Review

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Combination Therapies for Prostate Cancer: Novel Preclinical Combinations and Ongoing Clinical Trials

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Androgen receptor (AR) antagonists and androgen receptor pathway inhibitors (ARPIs) have long been cornerstones of systemic therapy for advanced prostate cancer (PC). This central role reflects the biological dependence of prostate cancer on AR signaling despite the marked molecular heterogeneity of the disease, which has limited the identification of broadly applicable therapeutic targets. However, the therapeutic landscape has expanded substantially in recent years with the introduction of novel treatment modalities, including immune checkpoint inhibitors, poly (ADP-ribose) polymerase (PARP) inhibitors, and radioligand therapy. Nevertheless, the clinical benefit of these therapies remains restricted to selected patient populations. Also, long-term efficacy is limited by both primary and acquired resistance. Consequently, increasing emphasis is laid on the development of rational combination strategies designed to enhance treatment responses, delay resistance, and improve patient outcomes. This review provides a comprehensive overview of recent advances in ARPI-based combination therapies by integrating evidence from both preclinical studies and clinical trials. Particular emphasis is placed on combinations targeting biological pathways that cooperate with AR signaling, including metabolic reprogramming, cancer stemness, canonical oncogenic signaling pathways, and diverse mechanisms of regulated cell death. Moreover, we summarize the current clinical evidence for combinations involving ARPIs with approved therapeutic modalities, including PARP inhibitors, chemotherapy, immunotherapy, and radioligand therapy. Although preclinical studies have identified numerous promising therapeutic combinations, translating these findings into clinical benefit is still highly challenging. The abundance of potential targets and the complexity of resistance mechanisms make it difficult to distinguish combinations with strong translational potential from those with limited clinical applicability. Consequently, most ongoing clinical trials have adopted a relatively conservative strategy by combining ARPIs with therapies with favorable safety profiles and established pharmacokinetic characteristics. This approach facilitates clinical development and regulatory implementation; however, continued investigation of mechanism-driven combinations emerging from preclinical research may be essential to identify more effective therapeutic strategies capable of overcoming resistance to AR-directed therapy. Strengthening the translational pipeline through rigorous mechanistic studies, biomarker-guided patient selection, and rational clinical trial design may be crucial for realizing the full potential of next-generation combination therapies in prostate cancer.

Keywords: ARPIs; combination therapy; PC

Introduction

Cancer development and progression are driven by the accumulation of genetic, epigenetic, and transcriptomic alterations disrupting normal cellular homeostasis. These alterations frequently involve the activation of oncogenes and the inactivation of tumor suppressor genes, leading to dysregulated signaling networks that promote uncontrolled proliferation, metabolic reprogramming, evasion of apoptosis, genomic instability, and metastatic progression [1]. Advances in molecular oncology have enabled the identification of actionable molecular drivers, resulting in the successful development of targeted therapies against several malignancies. Representative examples include estrogen receptor (ER)- and human epidermal growth factor receptor 2–targeted therapies for breast cancer, epidermal growth factor receptor (EGFR)-targeted therapies for non-small-cell lung cancer, and Kirsten rat sarcoma viral oncogene homologue (KRAS) inhibitors for selected pancreatic and colorectal cancers [2,3].

Unlike many solid tumors harboring recurrent, therapeutically actionable driver mutations, prostate cancer (PC) is characterized by marked molecular and clinical heterogeneity. Although recurrent genomic alterations involving genes such as speckle-type POZ protein (*SPOP*), phosphatase and tensin homolog (*PTEN*), tumor protein 53 (*TP53*), retinablastoma (*RB1*), and DNA damage repair (*DDR*) genes are frequently observed, their prevalence

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and clinical applicability vary considerably among patients [4,5]. In contrast, AR signaling remains the predominant molecular driver throughout prostate cancer progression and represents the principal therapeutic target in both hormone-sensitive and castration-resistant prostate cancer. Consequently, ARPIs, including second-generation antiandrogens and androgen biosynthesis inhibitors, constitute the foundation of systemic therapy for advanced prostate cancer. Despite substantial improvements in patient survival, most patients eventually develop resistance to AR-directed therapies, culminating in progression to castration-resistant prostate cancer (CRPC) [6,7]. This inevitable therapeutic resistance underscores the urgent need to develop treatment strategies capable of extending response duration and overcoming adaptive resistance mechanisms.

Resistance to ARPIs is a multifactorial process involving both AR-dependent and AR-independent mechanisms. Accumulating evidence demonstrates an interconnection between AR signaling and numerous oncogenic pathways regulating cellular metabolism, DNA damage response, cell-cycle progression, apoptosis, stemness, epigenetic remodeling, lineage plasticity, and interactions with the tumor microenvironment [8,9]. Reciprocal crosstalk between these pathways enables tumor cells to adapt to therapeutic pressure, thereby promoting disease progression despite continued AR inhibition. Consequently, simultaneous targeting of AR signaling and complementary molecular pathways represents a promising therapeutic strategy to enhance antitumor efficacy, suppress adaptive resistance, and promote durable clinical responses.

This biological rationale is reflected in the rapidly evolving clinical landscape of prostate cancer. Combination therapies have become a major focus of contemporary drug development, with numerous clinical trials evaluating ARPIs in combination with chemotherapy, poly(ADP-ribose) polymerase (PARP) inhibitors, radioligand therapy, immunotherapy, and emerging targeted agents [10,11]. To date, most clinically advanced combinations incorporate approved therapies with well-established safety profiles and pharmacokinetic characteristics, facilitating their translation into clinical practice. However, recent advances in molecular characterization of prostate cancer have accelerated the identification of potential therapeutic vulnerabilities. This has enabled the transition of a large number of mechanism-based combination strategies from preclinical research to early-phase clinical trials.

In this review, we comprehensively summarize recent advances in ARPI-based combination therapies for prostate cancer, encompassing both preclinical studies investigating novel therapeutic targets and ongoing or recently completed clinical trials (Fig. 1). Particular emphasis is placed on the molecular rationale for these combinations, the mechanisms by which they overcome resistance to AR-directed therapy, and their potential for clinical translation.

Preclinical ARPI-Based Combination Strategies

Combination With Metabolic Inhibitors

Enzalutamide, apalutamide, and darolutamide as second-generation ARPIs have improved clinical outcomes in patients with CRPC. However, most patients acquire resistance to ARPIs despite initial tumor regression. One attractive approach is to develop combination therapeutics with metabolic inhibitors to sensitize CRPC to ARPIs. Given the vital role of metabolic reprogramming in the development of resistance to AR-targeted therapies, several metabolic pathways, including glutamine metabolism, oxidative phosphorylation (OXPHOS), and lipid metabolism, have emerged as attractive therapeutic targets (Fig. 2). These metabolically reprogrammed cells become more sensitive to mitochondrial-targeted therapies such as glutaminase inhibitors, complex I inhibitors, and FASN inhibitors.

PC cells exhibit an increasing dependence on glutamine, unlike normal prostate cells. This is partly due to the suppression of glutamine synthase, which is a part of metabolic reprogramming driven by oncogenic pathways such as AR, MYC proto-oncogene, basic helix-loop-helix transcription factor (MYC), and mechanistic target of rapamycin (mTOR). Specifically, MYC plays a central role in glutamine metabolism by upregulating glutamine transporters alanine-serine-cysteine transporter 2 (ASCT2) and L-type amino acid transporter 1 (LAT1) and glutaminase (GLS) [12]. Treatment with the glutaminase inhibitor CB-839 significantly reduced proliferation of androgen-sensitive PC cells and CRPC cells and suppressed tumor growth in xenograft models [13]. Similarly, Blatt et al. [14] demonstrated that CB-839 treatment disrupted antioxidant defense, increased reactive oxygen species accumulation, and preferentially suppressed the growth of enzalutamide-resistant (EnzR) cells. Preclinical studies targeting mitochondrial metabolism have highlighted this pathway as a promising target in CRPC. EnzR PC cells exhibited elevated levels of OXPHOS and reduced levels of glycolysis compared with androgen-sensitive cells. Inhibition of OXPHOS with complex I inhibitor IACS-010759 significantly reduced cell growth and enhanced ARPI sensitivity [15]. More recent studies on mitochondrial metabolism revealed that HSP70 inhibitor JG-98 resensitized CRPC cells to ARPIs by suppressing aerobic respiration. HSP70 inhibition by JG-98 impaired mitochondrial translation and mitoribosome stability. As a result, the synthesis of electron transport chain (ETC) complex subunits was reduced, leading to impaired OXPHOS and decreased tumor growth. Furthermore, direct inhibition of ETC complexes I and II has also been shown to restore ARPI sensitivity [16].

