THERAPEUTIC ADVANCES in
Medical Oncology

Review

Capivasertib/Fulvestrant in patients with HR+, HER2-low or HER2-negative locally advanced or metastatic breast cancer

Ther Adv Med Oncol

2025, Vol. 17: 1–12

DOI: 10.1177/17588359251358947

Karam Aboud, Magda Meissner and Rob Jones

***Abstract*:** The landscape of breast cancer treatment continues to evolve. Survival rates have improved due to advancements in treatments such as endocrine therapy, cyclin-dependent kinase 4/6 inhibitors and targeted therapies. The PI3K/AKT/PTEN signalling pathway, frequently mutated in breast cancer, is a key target. Capivasertib, an AKT inhibitor, has shown promise in pre-clinical studies and clinical trials as monotherapy and in combination with Fulvestrant. The FAKTION trial demonstrated the efficacy and safety of Capivasertib with Fulvestrant, particularly in patients with PI3K/AKT/PTEN alterations. The Capitello 291 trial further supported the observed efficacy of Capivasertib with Fulvestrant in the FAKTION trial. Notably, Capivasertib plus Fulvestrant received Food and Drug Administration (FDA) approval in 2023 for ER-positive/HER2-negative breast cancer with PI3K/AKT/PTEN alterations. More recently, the National Institute for Health and Care Excellence (NICE) has also given approval for Capivasertib and Fulvestrant in this setting in May 2025. Moreover, evidence suggests further potential useful combinations of Capivasertib in other breast cancer settings, including triple-negative breast cancer. In conclusion, the evolving understanding of molecular pathways in breast cancer, coupled with successful clinical trials and regulatory approvals, positions Capivasertib plus Fulvestrant as a promising addition to standard care for ER-positive/HER2-negative breast cancer. Further research is required to compare the efficacy of available agents, explore the optimal sequence of treatment and establish the best drug combinations for ER-positive/HER2-negative breast cancer patients.

Keywords: breast cancer, combination therapy, hormone therapy, PI3K/Akt/mTOR inhibitor, targeted therapy

Received: 22 January 2024; revised manuscript accepted: 12 June 2025.

Introduction

Breast cancer is the most common cancer in females and the 4th most common cause of cancer death in the UK.[1] Since the 1970s, survival beyond 10 years from breast cancer has almost doubled. By 2010, almost 8 in 10 women survived their diagnosis of breast cancer by more than 10 years.[1] This is due to a combination of treatment improvements and disease stage distribution.[1]

Approximately two-thirds of breast cancer patients have ER (oestrogen receptor) positive, HER2 negative disease.[2] In the metastatic or advanced non-resectable setting, the first-line treatment for ER-positive/HER2-negative breast cancer is a combination of endocrine therapy (ET) with a cyclin-dependent kinase 4 and 6 inhibitor (CDK 4/6 inhibitor).[3] Patients with an impending organ crisis are generally treated with chemotherapy instead.[3] The choice of ET depends on the previous use of ET for each patient. Patients with no previous ET for breast cancer are treated with an aromatase inhibitor (AI) such as Letrozole, and patients who are currently taking an AI or stopped taking an AI less than 12 months ago are treated with an oestrogen receptor antagonist (Fulvestrant).[3]

Correspondence to:
Karam Aboud
Velindre Cancer Centre, Cardiff University School of Medicine, DCG, Velindre Road, Cardiff CF14 2TL, UK
karam.aboud@wales.nhs.uk

Magda Meissner
Rob Jones
Velindre Cancer Centre, Cardiff University School of Medicine, DCG, Cardiff, UK

There are a number of treatment options available in the metastatic second-line setting for ER-positive/HER2-negative breast cancer. Options include a combination of Fulvestrant and Alpelisib for PIK3CA mutated tumours, Exemestane-Everolimus, chemotherapy or PARP (Poly ADP-ribose polymerase) inhibitors if a germline BRCA mutation is present. Further Food and Drug Administration (FDA) approvals have been given to drugs based on the presence of genetic alterations in this setting. Capivasertib was approved for patients with any PIK3CA/AKT1/PTEN gene alterations, and Elacestrant was also approved for patients with ESR1 gene mutation following ET.[4,5] Additionally, antibody-drug conjugate drugs Datopotamab Deruxtecan and Sacituzumab Govitecan have been approved by the FDA for metastatic ER-positive/HER2-negative breast cancer.[6] Datopotamab Deruxtecan was approved for patients who have received prior ET and chemotherapy for unresectable or metastatic disease. Sacituzumab Govitecan also gained approval for patients who have received prior hormone therapy and at least two systemic therapies for ER-positive/HER2-negative metastatic breast cancer. Navigating therapeutic decisions for patients in this metastatic setting is complex. The choice between these agents is dependent on many factors, including efficacy within each subgroup of patients, side-effect profile of each drug, previous therapy, burden of disease, previous response to ET, patient fitness and patient preference.[3]

Multiple trials support the use of these agents in the standard of care pathway for advanced or metastatic ER-positive/HER2-negative breast cancer.[3] The use of ET to target the oestrogen receptor pathway in this setting is well established.[7] More recently, the clinical benefit of combining CDK4/6 inhibitors Palbociclib, Ribociclib and Abemaciclib to ET has been demonstrated in several trials with improvements in progression free survival (PFS) and overall survival (OS).[8–10] Moreover, there is evidence to support mTOR inhibition with Everolimus and PIK3CA inhibition with Alpelisib.[11,12]

