An Evaluation of Talazoparib Plus Enzalutamide for Metastatic Castration-Resistant Prostate Cancer

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Abstract

Introduction: Prostate cancer (PC) is the second most common cancer diagnosis among men worldwide, with poor prognosis in its advanced stage. Treatment strategies have evolved, including the use of androgen receptor signaling inhibitors (ARSIs) and poly (ADP-ribose) polymerase inhibitors (PARPis).

Areas covered: This review evaluates the clinical efficacy, safety, and future potential of combining talazoparib, a potent PARPi, with enzalutamide, a strong androgen receptor (AR) antagonist. The TALAPRO-2 trial demonstrated significant improvement in radiographic progression-free survival (rPFS) in metastatic castration-resistant prostate cancer (mCRPC) patients, particularly those with homologous recombination repair (HRR) gene mutations such as BRCA1/2.

Expert opinion: Emerging biomarkers like TMPRSS2-ERG and RB1 gene mutations are explored as potential predictors of response to PARPi/ARSI combination therapy. Although the combination of talazoparib and enzalutamide shows promise, challenges remain regarding patient selection and defining genomic markers for homologous recombination deficiency (HRD). Further investigation is needed to refine treatment strategies, including targeting non-HRR mutations, and to expand the role of this combination therapy in earlier stages of prostate cancer. A more personalized approach to therapy is crucial in optimizing outcomes for mCRPC patients.

INTRODUCTION

Prostate cancer (PC) represents a major health challenge, as it is the second most common cancer diagnosis among men worldwide, significantly impacting public health. [1] PC ranks as the third most diagnosed cancer worldwide, accounting for 7.3% of new cancer diagnoses and 3.8% of new deaths for cancer globally. [2] Among European countries, PC represent the most frequently diagnosed cancer among men and the fourth most diagnosed among all cancer types, accounting 470,000 new cases, with a cumulative risk of being diagnosed with PC before the age of 75 that is 8.2% (1 in 12 men), while the risk of prostate cancer death before the age of 75 is 1% (1 in 103 men). [3] Several therapeutic options are available in metastatic castration-resistant PC (mCRPC), including luteinising hormone-releasing hormone (LH-RH) analogs, taxane-based chemotherapy, androgen receptor signaling inhibitors (ARSIs), radium-223, radioligands and poly (ADP-ribose) polymerase inhibitors (PARPis). [4] Despite the dramatical improvement of the available therapies, prognosis of mCRPC remains poor, with a real-world median survival from diagnosis of 25.6 months. [5]

Genomic instability is a key hallmark of cancer and understanding the molecular patterns underlying PC is becoming fundamental to design new clinical trials and for a better patient's selection. [6] Cells have developed mechanisms to detect and repair DNA errors caused by genomic instability. In prostate cancer, one frequently altered pathway is the DNA damage response (DDR), which includes mutations in BRCA1/2 and other homologous recombination repair (HRR) genes. These DDR pathway alterations are especially common in prostate cancer patients [7] , and they have been found in around 10% of localized prostate cancers and 23-31% of patients with advanced prostate cancer. [8] Numerous DDR components play roles in the HRR pathway, both directly and indirectly. These include sensors of DNA damage such as ATR and ATM; signal mediator proteins like BRCA1, BRCA2, BARD1, PALB2, FANCL, and RAD54L; and effector proteins such as RAD51 and RAD54L that are directly involved in DNA repair through strand invasion and replication fork stabilization. Additionally, downstream signaling proteins like ATM, CHEK2, and

CHEK1 activate cell cycle checkpoints, while others such as CDK12 regulate the transcription of HRR genes. [7] [9] [10] These genomic alterations contribute to genomic instability, poorer prognosis, and an increased risk of metastatic disease. However, they also enhance the cancer's sensitivity to PARPis, significantly impact treatment strategies. [11] In this review we summarize the clinical characteristics of enzalutamide and talazoparib, their synergistic effects, the clinical efficacy and safety, and the future perspectives of this combination.

