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Original Article

PARP inhibitors on the move in prostate cancer: spotlight on Niraparib & update on PARP inhibitor combination trials

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Abstract: PARP inhibitors were recently introduced as a novel targeted therapy for biomarker positive metastatic castration resistant prostate cancer (mCRPC) patients, a population that inevitably acquires resistance to existing standard care regimens. Olaparib and rucaparib are now FDA-approved for mCRPC, while talazoparib and niraparib are advancing through the clinical stage of development. We highlight the recent results of the GALAHAD trial testing the efficacy of niraparib in mCRPC patients with DNA damage repair gene defects and compare its performance to key PARP inhibitor trials (PROFOUND, olaparib; TRITON2, rucaparib; TALAPRO-1, talazoparib). Finally, we briefly discuss recent updates on emerging PARP inhibitor and androgen receptor targeting combination trials as a novel treatment strategy for upfront treatment of mCRPC and in earlier disease settings.

Keywords: Prostate cancer, PARP inhibitors, DNA damage and repair, clinical trial

Introduction

Polyadenosine diphosphate ribose polymerase (PARP) inhibitors are a prominent treatment option for females with breast or ovarian cancer that have been utilized over the past decade. They were recently added to the treatment armamentarium for metastatic castration resistant prostate cancer (mCRPC) with the FDA approval of olaparib and rucaparib. While therapeutic options have diversified over the years, prostate cancer is still the second leading cause of cancer-related mortality for males in the United States [1]. Acquired resistance to androgen receptor (AR) antagonists and taxane chemotherapies eventually ensues, exemplifying the importance of identifying newer targeted therapies for patients with advanced disease.

PARP inhibitors introduce a precision medicine approach to mCRPC treatment by targeting the DNA damage repair (DDR) pathway. PARP proteins initiate single strand break (SSB) and double strand break (DSB) repair by binding to the site of damage, triggering a cascade of events. In the event of repair failure, DSBs form in response to multiple SSBs, terminating replication [2]. Normal cells repair DSBs in one of four ways: homologous recombination (HR), nonhomologous end joining, alternative nonhomologous end joining, or single-strand annealing [3]. *BRCA1/2* and *ATM* are known to play a crucial role in HR repair (HRR), and loss of function mutations in these genes result in the inability to repair DSBs, influencing cancer progression [2]. PARP inhibitor treatment of *BRCA*-deficient tumor cells takes advantage of their dysfunctional machinery: PARP inhibitors prevent the detection of SSBs, leading to DSBs. Patients without *BRCA1/2* mutations simply repair these DSBs and thus are not as sensitive to these inhibitors. However, given the inability to repair these DSBs in patients with HRR mutations, the DNA damage induced by PARP inhibitors results in enhanced cell death. This tactic is known as “synthetic lethality”, a situation in which two alterations are survivable when they occur independently but induce cell death when they occur simultaneously [4]. This relationship suggests that sensitivity to PARP inhibitors may be increased in nearly 25% of the mCRPC popu-

lation [5-7] who harbor germline or somatic HRR mutations, which are associated with aggressive disease or worse outcomes. This hypothesis was tested in the recent phase II trial for niraparib (GALAHAD) reported by Smith et al. in *The Lancet Oncology* [8].

GALAHAD phase II clinical trial

The GALAHAD study recruited mCRPC patients with disease progression post androgen deprivation therapy or a taxane chemotherapy and sequenced their blood and/or tumors to identify alterations to genes in the DDR pathway: *ATM, BRCA1, BRCA2, BRIP1, CHEK2, FANCA, HDAC2,* and *PALB2*. Analyses were completed within two cohorts: (1) patients with pathogenic germline or biallelic alterations in *BRCA1* or *BRCA2* and (2) patients with alterations to non-*BRCA* DDR genes. Participants were given 300 mg of niraparib daily, in 28-day cycles, until treatment was terminated due to predetermined conditions. The outcome was assessed by an objective response rate (ORR), defined as the proportion of patients with a partial or whole response according to RECIST version 1.1.

In the final efficacy analysis and with a median follow-up of 10.1 months, the ORR in the *BRCA* cohort was 34.2% (n=26 of 76; 95% CI 23.7-46.0), with two patients having a complete response, while the ORR was 10.6% (n=5 of 47; 95% CI 3.5-23.1) in the non-*BRCA* cohort. The trial also included circulating tumor cell (CTC) counts to assess niraparib outcome as CTC0 counts have been correlated with survival [9]. The GALAHAD trial is the first to prospectively test the clinical utility of this CTC0 endpoint as a potential biomarker of response, with 25% of the *BRCA* cohort demonstrating CTC response. The safety analysis portion of the trial found that common side effects of niraparib included nausea, anemia, and vomiting, while the more severe side effects were hematological, including anemia, thrombocytopenia, and neutropenia. These results suggest that niraparib has anti-tumor effects in heavily pretreated mCRPC patients with *BRCA* alterations and a tolerable safety profile. Due to their nature, clinical trials share common shortcomings, including limitations in population generalizability and inability to moderate participant compliance with trial guidelines. These influence our interpretation of the results and reinforce the need for real world data.