The frequency of PIK3CA mutations is approximately 40% in ER-positive/HER2-negative breast cancer patients.[12] Alpelisib is an inhibitor of the phosphoinositide 3-kinase-alpha (PI3Ka) isoform.[12] The SOLAR-1 phase III randomised trial compared Fulvestrant and Placebo with Fulvestrant and Alpelisib. In the PIK3CA-mutant cohort, Alpelisib resulted in a PFS of 11 months versus 5.7 for Fulvestrant and Placebo. However, this survival benefit for Alpelisib was not replicated in the cohort of patients without PIK3CA alterations.[12] The side effect profile of Alpelisib is an important consideration for clinicians considering this treatment for patients with PIK3CA alterations. Prominent grade 3 or above side effects observed in SOLAR-1 include hyperglycaemia, rash (20%) and diarrhoea (7%). Hyperglycaemia rates were particularly high with 65% of patients in the SOLAR-1 trial cohort developing hyperglycaemia of any grade. Rates of grade 3 and grade 4 hyperglycaemia were found to be 33% and 3.9% respectively in the study cohort. Additionally, patients with type 1 diabetes and uncontrolled type 2 diabetes were excluded from the trial, meaning it is difficult to ascertain the safety profile of Alpelisib for these patients. This can certainly limit the utility of Alpelisib for patients with these medical conditions. Assessment of risk versus benefit of Alpelisib, alternative treatment options available and careful monitoring for patients with a background of type 2 diabetes or risk factors for hyperglycaemia such as obesity are important considerations in clinic.

Evidence from the phase III BOLERO-2 trial and BOLERO-6 trial demonstrated a significant PFS benefit with the combination of Everolimus and Exemestane compared to monotherapy with either drug alone (7.8 months for combination vs 3.2 months for Exemestane alone; hazard ratio [HR]: 0.45; 95% CI: 0.35–0.54; $p < 0.0001$).[11,13] There is currently regulatory approval for the use of Exemestane and Everolimus for patients who have progressed on AI Letrozole or Anastrozole. However, there is limited evidence for the efficacy of Everolimus after CDK 4/6 inhibition, as studies on Everolimus were conducted prior to the availability of CDK 4/6 inhibitors.[14] There is, on the other hand, some evidence from retrospective observational studies suggesting that an improvement in OS observed for patients who had ET plus CDK 4/6 inhibition followed by Everolimus plus Exemestane is largely driven by the use of CDK 4/6 inhibition in this cohort.[14] Therefore, Everolimus plus Exemestane may be more suitable as a second or later line of ET therapy, though it is difficult to establish the exact benefit of these agents following CDK 4/6 inhibition due to the lack of evidence .

Of note, PIK3CA/AKT/mTOR alterations are not predictive of Everolimus benefit.[15] Considering both Everolimus and Alpelisib generally act on this pathway, there is no evidence comparing the efficacy of these agents directly against each other. There is also no data to guide the order in which these drugs should be used. Therefore, the choice of therapy between these two agents would depend on the PIC3CA status of the patient and the suitability of the side-effect profile to each individual patient. Significant grade 3 and 4 toxicities for Everolimus include stomatitis, dyspnoea, non-infectious pneumonitis and abnormal liver function tests, which occurred in 8%, 4%, 3% and 3% of patients, respectively.[13]

Elacestrant is an oral selective oestrogen receptor degrader which is indicated for the treatment of postmenopausal women with advanced or metastatic ESR1 mutant ER-positive/HER2-negative breast cancer following progression on at least one line of ET.[5] The phase III EMERALD trial explored the use of Elacestrant in ER-positive/HER2-negative breast cancer patients who had 1–2 lines of ET, including the use of CDK 4/6 inhibitors and 0–1 lines of prior chemotherapy.[16] The trial compared Elacestrant against the standard of care ET both in the overall cohort and in patients with an EST1 mutation. At 12 months, patients who received Elacestrant in the overall cohort achieved better PFS compared to standard of care ET and patients specifically receiving Fulvestrant (22%, 9% and 10% respectively; HR = 0.70; 95% CI: 0.55–0.88; $p = 0.002$). This improvement in PFS is more marked in the ESR1 mutant sub-cohort with patients achieving PFS rates of 27%, 8.2% and 8.4% for Elacestrant, standard of care ET and Fulvestrant, respectively (HR = 0.55; 95% CI: 0.39–0.77; $p = 0.0005$). This data provides insight into the activity of Elacestrant as a monotherapy but does not account for the fact that combination therapy is increasingly used as second line therapy, for example, Fulvestrant/Alpelisib combination in patients with PIK3CA alterations. Therefore, Elacestrant therapy may be better suited to patients who are candidates for monotherapy in later line settings. This data may encourage research to examine the role of Elacestrant combinations in the future. In terms of adverse events, Elacestrant showed a manageable toxicity profile. Nausea, fatigue and vomiting were the most common side effects, which occurred in 35%, 19% and 19% of patients, respectively. Grade 3/4 toxicities occurred in 27% of patients, with the most common toxicities being nausea (2.5%), back pain (2.5%) and elevated liver enzymes (2.1%).[16]

As discussed earlier, Datopotamab Deruxtecan Sacituzumab Govitecan are two antibody-drug conjugates that received FDA approval for patients who have received prior ET and chemotherapy for unresectable or metastatic disease. Sacituzumab Govitecan consists of an antibody targeting TROP-2 conjugated to a topoisomerase 1 inhibitor (SN-38). Datopotamab Deruxtecan is also targeted against TROP-2 and conjugated to Deruxtecan which is a different topoisomerase 1 inhibitor. Trial data from TROPiCS-02 trial on Sacituzumab Govitecan shows improved PFS (median PFS 5.5 months for Sacituzumab Govitecan vs 4 months for chemotherapy; HR: 0.66; $p = 0.0003$) and OS (median OS 14.4 months for Sacituzumab Govitecan vs 11.2 months for chemotherapy; HR 0.79; $p = 0.02$) in ER-positive/HER2-negative breast cancer patients who progressed on at least one line of ET, CDK4/6 inhibitors and 2–4 lines of chemotherapy compared to clinician's choice of chemotherapy (capecitabine, vinorelbine, gemcitabine or eribulin).[17] TROPION-Breast01 phase III trial data for Datopotamab Deruxtecan also shows improvements in PFS compared to clinician's choice of chemotherapy for patients who have already progressed on ET and at least one line of chemotherapy (median PFS 6.9 for Datopotamab Deruxtecan vs 4.9 for chemotherapy; HR: 0.63; $p < 0.0001$).[18] The benefits of PFS and OS for these agents must be balanced against the risks of toxicity of each agent. For example, Sacituzumab Govitecan had higher rates of grade 3 or more toxicities compared to clinician's choice chemotherapy (74% vs 60% respectively). Sacituzumab Govitecan had higher rates of neutropenia (51% vs 38%) and diarrhoea (9% vs 1%) compared to chemotherapy, meaning that assessment of the fitness and comorbidities of each patient is key when selecting appropriate therapy for each patient in this setting.[17]

