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Capivasertib: The Breakthrough Cancer Treatment of the Decade's

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Abstract:
Capivasertib (TRUQAP), a novel oral AKT inhibitor, targets the PI3K/AKT/mTOR pathway to overcome tumour resistance in advanced breast cancer.Capivasertib has a unique pyrrolopyrimidine derivative structure and is a highly strong ATP-competitive inhibitor of all three AKT isoforms (AKT1, AKT2, and AKT3).This article provides a thorough examination of capivasertib's synthesis, mechanisms of action, physical and chemical properties, and preclinical and clinical efficacy.Its advantages over existing treatments, possible adverse effects, and prospective use in combination therapy are examined.We also examine possible future paths for managing resistance, optimising the therapeutic advantages of capivasertib, and selecting the best patients using biomarkers.Preclinical research has demonstrated the potential of capivasertib in conjunction with endocrine therapy and anti-HER2 drugs. Its clinical importance is highlighted by the FDA's recent approval of TRUQAP in conjunction with Faslodex in November 2023 for advanced HR-positive and HER2-negative breast cancer.

Keywords: Capivasertib, AKT Inhibitor, Breast cancer, TRUQAP

Introduction:

The medical product capivasertib (AZD5363) is under study.AstraZeneca found capivasertib as a result of working with Astex Therapeutics(and its collaboration with Cancer Research Te chnology Limited and the Institute of Cancer Research).(1).With its first phase III study show ing "remarkable" outcomes against advanced breast cancer, capivasertib is the newest big dis covery in the field of cancer research.(2)A new selective ATP-competitive pan-AKT kinase in hibitor called capivasertib (AZD5363) works similarly against AKT1, AKT2, and AKT3 isof orms. Capivasertib has been shown in preclinical tests to be effective in breast cancer cell line s whether used alone or in combination with anti-HER2 drugs and endocrine therapy, particul arly in tumours that had PIK3CA or MTOR mutations.(3)With respectable preclinical tolerabi lity, AKT inhibitor-like pharmacodynamic properties, and a unique profile from other AKT in hibitors that have reached clinical development, AZD5363 stands out from the competition.(4)For oral use, TRUQAP is offered in round-shaped 160 mg and capsule-shaped 200 mg dose l evels as a beige-colored, film-coated, biconvex tablet.(5)The tablets also contain croscarmellose sodium, dibasic calcium phosphate, magnesium stearate, and microcrystalline cellulose. The film coat contains the following inactive ingredients: copovidone, hypromellose, iron oxide black, iron oxide red, iron oxide yellow, medium chain triglycerides, polydextrose, polyethylene glycol 3350, and titanium dioxide. (6)

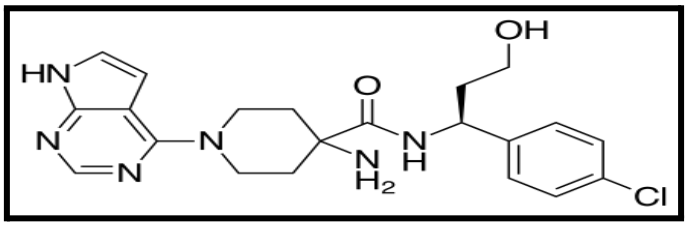
(7)


(8)

(9)

Physical and chemical data of capivasertib:

Structure:



IUPAC Name	4-Amino-N-[(1S)-1-(4-chlorophenyl)-3-hydroxypropyl]-1-(7H-pyrrolo[2,3-d]pyrimidin-
	4-yl)piperidine-4-carboxamide
Molecular formula	C21H25ClN6O2
Molecular weight	428.915 g/mol (10)
Appearance	White to off-white solid powder
Solubility	At pH levels less than 1.2, it dissolves readily in water, while at pH values more than 6.8, it becomes nearly insoluble. (6)

Table 1. Physical and chemical properties

Combination therapy of Capivasertib:

Approved Combinational therapy :

Combinational drug	Intervention	Dosage of drugs	Packaging	Marketed by
1.Capivasertib + Fulvestrant	HR+/HER2-Ne	400 mg of capiv asertib twice a d ay +	Capivasertib tablet +Fulvestrant injection vials	AstraZeneca Pharmaceuticals LP

	gative breast cancer	IM injection of 500 mg of fulve strant on days 1, 15, and 29,after that monthly		(11)

Table 2. Approved combination therapy Investigational

Combinational therapy :

