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ADISINSIGHT REPORT

Capivasertib: First Approval

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Abstract
Capivasertib (Truqap™) is an orally available, small-molecule pan-AKT inhibitor being developed by AstraZeneca for the treatment of various cancers, including breast and prostate cancers. Capivasertib received its first approval, in the USA, in November 2023 for use in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative, locally advanced or metastatic breast cancer with one or more *PIK3CA/AKT1/PTEN*-alterations following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy. Capivasertib is also under regulatory review for HR-positive, HER2-negative breast cancer in the EU and several other countries, and in phase III clinical development for use (in combination with other anti-cancer agents) in the treatment of triple-negative breast cancer, castration-resistant prostate cancer, and hormone-sensitive prostate cancer. This article summarizes the milestones in the development of capivasertib leading to this first approval for HR-positive, HER2-negative, locally advanced or metastatic breast cancer.

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Capivasertib (TRUQAP™): Key Points

A pan-AKT inhibitor is being developed by AstraZeneca for the treatment of various cancers, including HR-positive, HER2-negative breast cancer

Received its first approval on 16 November 2023 in the USA

Approved for use in combination with fulvestrant for the treatment of adult patients with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with one or more *PIK3CA/AKT1/PTEN*-alterations

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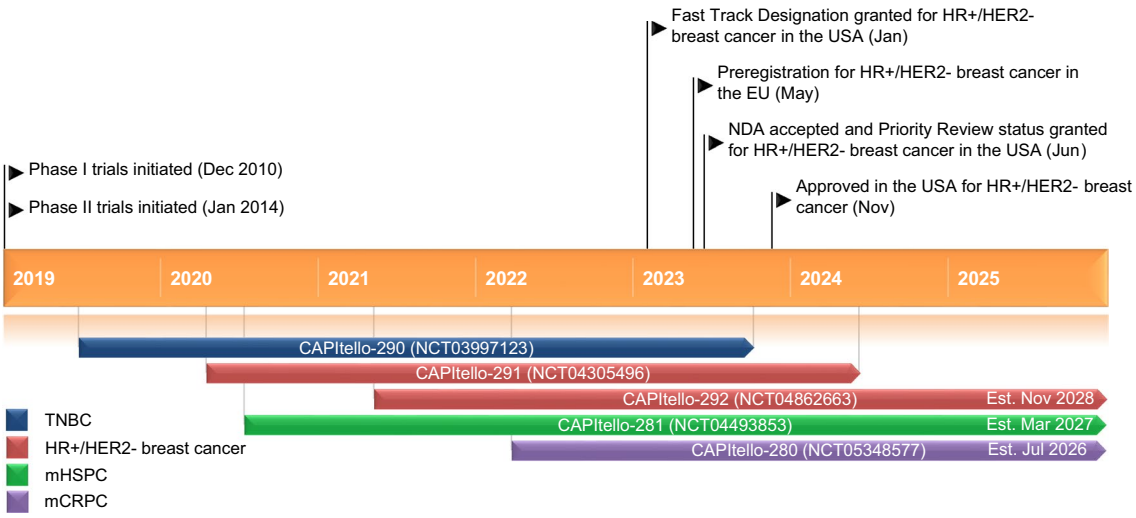
1 Introduction

With the growing recognition of the role that deregulation of the phosphatidylinositol-3-kinase (PI3K)/AKT pathway plays in the occurrence, development, and resistance of a wide range of cancers, the pathway has become a key focus for the development of a range of anti-cancer therapies [1, 2]. Alterations in PIK3/AKT pathway components [including phosphatase and tensin homolog (PTEN) loss, and mutations in *PIK3CA*, *PTEN* or *AKT1*] are found in almost 40% of solid tumor samples [1].

Capivasertib (Truqap™) is an orally available, small-molecule inhibitor of the serine/threonine protein kinase AKT [also known as protein kinase B (PKB)] being developed by AstraZeneca [3, 4]. Capivasertib inhibits all three isoforms of AKT (AKT1, AKT2, and AKT3), leading to the inhibition of phosphorylation of downstream AKT substrates [5, 6]. Following the demonstration of anti-tumor activity in preclinical studies (Sect. 2.1), capivasertib has been evaluated in numerous clinical trials (either as monotherapy, or in combination with other anti-cancer agents) as a potential treatment for a range of cancers (Sect. 2.3). In particular, the ongoing clinical research program is largely focused on tumors reliant on PI3K/AKT pathway signaling, and in tumors harboring biomarker alterations in this pathway [4].



