Novel therapeutic strategies for metastatic castration-resistant prostate cancer: Beyond androgen receptor pathway inhibition (Review)

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Abstract. Metastatic castration-resistant prostate cancer (mCRPC) remains a lethal disease due to universal resistance to androgen-receptor pathway inhibitors (ARPI). Tumor progression is orchestrated by a spectrum of androgen-receptor-independent drivers, including genomic alterations in DNA damage repair pathways, epigenetic shifts promoting lineage plasticity, metabolic adaptations and an immunosuppressive tumor microenvironment. This evolving understanding has catalyzed the development of novel therapeutic strategies. These include PARP inhibitors for tumors with homologous recombination repair deficiencies, protein kinase B inhibitors for the phosphatase and tensin homolog-loss subset, prostate-specific membrane antigen (PSMA)-targeted radioligand therapy, bispecific T-cell engagers, antibody-drug conjugates and immune checkpoint inhibitors. Furthermore, liquid biopsy profiling, PSMA-positron emission tomography-based radiomics and artificial intelligence platforms are enhancing real-time patient selection and response assessment. The present review synthesized these recent preclinical and clinical advances to delineate biomarker-driven, mechanism-based therapeutic sequencing and combination strategies for mCRPC in the post-ARPI era.

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Abbreviations: ADCs, antibody-drug conjugates; ADT, androgen deprivation therapy; AI, artificial intelligence; AKT, protein kinase B; AR androgen receptor; ARPI androgen-receptor pathway inhibitor; BiTE, bispecific T-cell engager; CAR-T, chimeric antigen receptor T cell; CRS, cytokine-release syndrome; ctDNA, circulating tumor DNA; DDR, DNA-damage response; DNR, dominant-negative receptor; FAP, fibroblast activation protein; GRPR, gastrin-releasing peptide receptor; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; MSI-H, microsatellite instability-high; NEPC, neuroendocrine prostate cancer; NHEJ, non-homologous end joining; ORR, objective response rate; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed death-ligand 1; PET, positron emission tomography; PI3K, phosphatidylinositol 3-kinase; PSMA, prostate-specific membrane antigen; PTEN, phosphatase and tensin homolog; rPFS, radiographic progression-free survival; RLT, radioligand therapy; SOC, standard of care; TMB, tumor mutational burden

Key words: metastatic castration-resistant prostate cancer, poly (ADP-ribose) polymerase inhibitors, prostate-specific membrane antigen theranostics, protein kinase B blockade, CDK12 loss, bispecific antibodies, antibody-drug conjugates

Contents

1. Introduction

Prostate cancer remained the second most commonly diagnosed malignancy in men worldwide in 2020, with an estimated 1.4 million new cases and 375,000 mortalities and up to 10% of patients already harbor distant metastases at presentation (1). Although androgen deprivation therapy (ADT) remains the cornerstone for advanced disease, progression

to metastatic castration-resistant prostate cancer (mCRPC) is almost universal and currently accounts for the majority of prostate-cancer-specific mortality. Despite the sequential approval of second-generation androgen-receptor pathway inhibitors (ARPI) such as abiraterone and enzalutamide, only a subset of patients achieves durable responses and objective radiologic progression is typically observed within 12-18 months, illustrating the urgent need for therapeutic strategies that operate independently of androgen-receptor (AR) blockade (2-4).

The molecular landscape underlying ARPI failure is heterogeneous. AR ligand-binding-domain missense mutations (such as L702H and T878A) and constitutively active splice variants, most frequently AR-V7, are detectable in circulating tumor DNA (ctDNA) in ≥25% of men with mCRPC and are strongly associated with shortened progression-free survival (PFS) on abiraterone or enzalutamide (5,6). Importantly, these resistance lesions are dynamic rather than static; deep sequencing of ctDNA sampled before and after ARPI reveals clonal selection and the emergence of polyclonal AR-variant-positive populations in two-thirds of progressing patients, a finding that corroborates earlier single-cell RNA-sequencing data from metastatic biopsies (7,8). While there is consensus that AR-V7 positivity predicts primary resistance, conflicting data exist regarding the prognostic value of low-frequency point mutations, partly because variant allele frequency thresholds and assay sensitivity differ across studies; nevertheless, the preponderance of evidence supports the use of ctDNA monitoring to guide early treatment switches (9).

Parallel to genomic escape, lineage plasticity has emerged as a cardinal mechanism of AR independence. Loss-of-function alterations in RB1 and TP53 cooperate to unlock an neuroendocrine prostate cancer (NEPC) transcriptional program characterized by ASCL1, ONECUT2 and chromogranin A overexpression; these tumors lose AR dependence, gain stem-like and mesenchymal traits and portend a median overall survival (OS) of <12 months (10-13). The frequency of treatment-emergent NEPC ranges from 15-20% in autopsy series but is reportedly lower (<8%) in imaging-based cohorts, a discrepancy that likely reflects both ascertainment bias and heterogeneous diagnostic criteria (14,15). Studies have identified the histone methyl-transferase NSD2 as a lineage-fidelity checkpoint whose overexpression sustains plasticity and confers resistance not only to ARPI but also to platinum-based chemotherapy, underscoring the need for epigenetic interventions (12,16).

Beyond cell-autonomous drivers, the tumor microenvironment is increasingly recognized as a driver of ARPI resistance. Single-cell profiling of phosphatase and tensin homolog (PTEN)/p53-deficient tumors revealed lactate-mediated suppression of macrophage phagocytosis; accordingly, pharmacologic blockade of glycolysis or PD-1 signaling restored immune clearance and delayed castration-resistant growth in murine models (17,18). Consistently, high TROP-2 and IL-8 expression, both linked to epithelial-mesenchymal transition, are associated with shorter PFS on taxanes and ARPI, providing a rationale for antibody-drug conjugates or CXCR1/2 inhibitors in combination protocols (19,20).

The growing number of actionable, non-AR targets has translated into early-phase clinical evaluation. Poly (ADP-ribose) polymerase (PARP) inhibitors have produced response rates of 30-50% in DNA-damage response (DDR)-mutated mCRPC, prompting phase III trials combining talazoparib with enzalutamide (21-23). Similarly, dual mTOR/DNA-PK inhibition (CC-115) and protein kinase B (AKT) blockade plus ARPI have shown preliminary efficacy in ARPI-naïve and ARPI-pretreated patients, although additive toxicity remains a concern (24-26). Finally, metronomic topotecan, by downregulating MAT2A and heat-shock proteins, suppressed EMT and synergized with docetaxel in xenograft models of aggressive-variant disease, an observation now being translated into an adaptive phase I/II trial (27,28). Major clinical guidelines, including those from the European Association of Urology and the National Comprehensive Cancer Network, have begun to incorporate these emerging therapeutic strategies, reflecting their increasing relevance in clinical practice (29,30).

Collectively, these data indicate that mCRPC is a molecularly heterogeneous disease in which AR-independent pathways, including genomic, epigenetic, metabolic and immune pathways, collectively orchestrate disease progression. The present review therefore synthesized recent pre-clinical and clinical evidence on therapeutic strategies that extend beyond AR axis inhibition, critically appraised conflicting results and delineated future directions for precision-oriented trials in this lethal phenotype. In simple terms, while existing reviews often focus on single therapeutic modalities or provide broad overviews, the present review uniquely integrated the latest evidence across multiple emerging classes of therapy, including PARP inhibitors, immunotherapy, radioligand therapy, Phosphatidylinositol 3-kinase (PI3K)/AKT inhibitors, antibody-drug conjugates and novel oral agents. By critically appraising conflicting data and emphasizing rational combination and sequencing strategies, the present review aimed to provide clinicians and researchers with a practical roadmap for navigating the increasingly complex therapeutic landscape of mCRPC in the post-ARPI era.

A comprehensive literature search was performed in the PubMed database to identify relevant peer-reviewed articles published between January 2019 and February 2026. The search strategy combined terms for metastatic castration-resistant prostate cancer ['mCRPC'(MeSH Terms) OR 'prostate cancer, castration-resistant'(MeSH Terms)] with keywords related to therapeutic strategies beyond androgen receptor pathway inhibition, including 'PARP inhibitors', 'immunotherapy', 'bispecific T-cell engagers', 'CAR-T', 'radioligand therapy', 'PSMA', 'AKT inhibitors', 'antibody-drug conjugates' and 'PROTACs'. The search was limited to articles published in English. Priority was given to phase II/III clinical trials, landmark studies, guideline-endorsed therapies and high-impact preclinical studies providing mechanistic insights into resistance or novel targets. The following types of articles were excluded: Conference abstracts, non-original research (such as, editorials, commentaries and letters to the editor), case reports and duplicate publications. Reference lists of included articles were manually screened to identify additional relevant studies.