The PI3K/AKT/PTEN signalling pathway

The PI3K/AKT/PTEN signalling pathway, which is also referred to as PI3K/PTEN/AKT/mTOR pathway, is the most commonly mutated signalling pathway in human cancer.[19] More than half of ER-positive/HER2-negative breast cancers harbour a mutation in this pathway.[20] The PI3K/

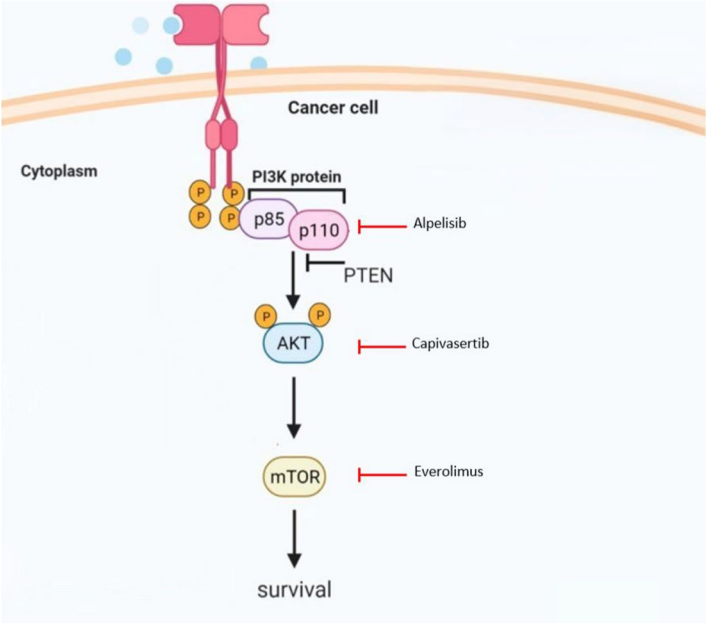

Figure 1. The action of select anti-cancer agents on the PI3K/AKT/PTEN signalling pathway in cancer cells. Inhibitory signalling or activity is denoted by ⊢.
Source: Figure adapted from work by Mishra et al. and used under Creative Commons Attribution 4.0 International license.[21]

AKT/PTEN pathway has a central role in cell proliferation, suppressing apoptosis and neovascularisation. Alterations in this pathway have been associated with treatment resistance and carcinogenesis.[20] As discussed above, several drugs targeting the PI3K/AKT pathway have made their way into the standard of care for advanced and metastatic ER-positive/HER2-negative breast cancer (Figure 1). More recently, several trials focused on targeting the AKT pathway to improve cancer treatment and survival. Capivasertib (AZD5363) is a novel AKT inhibitor that has shown significant promise in improving treatment for ER-positive/HER2-negative breast cancer.[20]

Mechanism of action

AKT is part of the AGC (cAMP-dependent, cGMP-dependent and protein kinase C) family of kinases. It has three different isoforms encoded by separate genes. These isoforms are preferentially expressed by different types of tissues in the body.[22] AKT can be over-activated in cancer cells by activating mutations in PIK3CA and AKT and inactivating mutations in PTEN tumour suppressor gene. AKT hyperactivity causes the activation of downstream substrates, eventually promoting cancer cell proliferation and growth.[20]

Capivasertib (AZD5363) is a potent AKT kinase competitive inhibitor that has similar activity against all three AKT isoforms. It exerts its effect by binding to the ATP binding site on the AKT kinase, reducing the phosphorylation of downstream effectors.[20]

Capivasertib in pre-clinical studies

The efficacy of Capivasertib in breast cancer has been shown in multiple preclinical studies.[23–25]

In vitro, Capivasertib was tested across 182 cell lines and showed persistent anticancer effects, particularly in ER-positive and HER2-positive breast cancer cell lines.[23] In vivo, Capivasertib was found to be effective in HER2-positive PIK3CA-mutated breast cancer xenografts. It also showed the synergy of therapy with anti-HER2 treatment with trastuzumab and lapatinib, as well as docetaxel chemotherapy.[23]

Pre-clinical studies also show that AKT can cause the phosphorylation of the oestrogen receptor in a ligand-independent fashion, which is linked with ET resistance.[26] AKT over activity has also been associated with altered oestrogen receptor transcription. Inhibition of AKT has been shown to reduce oestrogen receptor-related transcription

by reducing the recruitment of oestrogen receptors and CREB-binding protein coactivators to oestrogen response elements.[24] In ER-positive, endocrine-resistant cell lines, the combination of Capivasertib with ET using Fulvestrant, Anastrozole or Tamoxifen was found to have better outcomes than any of those agents alone in suppressing oestrogen receptor-mediated transcription. The combination of Capivarsertib and Fulvestrant exhibited inhibitory effects on oestrogen receptor-mediated growth in vivo and in vitro in ER-positive breast cancer xenografts. The growth suppression was better than either drug alone, and the same effect was exhibited for this combination in PIK3CA-mutated breast cancer xenografts.[24,25]