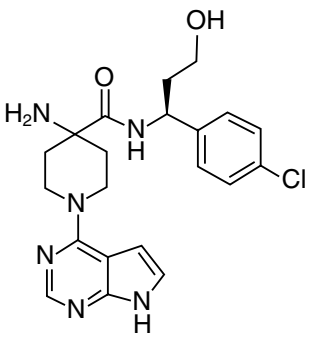
Key milestones in the development of capivasertib. *HER2-* human epidermal growth factor receptor 2-negative, *HR+* hormone receptor-positive, *mCRPC* metastatic castration-resistant prostate cancer, *mHSPC* metastatic hormone-sensitive prostate cancer, *NDA* New Drug Application, *TNBC* triple-negative breast cancer

Capivasertib received its first approval, in the USA, on 16 November 2023 for use in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative, locally advanced or metastatic breast cancer with one or more *PIK3CA*/*AKT1*/*PTEN*-alterations as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy [5, 7]. Prior to initiating capivasertib, fasting blood glucose and hemoglobin A1C levels should be evaluated, with further monitoring at regular intervals during treatment [5]. The recommended dosage of capivasertib, used in combination with fulvestrant, is 400 mg orally twice daily (approximately 12 h apart) for 4 days followed by 3 days off. Capivasertib can be taken with or without food. Treatment should be continued until disease progression or unacceptable toxicity [5]. Local prescribing information should be consulted for information on recommended dosage reductions or modifications for adverse reactions or for concomitant use with CYP3A inhibitors.

In addition to its approval in the USA, capivasertib is under regulatory review for HR-positive, HER2-negative breast cancer in China, Japan, and the EU, and in Australia, Brazil, Canada, Israel, Singapore, Switzerland, and the UK under the Project Orbis initiative [4]. Besides HR-positive, HER2-negative breast cancer, capivasertib is also currently in phase III clinical development for use (in combination with other anti-cancer drugs) in the treatment of triple-negative breast cancer (TNBC), castration-resistant prostate cancer (CRPC), and PTEN-deficient hormone-sensitive prostate cancer (HSPC), and has been assessed in several other malignancies, including B-cell non-Hodgkin lymphoma, endometrial cancer, and meningioma [4].

1.1 Company Agreements

Capivasertib was discovered by AstraZeneca following an earlier drug discovery research collaboration with Astex Therapeutics Ltd (now Astex Pharmaceuticals) and its collaboration with the Institute of Cancer Research and Cancer Research Technology Ltd [8]. An alliance between AstraZeneca and Astex Therapeutics to discover, develop, and commercialize novel small-molecule inhibitors of AKT for use as anti-cancer agents was announced in July 2005.



Chemical structure of capivasertib

2 Scientific Summary

2.1 Pharmacodynamics

Capivasertib inhibits all three isoforms of AKT (AKT1, AKT2, and AKT3), leading to the inhibition of phosphorylation of downstream AKT substrates, including GSK3β and PRAS40 [5, 6]. In tumors, AKT activation results from activation of upstream signaling pathways, mutations in *AKT1* and *PIK3CA*, and loss of PTEN function [1, 5]. In vitro, capivasertib has demonstrated activity against cell lines derived from a wide range of cancer types, including breast, prostate, endometrial, gastric, bladder, liver and hematologic cancers, and meningioma [6, 9–12]. Of note, a significant relationship between the presence of *PIK3CA* and/or *PTEN* mutations was observed [6]. Capivasertib has also demonstrated anti-tumor activity in mouse xenografts derived from various tumor types, including breast cancer [6, 13, 14], prostate cancer [11, 15], gastric cancer [12] and meningioma [9] xenograft models. Furthermore, capivasertib has demonstrated synergistic effects with a range of anti-cancer agents (including fulvestrant, enzalutamide, docetaxel, lapatinib and trastuzumab) in preclinical studies with cancer cell lines and xenograft models, including, in some cases, in settings where genetic alterations were not present [6, 12, 14–16].

2.2 Pharmacokinetics

Capivasertib exposure is approximately dose proportional over the dose range of 80–800 mg [5]. Maximum plasma concentrations (C_{max}) are achieved approximately 1–2 hours post dose; the absolute bioavailability is 29%. There is no clinically relevant food effect [17]. On the recommended 4 days on/3 days off dosing schedule, capivasertib steady-state concentrations are predicted to be reached on the third and fourth day of dosing each week, starting at week 2 [5]. On the off-dosing days, capivasertib plasma concentrations are approximately 0.5–15% of the steady-state C_{max} [5].

Capivasertib has a half-life of 8.3 hours [5]. Metabolism of the drug is primarily mediated by CYP3A4 and UGT2B7. Following a single radiolabeled oral dose of 400 mg, 50% of radioactivity was recovered in the feces and 45% was recovered in urine [5].

Capivasertib pharmacokinetics are not affected to a clinically relevant extent by race/ethnicity, sex, body weight (32–150 kg), age (26–87 years), mild hepatic impairment, or mild to moderate renal impairment [5]. The effects of moderate hepatic impairment on capivasertib pharmacokinetics are not fully characterized and the effects of severe renal impairment are unknown [5].

Concomitant use of strong or moderate CYP3A inhibitors with capivasertib may cause clinically significant increases in capivasertib exposure [5, 18]. Similarly, concomitant use of strong or moderate CYP3A inducers with capivasertib may cause clinically significant decreases in capivasertib exposure [5].

