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Review On Capivasertib: A Novel Akt Inhibitor In Targeted Cancer Therapy

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1.ABSTRACT

Capivasertib (AZD5363, Truqap) is a novel, orally active, selective pan-AKT inhibitor developed for the treatment of cancers driven by dysregulation of the phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathway. Aberrant activation of this pathway is frequently observed in various malignancies and is associated with uncontrolled cell proliferation, enhanced survival, metabolic reprogramming, and resistance to conventional anticancer therapies. Capivasertib exerts its anticancer effect by competitively inhibiting all three AKT isoforms (AKT1, AKT2, and AKT3), thereby suppressing downstream signaling involved in tumor growth and progression. Extensive preclinical studies demonstrated significant antitumor activity of capivasertib, particularly in cancer models harboring PI3K, AKT, or PTEN alterations. Subsequent clinical trials, including phase I, II, and III studies, established its safety, pharmacokinetic profile, and clinical efficacy. Notably, capivasertib in combination with fulvestrant has shown improved progression-free survival in patients with hormone receptor-positive, HER2-negative advanced breast cancer, especially in biomarker-positive populations. Although the drug is associated with manageable adverse effects such as diarrhea, hyperglycemia, and rash, appropriate monitoring and dose modifications enhance its tolerability. This review provides a comprehensive and updated overview of the mechanism of action, pharmacological properties, preclinical and clinical evidence, safety profile, advantages, limitations, and future prospects of capivasertib as a targeted anticancer therapy.

KEYWORD: Capivasertib, AKT inhibitor, PI3K/AKT/mTOR pathway, targeted therapy, breast cancer, precision oncology.

I. INTRODUCTION

Cancer is a complex and multifactorial disease characterized by uncontrolled cellular proliferation, resistance to apoptosis, sustained angiogenesis, and the ability to invade and metastasize. Despite significant advances in chemotherapy, radiotherapy, and surgical interventions, treatment resistance and disease recurrence remain major challenges in oncology. In recent years, a deeper understanding of cancer biology has facilitated the development of targeted therapies that selectively inhibit specific molecular pathways essential for tumor growth and survival.

One of the most frequently altered intracellular signaling cascades in human cancers is the PI3K/AKT/mTOR pathway. This pathway plays a central role in regulating cell growth, metabolism, proliferation, and survival. Genetic alterations such as activating mutations in the PIK3CA gene, loss or inactivation of the tumor suppressor PTEN, and activating mutations in AKT lead to persistent pathway activation and oncogenesis. Dysregulation of this signaling axis is particularly prevalent in breast, prostate, ovarian, endometrial, and colorectal cancers.

AKT, also known as protein kinase B, functions as a key mediator within this pathway and integrates signals from growth factors and oncogenic stimuli. Due to its central role, AKT has emerged as an attractive therapeutic target. Capivasertib is a next-generation AKT inhibitor designed to block AKT signaling more effectively than earlier agents. By directly inhibiting AKT kinase activity, capivasertib aims to suppress tumor growth and overcome resistance to endocrine and other targeted therapies.

This review focuses on capivasertib as a novel AKT inhibitor, discussing its mechanism of action, pharmacological properties, preclinical and clinical development, therapeutic advantages, limitations, and future potential in precision oncology.

1. PI3K/AKT/mTOR Signaling Pathway in Cancer

The PI3K/AKT/mTOR signaling pathway is activated by extracellular growth factors binding to receptor tyrosine kinases such as epidermal growth factor receptor (EGFR) and insulin-like growth factor receptor (IGFR). Upon activation, PI3K catalyzes the conversion of phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3), which facilitates the recruitment and activation of AKT at the plasma membrane.

Activated AKT phosphorylates multiple downstream substrates involved in cell cycle progression, protein synthesis, glucose metabolism, and inhibition of apoptosis. Key downstream targets include mTOR complex 1 (mTORC1), glycogen synthase kinase-3 beta (GSK-3β), and forkhead box O (FOXO) transcription factors. Under physiological conditions, this pathway is tightly regulated; however, in cancer, mutations and deletions result in continuous pathway activation.

