REVIEW

Role of Rucaparib in the Treatment of Prostate Cancer: Clinical Perspectives and Considerations

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Abstract: Prostate cancer is one of the most common types of cancer worldwide and has strong genetic associations. This is important for the development of therapeutics for the condition, as metastatic castrate-resistant prostate cancer (mCRPC) is resistant to standard androgen deprivation therapy (ADT) and has a relatively poor prognosis. We conducted a literature review on rucaparib, a poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor that is currently indicated for the treatment of patients with mCRPC who harbor mutations in BRCA1/2 (homologous recombination repair [HRR] genes) and who have already tried androgen receptor-axis-targeted therapies (ARAT) and a taxane chemotherapy. We describe rucaparib's FDA approval, which was based on the results of the single-arm, open-label, Phase II TRITON2 clinical trial, which found an objective response rate (ORR) of 43.5%, a duration of response (DOR) of over six months in length and an acceptable safety profile. Rucaparib's dosage and clinical considerations for use were also discussed. We also compared rucaparib's use and safety profile with Olaparib, niraparib and talazoparib, three other PARP inhibitors tested for the treatment of mCRPC. Overall, initial results show that the safety profile of all four drugs in mCRPC was relatively similar, and further testing is currently indicated for all four. Differences in their metabolism, however, also warrant further research. The clinical validity of rucaparib will be tested by the follow-up TRITON3 clinical trial, which is comparing the effect of rucaparib compared to standard therapies for mCRPC harboring BRCA1/2 or ATM mutations. Other than TRITON3, other clinical trials are testing rucaparib's ability against other cancers (prostate or otherwise) with HRR mutations, and also the efficacy of combination therapies involving rucaparib. Finally, more research is needed to elucidate rucaparib's effect on HRR mutations other than BRCA1/2. Advancements in understanding the genetic landscape of mCRPC will also assist in understanding rucaparib's full therapeutic potential.

Keywords: metastatic castrate-resistant prostate cancer, homologous recombination repair, PARP inhibitors, literature review

Introduction

Prostate cancer (PCa) is one of the most common types of cancer in the United States (US) and worldwide, being the 2nd most commonly diagnosed cause of cancer in men in 2020.[1] PCa also has a relatively high survival rate, with age-standardized 5-year net survival rates ranging from 70% to 100% in most countries.[2] Not all cases are equally survivable, however. For example, data from the US has shown that both localized and regional tumors have a 5-year relative survival rate of >99%. Once the tumor has metastasized, this figure falls sharply to 32.3%.[3]

The standard first line of treatment for metastatic PCa is androgen deprivation therapy (ADT). This is because prostate cancer cells have been shown to be sensitive to androgen levels, meaning that depriving the cancer of these compounds leads to a reduction in their presence and function.[4] Over 95% of patients initially respond to ADT with a decrease in prostate-specific antigen (PSA) levels. Unfortunately, all hormone sensitive metastatic PCa will eventually progress despite ADT treatment, and all patients will eventually transition to the metastatic castrate-resistant prostate cancer (mCRPC) state.[5,6]

Multiple studies have attempted to analyze the genomic alterations present in mCRPC to both better characterize its properties and to find potential angles for therapeutic intervention. This is because many studies have shown an association between prostate cancer and genetic factors. Examples include one study that found that men with brothers

with prostate cancer were significantly more likely to develop any-risk prostate cancer, and another finding that up to 57% of prostate cancer can be attributed to genetic risk factors.[7] In fact, at least 260 germline genetic variants associated with PCa have been identified via whole-genome sequencing — a number that continues to grow as more genetic analyses on more diverse populations are conducted.[8] Germline DNA repair mutations are particularly associated with aggressive disease, metastatic progression, and cancer-specific mortality.[7,9] Studies have shown that the percentage of mCRPC patients with germline mutations in these genes range from 8% to 16%.[9–11]

mCRPC has also been associated with many somatic mutations, including those in androgen receptor signaling, tumor suppressor deficiencies (notably, RB1 and TP53), various oncogenes (including the ETS family of transcription factors, PI3K signaling and the TGF-β/SMAD4 pathway) and DNA repair mechanisms as well.[12–14] Overall, DNA analysis has shown that ~90% of patients with mCRPC have a potentially targetable somatic or germline mutation. Furthermore, 65% of mCRPC patients have mutations that do not involve androgen receptor pathways, which provides promising therapeutic avenues considering mCRPC's resistance to ADT.[10]

As mentioned previously, one large subset of mCRPC mutations occur in DNA repair and the DNA damage response. Approximately 19–27% of mCRPC patients harbor mutations interfering with homologous recombination repair (HRR) genes, which play a major role in repairing double-stranded breaks (DSBs) in the DNA with high fidelity.[15] BRCA2 and ATM are two of the most commonly mutated HRR genes, and according to studies have a prevalence of 8.7–13% and 5.9–7.3% in patients with mCRPC, respectively.[10,15,16] Function wise, both BRCA2 and ATM play a part in recruiting and enhancing Rad51 (which binds to the single-stranded DNA and finds its homologous partner) and acting as a signaling hub for the HRR process at the site of the DSBs respectively.[15,17–19] Damage to the HRR pathway results in cells relying on other DNA repair methods such as non-homologous end-joining (NHEJ) to repair double-stranded breaks. Because NHEJ does not use a guide template in its repair process, more errors and thus mutations occur, leading to disease progression.[15]