2.3 Therapeutic Trials

Capivasertib has demonstrated activity against a range of cancers in clinical trials, as a single agent or as part of combination therapy. The recommended intermittent 4 days on/3 days off dosing schedule for capivasertib was

Features and properties of capivasertib

Alternative names	AZD5363; Truqap™
Class	Antineoplastics; piperidines; pyrimidines; pyrroles; small molecules
Mechanism of action	Proto oncogene protein c-akt inhibition
Route of administration	Oral
Pharmacodynamics	Inhibits all three forms of AKT (AKT1, AKT2, and AKT3), leading to the inhibition of phosphorylation of downstream AKT substrates
Pharmacokinetics	Steady-state AUC = 8069 h•ng/mL; C_{max} = 1371 ng/mL; T_{max} ≈ 1–2 h; absolute bioavailability = 29%; steady-state oral volume of distribution = 1847 L; plasma-to-blood ratio = 0.71; half-life = 8.3 h; steady-state oral clearance = 50 L/h; renal clearance = 21% of total clearance; metabolism primarily mediated by CYP3A4 and UGT2B7
Most common adverse events (incidence ≥ 20%), including laboratory anomalies	Diarrhea, cutaneous adverse reactions, increased random glucose, decreased lymphocytes, decreased hemoglobin, increased fasting glucose, nausea, fatigue, decreased leukocytes, increased triglycerides, decreased neutrophils, increased creatinine, vomiting, stomatitis
ATC codes	
WHO ATC code	L01X-E (Protein kinase inhibitors)
EphMRA ATC code	L1H (Protein kinase inhibitor antineoplastics)
Chemical name	4-amino-*N*-[(1S)-1-(4-chlorophenyl)-3-hydroxypropyl]-1-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamide

AUC area under the plasma concentration-time curve, C_{max} maximum plasma concentration, T_{max} time to C_{max}

determined in a phase I first-in-human trial (NCT01226316) in patients with advanced solid malignancies [19].

2.3.1 In Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer

The addition of capivasertib to fulvestrant therapy significantly prolonged progression-free survival (PFS) in patients with HR-positive, HER2-negative advanced breast cancer that had progressed during or after previous aromatase inhibitor therapy with or without a cyclin-dependent kinase (CDK) 4/6 inhibitor, based on the multinational, randomized, double-blind, placebo-controlled, phase III CAPItello-291 trial [20].

In total, 708 pre-, peri-, or post-menopausal women or men (median age 58 years, range 26–90 years) with HR-positive, HER2-negative locally advanced (i.e., primary inoperable) or metastatic breast cancer and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were enrolled in CAPItello-291 and randomized (1 : 1) to receive capivasertib plus fulvestrant or placebo plus fulvestrant [20]. Capivasertib 400 mg or matching placebo was administered orally twice daily on the recommended intermittent dosing schedule; fulvestrant 500 mg was administered intramuscularly every 14 days for three injections and every 28 days thereafter. Protocol-defined dose reductions of capivasertib (or placebo) were permitted for adverse events; dose reductions of fulvestrant were not permitted. Treatment was continued until disease progression or unacceptable toxicity. Pre- or peri-menopausal women also received a luteinizing hormone-releasing hormone agonist during the study drug treatment period. In the overall population, 77.3% of patients were postmenopausal women, 69.1% had previously received a CDK4/6 inhibitor for advanced disease, and 18.2% had previously received chemotherapy for advanced disease. In total, 289 of 708 patients (40.8%) in the overall population had tumors with alterations in *PIK3CA*, *AKT1*, or *PTEN* (determined by next-generation sequencing), hereafter referred to as the *PIK3CA*/*AKT1*/*PTEN*-altered population; 313 patients (44.2%) had confirmed *PIK3CA*/*AKT1*/*PTEN*-nonaltered tumors and 106 patients (15.0%) had unknown alteration status. The dual primary endpoint was investigator-assessed PFS in the overall population and in the *PIK3CA*/*AKT1*/*PTEN*-altered population [20].

The primary analysis, conducted after 551 events of disease progression or death, showed a significant increase in investigator-assessed PFS for capivasertib plus fulvestrant recipients versus placebo plus fulvestrant recipients, both in the overall population (median 7.2 months vs 3.6 months; hazard ratio for progression or death = 0.60; 95% CI 0.51–0.71; $p < 0.001$) and in the *PIK3CA*/*AKT1*/*PTEN*-altered population (median 7.3 months vs 3.1 months; hazard ratio = 0.50; 95% CI 0.38–0.65; $p < 0.001$). An exploratory analysis of investigator-assessed PFS in patients with confirmed *PIK3CA*/*AKT1*/*PTEN*-nonaltered tumors showed a hazard ratio of 0.79 (95% CI 0.61–1.02), indicating that the treatment effect observed in the overall population was primarily attributed to the results seen in the *PIK3CA*/*AKT1*/*PTEN*-altered population. PFS results based on assessment by blinded independent central review (BICR) were highly consistent with the primary endpoint findings. The investigator-assessed objective response rates (ORR) in the capivasertib plus fulvestrant and placebo plus fulvestrant groups, respectively, were 22.9% and 12.2% in the overall population and 28.8% and 9.7% in the *PIK3CA*/*AKT1*/*PTEN*-altered population. Overall survival data were immature at the primary analysis data cut-off. Estimated 18-month overall survival rates in the capivasertib plus fulvestrant and placebo plus fulvestrant groups, respectively, were 73.9% and 65.0% in the overall population and 73.2% and 62.9% in the *PIK3CA*/*AKT1*/*PTEN*-altered population [20].