Lipid metabolism is another important metabolic vulnerability in advanced PC. In particular, fatty acid synthase (FASN), a key enzyme involved in lipogenesis, is upregulated in PC, enhancing tumor growth and progression to CRPC. Recently, Nuzzo et al. [17] demonstrated

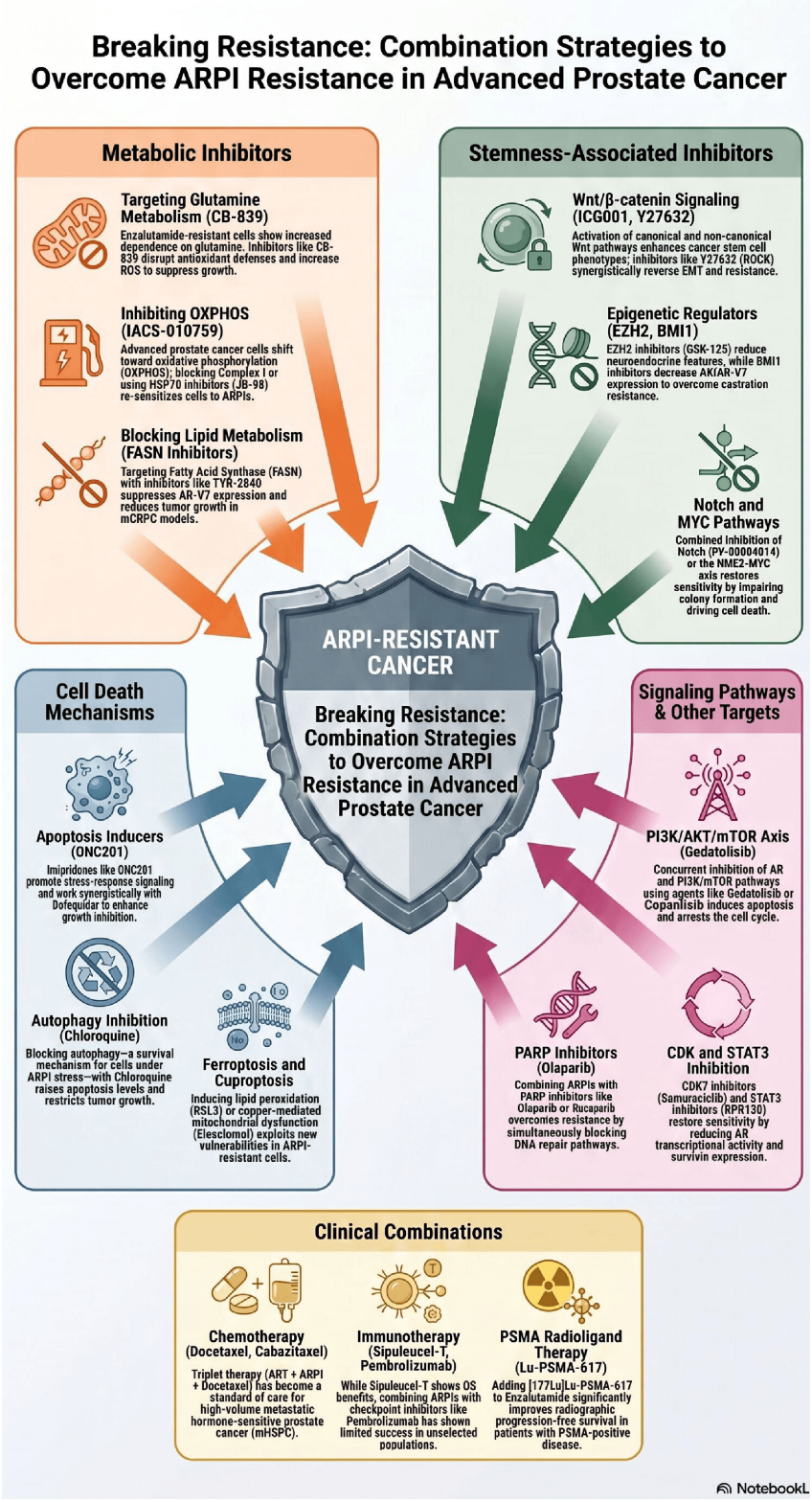


Fig. 1. Preclinical and clinical combination therapy landscape of prostate cancer. Preclinical combination strategies involving androgen receptor pathway inhibitors (ARPIs) with metabolic inhibitors, stemness-associated inhibitors, cell death pathway inducers, and inhibitors of common oncogenic pathways, as well as clinical combination strategies involving ARPIs with conventional chemotherapy, immunotherapy, and radioligand therapy. The authors conceived the figure and designed the prompt instructions, while AI was used to generate the draft figure using NotebookLM (Google LLC, CA, USA; https://notebooklm.google.com/) and optimized by OpenAI Prism (https://prism.openai.com/).

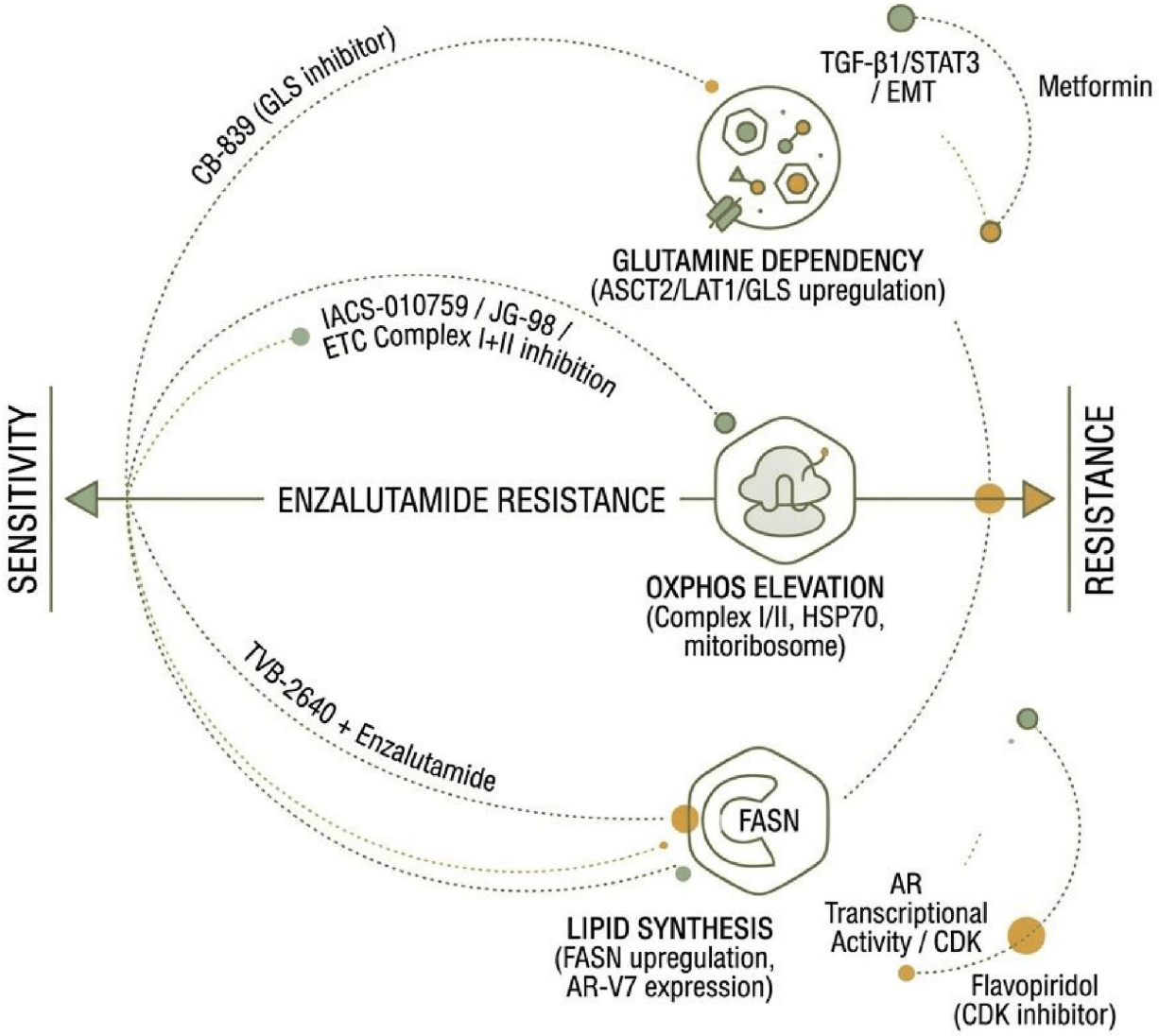


Fig. 2. Metabolic targets and their inhibitors. Overview of metabolic reprogramming mechanisms modulating enzalutamide sensitivity and resistance in advanced prostate cancer, including targeted pathways and respective inhibitors. The authors conceived the figure and designed the prompt instructions, while AI was used to generate the figure using Gamma (Gamma Tech, Inc., CA, USA; https://gamma.app/).

that the combination of FASN inhibitor TVB-2640 with enzalutamide significantly suppressed AR-V7 expression and reduced tumor growth in CRPC cells, organoid models, and patient-derived xenografts compared with enzalutamide monotherapy. After this encouraging preclinical study, a Phase I clinical trial (NCT05743621) is being conducted to investigate the translational potential of TVB-2640 in combination with enzalutamide in patients with metastatic castration-resistant prostate cancer (mCRPC). This trial currently focuses on safety, tolerability, and dose escalation [18].