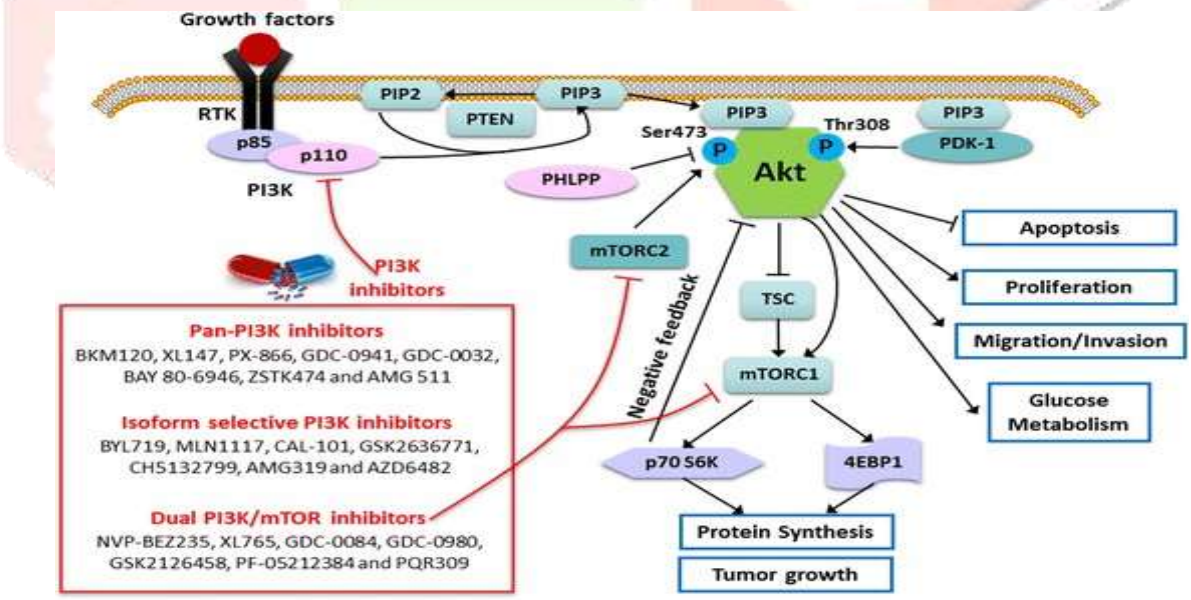

Fig 1: schematic diagram of pi3k\akt\mtor pathway

Loss of PTEN, a lipid phosphatase that negatively regulates PI3K signaling, is one of the most common alterations leading to hyperactivation of AKT. Persistent AKT signaling promotes tumor cell survival, angiogenesis, metastasis, and resistance to hormonal and cytotoxic therapies. Therefore, inhibition of AKT represents a rational and promising approach for targeted cancer therapy.

2. Mechanism of Action of Capivasertib

Capivasertib (AZD5363) is a potent, orally administered, ATP-competitive inhibitor of AKT that targets all three isoforms of the kinase—AKT1, AKT2, and AKT3. These isoforms play overlapping yet distinct roles in cancer cell survival, metabolism, and proliferation. Capivasertib binds to the catalytic ATP-binding pocket of AKT, preventing its phosphorylation and subsequent activation. As a result, downstream signaling events mediated by AKT are effectively suppressed.

