# PARP Inhibitors in Metastatic Prostate Cancer: Current Evidence and Future Directions

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**Abstract:** Inhibitors of poly(ADP-ribose) polymerase (PARPis) are an established treatment for homologous recombination repair gene-altered metastatic prostate cancer. The efficacy of PARPis—both as single agents and in combination with androgen receptor pathway inhibitors (ARPIs)—was first established in patients with metastatic castration-resistant prostate cancer (mCRPC, more recently termed androgen pathway modulation-resistant [APMR] prostate cancer), with the greatest benefit observed in *BRCA2*-altered disease. This review focuses on the more recently demonstrated evidence of the benefit of PARPis in combination with standard-of-care ARPIs and androgen deprivation therapy for patients with metastatic hormone-sensitive prostate cancer (mHSPC, also termed androgen pathway modulation-sensitive [APMS] prostate cancer) generated by the AMPLITUDE and TALAPRO-3 trials, which evaluated niraparib and talazoparib, respectively. How broadly PARPis will be incorporated into the clinical management of patients with mHSPC/APMS will depend on the perception of issues such as optimal patient eligibility (including biomarker selection), short- and long-term treatment-related adverse events, other available treatment options, and treatment sequencing. The review also examines future directions for PARPi therapy for the mHSPC/APMS disease state, including the ongoing EvoPAR-Prostate01 phase 3 registration trial evaluating the PARP1-selective agent saruparib.

Keywords
Androgen receptor pathway inhibitors, *BRCA* mutations, combination therapy, homologous recombination repair, metastatic hormone-sensitive prostate cancer, PARP inhibitors

## Introduction

Androgen deprivation therapy (ADT) was historically the standard of care for metastatic hormone-sensitive prostate cancer (mHSPC), more recently termed androgen pathway modulation-naive/sensitive (APMN/S) prostate cancer.[1] Intensification with an androgen receptor pathway inhibitor (ARPI), with or without docetaxel, is

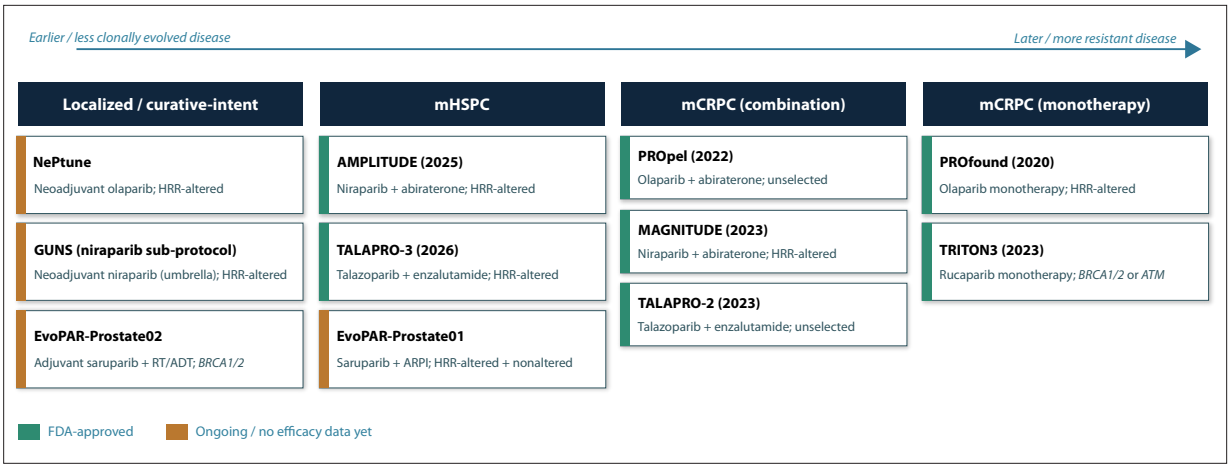



**Figure.** Selected key studies of PARP inhibitors in prostate cancer. Columns are ordered from left to right along the disease continuum (arrow), from localized, curative-intent disease through mHSPC/APMS to mCRPC/APMR, with mCRPC subdivided into ARPI-combination and later-line monotherapy settings. Clinical development has proceeded in the opposite direction, moving progressively to earlier in the disease course—from late-line monotherapy in mCRPC/APMR, to combination therapy in mCRPC and now mHSPC/APMS, to curative-intent localized disease. Trials are color-coded by status: FDA-approved (green), reported positive (teal), and ongoing (amber). Years indicate the years of primary endpoint (rPFS) publication; ongoing trials are undated.

ADT, androgen deprivation therapy; APMR, androgen pathway modulation-resistant; APMS, androgen pathway modulation-sensitive; ARPI, androgen receptor pathway inhibitor; *ATM*, ataxia-telangiectasia mutated; *BRCA*, breast cancer gene; HRR, homologous recombination repair; mCRPC/mHSPC, metastatic castration-resistant prostate cancer/metastatic hormone-sensitive prostate cancer; rPFS, radiographic progression-free survival; RT, radiotherapy.

now recommended because it improves progression-free survival (PFS) and overall survival (OS).[2] Nevertheless, benefit varies markedly, reflecting biological heterogeneity. Clinical presentations range from relatively indolent to rapidly progressive and lethal.