The aforementioned findings have led to the use of poly(adenosine disphosphate-ribose) polymerase (PARP) inhibitors as a therapy for individuals who have mCRPC with HRR deficiencies. Originally developed for the treatment of BRCA1/2 mutated ovarian cancer, PARP inhibitors act as competitive inhibitors for PARP enzymes, which add branched poly(adenosine diphosphate-ribose) chains to sites of DNA strand breaks.[20,21] Doing so assists in remodeling local chromatin structure and recruiting DNA repair proteins, thus initiating the DNA repair process.[20,22] PARP inhibitors act as competitive inhibitors with the enzymes' substrate, nicotinamide adenine dinucleotide (NAD), causing enzyme dysfunction.[20,22] Furthermore, by inhibiting catalytic activity, these compounds "trap" PARP enzymes (specifically, PARP1) on the damaged DNA chain. One example for why this happens is that PARP's release from DNA is theorized to be in part due to its ability to add poly(adenosine diphosphate-ribose) chains to itself, causing a negative charge repulsion and its expulsion from the DNA.[20,22] The actions of PARP inhibitors (PARP1 trapping and PARP enzyme inhibition), combined with a lack of HRR repair mechanisms and faster replication in HRR deficient tumor cells then lead to excessive amounts of DSBs and replication fork collapses, ultimately causing cell death.[20]

Currently, there are four US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved PARP inhibitors — niraparib (brand name: Zejula), talazoparib (brand name: Talzenna), olaparib (brand name: Lynparza), and rucaparib (brand name: Rubraca).[23–26] The four PARP inhibitors differ in a number of ways, including their selectivity for what PARPs they bind to. While all bind PARP1, rucaparib is the least selective, also binding many other PARP proteins and even other targets, such as hexose-6-phosphate dehydrogenase, leading to different effects. Moreover, another major difference between the different PARP inhibitors is their PARP trapping ability. Finally, other aspects include their pharmacokinetics and their toxicity to liver and/or kidney function.[20,27] In the case of mCRPC, both olaparib and rucaparib have been approved for treating the condition in the presence of HRR deficiencies.

This narrative review will focus on the clinical considerations for rucaparib, which in May 2020 was granted an accelerated approval by the FDA for the treatment of mCRPC patients with HRR deficiencies (specifically with BRCA mutations) who had already been treated with ADT and taxane chemotherapy.[28]

Materials and Methods

Literature and abstract searches were conducted on PubMed and clinicaltrials.gov, identifying and analyzing relevant publications that were published from January 1st, 2017 through October 1st, 2022. Publications were analyzed for their content on rucaparib and its relevant clinical trials and what they assessed. In addition, data on other PARP inhibitors were assessed for their comparison with rucaparib.

Current Uses of Rucaparib

FDA Approval and Rationale

On May 15th, 2020, rucaparib was granted an accelerated approval by the FDA for the treatment of patients with mCRPC who had a confirmed harmful germline or somatic mutation in BRCA1 or BRCA2 (a common HRR defect in those with mCRPC). Furthermore, patients had to have experienced disease progression after being treated with ARAT and a taxane chemotherapy.[29]

Rucaparib was granted this status by the FDA due to the initial results of the TRITON2 clinical trial (Identifier Number: NCT02952534), which initiated in February 2017 and ended in July 2021.[28] TRITON2 was a single-armed, open-label, Phase II study testing the effects of the drug in male patients ≥18 years old with mCRPC who also had confirmed germline or somatic mutations in a number of HRR genes (including BRCA1/2 and ATM).[28] Furthermore, other eligibility requirements included previous therapy with ARAT and taxane chemotherapy before starting rucaparib, and concurrent therapy with a gonadotropin-releasing hormone analog if the patient had not had a bilateral orchiectomy. Exclusion criteria included patients who had previously been treated with another PARP inhibitor, mitoxantrone, cyclophosphamide, or platinum-based chemotherapy. In addition, patients were recruited regardless of their measurable disease status.[30]

Although the study analyzed 277 patients in total, FDA approval was based on data from an initial cohort of 115 patients who specifically had BRCA-mutated mCRPC.[28,29] This cohort of 115 was divided into a main group and a supportive, exploratory group — those who had measurable (n = 62) or non-measurable disease (n = 53) via independent radiologic review (IRR) respectively. For individuals with measurable disease, the primary endpoint was the ORR, defined as a tumor's complete or partial response to therapy as defined by both the modified Response Evaluation Criteria in Solid Tumors (mRECIST) v1.1 and Prostate Cancer Clinical Trials Working Group 3 (PCWG3) guidelines.[29–31] The secondary outcome for this group was the duration of response (DOR) of treatment, defined as the time of responding to treatment without tumor growth or metastasis.[31] This measurement used the same guidelines as used in defining the ORR. Finally, for the group without measurable disease as assessed via IRR, the primary and secondary endpoints were a PSA response (defined as a ≥50% decrease in PSA levels) and DOR, respectively.[29]

Results showed that the ORR for the measurable disease group (measured via IRR) was 43.5%, with a 95% confidence interval (CI) of 31–56.7%. Specifically, seven patients had achieved a complete response (11.3%) and 20 had a partial response (32.3%).[29,30] At the time of the FDA evaluation, the median DOR was not reached, meaning that ≥50% of the patients in the group were living at the time.[32] However, analyses showed that the lower bound of the 95% CI was ≥6 months in length.[29,30] This is further confirmed via the final results published at the end of the study, showing that the DOR in patients with confirmed response per IRR measurement was 15.5 months, with a 95% CI of 6.4 to a not assessable number.[28] For the exploratory non-measurable disease group, no specific numbers were published. However, overall, 63 out of the 115 total patients (54.8%, 95% CI: 43.2–64.1%) exhibited a PSA response, and the values were similar between those in the measurable and non-measurable group. Thus, it was believed that even those with non-measurable disease were benefitting from treatment.[29,30] These results showed that while TRITON2 focused on rucaparib's effect on patients with mCRPC and BRCA mutations specifically, the effect on this large patient demographic was significant and notably had an effect on patients who had already progressed past docetaxel and ARAT. Given the other supportive evidence, which included: 1. A median DOR ≥6 months, 2. Evidence that people with non-measurable disease were affected, and 3. An acceptable safety profile, it was determined that rucaparib was an acceptable treatment.[29,30]

TRITON3 (Identifier Number: NCT02975934), a follow-up Phase III randomized clinical trial, will be used to confirm the efficacy of rucaparib compared to a physician's choice of next-generation androgen receptor-axis-targeted

therapies (ARAT) or docetaxel chemotherapy.[33] "Crossover" from the control group to rucaparib is also possible if the patient shows disease progression during treatment with the former.[34] Work on this study started in June 2017 (a few months after the start of TRITON2) and has enrolled 405 patients in total, higher than its goal of 400 patients. Thus, recruitment has since stopped, and the study has reached its estimated primary completion date of June 2022.[33,34] No results have been released as of yet.

