



CODEN [USA]: IAJPBB

ISSN : 2349-7750

INDO AMERICAN JOURNAL OF  
**PHARMACEUTICAL SCIENCES**

SJIF Impact Factor: 7.187

<https://doi.org/10.5281/zenodo.20512987>

Available online at: <http://www.iajps.com>

Research Article

**TARGETING THE PI3K/AKT/MTOR PATHWAY IN  
PROSTATE CANCER: OVERCOMING RESISTANCE VIA  
COMBINATION STRATEGIES**

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**Abstract:**

*Prostate cancer remains a leading malignancy in men worldwide, with aberrant activation of the PI3K/AKT/mTOR signaling pathway recognized as a central driver of disease progression and therapeutic resistance. Loss of PTEN and recurrent mutations in PIK3CA, AKT, and mTOR sustain oncogenic signaling, promoting castration-resistant prostate cancer (CRPC). The pathway's reciprocal crosstalk with androgen receptor (AR), MAPK, and WNT signaling underscores its role at the crossroads of multiple oncogenic networks, complicating monotherapy approaches. A wide spectrum of inhibitors—including pan-PI3K, isoform-selective PI3K, AKT, mTOR, and dual PI3K/mTOR agents—have demonstrated biological activity, yet clinical outcomes remain modest due to compensatory signaling and toxicity. Emerging strategies emphasize rational combination therapies, particularly with AR blockade, PARP inhibitors, immune checkpoint inhibitors, and chemotherapy, to enhance efficacy and overcome resistance. Novel dual-targeted agents such as PI3K/HDAC inhibitors further highlight the potential of multipathway inhibition in biomarker-defined patient populations. Collectively, these advances position PI3K-targeted therapies as a cornerstone of next-generation prostate cancer management, offering promise for durable outcomes in CRPC.*

**Key words :**PI3K, AKT, mTOR, PTEN, Resistance

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Please cite this article in press Fathima Rasma K et al., Targeting The Pi3k/Akt/Mtor Pathway In Prostate Cancer: Overcoming Resistance Via Combination Strategies..., Indo Am. J. P. Sci, 2026; 13(05).

**INTRODUCTION:**

Prostate cancer is characterized by abnormal cell growth in the prostate gland, commonly detected through elevated prostate-specific antigen (PSA) levels.<sup>1</sup> Early disease is often asymptomatic and slow-growing, but advanced stages may present with urinary difficulties, nocturia, retention, and back pain due to skeletal metastasis.<sup>2</sup> Established risk factors include older age, genetic predisposition, ethnicity, family history, and lifestyle influences such as diets high in saturated fats and red meat, low fruit and vegetable intake, obesity, inactivity, chronic inflammation, hyperglycemia, and environmental exposures.<sup>3</sup> Globally, prostate cancer is the second most frequently diagnosed malignancy in men, accounting for over 1.4 million new cases and 358,989 deaths in 2018.<sup>2</sup> Management strategies vary by stage: active surveillance for low-risk disease; radical prostatectomy or radiation therapy for localized cancer; androgen deprivation therapy for advanced disease; and, in metastatic or resistant cases, hormonal agents, chemotherapy, targeted therapies, immunotherapy, and radiopharmaceuticals.<sup>4</sup>

The PI3K/Akt/mTOR signaling pathway is a central intracellular cascade regulating cell survival, growth, and apoptosis. Following extracellular stimulation, PI3K translocates to the plasma membrane and generates phosphatidylinositol (3,4,5)-triphosphate (PIP3), which recruits Akt for activation by 3-phosphoinositide-dependent protein kinase-1.<sup>5</sup> Activated Akt and mTOR inhibit apoptosis, enhance cancer cell survival, and drive prostate cancer (PCa) progression. Dysregulation of this pathway is a hallmark of PCa, with PTEN inactivation representing a major mechanism underlying aberrant Akt activation.<sup>6</sup>

Akt activation is strongly associated with the development of androgen-independent prostate cancer (AIPC). Experimental studies have demonstrated that long-term culture of LNCaP cells in serum sustains Akt activation, promoting transition to an androgen-independent state. Clinically, activated Akt correlates with aggressive disease features and poor prognosis, underscoring its role in therapy resistance and disease progression. Consequently, the PI3K/Akt/mTOR axis is recognized as a critical target for therapeutic intervention in prostate cancer.<sup>7</sup>

