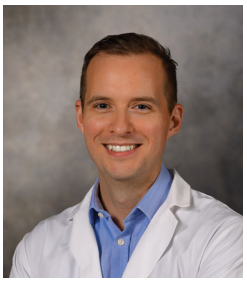
About the Author



Michael P. Kolinsky, MD, FRCPC

Dr. Kolinsky is a medical oncologist and clinical researcher at the Cross Cancer Institute, and an Associate Professor in the Department of Oncology at the University of Alberta in Edmonton, Canada. His primary clinical and research focus is on genitourinary and gynecologic cancers.

Affiliations: Cross Cancer Institute and University of Alberta, Edmonton, AB

The Evolution of PARP Inhibitors in Prostate Cancer

Michael P. Kolinsky, MD, FRCPC

Introduction

Poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors induce cell death in cancers by exploiting synthetic lethality, in which the combination of two defective cellular processes are lethal; however, either defect alone is not lethal.[1] PARP inhibitors impair the base excision repair pathway, which functions to repair single strand DNA breaks. Thus PARP inhibitors result in unrepaired single strand breaks, which are converted to double strand breaks during cellular replication. In a normally functioning cell, these double strand breaks are of little consequence, as the homologous recombination repair (HRR) pathway functions to repair these breaks efficiently and accurately. However, in the cellular background of defective HRR, classically through loss of *BRCA1* or *BRCA2* (*BRCA1/2*) protein function, the accumulation of these double strand breaks results in severe genomic stress and ultimately cell death.[2]

An extensive analysis of the early phase clinical trials of PARP inhibitors is beyond the scope of this review. However, it is worth noting the phase II TOPARP studies, were the first published trials investigating a PARP inhibitor in advanced prostate cancer. While the phase I studies of all clinically relevant PARP inhibitors were conducted in populations enriched for patients with mutations in *BRCA1/2*[3–6]; the key innovation of TOPARP was the demonstration of efficacy of the PARP inhibitor olaparib in metastatic castration-resistant prostate cancer (mCRPC) patients with defects in HRR genes other than *BRCA1* or *BRCA2*. The initial TOPARP-A study treated patients with mCRPC with olaparib in a single arm phase II design. The study's findings showed that patients with defects in a diverse range of genes, including *BRCA1, BRCA2, ATM, FANCA, CHEK2, PALB2, HDAC2, RAD51, MLH3, ERCC3, MRE11,* and *NBN,* had responses to treatment.[7] The larger TOPARP-B validation study enrolled 98 patients with mCRPC and pathogenic or likely pathogenic alterations in at least one of the following genes: *BRCA2, ATM, CDK12, PALB2, WRN, CHEK2, FANCA, FANCF, FANCM, ARID1A, ATRX, CHEK1, FANCG, FANCI, NBN,* or *RAD50*. Responses to treatment with olaparib were observed in 43 of the 98 enrolled patients. Response rates reported by gene subgroup analysis were *BRCA1/2*, 83.3%; *ATM*, 36.8%; *CDK12*, 25.0%; *PALB2*, 57.1%; and other, 20.0%. The median radiographic progression free survival in the intention to treat population was 5.5 months,

though this varied by gene subgroup as indicated: *BRCA1/2*, 8.3 months; *ATM*, 5.8 months; *CDK12*, 2.9 months; *PALB2*, 5.3 months; other, 2.8 months.[2] These results suggest a benefit of PARP inhibitors in a broader patient population beyond just patients with *BRCA1/2* alterations. Furthermore, the TOPARP trials have had a significant impact on the design of subsequent trials of PARP inhibitors in advanced prostate cancer.

Single agent PARP inhibitor trials:

Two phase III trials have been published that have evaluated the PARP inihibitors olaparib and rucaparib in patients with mCRPC.