Metformin, as an antidiabetic drug, enhanced the inhibitory effect of enzalutamide by modulating metabolic and signaling pathways. In EnzR PC models, metformin restored enzalutamide sensitivity by suppressing the TGF-β1/STAT3 signaling axis and reversing epithelial-to-mesenchymal transition (EMT). The combined treatment inhibited tumor proliferation more effectively than either drug alone [19].

Combination With Stemness-Associated Inhibitors

Accumulating evidence suggests that cancer stem cells (CSCs) contribute to therapeutic resistance against ARPIs and disease progression in PC by maintaining self-renewal, cell plasticity, and tumor heterogeneity. Thus, CSC-associated pathways are valuable targets to overcome therapeutic resistance [20]. Targeting these pathways, including canonical and noncanonical wingless-related integration site (Wnt) signaling, MYC, Notch, B-cell-specific Moloney murine leukemia virus integration site 1 (BMI1),

and enhancer of zeste homolog 2 (EZH2), may represent a promising strategy to overcome therapeutic resistance by suppressing the proliferation of CSC-like populations (Fig. 3). The activation of canonical Wnt/β-catenin signaling has been implicated in enzalutamide resistance through elevated AR signaling and an enhanced stemness phenotype. Inhibition of β-catenin using ICG001 restored enzalutamide sensitivity [21]. Chen et al. [22] demonstrated the role of the noncanonical Wnt pathway in enzalutamide-sensitive and EnzR prostate cancer cells. EnzR cells showed elevated levels of noncanonical Wnt activation through Wnt5a, ras homolog family member A (RhoA), and Rho-associated coiled-coil-containing protein kinase (ROCK) upregulation. Inhibition of ROCK using Y27632 effectively enhanced the antitumor activity of enzalutamide, leading to reduced tumor growth in xenograft models. Furthermore, the combination of enzalutamide and Y27632 synergistically reversed EMT and suppressed tumor growth in CRPC xenograft models. More recently, Fischetti et al. [23] investigated the therapeutic efficacy of combining enzalutamide with the EZH2 inhibitor GSK-126 in CRPC cell models. The combined treatment exerted substantial antitumor activity compared with either agent alone. Additionally, it reduced neuroendocrine features, a phenotype frequently associated with therapeutic resistance and disease progression. Besides suppressing tumor growth, combined AR and EZH2 inhibition potentiated antitumor immune responses by promoting T-cell function. The combination efficacy was reduced in immunodeficient models, highlighting its dependence on an intact immune system. Overall, these findings support the potential of combining AR-targeted therapy with epigenetic regulators of stemness to simultaneously overcome resistance and enhance antitumor immunity in advanced PC. Epigenetic regulators associated with stemness and lineage plasticity have emerged as potential therapeutic targets in CRPC. Although BMI1, a polycomb group (PcG) protein and epigenetic regulator, is widely recognized as a regulator of the stemness phenotype in PC, Zhu et al. [24] reported that BMI1 also played a key role in maintaining AR signaling, thereby promoting therapeutic resistance in CRPC. BMI1 directly stabilized AR and AR splice variants, resulting in sustained AR signaling in a noncanonical manner. Pharmacological inhibition of BMI1 decreased the expression of AR and AR-V7 and suppressed tumor growth in xenograft models that had developed resistance to castration and enzalutamide.

Further preclinical studies have evaluated the role of Notch signaling in the development of enzalutamide resistance. EnzR PC cells exhibited increased activation of the Notch pathway along with higher expression of Notch pathway effector proteins, including NOTCH1, Hes Family bHLH Transcription Factor 1 (HES1), and c-MYC. Combined treatment with the γ-secretase inhibitor PF-03084014 and enzalutamide enhanced cell death and impaired colony formation, ultimately resensitizing resistant prostate cancer cells to enzalutamide [25]. Researchers used a $CD133^{+}/CD44^{+}$ CSC-enriched population derived from therapy-resistant PC models to evaluate enzalutamide plus lupeol, a natural compound reported to inhibit AR signaling and stemness-associated pathways, including c-MYC, cellular FLICE (FADD-like IL-1β-converting enzyme)-inhibitory protein (c-FLIP), and T cell factor (TCF)/β-catenin signaling. In the combination treatment, lupeol reduced cell viability, migration, and tumor growth, and enhanced apoptosis and the efficacy of enzalutamide by downregulating AR, c-MYC, FLIP, and TCF activity [26]. MYC has emerged as a key driver of therapeutic resistance in CRPC. More recently, NME/NM23 nucleoside diphosphate kinase 2 (NME2) was identified as an important upstream regulator of MYC; elevated activities of both NME2 and MYC were observed in EnzR prostate cancer models. Furthermore, targeting MYC with MYCi975, together with the inhibition of NME2, restored therapeutic sensitivity in EnzR models, suggesting the NME2-MYC axis as a promising target to overcome therapeutic resistance in CRPC [27]. Furthermore, using a kinome-wide clustered regularly interspaced short palindromic repeats / CRISPR-associated protein 9 (CRISPR–Cas9) knockout screen, casein kinase 1 alpha (CK1α), polo-like kinase 1 (PLK1), and mTOR were identified as key regulators of enzalutamide response in prostate cancer cells [28]. The latest preclinical evidence suggests that the Hedgehog (Hh) pathway axis driven by PLK1, an upstream regulator of Hh, is a potential driver of stemness and enzalutamide resistance in metastatic PC. EnzR cells and tumor xenografts were treated with a combination of enzalutamide and vismodegib, a US Food and Drug Administration (FDA)-approved Hh signaling inhibitor. The combination treatment significantly inhibited tumor growth and promoted apoptosis both *in vitro* and *in vivo* [29].

Combination With Cell Death–Targeting Agents

Many research groups have highlighted that resistance to ARPIs is frequently supported by the activation of cellular survival mechanisms and inhibition of cell death pathways. Thus, combination strategies targeting cell death mechanisms have gained attention to promote distinct cell death pathways, including apoptosis, autophagy, ferroptosis, and cuproptosis, ultimately aiming to overcome therapeutic resistance in advanced PC (Fig. 4). Among these approaches, the activation of apoptotic signaling is a promising strategy to enhance the efficacy of AR-targeted agents. Combinations of the imipridones ONC201 and ONC206 with enzalutamide or darolutamide have been used to induce apoptosis. These combinations exerted synergistic effects, resulting in enhanced growth inhibition in CRPC cell lines and greater antitumor activity compared with either agent alone. Further, the combination treatments promoted stress-response signaling *in vivo*, demonstrating the potential of combining AR-targeted therapies with apoptosis in-