A substantial subset of metastatic prostate cancers harbor pathogenic alterations in genes associated with homologous recombination repair (HRR), most frequently *BRCA2*. HRR gene-altered disease, particularly *BRCA2*-altered disease, is associated with an aggressive phenotype and poor prognosis, including a higher Gleason grade, more frequent nodal and visceral involvement, and shorter cause-specific and metastasis-free survival.[3-5] PARP inhibitors (PARPis) are established treatments for HRR gene-altered metastatic castration-resistant prostate cancer (mCRPC), more recently termed androgen pathway modulation-resistant (APMR) prostate cancer, either as monotherapy after an ARPI or combined with an ARPI in ARPI-naive patients. AMPLITUDE and TALAPRO-3 have now reported the efficacy of adding niraparib and talazoparib (Talzenna, Pfizer), respectively, to ADT and ARPI doublet therapy in mHSPC, also termed androgen pathway modulation-sensitive (APMS) prostate cancer. This review examines the rationale, evidence, and unresolved questions that will determine how broadly PARPis are integrated into metastatic prostate cancer practice.

## Biological Rationale for PARP Inhibition in Prostate Cancer

PARP1 and PARP2 are enzymes that detect DNA damage and, using nicotinamide adenine dinucleotide ($NAD^+$) as a substrate, act to poly(ADP-ribosyl)ate histones and other proteins to recruit repair factors.[6] PARP inhibition and the trapping of PARP-DNA complexes block single-strand break repair, leading to replication fork collapse and double-strand breaks.[7] HRR-proficient cells can resolve this damage, whereas HRR-deficient cells, including those with biallelic loss of *BRCA1* or *BRCA2*, accumulate lethal genomic instability, the synthetic lethality underlying PARPi activity.[8,9] Here, the term *HRR gene-altered* denotes tumors carrying pathogenic alterations in HRR-associated genes, whereas *HRR-deficient* denotes functional loss of homologous recombination.

Germline or somatic HRR-associated gene alterations occur in approximately 25% of metastatic prostate cancers.[10] In a contemporary mHSPC/APMS cohort of 556 patients with paired somatic and germline sequencing, 28.6% had an HRR gene alteration (12.4% *BRCA1/2* and 16.2% non-*BRCA*), comparable with the reported frequencies in mCRPC/APMR.[11] Because these alterations are predominantly truncal,[12] screening in mHSPC/APMS identifies essentially the same targetable population and enables earlier intervention. PARPi

sensitivity is greatest with biallelic *BRCA2* loss; activity in other HRR genes is less consistent across agents, trials, and disease states.

Combining PARPis with ARPIs has also been proposed for tumors without HRR alterations. PARP1 is a cofactor for androgen receptor (AR)-driven transcription,[13] whereas AR signaling regulates components of DNA repair[14,15]; AR inhibition might therefore produce a "*BRCA*-like" state that increases PARPi susceptibility.[16,17] However, more recent preclinical[18] and clinical[19] evidence does not support synergistic antitumor activity.

## PARP Inhibitors in mCRPC/APMR

The US Food and Drug Administration (FDA) has approved 4 PARPis for prostate cancer. Rucaparib (Rubraca, pharma&) and olaparib (Lynparza, AstraZeneca) are approved as monotherapy for previously treated mCRPC/APMR. Olaparib plus abiraterone acetate and prednisone or prednisolone (AAP), niraparib plus abiraterone acetate (Akeega, Janssen Biotech) and prednisone or prednisolone, and talazoparib plus enzalutamide (Xtandi, Astellas) are approved as first-line ARPI combinations. Biomarker requirements vary by agent, setting, and region (Table 1).

The agents differ most notably in PARP-trapping potency. Talazoparib has the strongest preclinical trapping activity, followed by niraparib, with olaparib and rucaparib less potent.[7,20] PARP trapping stabilizes intrinsically cytotoxic PARP-DNA complexes in addition to inhibiting enzymatic activity. Veliparib causes minimal trapping and has demonstrated only modest prostate cancer activity,[7,21,22] supporting trapping as a potential driver of antitumor effect. Whether greater trapping translates into clinically meaningful efficacy is unestablished, although it may correlate with toxicity. Reported toxicity profiles vary across trials, but without a head-to-head clinical trial, comparisons are limited. PARP2 inhibition impairs hematopoiesis in animal models, so agents with stronger PARP2 inhibition may have increased hematologic toxicity,[23,24] although this requires validation in clinical studies. A computational and experimental analysis by Antolin and colleagues found that PARPis have varied off-target polypharmacologic kinase profiles, which may contribute to the varied side effect profiles observed.[25]

The mCRPC/APMR monotherapy trials provide the foundation for earlier treatment (Figure). In PROfound, olaparib improved radiographic PFS (rPFS; 7.4 vs 3.6 months; hazard ratio [HR], 0.34; *P*<.001) and OS (19.1 vs 14.7 months; HR, 0.69; *P*=.02), despite 67% control arm crossover, in patients with *BRCA1*, *BRCA2,* or *ATM* alterations after progression on an ARPI.[26,27] TRITON3 demonstrated rPFS benefit for rucaparib in *BRCA*-altered (HR, 0.50) and overall *BRCA*/*ATM* populations (HR, 0.61), but not in *ATM*-altered disease (HR, 0.95); roughly 55% of controls received docetaxel, making rucaparib the only PARPi shown to improve rPFS against a docetaxel-containing control.[28] Resistance is nevertheless inevitable and frequently develops through mechanisms including *BRCA2* reversion mutations that restore HRR function.[29,30]