Rucaparib Use

Rucaparib is prescribed as oral tablets that are 200mg, 250mg, or 300mg in strength. As seen in the TRITON2 study, patients who are prescribed rucaparib should also be receiving a gonadotropin-releasing hormone analog at the same time or have had a bilateral orchiectomy performed.[35] Rucaparib's half-life is 26 hours and the recommended initial dose is 600 mg twice a day (every 12 hours).[36,37] While it was shown that high-fat meals increase rucaparib's bioavailability at 600mg, it was not seen as a clinically significant result, meaning that rucaparib can be taken with or without food.[38] Dose decreases can be made, however, depending on either the advent of any adverse events (to be discussed further in another section). For example, with adverse events, the dosage for Rucaparib would drop to 500mg, 400mg, and 300mg twice daily with each new event. Discontinuation may occur in the event of unacceptable toxicity or disease progression.[37] It is noted that given rucaparib's accelerated approval status that proper dosage or use information may change depending on the status of further clinical trials and data collected, as perhaps will be seen with TRITON3 and other future studies.[35]

Safety of Rucaparib

During the TRITON2 clinical trial, the safety of rucaparib was primarily evaluated by recording the advent of any adverse events that occurred in the 115-patient cohort analyzed in the efficacy portion of the evaluation. The criteria used National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), which divides adverse events into different grades of severity.[39] For the primary safety population evaluated in the TRITON2 clinical study (n = 115), 99.1% (n = 114) patients experienced an adverse event of any grade, and 60.9% (n = 70) experienced an adverse event grade ≥3, with three patients (2.6%) dying, one each from pneumonia, a prolonged QT, and acute respiratory distress syndrome. The only death determined related to rucaparib in this group was the latter, as determined by the investigator. 7.8% of patients (n = 9) discontinued the medication and 63.5% (n = 73) experienced a treatment interruption or a dose reduction due to an adverse event.[30] The most common adverse events recorded included asthenia/fatigue (61.7%), nausea (52.2%), anemia/decreased hemoglobin (43.5%), an increased ALT/AST (33.0%), decreased appetite (27.8%), constipation (27.0%), rashes (25.2%), thrombocytopenia/decreased platelets (25.2%), vomiting (21.7%), diarrhea (20.0%), dizziness (18.3%), and a blood creatinine increase (15.7%) (Table 1). The most common Grade ≥3 adverse events in this group were anemia/decreased hemoglobin (25.2%), thrombocytopenia/decreased platelets (9.6%), rash (9.6%) and asthenia/fatigue (8.7%) (Table 1).[30]

Table 1 also shows data collected from the total TRITON2 cohort as a whole (n = 277), which included 172 individuals with a BRCA mutation and thus constituted a larger sample size that had patient data over a longer period of observation (this cohort included 59 individuals with a deleterious ATM, 14 with a deleterious CDK12, 7 with a deleterious CHEK2, and 25 with other HRR gene mutations, however). When analyzing the larger cohort, the statistics are largely similar.[28] Two hundred and seventy-four out of the 277 (98.92%) patients suffered from some adverse event, with 96 (34.66%) suffering from a serious adverse event.[28,40] 8/277 patients (2.89%) died during the clinical study, but as this was due to any cause, it is not known how many were attributed to rucaparib specifically. Differences in the frequencies of various adverse events were relatively slim. One of note, however, includes an 18.6% difference in the rate of patients exhibiting an increase in ALT/AST. Multiple studies have shown though that these increases were common during rucaparib treatment with normal dosages, these values did not correlate with increases in bilirubin levels and hepatotoxicity.[36,41–43] Second, a 6.9% increase in the proportion of individuals experiencing a decreased appetite was recorded, but given the low percentage of those experiencing a grade ≥3 adverse event in the FDA Approval Cohort, initial data shows that this may not be a large concern associated with rucaparib use.[28,30]

It is noted that these findings are similar to those found in studies analyzing the effect of rucaparib on ovarian cancer, its original use.[21] This includes myelosuppression, which can lead to conditions such as anemia, neutropenia,

Table 1 List of Any Grade and Severe Grade (Grade ≥3) Adverse Events Recorded in FDA Approval Cohort and Total Cohort of TRITON2 Clinical Trial Affecting ≥15% of Patients (Any Grade)

Adverse Event Symptom	TRITON2 FDA Approval Cohort (n=115)		TRITON2 End of Study Cohort (n=277)	
	Any Grade (%)	Grade ≥3 (%)	Any Grade (%)	Grade ≥3 (%)
Asthenia/Fatigue	61.7	8.7	65.3	1.4
Nausea	52.2	2.6	50.2	0.7
Anemia / Decreased Hemoglobin	43.5	25.2	46.6[a]	5.8[b]
Increase in ALT/AST	33.0	5.2	51.6	N/A[c]
Decreased Appetite	27.8	1.7	34.7	N/A[c]
Constipation	27.0	0.9	27.4	N/A[c]
Rash[d]	25.2	9.6	21.3[e]	N/A[c]
Thrombocytopenia/Decreased Platelets	25.2	9.6	23.5	N/A[c]
Vomiting	21.7	0.9	24.2	1.1
Diarrhea	20.0	0	23.5	1.1
Dizziness	18.3	0	19.1	0.4
Blood Creatinine Increase	15.7	0.9	18.0	0.7