The PI3K/AKT/mTOR signaling pathway is a critical intracellular cascade whose hyperactivation is strongly linked to tumor progression in multiple cancers, including breast, gastric, ovarian, colorectal, prostate, glioblastoma, and endometrial malignancies. PI3K serves as a central hub connecting upstream growth signals to downstream

processes such as protein synthesis, metabolism, inflammation, cell survival, motility, angiogenesis, and tumor progression. Structurally, PI3Ks are lipid kinases that phosphorylate the 3'-OH group of phosphatidylinositol at the plasma membrane. Identified more than 25 years ago in association with viral oncoproteins, PI3Ks are classified into three groups: class I, class II, and class III.<sup>8</sup>

Class IA enzymes consist of catalytic subunits (p110 $\alpha$ , p110 $\beta$ , p110 $\delta$ ) encoded by PIK3CA, PIK3CB, and PIK3CD, and regulatory subunits (p85 $\alpha$ , p55 $\alpha$ , p50 $\alpha$ , p85 $\beta$ , p55 $\gamma$ ) encoded by PIK3R1, PIK3R2, and PIK3R3. Class IB contains a single catalytic subunit, p110 $\gamma$ , with regulatory partners p84 and p101. Class II comprises three monomeric isoforms, whose roles remain less defined but are increasingly recognized in signal transduction. Class III is represented by Vps34, first discovered in yeast, which integrates nutrient-responsive signaling across eukaryotes<sup>8</sup>

PI3K activity is stimulated mainly by receptor tyrosine kinases, but also by GPCRs and oncogenes such as Ras, which directly interact with p110. Upon activation, PI3K converts PIP2 into PIP3, a second messenger that recruits pleckstrin homology (PH) domain-containing proteins to the membrane. Dysregulated PI3K signaling is frequent in cancer, with distinct oncogenic roles for its catalytic isoforms. Mutations in PIK3CA (p110 $\alpha$ ) are found in colon, lung, prostate, liver, and brain cancers, driving cell cycle progression and angiogenesis, thereby supporting metastasis. The p110 $\alpha$  isoform is essential for tumors driven by receptor tyrosine kinases and oncogenes, whereas p110 $\beta$  is critical for GPCR signaling and the development of high-grade prostatic intraepithelial neoplasia.<sup>9</sup>

In PTEN-deficient prostate cancer models, deletion of p110 $\beta$ —but not p110 $\alpha$ —suppressed tumorigenesis and reduced AKT phosphorylation. Consistent with recent findings, inhibition of p110 $\alpha$  has minimal impact in PTEN-null castration-resistant prostate cancer, whereas genetic or pharmacological targeting of p110 $\beta$  markedly impairs tumor progression. These observations highlight the isoform-specific contributions of PI3K catalytic subunits to oncogenesis and underscore their relevance as therapeutic targets.<sup>9</sup> The PI3K/AKT/mTOR pathway is among the most frequently altered signaling cascades in human cancers. In prostate cancer, aberrations often involve PTEN loss and mutations in components such as PIK3CA, AKT1, AKT2, and mTOR, which drive pathway hyperactivation, promote tumor progression, and contribute to treatment resistance.<sup>9</sup>

**PI3K/AKT/mTOR pathway and its dysregulation in prostate Cancer**

The PI3K/AKT/mTOR pathway is one of the most frequently altered signaling cascades in prostate cancer, with PTEN loss or mutation representing the predominant mechanism of aberrant activation. PTEN normally functions as a lipid phosphatase, converting PIP3 back to PIP2 and thereby restraining PI3K activity. Its inactivation leads to sustained AKT phosphorylation and persistent mTOR signaling, driving uncontrolled cell proliferation, metabolic reprogramming, and tumor progression. Beyond PTEN, mutations in PIK3CA (encoding p110 $\alpha$ ), AKT isoforms, and mTOR contribute to pathway hyperactivation. Isoform-specific dependence is particularly notable: in PTEN-deficient prostate cancer, deletion of p110 $\beta$ —but not p110 $\alpha$ —suppresses tumorigenesis, underscoring the unique role of p110 $\beta$  in castration-resistant disease. These molecular alterations collectively sustain oncogenic signaling and promote progression to advanced stages. Clinically, dysregulation of this pathway is strongly associated with androgen-independent prostate cancer (AIPC) and castration-resistant prostate cancer (CRPC). Experimental studies demonstrate that prolonged Akt activation in LNCaP cells promotes transition to androgen independence, while patient data show that activated Akt correlates with aggressive features and poor prognosis. Importantly, reciprocal crosstalk between AR and PI3K/AKT/mTOR signaling creates a feedback loop: AR inhibition upregulates PI3K/AKT activity, whereas PI3K blockade enhances AR signaling. This interplay undermines monotherapy approaches and explains why resistance to androgen receptor signaling inhibitors (ARSIs) is common in CRPC. Together, these findings highlight the pathway's dual role in driving tumor biology and mediating therapy resistance, making it a critical focus for targeted intervention in prostate cancer.<sup>11</sup>