2. Precision genomics: PARP inhibitors and DNA-damage response targeting

Genomic interrogation of mCRPC has revealed that ≥20% of tumors harbor deleterious alterations in genes involved in

homologous recombination repair (HRR), most frequently breast cancer susceptibility gene 2 (BRCA2), BRCA1, ATM serine/threonine kinase (ATM), partner and localizer of BRCA2 (PALB2) and cyclin-dependent kinase 12 (CDK12) (31,32). These lesions create a state of 'BRCAness' that compromises high-fidelity double-strand break repair and confers exquisite sensitivity to PARP inhibitors through synthetic lethality. The clinical validity of this concept has now been consolidated by three positive phase II/III trials (Profoundly, GALAHAD and TALAPRO-2) in which Olaparib, niraparib or talazoparib prolonged radiographic progression-free survival (rPFS) and OS compared with standard care or ARPI alone (33-35). Nevertheless, biomarker selection, combination strategy and resistance mechanisms remain areas of active debate; the key findings are summarized in Table I.

Biomarker algorithms: Germline vs. somatic, DNA vs. RNA, single vs. biallelic. Profoundly required a tumor tissue-based next-generation sequencing (NGS) panel and defined 'HRR-deficient' as pathogenic mutations in 15 prespecified genes; Olaparib reduced the risk of progression by 66% in the BRCA1/2 subgroup [hazard ration (HR) 0.34; 95% confidence interval (CI) 0.23-0.50] but failed to improve outcomes in ATM-altered tumors, highlighting locus-specific efficacy (35). Subsequent analyses of plasma ctDNA showed high concordance (91-94%) for BRCA1/2 and PALB2 alterations, yet sensitivity for ATM or CHEK2 was only 70-75%, suggesting that blood-first screening may miss a subset of actionable cases (36,37). Importantly, biallelic inactivation (second hit by mutation, deletion or loss-of-heterozygosity) appears critical: The objective response rate (ORR) to rucaparib was 44% among BRCA2 biallelic cases compared with 0% when only one allele was disrupted (38). RNA-based HRR deficiency signatures have therefore been developed to capture functional loss even in the absence of identifiable DNA mutations; in a retrospective series, 18% of HRR-wild-type tumors were classified as HRD-RNA+ and achieved similar rPFS benefit from niraparib as genomically defined carriers (39). Collectively, these data argue for an integrated DNA-plus-RNA diagnostic pipeline, although prospective validation is pending.

Combination with ARPI: Synergy or redundancy? Pre-clinical work demonstrated that AR signaling transcriptionally upregulates genes involved in DNA non-homologous end-joining; accordingly, enzalutamide impairs double-strand break repair and sensitizes prostate cancer cell lines to Olaparib irrespective of HRR status (40). The randomized PROpel and TALAPRO-2 trials translated this observation into the clinic: First-line Olaparib plus abiraterone or talazoparib plus enzalutamide improved median rPFS by 8.6 and 8.8 months, respectively, over ARPI alone in an 'all-comer' population (34,41). However, subgroup analyses revealed that the incremental benefit was largely confined to BRCA1/2-mutated tumors (rPFS; HR 0.20-0.23), whereas ATM or CDK12 alterations derived modest or no advantage, raising questions about overtreatment of non-BRCA patients (41,42). Moreover, grade ≥3 anemia and fatigue occurred in 30-40% of combination arms, necessitating dose reductions in roughly one-quarter of subjects. A matching-adjusted indirect comparison suggested similar efficacy between talazoparib-enzalutamide and niraparib-abiraterone in BRCA-mutated mCRPC, but lacked head-to-head safety data (43). Until biomarker-driven selection is refined, current regulatory approvals restrict the combination to BRCA1/2 carriers and European guidelines recommend sequential use when feasible to minimize toxicity (42,44).

Primary and acquired resistance: Genomic reversion, shielding pathways and the immune microenvironment. Despite robust initial responses, most patients progress within 12-18 months. Whole-genome sequencing of progressing lesions identified BRCA2 reversion mutations in 30-50% of cases, often sub-clonal at baseline and selected by therapy pressure (45). Reversion events restore the open reading frame and abolish PARP inhibitor sensitivity, explaining platinum cross-resistance and poor post-progression outcomes. Additional escape routes include compensatory activation of the non-homologous end joining (NHEJ) axis (LIG1, XLF over-expression) and loss of RNASEH2B, which overrides replication stress and diminishes PARP trapping (46,47). Concurrent RB1 deletion has been reported to confer PARP inhibitor resistance through replication fork stabilization, although conflicting data exist regarding its interaction with ATM loss (48). Finally, microsatellite instability-high (MSI-H) tumors with mono-allelic BRCA1/2 mutations appear intrinsically insensitive, presumably due to sufficient residual HRR activity, reinforcing the need for biallelic evaluation (49,50). The key mechanisms of action and acquired resistance to PARP inhibitors are summarized in Fig. 1.

Clinical sequencing and real-world effectiveness. Outside clinical trials, PARP inhibitor uptake is heterogeneous. A multinational chart review found that only 55% of patients with germline BRCA2 alterations received targeted therapy, with physician perception of limited efficacy in heavily pre-treated cases and reimbursement barriers cited as major obstacles (51). By contrast, an American registry showed that Olaparib re-challenge after platinum-based chemotherapy retained a 38% PSA50 response rate, suggesting that prior cytotoxic exposure does not irrevocably extinguish PARP dependence (37). Carboplatin remains an active alternative, achieving 61% radiographic response in BRCA2-mutated mCRPC, but median duration is short (4.8 months) and myelosuppression is substantial (52). Emerging data indicate that early introduction of PARP inhibition, immediately after ARPI failure, maximizes clinical benefit, supporting the current paradigm shift toward first-line use in biomarker-positive disease (34,35).

In summary, PARP inhibitors have transformed the therapeutic landscape of mCRPC by exploiting synthetic lethality in HRR-deficient tumors. Nevertheless, optimal implementation requires rigorous biomarker stratification, vigilant monitoring for genomic reversion and rational combination or sequencing strategies that balance efficacy with toxicity.

3. Immuno-oncology revival: Checkpoint inhibitors, bispecific antibodies and cellular therapy

Despite persistent immunological 'coldness' of prostate cancer, recent randomized and early-phase trials have re-ignited

Table I. Key clinical trials and studies on PARP inhibitors in mCRPC.

First author/s, year	Trial/study name	Drug(s) and design	Patient population and biomarkers	Key endpoints and results	(Refs.)
Smith *et al*, 2022	GALAHAD (Phase II)	Niraparib monotherapy	HRR-mutated mCRPC post ≥2 lines; DNA repair defects	ORR 30%; rPFS 5.5 months in BRCA1/2	(33)
Fizazi *et al*, 2024	TALAPRO-2 (Phase III)	Talazoparib + enzalutamide vs. enzalutamide	All-comer mCRPC 1st-line; HRR focus (BRCA1/2)	rPFS +8.8 months; HR 0.23 in BRCA-mutated	(34)
Mateo *et al*, 2024	Profoundly (Phase III)	Olaparib vs. physician's choice	BRCA1/2- or other HRR-mutated mCRPC post-ARPI/taxane	rPFS HR 0.34 (BRCA1/2); OS benefit in BRCA subgroup	(35)
Kim *et al*, 2023	ctDNA Concordance Study	Plasma NGS vs. tissue	mCRPC with BRCA1/2/PALB2/ATM; biallelic focus	91-94% concordance for BRCA; 70% for ATM	(36)
Triner *et al*, 2024	Olaparib Re-challenge Registry	Olaparib post-platinum	Previously platinum-exposed BRCA-mCRPC	PSA50 38%; durable in select cases	(37)
Fallah *et al*, 2024	Rucaparib Biallelic Analysis	Rucaparib monotherapy	BRCA2-mutated mCRPC; biallelic vs. monoallelic	ORR 44% biallelic vs. 0% monoallelic	(38)
Brown *et al*, 2023	HRD-RNA Signature Retrospective	Niraparib; RNA-based HRD	HRR-wild-type mCRPC; functional HRD via RNA	18% HRD-RNA+; similar rPFS to genomic carriers	(39)
Dong *et al*, 2023	Preclinical Synergy Model	Enzalutamide + Olaparib	Prostate cell lines; HRR-independent	AR signaling impairs DSB repair; synergy regardless of HRR	(40)
Clarke *et al*, 2025	PROpel (Phase III)	Olaparib + abiraterone vs. abiraterone	1st-line mCRPC a ll-comer; BRCA1/2 enrichment	rPFS +8.6 months; benefit confined to BRCA (HR 0.20)	(41)
Walmsley *et al*, 2024	BRCA2 Reversion WGS	Post-PARP progression biopsies	Progressing mCRPC on PARP; sub-clonal reversions	30-50% BRCA2 reversions; platinum cross-resistance	(45)
Miao *et al*, 2022	RB1 Deletion Interaction	PARP models with ATM loss	mCRPC organoids; fork stabilization	RB1 confers resistance; conflicts with ATM data	(48)
Sokol *et al*, 2022; Lenis *et al*, 2024	MSI-H Insensitivity Study	PARP in MSI-H tumors	Monoallelic BRCA1/2 + MSI-H mCRPC	Intrinsic insensitivity due to residual HRR	(49, 50)
Gratzke *et al*, 2025	Multinational Chart Review	PARP uptake real-world	Germline BRCA2 mCRPC; treatment barriers	55% received PARP; efficacy concerns in pretreated	(51)
Coquan *et al*, 2024	PRO-CARBO (Phase II)	Carboplatin monotherapy	DDR-altered mCRPC; BRCA2 focus	Radiographic ORR 61%; short duration (4.8 months)	(52)

mCRPC, metastatic castration-resistant prostate cancer; PARP, poly (ADP-ribose) polymerase; HRR, homologous recombination repair; BRCA, breast cancer gene; ATM, ataxia telangiectasia mutated; PALB2, partner and localizer of BRCA2; CDK12, cyclin-dependent kinase 12; rPFS, radiographic progression-free survival; OS, overall survival; ORR, objective response rate; ARPI androgen-receptor pathway inhibitor; ctDNA, circulating tumor DNA; NGS, next-generation sequencing; HRD, homologous recombination deficiency; WGS, whole-genome sequencing; MSI-H, microsatellite instability-high; DSB, double-strand break; NHEJ, non-homologous end joining; HR, hazard ratio.

interest in immuno-oncology once AR-targeted options are exhausted. Table II summarizes landmark studies discussed in this section, providing readers with a rapid overview of design, molecular selection criteria and efficacy signals.