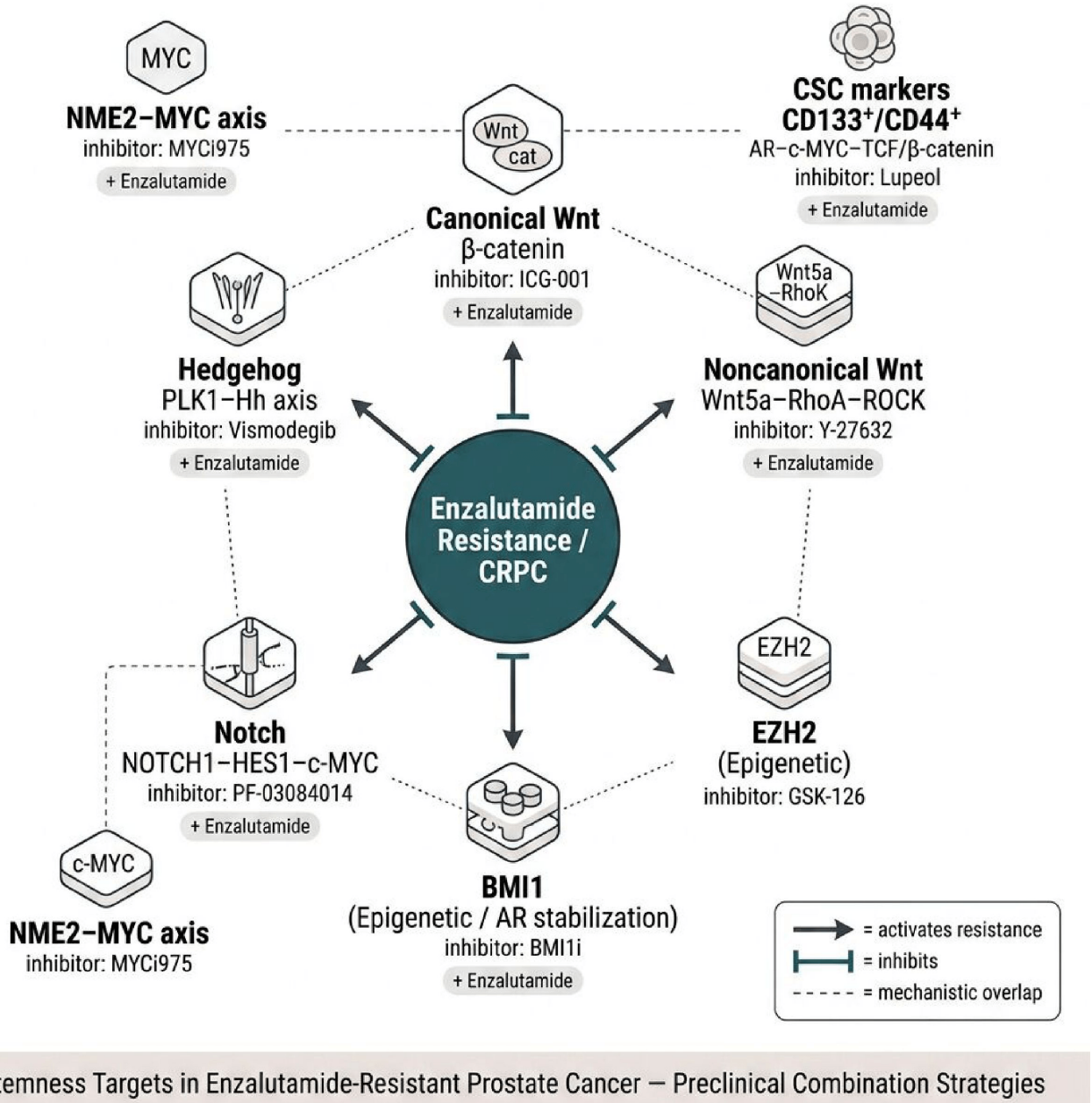


Fig. 3. Stemness targets and their inhibitors. Preclinical combination strategies targeting cancer stemness mechanisms to overcome enzalutamide resistance in advanced prostate cancer. The authors conceived the figure and designed the prompt instructions, while AI was used to generate the figure using Gamma (Gamma Tech, Inc., CA, USA; https://gamma.app/).

ducers to overcome therapeutic resistance [30]. Another approach is the inhibition of autophagy with ARPIs such as apalutamide and abiraterone. Researchers previously demonstrated the activation of autophagy as a mechanism of resistance to apalutamide [31]. The same research group evaluated the effect of a combination of chloroquine, as an autophagy inhibitor, with either apalutamide or abiraterone in xenograft models. The combination decreased the levels of autophagy markers and enhanced apoptosis, leading to higher tumor suppression compared with ARPI monotherapy *in vivo* [32]. Based on these findings, researchers further combined chloroquine with abiraterone, demonstrating that the combination decreased autophagic activity and restricted tumor growth more effectively than abiraterone alone in a PC xenograft model [33].

Another targeted cell death mechanism is ferroptosis mediated by the accumulation of lipid peroxidation and reactive oxygen species. Researchers focused on the role of ferroptosis in treatment-resistant PC cell models and xenografts. The expression of ferroptosis mediators, including solute carrier family 7 member 11 (SLC7A11), solute carrier family 3 member 2 (SLC3A2), and glutathione

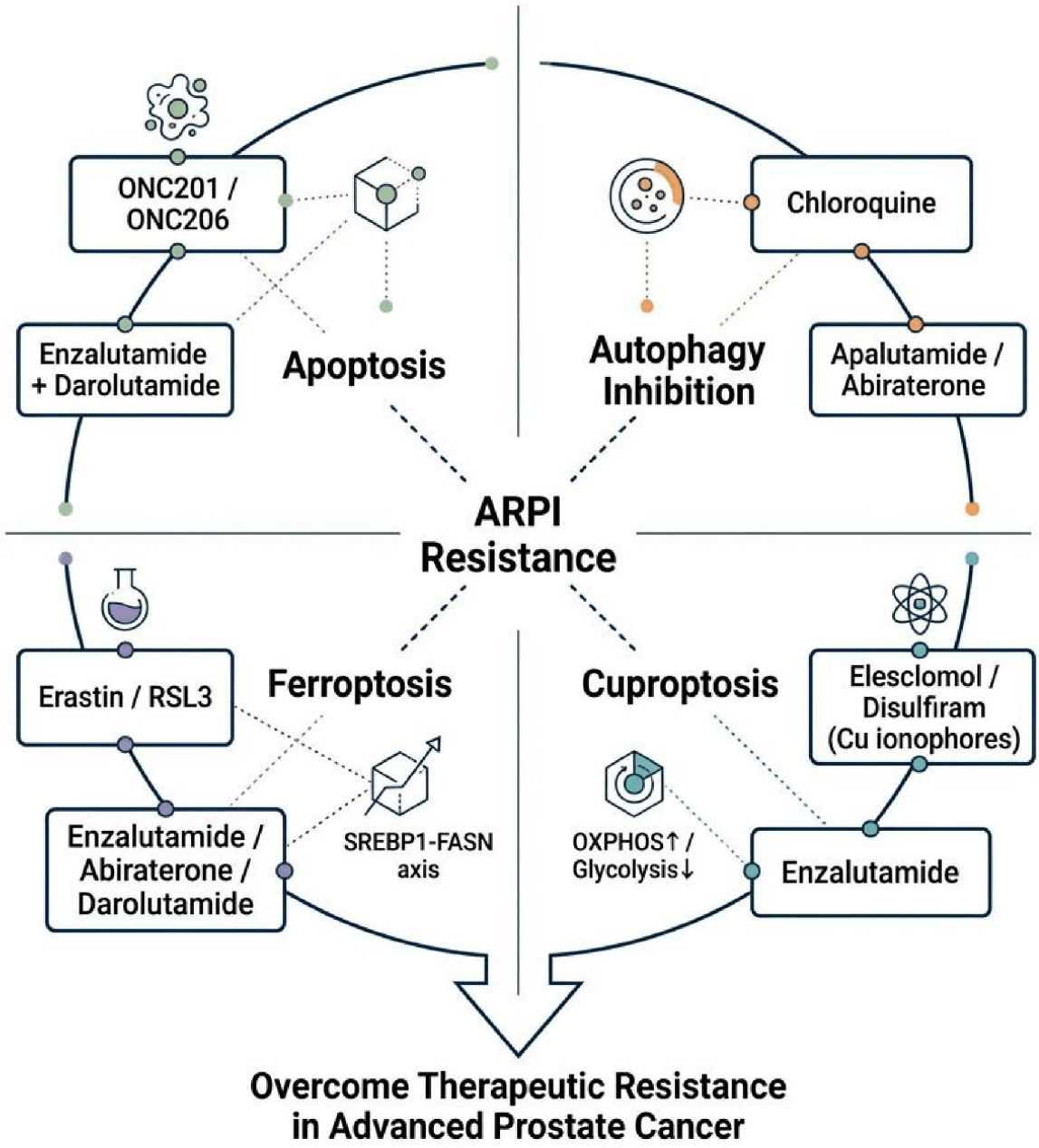


Fig. 4. Cell death mechanisms and inducers. Overview of cell death pathway modulation strategies—apoptosis, autophagy inhibition, ferroptosis, and cuproptosis—to overcome therapeutic resistance to ARPIs in advanced prostate cancer. The authors conceived the figure and designed the prompt instructions, while AI was used to generate the figure using Gamma (Gamma Tech, Inc., CA, USA; https://gamma.app/).

peroxidase 4 (GPX4), was observed in CRPC xenografts, indicating that these tumors remained susceptible to ferroptosis induction. Ferroptosis inducers erastin and ras-selective lethal 3 (RSL3) demonstrated marked antitumor activity in resistant models. Furthermore, the combinations of ferroptosis inducers with enzalutamide and abiraterone displayed stronger antitumor effects than ARPI monotherapy [34]. More recently, the antitumor effect of darolutamide with ferroptosis inducers, including erastin or RSL3, has been evaluated. Darolutamide inhibited the sterol regulatory element-binding protein 1 (SREBP1)–FASN axis, leading to increased lipid peroxidation and ferroptotic cell death. Combinations with darolutamide and ferroptosis inducers exhibited synergistic antitumor effects in PC cell lines, organoids, and xenografts compared with darolutamide-alone therapy [35].