The PROfound clinical trial compared olaparib to the investigators choice of either abiraterone acetate and prednisone (AAP) or enzalutamide in patients with mCPRC who were previously treated with AAP or enzalutamide, with prior taxane chemotherapy allowed. Patients in this trial must have had qualifying alterations in at least one gene of a 15 gene panel including *BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D,* and *RAD54L*, based on pre-screening tumour next generation sequencing (NGS). Patients with *BRCA1, BRCA2,* or *ATM* alterations were assigned to cohort A, and those with alterations in one of the other 12 genes were assigned to cohort B. The primary endpoint of this study was imaging-based progression free survival (ibPFS) in cohort A, and secondary endpoints included ibPFS in the overall population, response rates, and overall survival. Importantly, this trial allowed cross over to olaparib for patients with disease progression in the control arm. The PROfound trial met its primary endpoint by demonstrating an improved ibPFS in cohort A, with a median of 7.4 months for olaparib vs. 3.6 months for control (hazard ratio [HR], 0.34; 95% confidence interval [CI], 0.25 to 0.47; P<0.001).[8] A significant improvement in overall survival (OS) was also demonstrated in the cohort A population, with a median OS of 19.1 months for olaparib vs. 14.7 months for control (HR, 0.69; 95% CI, 0.50 to 0.97; P = 0.02),[9] despite 67% of cohort A patients in the control arm crossing over to receive olaparib. Results in cohort B were more modest, with a trend toward improvements in ibPFS and OS, with a median ibPFS of 4.8 months for olaparib vs. 3.3 months for control (HR 0.88, p value not reported), and a median OS of 14.1 months for olaparib vs. 11.5 months for control (HR 0.96, 95% CI 0.63 to 1.49, p value not reported). An exploratory gene-by-gene analysis of the PROfound trial has been published, and while limited by a small number of patients with alterations in many of the genes of interest, it is clear that the greatest benefit of olaparib is observed in patients with *BRCA2* alterations, with a modest if any benefit seen in patients with *ATM* alterations. The PROfound trial has led to the approval of olaparib by Health Canada for patients with mCRPC and alterations in *BRCA1, BRCA2,* and *ATM* genes based on findings from the cohort A population; whereas the FDA has approved olaparib in a broader population based on findings from the cohort A and B populations, except for patients with *PPP2R2A* alterations, who did not derive benefit from olaparib treatment.

The TRITON3 clinical trial[10] investigated rucaparib vs. a control arm of investigator's choice of therapy and was in many ways similar in design to the PROfound trial. Both trials investigated the use of a single agent PARP inhibitor compared to a control arm of standard therapies, in a previously treated mCRPC population. In both trials, patients underwent biomarker pre-screening for alterations in DNA repair genes. The primary end point of both trials was ibPFS. However, there were some key differences between the two trials. In the TRITON3 trial, the qualifying genetic alterations were limited to those in *BRCA1, BRCA2,* and *ATM* genes; eligible patients were those who received one line of prior androgen receptor pathway inhibitor (ARPI) and no prior taxane chemotherapy for mCRPC; and options in the control arm were AAP and enzalutamide, similar to the PROfound trial, but also included docetaxel. This final point is important to highlight, as a key criticism of the PROfound trial has been the choice of a relatively ineffective treatment as the control arm.[11] Indeed, in the TRITON3 trial, 56% of patients in the control arm were selected to receive docetaxel. In the overall population, rucaparib demonstrated a superior ibPFS with a median of 10.2 months for rucaparib vs. 6.4 months for control (HR, 0.61 95% CI, 0.47–0.80, p<0.001); with similar results observed in the *BRCA* subgroup, with a respective median ibPFS of 10.2 months for rucaparib vs. 6.4 months for control (HR,-0.50 95% CI 0.36–0.69, p<0.001). Similar to the PROfound trial, patients with *ATM* alterations were found to derive less benefit than that of those with *BRCA*, with a median ibPFS of 8.1 months for *BRCA* vs. 6.8 months for *ATM* (HR, 0.95, 95% CI, 0.59–1.52). Importantly,

the benefit of rucaparib was consistent when compared with either docetaxel or ARPI. The interim OS analysis has shown a trend toward improvement with a median OS of 23.6 months vs. 20.9 months (HR, 0.94, 95%.CI, 0.72–1.23) for rucaparib vs. control, respectively, in the overall population. Rucaparib had previously received FDA accelerated approval in mCRPC patients with *BRCA* alterations based on the phase II TRITON2 study, with the TRITON3 study supporting that approval. At the time of publication, rucaparib has not received Health Canada approval in this indication.