#### **Inhibitors of PI3K/AKT/mTOR signaling pathway**

Inhibitors targeting the PI3K/AKT/mTOR pathway have been developed in several forms, including pan-PI3K inhibitors, isoform-specific PI3K inhibitors, AKT inhibitors, mTOR inhibitors, and dual PI3K/mTOR inhibitors. These compounds have been tested in prostate cancer, particularly in castration-resistant disease where pathway activation is common. However, Shorning et al. (2020) point out that clinical outcomes have been modest, as single-agent therapy often leads to compensatory signaling and feedback activation of parallel pathways. They emphasize that while these inhibitors demonstrate biological activity, their limited efficacy and tolerability highlight the need for combination approaches, especially with androgen receptor blockade, to achieve more durable therapeutic benefit.<sup>12</sup>

### **The PI3K/AKT/mTOR Pathway at the Crossroads of AR, MAPK, and WNT Signaling**

#### **Introduction**

The PI3K/AKT/mTOR pathway represents one of the most frequently altered signaling cascades in prostate cancer. It functions as a central hub, integrating signals from androgen receptor (AR), MAPK, and WNT pathways. This positioning at the “crossroads” of multiple oncogenic networks explains its critical role in tumor progression and therapeutic resistance.

#### **Interaction with AR Signaling**

The androgen receptor remains the dominant driver of prostate cancer biology. A reciprocal feedback loop exists between AR and PI3K/AKT/mTOR: suppression of AR activity enhances PI3K/AKT signaling, while inhibition of PI3K/AKT/mTOR increases AR activity. This bidirectional relationship undermines monotherapy approaches and contributes to resistance against androgen deprivation and AR-targeted therapies.

#### **Interaction with MAPK Signaling**

The RAS/MAPK cascade promotes proliferation and survival through ERK activation. In prostate cancer, MAPK signaling cooperates with PI3K/AKT/mTOR to reinforce oncogenic growth. Genetic changes such as MAP3K7 deletion further strengthen this interaction, creating overlapping survival signals that complicate therapeutic targeting.

#### **Interaction with WNT Signaling**

Aberrant WNT/ $\beta$ -catenin signaling supports tumor stemness, migration, and progression. WNT interacts with both PI3K/AKT/mTOR and AR signaling, forming a cooperative network that sustains drug resistance. This integration allows tumors to bypass single-pathway inhibition, highlighting the importance of understanding WNT-PI3K-AR crosstalk for effective therapy design.<sup>9</sup>

#### **Therapeutic Implications**

Because PI3K/AKT/mTOR sits at the intersection of AR, MAPK, and WNT, inhibitors targeting this pathway alone have shown limited efficacy. Classes of inhibitors include pan-PI3K, isoform-specific PI3K, AKT, mTOR, and dual PI3K/mTOR agents, but their clinical impact has been modest due to toxicity and compensatory signaling. Rational combination strategies, particularly with AR blockades, are considered more promising for achieving durable therapeutic benefit.<sup>9</sup>

### Genetic Aberrations in the PI3K-AKT-mTOR Pathway in Prostate Cancer Are Diverse

Augmented phosphorylation and activation of key PI3K-AKT-mTOR pathway components, such as p-AKT and p-mTOR, have been consistently correlated with prostate cancer progression in clinical settings. Genomic and transcriptomic analyses reveal that genetic alterations and deregulated expression of PI3K pathway genes are highly prevalent, occurring in approximately 42% of primary and nearly all metastatic prostate cancers. Among these, PTEN loss-of-function represents the most frequent and critical driver of pathway deregulation. To comprehensively assess the frequency and diversity of PI3K-AKT-mTOR aberrations, three major prostate cancer genomic datasets (MSKCC/DFCI, TCGA, and SU2C-PCF IDT) were interrogated using cBioportal across 68 pathway-related genes. The analysis demonstrated that genetic alterations are widespread and often co-occur, with recurrent events including PTEN deletion/mutation (16.4–32.0%), DEPTOR amplification (5.1–21.4%), SGK3 mutation/amplification (5.6–20.5%), FOXO1/3 deletion (up to 15.2%), MAP3K7 deletion (5.9–14.8%), RRAGD deletion (6.5–14.4%), SESN1 mutation/deletion (5.4–13.6%), and PIK3CA mutation/amplification (5.5–11.5%). Less frequent but notable aberrations were also detected in AMPK subunits (PRKAB1/2 amplification) and regulators such as CAMKK2 and LKB1 deletion. Collectively, these findings underscore the central role of PI3K-AKT-mTOR pathway deregulation in prostate cancer biology, highlighting both the prevalence and heterogeneity of genetic events that contribute to disease progression.<sup>9</sup>