Combinational therapy	Study in clinical trials
1.Capivasertib + Olaparib	BRCA1/2 Mutated breast cancer
2.Capivasertib + Ipatasertib	Mutations in AKT (12)
3.Capivasertib + Paclitaxel	Metastatic triple-negative breast cancer (13)
4.Capivasertib + Trastuzumab deruxtecan	HER2+ and HER2- low breast cancer (14)
5.Capivasertib + Enzalutamide	Metastatic castration-resistant prostate cancer (15)
6.Capivasertib + Docetaxel	Metastatic castration-resistant prostate cancer (16)
7.Capivasertib + Abiraterone acetate	Metastatic castration-resistant prostate cancer (17)

Table 3. Investigational Combination therapy

Capivasertib is also undergoing phase III clinical development for use (in conjunction with ot her anti-cancer agents) in the treatment of triple-negative breast cancer, castration-resistant pr ostate cancer, and hormone-sensitive prostate cancer. It is also being reviewed for regulatory approval in the EU and a number of other countries for HR-positive, HER2-negative breast c ancer(18).By increasing sensitivity or overcoming resistance to HER2 inhibitors, capivasertib can improve the effectiveness of chemotherapy and reduce tumour size.In gastric cancer with a PI3KCA mutation, castrate-resistant prostate cancer (CRPC), and trastuzumab-resistant eso phageal squamous cell carcinoma, capivasertib has demonstrated reclinical efficacy either alo ne or in conjunction with other drugs.

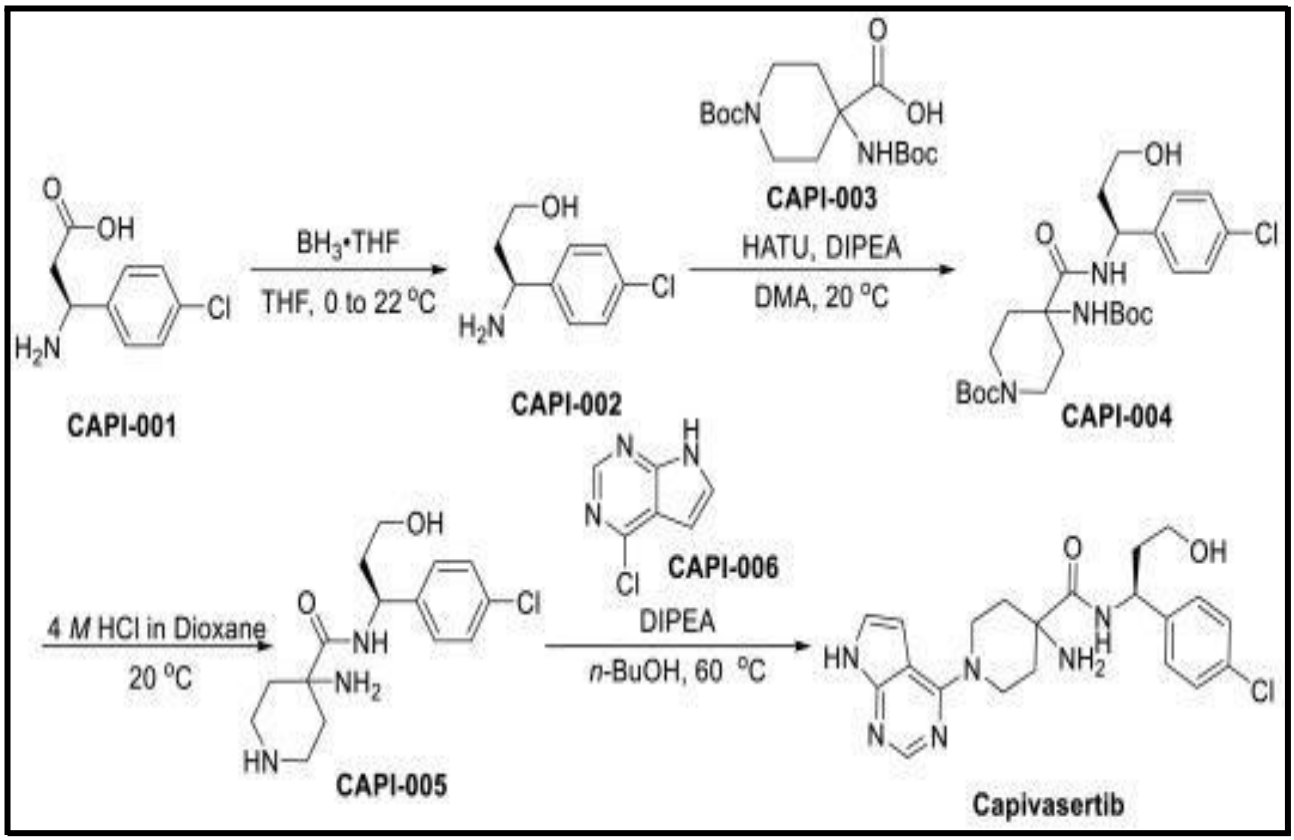
Moreover, research conducted in 2020 revealed that capivasertib, either by itself or in conjun ction with fullvestrant, was well tolerated and exhibited encouraging anticancer efficacy(12).I n the United States, capivasertib was first approved in November 2023 for use in conjunction with fulvestrant to treat adult patients with hormone receptor (HR)-positive, HER2-negative, locally advanced or metastatic breast cancer that has one or more PIK3CA/AKT1/PTEN mut ations.-differences after the completion of adjuvant therapy or recurrence on or within 12 mo nths of the end of at least one endocrine-based regimen in the metastatic context.(11)(18)Trap et al. assessed capivasertib and the PARP inhibitor (PARPi), olaparib, in a phase 1 trial since preclinical studies showed a synergy between poly(ADP-ribose) polymerase (PARP) and PI3 Ki.They found capivasertib to be both well-tolerated and safe. Moreover, anticancer activity was shown in patients with germline BRCA1/2 mutations as well as BRCA1/2 wild-