Immune-checkpoint blockade, long-term follow-up of KEYNOTE-199, CheckMate-9KD and COSMIC-021. Pembrolizumab monotherapy produced an ORR of 5-9% in unselected mCRPC, but long-term data from KEYNOTE-199

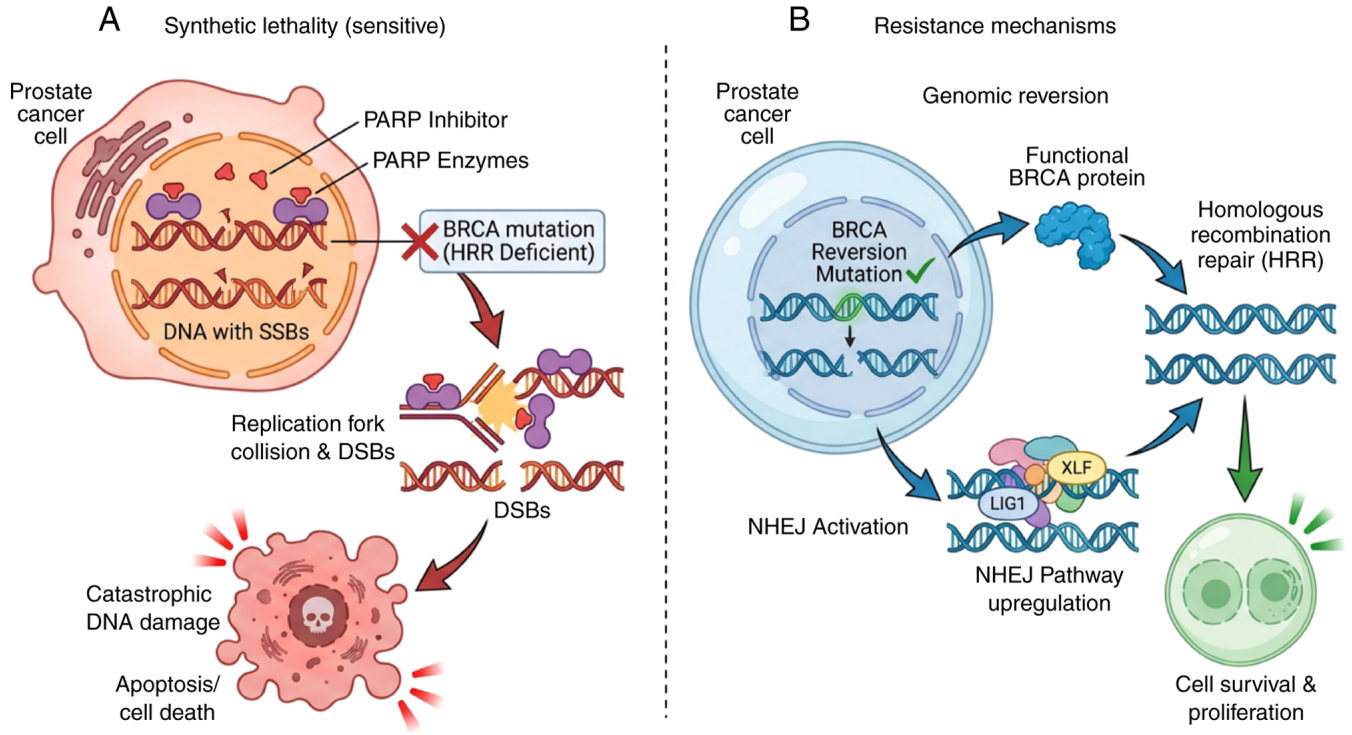

Figure 1. Mechanism of action and acquired resistance to PARP Inhibitors in prostate cancer. (A) Synthetic lethality in BRCA-mutant prostate cancer cells. PARP inhibition traps PARP enzymes on single-strand DNA breaks, leading to replication-associated DSBs. Due to defective HRR, these DSBs accumulate, causing cell death. (B) Mechanisms of resistance. Tumors may acquire resistance through genomic reversion mutations that restore functional BRCA protein and HRR capability, or through the upregulation of alternative repair pathways, such as NHEJ, mediated by proteins such as LIG1 and XLF, leading to cell survival. PARP, poly (ADP-ribose) polymerase; BRCA, breast cancer gene; DSBs, double-strand breaks; HRR, homologous recombination repair NHEJ, non-homologous end joining; LIG1, DNA ligase 1; XLF, XRCC4-like factor.

cohorts B and C (n=364) now show that 34% of responders remained progression-free at 24 months, with median OS 9.5 months (53). These durable remissions are almost exclusively confined to tumors displaying MSI-H or high tumor mutational burden (TMB-H) (50). Similarly, CheckMate-9KD combining nivolumab plus docetaxel improved PSA-50 response rate to 42 compared with historical 28-32% with docetaxel alone; however, after 40 months of follow-up, OS was only modestly prolonged (HR 0.78; 95% CI 0.60-1.02) (54). COSMIC-021 tested cabozantinib-atezolizumab in 62 chemotherapy-naïve mCRPC patients: ORR 19%, median rPFS 6.8 months, but again benefit clustered in patients with bone-predominant disease and high circulating programmed death-ligand 1(PD-L1) (55). Collectively, these mature datasets confirm that checkpoint inhibitors (CPI) can yield meaningful disease control, yet objective responses remain <20% in an unselected population, underlining the necessity of predictive biomarkers.

Predictive biomarkers, MSI-H, TMB-H, CDK12 loss and PD-L1 combined positive score. Pooling 1,596 tumor samples from the aforementioned trials, CDK12 biallelic loss emerged as the strongest genomic predictor of CPI benefit (ORR 29%; disease-control rate 67%), outperforming MSI-H (7% of cases; ORR 44%) and TMB-H ≥10 mut/Mb (5%; ORR 37%) (50,56). Notably, CDK12-deficient tumors display a unique 'focal tandem duplication' signature that generates abundant neo-antigens and T-cell infiltration, explaining their CPI sensitivity (57,58). Conversely, single-copy CDK12 loss or BRCA1/2 mono-allelic alteration did not enrich responses (49). PD-L1 combined positive score ≥10 was only modestly associated with efficacy (positive predictive value 28%) and its expression was dynamically downregulated by androgen-deprivation therapy (59). Multiplex immunohistochemistry further revealed that co-staining of CD68+ macrophages with PD-L1 predicted primary resistance, suggesting that myeloid-driven immune suppression overrides T-cell re-invigoration (60). Thus, composite models incorporating CDK12 status, TMB and myeloid score currently offer the highest discriminatory power for patient selection.

Prostate-specific membrane antigen (PSMA) or STEAP1 directed bispecific T-cell engager. Bispecific T-cell engagers link CD3 on T lymphocytes to prostate-restricted antigens, thereby bypassing MHC-restricted recognition. Acapatamab (AMG 160), a half-life-extended PSMAxCD3 molecule, induced PSA-50 responses in 22% of 62 heavily pre-treated mCRPC patients; median rPFS was 4.6 months and grade ≥3 cytokine-release syndrome (CRS) occurred in 10% of cycles, mitigated by step-up dosing (61). Comparable efficacy was observed with pasotuxizumab (STEAP1 x CD3) in a phase I trial (n=41): ORR 24%, but CRS remained frequent (15% grade ≥3) (62). Xaluritamig, a bivalent PSMA-engager currently in dose-escalation, showed early signals of activity (PSA-50 31%) at the 4 μg/kg cohort with only 4% CRS, possibly reflecting optimized CD3 affinity (63). Across studies, patients with prior CPI exposure retained similar response rates, arguing for non-overlapping resistance mechanisms. Peripheral T-cell

Table II. Landmark studies in immuno-oncology for mCRPC.