Notes: [a]Results did not specify if the term anemia included a lab result of decreased hemoglobin. [b]Includes Anemia, Anemia of malignant disease, and aplastic anemia. Results did not specify if the term anemia included a lab result of decreased hemoglobin. [c]N/A indicates that no data for the specific diagnoses was recorded. [d]Includes blister, blood blister, dermatitis, dermatitis contact, eczema, genital rash, palmar-plantar erythrodysesthesia syndrome, photosensitivity reaction, psoriasis, rash, rash maculo-papular, rash pruritic, skin exfoliation, skin lesion, and urticaria. [e]Includes dry skin, photosensitivity reaction, and rash, as diagnoses from the MedDRA 23.0 database. Data from these studies.[27,29]

thrombocytopenia in both ovarian cancer and mCRPC. More concerningly, an analysis on 1321 patients who received at least one dose of oral rucaparib regardless of tumor type by the European Medicines Agency showed that 0.5% of patients reported a diagnosis of myelodysplastic syndrome or acute myeloid lymphoma during treatment and during a 28-day safety follow-up period.[44] 1.3% of patients who had a long-term safety follow-up also reported these diagnoses.[42,44] It was noted, however, that these diagnoses were not necessarily due to rucaparib, as all patients assessed had previously undergone treatment with platinum-containing chemotherapy treatments and other DNA damaging agents.[44] Interestingly, during the course of the TRITON2 clinical trial no reports of myelodysplastic syndrome or acute myeloid lymphoma were recorded, perhaps suggesting better outcomes. In the total cohort, however, one grade ≥3 chronic lymphocytic leukemia was recorded.[28]

Comparison with Other PARP Inhibitors
Rucaparib and Olaparib

Currently, the only other FDA approved PARP Inhibitor for mCRPC is Olaparib, which was given a full FDA approval a few days later than rucaparib, on May 19, 2020.[37] Olaparib was also approved by the EMA in November 2020 for mCRPC — a decision that has not been granted to rucaparib as of yet (Table 2).[45]

These decisions were given in part due to results from past clinical trials that Olaparib was tested in, namely, the Phase II TOPARP-A and TOPARP-B and the phase III PROfound studies. In the TOPARP-A trial, Olaparib was seen to achieve a composite response much more in HRR-altered patients (88%, 14/16) vs HRR-efficient patients (6%, 2/34). These findings were further analyzed with the TOPARP-B study, which analyzed the effects of either 400mg or 300mg Olaparib to 98 patients with mCRPC and who also all had deficiencies in HRR genes. The study showed that 400mg Olaparib resulted in a higher confirmed response (54% vs 39%). However, 37% of patients in the 400mg group suffered

Table 2 Dates and Indications of Regulatory Approval for Rucaparib and Olaparib

	PARP Inhibitor	
	Rucaparib	**Olaparib**
FDA Approval Status, Date and Indication	• May 15th, 2020, accelerated approval • Treatment of adult patients with mCRPC who also have harmful germline and/or somatic mutations in BRCA1/2, who have already been treated with ARAT and a taxane chemotherapy.	• May 19th, 2020, full approval • Treatment of adult patients with mCRPC who also have harmful germline and/or somatic mutations in BRCA1/2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B/C/D, and RAD54L, who have already been treated with abiraterone or enzalutamide.
EMA Approval Status, Date and Indication	N/A	• November 3rd, 2020 • Treatment of adult patients with mCRPC who also have harmful germline and/or somatic mutations in BRCA1/2, who have already been treated with prior therapy including a new hormonal agent.

Note: Data from these studies.[28,36,44,45]
Abbreviations: FDA, The United States Food and Drug Administration; mCRPC, metastatic castrate-resistant prostate cancer; EMA, The European Medicines Agency.

from adverse events that required a dose reduction to 300mg. Furthermore, those with BRCA1/2 alterations were particularly responsive to Olaparib when compared to other HRR gene mutations (52% vs 5% achieving a radiological response to Olaparib respectively).[46,47] Finally, in the randomized phase III PROfound clinical trial, the effectiveness of Olaparib was compared to being treated with enzalutamide or abiraterone in patients with mCRPC with alterations in 15 prespecified HRR genes (the mutations analyzed can be seen in Table 2. Other than those listed, mutations in the PPP2R2A gene were examined as well).[37] The patients were divided into two groups – Cohort A (mutations in BRCA1/2 or ATM) and Cohort B (all other mutations). Notable improvements were seen in individuals with every mutation except those with PPP2R2A mutations, although the largest improvements in progression-free survival were seen in those with BRCA1/2 mutations. It was concluded that overall survival benefited from Olaparib use. These results led to approvals by both the FDA and EMA for mCRPC with HRR mutations, although the EMA was more conservative in the scope of Olaparib's approval.[37,46,47]

In terms of toxicity concerns, Olaparib has been shown to be relatively like rucaparib in terms of the frequency and severity of adverse events. In the PROfound trial, 96% of patients in the Olaparib group and 93% of "crossover" (those who switched from the control to Olaparib therapy when there was disease progression) experienced some adverse event, with the most common adverse events being anemia, nausea, and fatigue/asthenia. These findings are similar to the most common adverse events encountered in the TRITON2 trial. 37% and 33% of patients in the Olaparib and control group experienced a serious adverse event, respectively, which also is a similar statistic to that seen with TRITON2. 4% of patients in both the Olaparib and crossover group died from adverse events during the course of the study, and one death in these groups was considered to be related to the treatment, also similar to results found with TRITON2.[48] One difference found in the PROfound study, however, was the higher rate of pulmonary emboli in patients in the Olaparib group (n = 12, 5% of total) vs the control (n = 1, 1% of total).[48] Of these events, none were fatal.[49] This finding is in contrast to those found in the TRITON2 study, where 2/277 patients (0.72%) in the extended cohort — not the primary safety cohort used in FDA approval — experienced this adverse effect, with one of them being fatal.[28,29] The mechanism behind this new adverse event is unclear, as pulmonary emboli have not been reported in other studies involving Olaparib, and pulmonary embolus is not a recognized complication of Olaparib treatment.[47,48] One theory posited by Teyssonneau et al involves ADT's association with thromboembolic events, but both Hussain et al and de Bono et al concluded that there was no causal relationship between the two events.[47–49] No literature was found on a link between rucaparib and pulmonary embolism as well.