The next target is cuproptosis, which is a form of regulated cell death mediated by copper accumulation and mitochondrial dysfunction. Enzalutamide reprogrammed cellular metabolism in PC through increased OXPHOS and re-

duced glycolysis, thereby rendering the cells more susceptible to cuproptosis. Combinations of enzalutamide with the copper ionophores elesclomol and disulfiram displayed stronger antitumor activity in EnzR cells [36].

Combination With Common Oncogenic Pathway Inhibitors

Accumulating evidence shows that the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) /mTOR axis is one of the drivers of therapeutic resistance in PC (Fig. 5). Previous studies demonstrated synergistic antitumor effects of the combination of enzalutamide and the Akt inhibitor AZD5363 in PC cell lines and CRPC xenografts. The combination treatment enhanced apoptosis and sustained tumor regression more than enzalutamide alone [37]. Subsequent studies extended this concept using a combination of darolutamide with the pan-PI3K inhibitor copanlisib, which inhibited the expression of PI3K isoforms, including PI3Kα, PI3Kβ, PI3Kδ, and PI3Kγ. Concurrent inhibition of AR and PI3K/Akt/mTOR pathways resulted in superior effects, including induction of apoptosis and suppression of tumor growth in AR^+ PC cell lines and androgen-sensitive patient-derived PC models [38]. Lately, another group of researchers evaluated the simultaneous use of a pan-PI3K inhibitor and darolutamide. They reported the antiproliferative effects of the combination of pan-PI3K/mTOR inhibitor gedatolisib with darolutamide in both PTEN-deficient and $PTEN^+$ PC, including AR^+ cells adapted to long-term darolutamide treatment. The combination treatment produced stronger antitumor and cytotoxic effects than either monotherapy in both darolutamide-sensitive and darolutamide-adapted cells. The antitumor effect of combination treatment was associated with the inhibition of AR and PI3K/Akt/mTOR signaling, leading to cell-cycle arrest, increased apoptosis, and suppression of glucose and lipid metabolism [39]. Angiogenesis-associated signaling pathways are attractive targets to delay or overcome therapeutic resistance in advanced PC. The expression of chemokine receptor C-X-C chemokine receptor type 7 (CXCR7) was activated following enzalutamide treatment in CRPC models. Thus, the researchers targeted CXCR7 with a selective inhibitor, CCX771, in combination with enzalutamide. The combination treatment decreased EGFR and Akt signaling and reduced Vascular endothelial growth factor receptor (VEGFR) expression, resulting in the inhibition of the angiogenic pathway. Also, tumor cell migration was reduced and tumor growth suppression increased in vertebral-Cancer of the Prostate (VCaP) xenografts and patient-derived xenograft models after combination treatment. Collectively, the combination of enzalutamide and CXCR7 inhibitor had a better suppressive effect on cancer cell proliferation compared with either agent alone [40].

Beyond the inhibition of angiogenic pathways, combination strategies involving AR-targeted agents and chemotherapy have gained considerable attention. Mout et al. [41] investigated whether persistent AR pathway inhibition can enhance the efficacy of taxane-based chemotherapy in CRPC. They evaluated the combination of enzalutamide and cabazitaxel in both an AR-positive CRPC model and an EnzR VCaP model. Despite the limited antiproliferative effect of enzalutamide alone, persistent enzalutamide treatment with cabazitaxel prolonged tumor control and improved therapeutic responses in both xenograft and patient-derived models. Besides persistent AR blockade, incomplete AR suppression has been identified as a leading cause of therapeutic resistance. Researchers used a combination of enzalutamide and AR antagonists to achieve complete AR blockade. They combined enzalutamide with tautomycin: the former inhibited the activity of residual AR signaling, whereas the latter enhanced the degradation of both full-length AR and AR-V7. This dual treatment exerted greater tumor-suppressive effects in PC cell lines than either treatment alone [42].

STAT3 has emerged as an important mediator of therapeutic resistance in prostate cancer. The activation of STAT3 has been implicated in resistance to antiandrogens such as enzalutamide and bicalutamide; the inhibition of STAT3 can reverse this resistance. The constitutive activation of STAT3 promoted tumor cell survival, proliferation, stemness-associated traits, and resistance to apoptosis. Hellsten et al. [43] reported that combining enzalutamide with the STAT3 inhibitor GPB730 significantly increased growth inhibition in both androgen-sensitive and CRPC models. The combination treatment suppressed AR-associated transcriptional programs and reduced the expression of c-MYC and survivin. These findings suggested that the inhibition of STAT3 signaling restored sensitivity to AR-targeted therapies.

Cyclin-dependent kinases (CDKs) have emerged as attractive therapeutic targets for overcoming resistance to AR-targeted therapies due to their vital roles in cell-cycle regulation and transcriptional control. Constantin et al. [44] evaluated the use of the CDK7 inhibitor CT7001 (samuraciclib) in CRPC models and reported that CDK7 inhibition suppressed proliferation and induced apoptosis. Additionally, combined treatment with the CDK7 inhibitor and enzalutamide resulted in greater inhibition of tumor growth than either monotherapy, suggesting that the dual targeting of AR signaling and cell-cycle progression can improve therapeutic responses in advanced prostate cancer. Building on the rationale of CDK targeting, Matsuoka et al. [45] identified flavopiridol as a potent CDK inhibitor, among a broad spectrum of inhibitors, which was capable of suppressing tumor growth in patient-derived xenograft models. The antitumor activity of flavopiridol was associated with reduced AR transcriptional activity, further supporting the concept that CDK inhibition can enhance the efficacy of AR-targeted therapies and sustain tumor growth inhibition and overcome therapeutic resistance.