Three phase 3 trials then evaluated first-line PARPi/ARPI combinations. In both PROpel (olaparib plus AAP) and MAGNITUDE (niraparib plus AAP), rPFS was improved without a significant OS benefit, with the advantage largely confined to *BRCA1/2*-altered disease.[19,31-33] TALAPRO-2 (talazoparib plus enzalutamide) alone demonstrated a significant OS benefit in a biomarker-unselected population: 45.8 months (95% CI, 39.4-50.8) vs 37.0 months (95% CI, 34.1-40.4; HR, 0.80; 95% CI, 0.66-0.96; *P*=.016).[34,35] Benefit was concentrated in HRR gene-altered disease (HR, 0.55; 95% CI, 0.36-0.83; *P*=.0035), whereas the HRR-nonaltered/unknown subgroup did not independently show a significant OS benefit (HR, 0.88; 95% CI, 0.71-1.08; *P*=.22). The latter subgroup comprised 636 of 805 patients (79%) and pooled HRR-nonaltered with untested or test-failed patients in a single randomization stratum; *BRCA1/2* alterations were present in only 7% to 8% of the cohort overall.[34] Because status was assigned almost entirely on the basis of tumor tissue, with concurrent circulating tumor DNA (ctDNA) testing available in only a minority, misclassified HRR-altered patients would have carried a genuine effect into this stratum and biased its estimate toward apparent benefit; an exploratory analysis confined to the 314 patients HRR-negative on both tissue and ctDNA testing was likewise not significant (HR, 0.78; 95% CI, 0.58-1.05).[35]

The approved populations differ by region. For monotherapy, gene eligibility is broadest in the United States and narrows through Canada to the European Union; rucaparib is indicated only in the United States. In PROpel, olaparib plus AAP improved rPFS in the intention-to-treat population (HR, 0.66; 95% CI, 0.54-0.81), but in exploratory analyses the benefit was concentrated in the 85 patients with *BRCA*-altered disease (rPFS HR, 0.24; 95% CI, 0.12-0.45). The 711 patients without a detected *BRCA* alteration showed only a modest rPFS difference (HR, 0.77; 95% CI, 0.63-0.96) and no survival benefit (HR, 0.92; 95% CI, 0.74-1.14).[36] A majority of the members of the FDA Oncologic Drugs Advisory Committee voted to restrict the indication accordingly, and regulators in the United States and Canada limit the olaparib and niraparib combinations to *BRCA*-altered disease (Table 1).[36,37]

FDA reviewers have set out the reasoning behind restricting talazoparib/enzalutamide to HRR gene-altered

**Table 1.** Approved PARP Inhibitor Indications and Required Biomarkers, by Disease Setting and Region

| Agent/regimen | United States (FDA) | Canada | European Union (EMA) |
|---|---|---|---|
| ***Castration-resistant (mCRPC) — single agent, after prior ARPI*** | | | |
| Olaparib | HRR gene panel (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1, CDK12, CHEK1, CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*) | *BRCA1/2* or *ATM* | *BRCA1/2* |
| Rucaparib | *BRCA1/2* | Not approved | Not approved |
| ***Castration-resistant (mCRPC) — combination, first-line*** | | | |
| Olaparib + abiraterone | *BRCA1/2* | *BRCA1/2* | No biomarker restriction |
| Niraparib + abiraterone | *BRCA1/2* | *BRCA1/2* | *BRCA1/2* |
| Talazoparib + enzalutamide | HRR gene-mutated | HRR gene-mutated | No biomarker restriction |
| ***Hormone-sensitive (mHSPC) — combination (with ADT)*** | | | |
| Niraparib + abiraterone | *BRCA2* | Not approved | *BRCA1/2* |
| Talazoparib + enzalutamide | HRR gene-mutated | Not approved | Not approved |

ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; *ATM*, ataxia-telangiectasia mutated; *BRCA*, breast cancer gene; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer.

disease.[38] The all-comers cohort met its rPFS endpoint (HR, 0.63; 95% CI, 0.51-0.78; *P*<.0001), but the effect size was judged modest, the survival data were immature, and the risk-to-benefit balance was unfavorable in a broad, minimally symptomatic population. Including the non-*BRCA* HRR gene-altered population was less straightforward; its exploratory rPFS estimate (HR, 0.72; 95% CI, 0.49-1.07) fell well short of that in *BRCA*-altered disease (HR, 0.20; 95% CI, 0.11-0.36), but the prespecified HRR-altered population had met its endpoint and the agency was unwilling to act on small exploratory subgroups, with the weaker supporting evidence reflected in the label. In contrast, the European Medicines Agency (EMA) approved olaparib and talazoparib combinations without biomarker restriction, reflecting their biomarker-unselected primary endpoints. The EMA regarded the subgroup analyses as underpowered and hypothesis-generating, and it did not consider the evidence of treatment heterogeneity sufficient to warrant a narrower indication.[37] These regional variations illustrate the ongoing uncertainty about whether benefit beyond *BRCA1/2*-altered disease is sufficient to justify biomarker-unselected treatment. The hormone-sensitive indications are included here for completeness and are discussed in the following section.

Together, these mCRPC/APMR trials identify which patients derive the greatest benefit and raise 3 debates that carry directly into the hormone-sensitive setting:

**1. Patient selection.** It is unclear whether the minimal to modest activity in unselected populations justifies routine combination therapy, or whether the benefit is sufficiently concentrated in HRR gene-altered—and particularly *BRCA*-altered—disease to make biomarker selection mandatory. The regulatory divergence described above reflects genuine uncertainty about the benefit in the non-*BRCA* HRR gene-altered and unselected populations.

**2. Differences in HRR gene panel composition.** The trials do not test a common biomarker. Approved indications range from *BRCA1/2* alone (rucaparib) to a 14-gene HRR panel (olaparib), and the combination trials applied differing definitions of HRR gene alteration, complicating cross-trial comparison.

**3. Differential benefit by HRR gene alteration.** The hierarchy of effects across *BRCA2*, other HRR gene-altered, and HRR gene-non-altered disease argues against treating HRR alterations as a single biomarker. These gene-level signals should, however, be interpreted with caution because they derive from small subgroups analyzed with univariate rather than multivariate methods, and largely from post hoc and regulatory (FDA-level) analyses rather than from prespecified endpoints.