PARP inhibitor and ARPI combinations trials:

A number of trials have evaluated PARP inhibitors in combination with, as opposed to progression after, first line ARPIs. In contrast to the single agent trials however, these trials tested PARP inhibitors in a broader "all-comers" population, with biomarker stratification as opposed to selection. This approach was supported by pre-clinical evidence suggesting that ARPI therapy may induce a homologous recombination (HR) deficient state, which sensitizes cancers without genomic HRR defects to PARP inhibitors.[12,13] This hypothesis was further supported by the phase II Study 08, in which ARPI naive mCRPC patients were treated with AAP with either placebo or olaparib.[14] The study population did not undergo biomarker pre-screening. However, tumour and germline NGS was performed, and biomarker status (presence or absence of a pathogenic HRR gene alteration) was used in an exploratory analysis. The study demonstrated that the experimental treatment improved rPFS, with a median of 13.8 months for the experimental treatment arm vs. 8.2 months for the control arm (HR 0.65, 95% CI 0.44–0.97, p=0.034) with a consistent benefit across HRR biomarker status.

Following the findings of Study 08, three phase III trials have been published using a similar therapeutic strategy, though with slightly different designs.

PROpel, essentially the phase III extension of Study 08, evaluated the combination of AAP with either placebo or olaparib. The drugs were administered at standard doses for single agent use in mCPRC patients without prior exposure to ARPI or docetaxel for mCRPC.[15] While ARPI use other than AAP in earlier disease states was allowed, only one patient in the experimental arm received a prior ARPI, therefore this population should be considered ARPI naive. The primary end point of the trial was investigator-assessed ibPFS in the intention-to-treat population. The biomarker status was determined after enrolment (i.e. was not used as a prospective stratification factor). The biomarker status was determined using tumour tissue, ctDNA, and whole blood NGS. Patients were categorized by *BRCA* mutational status, as well as HRR mutational status, based on a 14 gene panel. Among the 399 patients who were randomized, ibPFS was significantly improved, with a median of 24.8 months for the experimental arm vs. 16.6 months for the control arm (HR, 0.66, 95% CI 0.54–0.81, p<0.001). This finding was consistent across all subgroups, though a greater benefit was apparent in the HRRm subgroup (median ibPFS not reached in the experimental arm vs. 13.9 months in the control arm; HR, 0.50 95% CI 0.34–0.73) vs the non-HRRm subgroup (median ibPFS of 24.1 months in the experimental arm vs 19.0 months in the control arm; HR, 0.76, 95% CI 0.60–0.97). The updated final OS analysis demonstrated a trend toward OS benefit, with a median OS of 42.1 months vs 34.7 months for the experimental and control arms, respectively. While this is an important numerical difference, it failed to reach statistical significance.[16] It is important to note that this study was conducted when access to standard of care PARP inhibitors was limited; and only 1% of patients in each arm subsequently received a PARP inhibitor.

TALAPRO-2 was a phase III trial that evaluated the combination of enzalutamide 160 mg daily with either placebo or talazoparib 0.5 mg daily, (whereas the standard single agent dose of talazoparib is 1 mg daily) in mCRPC patients with no prior mCRPC therapy, though prior docetaxel, abiraterone, or orteronel therapies were allowed in the mCSPC setting. In contrast to the PROpel trial, the biomarker status was defined prospectively during the trial screening procedures and was used as a stratification factor. Patients underwent tumour tissue and ctDNA analysis to classify their HRR mutational status based on a 12 gene panel. The primary endpoint of the study was rPFS that was assessed by a blinded independent central review. This study randomized 805 patients, of which only 50 were previously treated with an ARPI. The results of the TALAPRO-2 study were consistent with those from the PROpel trial, with a significant improvement in rPFS in the intention-to-treat population, with a median

rPFS not reached for the experimental arm vs. 21.9 months for the control arm (HR, 0.63, 95% CI 0.51–0.78, p<0.0001). Similar to the PROpel trial, a benefit was observed irrespective of biomarker status, with the greatest benefit observed in the BRCAm subgroup (HR, 0.23, 95%CI 0.10–0.53, p=0.0002), followed by the non-BRCA HRRm subgroup (HR, 0.66; 0.39–1.12, p=0.12), with the non-HRRm or unknown subgroups showing the least benefit (HR 0.70, 95%CI 0.54–0.89, p=0.0039). Overall survival data is not yet mature.

