy. The gene panel included in this study includes *BRCA1/2*, *ATM*, *FANCA*, *PALB2*, *CHEK2*, *BRIP1*, and *HDAC2*. Interestingly, eligibility for this trial uses a liquid-based (ctDNA) assay for assessment of mutational status, and only patients with biallelic HRD mutations are permitted to enroll. The primary end-point for the study is ORR, and a secondary endpoint includes a composite response rate (RR) encompassing objective response, circulating tumor cell conversion, or PSA decline by 50% or more. An interim analysis reported in September 2019 showed an ORR of 41% for 29 patients enrolled with bi-allelic *BRCA1/2* mutations, and a 9% ORR for 22 patients with other bi-allelic HRD mutations.²⁹ The composite response rate was 63% for 46 patients for *BRCA1/2* alterations, and 17% for 35 patients for non-*BRCA1/2* alterations. The most significant reported side effects were hematologic (grade 3/4 anemia 25%, and thrombocytopenia 15%), along with non-hematologic effects including asthenia and hypertension. Niraparib is now being tested definitively in the phase III MAGNITUDE study, which is a randomized trial of niraparib plus abiraterone versus abiraterone alone (plus placebo) in men with metastatic CRPC.

Talazoparib

An interim analysis of the phase II TALAPRO-1 study was first reported at the 2020 GU ASCO symposium,³⁰ and was updated at the annual ASCO 2020 meeting.³¹ In TALAPRO-1, patients with mCRPC harboring mono- or bi-allelic alterations in one of the 11 pre-specified HRD genes were treated with talazoparib, with the primary outcome of overall ORR of 28% (21/75 patients). All patients had an HRD mutation, with differences noted in ORR depending on mutation type. For patients with *BRCA1/2* mutations, an ORR of 43.9% (18/41 patients) was noted while an ORR of 11.8% (2/17 patients) was noted for *ATM* mutations. The most commonly reported adverse events

were anemia, nausea, anorexia, and asthenia. Talazoparib is currently being tested definitively in the phase III TALAPRO-2 study, which is a randomized trial of talazoparib plus enzalutamide versus enzalutamide alone (plus placebo) in men with metastatic CRPC.

Combination Strategies with PARPi and Other Agents

PARPi have also been studied in combination with a number of other different agents. An interaction between androgen receptor signaling and synthetic lethality with PARPi has been proposed.^{32,33} In vitro data suggest that androgen deprivation impairs NHEJ and initiation of double-stranded break repair.^{34,35} Further data have demonstrated that combination treatment of bicalutamide plus olaparib in murine xenograft models leads to a decrease in tumor burden while single-agent treatment did not.³² This is being explored through a number of ongoing studies combining PARPi with second-generation antiandrogen therapies. A phase II study combining abiraterone and olaparib versus abiraterone alone in patients unselected for mutational status found an increase in rPFS in the olaparib plus abiraterone arm (13.8 months versus 8.2 months) compared to the abiraterone alone arm.³⁶ The phase III PROpel trial is being conducted to analyze olaparib in combination with abiraterone as first-line therapy in patients with mCRPC. The primary end-point for this study is rPFS. Ongoing trials with additional PARPi agents are also being completed in combination with second-generation androgen therapy. The phase III MAGNITUDE study with niraparib and abiraterone is being conducted in both patients with and without HRD alterations. The phase III TALAPRO-2 study is investigating the combination of talazoparib and enzalutamide in patients with mCRPC. The initial phase of dose finding has been completed, and the study is currently enrolling patients. For this study, there are also biomarker-positive and biomarker-negative cohorts being enrolled. Finally, the phase II NCI 9012 trial randomized mCRPC patients to abiraterone or abiraterone plus veliparib. This was a negative trial without a significant difference in rPFS in the combination abiraterone-veliparib arm.³⁷ In summary, PARPi in combination with second-generation antiandrogens are a potential combination therapy, which would greatly increase the patient population benefiting from PARPi. Multiple trials are currently being conducted and there may be differences in outcomes depending on the PARPi (or the combinatorial hormonal therapy partner) being investigated.

Combination therapy with PARPi and immunotherapy has also been proposed based on preclinical work linking DNA damage and immune activation. One proposed mechanism is that DNA damage leads to immune activation through the enhancement of stimulator of interferon genes (STING).³⁸ Multiple mechanisms have been proposed to connect DNA damage to immune activation in breast cancer, including STING activation and increased CD8+ tumor-infiltrating lymphocytes; an indicator of response to immunotherapy.³⁹ In cells lines, PARPi are shown to increase DNA damage leading to cytosolic DNA and ultimately STING activation. Combination therapy with talazoparib and anti-PD-L1 therapy has been shown to lead to increased survival in mouse syngeneic models of colorectal and ovarian cancer.⁴⁰ In prostate cancer, a phase I/II study of durvalumab plus olaparib in mCRPC was done with early indicators of response and adequate safety. Nine of the 17 patients had a decrease in PSA by 50% or greater. Toxicities reported include grade 3/4 anemia, lymphopenia, infection, and nausea. Additionally, 4 of the 17 patients had immune-related adverse events.⁴¹ The KEYNOTE-365 study is a phase I/II study of pembrolizumab plus olaparib in mCRPC patients who previously received docetaxel. Of note, 26% of patients had PD-L1+ disease. Results showed similar safety profiles to the individual agents, a PSA response of 8.5% (7/82 patients) and an ORR of 8.3% (2/24 patients).⁴² The KEYLYNK-010 is a phase III study comparing pembrolizumab plus olaparib versus abiraterone or enzalutamide in mCRPC patients who have progressed on chemotherapy (docetaxel) and one second-generation antiandrogen therapy in patients unselected for HRD alterations. A similar study (CheckMate 9KD) is testing the combination of rucaparib plus nivolumab in mCRPC patients that are unselected for HRD defects. These ongoing studies will help delineate the interaction of immunotherapy with PARPi and the potential synergistic effects.