The pre-clinical data discussed above provided a rationale to further explore the simultaneous inhibition of AKT and ER pathways to improve outcomes of ER-positive breast cancer treatment. There is further pre-clinical evidence for the efficacy of Capivasertib as a single agent or in combination for several tumours, including prostate, gastric, oesophageal and non-small cell lung cancer.[27–31]

Clinical trials of Capivasertib

Capivasertib as monotherapy in breast cancer

Capivasertib as a monotherapy was first trialled in a first-in-human phase I study in late 2010 [ClinicalTrials.gov identifier: NCT01226316]. Ninety patients with breast, gynaecological, lung and other solid cancers were recruited. Patients with AKT1/PIK3CA or PTEN mutations in these tumour types were included in the study. The study recommended a Capivasertib dose of 480 mg twice daily on a 4-days-on, 3-days-off schedule.[32] This dose was used in phase II expansion in PIK3CA-mutated breast and gynaecological cancers.[33] Forty percent of patients in the PIK3CA-mutated breast cancer cohort achieved a reduction in tumour size, with a further 4% of patients achieving radiological responses. The phase II study concluded that Capivasertib achieved target modulation, and sufficient responses were observed to provide proof of concept.[33]

The most common AKT mutation is the E17K mutation, which causes a glutamic acid to lysine substitution. This mutation is present in 3%–4% of breast cancer tumours and represents approximately 90% of the mutations in the AKT gene.[34] Phase I and II studies evaluated Capivasertib for AKT E17K mutant solid cancer patients.[32,35] The study cohorts included 20 out of 52, and 15 out of 35 patients with ER-positive breast cancers. The phase I study reported a median PFS of 5.5 months and a 20% objective response rate (ORR) in a heavily pre-treated cohort with a median of five lines of previous therapy. The phase II study reported the same PFS with a similar ORR of 28.6% which was also a heavily pre-treated patient cohort with a median of four previous lines of therapy.[32,35]

These early phase trials also reported on the safety profile of Capivasertib as a single agent. The most common adverse event (AE) of any grade was diarrhoea, which occurred in up to 80% of patients. Nausea, fatigue and vomiting occurred in up to 56%, 41% and 44% of patients, respectively. In both studies, hyperglycaemia and maculopapular rash were reported and occurred in up to 41% and 31%, respectively. The most common grade $\geqslant$3 AE were hyperglycaemia, diarrhoea and maculopapular rash, which occurred in up to 24.1%, 17.2% and 15.5% of patients.[32,33]

It is worth noting that most studies excluded patients with diabetes, so it is difficult to determine the precise safety profile in the diabetic population from this data. Generally, studies reported Capivasertib as a well-tolerated agent with mainly self-limiting gastrointestinal AEs, such as rash and hyperglycaemia, which responded well to metformin treatment. Furthermore, studies did not report any clinically significant cardiac side effects.[32,33,36]

Capivasertib in combination with Fulvestrant in breast cancer

The combination of Capivasertib with Fulvestrant was first investigated in the dose expansion cohort of the NCT01226316 trial, the first trial to investigate Capivasertib as monotherapy, as discussed earlier [ClinicalTrials.gov identifier: NCT01226316]. However, this was limited to patients with AKT1 E17K mutated ER-positive/HER2-negative metastatic breast cancer. Sixty-three patients were included in the expansion cohort with E17K ER-positive/HER2-negative metastatic breast cancer patients. These patients were heavily pre-treated with a median of 6 lines of previous therapy in the overall cohort, including a median of 3 lines of chemotherapy and 3 lines of ET. Forty-three patients received combination treatment with

Fulvestrant and Capivasertib, of which 15 participants were Fulvestrant naïve, and the rest were previously treated with Fulvestrant. The data from these 43 patients was compared with 20 patients who received Capivasertib monotherapy. ORR was 20% for the Capivasertib monotherapy and the Fulvestrant naïve cohorts and 36% (95% CI: 19–56) in the Fulvestrant pre-treated cohort. Median PFS was similar across all cohorts and reported as 5.4 (3–7), 5.6 (2–14) and 5 (3–8) months in the Capivasertib monotherapy, the Fulvestrant naïve and Fulvestrant pre-treated cohorts, respectively (Table 1).[37]

A further expansion cohort of the NCT01226316 trial explored the combination of Capivasertib and Fulvestrant. This cohort consisted of 31 metastatic or advanced breast cancer patients with PTEN mutations. Only three patients had ER-positive/HER2-positive disease, and the rest had ER-positive/HER2-negative disease. Median PFS was reported as 2.6 (1–4) months in the Fulvestrant naïve cohort ($n = 12$) and 4.1 (2–7) months in the Fulvestrant pre-treated cohort ($n = 19$). It is worth noting that 87% of the study cohort had visceral metastasis at baseline. There were also distinct differences in the characteristics of the Fulvestrant naïve and the Fulvestrant pre-treated cohorts. The Fulvestrant naïve cohort had a higher proportion of patients who were pre-treated with first-line chemotherapy compared to the pre-treated group (38% vs 12% respectively). This study was not designed to compare efficacy across these groups. The study authors also reflect that the Fulvestrant naïve group may have had more aggressive disease at baseline. Furthermore, the clinical response rates across the groups defined as partial or complete response or stabilisation at ⩾24 weeks were generally similar despite the differences in ORR. Considering these factors, the results of this study relating to Fulvestrant naïve and the Fulvestrant pre-treated cohorts should be interpreted with caution.