The MAGNITUDE trial, which investigated AAP at standard dosing with either placebo or niraparib 200 mg daily (standard single agent dose of niraparib is 300 mg, or 200 mg in patients <77 kg or baseline platelet count <150,000/uL) included design elements that were distinct from the other combination trials. Similar to the TALAPRO-2 trial, patients underwent prospective biomarker analysis prior to randomization, using tumour tissue, ctDNA, and whole blood to determine HRR gene mutation status, though in this trial a 9 gene panel was used. Unlike the other trials, however, patients were allocated to and analyzed in two distinct cohorts. The HRR+ cohort included patients who had at least one pathogenic alteration in at least one gene, and the HRR- cohort included patients with no pathogenic alterations. An additional unique aspect of this trial was that up to 4 months of AAP treatment for mCPRC was allowed prior to randomization to allow time for HRR biomarker testing, which 23% of patients on the trial had received. The primary endpoint of this trial for both cohorts was rPFS assessed by a blinded independent central review. In the HRR+ cohort that included 212 randomized patients, rPFS was significantly prolonged, with a median of 16.6 months in the experimental arm vs. 10.9 months in the control arm (HR, 0.53, 95% CI 0.36–0.79). However, on subgroup analysis, this finding was largely driven by the patients with *BRCA* mutations (HR 0.55, 95% CI 0.38–0.81), and patients with other non-BRCA HRR mutations demonstrating minimal if any benefit (HR, 0.99, 95% CI 0.68–1.45). Outcomes in the secondary endpoints all favoured the experimental arm. In the HRR- cohort, a futility analysis was performed after 233 patients were randomized. This analysis used both the time to PSA progression and rPFS as individual endpoints. In addition, these two measures were also used together as a composite endpoint. Futility was declared for this cohort ,with the composite endpoint showing no benefit of niraparib (HR, 1.09, 95%, 95% CI 0.75–1.57, p=0.66).

The reasons why the MAGNITUDE trial failed to demonstrate an rPFS benefit of adding niraparib to AAP in patients without *BRCA* alterations are not known but may include the following: The drug itself, which seems unlikely given that niraparib has demonstrated comparable efficacy to other PARP inhibitors as a single agent in both prostate and ovarian cancer. The reduced dose of niraparib, again this is unlikely given that the 200 mg starting dose has been used in ovarian cancer trials in patients with a baseline weight of <77 kg or a platelet count of <150,000 uL and that this dose has shown a similar efficacy to the 300 mg dose; [17,18] or the different design of the trial itself. In contrast, the consistent results demonstrated in the PROpel and TALAPRO-2 trials leaves little doubt that the benefits of these therapies exist across patient subgroups. The controversy associated with these trials is rather whether the benefit observed in the non-BRCA patient population can translate into a meaningful clinical benefit. At present, this remains an academic question, as both olaparib and niraparib have only been approved by Health Canada for use in combination with a first line AAP in patients with mCRPC and pathogenic *BRCA1/2* alterations.

Approach to patients:

Most Canadian jurisdictions now have access to tumour and/or germline NGS for *BRCA1, BRCA2,* and *ATM* at a minimum, with many using broader gene panels. I believe that, where available, all patients with mCRPC should undergo NGS testing, as well as those in earlier disease states that are likely to progress to mCRPC, such as mCSPC and nmCRPC.

A key distinction is whether patients have previously been treated with an ARPI in an earlier disease state. While prior ARPI therapy was allowed in the combination trials, the vast majority of patients on these trials were ARPI naive and therefore the results of these trials should only be applied to this population.

ARPI naive patients:

Let us first consider a patient with mCRPC with a pathogenic or likely pathogenic (also referred to as Tier I or Tier II) alteration in *BRCA1* or *BRCA2* identified on tumour or germline NGS who has not yet received an ARPI. First line mCRPC options for this patient would include