CASPAR, which was evaluating enzalutamide plus rucaparib in biomarker-unselected first-line mCRPC/APMR, was discontinued in 2023 following changes in

the treatment landscape.[39] Truly ARPI-naive first-line mCRPC/APMR is increasingly uncommon, shifting attention to PARPi treatment in mHSPC/APMS.

## PARP Inhibitors in mHSPC/APMS

### *Rationale*

ARPIs with ADT are the standard first-line treatment for mHSPC/APMS.[2] PARPis have similarly been moved to earlier in the disease course in other cancer types, including as maintenance in newly diagnosed advanced ovarian cancer after a response to first-line platinum therapy,[40,41] prompting assessment of ARPI/PARPi combinations in mHSPC/APMS. The rationale for moving PARPis upstream is in any case not a simple extrapolation from mCRPC/APMR; the 2 settings differ in disease burden, clonal architecture,[42] and prognosis[5] and must be assessed directly rather than assumed.

Several arguments favor earlier use. Hormone-sensitive disease is less genomically heterogeneous, with fewer co-occurring *TP53*, *RB1*, and *PTEN* alterations that may modify response,[5,43] and secondary *BRCA2* reversion mutations are less likely to occur before the selective pressure of prior therapy.[29] Earlier intensification with docetaxel or an ARPI has also historically yielded larger and more durable survival benefits than equivalent intensification in mCRPC/APMR.[44-46] Set against this finding, combination therapy may overtreat patients in whom durable control would be achieved on ADT-ARPI alone, and PARPis carry a recognized risk of hematologic toxicity, including the uncommon late complications of myelodysplastic syndrome and acute myeloid leukemia.[47] The trade-off turns partly on attrition; many patients receive no systemic therapy beyond an ARPI, so a biomarker-selected patient who is not offered a PARPi upfront may never receive it,[48] whereas a sequential strategy reserving PARPis for mCRPC/APMR would spare those who would not benefit years of treatment. OS and subsequent therapy are therefore central to interpreting these trials, as is the population; in patients with *BRCA*-altered disease, a subgroup with a particularly poor prognosis, earlier use is more readily justified, whereas in non-*BRCA* disease, the benefit may be too marginal to warrant the added toxicity.

### *AMPLITUDE*

AMPLITUDE randomized 696 patients with HRR-altered mHSPC/APMS to niraparib plus AAP or placebo plus AAP.[10] rPFS testing was done hierarchically, proceeding only after each preceding endpoint had been met: *BRCA1/2*, then the HRR effector cohort (*BRCA1/2*, *BRIP1*, *PALB2*, *RAD51B,* and *RAD54L*), and then the intention-to-treat population. *BRCA1/2* alterations occurred in 387 patients (56%) and HRR effector alterations in 456 (66%). The primary endpoint was met in all 3 cohorts: HR, 0.52 (95% CI, 0.37-0.72) in *BRCA1/2*, 0.57 (95% CI, 0.42-0.77) in HRR effector genes, and 0.63 (95% CI, 0.49-0.80) in the intention-to-treat population. OS data are immature but favor the combination (*BRCA1/2* HR, 0.75; *P*=.15), and safety was consistent with that in MAGNITUDE.[49]

The FDA exploratory *BRCA2* analysis reported an rPFS HR of 0.46 (95% CI, 0.32-0.66), whereas the non-*BRCA2* population did not show significant benefit (HR, 0.88; 95% CI, 0.63-1.24).[50] The FDA therefore approved niraparib plus AAP for *BRCA2*-altered mHSPC/APMS in December 2025. Together with MAGNITUDE, PROpel, and TALAPRO-2, this trial again raises the question of whether PARPi/ARPI benefit is driven primarily by *BRCA2*-altered disease.[32,34,49] The HRR effector subgroup was intended to capture genes that act immediately at the double-strand break and whose biology more closely resembles *BRCA* biology[10]; *CDK12*, *CHEK2*, and *FANCA* were excluded. Biology within this group is unlikely to be uniform, and except for *BRCA2*, AMPLITUDE was not powered at the single-gene level.[51]

### *TALAPRO-3*

TALAPRO-3 randomized 599 patients with alterations in 1 of 12 HRR genes to talazoparib plus enzalutamide or placebo plus enzalutamide.[52] Investigator-assessed rPFS improved overall (HR, 0.48; 95% CI, 0.36-0.65; *P*<.001), in the *BRCA* subgroup (HR, 0.37; 95% CI, 0.22-0.61), and in the prespecified non-*BRCA* population (HR, 0.57; 95% CI, 0.39–0.82). The panel comprised *ATM*, *ATR*, *BRCA1*, *BRCA2*, *CDK12*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2,* and *RAD51C*, with *BRCA* status used for stratification; this prespecified non-*BRCA* analysis is an important distinction from AMPLITUDE.

Exploratory single-gene estimates favored talazoparib for *CDK12* (HR, 0.28; 95% CI, 0.12-0.60), *BRCA2* (HR, 0.35; 95% CI, 0.20-0.62), and *ATM* (HR, 0.43; 95% CI, 0.24-0.79), but they were inconclusive for *BRCA1* (HR, 0.71), *ATR* (HR, 0.79), and *CHEK2* (HR, 0.63). These post hoc, univariate analyses were not adjusted for multiplicity and often involved small samples, including only 27 patients with *BRCA1*-altered disease. *ATM* provides the clearest contrast with mCRPC/APMR, in which PARPi monotherapy produced no evident benefit in PROfound, TRITON3, or the pooled FDA analysis.[51] *CDK12* results in mCRPC/APMR have been mixed, and *BRCA1* may differ from *BRCA2* because it is more often monoallelic and therefore not functionally HRR-deficient.