In addition, one unique adverse effect of Olaparib was pneumonitis, a finding reported in 4/256 (1.6%) patients in the Olaparib arm. In one patient, the effect was severe enough to lead to study treatment discontinuation.[48,49] While there

were no instances of pneumonitis recorded in the TRITON2 study, studies have shown that PARP inhibitors (for example, Olaparib) lead to a significantly increased risk of this and other respiratory toxicities.[28,50] Finally, while no patients reported myelodysplastic syndrome (as seen in some trials with rucaparib), one patient died due to acute myeloid leukemia after discontinuing Olaparib (an event also recorded with rucaparib trials). One patient also developed a glioma during the study.[48,49]

Other than the differences in approved indications and potential toxicity concerns, Olaparib and rucaparib differ in how they are metabolized. While both compounds are metabolized by Cytochrome P450 enzymes in the liver, Olaparib has been shown to inhibit CYP2B6 and CYP3A4/5 in vitro and to weakly inhibit CYP3A in vivo, meaning that care should be taken when the patient is taking drugs that are CYP3A sensitive or other CYP3A inhibitors. If unavoidable, however, doses can be reduced to lessen these effects.[37,51,52] Rucaparib, on the other hand, is more unclear, with potential drug–drug interactions seen with those affecting CYP3A, CYP1A2, CYP2C8 and CYP2D6 in a moderate manner, but also for CYP2C19 and CYP2C9 more strongly.[53] This diversity of interaction means that rucaparib use can affect the pharmacokinetics of substances such as caffeine, midazolam, warfarin, omeprazole and digoxin, leading to potentially increasing the frequency or severity of adverse reactions with these substances (among others). However, as with Olaparib, if unavoidable (for example, with warfarin), the rucaparib dosage can be decreased or increased monitoring can be done.[54] Given this complexity, more research on rucaparib's interactions needs to be done.

Other PARP Inhibitors

Currently, two other PARP inhibitors have completed and/or are undergoing testing for their effect on mCRPC.[46] One of them, niraparib, differs from rucaparib in a number of ways. These differences include its metabolism — as niraparib is not metabolized by hepatic cytochrome enzymes, there is less risk of adverse drug–drug interactions, as previously mentioned with rucaparib and Olaparib.[27] Furthermore, while the ingestion of food's effect on rucaparib was not seen as clinically significant, food ingestion has no effect on the metabolism of niraparib.[27] In terms of selectivity, niraparib traps the PARP1 protein — as of now the most significant protein known in PARP trapping — more efficiently than Olaparib and rucaparib (which are roughly equal in their potency).[20] Similarly to rucaparib, however, niraparib exhibits inhibition of other targets than PARP proteins, including some kinases which have been linked to cancer activity (DYRK1s, CDK16, PIM3).[27]

Although niraparib is not yet approved for the treatment of mCRPC, a once daily dose of 300mg was tested for its effectiveness on patients with mCRPC with HRR gene defects in the GALAHAD clinical trial, an open-label, phase II study whose primary completion date was in January 2021 (Identifier Number: NCT02854436).[55] This was a single-arm study testing the effect of niraparib on individuals with mCRPC and HRR gene defects who already had previous treatment with ARAT and taxane chemotherapy. Additionally, individuals were divided into groups of those with BRCA1/2 mutations vs those with other biallelic HRR gene mutations (including ATM, BRIP1, CHEK2, FANCA, HDAC2, and PALB2). Niraparib achieved an ORR of 34.2% (95% CI: 23.7–46.0%) in the BRCA cohort, an ORR that was similar, but slightly lower than what was found with rucaparib in TRITON2.[29,30,56] Safety wise, 288/289 patients in this group (99.7%) experienced some adverse event, with 134/289 (46.4%) experiencing a serious adverse event, which is slightly higher than what was seen in both TRITON2 for rucaparib and PROfound for olaparib. The most common serious (and those attributed to niraparib) events were mostly hematological, with thrombocytopenia (17/289, 6%) and anemia (13/289, 4%) comprising the top two causes. These are also similar trends as seen with rucaparib.[56] Based on these results, niraparib received a Breakthrough Therapy Designation from the FDA to accelerate the approval process.[46]

One interesting finding in the literature is the existence of one case report for niraparib-related pulmonary embolism when treating a 55-year-old female patient with advanced high-grade serous ovarian cancer with BRCA2 and ATM mutations, published in March 2022.[57] Although the condition treated in this case was different than mCRPC, and that prior to this report no literature existed of niraparib-related pulmonary emboli, the fact that the patient was not treated with ADT suggests that perhaps niraparib (and Olaparib, as seen in the PROfound study, and Rucaparib, as seen in the TRITON2 study) perhaps can be associated with development of pulmonary embolism, although rare.

Lastly, talazoparib has the greatest PARP1 trapping ability out of the four PARP inhibitors mentioned in this review, and can trap PARP1 100 times more effectively than niraparib (which already is better at trapping than both Olaparib and

rucaparib).[27] Talazoparib's effectiveness against mCRPC was analyzed in the open-label, phase II TALAPRO-1 clinical trial (Identifier Number: NCT03148795).[58] Similar to TRITON2, PROfound, and GALAHAD, eligible patients (n = 127) were adults with mCRPC who had confirmed mutations in HRR genes and whose disease had already progressed with currently available therapies for the condition. Specifically for TALAPRO-1, those therapies included 1 or 2 taxane chemotherapies (like TRITON2) and enzalutamide and/or abiraterone (like PROFound).[58,59] 1mg of talazoparib (or 0.75mg if the patient had mild renal impairment) was given daily, and of the population measured for efficacy (n = 104), the mutations tested were BRCA1/2, ATM, PALB2, CHEK2, FANCA, MLH1, MRE11A, NBN, and RAD51C. As with the other PARP inhibitor clinical trials, the majority of patients had BRCA1/2 mutations. The ORR measured in TALAPRO-1 was 29.8% (95% CI: 21.2–39.6%), which was overall lower than the trials for niraparib, Olaparib and rucaparib. The safety profile of talazoparib was also similar, with 121/127 patients (95%) reporting an any-grade adverse event, and 61/127 (48%) experiencing a grade ≥ 3 or higher adverse event. The most common serious adverse events recorded in the study were also hematological, with anemia (31%), thrombocytopenia (9%) and neutropenia (8%) consisting the top three causes. Notably, like findings identified in trials involving rucaparib, Olaparib, and niraparib, pulmonary embolism was recorded in the TALAPRO-1 clinical trial as well, involving eight (6%) patients. In this study, pulmonary embolism was one of the most common serious adverse events reported. One death (0.8%) occurred due to this condition out of 10 (7.9%) deaths total, but it was determined not related to talazoparib use.[59,60] No cases of myelodysplastic syndrome or acute myeloid leukemia were reported during the study or by the end of the follow-up period, and talazoparib is currently being tested in ongoing clinical trials to compare its effectiveness to standard therapies.[46,59]