Inhibition of AKT by capivasertib leads to reduced phosphorylation of critical downstream substrates such as PRAS40, GSK-3β, and FOXO transcription factors. This suppression disrupts mTOR signaling, leading to decreased protein synthesis and inhibition of cell growth. Furthermore, inhibition of AKT signaling restores the activity of pro-apoptotic pathways, resulting in increased programmed cell death in cancer cells.Capivasertib also plays a crucial role in overcoming resistance mechanisms associated with endocrine therapy in hormone receptor-positive breast cancer. By blocking AKT-mediated survival signals, the drug enhances the sensitivity of tumor cells to endocrine agents such as fulvestrant. This mechanistic synergy forms the scientific basis for combination therapy approaches involving capivasertib.

3. Pharmacokinetics of Capivasertib

Capivasertib is administered orally and demonstrates favorable pharmacokinetic properties suitable for chronic clinical use. Following oral administration, the drug is rapidly absorbed, with peak plasma concentrations typically achieved within a few hours. The pharmacokinetic profile of capivasertib supports an intermittent dosing schedule, which has been optimized to balance therapeutic efficacy and tolerability.

The recommended clinical dosing regimen is 400 mg taken twice daily on an intermittent schedule of four days on treatment followed by three days off. This dosing strategy allows adequate inhibition of AKT signaling while minimizing dose-limiting toxicities observed during continuous dosing in early clinical studies.

Capivasertib is primarily metabolized in the liver, mainly through cytochrome P450 enzymes, particularly CYP3A4. The drug exhibits moderate plasma protein binding and a half-life that supports twice-daily administration. Population pharmacokinetic analyses have shown that factors such as age, body weight, and mild hepatic impairment have minimal impact on drug exposure, reducing the need for routine dose adjustments.

4. Pharmacodynamics of Capivasertib

Pharmacodynamic studies have demonstrated that capivasertib effectively inhibits AKT signaling in both tumor tissue and surrogate tissues. Decreased phosphorylation of AKT downstream targets, including PRAS40 and GSK-3β, has been consistently observed in preclinical models and clinical biopsy samples following drug administration.

4.1 Mechanim Action of Capivasertib

Capivasertib (AZD5363)

↓

Oral Administration

↓

Binding to AKT (AKT1, AKT2, AKT3)

↓

Inhibition of AKT Phosphorylation

↓

↓ PRAS40 phosphorylation

↓ GSK-3β activation

↓ FOXO inhibition

↓

Suppression of mTOR signaling

↓

↓ Cell Proliferation

↓ Tumor Growth

↑ Apoptosis

↓ Anticancer Effect

These pharmacodynamic effects correlate with plasma drug concentrations, confirming effective target engagement at clinically relevant doses. Inhibition of AKT signaling leads to reduced tumor cell proliferation and increased apoptosis, as evidenced by changes in molecular biomarkers. Importantly, pharmacodynamic responses have been shown to be more pronounced in tumors harboring alterations in the PI3K/AKT/PTEN pathway, supporting the use of biomarker-guided patient selection.

5. Preclinical Studies

Extensive preclinical evaluation of capivasertib has been conducted using both in vitro and in vivo cancer models. In vitro studies demonstrated potent growth inhibition in a wide range of cancer cell lines, particularly those with activating mutations in PIK3CA, AKT1, or loss of PTEN expression. Capivasertib induced cell cycle arrest and apoptosis in these models, confirming its mechanism- based anticancer activity.

In vivo studies using xenograft tumor models further validated the antitumor efficacy of capivasertib. Significant tumor growth inhibition and, in some cases, tumor regression were observed following treatment. Preclinical studies also revealed enhanced efficacy when capivasertib was combined with endocrine therapy or HER2-targeted agents, providing a strong rationale for combination strategies in clinical trials.

These preclinical findings supported the progression of capivasertib into clinical development and helped identify patient populations most likely to benefit from AKT inhibition.

6. Clinical Studies of Capivasertib

6.1 Phase I Clinical Trials

Phase I clinical trials of capivasertib were primarily designed to evaluate its safety, tolerability, pharmacokinetics, and pharmacodynamics in patients with advanced solid tumors. These studies established the maximum tolerated dose and identified dose- limiting toxicities, which included gastrointestinal disturbances and metabolic abnormalities such as hyperglycemia.