ENZALUTAMIDE MONOTHERAPY

Enzalutamide is a second-generation inhibitor of androgen receptor signaling, approved from the US FDA in 2012. [12] Enzalutamide blocks several key steps in the androgen receptor (AR) signalling pathway, including androgen binding to the AR, nuclear translocation of activated AR and binding of activated AR with DNA. [13] Based on extensive clinical trial data and real-world evidence, oral enzalutamide, administered at a dose of 160 mg once daily, has been shown to be an effective and generally well-tolerated treatment for a broad population of patients with CRPC. [14] This encompasses patients with both metastatic and nonmetastatic forms of the disease, as well as patients who are either chemotherapy-naive or have previously undergone docetaxel chemotherapy. Enzalutamide is also becoming a key treatment option for men with nonmetastatic CRPC at high risk of developing metastases, and it remains an important first-line therapy for metastatic CRPC, regardless of prior chemotherapy use. [15] [16] [17] The efficacy of enzalutamide monotherapy in the treatment of mCRPC is supported by the findings from the AFFIRM trial [17], which focused on post-docetaxel patients, and the PREVAIL trial [16], which examined the effects of enzalutamide prior to chemotherapy. Enzalutamide is also available as a first line treatment of metastatic hormone-sensitive prostate cancer (mHSPC). [18]

TALAZOPARIB MONOTHERAPY

PARP inhibitors as monotherapy are a recognized standard of care for patients with advanced-stage prostate cancer. [19] Talazoparib is the most effective PARP inhibitor in trapping PARP1 and PARP2

at sites of DNA single-strand breaks. [20] This action hinders DNA replication and transcription, resulting in the development of double-strand DNA breaks and subsequent cell death. [20] Even if it is not yet approved for mCRPC, talazoparib obtained positive results as a monotherapy. The phase 2 TALAPRO-1 study enrolled 127 patients and demonstrated that monotherapy with the PARP inhibitor talazoparib (1 mg daily; 0.75 mg if moderate renal impairment) exhibited durable antitumor activity and a favorable risk-benefit profile in patients with heavily pretreated metastatic castration-resistant prostate cancer (mCRPC) harboring HRR pathway alterations that passed validation requirements: ATM, ATR, BRCA1, BRCA2, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, and RAD51C. [21 22] The primary endpoint of the study was primary objective response rate, assessed by investigator and by blinded independent central review. Key secondary endpoints were time to objective response and the duration of response, radiographic progression free survival (rPFS) and overall survival (OS). Other secondary endpoints: proportion of patients with a decrease of 50% or more of PSA levels, time to PSA progression, the proportion of patients with conversion of circulating tumor cell count and patient reported outcomes as per BPI-SF. In this trial, patients showed an objective response rate (ORR) of 29.8% (31 of 104 patients; 95% CI 21.2–39.6). The median time to objective response was 3.4 months (IQR 1.8–5.4) and the median duration of response was 12.8 months (95% CI 6.5 to not evaluable). The median rPFS was 5.6 months (95% CI; 3.7 – 8.8) in the all-comers' cohort, with a longer rPFS in the BRCA 1-2 mutated group (11.2 months; 95% CI, 7.5 – 19.2) and a shorter rPFS in the ATM mutated group (3.5 months; 95% CI, 1.7-8.3). [22] The most common grade 3 and 4 adverse events were anemia (31%), thrombocytopenia (9%), and neutropenia (8%). Serious treatment-related adverse events were reported in 34% of patients, with no treatment-related deaths. [21 22]