Furthermore, PARPi have been investigated in combination with cytotoxic chemotherapy in solid tumors, with mixed results and concern for increased toxicity.⁴³ In prostate cancer, veliparib has been combined with temozolomide based on preclinical data in a small 25-patient single-arm study in mCRPC, with minimal clinical benefit achieved.⁴⁴ Therefore, the combination of chemotherapy plus PARPi in mCRPC is not being developed further at this time. Rather than combined with chemotherapy, a phase II study is being done with olaparib as maintenance therapy following treatment with cabazitaxel and carboplatin.

Additional combination trials are being completed with the goal to increase DNA damage through a variety of mechanisms. Such trials include the phase II study combining olaparib with ceralasertib, which targets the ATR (ataxia-telangiectasia and Rad3-related) protein. In vitro combination studies in ATM-deficient cell lines have shown synergy between PARP and ATR inhibitors.⁴⁵ Supraphysiologic (high-dose) testosterone is also being combined with olaparib in a phase II trial with the goal of increasing DNA damage with combination therapy.⁴⁶ Finally, in vitro and in vivo data have demonstrated increased cytotoxicity with the combination of DNA methyltransferase inhibitors (DNMTi) and PARPi.⁴⁷ DNMTi become incorporated into the DNA, trap DNMT enzymes, and also enhance PARP trapping when used in combination with a PARPi. This leads to an increase in double-strand DNA breaks and cytotoxicity. A phase I trial of a novel oral DNMTi plus talazoparib is being conducted in breast cancer patients (NCT04134884), and similar trials are currently being designed for patients with *BRCA1/2* wild-type mCRPC.

Finally, it is proposed that PARPi may augment the DNA damaging effects of ionizing radiation or radiopharmaceutical agents. In vivo studies combining fractionated radiation plus PARPi show promising data with increased tumor toxicity.⁴⁸ Radium-223 is a targeted alpha-particle therapy which has shown a survival benefit for prostate cancer patients with symptomatic bone metastases.⁴⁹ Two early-phase trials have been initiated combining radium-223 with PARPi in patients with mCRPC with known bone metastasis.⁵⁰ A Phase 1b study was presented at ASCO 2020 combining radium-223 with niraparib in patients with mCRPC.⁵¹ Combination therapy was considered to have adequate safety, with the most common grade ≥ 3 adverse events being cytopenias and hypertension. A secondary analysis of $\geq 50\%$ PSA response was 10% (3 of 30 patients) in the full cohort and was even higher at 14–30% (dose-dependent) in the chemotherapy-naïve group. Further studies are warranted, and indeed, others are currently ongoing to combine olaparib plus radium-223 as well. Combination studies involving PARPi are summarized in Table 2.

Limitations of the Current Data

The above studies use a variety of different primary outcome measurements. A number of studies use a composite primary end-point. Composite end-points can make it difficult to interpret results and understand what component

is driving the results. The field of PARPi has been rapidly evolving and many studies have been reported as interim results at international meetings but have not yet been published in peer-reviewed journals. An additional limitation to the listed studies is the variety of inclusion criteria based on tumor genetics to define HRD. The wide variety of definitions of HRD genes included in different studies and specific cohorts make it difficult to interpret the significance of mutations in genes such as *ATM*. *ATM* was included with *BRCA1* and *BRCA2* for cohort A of the PROfound study with unclear biologic reasoning.²⁴ While both olaparib and rucaparib have been approved by the FDA for use in prostate cancer, this is specific for drug approval in the United States and not in other parts of the world. Finally, no phase III studies, which are the standard for the adequate assessment of a therapy, have been reported for combination studies with PARPi.

Unanswered Questions and Future Directions

PARPi induce cytotoxicity through the novel mechanism of synthetic lethality in the appropriate genetic background. Robust data exists for the role of PARPi in patients with multiple tumor types with underlying HRD alterations, specifically *BRCA1/2* mutations. Due to the growing evidence of the efficacy of PARPi in prostate cancer, including a survival benefit for a subset of patients with *BRCA1/2* and *ATM* mutations in the PROfound study, the FDA approved olaparib for mCRPC patients with somatic and/or germline HRD alterations who have progressed through enzalutamide or abiraterone. Rucaparib was also approved in the setting of *BRCA1/2* mutation-positive patients with mCRPC who have progressed on androgen receptor therapy and taxane therapy. Rucaparib was approved on an accelerated basis and confirmatory studies (eg TRITON3) will be needed for full approval. These two approvals are a big step forward for our patients with HR-deficient prostate cancer, but also highlight the need to understand additional biomarkers of response to PARPi better than we currently do.