First author/s, year	Trial/study name	Modality and design	Patient population and biomarkers	Key endpoints and results	(Refs.)
Yu *et al*, 2022	KEYNOTE-199 (Phase II, long-term)	Pembrolizumab monotherapy	Unselected mCRPC (n=364); MSI-H/TMB-H	ORR 5-9%; 34% PFS at 24 months in MSI-H	(53)
Fizazi *et al*, 2022	CheckMate-9KD (Phase II)	Nivolumab + docetaxel	Chemo-naïve mCRPC; all-comer	PSA50 42%; OS HR 0.78 (modest)	(54)
Agarwal *et al*, 2022	COSMIC-021 (Phase Ib)	Cabozantinib + atezolizumab	Chemo-naïve mCRPC (n=62); PD-L1 high	ORR 19%; rPFS 6.8 months in bone-predominant	(55)
Liang *et al*, 2024; Tien *et al*, 2024	CDK12 Signature Study	CDK12 loss models	mCRPC with tandem duplications	Neo-antigen generation; T-cell infiltration	(57, 58)
Sommer *et al*, 2022	PD-L1 Dynamics IHC	ADT impact on PD-L1	mCRPC tissues; CPS ≥10	Modest PPV 28%; ADT downregulates PD-L1	(59)
Lyu *et al*, 2025	Myeloid Suppression Multiplex	CPI-resistant tumors	PTEN/p53-deficient mCRPC; CD68+PD-L1	Macrophage co-staining predicts resistance	(60)
Dorff *et al*, 2024	Acapatamab Phase I	PSMAxCD3 BiTE	Heavily pretreated mCRPC (n=62)	PSA50 22%; rPFS 4.6 months; CRS 10% G3	(61)
Bhatia *et al*, 2023	Pasotuxizumab Phase I	STEAP1xCD3 BiTE	mCRPC (n=41); STEAP1 expression	ORR 24%; CRS 15% G3	(62)
Lim *et al*, 2023	Xaluritamig Dose-Escalation	PSMAxCD3 BiTE	mCRPC; optimized CD3 affinity	PSA50 31%; CRS 4% at 4 μg/kg	(63)
King *et al*, 2024	T-Cell Expansion Correlative	BiTE-treated cohorts	mCRPC post-CPI; CD14+HLA-DRlo monocytes	T-cell peak day 8-10; monocytes predict progression	(64)
Narayan *et al*, 2022	PSMA-CAR-T Phase I (NCT03089203)	Armored PSMA-CAR-T + TGF-β DNR	mCRPC post-lymphodepletion (n=12)	PSA50 in 25%; >18-month response in 1; bone trafficking	(66)
Wang *et al*, 2022; Wu *et al*, 2022	B7-H3 CAR-NK Preclinical	Dual PSMA/B7-H3 CAR-NK	PSMA-negative variants in models	Eradication of escape variants	(67, 68)
Stein *et al*, 2024	PSCA-CAR-T Phase I (BPX-601)	PSCA-CAR-T + rimiducid	mCRPC (n=11); antigen-low relapse	Stabilization in 45%; limited persistence	(69)

mCRPC, metastatic castration-resistant prostate cancer; CPI, checkpoint inhibitor; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; MSI-H, microsatellite instability-high; TMB-H, tumor mutational burden-high; CDK12, cyclin-dependent kinase 12; PD-L1, programmed death-ligand 1; CPS, combined positive score; IHC, immunohistochemistry; BiTE, bispecific T-cell engager; PSMA, prostate-specific membrane antigen; STEAP1, six-transmembrane epithelial antigen of prostate 1; CRS, cytokine release syndrome; CAR-T, chimeric antigen receptor T cell; TGF-β, transforming growth factor beta; DNR, dominant-negative receptor; PSCA, prostate stem cell antigen.

expansion peaked at day 8-10 and was associated with clinical benefit; conversely, baseline immunosuppressive monocytes (CD14+HLA-DRlo) predicted progression despite bispecific T-cell engager (BiTE) therapy (64,65). These data position PSMA/STEAP1 BiTEs as an active, chemotherapy-free option post-AR pathway inhibition, with CRS remaining the principal on-target toxicity.

Armored CAR-T/CAR-NK cells, PSMA, B7-H3 and PSCA targets. Autologous PSMA-directed chimeric antigen receptor T cell (CAR-T) incorporating a TGF-β dominant-negative receptor (DNR) demonstrated feasibility in a first-in-human phase I study (NCT03089203). Among 12 mCRPC subjects treated after lymphodepleting cyclophosphamide/fludarabine, three achieved ≥50% PSA decline; one patient maintained response >18 months and trafficking to bone lesions was confirmed by 89Zr-CAR positron emission tomography (PET) (66). Notably, PSMA down-modulation on malignant cells emerged as a dominant escape route, prompting combinatorial strategies, such as concurrent B7-H3-CAR-NK92 infusion, which eradicated PSMA-negative variants in murine models (67,68). Phase I testing of PSCA-CAR-T cells (BPX-601) coupled with rimiducid-mediated survival signaling yielded disease stabilization in 5/11 subjects; however, antigen-low relapse and limited *in vivo* persistence were observed (69). Manufacturing improvements, switching to a CD19-CAR-like hinge/spacer, adding IL-15 secretion cassette and knocking out endogenous PD-1, enhanced expansion 30-fold and overcame

PD-L1-mediated inhibition in pre-clinical experiments (70). Centralized, closed-system production currently has a median vein-to-vein time of 12 days (range, 10-15 days). from leukapheresis to release (66); hospital-based point-of-care electroporation is being explored to shorten vein-to-vein time to <7 days. Collectively, while CAR-based immunotherapy remains experimental in prostate cancer, early signals of activity and iterative engineering provide a clear roadmap toward larger efficacy studies.

Taken together, the immuno-oncology field in mCRPC has moved from blanket CPI administration to precision-guided interventions. CDK12 loss, MSI-H and TMB-H define a molecularly-enriched niche where pembrolizumab or nivolumab can deliver durable remissions. For the broader patient population, PSMA- or STEAP1-directed BiTEs offer immediate, clinically-meaningful PSA responses, albeit with manageable CRS. Finally, armored CAR-T/CAR-NK platforms tackling PSMA, B7-H3 and PSCA are poised to circumvent antigen escape and immunosuppression. Ongoing randomized trials combining these agents with PARP inhibitors or radioligands (NCT04592237, NCT05122895) will definitively test whether immunotherapy can become a backbone rather than a salvage strategy in mCRPC.

4. Radioligand therapy: PSMA-targeted β- and α-emitters

The concept of theranostics, linking molecular imaging to targeted radionuclide therapy, has matured most rapidly in prostate cancer through agents directed against PSMA. Over the past five years, both β-emitting 177Lu-PSMA-617 and the α-emitter 225Ac-PSMA have moved from compassionate-use programs to randomized phase 3 trials and national reimbursement lists. Table III provided an at-a-glance comparison of the key trials and real-world series discussed below.

177Lu-PSMA-617: VISION and PSMAfore outcomes updated to 2024. In the multinational VISION study, 831 patients with PSMA-positive mCRPC who had progressed on ≥1 ARPI and 1-2 taxane regimens were randomized to 177Lu-PSMA-617 (7.4 GBq q 6 weeksx6) plus protocol-permitted standard-of-care (SOC) or SOC alone (71,72). The primary analysis showed a 38% reduction in mortality (HR 0.62; 95% CI 0.52-0.74) and a 60% improvement in rPFS (71). With ≥4 years of follow-up, median OS has now reached 15.3 months compared with 11.3 months for controls and landmark OS at 24 months is 28.4 vs. 18.7% (72). Subgroup exploration reveals that patients with HRR defects derive the largest absolute gain (HR 0.48), whereas liver-metastatic or PSMA-negative/FDG-positive tumors show no benefit (73,74). Real-world evidence from the German RALU registry (n=424) mirrors these efficacy signals (median OS 14.1 months) but records higher rates of grade 3-4 thrombocytopenia (11%) than reported in VISION (4%), attributable to heavier pre-treatment and lower baseline hemoglobin (75). Taken together, 177Lu-PSMA-617 has become the reference β-emitter for late-line mCRPC, although optimal sequencing and patient selection continue to be refined.

Up-front combinations: 177Lu-PSMA + ARPI (ENZA-p) and + pembrolizumab (PRINCE). Moving 177Lu-PSMA-617 earlier in the disease course is being pursued to forestall resistance. The single-arm phase II ENZA-p trial enrolled 72 chemotherapy-naïve mCRPC patients who received enzalutamide 160 mg daily concomitantly with 6 cycles of 177Lu-PSMA-617 (76). PSA50 response was 94%, median rPFS 19.9 months and 2-year OS 81%. Notably, enzalutamide upregulated PSMA expression on baseline PET (median SUVmax 18.4-26.3; P=0.003), possibly enhancing ligand delivery (77). Randomized confirmation is underway in the PSMA study (NCT04720157) that couples 177Lu-PSMA-617 with SOC ARPI + ADT in metastatic hormone-sensitive disease (78). Immune priming by radioligands is also being explored: The Australian PRINCE cohort treated 40 mCRPC patients with 177Lu-PSMA-617 + pembrolizumab every 3 weeks for 2 years, yielding PSA50 67% and median rPFS 14.2 months, although grade 3-4 xerostomia reached 15%. Early translational data suggest increased peripheral CD8+PD-1+T-cell expansion, providing rationale for the randomized phase II IPRLuS trial (NCT05890859). Collectively, these studies position 177Lu-PSMA-617 as a combinatorial backbone rather than a monotherapy endpoint.