### *Interpreting the Trials in Context*

AMPLITUDE and TALAPRO-3 use the same treatment strategy but differ sufficiently to limit comparisons of

**Table 2.** Phase 3 Trials of PARP Inhibitor Plus ARPI Combinations in mHSPC/APMS

| Characteristic | AMPLITUDE (NCT04497844) *Niraparib + AAP* | TALAPRO-3 (NCT04821622) *Talazoparib + enzalutamide* | EvoPAR-Prostate01 (NCT06120491) *Saruparib + ARPI* |
|---|---|---|---|
| **Regimen** | Niraparib + AAP | Talazoparib + enzalutamide | Saruparib (PARP1-selective) + physician's choice ARPI |
| **Sample size and eligibility** | 696; HRR-altered, 9-gene panel | 599; HRR-altered, 12-gene panel | 1889; separate HRR-altered (~30%) and nonaltered (~70%) cohorts; 9-gene panel |
| **Prior ADT / prior therapy window**[a] | ≤6 months of prior ADT, ≤45 days of AAP | ≤3 months of ADT, ± an approved ARPI, in the mHSPC/APMS setting | <4 months of prior ADT for metastatic disease |
| **Prior docetaxel permitted** | ≤6 cycles; received by 16% | No | No |
| **Volume/risk stratification** | Stratified by disease volume (high vs low), prior docetaxel, and alteration type (*BRCA2* vs *CDK12* vs other) | Stratified by disease volume (high vs low), de novo vs relapsed disease, and *BRCA* vs non-*BRCA* status | Disease volume and physician's choice of ARPI. HRR gene-altered cohort: *BRCA1/2* mutation status<br>Non-HRR gene-altered cohort: metastatic (M1) disease at initial prostate cancer diagnosis (yes vs no) |
| **Results to date (as of September 2026)** | rPFS positive (HR 0.63 overall, 0.52 in *BRCA1/2* subgroup) | rPFS positive (HR 0.48 overall, 0.37 in *BRCA* subgroup) | Active, not recruiting (estimated primary outcome completion 2027) |

[a]Prior PARP inhibitors were excluded in all trials. EvoPAR-Prostate01 permitted prior ARPI or chemotherapy for localized disease.

AAP, abiraterone acetate plus prednisone; ADT, androgen deprivation therapy; APMS, androgen pathway modulation-sensitive; ARPI, androgen receptor pathway inhibitor; HR, hazard ratio; HRR, homologous recombination repair; mHSPC, metastatic hormone-sensitive prostate cancer; PARP, poly(ADP-ribose) polymerase; rPFS, radiographic progression-free survival.

direct efficacy (Table 2), and their gene panels overlap in the case of only 6 genes (Table 3). *ATM* was included in TALAPRO-3 but excluded from AMPLITUDE, likely reflecting its low activity in prior mCRPC/APMR studies. TALAPRO-3 reported a prespecified non-*BRCA* benefit (HR, 0.57), whereas AMPLITUDE's post hoc non-*BRCA1/2* estimate showed little benefit (HR, 0.81).[10,52] The 2 subgroups were not equivalent, however; TALAPRO-3 also included *ATM*, *ATR*, *MLH1*, *MRE11A, NBN,* and *RAD51C*.

Concomitant and permitted prior therapies also differed. The ARPI backbones, AAP in AMPLITUDE and enzalutamide in TALAPRO-3, have not been compared directly in mHSPC/APMS; the closest evidence is the crossover trial by Khalaf and colleagues, which examined their sequencing in mCRPC/APMR.[53] AMPLITUDE permitted up to 6 months of prior ADT, 45 days of AAP, and 6 docetaxel cycles, whereas TALAPRO-3 permitted 3 months of ADT with or without an ARPI and excluded docetaxel because of overlapping toxicity and sequencing uncertainty.[54] Both trials stratified by CHAARTED volume and HRR status and enrolled predominantly aggressive disease; TALAPRO-3 was 84% de novo and 70% high-volume, and AMPLITUDE was 78% high-volume. Only AMPLITUDE included chemotherapy-exposed patients (16%), consistent with real-world uptake in the United States.[55,56] AMPLITUDE also carried more *BRCA1/2*-altered disease (56% vs 35%). Notably, AMPLITUDE had a shorter control arm median rPFS of 29.5 months vs 45.8 months in TALAPRO-3.

Pharmacodynamic differences may nevertheless contribute. In the mCRPC/APMR setting, talazoparib plus enzalutamide improved both rPFS and OS in TALAPRO-2, whereas niraparib plus AAP produced no significant OS benefit in MAGNITUDE.[33,35] Similarly, in mHSPC/APMS, TALAPRO-3 produced a numerically lower overall HR despite lower *BRCA* enrichment, which is consistent with a stronger non-*BRCA* effect and potentially with talazoparib's greater trapping potency.[57] If this instead reflects broad cytotoxicity without a target-specific effect, docetaxel might be similarly effective, and direct comparison would be warranted.

These observations do not establish talazoparib as intrinsically more active. HRs cannot be compared directly, the rPFS difference in the control arm reflects distinct populations and treatment contexts, and the non-*BRCA* panels were not equivalent. Greater trapping may also increase toxicity; anemia occurred in 71% of talazo-

parib-treated patients in TALAPRO-3 (51% grade ≥3) and 52% of niraparib-treated patients in AMPLITUDE (29% grade ≥3). Establishing differential activity within *BRCA2* or more broadly would require mature OS and quality-of-life data, and ultimately a head-to-head comparison.