Clinically meaningful activity for capivasertib in combination with fulvestrant in the treatment of estrogen receptor (ER)-positive metastatic breast cancer was earlier demonstrated in the first-in-human phase I trial (NCT01226316) in expansion cohorts of patients with tumors harboring *AKT1*^{E17K} [21] or *PTEN* [22] mutations. Subsequently, the efficacy of capivasertib in combination with fulvestrant was investigated in the randomized, double-blind, placebo-controlled, phase II FAKTION trial in patients with ER-positive, HER2-negative, aromatase inhibitor-resistant advanced breast cancer [23]. The FAKTION trial provided evidence that the addition of capivasertib to fulvestrant can improve both PFS and overall survival in this patient population [23, 24]. It should be noted, however, that no participants in the trial had received previous CDK4/6 inhibitor therapy [23, 24], now part of standard-of-care therapy in this disease setting [25].

In total, 140 postmenopausal women with ER-positive, HER2-negative locally advanced or metastatic breast cancer and an ECOG performance status of 0–2 were enrolled in FAKTION and randomized (1 : 1) to receive capivasertib plus fulvestrant or placebo plus fulvestrant [23]. Fulvestrant 500 mg was administered intramuscularly on day 1 of every 28-day cycle, with an additional loading dose administered on cycle 1 day 15. Capivasertib 400 mg or matching placebo was administered using the recommended dosing schedule, with dosing commencing on cycle 1 day 15. Study treatment was continued until disease progression or unacceptable toxicity. The primary endpoint was investigator-assessed PFS in the full analysis set on an intent-to-treat (ITT) basis [23].

At the time of the primary analysis, conducted after 112 events of disease progression or death, investigator-assessed PFS was significantly longer in the capivasertib plus fulvestrant group compared with the placebo plus fulvestrant group (median 10.3 months vs 4.8 months; hazard ratio for progression or death = 0.58; 95% CI 0.39–0.84; $p = 0.0044$) [23]. The ORRs in the capivasertib plus fulvestrant and placebo plus fulvestrant groups, respectively, were 29% and 8%

[odds ratio (OR) = 4.42; 95% CI 1.65–11.84; $p = 0.0031$]. Overall survival data were immature at the primary analysis data cut-off [23]. In an updated analysis with 5 years of follow-up, a significant improvement in overall survival was seen for capivasertib plus fulvestrant compared with fulvestrant alone (29.3 months vs 23.4 months; hazard ratio for death = 0.66; 95% CI 0.45–0.97; $p = 0.035$) [24]. In the updated analysis, a prespecified exploratory analysis was performed based on subgroups of patients with *PIK3CA/AKT1/PTEN*-altered and -nonaltered tumors (determined using a combination of next-generation sequencing, pyrosequencing, and digital-droplet PCR test results for *PIK3CA* and *AKT1*). In the *PIK3CA/AKT1/PTEN*-altered subgroup ($n = 76$), median PFS was 12.8 months in capivasertib plus fulvestrant recipients and 4.6 months in placebo plus fulvestrant recipients (HR = 0.44; 95% CI 0.26–0.72; $p = 0.0014$); in the *PIK3CA/AKT1/PTEN*-nonaltered subgroup ($n = 64$), median PFS was 7.7 months in capivasertib plus fulvestrant recipients and 4.9 months in placebo plus fulvestrant recipients (HR = 0.70; 95% CI 0.40–1.25; $p = 0.23$) [24].

According to the randomized, double-blind, placebo-controlled, phase II expansion portion of the BEECH trial in patients with ER-positive, HER2-negative advanced or metastatic breast cancer, the addition of capivasertib to paclitaxel had no significant effect on PFS in the overall population ($n = 110$) or in a subpopulation of patients ($n = 51$) with a *PIK3CA* mutation [26].

2.3.2 In Triple-Negative Breast Cancer

The addition of capivasertib to first-line paclitaxel therapy significantly prolonged PFS in patients with metastatic TNBC, based on the randomized, double-blind, placebo-controlled, phase II PAKT trial [27].

In total, 140 women (median age 54 years) with untreated metastatic triple-negative (i.e., ER-negative, progesterone receptor-negative, and HER2-negative) breast cancer were enrolled in PAKT and randomized (1 : 1) to receive paclitaxel plus capivasertib or paclitaxel plus placebo [27]. Paclitaxel 90 mg/m^2 was administered by intravenous infusion over approximately 1 h on days 1, 8, and 15 of each 28-day treatment cycle; capivasertib 400 mg or placebo was administered orally twice daily on days 2 to 5 of weeks 1, 2, and 3 of each 28-day cycle. Treatment was continued until disease progression or unacceptable toxicity. Patients with previous systemic therapy for locally advanced or metastatic disease were excluded; however, previous adjuvant or neoadjuvant chemotherapy was permitted provided that taxane-based therapy had been completed ≥ 12 months before randomization. In the ITT population, 69% of patients had visceral involvement, 46% had metastases in three or more organs, and 77% had received adjuvant or neoadjuvant chemotherapy, including 57% with prior taxane-based therapy. The primary endpoint was investigator-assessed PFS [27].