The combination of Capivasertib and Fulvestrant was generally better tolerated with fewer AEs of any grade and of grade ⩾3 compared to Capivasertib alone. This is likely to be in part due to the different dosing schedule of oral Capivasertib 400 mg twice daily for 4 days then 3 days off in combination with Fulvestrant compared to 480 mg dosing in the same schedule for Capivasertib alone. This study added to the evidence base in support of the value of Capivasertib and Fulvestrant in ER-positive/HER2-positive metastatic breast cancer.[38]

BEECH trial is one of the first randomised phase II trials that examined the role of Capivasertib in combination with other agents in advanced or metastatic ER-positive/HER2-negative breast cancer. Patients had a median of two lines of previous anti-cancer therapy, with 74.5% of patients having had prior ET. Patients were randomised to receive paclitaxel chemotherapy with placebo or with Capivasertib. There was also a subgroup analysis of a PIK3CA-mutated subpopulation within the study. Unfortunately, whilst the combination of paclitaxel with Capivasertib was found relatively well tolerated by the patient cohort, no benefit in PFS or OS was demonstrated by the trial in the overall population or the sub-group analysis.[39]

The phase I/II FAKTION trial was the first randomised trial to investigate the combination of Fulvestrant and Capivasertib for ER-positive/HER2-negative metastatic or locally advanced breast cancer after progression on AI.[40] The trial started with a dose escalation phase I followed by a double-blind randomised phase II trial. In phase II, 140 patients were randomised to receive Fulvestrant plus Placebo (71 patients) or Fulvestrant plus Capivasertib (69 patients). Patients recruited had a median of one line of prior ET therapy with approximately a third of patients having had two or more lines of ET. Twenty-five percent of patients in the combination arm and 28% of patients in the Fulvestrant arm also had prior chemotherapy in the metastatic setting. The subsequent subgroup analyses included patients with PIK3CA mutations and PTEN loss, as well as those who were wild-type. Mutation analysis was done by digital droplet PCR to detect hotspot mutations on PIK3CA exons 9 or 20 in tumour tissue or blood. PTEN status was established via immunohistochemistry of tumour tissue. Tissue from the archival primary tumour or previous metastatic tissue biopsy was used in this study. Blood specimens were taken at enrolment of the trial. The method of sample analysis was changed from pyrosequencing to digital PCR during the trial to enable greater sensitivity for mutation testing. Fourteen patient samples had insufficient material for re-analysis using digital PCR. In cases where PIK3CA status was changed by reanalysis using digital PCR, the participant data was analysed

Table 1. Clinical trials of Capivasertib combinations in ER-positive/HER2-positive advanced breast cancer.

Trial	Cohort within study	Treatment arm	Median PFS (months)	PFS HR (95% CI)	Median OS (months)	OS HR (95% CI)
NCT01226316 (phase I)	Overall cohort	Capivasertib monotherapy	5.4 (3–7)	–	–	–
	Overall cohort	Capivasertib + Fulvestrant (All)	5.6 (2–14)	–	–	–
	Overall cohort	Capivasertib + Fulvestrant (Naïve)	5.0 (3–8)	–	–	–
BEECH (phase Ib–II)	Overall cohort	Capivasertib + Paclitaxel	10.9	0.80 ($p = 0.308$)	–	–
	Overall cohort	Placebo + Paclitaxel	8.4	–	–	–
	PIK3CA altered	Capivasertib + Paclitaxel	10.9	1.11 ($p = 0.760$)	–	–
	PIK3CA altered	Placebo + Paclitaxel	10.8		–	–
FAKTION (phase II)	Overall cohort	Capivasertib + Fulvestrant	10.3 (5.0–13.4)	0.56 (0.38–0.81); $p = 0.0023$	29.3 (23.7–39.0)	0.66 (0.45–0.97); $p = 0.035$
	Overall cohort	Placebo + Fulvestrant	4.8 (3.1–7.9)	–	23.4 (18.7–32.7)	–
	PI3K/AKT/PTEN pathway-altered subgroup	Capivasertib + Fulvestrant	12.8 (6.6–18.8)	0.44 (0.26–0.72); two-sided $p = 0{\cdot}0014$	38.9 (23.3–50.7)	0.46 (0.27–0.79); two-sided $p = 0.0047$
	PI3K/AKT/PTEN pathway-altered subgroup	Placebo + Fulvestrant	4.6 (2.8–7.9)	–	20.0 (14.8–31.4)	–
Capitello 291 (phase III)	Overall cohort	Capivasertib + Fulvestrant	7.2	0.6 (0.51–0.71); $p < 0.001$	Not reached	–
	Overall cohort	Placebo + Fulvestrant	3.6	–	Not reached	–
	PI3K/AKT/PTEN pathway-altered subgroup	Capivasertib + Fulvestrant	7.3	0.5 (0.38–0.65); $p < 0.001$	Not reached	–
	PI3K/AKT/PTEN pathway-altered subgroup	Placebo + Fulvestrant	3.1	–	Not reached	–

HR, hazard ratio; OS, overall survival; PFS, progression free survival.

based on the latter test. Median PFS was reported as 10.3 months (95% CI: 5.0–13.2) in the Fulvestrant plus Capivasertib combination group versus 4.8 months (95% CI: 3.1–7.7) in the Fulvestrant plus Placebo group. The trial met its primary endpoint with an adjusted HR of 0.58 (0.39–0.85, $p = 0.0049$) favouring the Capivasertib plus Fulvestrant group. Initial subgroup analysis showed the PFS demonstrated with Fulvestrant and Capivasertib was maintained in the PIK3CA/PTEN wild-type group (HR: 0.56, 95% CI: 0.33–0.96, $p = 0.035$) but not in the PIK3CA/PTEN mutation carrying cohort (HR: 0.59, 95% CI: 0.34–1.03, $p = 0.064$). In terms of safety profile, data from the trial showed that Capivasertib is a relatively well-tolerated agent. Only 12% of patients had to discontinue Capivasertib due to toxicity. The most common grade ⩾3 AEs in the Capivasertib group were hypertension (32%), rash (20%) and diarrhoea (14%).[40]