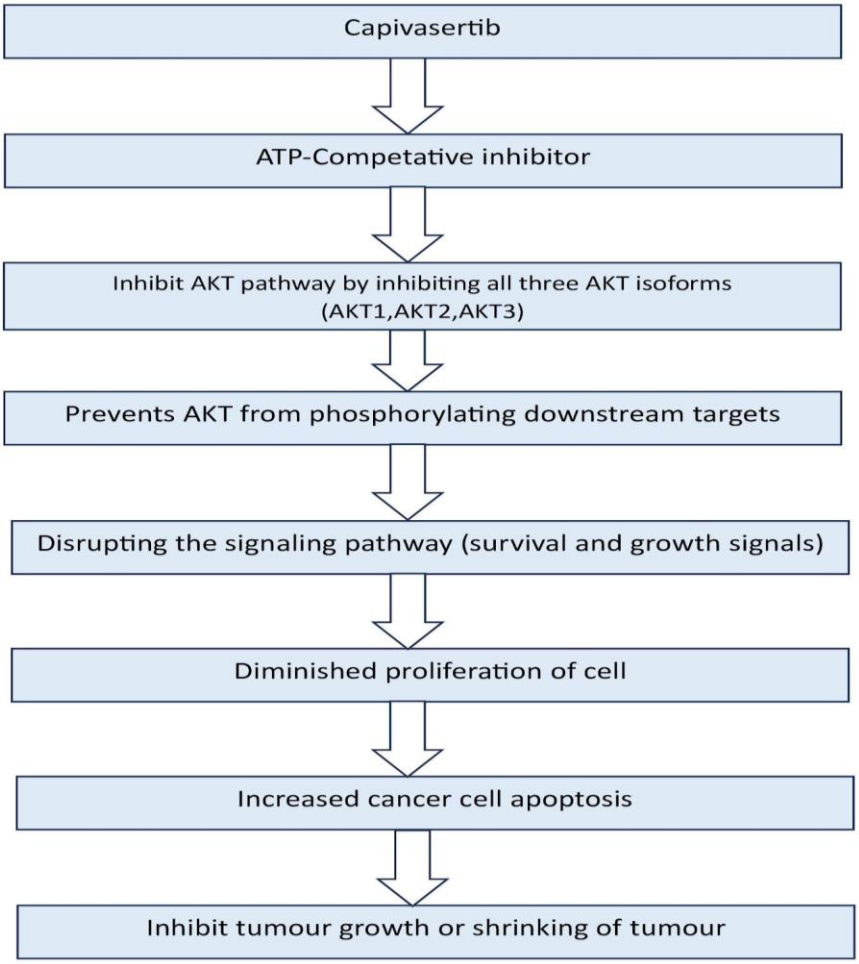
type, wit h or without somatic DNA damage repair gene (DDR) and/or changes to the PI3K/AKT path way.It is important to note that extensive genomic investigations of human cancer have show n that the most prevalent AKT mutation, AKT1-E17K, enhances the effectiveness of AKT inh ibitor therapy in solid tumours.Therefore, a combination of drugs may be needed to fully utili se capivasertib in AKT1-mutant malignancies.Patients with mutations in AKT can take capiv asertib with ipatasertib; patients with mutations or deletions in PTEN can take the leuprolide Acetate or Abiraterone with capivasertib. The co-primary goals of this combination treatment were capivasertib's safety and tolerability.(12)