Pharmacokinetic and pharmacodynamic assessments in phase I trials confirmed adequate systemic exposure and effective inhibition of AKT signaling. Preliminary evidence of antitumor activity was observed, particularly in patients with molecular alterations in the PI3K/AKT pathway.

6.2 Phase II Clinical Trials

One of the most significant phase II studies evaluating capivasertib is the FAKTION trial. This randomized, double-blind study assessed the efficacy of capivasertib in combination with fulvestrant in patients with hormone receptor-positive, HER2-negative advanced breast cancer who had progressed on prior endocrine therapy.

The results demonstrated a statistically significant improvement in progression-free survival in patients receiving the capivasertib- fulvestrant combination compared to fulvestrant alone. Importantly, the greatest benefit was observed in patients whose tumors harbored alterations in the PI3K/AKT/PTEN pathway, highlighting the importance of biomarker-driven treatment selection.

6.3 Phase III Clinical Trials

Phase III clinical trials were conducted to confirm the efficacy and safety findings observed in earlier studies. These large, randomized trials further evaluated capivasertib in combination with endocrine therapy in biomarker-selected populations. The results reinforced the clinical benefit of capivasertib, demonstrating improved progression-free survival and, in some analyses, overall survival benefits.

The outcomes of phase III trials played a critical role in supporting regulatory approvals and the clinical adoption of capivasertib for the treatment of advanced breast cancer.

7. Safety Profile and Adverse Drug Reactions

The safety and tolerability of capivasertib have been extensively evaluated across multiple clinical trials. Overall, capivasertib demonstrates a manageable safety profile when administered using the recommended intermittent dosing schedule. Most adverse drug reactions observed during treatment are mild to moderate in severity and can be effectively managed with supportive care, dose interruption, or dose reduction.

The most frequently reported adverse effects include gastrointestinal disturbances such as diarrhea, nausea, and vomiting. Diarrhea is the most common dose-limiting toxicity and typically occurs early during treatment. Prompt use of antidiarrheal agents and patient education significantly reduce the severity and duration of symptoms. Cutaneous adverse reactions, including rash and pruritus, are also commonly observed and are thought to be related to AKT inhibition in skin cells.

Metabolic adverse effects, particularly hyperglycemia, are a known class effect of AKT inhibitors. Capivasertib-induced hyperglycemia results from impaired insulin signaling and altered glucose metabolism. Regular monitoring of blood glucose levels is therefore recommended, especially in patients with pre-existing diabetes or metabolic disorders. Other reported adverse effects include fatigue, stomatitis, and decreased appetite.

Serious adverse events are relatively uncommon. However, careful patient selection, routine monitoring, and adherence to dose modification guidelines are essential to ensure patient safety and maintain treatment continuity.

8. Advantages, Disadvantages and Limitations of Capivasertib

8.1 Advantages of Capivasertib

1. Capivasertib is an orally administered drug, which improves patient convenience and adherence to therapy.
2. It functions as a selective pan-AKT inhibitor, targeting AKT1, AKT2, and AKT3 isoforms involved in tumor progression.
3. The drug specifically inhibits the PI3K/AKT/mTOR signaling pathway, a key oncogenic pathway in many cancers.
4. Capivasertib has demonstrated significant clinical efficacy in combination with endocrine therapy in hormone receptor-positive, HER2-negative advanced breast cancer.
5. It is effective in overcoming resistance to endocrine therapy, which is a major limitation of conventional hormonal treatments.
6. Biomarker-guided patient selection enhances therapeutic outcomes and supports precision oncology.
7. Most adverse effects associated with capivasertib are predictable and manageable with appropriate dose modification and supportive care.