### PI3K Targeted treatment for prostate cancer

Aberrant activation of the PI3K-AKT-mTOR pathway is a defining feature of prostate cancer progression. Clinical and genomic profiling demonstrates that pathway deregulation occurs in ~42% of primary and nearly all metastatic prostate cancers, with PTEN loss-of-function as the most frequent driver. Additional recurrent genetic events include alterations in DEPTOR, SGK3, FOXO1/3, MAP3K7, RRAGD, SESN1, PIK3CA, and PDPK1, underscoring the heterogeneity and co-occurrence of PI3K-AKT-mTOR aberrations in patient cohorts

Functionally, mTOR activation suppresses glycogen synthase kinase-3 (GSK-3) and caspase-3 signaling, reducing reactive oxygen species (ROS) production and thereby inhibiting apoptosis, which sustains tumor survival and therapeutic resistance. Cancer stem cells (CSCs), the subpopulation responsible for recurrence and metastasis, are particularly

dependent on PI3K-AKT-mTOR signaling. Targeted inhibition of mTOR has therefore emerged as a promising therapeutic strategy. Pre-clinical and clinical studies show that mTOR inhibitors reduce CSC viability, diminish tumor sphere formation, enhance radio- and chemo-sensitivity, and restore apoptotic signaling, ultimately counteracting drug resistance and improving treatment efficacy in prostate cancer<sup>13</sup>

### PI3K inhibitors

A variety of pan-PI3K inhibitors such as buparlisib and pictilisib have proven effective in both preclinical models and clinical trials. Furthermore, several isoform-selective inhibitors, like alpelisib, specifically targets PI3K $\alpha$ , have also received considerable clinical attention. **Perifosine**

Perifosine is distinguished by its unique mechanism of targeting the pleckstrin homology domain of AKT, which prevents AKT translocation to the plasma membrane and subsequent activation. Unlike ATP-competitive inhibitors, this mode of action allows effective disruption of survival signaling pathways, leading to reduced proliferation and enhanced apoptosis in prostate cancer cells

### GSK-690693

GSK-690693 exhibits its uniqueness as a pan-AKT inhibitor capable of targeting multiple AKT isoforms simultaneously. This broad-spectrum inhibition results in comprehensive suppression of AKT-mediated signaling pathways, thereby effectively reducing tumor cell growth and promoting apoptosis in prostate cancer models.

### GDC-0941

GDC-0941 is unique in its upstream targeting of the PI3K pathway as a pan-class I PI3K inhibitor. By inhibiting PI3K activity, it blocks the entire downstream PI3K/AKT signaling cascade, leading to suppression of tumor growth, angiogenesis, and survival pathways, with enhanced efficacy observed in combination therapies.

### Arctigenin

Arctigenin stands out due to its dual mechanism involving inhibition of the PI3K/AKT/mTOR pathway along with induction of reactive oxygen species (ROS). This combined action promotes apoptosis, autophagy, and inhibition of metastasis, making it a multi-functional anti-cancer agent in prostate cancer.

### Thymoquinone

Thymoquinone is uniquely characterized by its multi-targeted activity, simultaneously modulating PI3K/AKT and other signaling pathways such as

ERK. This enables it to induce apoptosis, inhibit angiogenesis, and enhance chemosensitivity, highlighting its potential as an adjunct therapeutic agent in prostate cancer treatment<sup>14</sup>

### Dual pathway inhibitors

**CUDC-907 (dual PI3K/HDAC inhibitor)** By simultaneously blocking PI3K signaling and histone deacetylase activity, CUDC-907 exerts potent antitumor effects in castration-resistant prostate cancer. It drives apoptosis through modulation of survival proteins and induces DNA damage by suppressing repair regulators, leading to marked tumor growth inhibition in xenograft models.<sup>15</sup>

### AZD8186 (dual PI3K $\beta/\delta$ inhibitor, often paired with MEK blockade)

This agent targets PI3K $\beta/\delta$  isoforms, crucial in PTEN-wild-type prostate cancer, and shows enhanced potency when combined with selumetinib (MEK inhibitor). The dual pathway inhibition effectively reduces proliferation, promotes apoptosis, and suppresses resistant tumor growth, encouraging tolerability in preclinical studies.<sup>16</sup>