### *EvoPAR-Prostate01*

Saruparib is highly selective for PARP1, the primary mediator of PARPi antitumor effects, while largely sparing PARP2.[58] Because PARP2 supports hematopoiesis, this feature is expected to reduce the anemia and thrombocytopenia that frequently limit the dose intensity of dual PARP1/2 inhibitors. PETRANHA demonstrated acceptable toxicity in metastatic prostate cancer,[59] potentially widening the therapeutic index for prolonged treatment in mHSPC/APMS.

EvoPAR-Prostate01 (NCT06120491) is an ongoing phase 3 trial of saruparib plus physician's choice of AAP, darolutamide (Nubeqa, Bayer HealthCare), or enzalutamide in 1889 patients with mHSPC/APMS.[60] Cohort assignment uses prospective testing of tumor tissue and ctDNA, with HRR gene-altered and HRR gene-non-altered cohorts accounting for approximately 30% and 70% of the planned enrollment, respectively. Unlike AMPLITUDE and TALAPRO-3, EvoPAR-Prostate01 tests biomarker-negative disease in a prespecified cohort and permits different ARPI backbones. No efficacy data are available; primary completion is estimated for 2027. The design will establish whether the benefit extends to biomarker-negative disease and whether a better-tolerated, PARP1-selective inhibitor can sustain earlier, prolonged combination treatment.

## Unresolved Questions for PARP Inhibitors in mHSPC/APMS

### *Patient Selection*

How broadly PARPis should be used remains a subject of debate. The narrowest approach restricts treatment to *BRCA2*-altered disease, in which prognosis is poorest and benefit most consistent, underpinning the FDA approval of niraparib plus AAP in mHSPC/APMS.[50] TALAPRO-3 supports a broader HRR-based approach through its non-*BRCA* result,[52] although benefit across *CDK12*, *ATM*, *BRCA1*, *ATR*, and *CHEK2* was uneven and based on exploratory post hoc analyses. Without demonstrated OS benefit, selection in non-*BRCA* disease must weigh age, comorbidity, disease volume, prognosis, and alternatives. Biomarker-negative use requires a positive non-HRR cohort in EvoPAR-Prostate01.

*CDK12* and *ATM* are the most notable non-*BRCA* signals because their subgroups were relatively large and their point estimates favored talazoparib, whereas *BRCA1*, *ATR,* and *CHEK2* did not reach significance. This distinction is clinically important; broadening eligibility across all HRR-associated genes would treat heterogeneous biology as a single predictive category. Mature OS and quality-of-life data may determine whether the rPFS gain in these groups is sufficient.

The implementation of ARPI/PARPi combinations depends on identifying eligible patients through testing, but most of the 11,927 US patients studied from 2015 to 2022 did not undergo genetic testing.[61] Where testing is performed, tissue and ctDNA assays differ between trials,[62] and a small tumor fraction can produce false-negative results.[63,64] The contrasting gene panels also mean that a patient may meet one trial definition but not another, even before regional labels are applied; molecular selection will improve outcomes only if testing is routine and negative results are technically reliable.

### *Integration With Triplet Therapy*

ARASENS and PEACE-1 established that the combination of ADT, an ARPI, and docetaxel improves survival in mHSPC/APMS when compared with ADT plus docetaxel.[65,66] ARASENS enrolled a population with predominantly de novo, high-volume disease and suggested benefit across risk groups, with less precise low-volume estimates.[67] PEACE-1 enrolled only de novo disease and showed the clearest benefit in high-volume disease.[66] Docetaxel triplet therapy is consequently recommended predominantly in de novo high-volume or high-risk disease, although its benefit vs an ARPI doublet is unproven[2] and real-world uptake remains limited.[56]

The Alliance ASPIRE trial randomizes patients to ADT plus apalutamide (Erleada, Janssen Biotech), with or without docetaxel, with OS as the primary endpoint.[68] TRIPLE-SWITCH (SWOG/CCTG-PR26; NCT06592924) uses a response-adapted design, randomizing patients with a prostate-specific antigen level of at least 0.2 ng/mL after 6 to 12 months of ADT and at least 4 months of an ARPI to docetaxel or continued ADT-ARPI, again with OS as the primary endpoint.[69] Many patients with *BRCA2*-altered disease may meet criteria for both docetaxel triplet and PARPi-ARPI therapy. Adding a PARPi to ADT-ARPI has level 1 evidence of benefit in *BRCA2*-altered disease. Where docetaxel is strongly favored, AMPLITUDE provides limited evidence after prior docetaxel because only 16% received it, whereas TALAPRO-3 excluded prior docetaxel, partly because of overlapping toxicity and sequencing uncertainty.[10,52] No trial tested concomitant docetaxel, so optimal selection and sequencing, as well as any role for quadruplet therapy, remain unknown. PSMAddition assessed lutetium Lu 177 vipivotide tetraxetan ([$^{177}$Lu]