TALAZOPARIB AND ENZALUTAMIDE

Synergistic effects

Enzalutamide is a strong AR antagonist that works by competitively inhibiting androgen binding to the androgen receptor (AR). This inhibition effectively blocks the receptor's ability to function as a transcription factor within the tumor environment. [23] Preclinical studies indicate at least four mechanisms of interaction between the AR, a key driver of prostate cancer cell growth, and PARP, supporting the rationale for their combined inhibition (Image 1.). [23] [24] [25] First, the retinoblastoma (RB1) tumor suppressor gene is located near BRCA2, and thus, the loss of RB1 often coincides with the loss of BRCA2. [26] The co-deletion of BRCA2 and RB1 is common and is linked to tumor progression and resistance to AR-targeted therapies.[27] When both RB1 and BRCA2 are lost, PARP inhibitors may exert selective pressure on cells with this co-deletion, making the tumor more responsive to ARSIs. [28] Early combination therapy with PARP inhibitors and ARSIs may even prevent RB1 loss, potentially delaying resistance to ARSIs. [28] Additionally, AR inhibition has been associated with an increase in PARP activity, potentially enhancing sensitivity to PARP inhibition. [28] PARP inhibitors also reduce AR activity, decreasing the expression of AR target genes. [28]Finally, AR inhibition may result in a state of BRCAness by downregulating HRR gene expression. [28]

Talazoparib plus enzalutamide: the TALAPRO-2

The synergistic effects of talazoparib and enzalutamide were tested in the phase 3 clinical trial TALAPRO-2, a randomized, double-blind, placebo-controlled trial evaluating talazoparib plus enzalutamide vs enzalutamide. Patients were randomly assigned to receive enzalutamide 160 mg once daily plus either talazoparib 0.5 mg or placebo once daily. [29] [30] The primary endpoint was rPFS by independent central review. Key secondary endpoints were OS, rPFS by investigator assessment, objective response rate (ORR) and duration of response, PSA response of 50% or greater. [30]All patients underwent prospective testing for HRR alterations with FoundationOne CDx or FoundationOne Liquid CDx. The following genes involved in the HRR pathway were tested: BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12. Enrollment was conducted into two independently powered cohorts: a general all-comers

cohort (N = 805; 169 were HRR-deficient) and then with a cohort specifically composed of HRR-deficient patients (N = 230). [31] Patients with BRCA alterations represent 7% in the talazoparib group and 8% in the placebo group and were not over-represented. [32]

Clinical efficacy

At the data cut-off August 16, 2022 median rPFS was not reached (95% CI, 27.5 months – not reached) in the talazoparib group and was 21.9 months (16.6–25.1) in the placebo group with a 37% reduced risk of radiographic progression in the treatment group with talazoparib and enzalutamide (HR 0.63; 95% CI 0.51–0.78; p<0.0001). In the HRR mutated patients' subgroup a decrease of 56% in the risk of rPFS was detected (HR 0.46; 95% CI 0.30 – 0.70; p = 0.0003). [31] Patients in the talazoparib group with BRCA gene alterations had a 77% lower risk of radiographic progression or death (HR 0.23; 95% CI 0.10 – 0.53; p = 0.0002). Despite overall survival data were immature, the HR for death was 0.89 (95% CI 0.69–1.14; p = 0.35), in favour of talazoparib plus enzalutamide. [31]

Safety evaluation

In the TALAPRO-2 study, treatment-emergent adverse events (TEAEs) resulted in dose interruptions and reductions of talazoparib in 62% and 53% of patients, respectively, compared to 21% and 7% in the placebo group. Despite these interruptions and reductions, the rate of permanent discontinuation due to TEAEs was 19% for those receiving talazoparib, versus 12% for the placebo group. [31 33] The most common hematological TEAEs were anemia, occurred in 65.8 % of patients (43.4 % were grade 3), neutropenia in 35.7 % (with 17.1 % grade 3) and thrombocytopenia in 24.6 % (the most were grade 1, occurred in 10%). Considering anemia, the median time to onset of grade 3 or more TEAE was 3.3 months, with a median duration of 16 days. [34] As a result, it is recommended to actively monitor patients for anemia during the first 3–4 months of treatment. For the first occurrence of grade 3–4 anemia, a temporary pause in treatment is advised, followed by a dose reduction if the anemia recurs, enabling most patients to continue PARP inhibitor therapy without needing permanent discontinuation. Anemia was managed through supportive care