### Sapanisertib (dual PI3K/AKT/mTOR inhibitor)<sup>17</sup>

Sapanisertib is a second-generation inhibitor of both mTORC1 and mTORC2 that enables functional dual inhibition within the PI3K/AKT/mTOR signaling pathway. By blocking mTORC2, it prevents AKT phosphorylation, thereby suppressing a key downstream effector of PI3K signaling and partially overcoming feedback activation commonly seen with selective mTORC1 inhibitors. This creates a broader pathway blockade that resembles dual PI3K/mTOR inhibition, leading to reduced cell proliferation and increased apoptosis in prostate cancer models. However, because it does not directly inhibit PI3K, upstream signaling may remain active, which limits its full dual-target potential and supports its use in combination strategies to achieve more complete pathway suppression.

### Combination therapy

#### Darolutamide with Copanlisib

The combination of darolutamide and copanlisib showed the most potent antitumor activity through dual inhibition of androgen receptor and PI3K signaling. It significantly reduced cell proliferation and induced apoptosis in prostate cancer cells, as indicated by increased caspase-3/7 activation, PARP cleavage, and BBC3 upregulation. Additionally, it suppressed androgen-response and mTORC1 signaling pathways and induced DNA damage. In

vivo studies further demonstrated superior tumor growth inhibition and enhanced apoptosis compared to monotherapy, confirming strong synergistic efficacy<sup>1</sup>

#### Darolutamide with Apatolisib

The darolutamide apitolisib combination effectively targeted both androgen receptor and PI3K/mTOR pathways, leading to reduced proliferation and increased apoptosis in androgen-sensitive prostate cancer cells. The treatment exhibited synergistic activity compared to single agents; however, its overall efficacy was lower than the copanlisib combination, requiring higher concentrations to achieve similar biological effects, indicating comparatively weaker potency<sup>18</sup>

#### PI3K/AKT inhibitors with PARP inhibitors

Blocking PI3K/AKT signaling suppresses homologous recombination repair proteins (BRCA1/2, RAD51), making tumor cells more dependent on PARP. Trials with capivasertib with olaparib and apelisib + olaparib showed manageable toxicity and partial responses, even in patients without DNA repair defects, highlighting the potential of dual targeting in biomarker-selected groups.

#### PI3K/AKT/mTOR inhibitors with AR blockade

Because AR and PI3K/AKT/mTOR pathways form compensatory feedback loops, combining inhibitors with androgen receptor antagonists (like abiraterone or enzalutamide) has yielded the best results in PTEN-deficient mCRPC, improving radiographic progression-free survival in Phase III trials.

#### PI3K/AKT/mTOR inhibitors with immune checkpoint inhibitors

This pathway regulates PD-L1 expression and T-cell function, shaping the tumor immune microenvironment. Early studies in glioma suggest synergy between PI3K/mTOR inhibitors and PD-1/PD-L1 blockade, and preclinical prostate cancer data indicate potential benefit in immune-excluded tumors, though robust clinical evidence in PCa is still lacking.

#### PI3K/AKT/mTOR inhibitors with chemotherapy (docetaxel)

Combination with chemotherapy aims to overcome resistance mechanisms in castration-resistant disease. Preclinical models show enhanced tumor suppression when PI3K/AKT/mTOR inhibitors are paired with docetaxel, though clinical translation remains under investigation.<sup>19</sup>

### Future Directions

The development of dual-targeted agents such as CUDC-907 underscores the therapeutic potential of simultaneously inhibiting PI3K signaling and epigenetic regulators like HDACs in prostate cancer. Preclinical evidence demonstrates that this approach can suppress tumor growth, induce apoptosis, and overcome resistance mechanisms associated with single-pathway blockade. Importantly, the study highlights compensatory ERK activation as a resistance driver, suggesting that rationally designed multi-pathway inhibition strategies will be essential to achieve durable responses in castration-resistant prostate cancer (CRPC).<sup>20</sup>

Looking forward, the integration of dual PI3K/HDAC inhibitors into biomarker-defined patient populations offers a promising avenue for precision oncology. Future clinical trials should incorporate genomic profiling to identify PTEN-deficient and PI3K-activated tumors most likely to benefit, while also exploring combination regimens that intercept compensatory cascades such as MAPK and AR signaling. Adaptive dosing strategies to mitigate toxicity, alongside translational endpoints to validate pathway blockade, will be critical for clinical success. Collectively, these advances position dual-targeted PI3K/HDAC inhibition as a cornerstone of next-generation prostate cancer therapy, with the potential to transform modest benefits into durable outcomes.<sup>20</sup>

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