**Table 3.** Clinical Trial Gene Eligibility Across mHSPC/APMS Trials

| Gene | Functional category | PARPi sensitivity[a] | AMPLITUDE | TALAPRO-3 | EvoPAR-Prostate01 |
|---|---|---|---|---|---|
| *ATM* | DNA damage signaling | Limited | — | ✓ | ✓ |
| *ATR* | DNA damage signaling | Uncertain | — | ✓ | — |
| *BARD1* | Core HRR | Moderate | — | — | ✓ |
| ***BRCA1*** | Core HRR | Strong | ✓ | ✓ | ✓ |
| ***BRCA2*** | Core HRR | Strong | ✓ | ✓ | ✓ |
| *BRIP1* | Interstrand-crosslink repair (FA pathway) | Uncertain | ✓ | — | — |
| ***CDK12***[b] | Transcription-coupled DDR | Conflicting | ✓ | ✓ | ✓ |
| *CHEK2* | DNA damage signaling | Limited | ✓ | ✓ | — |
| *FANCA* | Interstrand-crosslink repair (FA pathway) | Uncertain | ✓ | ✓ | — |
| *MLH1** | Mismatch repair | Uncertain | — | ✓ | — |
| *MRE11A* | DSB end resection (MRN complex) | Uncertain | — | ✓ | — |
| *NBN* | DSB end resection (MRN complex) | Uncertain | — | ✓ | — |
| ***PALB2*** | Core HRR | Strong | ✓ | ✓ | ✓ |
| *RAD51B* | Core HRR | Moderate | ✓ | — | ✓ |
| *RAD51C* | Core HRR | Moderate | — | ✓ | ✓ |
| *RAD51D* | Core HRR | Moderate | — | — | ✓ |
| *RAD54L* | Core HRR | Moderate | ✓ | — | — |

*Mismatch repair genes are distinct from canonical HRR, but *MLH1* is included because it was part of the TALAPRO-3 eligibility panel.

"✓" indicates a qualifying (eligibility) gene; "—" indicates that the gene is not in the panel. Gene symbols in boldface type (*BRCA1*, *BRCA2*, *CDK12*, *PALB2*) are the only ones qualifying across all 3 trials. *ATM* was excluded from AMPLITUDE but was eligible in TALAPRO-3 and EvoPAR-Prostate01.

[a]PARPi sensitivity is a qualitative summary for each gene, drawn mainly from the by-gene analyses in castration-resistant (APMR) disease (PROfound,[26] TRITON2[90] and TRITON3,[28] TALAPRO-2,[34] MAGNITUDE[49]), and the FDA pooled analysis,[51] which report outcomes at the level of individual genes. The hormone-sensitive (APMS) trials (AMPLITUDE[10] and TALAPRO-3[52]) both show a clear benefit in BRCA-altered disease; their estimates for individual non-*BRCA* genes are exploratory and underpowered, so these trials are cited in support of the *BRCA* rating rather than as the source for the other genes' ratings.

[b]*CDK12* functions in transcription-coupled regulation of DDR gene expression rather than directly in HRR. In the AMPLITUDE trial, it was a randomization stratification factor (*BRCA2* vs *CDK12* vs other) and lies outside the HRR effector subgroup, contributing only to the all-HRR intention-to-treat analysis. PARPi sensitivity is reported inconsistently. The FDA pooled analysis[51] found a significant rPFS benefit (HR, 0.50), whereas earlier individual trial data indicated limited activity; hence, the "Conflicting" designation.

Functional categories denote each gene's primary role in the DNA damage response: DNA damage signaling and DSB end resection,[91] core HRR,[92] interstrand-crosslink repair (Fanconi anemia pathway),[93] transcriptional regulation of DDR genes,[94] and mismatch repair.[95] Several core HRR genes (*BRCA1*, *BRCA2*, *PALB2*, *RAD51C*) are also formally Fanconi anemia genes but are classified here by their primary HR role.

APMR, androgen pathway modulation–resistant; APMS, androgen pathway modulation-sensitive; *ATM*, ataxia-telangiectasia mutated; DDR, DNA damage response; DSB, double-strand break; FA, Fanconi anemia; FDA, US Food and Drug Administration; HR, hazard ratio; HRR, homologous recombination repair; mHSPC, metastatic hormone-sensitive prostate cancer; MRN, MRE11-RAD50-NBS1 complex; PARPi, poly(ADP-ribose) polymerase inhibitor; rPFS, radiographic progression-free survival.

Lu-PSMA-617; Pluvicto, Novartis) in PSMA positron emission tomography (PET)-positive disease, and CAPItello-281 investigated capivasertib (Truqap, AstraZeneca) plus abiraterone in *PTEN*-deficient disease; both reported positive rPFS results in predominantly high-risk mHSPC/APMS and complicate the picture further.[70-72] Their sequencing with PARPi treatment in *BRCA2*-altered disease is untested.[71,73]

### *Balancing Risk and Benefit*

In AMPLITUDE, grade 3 or higher adverse events occurred in 75% of patients in the niraparib arm, including anemia in 52% (29% grade ≥3; approximately 25% transfused) and hypertension in 45% (27% grade ≥3); treatment was discontinued in 15% vs 10% in the control arm. In TALAPRO-3, grade 3 or higher events occurred in 81% of patients in the talazoparib arm, with anemia in 71% (51% grade ≥3; 40% transfused), leading to talazoparib interruption in 42% of patients and dose reduction in 45%; permanent discontinuation (any cause) occurred in 19% vs 10%. Patients requiring transfusion received a median of 2 packed red cell transfusions in both trials.[10,52] This burden requires close surveillance, consideration of blood bank supply in cost-effectiveness analyses,[74] and research into mitigation strategies including lower-dose or interrupted PARPi regimens.