225Ac-PSMA α-therapy: efficacy, nephrotoxicity and dosimetry from the WARMTH registry. Actinium-225 delivers high-linear-energy-transfer α-particles (50-80 keV μm^{-1}) over a 50-80 μm range, inducing complex DNA double-strand breaks. A 2024 multi-center retrospective analysis of 233 patients enrolled in the WARMTH registry reported a PSA50 response of 68% with 225Ac-PSMA-617 (100 kBq kg^{-1}; q 8 weeks) after prior 177Lu-PSMA failure (79). Median OS was 14.7 months; importantly, 24% of β-refractory subjects achieved >90% PSA decline, underscoring non-cross-resistance. Objective imaging response (RECIP 1.0) occurred in 42% of soft-tissue lesions, but complete responses were rare (3%). Dose-limiting toxicities mirrored earlier compassionate-use series: grade ≥2 xerostomia 35%, grade ≥3 anemia 15% and grade ≥3 nephrotoxicity 4% (80,81). Renal dosimetry showed mean cortex absorbed dose 0.40 Gy MBq^{-1}, below the 23-Gy safety threshold, yet sequential 177Lu/225Ac 'cocktail' regimens amplified marrow exposure, leading to grade 3 thrombocytopenia in 19 vs. 8% with 225Ac alone (82). Salivary-gland sparing via competitive amino-acid infusion reduced parotid dose by 28% without compromising tumor uptake in a pilot study (n=20) (79). Long-term leukemia risk remains uncertain; no therapy-related MDS has been reported with <3-year follow-up, but systematic surveillance is mandated. Overall, 225Ac-PSMA is positioned as a potent salvage option after β-emitter failure, with ongoing trials (AcPel-III, NCT05772897) exploring earlier use.

Alternative targets and emerging theranostics: GRPR, B7-H3 and fibroblast-activation-protein (FAP). PSMA-negative progression occurs in 10-15% of patients and limits further radioligand options. The gastrin-releasing-peptide receptor (GRPR) is overexpressed in >80% of primary prostate cancers. A first-in-human study of 177Lu-RM2 (GRPR antagonist) in 12 mCRPC patients demonstrated tumor uptake (SUVmax 9-14) and disease stabilization in 50%, with no grade >1 neurotoxicity (83). B7-H3, an immune-checkpoint molecule, is being targeted with 131I-omburtamab; preliminary imaging showed favorable tumor-to-blood ratios (15:1)

Table III. Radioligand therapy studies: PSMA-targeted agents in mCRPC.

First author/s, year	Trial/study name	Agent and design	Patient population and selection	Key endpoints and results	(Refs.)
Sartor *et al*, 2021; Chi *et al*, 2024	VISION (Phase III, 2024 update)	177Lu-PSMA-617 + SOC vs. SOC	PSMA+ mCRPC post-ARPI/taxane (n=831)	OS 15.3 vs. 11.3 months (HR 0.62); rPFS +60%	(71, 72)
Rahbar *et al*, 2023	RALU Registry (Real-World)	177Lu-PSMA-617	mCRPC post-223Ra (n=424)	OS 14.1 months; thrombocytopenia 11% G3-4	(75)
Emmett *et al*, 2024; Staniszewska *et al*, 2021	ENZA-p (Phase II)	177Lu-PSMA-617 + enzalutamide (n=72)	Chemo-naïve mCRPC 19.9 months; PSMA	PSA50 94%; rPFS upregulation	(76, 77)
Rathke *et al*, 2024; Sathekge *et al*, 2024	WARMTH Registry (Retrospective)	225Ac-PSMA-617	Post-177Lu failure mCRPC (n=233)	PSA50 68%; OS 14.7 months; xerostomia 35% G2	(79, 81)
Khreish *et al*, 2020	Compassionate-Use Series	225Ac-PSMA-617	β-refractory mCRPC	>90% PSA decline in 24%; nephrotoxicity 4% G3	(80)
Delker *et al*, 2023	Sequential 177Lu/225Ac Dosimetry	Cocktail regimen	mCRPC; multi-isotope SPECT	Marrow toxicity ↑19%; parotid dose-28% with amino acids	(82)
Kurth *et al*, 2020	177Lu-RM2 First-in-Human	GRPR-targeted 177Lu	PSMA-mCRPC (n=12)	SUVmax 9-14; stabilization 50%; no G>1 toxicity	(83)
Zhao *et al*, 2022	131I-Omburtamab Pilot	B7-H3-targeted	PSMA-negative lesions	Tumor:blood 15:1; favorable uptake	(84)
Fendler *et al*, 2022	90Y-FAPI-46 Pilot	FAP-targeted	PSMA-/FDG+ mCRPC (n=9)	PSA50 33%; transient liver elevation	(85)

mCRPC, metastatic castration-resistant prostate cancer; PSMA, prostate-specific membrane antigen; SOC, standard of care; ARPI androgen-receptor pathway inhibitor; rPFS, radiographic progression-free survival; OS, overall survival; HRR, homologous recombination repair; FDG, fluorodeoxyglucose; PET, positron emission tomography; RECIP, Response Evaluation Criteria in PSMA Imaging; SUVmax, maximum standardized uptake value; GRPR, gastrin-releasing peptide receptor; B7-H3, B7 homolog 3; FAP, fibroblast activation protein; SPECT, single-photon emission computed tomography.

in PSMA-negative lesions (84). Finally, FAP ligands labelled with 68Ga/177Lu or 90Y are under evaluation for stroma-rich tumors. In a 2024 pilot, 90Y-FAPI-46 yielded PSA50 33% in 9 PSMA-negative/FDG-positive patients, albeit with transient liver-enzyme elevation (85). Table III summarized isotope choices, administered activities and organ dose constraints for these exploratory vectors.

Collectively, radioligand therapy has evolved from a late-line salvage tool to an integral component of sequential, biology-driven management of mCRPC. The 2024 data confirm 177Lu-PSMA-617 as an efficacy anchor, while 225Ac-PSMA extends benefit to β-refractory disease and novel targets offer options for PSMA escape. Ongoing randomized trials will clarify optimal sequencing, combination partners and long-term safety.

5. PI3K-AKT-PTEN axis and adjacent kinase pathways

Alterations in the PI3K-AKT-mTOR signaling cascade are among the most common oncogenic drivers in mCRPC, affecting 40-50% of cases via PTEN loss, PIK3CA mutations, or receptor tyrosine kinase amplification (86,87). This pathway drives anabolic metabolism, cell survival and AR crosstalk, fueling resistance to ARPI and taxanes, thus justifying isoform-selective AKT inhibitors for synthetic lethality in PTEN-deficient tumors (88,89). Phase III trials such asIPATential150 and CAPItello-281 confirm benefits, with ipatasertib or capivasertib plus abiraterone/enzalutamide extending rPFS and OS in biomarker-enriched groups (90,91). Challenges remain in ctDNA-guided selection and managing hyperglycemia; key studies are summarized in Table IV.

Biology of PTEN loss. PTEN deletion occurs in 30-50% of primary prostate cancers and up to 70% of mCRPC specimens, making it one of the most frequent genomic drivers beyond AR amplification (92,93). The resulting constitutive PI3K-AKT signaling phosphorylates and excludes FOXO1 from the nucleus, thereby relieving transcriptional repression of AR target genes and sustaining ligand-independent AR activity (94,95). Conversely, AR signaling transcriptionally upregulates PIK3CA and PIK3CB, establishing a forward-feedback loop that maintains PI3K-AKT output even under castrate androgen levels (86,96).

Table IV. Studies on PI3K/AKT inhibitors, ADCs and Emerging Agents in mCRPC.

First author/s, year	Trial/study name	Agent and design	Patient population and biomarkers	Key endpoints and results	(Refs.)
Sweeney *et al*, 2021; de Bono *et al*, 2025	IPATential150 (Phase III, 2024)	Ipatasertib + abiraterone vs. placebo	mCRPC 1st-line (n=1101); PTEN-loss	rPFS 19.2 vs. 14.7 months (HR 0.57 PTEN-loss)	(90, 91)
Vidotto *et al*, 2023	ctDNA PTEN Analysis	Ipatasertib correlative	mCRPC; biallelic PTEN (copy ≤0.5)	Maximal sensitivity with biallelic loss	(98)
Rescigno *et al*, 2024	CAPItello-281 (Phase III, interim)	Capivasertib + enzalutamide	Post-docetaxel mCRPC (n=888); PTEN 42%	OS 26.8 vs. 21.3 months (HR 0.64 PTEN-loss)	(99)
Matsubara *et al*, 2023	Safety Pooled Analysis	AKTis (ipatasertib/ capivasertib)	mCRPC cohorts (n>900)	G3 diarrhea 15-20%; loperamide reduces mods 28%→11%	(100)
Liu *et al*, 2022	Hyperglycemia Management	AKTis + metformin	mCRPC with BMI>30	Normalization in 78%; no discontinuation	(102)
Scribner *et al*, 2020	Vobramitamab Phase I	B7-H3 ADC	Post-ARPI mCRPC (n=78)	ORR 34%; PFS 7.2 months; neuropathy 19% G2	(106)
Bardia *et al*, 2021	TROPHY-U-01 Cohort	Sacituzumab govitecan (Trop-2 ADC)	Heavily pretreated mCRPC (n=31)	ORR 32%; PFS 5.6 months; neutropenia 23% G3	(107)
Milowsky *et al*, 2016	MLN2704 Phase I	STEAP1 ADC (maytansinoid)	ARPI-refractory mCRPC (n=37)	ORR 8%; PSA50 14%; neuropathy 9% G1	(108)
Rathkopf *et al*, 2025	ARV-110 Phase I/II	AR PROTAC (bavdegalutamide)	AR-mutated mCRPC (n=46)	PSA50 46% in mutants; fatigue 18% G2	(112)
Rathkopf *et al*, 2025	CC-94676 Phase I	AR PROTAC	Heavily pretreated mCRPC	PSA50 38%; >95% AR degradation	(113)

mCRPC, metastatic castration-resistant prostate cancer; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; PTEN, phosphatase and tensin homolog; rPFS, radiographic progression-free survival; OS, overall survival; ctDNA, circulating tumor DNA; ADC, antibody-drug conjugate; B7-H3, B7 homolog 3; ORR, objective response rate; PFS, progression-free survival; STEAP1, six-transmembrane epithelial antigen of prostate 1; AR androgen receptor; PROTAC, proteolysis-targeting chimera; CYP11A1, cytochrome P450 family 11 subfamily A member 1; AR-V7 androgen receptor splice variant 7; HR, hazard ratio.