The primary analysis (median follow-up of 18.2 months), conducted after 112 events of disease progression or death, showed a significant increase in investigator-assessed PFS for paclitaxel plus capivasertib recipients versus paclitaxel plus placebo recipients (median 5.9 months vs 4.2 months; hazard ratio for progression or death = 0.74; 95% CI 0.50–1.08; 1-sided $p = 0.06$; 2-sided $p = 0.11$), meeting the predefined significance level (1-sided $p = 0.10$) [27]. Overall survival data were immature at the time of the primary analysis but suggested a benefit for paclitaxel plus capivasertib over paclitaxel plus placebo (median overall survival of 19.1 months vs 12.6 months; hazard ratio = 0.61; 95% CI 0.37–0.99; 2-sided $p = 0.04$). At the primary analysis, the benefit of capivasertib appeared to be more pronounced in patients with *PIK3CA/AKT1/PTEN*-altered tumors, with prespecified analyses showing median PFS in the paclitaxel plus capivasertib and paclitaxel plus placebo groups, respectively, of 9.3 months and 3.7 months (HR = 0.30; 95% CI 0.11–0.79; 2-sided $p = 0.01$) in the *PIK3CA/AKT1/PTEN*-altered subgroup and 5.3 months and 4.4 months (HR = 1.13; 95% CI 0.70–1.82; 2-sided $p = 0.61$) in the *PIK3CA/AKT1/PTEN*-nonaltered subgroup [27]. However, an updated analysis (median follow-up of 40.0 months) found no meaningful differences in terms of the benefit of capivasertib between patients with *PIK3CA/AKT1/PTEN*-altered and -nonaltered tumors [28]. In the updated analysis, overall survival was numerically longer in the paclitaxel plus capivasertib group compared with the paclitaxel plus placebo group in the overall population (median 19.1 months vs 13.5 months; hazard ratio = 0.70; 95% CI 0.47–1.05; $p = 0.085$), and in both the *PIK3CA/AKT1/PTEN*-altered (hazard ratio = 0.58; 95% CI 0.21–1.58; $p = 0.290$) and *PIK3CA/AKT1/PTEN*-nonaltered (hazard ratio = 0.74; 95% CI 0.47–1.18; $p = 0.207$) subgroups [28].

The phase Ib/II BEGONIA trial is an ongoing two-part, open-label platform study evaluating the safety and efficacy of durvalumab in combinations with other anti-cancer agents in the treatment of locally advanced or metastatic TNBC [29]. Although not designed to compare activity across treatment groups, the ORR among patients treated with durvalumab, paclitaxel, and capivasertib triple therapy (53.3%) was similar to the ORR for patients treated with durvalumab plus paclitaxel alone (56.5%) [29].

2.3.3 In Metastatic Castration Resistant Prostate Cancer

The randomized, double-blind, placebo-controlled, phase II ProCAID trial, although failing to meet its primary endpoint of composite PFS, provided evidence that the addition of capivasertib to docetaxel and prednisolone could potentially improve overall survival in patients with metastatic CRPC [30, 31]. Validation of the finding of an overall survival benefit is being pursued in the phase III CAPItello-280 trial in patients with metastatic CRPC who have not received prior chemotherapy

for metastatic CRPC but whose disease has progressed despite treatment with an androgen receptor-targeted agent (ARTA) (Sect. 2.6) [32].

In total, 150 patients (median age 69 years) were enrolled in ProCAID and randomized (1 : 1) to receive capivasertib or matching placebo, with all patients also receiving docetaxel and prednisolone [31]. Study treatment was administered for up to ten 21-day cycles, with docetaxel 75 mg/m^2 administered intravenously on day 1, oral prednisolone 5 mg administered twice daily on days 1–21, and oral capivasertib 320 mg or matching placebo administered twice daily on a 4 days on/3 days off schedule from day 2 of each cycle. Prior treatment with hormonal therapies was permitted; patients with previous chemotherapy for metastatic CRPC were excluded. The primary endpoint was investigator-assessed composite PFS, which included prostate-specific antigen progression events [31].