PARP inhibitor cross comparison

This trial is the first to prove the efficacy of niraparib in mCRPC patients, adding another potential PARP inhibitor to the clinic. **Table 1** compares the results of the four PARP inhibitors (niraparib vs olaparib, rucaparib, and talazoparib) and their representative trials (GALAHAD vs PROFOUND [10, 11], TRITON2 [12, 13], and TALAPRO-1 [14], respectively). Although anti-tumor activity data from these trials appear to be similar, there are important differences in the study designs for these trials, including the method of determining genomic alteration, type of DDR-HRR gene alterations eligible for enrollment, prior treatment conditions, requirement for measurable soft-tissue disease at enrollment, and assessments of response. This is reflected in the distinct FDA approvals of the first PARP inhibitors for mCRPC: rucaparib was approved for patients harboring deleterious *BRCA1/2* (germline and/or somatic) mutations after progression on an AR-targeting agent and taxane-based chemotherapy, while olaparib is more broadly indicated for patients with any deleterious or suspected deleterious germline or somatic HRR gene mutations post AR-targeting therapy. While all four studies reinforced the potential benefit of PARP inhibitors in *BRCA* mutation-associated mCRPC, not all patients with HRR alterations benefit equally from PARP inhibition. In the TRITON2 study, early evidence suggested that *ATM, CDK12,* and *CHEK2* mutations are associated with a minor response to rucaparib, while alterations in other DDR genes (*PALB2, FANCA, BRIP1*, and *RAD51B)* may improve sensitivity to PARP inhibition [13]. The TALAPRO-1 trial demonstrated that PARP inhibition could be extended beyond the *BRCA1/2* sub-population, with responses also observed in those with alterations in *PALB2* and *ATM* [14]. Moreover, a recently published retrospective analysis on the efficacy of PARP inhibition in cancers with *BRCA1/2* mutations revealed that PARP inhibitor efficacy is decreased in *BRCA1*- versus *BRCA2*-altered mCRPC (PSA response as primary endpoint, 23% vs 63% respectively, *P*= 0.01) [15]. In a study on the in vivo potency and PARP trapping of each PARP inhibitor, the potency of each PARP inhibitor was ranked from highest to lowest: talazoparib > rucaparib > olaparib > niraparib [16]. Whether this translates to anti-tumor activity and/or correlates to improved duration of clinical outcome in prostate cancer remains to be determined.

Table 1. Comparison of PARP inhibitors recently investigated in mCRPC trials

	Olaparib	Rucaparib	Niraparib	Talazoparib
FDA approval	OC; BC; PaC; mCRPC (2020)	OC; mCRPC (2020)	OC	BC
Approved indication for mCRPC	mCRPC w/*BRCA1/2* & other HRR mutations[a] & post NHT	mCRPC w/*BRCA1/2* mutations & post taxane + NHT	-	-
Trial Name (Identifier)	PROFOUND (phase III) NCT02987543	TRITON2 (phase II) NCT02952534	GALAHAD (phase II) NCT02854436	TALAPRO-1 (phase II) NCT03148795
Biomarker status	Cohort A: *BRCA/ATM* Cohort B: other HRR[a]	*BRCA1/2* & non-*BRCA*[b]	*BRCA1/2* cohort & non-*BRCA* cohort[c]	DDR alterations[d]
Primary endpoint	PFS	ORR	ORR	ORR
ORR (%)	(olaparib vs control) Cohort A: 33% vs 2% Overall (A + B): 22% vs 4%	*BRCA*: 43.5%	*BRCA*: 34.2% non-*BRCA*: 10.6%	*BRCA:* 46% *PALB2*: 25% *ATM:* 12% Overall: 30%
PFS	Cohort A: 7.4 mo vs 3.6 mo Overall: 5.8 mo vs 3.5 mo	*BRCA*: 9 mo	*BRCA*: 5.52 mo non-*BRCA*: 3.71 mo	*BRCA:* 11.2 mo *PALB2:* 5.6 mo *ATM:* 3.5 mo Overall: 5.6 mo
OS	Cohort A: 19.1 mo vs 14.7 mo Overall: 17.3 mo vs 14.0 mo	N/A	*BRCA*: 10.87 mo non-*BRCA*: 9.63 mo	*BRCA*: 24 mo *PALB2:* 16 mo *ATM*: 12.2 mo Overall: 16.4 mo
REFS	[10]; [11]	[12]; [13]	[8]	[14]

Abbreviations: BC, breast cancer; mCRPC, metastatic castration resistant prostate cancer; NHT, novel hormonal therapy (abiraterone or enzalutamide); OC, ovarian cancer; ORR, objective response rate; OS, overall survival; PaC, pancreatic cancer; PFS, progression free survival. [a]*ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L.* [b]*ATM, BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L.* [c]*ATM, BRIP1, CHEK2, FANCA, HDAC2, PALB2.* [d]*ATM, ATR, BRCA1, BRCA2, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C.*