Single-cell RNA-sequencing of PTEN-null tumors further reveals reciprocal activation of the MAPK module, via AKT-mediated phosphorylation of CRAF at S338 and ERK-dependent phosphorylation of AKT at S473, amplifying mitogenic and survival signals (97). Integrated copy-number and transcriptomic analyses demonstrate that concurrent PTEN loss and ERG rearrangement cooperate to repress epithelial differentiation genes (such as CDH1 and KRT5) while inducing mesenchymal and stem-like signatures (VIM, CD44 and SOX2) that predict early metastatic relapse (87,88). Notably, PTEN-deficient organoids show heightened sensitivity to PI3Kβ-selective blockade (GSK2636771), with complete growth arrest only when combined with MEK inhibition, underscoring the functional relevance of PI3K-MAPK crosstalk (89).

Phase-III evidence. The IPATential150 trial randomized 1101 asymptomatic or mildly symptomatic mCRPC patients 1:1 to ipatasertib (400 mg; QD) plus abiraterone/prednisone compared with placebo plus abiraterone (90). After 42-month follow-up, median rPFS was 19.2 vs. 14.7 months (HR 0.73; 95% CI 0.61-0.88) in the intention-to-treat cohort; however, the benefit was confined to the 521 patients with PTEN-loss tumors (HR 0.57; 95% CI 0.43-0.74), whereas PTEN-normal patients derived no significant advantage (HR 0.95; 95% CI 0.70-1.27) (91). Biomarker-rich ctDNA analyses confirmed that biallelic PTEN disruption (copy-number ≤0.5) was required for maximal ipatasertib sensitivity, while mono-allelic loss or PTEN-wild-type status predicted primary resistance (98).

Similarly, the CAPItello-281 phase-III study evaluated capivasertib (320 mg BDI, 4-days-on/3-days-off) plus enzalutamide in 888 post-docetaxel mCRPC patients (99). Interim results (data-cut May 2024) demonstrated improved median OS from 21.3 to 26.8 months (HR 0.78; 95% CI 0.65-0.95) regardless of PTEN status, yet the magnitude of benefit was again greatest in the 42% of tumors with PTEN loss (HR 0.64; 95% CI 0.48-0.85) (99). Collectively, these data establish PTEN loss as an enrichment biomarker for first-line AKT inhibition, although heterogeneity in control-arm outcomes across geographic regions highlights the need for prospective validation (91).

Safety profile. Pooled safety datasets from IPATential150 (n=547; ipatasertib) and CAPItello-281 (n=443; capivasertib)

reveal class-characteristic toxicities (100,101). Grade ≥3 diarrhea occurred in 20% (ipatasertib) and 15% (capivasertib) of patients, with median time-to-onset of 8 days; prompt loperamide initiation (4 mg at first loose stool, then 2 mg q 4 h) reduced dose-modification rates from 28-11% (100). Hyper-glycaemia (fasting glucose >250 mg/dl) was documented in 12 and 10% respectively, predominantly in patients with baseline BMI >30 kg/m^2; metformin initiation at 500 mg BID together with dietary counseling normalized glucose in 78% of cases without AKTi discontinuation (101). Maculo-papular rash (grade ≥2; 18 vs. 14%) followed a typical sun-exposed distribution; prophylactic emollients and topical corticosteroids (mometasone 0.1% BID) decreased severe cutaneous events to <5% in a prespecified sub-study (101). No cumulative cardiotoxicity was observed; however, periodic ECG monitoring is advised because AKT inhibition can prolong QTc by 10-15 msec (102).

Combinatorial rationale: AKTi + PARPi to overcome reciprocal resistance. Pre-clinical models demonstrate that PTEN loss impairs homologous-recombination repair via AKT-mediated phosphorylation and nuclear exclusion of RAD51 and BRCA2, thereby inducing a 'BRCAness' phenotype that sensitizes to PARP inhibition (103,104). Conversely, PARPi-induced replication stress activates AKT through PI3K-dependent feedback, providing a mechanistic rationale for dual blockade (105). In PTEN-null murine prostate allografts, ipatasertib + Olaparib achieved complete responses in 9/12 tumors vs. 0/12 with either agent alone, accompanied by sustained DNA-damage signaling (γH2AX foci >24 h) and T-cell infiltration (CD8$^+$/FoxP3$^+$ ratio ↑3.2-fold) (105).

Early-phase clinical translation is underway: The phase-Ib RE-ACTIVATE trial (NCT04380265) combined capivasertib with Olaparib after ARPI failure; among 28 PTEN-loss patients, PSA50 responses were observed in 54% and median rPFS was 8.7 months, with grade ≥3 adverse events limited to anemia (18%) and diarrhea (14%) (99). Pharmacodynamic ctDNA analyses confirmed downregulation of PI3K-AKT and DDR gene signatures only in the combination arm, supporting on-target synergy (99). Ongoing randomized studies (such as CAPItello-292 and NCT05654623) will definitively test whether AKTi + PARPi can postpone the emergence of genomic-reversion resistance and extend survival in biomarker-selected mCRPC.

6. Antibody-drug conjugates and emerging oral molecular agents

The therapeutic landscape of mCRPC is rapidly expanding beyond AR axis inhibition. Antibody-drug conjugates (ADCs) and novel oral agents targeting alternative oncogenic drivers have entered clinical evaluation, offering mechanistically distinct options for AR-independent disease. The following sections critically appraised the most advanced candidates, with emphasis on efficacy signals, neurotoxicity profiles and early biomarker data. A concise overview is provided in Table IV and the distinct mechanisms of action for PROTAC degraders and antibody-drug conjugates are illustrated in Fig. 2.

ADCs pipeline: B7-H3, Trop-2 and STEAP1

Vobramitamab duocarmazine (B7-H3-directed ADCs). In a first-in-human phase I study (NCT04145622) enrolling 78 mCRPC patients who had progressed on ≥1 AR-pathway inhibitor, vobramitamab demonstrated a 34% ORR and 67% PSA50 decline at the recommended phase-II dose (2.5 mg kg^{-1} every 3 weeks) (106). Median PFS was 7.2 months; however, grade-2 peripheral neuropathy occurred in 19% of subjects, prompting implementation of a mandatory dose-reduction algorithm after cycle 3. ctDNA profiling revealed B7-H3 copy-number gain as a putative response predictor (OR 2.8, P=0.03), although these genomic data remain to be validated prospectively.

Sacituzumab govitecan (Trop-2-directed, SN-38 ADCs). Updated results of the TROPHY-U-01 cohort (n=31) showed a 32% ORR and median PFS of 5.6 months in heavily pre-treated mCRPC (107). Notably, responses were observed irrespective of Trop-2 membrane H-score, questioning the utility of immunohistochemistry-based patient selection. Grade ≥2 neuropathy was infrequent (6%), but neutropenia (all-grade 58%, grade ≥3 23%) emerged as the dose-limiting toxicity, requiring primary G-CSF prophylaxis in subsequent trials. Comparative transcriptomics identified MYC amplification as a resistance hallmark, providing rationale for combination with PI3K/AKT inhibitors currently under investigation.

MLN2704 (STEAP1-directed, maytansinoid ADC). In the first-in-human phase I study reported by Milowsky *et al* (108) (n=37), MLN2704 demonstrated modest single-agent activity in AR-pathway-inhibitor-refractory mCRPC, with 8% objective responses and 14% of patients achieving ≥50% PSA decline. Median PFS was 3.7 months. Notably, peripheral neuropathy was limited to grade 1 in 9% of subjects, supporting further exploration of split-dosing or combination strategies. STEAP1 membrane expression by IHC did not correlate with clinical benefit, highlighting the need for alternative patient-selection biomarkers. Collectively, these studies indicate that ADCs can elicit clinically meaningful AR-independent responses; however, the heterogeneity of target expression, discordance between target levels and activity and non-negligible neuro-toxicity underscore the need for refined patient-selection algorithms.