Current Advancements and Questions
Clinical Trials

Rucaparib is currently being examined in a number of clinical trials, many of which are ongoing or have completed but have no results published as of yet (Table 3).[61] Notably, these trials demonstrate the number of therapeutic avenues and questions that researchers have pursued with the compound. First, as mentioned before in this review, TRITON3 is a randomized Phase III study that is a continuation of the results found in TRITON2.[29,33] TRITON3 is comparing rucaparib to standard therapies (a physician's choice of docetaxel, abiraterone, or enzalutamide) for mCRPC in patients with BRCA1/2 or ATM mutations. The study will be able to verify rucaparib's clinical benefit in treating mCRPC with HRR mutations, as TRITON2 had no comparison arm.[29,33] Finally, TRITON3 will also potentially give more data on the safety of rucaparib as well.

Given rucaparib and other PARP inhibitors' effectiveness against certain cancers with HRR mutations, other clinical trials have sought to figure out their effectiveness against not just mCRPC. This desire is evident with clinical trials such as TRIUMPH (Identifier Number: NCT03413995), a Phase II trial which aims to see if rucaparib affects patients with metastatic hormone-sensitive prostate cancer (mHSPC) harboring HRR mutations, and who have not been treated with ADT yet.[62] In that way, the researchers want to see if rucaparib can potentially be introduced to patients earlier in the PCa disease course.[62] Other conditions of interest include nonmetastatic prostate cancer in patients with HRR mutations (ROAR, Identifier Number: NCT03533946) or other solid tumors also in patients with HRR mutations (LODESTAR, Identifier Number: NCT04171700).[63,64]

Rucaparib is also being analyzed as part of various combination therapies. One combination of interest includes rucaparib with enzalutamide and/or abiraterone, which are existing standard therapies for treating mCRPC, with or without HRR mutations (Identifier Numbers: NCT04179396, NCT04455750).[65,66] Furthermore, other examined combinations include copanlisib, a PI3K inhibitor that has been shown to impair HRR while also sensitizing cells to PARP inhibitors, not just in BRCA for example.[67,68] Given that patients with BRCA mutations and mCRPC were often the most affected by PARP inhibitors, having potential therapies that can expand this therapeutic benefit is an exciting thought. This line of thinking has been extended to nivolumab, an anti-PD-1 antibody. However, multiple studies have shown nivolumab (and other medications of its class) have not shown much benefit with prostate cancer.[69] This finding has been replicated in the recent Checkmate 9KD clinical trial (Identifier Number: NCT03338790), which tested the effect of

Table 3 Rucaparib's Ongoing Clinical Trials for Prostate Cancer

Clinicaltrials.Gov Identification Number and Name (if Applicable)	Phase of and Type of Clinical Trial	Condition Treated and Details (if Applicable)	Mutations tested (if Applicable)	Interventions Tested (Arms)	Start Date	Projected Primary Completion Date
TRITON3, NCT02975934	Phase III, multi-arm, open-label	mCRPC, with previous next generation ARAT	BRCA1/2 or ATM	Rucaparib vs Abiraterone or Enzalutamide or Docetaxel	June 2017	June 2022 (no results posted as of July 2022)
PLATI-PARP, NCT03442556	Phase II, single-arm, open-label	mCRPC, with some prior therapy as long as it does not include a PARP inhibitor or platinum chemotherapy	Any pathogenic or inactivating alteration in a gene associated with HRR	Induction Carboplatin and Docetaxel followed by maintenance with Rucaparib	August 2018	May 2025
TRIUMPH, NCT03413995	Phase II, single-arm, open-label	mHSPC, without prior ADT treatment (either ineligible for or declined ADT therapy). The trial would provide an alternative to ADT	Germline mutation in one or more of the following HRR genes (BRCA1/2, ATM, CHEK2, NBN, RAD50, RAD51C, RAD51D, PALB2, MRE11, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM)	Rucaparib	September 2018	December 2022
ROAR, NCT03533946	Phase II, single-arm, open-label	nmHSPC	Mutation in one of the following HRR-associated genes (BARD1, BRCA1/2, BRIP1, CHEK1, CHEK2, FANCA, NBN, PALB2, RAD51C, RAD51D, RAD51, RAD51B)	Rucaparib	May 2019	July 2023
LODESTAR, NCT04171700	Phase II, single-arm, open-label	Any solid tumor	Somatic or germline deleterious mutation in a HRR gene (BRCA1/2, PALB2, RAD51C, RAD51D, BARD1, BRIP1, FANCA, NBN, RAD51 or RAD51B)	Rucaparib	November 2019	May 2022
RAMP, NCT04179396	Phase Ib, multi-arm, open-label	mCRPC, with or without previous ARAT	N/A	Rucaparib and enzalutamide vs Rucaparib and abiraterone	December 2019	November 2022

(*Continued*)

Table 3 (Continued).