Synthesis:

The following scheme shows the steps involved in synthesising capivasertib :

1. By reducing the carbonyl group of propanoic acid CAPI-001, CAPI-002 was produce d.
2. It was then further condensed to produce amide CAPI-004 using carboxylic acid CAP I-003.
3. In an acidic environment, CAPI-004 was deprotected to produce the amine CAPI-005.
4. Finally, 4-chloropyrimidine CAPI-006 was used to nucleophilically substitute CAPI-0 05 in order to produce Capivasertib(19).





Mechanism of action:

In human malignancies, the most often changed signalling route is the phosphatidylinositol-3kinase (PI3K)/Akt (PI3K/AKT) pathway.A crucial component of the AGC kinase family, Akt is composed of three isoforms, each of which is encoded by a different gene: Akt1 is highly e xpressed in most tissues, Akt2 is primarily expressed in metabolic tissues like the liver, skelet al muscle, and adipose tissue, and Akt3 is enriched in the brain and testis.AKT signalling is n ot only critical for cancer but also for many other normal physiological functions, including g lucose homeostasis, heart function, coronary angiogenesis, endothelial nitric oxide production , and brain synaptic transmission.

AKT activating mutations, activating PI3K catalytic subunit mutations, PTEN loss, and other mechanisms can all cause Akt to become hyper-activated in cancer cells.AKT activation is lin ked to a poor prognosis and resistance to anticancer therapy.There's a good reason to focus on the essential elements of the PI3K/AKT pathway accordingly. Although patients with advanc ed HR-positive breast cancer are already treated with mTOR and PI3K inhibitors that are lice nsed by the FDA, AKT is a new target that can be treated with medicationThere are two prim ary subgroups of AKT inhibitors: ATP competitors, which involve ATP competition to bind w ith Akt kinase at the ATP binding site; and allosteric inhibitors, which target the PH-domain a nd stop AKT from migrating to the plasma membrane, where upstream kinases activate AKT, thereby locking AKT in an inactive form.Capivasertib is a member of the most extensively re searched class of ATP-competitive inhibitors.(3)