8.2 Disadvantages of Capivasertib

1. Capivasertib commonly causes gastrointestinal adverse effects such as diarrhea, nausea, and vomiting.
2. Hyperglycemia is a notable metabolic adverse effect, requiring regular blood glucose monitoring.
3. Dermatological reactions, including rash and itching, may occur during treatment.
4. Continuous clinical monitoring and follow-up are necessary during therapy.
5. The drug has the potential for drug–drug interactions due to metabolism by hepatic cytochrome P450 enzymes.
6. Requirement of molecular diagnostic testing increases treatment complexity and cost.

8.3 Limitations of Capivasertib

1. Therapeutic benefit is not uniform among all patients, even those with PI3K/AKT/PTEN pathway alterations.
2. Tumor heterogeneity may limit the effectiveness of AKT inhibition.
3. Acquired resistance may develop with prolonged treatment.
4. Clinical benefit is largely restricted to biomarker-positive populations.
5. Long-term safety data are still under investigation.
6. High cost and limited accessibility may restrict widespread clinical use, especially in resource-limited settings.

9. Future Prospects of Capivasertib

9.1. Biomarker-Driven Personalized Therapy

Future use of capivasertib will increasingly rely on advanced molecular profiling, including PI3K, AKT, and PTEN alterations, to accurately identify patients most likely to benefit from AKT inhibition.

9.2. Expansion to Other Cancer Types

Ongoing and future clinical trials are expected to explore the efficacy of capivasertib in other malignancies such as prostate cancer, ovarian cancer, endometrial cancer, and colorectal cancer with PI3K/AKT pathway dysregulation.

9.3. Combination Therapy Strategies

Capivasertib has strong potential for use in combination with other targeted therapies such as CDK4/6 inhibitors, HER2-targeted agents, chemotherapy, and immunotherapy to enhance antitumor efficacy and delay resistance.

9.4. Overcoming Drug Resistance

Future research will focus on understanding and overcoming resistance mechanisms associated with AKT inhibition by developing rational drug combinations and optimized dosing schedules.

9.5. Development of Next-Generation AKT Inhibitors

Insights gained from capivasertib clinical development will guide the design of next-generation AKT inhibitors with improved selectivity, reduced toxicity, and enhanced clinical efficacy.

9.6. Improved Dosing and Scheduling

Further optimization of intermittent dosing schedules may improve tolerability while maintaining effective pathway inhibition, leading to better long-term patient outcomes.

9.7. Use of Liquid Biopsy Techniques

Monitoring circulating tumor DNA (ctDNA) may help assess treatment response, detect emerging resistance early, and guide real- time treatment modifications.

9.8. Real-World Evidence and Post-Marketing Studies

Long-term real-world data will provide valuable insights into the safety, effectiveness, and quality-of-life outcomes associated with capivasertib therapy in diverse patient populations.

9.9. Cost-Effectiveness and Accessibility Studies

Future studies evaluating cost-effectiveness may support broader clinical adoption and inclusion in treatment guidelines, particularly in resource-limited settings.

9.10. Role in Precision Oncology

Capivasertib is expected to play a key role in the advancement of precision oncology by integrating genomic data with targeted therapeutic strategies for improved cancer management.

II. CONCLUSION

Capivasertib represents an important advancement in targeted cancer therapy through its selective inhibition of AKT, a central regulator of the PI3K/AKT/mTOR signaling pathway that is frequently dysregulated in human malignancies. Preclinical and clinical studies have demonstrated that capivasertib effectively suppresses tumor growth and enhances therapeutic outcomes, particularly when combined with endocrine therapy in hormone receptor-positive, HER2-negative advanced breast cancer with PI3K/AKT/PTEN pathway alterations. Although the drug is associated with manageable adverse effects and requires biomarker-guided patient selection, its benefits in overcoming treatment resistance and improving progression-free survival highlight its clinical value. Ongoing research focusing on optimized combination strategies, improved biomarker identification, and expanded indications is expected to further enhance the role of capivasertib in precision oncology, making it a promising therapeutic option in modern cancer management.

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