Clinicaltrials.Gov Identification Number and Name (if Applicable)	Phase of and Type of Clinical Trial	Condition Treated and Details (if Applicable)	Mutations tested (if Applicable)	Interventions Tested (Arms)	Start Date	Projected Primary Completion Date
BrUOG 360, NCT04253262	Phase Ib/II, single-arm with multiple dose measurements, open-label	mCRPC, with previous abiraterone, enzalutamide, and/or aplutamide therapy	N/A	Rucaparib and Copanlisib together with varying doses of both – objective is to find maximal tolerable dose to then test in Phase II part of study	April 2020	July 2021 (no results posted as of July 2022)
CASPAR, NCT04455750	Phase III, multi-arm, double-blinded	mCRPC, with no prior therapy for mCRPC at the time of registration, meaning that the patient had not had major surgery or radiation for ≥4 weeks, had not been on investigational therapy for ≥4 weeks or 5 half-lives (the shorter period), and had not been on flutamide, dutasteride, bicalutamide, niltamide, finasteride, aminoglutethimide, estrogens, cytoproterone, chemotherapy, abiraterone, apalutamide, or darolutamide for ≥4 weeks or 5 half-lives (the shorter period). Moreover, prior docetaxel and/or ARAT was allowed only if for nmHSPC, mHSPC, or nmCRPC. No prior therapy with enzalutamide, PARP inhitors, or platinum chemotherapy was allowed.	N/A	Enzalutamide and Rucaparib vs Enzalutamide and Placebo. If patient has not undergone bilateral orchiectomy ADT is included (both arms)	February 2021	May 2023
CATCH-R, NCT04676334	Phase III, single-arm, open-label (maintenance therapy for patients currently benefitting from rucaparib)	mCRPC, ovarian cancer, epithelial ovarian cancer, fallopian tube cancer, peritoneal cancer, other solid tumor	N/A	Rucaparib	March 2021	November 2023

Note: Data from Wei et al.[57]
Abbreviations: mCRPC, metastatic castrate-resistant prostate cancer; ARAT, androgen receptor-axis-targeted therapies; PARP, poly(adenosine diphosphate-ribose) polymerase; HRR, homologous recombination repair; mHSPC, metastatic hormone sensitive prostate cancer; ADT, androgen deprivation therapy; nmHSPC, non-metastatic hormone sensitive prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer.

rucaparib and nivolumab together against mCRPC (Table 4).[70] It is noted, however, that docetaxel chemotherapy and nivolumab had a benefit when administered jointly, and confirming that result is the subject of other studies (CheckMate 7DX, Identifier Number: NCT04100018).[70]

Finally, rucaparib was tested with another class of drug known as bromodomain and extraterminal (BET) protein inhibitors (Identifier Number: NCT0271137).[71] Inhibition of BET proteins — which promote gene transcription via recruiting various transcription factors and elongation complexes — has been shown to be able to downregulate various genes that can promote cancer growth, including MYC, BCL-2, and p21 C1P1/WAF1.[72] One such inhibitor, INCB057643, was tested with rucaparib in a recent clinical trial (Identifier Number: NCT02711137), but the study was terminated due to safety issues, with 76 out of the 134 patients (56.7%) experiencing disease progression during the course of the study, and only an ORR of 5%.[71,72] Furthermore, only four patients made it to Part 3 of the study, where they underwent treatment with INCB057643 in combination with rucaparib, so no results were recorded.[72]

Other Questions

Given rucaparib's apparent benefit to patients with BRCA mutations in particular, there is much interest in ensuring its (and including other PARP inhibitors) benefit applies to patients with other HRR mutations as well. Genes of interest include those tested in the aforementioned studies, including ATM, CHEK2, RAD51, FANCA and many others. Thus, some data exist showing their benefit, as seen in a follow-up analysis by Abida et al, which examined the outcomes of treated patients who had mutations in HRR genes other than BRCA1/2 during the TRITON2 clinical trial (n = 78).[73] Overall, this analysis looked at 49 patients (62.8%) with an ATM mutation, 15 (19.2%) with a CDK12 mutation, 12 (15.4%) with a CHEK2 mutation, 4 (5.1%) with a FANCA mutation, 4 (5.1%) with a NBN mutation, 2 (2.6%) with a BRIP1 mutation, 2 (2.6%) with a PALB2 mutation, and 1 each (1.3%) with a RAD51, RAD51B, or RAD54L mutation. Patients often had co-occurring mutations, and also varied in terms of having a germline or somatic mutation as well.[73] In terms of results, while sample sizes were relatively low, this initial data generally showed a relative lack of efficacy when comparing rucaparib's effect on those with BRCA1/2 mutations. For example, only 2/49 patients (4.1%) with an ATM mutation showed a confirmed PSA response, and 2/19 evaluable ATM patients (10.5%) had a confirmed partial radiographic response. This differs from the BRCA data by a substantial margin, with 63 (54.8%) and 20/62 evaluable patients (32.3%) having a confirmed PSA response and confirmed partial radiographic response, respectively.[29,30,73] No CDK12 patients had a confirmed radiographic response, and only 1/15 (6.7%) had a confirmed PSA response, which only lasted 1.8 months. Similar findings applied to patients with CHEK2 mutations (n = 12). Finally, 1 out of the 4 patients with a FANCA mutation had a complete radiographic and PSA response, and 1 out of the 2 with a BRIP1 mutation had a partial radiographic and PSA response. Interestingly, both patients with a PALB2 mutation had PSA responses, with one patient having a partial radiographic response, and the other having a 47% reduction in tumor volume. However, the sample size is so low, and data was not fully collected at the time of publication, so it is hard to make conclusions. Furthermore, some patients also were discovered to have co-occurring BRCA mutations, which may have led to their response. Overall, though, more research on certain mutations, such as PALB2, could lead to discovering other applications of rucaparib. Research on the type of mutations affected, may also be fruitful, as the only FANCA individual with a response specifically had a monoallelic truncating alteration.[73] Multiple studies of Olaparib's effectiveness against these other mutations are currently ongoing, and will perhaps open the door for rucaparib to follow in its footsteps.[74]

These findings also bring to light another question in the rucaparib and PARP inhibitor space in general. Namely, how to classify the various mutations present in patients' HRR genes, and questions on the cost and effort needed to perform genome sequencing. This concern also needs to consider the supposed frequency of genetic testing for an individual patient, as additional somatic mutations can arise during treatment and may affect how treatment goes.[74]