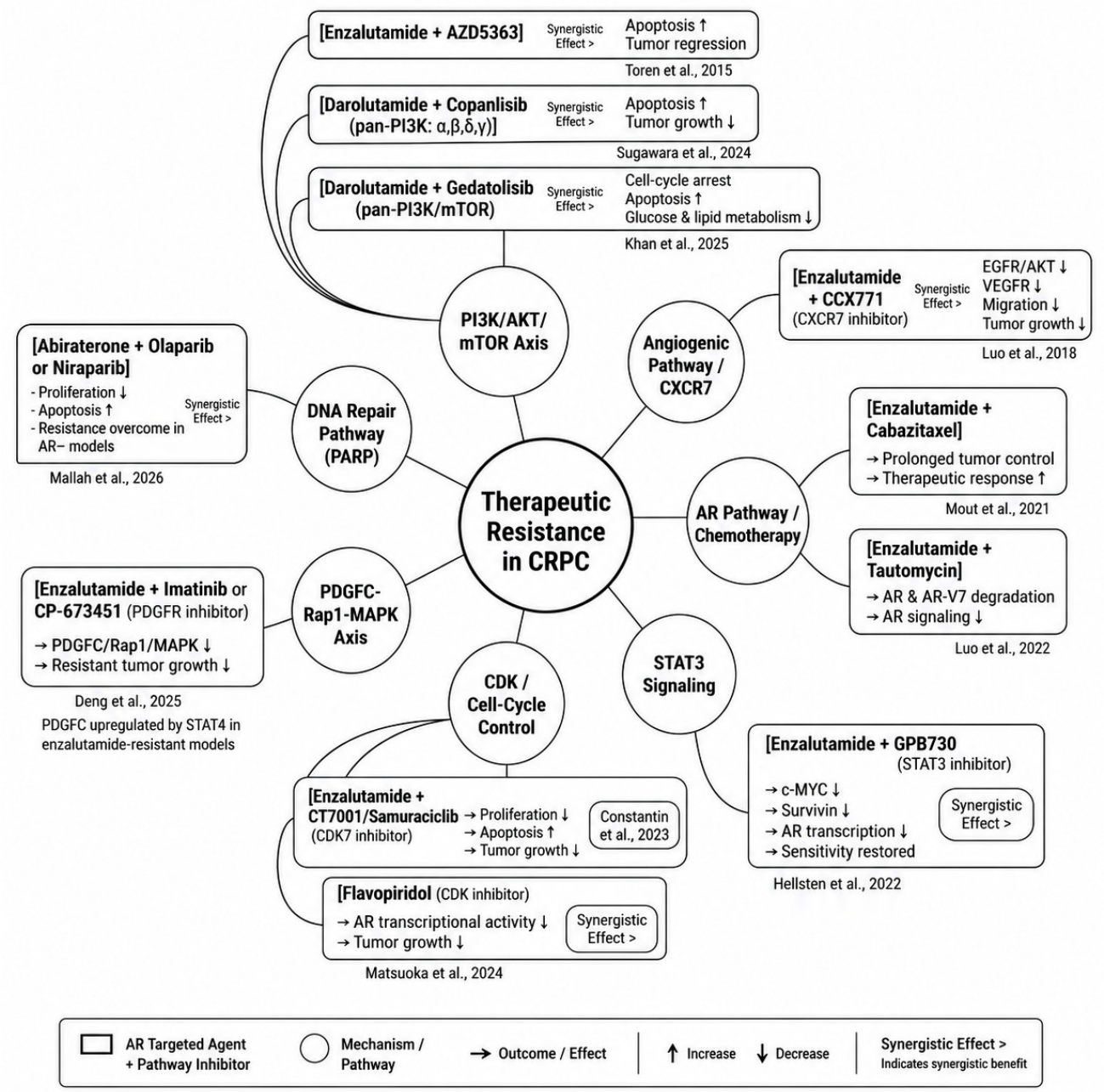


Fig. 5. Common oncogenic pathways and their inhibitors. Overview of combination strategies targeting common oncogenic and signaling pathways—PI3K/Akt/mTOR, DNA repair (PARP), angiogenesis, CDK/cell cycle control, and STAT3 signaling—to overcome therapeutic resistance in CRPC. The authors conceived the figure and designed the prompt instructions, while AI was used to generate the figure using Gamma (Gamma Tech, Inc., CA, USA; https://gamma.app/) and optimized by OpenAI Prism (https://prism.openai.com/). PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; mTOR, mechanistic target of rapamycin; CDK, Cyclin-dependent kinase; STAT3, signal transducer and activator of transcription 3; CRPC, castration-resistant prostate cancer.

Platelet-derived growth factor C (PDGFC) has recently emerged as a potential contributor to cancer progression and therapeutic resistance. Deng et al. [46] demonstrated that PDGFC expression was markedly elevated in EnzR prostate cancer models and transcriptionally upregulated by STAT4. Increased PDGFC expression promoted tumor growth by activating the downstream PDGFR–Ras-related protein 1/mitogen-activated protein kinase (Rap1–MAPK) signaling pathway. The genetic silencing of PDGFC using shRNA, as well as pharmacological inhibition of PDGFR with imatinib or CP-673451, enhanced the antitumor efficacy of enzalutamide and suppressed the growth of resistant tumors. Inhibition of the PDGFC–Rap1–MAPK axis restored sensitivity to enzalutamide and significantly impaired tumor progression in preclinical models. Collectively, these findings high-

light PDGFC-mediated signaling as a potentially targetable adaptive resistance mechanism in CRPC.

Targeting DNA repair pathways has also emerged as a promising strategy to enhance the efficacy of ARPIs. Mallah et al. [47] investigated the combination of abiraterone with the PARP inhibitors olaparib and niraparib in resistant metastatic prostate cancer cells. The combination treatment led to greater reductions in cell proliferation and tumor growth than either agent alone and significantly overcame resistance in both *in vitro* and xenograft models. These effects were observed in AR-negative prostate cancer models, suggesting that the therapeutic benefit did not solely depend on AR signaling. Mechanistic analyses indicated that the enhanced antitumor activity was primarily associated with increased apoptotic cell death. These findings supported the concept that simultaneous inhibition of AR signaling and DNA repair pathways can provide therapeutic benefit even after the development of resistance to AR-targeted therapy.

Clinical ARPI-Based Combination Therapies

ARPIs and Immune Therapies

Major completed and ongoing clinical trials evaluating combination therapies are summarized in Table 1 (Ref. [48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65]).

Immunotherapy has emerged as a transformative treatment modality for several malignancies over the past decade. However, its clinical efficacy in prostate cancer remains limited. Prostate cancer is generally considered an immunologically "cold" tumor, characterized by low T-cell infiltration, a low tumor mutational burden, and an immunosuppressive tumor microenvironment. Therefore, only a small subset of patients derives meaningful benefit from immunotherapeutic approaches. These limitations have prompted extensive investigation into combination strategies aimed at enhancing antitumor immune responses [66].

Sipuleucel-T is the first immunotherapy approved for treating prostate cancer. It is an autologous cellular vaccine generated through *ex vivo* activation of peripheral blood mononuclear cells with prostatic acid phosphatase fused to granulocyte–macrophage colony-stimulating factor, resulting in the activation of antigen-presenting cells. Based on a significant improvement in overall survival (OS) in patients with mCRPC, Sipuleucel-T received FDA approval in 2010. Despite prolonging OS, treatment with Sipuleucel-T did not significantly improve progression-free survival (PFS) or prostate-specific antigen (PSA) response rates [67].

Given the immunomodulatory effects of androgen deprivation therapy (ADT), the optimal sequencing of ADT and Sipuleucel-T has been investigated. The STAND trial demonstrated that administering Sipuleucel-T before initiating ADT in men with hormone-sensitive biochemically recurrent prostate cancer at high risk of metastasis elicited significantly greater and more durable antitumor immune responses than the reverse treatment sequence. Specifically, patients receiving Sipuleucel-T before ADT exhibited approximately twofold higher antigen-specific T-cell proliferation compared with those treated with ADT before Sipuleucel-T [68].

The combination of Sipuleucel-T with ARPIs, including abiraterone acetate and enzalutamide, has also gained considerable clinical interest. Retrospective analyses have suggested that patients receiving a combination of Sipuleucel-T and ARPI therapy experience significantly longer median OS than those treated with ARPI monotherapy (30.4 vs 14.3 months). Although these findings support a potential synergism between immune activation and AR blockade, no combination regimen involving Sipuleucel-T has yet been incorporated into routine clinical practice [69].

Immune checkpoint inhibitors (ICIs) represent the most widely used class of cancer immunotherapies. They are broadly categorized into programmed cell death protein 1 inhibitors (e.g., pembrolizumab, nivolumab, and cemiplimab), programmed death-ligand 1 (PD-L1) inhibitors (e.g., atezolizumab, avelumab, and durvalumab), and cytotoxic T-lymphocyte-associated protein 4 inhibitors (e.g., ipilimumab) [66].

Despite their success in several solid tumors, the clinical utility of ICIs in prostate cancer has been limited. Currently, pembrolizumab is the only ICI approved for prostate cancer. It is indicated exclusively for patients with mCRPC harboring high microsatellite instability or deficient mismatch repair. Since these molecular alterations are present in only approximately 2%–5% of prostate cancer cases, most efforts have focused on expanding the population of patients who may benefit from checkpoint inhibition through rational combination therapies [70].

Among ICIs, pembrolizumab has been extensively evaluated in combination with enzalutamide. The KEYNOTE-199 trial investigated the use of pembrolizumab in patients with mCRPC who had progressed on enzalutamide and demonstrated only modest antitumor activity [71]. Subsequently, the KEYNOTE-365 trial evaluated the use of pembrolizumab plus enzalutamide in patients with mCRPC following disease progression or intolerance to abiraterone acetate. Although the combination exhibited manageable safety, it failed to demonstrate a clinically meaningful improvement compared with the historical outcomes of enzalutamide alone [48]. Furthermore, the Phase III KEYNOTE-641 trial did not demonstrate a survival benefit from adding pembrolizumab to enzalutamide, indicating that checkpoint inhibition does not improve clinical outcomes in unselected patients with mCRPC [49].

The efficacy of pembrolizumab has also been investigated in the metastatic hormone-sensitive prostate cancer (mHSPC) setting. Clinical trials comparing ADT plus enzalutamide with or without pembrolizumab also

Table 1. Major completed and ongoing clinical trials evaluating combination therapies in advanced prostate cancer.