Oral first-in-class agents: CYP11A1, AR-V7 Splice and PROTAC inhibitors

Orteronel (CYP11A1 inhibitor). The randomized phase III SWOG-1216 trial (n=1,279) showed a non-significant OS benefit (median 81.1 vs. 70.2 months; HR 0.86; P=0.06) when orteronel was added to ADT in hormone-sensitive disease; however, subset analysis revealed significant OS prolongation in high-volume disease (HR 0.75; P=0.009) (109). Adrenal insufficiency (grade ≥3 7%) and hypertension (20%) were manageable with mandated morning cortisol monitoring. Circulating steroid metabolomics demonstrated near-complete suppression of intratumoral androstenedione, corroborating on-target CYP11A1 blockade (110).

AR-V7 splice inhibitors. Although no selective AR-V7 antagonist has advanced beyond phase I, the oral splice-switching oligonucleotide EPI-7386 reduced AR-V7 transcript by >90% in patient-derived xenografts, restoring enzalutamide sensitivity (111). In a 21-patient expansion cohort, PSA50 was 24% and median PFS 3.8 months, with

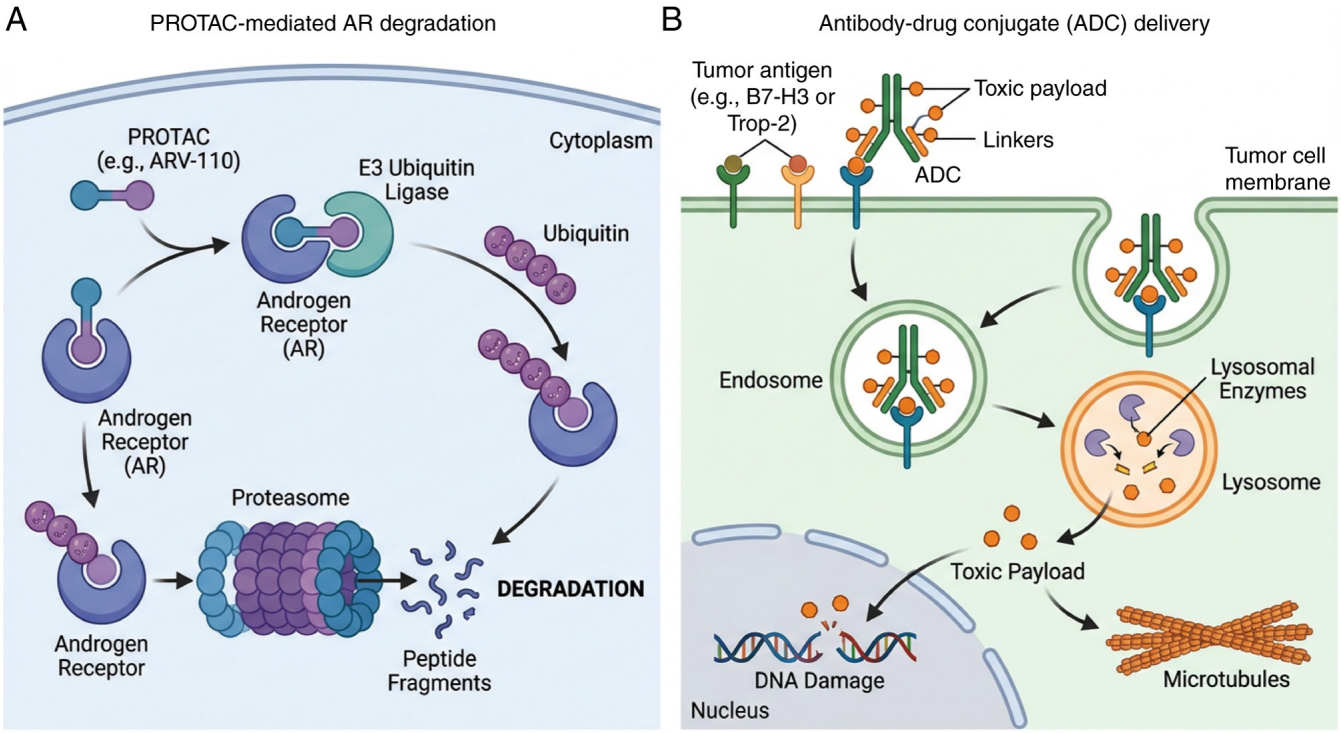

Figure 2. Mechanisms of action for emerging therapeutic classes: PROTACs and ADCs. (A) PROTACs, such as ARV-110, utilize a dual-binding mechanism to recruit E3 ubiquitin ligases specifically to the AR. This results in AR polyubiquitination and subsequent destruction by the proteasome, rather than just inhibition. (B) ADCs act as targeted delivery systems. They bind to specific tumor surface antigens (such as B7-H3 and Trop-2), triggering internalization. Once inside the cell, lysosomal enzymes cleave the linker, releasing a potent cytotoxic payload directly into the cancer cell. PROTACs, proteolysis-targeting chimeras; ADCs, antibody-drug conjugates; AR, androgen receptor.

no dose-limiting neuropathy; however, heterogeneous AR-V7 detection across ctDNA platforms limited biomarker enrichment, highlighting the need for standardized assays.

AR PROTAC degraders (ARV-110, CC-94676). Bavdegalutamide (ARV-110) achieved PSA50 of 46% in AR ligand-binding-domain mutated tumors (n=46) at the recommended phase-II dose (420 mg QD) (112). Notably, responses were retained in F877L and L702H AR mutants conferring enzalutamide resistance. Grade 2 fatigue (18%) and grade 1 dysgeusia (22%) were the dominant toxicities, without neurotoxicity. Similarly, CC-94676 induced ≥50% PSA reduction in 38% of heavily pre-treated mCRPC, including 27% with prior taxane and novel hormonal therapy (113). Pharmacodynamic modelling demonstrated >95% AR degradation within 48 h, sustained for ≥7 days, supporting once-weekly dosing that is being tested in an ongoing randomized phase II trial (NCT05828684).

Glucocorticoid receptor antagonists to counter glucocorticoid receptor (GR) bypass. Upregulation of GR has been identified as a canonical bypass mechanism after potent AR suppression. Relacorilant, a selective GR modulator, combined with enzalutamide in a phase Ib/II study (n=60) yielded PSA50 of 35% and median PFS of 5.5 months in enzalutamide-refractory patients (114). Importantly, GR nuclear translocation was reduced by 68% in on-treatment biopsies, paralleling clinical benefit. Hypertension and hypokalemia (all-grade 15%) were reversible with dose interruption and no neurotoxicity was reported. Comparative transcriptomics revealed suppression of GR-driven FKBP5 and SGK1 transcriptional programs exclusively in responders, providing a pharmacodynamic biomarker for patient selection that is being prospectively validated in the randomized phase II GRASP trial (NCT06153864).

7. Rational combinations and sequencing in the post-ARPI landscape

With androgen-deprivation therapy and ARPIs now foundational in mCRPC management, the central clinical question has shifted to optimal sequencing after their failure. The emergence of PARP inhibitors, radioligand therapy and immunotherapy has created a complex treatment landscape. The marked molecular heterogeneity of mCRPC necessitates a move from empirical switching to biomarker-guided, mechanism-based strategies. This approach must carefully balance efficacy against the risks of cumulative toxicity and cross-resistance.

PARP inhibitor plus ARPI: A BRCA1/2-exclusive paradigm. Final analyses of PROpel (n=796) and TALAPRO-2 (n=399) confirm that the addition of Olaparib or talazoparib to first-line abiraterone or enzalutamide reduces the risk of radiographic progression by 60-70% only in patients with deleterious BRCA1/2 alterations (HR 0.20 and 0.23, respectively) (115,116). No incremental benefit was observed for ATM or CDK12 mono-allelic lesions and exploratory ctDNA copy-number analysis showed that biallelic inactivation (copy-number ≤0.5) was required for maximal sensitivity (38). Grade ≥3 anemia occurred in 38% of combination arms, mandating dose reductions in 28% of subjects; however, no excess cardiotoxicity was

recorded after 5-year follow-up (117). Consequently, current European guidelines restrict front-line PARP-ARPI combination to BRCA1/2 carriers and recommend sequential PARP monotherapy after ARPI failure for other HRR genotypes when marrow reserve is limited (29).

Taxane re-challenge vs. 177Lu-PSMA-617: Sequencing after ARPI failure. The outcome-adaptive ProBio platform trial randomized 1 102 men with progression on ARPI to cabazitaxel or crossover ARPI (118). Cabazitaxel improved median OS from 11.2 to 14.8 months (HR 0.68; P=0.004), but a significant interaction test showed no benefit in patients with DNA-repair defects (pinteraction=0.04). Conversely, the updated VISION dataset (n=831) demonstrates that 177Lu-PSMA-617 achieves a 60% PSA50 response after taxane failure and prolongs OS regardless of HRR status (HR 0.62) (119,120). Real-world German and US registries further show that baseline platelet count $<100x10^9l^{-1}$ predicts grade ≥3 thrombocytopenia in 27% of cycles, whereas prior PARP exposure does not compromise subsequent PSMA efficacy (121,122). Taken together, cabazitaxel is favored in genomically unselected, fit patients, while 177Lu-PSMA-617 offers an equally efficacious and safer bridge when marrow reserve is compromised.