A subsequent analysis of FAKTION data was published in 2022 after a median follow-up of 58.5 months in the Fulvestrant plus Capivasertib group and 62.3 months in the Fulvestrant plus Placebo group. The updated PFS was consistent with the primary analysis PFS of 10.3 months in the double agent group versus 4.8 months for the Fulvestrant plus Placebo group (adjusted HR 0.56, 95% CI: 0.38–0.81, $p = 0.0023$). The updated analysis also revealed a statistically significant median OS of 29.3 months (95% CI: 23.7–39.0) versus 23.4 months (95% CI: 18.7–32.7). Adjusted HR was reported as 0.66 (95% CI: 0.45–0.97; two-sided $p = 0.035$).[40,41]

The FAKTION team also applied an expanded biomarker panel to comprehensively report on any PI3K/AKT/PTEN pathway alterations using next-generation sequencing (NGS). This NGS analysis revealed that 54% of the study cohort had PI3K/AKT/PTEN alterations compared with 42% in the primary analysis. There was, however, some missing data in the study, meaning some patients had unknown mutation status. Nine patients in the Fulvestrant plus Capivasertib group and eight patients in the Fulvestrant plus Placebo group were missing PTEN results. All patients had either a result from blood or tissue testing for meaning no PIK3CA mutation status data was missing. Median OS for the expanded PI3K/AKT/PTEN pathway alterations group was 38.9 months (95% CI: 23.3–50.7) compared with 20 months (95% CI: 14.8–31.4) for the Placebo group (adjusted HR 0.46, 95% CI: 0.27–0.79; two-sided $p = 0.0047$). Interestingly, no statistically significant difference was demonstrated in PFS or OS in the PI3K/AKT/PTEN pathway wild-type group. The reason for this is likely to be that the expanded biomarker panel identified PI3K/AKT/PTEN alterations in 25% of the tumours originally categorised as wild-type. Given that the updated data after the re-categorisation of these patients based on the expanded biomarker panel showed statistically significant benefits only in the pathway-altered group, the original analysis would have over-exaggerated survival benefits in the wild-type group. This data suggests that the Capivasertib/Fulvestrant combination is predominantly beneficial to PI3K/AKT/PTEN altered breast cancer tumours. However, the authors of FAKTION noted that it is a relatively small trial, and further clinical trials are required to ascertain this. Furthermore, the FAKTION trial does not provide any data as to whether patients would respond to the Capivasertib/Fulvestrant combination after progressing on ET with CDK4/6 inhibition.[41]

Capitello 291 is a double-blind, randomised phase III trial for advanced or metastatic ER-positive / HER2-negative breast cancer.[42] It included patients who progressed on AI therapy with or without previous CDK4/6 inhibitor therapy. 708 patients were included and randomly assigned to receive either Fulvestrant plus Placebo or Capivasertib plus Fulvestrant. 355 patients were recruited into the Capivasertib/Fulvestrant group, and 353 patients were recruited into the Placebo/Fulvestrant group. 16.3% of patients in the Capivasertib/Fulvestrant group and 13.6% of patients in the Fulvestrant/Placebo group had an unknown status for PI3K/AKT pathway. Tissue samples were analysed by next-generation sequencing after randomisation for the trial. The reported PFS was 7.2 months in the Capivasertib/Fulvestrant group compared with 3.6 months in the Fulvestrant/Placebo group (HR 0.6; 95% CI: 0.51–0.71; $p < 0.001$). The study also carried out an exploratory analysis of the PI3K/AKT pathway-altered cohort within the study. Median PFS was 7.3 months in the Capivasertib/Fulvestrant group compared with 3.1 months in the Fulvestrant/Placebo group (HR 0.5; 95% CI: 0.38–0.65; $p < 0.001$). Even though this seems to suggest that the activity of the Capivasertib/Fulvestrant combination extends beyond the PI3K/AKT-altered population, the survival benefit for the Capivasertib/Fulvestrant combination in the overall population is largely driven by the

PI3K/AKT-altered population within the overall population.[42] This is highlighted by the lack of a statistically significant PFS benefit in the PI3K/AKT non-altered cohort in the sub-group analysis conducted by the study. The improved efficacy in the PI3K/AKT-altered pathway population as compared to the PI3K/AKT pathway non-altered population is in keeping with findings from FAKTION trial. It is also in keeping with the biologic rational that AKT inhibition would preferentially be more beneficial where there is increased AKT signalling through PI3K/AKT pathway alterations. The clinical activity of Capivasertib/Fulvestrant combination in PI3K/AKT altered and non-altered breast cancer is in keeping with the preclinical data on Capivasertib discussed earlier.[24] Furthermore, the communication between the ER receptor pathway and the PI3K/AKT pathway can limit the activity of monotherapy so that simultaneous inhibition could improve therapeutic outcome.[42] Further research into the efficacy of Capivasertib in ER-positive/HER2-negative PI3K/AKT pathway non-altered breast cancer before definitive conclusions can be drawn regarding this.

The Capitello 291 trial also reported that the combination of Capivasertib and Fulvestrant was relatively well tolerated by patients. The most common AE of any grade was diarrhoea at 72.4%. Rash was 38.0%, nausea 34.6% and hyperglycaemia 16.3%. The rate of grade 3 AEs in the overall population was 39.2% and grade 4 was 2.5%. No deaths were attributed to Capivasertib/Fulvestrant by trial investigators.[42] While direct comparisons are difficult due to different study designs, Capivasertib plus Fulvestrant generally compares favourably in terms of AEs to other agent-ET combinations available in standard of care, including Alpelisib/Fulvestrant and Everolimus/Exemestane.[12,42] For example, the Capivasertib/Fulvestrant combination had a lower incidence of hyperglycaemia compared to Alpelisib/Fulvestrant.[12] This may be partially down to the intermittent dosing of Capivasertib as per the trial schedule. This is important to note when selecting candidate patients for Capivasertib-based therapy in clinic, for example, diabetic patients with poor blood sugar control may tolerate Capivasertib better than Alpelisib due to the lower incidence of hyperglycaemia. The introduction of better-tolerated anticancer agents to the standard of care gives patients a better quality of life and may potentially open the door for further combinations of anticancer agents.