Trial	Year of publication/ reporting	Phase	Population	Treatment	Biomarker	*n*	Primary endpoint	Median follow-up	Key findings	Status	Reference
Immunotherapy-based combinations											
KEYNOTE-365	2024	Ib/II	mCRPC	Pembrolizumab + Enzalutamide	None	102	Safety/PSA	51 mo	Limited efficacy	Completed	[48]
KEYNOTE-641	2025	III	mCRPC	Pembrolizumab + Enzalutamide	None	1243	rPFS, OS	~28 mo	Negative	Negative	[49]
IMbassador250	2022	III	mCRPC	Atezolizumab + Enzalutamide	None	759	OS	34 mo	Negative	Negative	[50]
STARVE-PC	2021	II	mCRPC	Nivolumab + Ipilimumab ± Enzalutamide	None	100	PSA response	14 mo	No added benefit	Completed	[51]
ARPI- and chemotherapy-based combinations											
ENZAMET	2023	III	mHSPC	ADT + Enzalutamide + Docetaxel	None	1125	OS	68 mo	Improved OS	Practice-changing	[52]
PEACE-1	2022	III	de novo mHSPC	ADT + Docetaxel ± Abiraterone	None	1173	rPFS, OS	4.4 y	Improved rPFS and OS	Practice-changing	[53]
ARASENS	2025	III	mHSPC	ADT + Docetaxel ± Darolutamide	None	1306	OS	43.7 mo	Reduced death risk	Approved	[54]
PARP inhibitor–based combinations											
PROpel	2022	III	mCRPC	Olaparib + Abiraterone	All	796	rPFS	24.8 mo	Improved rPFS	Approved	[55]
MAGNITUDE	2023	III	HRR+ mCRPC	Niraparib + Abiraterone	HRR+	423	rPFS	26.8 mo	Benefit in HRR+	Approved	[57]
TALAPRO-2	2023	III	mCRPC	Talazoparib + Enzalutamide	All	805	rPFS	24.9 mo	Improved rPFS	Approved	[56]
AMPLITUDE	2025	III	HRR+ mCSPC	Niraparib + Abiraterone + ADT	HRR+	696	rPFS	30.8 mo	Improved rPFS	Approved	[58]
TALAPRO-3	2026	III	HRR+ mCSPC	Talazoparib + Enzalutamide + ADT	HRR+	~550	rPFS	Ongoing	Recruiting	Ongoing	[59]

Table 1. Continued.

Trial	Year of publication/ reporting	Phase	Population	Treatment	Biomarker	*n*	Primary endpoint	Median follow-up	Key findings	Status	Reference
EvoPAR-Prostate01	2026	III	mHSPC	Saruparib + physician's choice ARPI + ADT	HRRm and non-HRRm	~1800 (planned; 550 HRRm, 1250 non-HRRm)	rPFS (primary); OS (key secondary)	Ongoing	Global registrational trial evaluating first-line PARP inhibition in mHSPC	Ongoing	[61]
PETRANHA	2026	I/IIa	mHSPC	Saruparib + ARPI + ADT	HRRm and non-HRRm	93	Safety, ORR, uPSA response	Ongoing	Demonstrated encouraging activity with manageable safety; supports Phase III development regardless of HRR status	Ongoing/positive early results	[60]
Radioligand and targeted therapies											
ENZA-p	2024	II	mCRPC	177Lu-PSMA-617 + Enzalutamide	PSMA+	162	PSA-PFS	20 mo	Delayed progression	Positive	[62]
PSMAddition	2025	III	mHSPC	177Lu-PSMA-617 + ARPIs + ADT	PSMA+	1126	rPFS	Interim	Positive interim	Ongoing	[63]
CAPItello-281	2026	III	PTEN-deficient mHSPC	Capivasertib + Abiraterone + ADT	PTEN	~1000	rPFS	Ongoing	Recruiting	Ongoing	[65]
TulmiSTAR-02 (NCT07190300)	2026	I/II	mHSPC	Tulmimetostat + darolutamide or tulmimetostat + abiraterone + ADT	None	181 (estimated)	Phase I: recommended dose for expansion, safety, and tolerability; Phase II: biochemical response rate; secondary endpoints include rPFS and OS	Not yet available	Evaluates EZH1/2 inhibition as a novel targeted combination with ARPIs in mHSPC	Ongoing; recruiting	[64]

PSA, prostate-specific antigen; rPFS, radiographic progression-free survival; OS, overall survival; mHSPC, metastatic hormone-sensitive prostate cancer; ADT, androgen deprivation therapy; ORR, objective response rate; PSMA, prostate-specific membrane antigen; PTEN, phosphatase and tension homolog; EZH1/2, enhancer of zeste homolog 1/2.

failed to demonstrate additional clinical benefit from pembrolizumab [72]. Collectively, these findings indicate that, despite a strong biological rationale, combining pembrolizumab with AR pathway inhibition has not translated into improved clinical outcomes in either mCRPC or mHSPC. Future studies should focus on improved patient selection through predictive biomarkers and the development of novel combination strategies capable of overcoming the immunologically cold tumor microenvironment characteristic of prostate cancer.

Although atezolizumab has not been approved for treating prostate cancer, its combination with enzalutamide was evaluated in the Phase III IMbassador250 trial in patients with mCRPC. The addition of atezolizumab to enzalutamide did not improve OS compared with enzalutamide monotherapy, and hence the trial failed to meet its primary endpoint. Despite the overall negative outcome, exploratory biomarker analyses identified subgroups of patients who derived greater benefit from combination therapy. Specifically, elevated PD-L1 expression, increased infiltration of CD8+ T cells, and an interferon-γ-related gene expression signature were associated with improved PFS. Although these biomarker-defined populations represent only a small proportion of patients with mCRPC, these findings underscore the importance of biomarker-driven patient selection for future immunotherapy-based combination strategies [50].

Another approach to enhancing antitumor immunity involves combining ICIs with distinct mechanisms of action. The Phase II STARVE-PC (Study of Combined Immune Checkpoint Blockade for AR-V7–Expressing Metastatic Castration-Resistant Prostate Cancer) trial evaluated dual immune checkpoint blockade with nivolumab and ipilimumab, with or without the addition of enzalutamide, in patients with mCRPC who had progressed on prior enzalutamide therapy. Although the study was limited by its relatively small sample size, the addition of enzalutamide to dual checkpoint inhibition did not improve clinical outcomes compared with nivolumab plus ipilimumab alone [51].

Overall, the available clinical evidence indicates that combining ARPIs with ICIs has not yielded meaningful clinical benefit in unselected patients with advanced prostate cancer. Nevertheless, several important questions remain unresolved. Future studies should determine whether biomarker-guided patient selection can identify subgroups more likely to respond to combination therapy and whether recently developed or next-generation ICIs, novel immunotherapeutic agents, or alternative combination strategies can overcome the immunologically “cold” tumor microenvironment characterizing prostate cancer.

Taxanes and ARPIs

Taxanes represent a cornerstone of systemic chemotherapy for advanced prostate cancer, particularly in patients with mCRPC. The two taxanes currently approved for prostate cancer treatment, docetaxel and cabazitaxel, exert their antitumor effects primarily by stabilizing microtubules, thereby disrupting mitotic spindle dynamics and inhibiting cell division. Besides their cytotoxic activity, taxanes impair AR signaling by preventing microtubule-dependent AR nuclear translocation, resulting in the suppression of AR-mediated transcriptional activity. Docetaxel was approved for treating mCRPC in 2004, followed by cabazitaxel in 2010.

The introduction of second-generation ARPIs provided an effective alternative to taxane chemotherapy, leading to substantial changes in the therapeutic landscape of advanced prostate cancer. More recently, treatment strategies have shifted toward the earlier integration of ARPIs with taxane-based chemotherapy in patients with mHSPC. This approach aims to achieve more profound suppression of AR signaling and delay, or potentially prevent, progression to castration-resistant prostate cancer.

The ENZAMET trial evaluated the addition of enzalutamide to ADT in patients with mHSPC and demonstrated a significant improvement in long-term OS after a median follow-up of approximately 6 years. Although the evaluation of triplet therapy was not the primary objective of the trial, a prespecified subgroup analysis examined patients who received concurrent docetaxel. In this subgroup, the addition of enzalutamide was associated with a hazard ratio for OS of 0.82 (95% CI, 0.63–1.06), which did not reach statistical significance. However, as concurrent docetaxel use was not randomized and the trial was not powered to compare triplet versus doublet therapy, these findings should be interpreted cautiously and do not definitively exclude a potential benefit of triplet therapy [52,73,74,75].

In contrast, several subsequent Phase III trials have demonstrated clear clinical benefits of combining ARPIs with ADT and docetaxel. The PEACE-1 trial showed that the addition of abiraterone acetate to ADT and docetaxel significantly prolonged radiographic PFS and OS in patients with *de novo* high-volume mHSPC [53]. Similarly, the ARASENS trial demonstrated that the addition of darolutamide to ADT and docetaxel significantly reduced the risk of death compared with ADT plus docetaxel alone, thus establishing a substantial OS benefit [54,76]. Collectively, these findings support the concept of treatment intensification through triplet therapy and have established the combination of ADT, docetaxel, and selected ARPIs as a standard-of-care option for appropriately selected patients with mHSPC, particularly those with high-volume or *de novo* metastatic disease.