measures (including transfusions) and dose adjustments, making it the most frequent adverse event leading to dose reductions (43%) and treatment discontinuation (8%). [33] The three most common non-hematologic treatment-emergent adverse events (TEAEs) observed were fatigue, affecting 33.7% of patients (with 4.0% classified as grade 3), back pain, reported by 22.1% of patients (with 2.5% grade 3), and decreased appetite, experienced by 21.6% of patients (with 1.3% grade 3). [34] The occurrence of serious TEAEs was 39% in patients treated with talazoparib plus enzalutamide, compared to 27% in those receiving placebo plus enzalutamide. In the talazoparib and enzalutamide group, 3% of patients died due to adverse events, though none of these deaths were deemed related to the treatment. [30] In the all-comers' population of the TALAPRO-2 trial, venous embolic and thrombotic events were observed in 4% of patients receiving talazoparib, with 3% experiencing pulmonary embolism. In comparison, less than 1% of patients in the placebo arm reported such events. [30] The safety profile of talazoparib combined with enzalutamide in the TALAPRO-2 HRR-deficient population aligned with the findings observed in the all-comers population. [33]

Agencies Approvals

FDA approved the association of talazoparib and enzalutamide as a first-line treatment in HRRm mCRPC patients [29] Despite a statistically significant rPFS improvement in the all-comers, the FDA did not consider the rPFS magnitude clinically meaningful in the context of the broad indication, combination treatment, and safety profile. [29]

The European Commission (EC), following the positive opinion expressed by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA), approved Talazoparib + Enzalutamide for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated regardless of the HRR status. [35]

Conclusion: an analysis of the data presented in the review

The combination therapy with talazoparib and enzalutamide is a valid first-line option for patients with mCRPC. However, special attention must be given to the adverse events associated with PARP inhibitors, particularly during the first few months of treatment.

EXPERT OPINION

Advancing PARP inhibitors earlier in the treatment strategy for mCRPC could offer enhanced benefits. The TALAPRO-2 trial investigated the effectiveness of talazoparib in combination with enzalutamide as a first-line therapy for men with mCRPC, both in the overall population and in those with DDR alterations. While the survival benefit is well-established in the BRCA-mutated population, there is some variability in the degree of benefit observed in the HRR-mutated population and in those without HRR mutations. The FDA approved the combination for HRR mutated only, but even within the HRR-mutated population, certain subgroups did not experience a PFS or OS benefit (e.g., those with ATM or CHEK2 mutations). [29] In the context of increasingly precise medicine, it is valuable to investigate the presence of additional subgroups beyond HRR mutations that could potentially benefit from PARP inhibitor and ARSI combination therapies.

Emerging biomarkers of efficacy

HRD

There is currently limited consensus on the parameters that define the HR status of a sample, and the specific combination of molecular markers required to classify tumors as homologous recombinations deficient (HRD). [36] DDR mutations alone do not fully capture the complexity of a patient's HRD status. Moreover, genomic testing for DDR mutations faces several inherent challenges, including reversion mutations, gene loss, epigenetic regulation, and potentially predictive mutations from other genes. This is particularly relevant in prostate cancer (PCa), where biallelic gene loss is often driven exclusively by somatic events. [37] Recent years have seen the emergence of multiple tests for HRD status. For instance, using the mutational signature-based

algorithm HRDetect (designed to identify BRCA1/BRCA2-deficient tumors), HRD tumors have been detected without the presence of homologous recombination repair (HRR) mutations.[38] This provides a basis for hypothesizing that alternative factors may contribute to HRD broadening. [38]

The HRD score is a test that measures chromosomal abnormalities, which reflect defects in the upstream precise repair of DNA double-strand breaks. This score is determined by combining three SNP-based assays: loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale state transitions (LST), each representing a distinct form of major genomic aberration. [39] In summary, HRD score directly reflects the impact of impaired HRR function (genomic scar), regardless of which specific component of the pathway is disrupted. [37] Investigating HRD to identify a "genomic scar" in prostate cancers that may be more responsive to PARP inhibitors would be highly valuable.