In the primary endpoint analysis, the addition of capivasertib to docetaxel and prednisolone did not reduce the risk of progression or death compared with docetaxel and prednisolone alone (median composite PFS of 7.0 months vs 6.6 months; hazard ratio = 0.92; 80% CI 0.73–1.16; 1-sided $p = 0.32$) [31]. Median overall survival was 31.15 months in the docetaxel and prednisolone plus capivasertib group and 20.27 months in the docetaxel and prednisolone alone group (hazard ratio = 0.54; 95% CI 0.34–0.88; 2-sided $p = 0.01$) [31]. In an updated overall survival analysis, conducted when 66% of patients had died, median overall survival was 25.3 months in the docetaxel and prednisolone plus capivasertib group and 20.3 months in the docetaxel and prednisolone alone group (hazard ratio = 0.70; 95% CI 0.47–1.05; nominal $p = 0.09$) [30]. In an exploratory analysis in the subgroup of patients ($n = 101$) who had received abiraterone and/or enzalutamide prior to entering the study, median overall survival was 25.0 months in the docetaxel and prednisolone plus capivasertib group and 17.6 months in the docetaxel and prednisolone alone group (hazard ratio = 0.57; 95% CI 0.36–0.91; $p = 0.02$), suggesting that the addition of capivasertib to docetaxel and prednisolone may be particularly beneficial in patients previously treated with an ARTA [30].

2.3.4 In B-Cell Non-Hodgkin Lymphoma

Preliminary efficacy data from the open-label, phase II CAPITAL trial demonstrated single-agent activity for capivasertib in patients with relapsed or refractory B-cell non-Hodgkin lymphoma [33]. At data cut-off in the preliminary analysis, 15 patients (median age 55 years) with heavily pretreated (median three prior lines of therapy) follicular lymphoma ($n = 11$), marginal zone lymphoma ($n = 2$), or mantle cell lymphoma ($n = 2$) had received treatment with oral capivasertib 480 mg twice daily on the recommended dosing schedule until disease progression or unacceptable toxicity. With a median follow-up of 5 months, the ORR among the 13 patients (11 evaluable) with follicular lymphoma or marginal zone lymphoma was 54%, including one patient with a complete response and six patients with a partial response. Neither of the patients with mantle cell lymphoma were evaluable at data cut-off [33].

2.3.5 Other Trials

Several other trials have investigated the efficacy of capivasertib in the treatment of advanced solid tumors, either as monotherapy or in combination with other anti-cancer agents, with activity observed in a range of cancer types.

In the phase I first-in-human trial (NCT01226316), response rates for monotherapy with capivasertib 480 mg twice daily using the recommended dosing schedule in patients with *PIK3CA*-mutated ER-positive breast cancer and gynecologic cancers were modest (< 10%) [19]. However, in an expansion of the study in 52 patients with *AKT1*^{E17K}-mutant tumors and a median of five prior lines of therapy, confirmed partial responses were observed in nine patients (17.3%), including patients with ER-positive breast ($n = 4$) and endometrial ($n = 2$) cancers, cervical cancer ($n = 1$), TNBC ($n = 1$), and lung adenocarcinoma ($n = 1$) [34]. Unconfirmed partial responses occurred in four (7.7%) additional patients, including one patient with anal adenocarcinoma [34]. Comparable results were observed in the National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) subprotocol EAY131-Y trial (NCT04439123) in patients with metastatic *AKT1*^{E17K}-mutant tumors treated with capivasertib [35]. The ORR (primary endpoint) in the trial was 28.6%, with responses observed in 10 of 35 evaluable patients, including a complete response in a patient with endometrioid endometrial adenocarcinoma and partial responses observed in patients with HR-positive/*ERBB2*-negative breast cancer ($n = 7$), uterine leiomyosarcoma ($n = 1$), and oncocytic parotid gland carcinoma ($n = 1$) [35].

Two cohorts of patients in the multicohort, phase IIa plasmaMATCH platform trial in patients with advanced breast cancer received treatment involving capivasertib [36]. In cohort C, which comprised patients with ER-positive breast cancer with *AKT1* mutations treated with capivasertib 400 mg plus fulvestrant, four (22%) of 18 patients had a response, meeting the target number to infer activity. On the other hand, in cohort D, which comprised patients with ER-negative breast cancer treated with capivasertib 480 mg, two (11%) of 19 patients had a response, failing to meet the target number to infer activity [36].

Capivasertib has also been investigated in combination with the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib [37, 38]. In a phase I trial (NCT02338622) in 64 patients with advanced solid tumors treated with capivasertib plus olaparib, 25 (44.6%) of 56 evaluable patients had clinical benefit (defined as a complete or partial response, or stable disease for ≥ 4 months) [38]. Patients in the trial

had received a median of four prior systemic therapies and had a range of advanced solid malignancies, including ovarian cancer ($n = 25$), breast cancer ($n = 18$), pancreatic cancer ($n = 5$), CRPC ($n = 4$) and others ($n = 12$) [38]. In a separate phase I trial (NCT02208375) in 38 patients with advanced ovarian ($n = 16$), endometrial ($n = 11$), or TNBC ($n = 11$) treated with capivasertib plus olaparib, partial responses were observed in six (19%) of 32 evaluable patients, including four (44%) of nine evaluable patients with endometrial cancer [37].