ARPIs and PARP Inhibitors

PARP inhibitors have become an integral component of precision medicine for advanced prostate cancer, particularly in tumors harboring defects in homologous recombination repair (HRR). Olaparib was the first PARP in-

hibitor approved for treating mCRPC, receiving regulatory approval in 2020 for patients with deleterious alterations in HRR-related genes, including BRCA1 DNA repair associated (*BRCA1*), *BRCA2*, and ataxia-telangiectasia mutated (*ATM*) [77]. Subsequently, in 2023, the combination of olaparib and abiraterone was approved for patients with BRCA-mutated mCRPC, reflecting the growing clinical interest in combining PARP inhibition with ARPIs [55].

Since then, several additional PARP inhibitor–based regimens have entered clinical practice. Rucaparib was approved following the TRITON2 and TRITON3 clinical trials, whereas the combination of talazoparib and enzalutamide gained approval for patients with HRR-deficient mCRPC based on the TALAPRO-2 trial [56,78]. Likewise, the combination of niraparib and abiraterone was approved in 2023 for patients with HRR-altered mCRPC [57]. More recently, the indications for PARP inhibitor–based therapy have expanded to include selected patients with mCSPC, particularly those harboring BRCA2 alterations, following the encouraging results of the AMPLITUDE and MAGNITUDE trials [58,79].

Given the success of these combinations in mCRPC, ongoing clinical trials are investigating whether PARP inhibitors can be incorporated earlier in the disease course. The Phase III TALAPRO-3 trial is evaluating the efficacy of talazoparib combined with enzalutamide in patients with mCSPC to determine whether this combination can further delay disease progression when administered in the hormone-sensitive setting [59].

The development of next-generation PARP inhibitors has focused on improving target selectivity while minimizing treatment-related toxicity. Saruparib, a highly selective PARP1 inhibitor, represents one such agent currently undergoing clinical evaluation. The Phase I/II PETRANHA trial is investigating the efficacy of triplet therapy consisting of ADT, an ARPI (enzalutamide, abiraterone, or darolutamide), and saruparib in patients with mHSPC. Early clinical results have demonstrated encouraging objective response rates irrespective of HRR mutation status, suggesting that selective PARP1 inhibition can provide therapeutic benefit beyond biomarker-defined populations [60]. Similarly, the EvoPAR-Prostate01 trial is evaluating the use of saruparib in combination with standard ARPI therapy in patients with mHSPC stratified according to HRR mutation status, thereby providing further insight into the potential role of PARP inhibition in both HRR-mutant and HRR-proficient disease [61].

Although several combinations of PARP inhibitors and ARPIs have already been incorporated into the treatment paradigm for mCRPC, their role in mHSPC is still under investigation. Ongoing studies should determine whether earlier implementation of these combinations can further improve clinical outcomes and delay progression to castration-resistant disease. In parallel, the emergence of next-generation PARP1-selective inhibitors offers an opportunity to enhance therapeutic efficacy while reducing toxicity, making their integration with second-generation ARPIs a promising direction for future clinical development.

ARPIs and Prostate-Specific Membrane Antigen–Based Therapies

Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein highly overexpressed in prostate cancer, particularly in advanced and metastatic disease. Its restricted expression in normal tissues and abundant expression in prostate cancer cells have established PSMA as an attractive target for both molecular imaging and targeted therapy. To date, the only clinically approved PSMA-targeted therapeutic modality is radioligand therapy with 177Lu-PSMA-617, which received regulatory approval in 2022 for treating patients with mCRPC based on the VISION trial [80,81].

The combination of PSMA-targeted radioligand therapy with ARPIs has recently emerged as a promising therapeutic strategy. The Phase II ENZA-p trial evaluated the addition of 177Lu-PSMA-617 to enzalutamide in patients with mCRPC. Compared with enzalutamide monotherapy, the combination demonstrated improvements in OS and quality-of-life outcomes, supporting the potential synergistic interaction between AR inhibition and PSMA-targeted radioligand therapy [62,82].

Given these encouraging findings, PSMA-targeted therapy is now being investigated in earlier stages of disease. The Phase III PSMAddition trial evaluated the addition of 177Lu-PSMA-617 to the current standard of care, comprising ADT plus an ARPI, in patients with PSMA-positive mHSPC. Preliminary Phase III results demonstrated a significant improvement in radiographic progression-free survival (rPFS), suggesting that incorporation of PSMA-targeted radioligand therapy into first-line treatment may further improve disease control in selected patients [63].

Additional PSMA-targeted therapeutic strategies are also under clinical investigation. The ongoing Phase I/II trial (NCT03724747) is evaluating the safety and efficacy of the investigational PSMA-Targeted Thorium Conjugate (BAY 2315497) in combination with darolutamide in patients with mCRPC. This approach employs an alpha-emitting radionuclide conjugated to a PSMA-targeting ligand with the aim of enhancing tumor-specific cytotoxicity while minimizing off-target toxicity. The clinical results from this study are awaited [83].

Additionally, several novel targeted combinations with ARPIs are currently undergoing clinical evaluation. The recently initiated Tulmimetostat-02 (TulmiSTAR-02) trial is investigating tulmimetostat, EZH1/2 inhibitor, in combination with either darolutamide or abiraterone in patients with mHSPC. The study, recently presented at the 2026 American Society of Clinical Oncology (ASCO) An-

nual Meeting, is currently ongoing, and its efficacy data have not yet been reported [64].

Another important investigational strategy is represented by the Phase III CAPItello-281 trial, which is evaluating the addition of capivasertib, a selective Akt inhibitor, to abiraterone in combination with ADT for patients with mHSPC. Although recurrent oncogenic mutations are relatively uncommon in prostate cancer, the loss of PTEN, a key negative regulator of the PI3K/Akt signaling pathway, represents one of the most frequent molecular alterations and defines a biologically distinct disease subtype. Consequently, the inhibition of Akt signaling may provide a rational therapeutic approach for patients with PTEN-deficient tumors and further enhance the efficacy of AR pathway inhibition [65].

Collectively, these ongoing studies illustrate the expanding landscape of combination therapies integrating ARPIs with targeted agents directed against complementary oncogenic pathways. PSMA-targeted radioligand therapy has already demonstrated encouraging clinical activity. However, the therapeutic potential of emerging approaches—alpha-emitting PSMA-targeted conjugates, epigenetic modulators, and PI3K/Akt pathway inhibitors—remains to be established in prospective randomized clinical trials. The results of these studies may help determine whether these combinations can further improve long-term outcomes and extend the benefits of treatment intensification to broader populations of patients with advanced prostate cancer.

Conclusions

Combination therapies have become an integral component of the therapeutic landscape for prostate cancer, with several doublet and triplet regimens already incorporated into clinical practice. Numerous additional strategies are under evaluation in preclinical studies and clinical trials. Despite this progress, most clinically approved combinations rely on integrating existing standard-of-care therapies rather than introducing novel therapeutic partners or mechanistically innovative approaches. This underscores the need to identify promising combination strategies through robust preclinical research and establish more efficient translational pipelines that facilitate their progression into clinical evaluation and eventual routine practice.

Another key consideration is the optimal timing of combination therapy. Given that intrinsic and acquired resistance to single-agent treatments continue to limit long-term therapeutic efficacy, whether introducing rational combination regimens earlier in the treatment algorithm can delay resistance, prolong disease control, and ultimately improve patient outcomes remains unclear. Addressing these questions may require well-designed translational studies and prospective clinical trials aimed not only at evaluating novel combinations but also at defining the most effective treatment sequence, patient selection criteria, and biomarker-driven strategies. Such efforts have the potential to enhance the clinical benefits of combination therapies and further improve outcomes for patients with prostate cancer.

Availability of Data and Materials

Not applicable.

Author Contributions

UD designed the study; UD and RES collected and analyzed the data. UD and RES have been involved in drafting the manuscript and both authors have been involved in revising it critically for important intellectual content. Both authors gave final approval of the version to be published. Both authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

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The authors declare no conflict of interest.

Declaration of Generative AI and AI-Assisted Technologies in Manuscript Preparation

During the preparation of this manuscript, the authors used ChatGPT for language checking/grammar correction The authors conceived the figure and designed the prompt instructions, while AI was used to generate the draft figures with NotebookLM (Google LLC; accessed on 30 June 2026) and Gamma (Gamma Tech, Inc.; accessed on 30 June 2026). The resulting figure was subsequently optimized and finalized using OpenAI Prism (https://prism.openai.com/; accessed on 22 September 2026). After using AI-assisted tools, the authors thoroughly reviewed, verified, and revised all content to ensure accuracy and originality.

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