While for *BRCA1/2*, the evidence is growing that alterations in these genes are a strong predictor of a favorable response to PARPi, it is still unclear how HRD genes broadly should be classified. Different trials are using different panels of genes involved in the wider pathway of DNA repair to determine HRD status and are seeing variable results and inconsistent outcomes with

Table 2 Selected Combination Studies Involving PARP Inhibitors

| Class of Agent Combined with PARPi | Trial | PARPi | Combined Agent |
|--|--|----------------------|-------------------------------------|
| Second-generation antiandrogen therapy | Phase II [NCT01972217] Study start date 4/1/2014 Enrollment 158 patients | Olaparib | Abiraterone |
| | Phase III/PROpel [NCT03732820] Study start date 10/31/2018 Estimated enrollment 720 patients | Olaparib | Abiraterone |
| | Phase III/MAGNITUDE [NCT03748641] Study start date 1/25/2019 Estimated enrollment 1000 patients | Niraparib | Abiraterone |
| | Phase III/TALAPRO-2 [NCT03395197] Study start date 12/18/2017 Estimated enrollment 1037 patients | Talazoparib | Enzalutamide |
| Immunotherapy | Phase I/II [NCT02484404] Study start date 6/29/2015 Estimated enrollment 384 patients | Olaparib | Durvalumab |
| | Phase II/KEYNOTE-365 [NCT02861573] Study start date 11/17/2016 Estimated enrollment 400 patients | Olaparib | Pembrolizumab |
| | Phase III/KEYLYNK-010 [NCT03834519] Study start date 5/2/2019 Estimated enrollment 780 patients | Olaparib | Pembrolizumab |
| | Phase II/CheckMate 9KD [NCT03338790] Study start date 12/15/2017 Estimated enrollment 330 patients | Rucaparib | Nivolumab |
| Radiopharmaceutical | Phase I/II/COMRADE [NCT03317392] Study start date 10/12/2018 Estimated enrollment 112 patients | Olaparib | Radium-223 |
| | Phase Ib/II [NCT03076203] Study start date 10/22/2017 Enrollment 14 patients | Niraparib | Radium-223 |
| Chemotherapy | Phase Ib/II [NCT04019327] Study start date 7/11/2019 Estimated enrollment 55 patients | Talazoparib | Temozolomide |
| | Phase II [NCT03263650] Study start date 10/3/2017 Estimated enrollment 96 patients | Olaparib maintenance | Cabazitaxel and Carboplatin |
| High-dose testosterone | Phase II [NCT03516812] Study start date 8/29/2018 Estimated enrollment 30 patients | Olaparib | Testosterone enanthate or cypionate |
| ATR-targeted agent | Phase II [NCT03787680] Study start date 10/31/2019 Estimated enrollment 47 patients | Olaparib | Ceralasertib |

respect to specific gene alterations. This may be partly due to the differences in the PARPi themselves, but also in part due to the different effects each gene alteration has on DNA damage and repair. Additionally, the field is still

grappling with the best way to classify individual alterations within a given gene and determining those which are bystander alterations versus truly pathogenic drivers. Ultimately, a functional marker of HRD through a test

that does not depend on gene sequencing would be beneficial to expand and clarify the patient population which will benefit (or not) from PARPi treatment.

Combination strategies of PARPi with agents selected based on synergistic pre-clinical data will also be an important strategy to expand the population that may benefit from PARPi therapies. Pre-clinical data have shown a link between DNA damage and immune activation that is being leveraged by combining PARPi with checkpoint-targeting immunotherapy. While early studies are promising, additional data from KEYLINK-010 and CheckMate 9KD will help to clarify the role of immunotherapy combined with PARPi treatment. In addition, it will be interesting to determine whether the addition of an immune checkpoint inhibitor will also be able to improve the efficacy (and duration of response) of PARPi treatment in HR-deficient cancers, especially those with non-*BRCA1/2* HRD mutations.

Finally, the majority of the data for PARPi have been in patients with mCRPC, but given the positive results in this context, it will be interesting to see results from studies in earlier disease states ranging from neoadjuvant/adjuvant therapy for localized disease, to biochemical recurrence (ie micrometastatic disease), to metastatic hormone-sensitive prostate cancer. It will also be important to answer the question of whether androgen deprivation therapy is even necessary for PARP inhibitors to work in prostate cancer; preliminary data suggest that PARPi demonstrate efficacy in the hormone-naïve state even when used as monotherapies (without concurrent medical castration). Studies in early-stage disease will have to be approached with caution given the known side effects of cytopenias and concern for secondary MDS/AML which may be worsened with longer term therapy and longer survival. In this fashion, PARP inhibition will become a realization of personalized medicine in prostate cancer moving forward.

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