Key clinical trials of capivasertib

Identifier(s)	Indication	Phase	Drug(s)	Location(s)	Sponsor(s)	Status
NCT04305496; CAPItello-291	Advanced HR+/HER2- breast cancer	III	Capivasertib; fulvestrant; placebo	Multinational	AstraZeneca	Active
NCT04862663; CAPItello-292	Advanced HR+/HER2- breast cancer	III	Capivasertib; fulvestrant; palbociclib; ribociclib; abemaciclib	Multinational	AstraZeneca	Recruiting
NCT01992952; FAKTION	Advanced HR+/HER2- breast cancer	I/II	Capivasertib; fulvestrant; placebo	UK	Velindre NHS Trust	Active
NCT01625286; BEECH	Advanced HR+/HER2- breast cancer	I/II	Capivasertib; paclitaxel; placebo	Multinational	AstraZeneca	Completed
NCT03997123; CAPItello-290	Advanced TNBC	III	Capivasertib; paclitaxel; placebo	Multinational	AstraZeneca	Active
NCT02423603; PAKT	Advanced TNBC	II	Capivasertib; paclitaxel; placebo	France, Georgia, Hungary, Republic of Korea, Romania, UK	Queen Mary University of London	Completed
NCT03742102; BEGONIA	Advanced TNBC	I/II	Capivasertib; durvalumab; oleclumab; paclitaxel; trastuzumab deruxtecan; datopotamab deruxtecan	Canada, Poland, Republic of Korea, Taiwan, UK, USA	AstraZeneca	Recruiting
NCT03801369	Advanced TNBC	II	Capivasertib; ceralasertib; durvalumab; olaparib; selumetinib	USA	OHSU Knight Cancer Institute	Recruiting
NCT05348577; CAPItello-280	mCRPC	III	Capivasertib; docetaxel; placebo	Multinational	AstraZeneca	Recruiting
NCT04087174	mCRPC	I	Capivasertib; enzalutamide; abiraterone	Spain, USA	AstraZeneca	Completed
NCT02525068; RE-AKT	mCRPC	II	Capivasertib; enzalutamide; placebo	UK	Institute of Cancer Research, UK	Completed
NCT02121639; ProCAID	mCRPC	I/II	Capivasertib; docetaxel; prednisolone; placebo	UK	University Hospital Southampton NHS Foundation Trust	Completed
NCT04493853; CAPItello-281	mHSPC with PTEN deficiency	III	Capivasertib; abiraterone acetate; placebo	Multinational	AstraZeneca	Recruiting
NCT05008055; CAPITAL	R/R B-NHL	II	Capivasertib	Canada, Denmark, France, Republic of Korea, Spain, UK, USA	AstraZeneca	Active
NCT02523014	Progressive meningioma	II	Capivasertib; vismodegib; FAK inhibitor GSK2256098; abemaciclib	USA	Alliance for Clinical Trials in Oncology	Recruiting
NCT02208375	Advanced solid cancers	I/II	Capivasertib; olaparib; vistusertib	USA	M.D. Anderson Cancer Center	Active
NCT01226316	Advanced solid cancers	I	Capivasertib	Multinational	AstraZeneca	Active
NCT04439123	Cancers with *AKT* genetic changes	II	Capivasertib	USA	National Cancer Institute	Active

B-NHL, B-cell non-Hodgkin lymphoma, *HER2-* human epidermal growth factor receptor 2-negative, *HR+* hormone receptor-positive, *mCRPC* metastatic castration-resistant prostate cancer, *mHSPC* metastatic hormone-sensitive prostate cancer, *NHS* National Health Service, *OHSU* Oregon Health & Science University, *PTEN* phosphatase and tensin homolog, *R/R* relapsed or refractory, *TNBC* triple-negative breast cancer

2.4 Adverse Events

Based on data from the phase III CAPItello-291 trial (Sect. 2.3.1) in patients with HR-positive, HER2-negative advanced breast cancer, capivasertib has manageable tolerability when used in combination with fulvestrant [20]. In the trial, the most common (incidence ≥ 20%) adverse events of any grade in the capivasertib plus fulvestrant group were diarrhea (incidence 72.4% vs 20.0% in the placebo plus fulvestrant group), rash (grouped term, includes rash, rash macular, maculopapular rash, rash papular, and rash pruritic; 38.0% vs 7.1%), nausea (34.6% vs 15.4%), fatigue (20.8% vs 12.9%), and vomiting (20.6% vs 4.9%). The most common adverse events of grade ≥ 3 severity were rash (grouped term; 12.1% vs 0.3%), diarrhea (9.3% vs 0.3%), and hyperglycemia (2.3% vs 0.3%). Serious adverse events occurred in 16.1% of capivasertib plus fulvestrant recipients versus 8.0% of placebo plus fulvestrant recipients. Adverse events resulting in death occurred in four patients in the capivasertib plus fulvestrant group (acute myocardial infarction, cerebral hemorrhage, aspiration pneumonia, and sepsis in one patient each) and in one patient in the placebo plus fulvestrant group (Covid-19), none of which were considered to be related to study treatment. Adverse events leading to dose interruption occurred in 34.9% versus 10.3% of patients, adverse events leading to dose reduction occurred in 19.7% versus 1.7% of patients, and adverse events leading to treatment discontinuation occurred in 13.0% versus 2.3% of patients in the respective groups [20].