ARPI monotherapy, ARPI plus PARP inhibitor combination therapy, or docetaxel. The first consideration is that patients with *BRCA* alterations have worse outcomes on ARPI therapy compared to patients with *BRCA* wildtype. This has been conclusively demonstrated in the PROpel and TALAPRO-2 studies in which rPFS was significantly shorter for patients with HRR+ compared to HRR- patients treated on the control arms of these trials. The combination trials definitively show improved efficacy of combination therapy as measured by rPFS, as well as a number of other secondary endpoints, including response rate, time to subsequent therapy, and PFS2. However, some authors debate whether this benefit can justify exposing patients to the significantly increased cost and toxicity associated with PARP inhibitors.[19] For instance, PARP inhibitors are associated with increased toxicity, particularly hematologic toxicity, and nausea. These adverse effects are generally manageable with supportive treatment, treatment interruptions, and/or dose reduction, as evidenced by only modestly increased rates of treatment discontinuation in the combination trials. Reassuringly, combination therapy did not have a negative impact on patients' reported quality of life outcomes as described in the PROpel and MAGNITUDE trials. Undoubtedly the financial cost of combination therapy is significantly higher than that of sequential monotherapy use. While AAP is now available as a generic medication, significantly reducing its cost, the cost of olaparib for a 28-day cycle is $7380CAD,[20] with a median duration of exposure to olaparib of 17.5 months in the PROpel trial and 7.4 months in the PROfound trial. Additionally, OS benefit has not been demonstrated in any of the trials conducted thus far. And because so few patients received PARP inhibitors after progression (approximately 2% in both PROpel and TALAPRO-2 trials, and in the MAGNITUDE trial, 1% in the experimental arm, and 20% in the control arm), even a survival advantage would not address the question of whether combination therapy is superior to sequential monotherapies. On the other hand, delaying progression is an important goal for both clinicians and patients, and the magnitude of benefit observed in these trials is clinically meaningful. Therefore, in my opinion, all eligible patients should be considered for combination ARPI and PARP inhibitor therapy when it is available in the first line mCRPC setting if no prior ARPI has been received in earlier disease states. Moreover, a balanced discussion of the risks and benefits should take place to facilitate a shared decision-making process between the patient and clinician. However, for patients who are not willing to undergo the additional monitoring required for these combination therapies, for those who desire a decreased pill or side effect burden, or in situations in which financial cost is a limiting factor, sequential monotherapies with ARPI followed by a PARP inhibitor remains a reasonable therapeutic strategy.

There is no available data that compares the efficacy of first line ARPI and PARP inhibitor combinations to docetaxel for mCRPC patients; however, the TRITON3 trial demonstrated that rucaparib was superior to docetaxel in a cohort of patients with *BRCA* or *ATM* alterations after progression on ARPI. Therefore, I think it is a reasonable extrapolation that combination therapy is likely preferable to docetaxel in the ARPI naive setting. However, there are some clinical settings in which docetaxel may remain a treatment option, such as patients with a very low PSA relative to the burden of metastatic disease, in such cases ARPI therapies tend to have limited efficacy.

APRI pre-treated patients:

Patients with mCRPC previously exposed to an ARPI should be considered for PARP inhibitor monotherapy, especially considering that this was the population studied in the PROfound and TRITON3 clinical trials. Both trials primarily studied patients with pathogenic alterations in *BRCA1, BRCA2,* or *ATM*; at present, olaparib is approved by Health Canada for this indication, and rucaparib is not approved.

In my opinion, the choice of when to use olaparib depends on the gene alteration present, what other therapies are available, and patient factors, including their preferences. For patients with *BRCA* alterations, I preferentially use olaparib over other therapies based on the PROfound and TRITON3 trials that demonstrated benefit over second line ARPI, and the TRITON3 trial, which showed benefit over docetaxel. While there is no direct comparison, the objective response rate of 44% and the PSA50% response rate of 62%, respectively, that were observed in the PROfound trial[8] in *BRCA* patients compare favourably with findings that have been demonstrated in the registration trials for radium 223,[21] cabazitaxel,[22] and Lu-177-PSMA-617.[23] Additionally, most patients value an oral therapy for its convenience over intravenous therapies.

My approach to patients with *ATM* alterations follows a similar logic as noted above, but given the very modest efficacy demonstrated in the PROfound trial for this subgroup, with an objective response rate of 10% and a PSA 50% response rate of 13%,[8] with similar results noted in the TRITON3 trial, I generally recommend other agents, such as taxane chemotherapy, prior to olaparib. However, I consider using olaparib in patients who may not be fit for, or those who chose to avoid or delay, cytotoxic chemotherapy as long as they are asymptomatic or minimally symptomatic with a relatively low disease burden, such that if disease progression occurs it is not likely to cause significant clinical deterioration.

Conclusions

The introduction of PARP inhibitors in the management of advanced prostate cancer has been a significant breakthrough that offers benefits to patients. With numerous active and ongoing trials, this is a rapidly evolving field and we can anticipate further shifts in treatment approaches. As with other therapeutic agents, we may witness the introduction of PARP inhibitors into earlier disease states, such as metastatic castration sensitive prostate cancer. As always, when making treatment decisions in collaboration with patients, it is important to balance the efficacy of these treatments with their side effect burden and financial cost.

Correspondence

Dr. Michael P. Kolinsky
Email: Michael.Kolinsky@albertahealthservices.ca

Financial Disclosures

Honoraria/consulting fees: AstraZeneca, Astellas, Bayer, BMS, Eisai, EMD Serono, Ipsen, Janssen, and Merck.

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