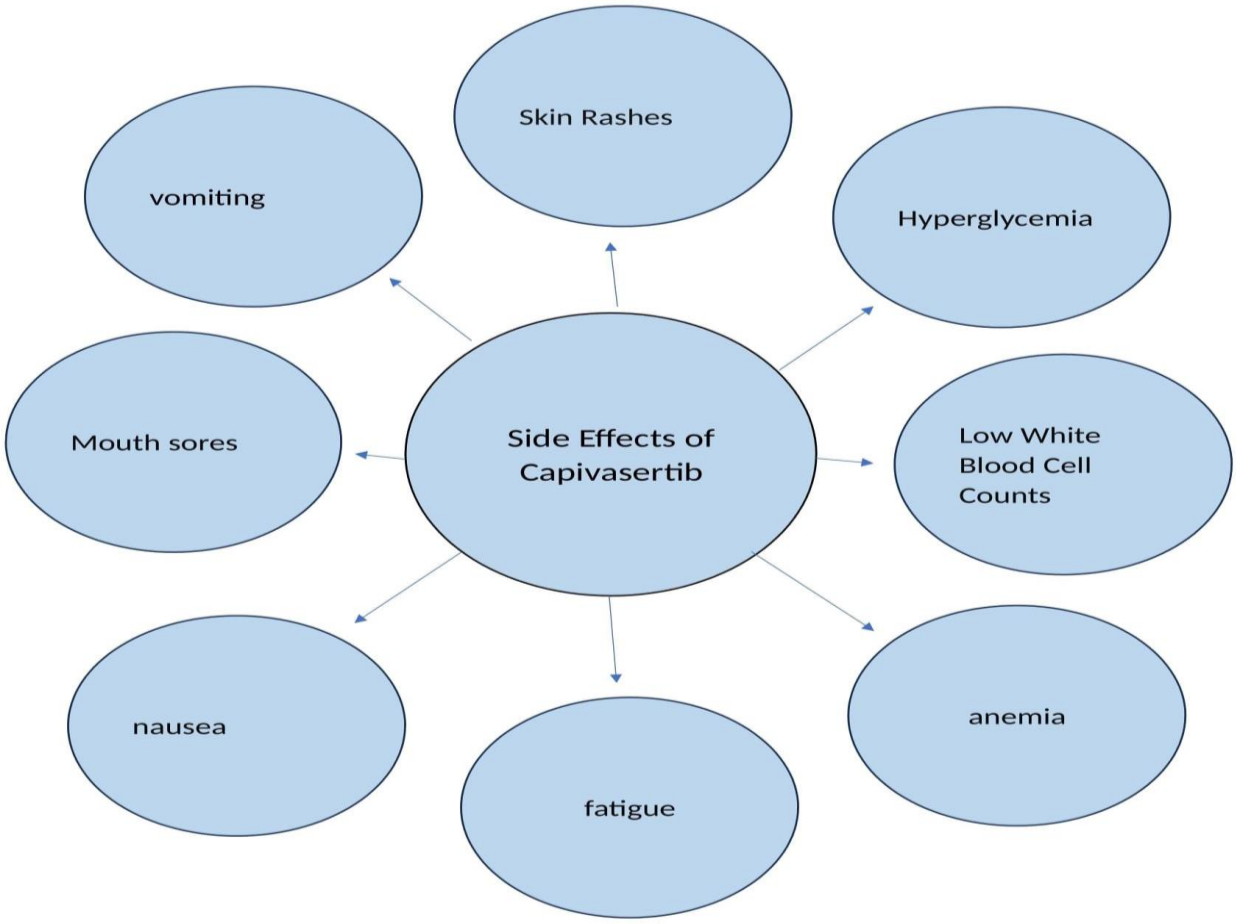
Capivasertib prevents downstream AKT substrates from being phosphorylated by inhibiting t he activity of all three isoforms of serine/threonine kinase AKT (AKT1, AKT2, and AKT3)(2 0).AKT1 and AKT2 play different roles in cancer cells. While AKT1 promotes tumour start a nd growth while suppressing apoptosis, AKT2 controls cytoskeleton dynamics, which favours invasiveness and metastatization. Though it has been suggested that AKT3 hyperactivation may stimulate cell proliferation, its involvement in cancer is still debatable.(21)The AKT1 en zyme is Inhibited by capivasertib

blocks this important signalling system, which stops the mechanisms that support the prolifer ation and resistance of cancer cells.

capivasertib at different doses to assess its effects; a dose-dependent inhibitory impact was sh own by the increasing decrease in cell viability as the tested agent's concentration dose. Incre ased capsivasertib dosages led to increased inhibition. Capivasertib therapy inhibits cell grow th, induces cell cycle arrest, and promotes cell death, according to further research.(22)The d ysregulation of PI3K/AKT/mTOR signalling in a broad spectrum of solid and haematological cancers is caused by mutations in several signalling components.(23)

Adverse effects :

Truqap exhibiting some potential adverse effects like : (24)



Advantages of capivasertib :

1. Distinct modes of action, such as selective inhibition, PI3K/AKT pathway targeting, o r decreased toxicity in contrast to non-selective P13K inhibitors.(25)

2. Capivasertib was safe and effective for solid tumours like BC.(26)
3. It increased progression free survival (PFS) and improved overall survival (OS)(12).
4. Targeted treatment for tumours dependent on AKT is identified through biomarker-dri ven development.(27)
5. It has advantageous pharmacokinetics and oral bioavailability. (28)
6. The combination therapies seemed to improve both activity and tolerability.(29)
7. In ovarian cancer, olaparib response rates were higher with capivasertib(30)
8. HER2 inhibitor resistance can be overcome or sensitivity increased with capivasertib.(12)

Future prospective of capivasertib :

When treating advanced cancers, such as breast cancer, capivasertib is a promising intervention that has demonstrated notable safety and efficacy. To realise the full potential of this medication, however, larger sample size trials and different combination therapies should be the main focus of future research. Future research ought to take into consideration the drawbacks of earlier studies, including clinical heterogeneity, small sample sizes, length of follow-up, etc.(31) Also investigating capivasertib in additional types of cancer.

Investigating the use of capivasertib in conjunction with additional targeted agents.

The creation of biomarkers for patient selection and overcoming the Capivasertib resistance. **Conclusion:** Capivasertib is a potential AKT inhibitor that has shown promise in treating breast cancer, es pecially when used in combination regimens. Other cancer types, such as metastatic castratio n-resistant prostate cancer, ovarian cancer, etc., can benefit from its therapeutic potential.

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