Patients with insulin-dependent diabetes were excluded from CAPItello-291 [20]. Grade 3 hyperglycemia occurred in seven (2.0%) capivasertib plus fulvestrant recipients (and in one placebo plus fulvestrant recipient) in the trial; grade 4 hyperglycemia occurred in one (0.3%) capivasertib plus fulvestrant recipient (and in no placebo plus fulvestrant recipients) [20]. Forty-five percent of capivasertib plus fulvestrant recipients with hyperglycemia in CAPItello-291 required treatment with anti-hyperglycemic medication, with two thirds of those patients remaining on these medications at study treatment discontinuation or last follow-up [5].

Serious cutaneous adverse reactions were reported among capivasertib plus fulvestrant recipients in CAPItello-291, including serious events of maculopapular rash (in 5 patients), erythema multiforme (1 patient), and drug reaction with eosinophilia and systemic symptoms (DRESS; 1 patient) [20].

2.5 Companion Diagnostic

FoundationOne®CDx is a qualitative next-generation sequencing-based in vitro diagnostic test for detection of substitutions, insertion and deletion alterations, and copy number alterations in 324 genes and select gene rearrangements [39]. It is US FDA-approved as a companion diagnostic for identifying candidates for treatment with capivasertib in accordance with the approved drug labeling [39].

2.6 Ongoing Clinical Trials

In addition to the trials discussed in Sect. 2.3, capivasertib (including as part of combination therapy) is being evaluated in a wide range of ongoing clinical trials in a variety of cancers, including several phase III trials that are underway. Among these is the phase III portion of the randomized, open-label CAPItello-292 trial (NCT04862663), which is evaluating the efficacy, safety, and degree of added benefit of capivasertib combined with fulvestrant and investigator's choice of CDK4/6 inhibitor (palbociclib or ribociclib) in patients with locally advanced or metastatic HR-positive, HER2-negative breast cancer with no prior endocrine therapy in the advanced setting. The primary endpoint of CAPItello-292 is PFS as assessed by BICR. An initial dose-finding phase Ib portion of the trial identified capivasertib 400 mg twice daily for 4 days followed by 3 days off, palbociclib 125 mg once daily for 21 days of each 28-day cycle, and fulvestrant 500 mg every 28 days plus a loading dose on cycle 1 day 15 as the recommended phase III dose (RP3D) of the capivasertib, palbociclib, and fulvestrant triple combination [40]. Eligibility criteria in the phase Ib portion of the trial included having had at least one prior endocrine therapy in the advanced setting or disease recurrence within 12 months of completing (neo)adjuvant endocrine therapy. Preliminary response data from the phase Ib portion of the trial have suggested evidence of clinical activity of this combination at the RP3D, with some partial responses observed (including in patients with prior CDK4/6 inhibitor and/or fulvestrant therapy) [40].

Following on from the phase II PAKT trial (Sect. 2.3.2), CAPItello-290 (NCT03997123) is a randomized, double-blind, placebo-controlled, multinational phase III trial to evaluate the efficacy and safety of capivasertib in combination with paclitaxel in the first-line treatment of patients with locally advanced or metastatic TNBC in an unselected population [41]. CAPItello-290 is in the final stages of follow-up for the primary endpoint of overall survival. The trial will also explore potential predictive markers of sensitivity to the combination of capivasertib and paclitaxel [41].

CAPItello-280 (NCT05348577) is a randomized, double-blind, placebo-controlled, multinational phase III trial underway to evaluate the efficacy and safety of capivasertib plus docetaxel and steroid therapy versus placebo plus docetaxel and steroid therapy in patients with metastatic CRPC who

have not received prior chemotherapy for metastatic CRPC but whose disease has progressed despite treatment with an ARTA in any setting [32]. The CAPItello-280 primary endpoint is overall survival, with the aim to further evaluate and confirm the findings from the phase II ProCAID trial (Sect. 2.3.3).

In the HSPC setting, CAPItello-281 (NCT04493853) is a randomized, double-blind, placebo-controlled, multinational phase III trial underway to evaluate the efficacy and safety of capivasertib plus abiraterone versus placebo plus abiraterone, on a background of androgen deprivation therapy, in patients with de novo metastatic HSPC with PTEN-deficient tumors [42]. The primary endpoint of CAPItello-281 is radiographic PFS.

Several multicohort platform trials involving capivasertib are also underway, including: the phase II Molecular Analysis for Therapy Choice (MATCH) trial (NCT02465060) in advanced refractory solid tumors, lymphomas, or multiple myeloma; the phase II plasmaMATCH trial (NCT03182634) in advanced breast cancer [36]; the phase I/II VIKTORY trial in metastatic gastric cancer [43]; a phase II trial (NCT03660826) in recurrent or refractory endometrial cancer; and the phase II National Lung Matrix Trial (NCT02664935) in non-small cell lung cancer [44].

3 Current Status

Capivasertib received its first approval, in the USA, on 16 November 2023 for use in combination with fulvestrant for the treatment of adult patients with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with one or more *PIK3CA*/*AKT1*/*PTEN*-alterations as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy [5, 7].

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Declarations

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