Immuno-oncology: CDK12 loss and MSI-H define the responsive niche. Long-term follow-up of KEYNOTE-199 and CheckMate 9KD shows that pembrolizumab or nivolumab combinations yield durable 24-month responses exclusively in microsatellite-instable (MSI-H; 7% of mCRPC) or CDK12 biallelic-loss (10%) tumors (54,123). A pooled analysis of 1,596 biopsies revealed objective response rates of 44, 37 and 29% for MSI-H, TMB-high and CDK12-loss subgroups, respectively, while PD-L1 ≥10% conferred only modest enrichment (ORR 28%) (124). Notably, prior PARP or ARPI exposure did not impair subsequent checkpoint efficacy, suggesting non-overlapping resistance mechanisms (123). Consequently, upfront molecular profiling is warranted to identify the 17% of patients eligible for immunotherapy; for the remainder, continued ARPI beyond progression or switch to taxane remains standard.

PI3K/AKT inhibition. The phase-III IPATential150 and CAPItello-281 trials establish that ipatasertib or capivasertib plus ARPI improves radiographic progression-free survival only in PTEN-loss tumors (HR 0.57 and 0.64, respectively) (125,126). Mono-allelic loss or PTEN-wild-type disease showed no benefit (HR 0.95-1.02), underscoring the necessity of centralized immunohistochemistry or ctDNA copy-number ≤0.5 for patient selection (127,128). Cross-study safety synthesis revealed grade ≥3 diarrhea in 15-20% of patients; protocolized loperamide prophylaxis reduced dose modifications from 28 to 11% (18,129). Emerging data further indicate that AKT inhibition sensitizes PTEN-null tumors to subsequent PARP blockade by restoring homologous-recombination efficiency, providing rationale for AKT-PARP sequences now being tested in phase-II trials (47,130).

8. Future directions

The therapeutic landscape of mCRPC is evolving rapidly, driven by advances in precision imaging, liquid biopsy and mechanism-based combination therapies. Yet, several persistent challenges continue to limit durable disease control. Looking forward, meaningful progress will likely hinge on three key areas: Adapting treatment in real time to clonal evolution, harmonizing molecular and imaging biomarkers for response assessment and targeting non-AR oncogenic drivers that emerge after AR pathway inhibition.

One major area of uncertainty lies in the dynamic nature of PSMA expression. Emerging evidence from serial 68Ga-PSMA PET/CT imaging reveals that ADT can acutely upregulate PSMA uptake, while subsequent exposure to enzalutamide or abiraterone may lead to downregulation in progressing lesions (131-133). These fluctuations have direct clinical implications, as the efficacy of PSMA radioligand therapy (RLT) is closely linked to baseline SUVmax and total tumor burden (134-137). To address this, a multi-tracer PET strategy, incorporating early and delayed 68Ga-PSMA scans alongside 18F-FDG or 18F-PSMA-1007 imaging, could serve as a dynamic decision-making tool to guide treatment selection at each stage of disease progression (138-140). Such an approach has already shown promise in improving lesion detectability in biochemical recurrence (141,142) and ongoing trials are now testing its utility in the metastatic setting (NCT05654623).

Parallel to imaging advances, the integration of liquid biopsy metrics is transitioning from exploratory to clinical validation. For instance, a ctDNA fraction ≥5% prior to PSMA-RLT has been independently associated with shorter OS (143), while longitudinal monitoring of AR copy number changes can anticipate abiraterone resistance earlier than PSA trends (144,145). When combined with PET-derived parameters such as whole-body PSMA tumor volume (PSMA-TV) and total lesion PSMA (TL-PSMA), these molecular data markedly enhance prognostic accuracy (146,147). A notable example is the ongoing international trial (NCT05122895), which pairs PSMA-PET/CT-guided biopsies with ultra-deep ctDNA sequencing to track clonal evolution under 177Lu-PSMA-617. Early findings suggest that BRCA2 reversion mutations emerge selectively in lesions with deep PSA responses, hinting at a transient antigen-negative escape mechanism following α-particle irradiation (148,149). These insights highlight the need for integrative models that fuse imaging radiomics with genomic variant dynamics to anticipate resistance patterns.

Efforts to refine the therapeutic index of PSMA-RLT are also gaining momentum. Lesion-level dosimetry has shown that absorbed doses ≥23 Gy predict >90% PSA50 responses, yet toxicity to salivary glands and renal cortex remains a limiting factor (150,151). Data from the WARMTH registry indicate that weight-based 225Ac-PSMA dosing (100 kBq kg^{-1}) following 177Lu-PSMA priming achieves comparable antitumor efficacy with reduced marrow toxicity, suggesting that sequential α-β emitter regimens may optimize the therapeutic window (148,150). Furthermore, preclinical studies have demonstrated that PTEN loss induces a 'BRCAness' phenotype via AKT-mediated suppression of RAD51, sensitizing tumors to PARP inhibition (152,153). Early-phase trials combining the AKT inhibitor capivasertib with Olaparib post-PSMA-RLT have reported PSA50 responses in 54% of DDR-naïve patients, without excess grade ≥3 anemia (154). These findings are now being formally tested in randomized

phase II studies (CAPItello-292 and NCT05654623) to determine whether AKT-PARP sequencing can delay the emergence of BRCA2 reversion mutations that compromise both PARP and PSMA-targeted therapies (149,155).

Beyond DNA repair modulation, the immune microenvironment is increasingly recognized as a modifiable determinant of PSMA-RLT efficacy. Pre-therapy $CD8^+$ tumor-infiltrating lymphocyte density ≥200 cells mm^{-2}, as assessed by PSMA-PET-guided biopsy, has been associated with prolonged progression-free survival when 177Lu-PSMA-617 is combined with pembrolizumab (132,140). Conversely, high PSMA expression itself has been linked to immunosuppressive myeloid infiltrates, suggesting that radiation-induced antigen release may only translate into durable benefit when PD-1/PD-L1 signaling is concurrently inhibited (138,156). The PRINCE trial (NCT03658447) is currently evaluating triplet therapy consisting of 177Lu-PSMA-617, nivolumab and ipilimumab. Interim results show manageable grade-3 colitis (8%) and objective soft-tissue responses in 42% of MSI-high patients (132), reinforcing the rationale for immune-biomarker stratification prior to PSMA-RLT, akin to the CDK12-loss enrichment model now used for first-line pembrolizumab (157,158).

Finally, the integration of artificial intelligence (AI) is poised to harmonize these complex, multimodal datasets. Deep learning models trained on 68Ga-PSMA-PET/CT can now segment whole-body tumor burden with Dice coefficients >0.91, surpassing manual delineation by expert readers (159,160). When fused with clinical variables such as PSA, alkaline phosphatase and ctDNA fraction, AI-derived risk scores predict OS post-PSMA-RLT with C-indices ≥0.80 (161,162). Prospective validation of such integrative algorithms within adaptive trial platforms (such as the outcome-adaptive ProBio study) is expected to accelerate biomarker-driven therapy switching and minimize exposure to ineffective treatments (163,164).

Taken together, these converging research directions suggest that the future of mCRPC management will be defined by real-time, multi-omic decision frameworks that transcend traditional AR-centric paradigms. Realizing this potential will require coordinated international efforts to standardize PET acquisition protocols, ctDNA assay thresholds and AI model transparency, ensuring that the promise of precision oncology is translated into routine clinical practice rather than remaining confined to high-resource centers.

As a narrative review, the present study has several inherent limitations. The literature search and selection process, while comprehensive and based on PubMed-indexed publications, was not conducted as a formal systematic review with a pre-registered protocol. Therefore, the possibility of selection bias cannot be entirely excluded and some relevant studies may have been inadvertently omitted. The synthesis of evidence is qualitative and descriptive rather than quantitative; no meta-analysis was performed and the absence of pooled effect sizes limits the ability to draw definitive conclusions about the magnitude of treatment benefits across studies. Furthermore, the rapid pace of publication in this field means that some emerging data, particularly from ongoing clinical trials, may not yet be mature enough for inclusion. Despite these limitations, the conclusions presented in the present review are drawn directly from the synthesized evidence and reflect a balanced interpretation of the available data, critically appraising both positive findings and conflicting results. The conclusions are intended to provide a framework for understanding current therapeutic strategies and guiding future research, rather than serving as definitive clinical recommendations. The present review aimed to provide a balanced and up-to-date overview of the therapeutic landscape, critically appraising conflicting results and highlighting areas of consensus and ongoing debate.

9. Conclusions

MCRPC is increasingly recognized as a molecularly heterogeneous disease driven by diverse, non-AR oncogenic pathways. Precision strategies targeting DDR defects, PI3K/AKT alterations, lineage plasticity, immune evasion and PSMA expression have entered clinical practice, yielding biomarker-defined survival gains. Future progress will hinge on real-time integration of multimodal liquid biopsies, PSMA-PET radiomics and AI-guided adaptive trials to anticipate clonal evolution, optimize sequencing and extend precision therapy beyond AR axis inhibition.

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Authors' contributions

YW was responsible for conceptualization, literature search, data analysis, original draft preparation and figure/table design. YX was responsible for critical revision of the manuscript for important intellectual content, supervision of data interpretation and validation of clinical insights. QZ was responsible for overall study design, final manuscript review and editing, project coordination and approval of the final version for submission. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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