Emerging combination therapies

Establishing new therapies is crucial for mCRPC patients due to the inevitable development of resistance to existing treatments. The findings of the GALAHAD trial contribute directly to building treatment options for a vulnerable population, specifically those who are heavily pretreated (>3 lines of systemic therapies) or have visceral metastases to areas such as the liver, which are linked with poor survival [17]. At advanced stages of disease, mutations accumulate and add complexity to the profile of the tumor, resulting in the cancer likely having more than one driver which could be more adequately managed by a combination approach. Despite the growing number of FDA-approved treatments for first line mCRPC, there is a critical unmet need for developing novel treatment options after frontline next generation hormonal agent (NHA) resistance occurs. We expect that this need will be fulfilled through an increase in clinically available combination therapies. A rational potential combination is adding a targeted agent to a NHA regimen, reintroducing and extending sensitivity to an existing standard of care treatment.

Optimal treatment sequencing in the mCRPC space has yet to be determined and no combination targeted therapies are currently approved. Thus, new and emerging PARP inhibitor combinations represent an attractive strategy due to the possibility of extending NHA sensitivity. Preclinical evidence and early phase studies suggest that co-inhibition of AR and PARP promotes synthetic lethality with enhanced activity and interdependency between both pathways, thus providing the rationale for clinical development of a co-targeting AR/PARP approach [18-20]. The potential treatment combination of a PARP inhibitor (PARPi) plus a NHA is on the horizon with several ongoing phase III trials (**Table 2**). There are currently four phase III trials investigating a PARPi with NHA as first-line treatment for previously untreated mCRPC. Two trials combine a PARPi with abiraterone (niraparib/MAGNITUDE; olaparib/PROPEL), while two other trials pair enzalutamide with either rucaparib (CASPAR) or talazoparib (TALAPRO-2). Results of the PARPi/Abi combination trials were recently reported at ASCO 2022 Genitourinary Symposium. In the MAGNITUDE study, the combination of niraparib/Abi led to a 47% improvement in the rPFS of patients with BRCA1/2 mutations and a 27% improvement across all HRR biomarker-positive patients [21]. The PROPEL trial reported a 34% reduced risk of disease progression in the olaparib/Abi combination arm with a signifi-

Table 2. Ongoing phase 3 trials of PARP inhibitors in combination with androgen targeted therapy in prostate cancer

Clinical Trial # (Trial Name)	Drug Combination	Patient Population	Primary Endpoint	Biomarker Selected Enrollment	Primary Completion Date
NCT03748641 (MAGNITUDE)	Niraparib + Abi vs Abi + placebo	mCRPC	rPFS	No	October 2021
NCT03732820 (PROPEL)	Olaparib + Abi vs Abi + placebo	mCRPC	rPFS	No	July 2021
NCT04455750 (CASPAR)	Rucaparib + Enz vs Enz + placebo	mCRPC	rPFS; OS	No	May 2023
NCT03395197 (TALAPRO2)	Talazoparib + Enz vs Enz + placebo	mCRPC	rPFS; OS	Yes	March 2022
NCT04497844 (AMPLITUDE)	Niraparib + Abi vs Abi + placebo	mCSPC	rPFS	Yes	November 2024
NCT04821622 (TALAPRO3)	Talazoparib + Enz vs Enz + placebo	mCSPC	rPFS	Yes	December 2024

Abbreviations: Abi, abiraterone; Enz, enzalutamide; mCRPC, metastatic castration resistant prostate cancer; mCSPC, metastatic castration sensitive prostate cancer; OS, overall survival; rPFS, radiographic progression free survival.

cantly improved rPFS of 24.8 months (versus 16.6 months in the abiraterone alone arm), irrespective of the HRR status [22]. Whether this translates to an improvement in overall survival remains to be seen. There are also ongoing trials evaluating PARPi combinations in the metastatic, castration-sensitive setting, including studies of niraparib with abiraterone (AMPLITUDE) and talazoparib plus enzalutamide (TALAPRO3) for patients with deleterious HRR mutations. Results from these ongoing trials will not only shed light on the efficacy of a PARPi plus NHA regimen but also address any dose-limiting or emergent toxicities associated with drug-drug interactions.

Conclusion

Advances in imaging and genetic testing coupled with the emergence of potential novel treatment combinations continue to advance progress within the metastatic prostate cancer field. We wait to see whether niraparib will continue to expand the role of targeted therapies for mCRPC, specifically in combination with abiraterone, as its single agent potency thus far is lower compared to its counterparts. Identification of treatment response and resistance biomarkers in addition to expansion of genomic technologies will lead to improved patient selection and help guide treatment decisions. While increasing patient access to these therapies may be a challenge, the availability of numerous therapeutic options will inevitably help patients live longer with advanced prostate cancer.

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Disclosure of conflict of interest

None.

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