TMPRSS2-ERG

TMPRSS2 is located on chromosome 21q22.3, this gene encodes an androgen-inducible serine protease predominantly found in semen. It is most abundantly expressed in the adult prostate, with lower expression levels observed in tissues such as the gut, breast, ovary, kidney, heart, and lung. [40]

AR signaling controls the expression of genes like TMPRSS2 and PSA in both normal prostate cells and prostate cancer cells. [41] Therefore, the suppression of AR signaling is a key objective in prostate cancer therapy. Androgen deprivation and anti-androgen treatments inhibit AR signaling and can impair homologous recombination (HR) genes, and enzalutamide has been shown to induce a BRCAness-like state.[42] In vitro and in vivo preclinical studies showing that ERG interacts with tubulin and alters microtubule dynamics leading to impaired docetaxel or cabazitaxel engagement, detection of TMPRSS2-ERG fusion in the blood of CRPC patients is predictive of resistance to taxanes. [43]

RB1

The RB1 gene is the first human tumor suppressor gene to be described [44] and, in PC, the loss of RB1 is frequently linked to resistance to ARSIs. [44] [45]Furthermore, research has demonstrated that BRCA2 germline mutations are frequently linked to RB1 heterozygous deletions in prostate cancer. [46] [47] Additionally, a study revealed that the co-loss of BRCA2 and RB1 in human prostate cancer cells triggers an epithelial-to-mesenchymal transition, which is linked to a more aggressive disease phenotype, facilitating tumor cell extravasation and driving metastatic progression toward fatal outcomes. [27]

We also shed light on recent findings from a post-hoc analysis of the TALAPRO-2 all-comers cohort, presented by Piulats et al. at the 2024 American Association for Cancer Research (AACR) annual meeting [48]. The study examined the rPFS benefit of talazoparib plus enzalutamide compared to placebo plus enzalutamide in patients with mutations in specific non-HRR genes, irrespective of HRR gene mutations. Notably, alterations in the TMPRSS2-ERG and RB1 genes (found in 30% and 3% of the cohort, respectively) emerged as potential predictive biomarkers for differential efficacy, favoring the combination of talazoparib and enzalutamide. The authors propose that PARP inhibitors may create a synthetically lethal interaction with TMPRSS2-ERG, potentially overcoming RB1-mediated resistance to enzalutamide. This study highlights the role of mutations outside the HRR pathway that may confer clinical benefit when combining PARP inhibitors and ARSIs. It is important to note, however, that the clinical impact of TMPRSS2-ERG mutations could be associated with the co-loss of RB1 and BRCA2 on chromosome 13. [48]

Conclusions

The abovementioned emerging molecular targets shed light on the need to look beyond the concept of HRR. We think that these molecular targets might warrant further consideration by regulatory agencies and in future clinical trials. This would be important to better define the pool of patients who could benefit from enzalutamide in combination with talazoparib, especially considering the

potential future shift of the combo to the first line in the setting of hormone sensitive prostate cancer (HSPC) [49] , and the need for an increasingly precise and patient-tailored approach to oncology.