Long-term toxicity carries greater weight in mHSPC/APMS because survival is considerably longer than in mCRPC/APMR. Median OS is approximately 2 to 3 years in contemporary mCRPC/APMR cohorts,[75,76] 4 to 5 years in high-volume mHSPC/APMS treated with ADT and docetaxel,[77] and approximately 8 years in low-volume disease after prior local therapy.[78] In TALAPRO-3, myelodysplastic syndrome occurred in 3 patients on talazoparib and 1 control patient, and acute myeloid leukemia in 2 patients vs none.[52] CHAARTED reported that 25.9% of the docetaxel-treated patients were alive at 10 years,[79] emphasizing the relevance of uncommon late toxicities. The larger toxicity differences in TALAPRO-3 are consistent with the association of greater trapping potency with greater marrow toxicity; tolerability may therefore influence agent choice and the timing of PARPi administration. Longer follow-up and single-gene OS data are essential when efficacy is marginal. Patient preferences should influence treatment choice even in *BRCA2*-altered disease, in which efficacy is greatest.[51]

Prolonged survival also increases treatment duration. First-line ovarian maintenance PARPi administration is time-limited,[80] whereas the EORTC GUCG 2238 (De-Escalate) trial (NCT05974774) is prospectively testing the interruption of ADT and an ARPI after a deep response.[81] Whether shorter PARPi treatment preserves efficacy has not been assessed and warrants a dedicated trial.

## Future Directions

### *Combination Strategies*

PARPis and PSMA-targeted radioligand therapy have complementary effects on DNA damage and repair. LuPARP demonstrated encouraging activity and manageable toxicity with a PARPi plus [$^{177}$Lu]Lu-PSMA-617 in mCRPC/APMR, although overlapping myelosuppression may limit treatment.[82] Immunotherapy evidence is weaker; despite a rationale involving DNA damage and cGAS–STING pathway signaling,[83,84] KEYLYNK-010 (pembrolizumab [Keytruda, Merck] plus olaparib) failed to improve rPFS or OS in biomarker-unselected mCRPC/APMR.[85] In contrast, CheckMate 9KD (nivolumab plus rucaparib) suggested activity, predominantly in HRR gene-altered (particularly *BRCA1/2*-altered) tumors.[86] In mHSPC/APMS, PSMAddition showed an rPFS benefit (HR, 0.72) when [$^{177}$Lu]Lu-PSMA-617 was added to ADT-ARPI, making sequencing or combination with a PARPi the nearer-term question.[70]

### *Biomarker Evolution*

Biomarker development must refine the HRR panels and ctDNA assays already determining eligibility. Non-*BRCA* benefit is heterogeneous, requiring standardized gene definitions and harmonized assays. Serial ctDNA could extend testing from baseline selection to dynamic treatment guidance by detecting reversion mutations before the radiographic progression and changes in tumor fraction that signal response or escape,[29,64] but this requires prospective validation. Current panels may miss cryptic HRR loss when monoallelic carriers without functional HRR deficiency are selected, and no HRD score has been validated for prostate cancer; scores developed for breast and ovarian cancer are not transferable. Distinguishing genotype from functional HRR deficiency is central to extending treatment beyond *BRCA2*, particularly because clinical benefit from non-*BRCA* alterations varies across trials. Prospective biomarker-adaptive trials could test whether treatment changes based on serial molecular information improve outcomes.

### *Earlier Disease States*

Positive mHSPC/APMS trials have prompted evaluation in high-risk localized and locally advanced disease.[10,52] The phase 2 single-arm NePtune trial is assessing neoadjuvant olaparib plus a luteinizing hormone-releasing hormone (LHRH) agonist before prostatectomy in selected cases of HRR gene-altered disease, whereas the adaptive multi-arm phase 2 GUNS trial is assigning HRR gene-altered patients to niraparib, an LHRH agonist, and AAP; both are expected to be completed later in 2026. EvoPAR-Prostate02 (NCT06952803) is evaluating

saruparib in *BRCA1/2*-altered high-risk nonmetastatic disease after radiotherapy or prostatectomy, with metastasis-free survival the primary endpoint. Cohort A adds saruparib or placebo to continuous ADT in patients after primary radiotherapy, or after prostatectomy and salvage radiotherapy, for high-risk biochemical recurrence; cohort B adds saruparib or placebo to continuous ADT plus abiraterone after radiotherapy for very high-risk, locally advanced disease. Primary completion is expected in 2033 and overall completion in 2036.

These studies are limited by the low prevalence of *BRCA*—3.1% in localized vs 10.6% in de novo metastatic disease[87]—and the lack of a validated short-term pathologic surrogate.[1] Pathologic complete response occurs in only 4% to 13% of early-phase neoadjuvant studies.[88,89] The composite endpoint of pathologic complete response or measurable residual disease is more frequent, although its reported rate depends heavily on the definition used.[88] In PROTEUS, the treatment effect on metastasis-free survival was significant when defined by PSMA PET/computed tomography but not by conventional imaging alone.[89] Definitive trials must therefore rely on longer-term survival outcomes, thereby increasing study duration and cost and making participant retention more difficult.

## Conclusion

PARPis are established treatments for HRR-altered prostate cancer across metastatic disease states, from late mCRPC/APMR to selected patients with mHSPC/APMS receiving AR-directed combination therapy. Substantial debate remains regarding patient selection, risk vs benefit in earlier disease, and treatment choice in an increasingly complex field. Longer-term follow-up of AMPLITUDE and TALAPRO-3 and the completion of EvoPAR-Prostate01 will help resolve these questions.

***Disclosures***

*Drs McKendry and Maurice-Dror have nothing to declare. Dr Chi reports consulting/advisory roles with AbCellera, Amgen, Astellas, AstraZeneca, Bayer, BMS, Chugai Pharmaceutical, Curium Pharma, GSK, Janssen, Lilly, Merck, Novartis, Pfizer, and Roche; and institutional research funding from Amgen, Astellas, AstraZeneca, Bayer, BMS, Janssen, Lilly, Merck, Novartis, Pfizer, and Roche. This paper was not funded.*

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