Conclusion and future directions

The FAKTION and Capitello 291 trials provided clinically meaningful evidence on the efficacy of Capivasertib with Fulvestrant in ER-positive/HER2-negative breast cancer. OS data from the Capitello 291 trial is awaited. In May 2025, National Institute for Health and Care Excellence (NICE) have given approval for Capivasertib plus Fulvestrant for patients with ER-positive/HER2-negative locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN-alterations after progression or recurrence on a CDK 4/6 inhibitor plus an AI.[43] This follows the United States FDA approval in 2003 for Capivasertib plus Fulvestrant for patients with ER-positive/HER2-negative locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN-alterations after progression on at least one ET.[4] The FDA based their approval for the PIK3CA/AKT1/PTEN-alterations cohort of patients on data from the Capitello 291 trial, which showed an HR of 0.50 (95% CI: 0.38–0.65) compared to an HR of 0.79 (95% CI: 0.61–1.02) in the PIK3CA/AKT1/PTEN-non-altered cohort. The FDA decided that this data shows that the overall benefit shown in the study was primarily driven by the benefit of the PIK3CA/AKT1/PTEN-altered cohort.[4] It is worth noting that Capitello 291 was not powered to evaluate the efficacy within the PIK3CA/AKT1/PTEN-non-altered cohort. Considering that up to 40% of metastatic breast cancer patients in this setting may not have PIK3CA/AKT1/PTEN alterations, approval of Capivasertib combinations in this population may expose a significant proportion of the patient cohort to treatment toxicity without confirmation of specific efficacy within this sub-cohort of patients. The addition of this drug combination to a standard of care setting is a very promising step for patients and further research is required to establish the role of Capivasertib combinations in this and other settings.

Efforts are ongoing to capitalise on the success of Capivasertib plus Fulvestrant in this and other settings. The Capitello 292 trial is an ongoing phase Ib/III trial which is aiming to build on the notion that concurrent blockade of PI3K/AKT/mTOR and CDK4/6 with ET by using Capivasertib, Palbociclib and Fulvestrant may provide clinical benefit and reduce ET resistance in ER-positive/HER2-negative locally advanced or metastatic breast cancer [ClinicalTrials.gov identifier: NCT04862663]. Positive findings from this study could pave the way for this

combination and potentially move Capivasertib closer to first line setting.

There is also evidence of the potential use of Capivasertib for other types of breast cancer. The phase II PAKT study provided evidence of PFS and OS benefit of adding Capivasertib to paclitaxel in patients with locally advanced or metastatic triple-negative breast cancer, particularly within the PIK3CA/AKT1/PTEN-altered population. The Capitello 290 study further examines the benefit of this combination in phase III without selecting PIK3CA/AKT1/PTEN alterations. The results of Capitello 290 are still awaited [ClinicalTrials.gov identifier: NCT03997123].[44]

There are a limited number of studies to inform the optimal sequence of the newer agents available for patients with ER-positive/HER2-negative breast cancer. There is also limited evidence available to compare agents within one class or comparing one class against another. Future studies to inform clinical decisions regarding these agents are critical to improve patient outcome and reduce the burden of treatment toxicity for patients.[45]

In summary, there is a growing body of evidence on the use of Capivasertib plus Fulvestrant for locally advanced and metastatic ER-positive/HER2-negative breast cancer. Randomised clinical phase II and III trials have built upon preclinical data for drugs targeting the PI3K/AKT/mTOR pathway to illustrate the significant clinical benefit in OS of this combination of drugs in this setting. Recent regulatory approval in the United States is the latest success to date, with many trials ongoing to explore the use of Capivasertib in different settings and tumour sites.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Karam Aboud: Conceptualisation; Data curation; Writing – original draft; Writing – review & editing.

Magda Meissner: Writing – review & editing.

Rob Jones: Conceptualisation; Writing – review & editing.

Acknowledgements
None.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests
The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: M.M. is an author on FAKTION trial. R.J. is an author and C.I. of FAKTION trial.

Availability of data and materials
Not applicable.

ORCID iDs
Karam Aboud https://orcid.org/0009-0000-8491-2178

Magda Meissner https://orcid.org/0000-0001-5897-0219

Rob Jones https://orcid.org/0000-0003-3576-9496

References

1. Cancer Research UK. Breast cancer statistics [Internet], https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer (2015, accessed 29 November 2023).
2. SEER. Female breast cancer subtypes – cancer stat facts [Internet], https://seer.cancer.gov/statfacts/html/breast-subtypes.html (accessed 29 November 2023).
3. Gennari A, André F, Barrios CH, et al. ESMO Clinical practice guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol* 2021; 32(12): 1475–1495.
4. Center for Drug Evaluation and Research. FDA approves Capivasertib with Fulvestrant for breast cancer. FDA, https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-capivasertib-fulvestrant-breast-cancer (2023, accessed 29 November 2023).