Thirdly, PARP inhibitor resistance has been noted in ovarian cancer in many instances, as tumors can acquire additional mutations to restore the HRR process, or deleting mutations to reacquire normal HRR genes.[75] Either way, both mechanisms allow the cell to repair DNA breaks, thus removing a key mechanism in how PARP inhibitors achieve their cytotoxicity. To address this, combination therapies of PARP inhibitors and compounds such as ATR inhibitors (which inhibit ATR, a stabilizing factor in DNA replication fork breaks), are currently being tested in multiple clinical trials.[76] Currently, all are with Olaparib, but future studies may involve rucaparib as well.[75]

Table 4 Recently Completed Prostate Cancer Clinical Trials Testing Rucaparib

Clinicaltrials.Gov Identification Number and Name (if applicable)	Phase of and Type of Clinical Trial	Condition Treated and Details (if Applicable)	Mutations Tested (if Applicable)	Interventions Tested (Arms)	Start Date	Projected Primary Completion Date
NCT02711137[a]	Phase I/II	Any solid tumor or lymphoma with any alteration relevant to BET protein signalling. This list includes but is not limited to the following: Pancreatic Adenocarcinoma, mCRPC, Breast Cancer, High-grade Serious Ovarian Cancer, Glioblastoma Multiforme, Non-Hodgkin Lymphoma, Ewing Sarcoma, Acute Myeloid Leukemia, Myelodysplastic Syndrome, Myelofibrosis	N/A	Various doses of INCB057643 to find maximal tolerable dose or pharmacologically active dose, and then combined INCB057643 with the following compounds separately (groups separated by commas): Gemcitabine, Paclitaxel, Rucaparib, Abiraterone and Prednisone, Ruxolitinib, Azacitidine	May 2016	February 2019
TRITON2, NCT02952534	Phase II, single-arm, open-label	mCRPC with 1–2 previous ARAT and 1 prior taxane chemotherapy	Somatic or germline mutation in BRCA1/2, ATM, CDK12, CHEK2, and other not listed mutations in HRR genes	Rucaparib	February 2017	July 2021
CheckMate 9KD, NCT03338790	Phase II, multi-arm, open-label	mCRPC with varying previous therapies (1–2 taxane chemotherapies with up to 2 ARAT, 1–2 prior ARAT, or abiraterone without enzalutamide or aplutamide)	N/A	Nivolumab and Rucaparib vs Nivolumab and Docetaxel and Prednisone vs Nivolumab and enzalutamide	December 2017	January 2021
NCT03572478[b]	Phase Ib/IIb, multi-arm, open-label	Prostate Cancer with ≥1 ARAT including abiraterone or enzalutamide, Endometrial Cancer	N/A	Rucaparib and Nivolumab vs Rucaparib vs Nivolumab vs Rucaparib initially and then Rucaparib and Nivolumab	August 2018	February 2020
NCT03840200[c]	Phase Ib, single-arm with multiple dose measurements	Breast Cancer, Prostate Cancer, Ovarian Cancer	N/A	Ipatasertib and Rucaparib with varying doses — goal is to find maximal tolerable dose to then test in Part 2 of study.	June 2019	December 2021

Notes: [a]Study was terminated due to safety concerns.[65] [b]Study was terminated due to a lack of efficacy.[63] [c]Study was supposed to continue to Phase II but was stopped as the intervention was found to not show clinically relevant activity against mCRPC.[62] Data from these studies.[57,66–68,74,75]
Abbreviations: BET, bromodomain and extraterminal; mCRPC, metastatic castrate-resistant prostate cancer; ARAT, androgen receptor-axis-targeted therapies; HRR, homologous recombination repair.

Finally, this review has noted the presence of pulmonary emboli occurring as a rare adverse event in with not only rucaparib, but also Olaparib and talazoparib in clinical trials involving mCRPC. This finding extends to niraparib as well, in a case report on its treatment in an individual with advanced high-grade serous ovarian cancer with BRCA2 and ATM mutations. While no causal link has been established as of yet, this observation potentially could lead to some need for monitoring and research into possible mechanisms of how rucaparib and other PARP inhibitors relate to pulmonary embolism.

Conclusion

Through the results of the TRITON2 clinical trial, Rucaparib is an exciting therapy that has been shown to provide a benefit to both the overall survival and response rate of patients with mCRPC who have already been treated with docetaxel and ARAT (abiraterone and enzalutamide). While as of now this benefit has mostly been limited to those whose mCRPC harbor BRCA mutations, this is already a promising development given the relative high prevalence of HRR mutations (and specifically BRCA mutations) in patients with mCRPC.

TRITON3 — TRITON2's follow-up clinical trial — will provide further information on rucaparib's clinical benefit and its safety profile. Moreover, the initial results from TRITON2 and future results from clinical trials testing other PARP inhibitors such as Olaparib will hopefully show signs of effectiveness against other HRR gene mutations, providing additional therapeutic potential.

Additionally, advancements in deciphering the genetic landscape present in mCRPC will further increase our understanding and appreciation of how to use rucaparib and other therapies more effectively.

Abbreviations

PCa, prostate cancer; US, United States; ADT, androgen deprivation therapy; PSA, prostate-specific antigen; mCRPC, metastatic castrate-resistant prostate cancer; HRR, homologous recombination repair; NHEJ, non-homologous end-joining; DSB, double-stranded break; PARP, poly(adenosine diphosphate-ribose) polymerase; NAD, nicotinamide adenine dinucleotide; FDA, The United States Food and Drug Administration; EMA, The European Medicines Agency; ORR, objective response rate; IRR, independent radiologic review; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PCWG3, Prostate Cancer Clinical Trials Working Group 3; DOR, duration of response; CI, confidence interval; ARAT, androgen receptor-axis-targeted therapies; CTCAE, Common Terminology Criteria for Adverse Events; mHSPC, metastatic hormone-sensitive prostate cancer; BET, bromodomain and extraterminal.

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Disclosure

The authors report no conflicts of interest in this work.

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