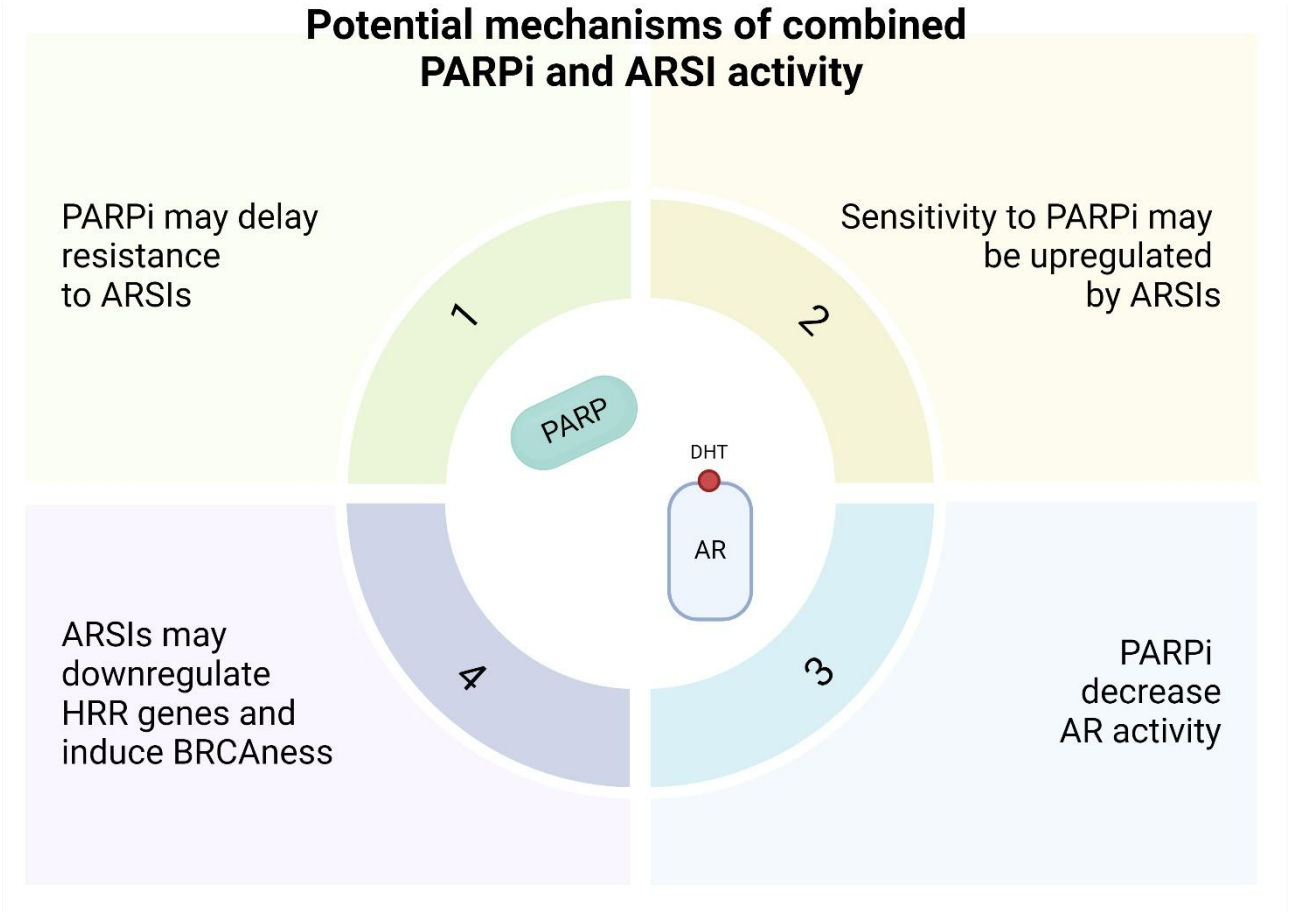

Image 1. Potential mechanisms of combined PARPi and ARSI activity. Created with Biorender ®.

PARPi: poly (ADP-ribose) polymerase inhibitors; ARSI: androgen receptor signal inhibitor; AR: androgen receptor; HRR: homologous recombination repair.

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