5. Center for Drug Evaluation and Research. FDA approves Elacestrant for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer. FDA, https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-elacestrant-er-positive-her2-negative-esr1-mutated-advanced-or-metastatic-breast-cancer (2023, accessed 17 March 2025).
6. Mullard A. FDA approves TROP2-targeted antibody–drug conjugate for breast cancer. *Nat Rev Drug Discov* 2025; 24(3): 159–159.
7. Maximov PY, Lee TM and Jordan VC. The discovery and development of selective estrogen receptor modulators (SERMs) for clinical practice. *Curr Clin Pharmacol* 2013; 8(2): 135–155.
8. Finn RS, Martin M, Rugo HS, et al. Palbociclib and Letrozole in advanced breast cancer. *N Engl J Med* 2016; 375(20): 1925–1936.
9. Im SA, Lu YS, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med* 2019; 381(4): 307–316.
10. Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol* 2017; 35(32): 3638–3646.
11. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2012; 366(6): 520–529.
12. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med* 2019; 380(20): 1929–1940.
13. Jerusalem G, de Boer RH, Hurvitz S, et al. Everolimus plus Exemestane vs Everolimus or capecitabine monotherapy for estrogen receptor-positive, HER2-negative advanced breast cancer: the BOLERO-6 randomized clinical trial. *JAMA Oncol* 2018; 4(10): 1367–1374.
14. Rozenblit M, Mun S, Soulos P, et al. Patterns of treatment with Everolimus Exemestane in hormone receptor-positive HER2-negative metastatic breast cancer in the era of targeted therapy. *Breast Cancer Res* 2021; 23(1): 14.
15. Burstein HJ, Somerfield MR, Barton DL, et al. Endocrine treatment and targeted therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: ASCO guideline update. *J Clin Oncol* 2021; 39: 3859–3877.
16. Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: results from the randomized phase III EMERALD trial. *J Clin Oncol* 2022; 40(28): 3246–3256.
17. Rugo HS, Bardia A, Marmé F, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol* 2022; 40(29): 3365–3376.
18. Bardia A, Jhaveri K, Im SA, et al. Datopotamab deruxtecan versus chemotherapy in previously treated inoperable/metastatic hormone receptor-positive human epidermal growth factor receptor 2-negative breast cancer: primary results from TROPION-Breast01. *J Clin Oncol* 2025; 43(3): 285–296.
19. Millis SZ, Ikeda S, Reddy S, et al. Landscape of phosphatidylinositol-3-kinase pathway alterations across 19 784 diverse solid tumors. *JAMA Oncol* 2016; 2(12): 1565–1573.
20. Andrikopoulou A, Chatzinikolaou S, Panourgias E, et al. The emerging role of Capivasertib in breast cancer. *Breast* 2022; 63: 157–167.
21. Mishra R, Patel H, Alanazi S, et al. PI3K inhibitors in cancer: clinical implications and adverse effects. *Int J Mol Sci* 2021; 22(7): 3464.
22. Wang Q, Chen X and Hay N. Akt as a target for cancer therapy: more is not always better (lessons from studies in mice). *Br J Cancer* 2017; 117(2): 159–163.
23. Davies BR, Greenwood H, Dudley P, et al. Preclinical pharmacology of AZD5363, an inhibitor of AKT: pharmacodynamics, antitumor activity, and correlation of monotherapy activity with genetic background. *Mol Cancer Ther* 2012; 11(4): 873–887.
24. Ribas R, Pancholi S, Guest SK, et al. AKT antagonist AZD5363 influences estrogen receptor function in endocrine-resistant breast cancer and synergizes with Fulvestrant (ICI182780) in vivo. *Mol Cancer Ther* 2015; 14(9): 2035–2048.
25. Fox EM, Kuba MG, Miller TW, et al. Autocrine IGF-I/insulin receptor axis compensates for inhibition of AKT in ER-positive breast cancer cells with resistance to estrogen deprivation. *Breast Cancer Res* 2013; 15(4): R55.
26. Campbell RA, Bhat-Nakshatri P, Patel NM, et al. Phosphatidylinositol 3-kinase/AKT-mediated activation of estrogen receptor alpha: a new model for anti-estrogen. *J Biol Chem* 2001; 276(13): 9817–9824..
27. Toren P, Kim S, Cordonnier T, et al. Combination AZD5363 with enzalutamide

significantly delays enzalutamide-resistant prostate cancer in preclinical models. *Eur Urol* 2015; 67(6): 986–990.

28. Thomas C, Lamoureux F, Crafter C, et al. Synergistic targeting of PI3K/AKT pathway and androgen receptor axis significantly delays castration-resistant prostate cancer progression in vivo. *Mol Cancer Ther* 2013; 12(11): 2342–2355.
29. Li J, Davies BR, Han S, et al. The AKT inhibitor AZD5363 is selectively active in PI3KCA mutant gastric cancer, and sensitizes a patient-derived gastric cancer xenograft model with PTEN loss to Taxotere. *J Transl Med* 2013; 11: 241.
30. Wu X, Zhang J, Zhen R, et al. Trastuzumab anti-tumor efficacy in patient-derived esophageal squamous cell carcinoma xenograft (PDECX) mouse models. *J Transl Med* 2012; 10: 180.
31. Puglisi M, Thavasu P, Stewart A, et al. AKT inhibition synergistically enhances growth-inhibitory effects of gefitinib and increases apoptosis in non-small cell lung cancer cell lines. *Lung Cancer* 2014; 85(2): 141–146.
32. Hyman DM, Smyth LM, Donoghue MTA, et al. AKT inhibition in solid tumors with AKT1 mutations. *J Clin Oncol* 2017; 35(20): 2251–2259.
33. Banerji U, Dean EJ, Pérez-Fidalgo JA, et al. A phase I open-label study to identify a dosing regimen of the pan-AKT inhibitor AZD5363 for evaluation in solid tumors and in PIK3CA-mutated breast and gynecologic cancers. *Clin Cancer Res* 2018; 24(9): 2050–2059.
34. Cosmic. COSMIC—catalogue of somatic mutations in cancer, https://cancer.sanger.ac.uk/cosmic (accessed 29 November 2023).
35. Kalinsky K, Hong F, McCourt CK, et al. Effect of Capivasertib in patients with an AKT1 E17K-mutated tumor. *JAMA Oncol* 2021; 7(2): 1–8.
36. Voronova V, Cullberg M, Delff P, et al. Concentration-QT modelling shows no evidence of clinically significant QT interval prolongation with Capivasertib at expected therapeutic concentrations. *Br J Clin Pharmacol* 2022; 88(2): 858–864.
37. Smyth LM, Tamura K, Oliveira M, et al. Capivasertib, an AKT kinase inhibitor, as monotherapy or in combination with Fulvestrant in patients with AKT1E17K-mutant, ER-positive metastatic breast cancer. *Clin Cancer Res* 2020; 26(15): 3947–3957.
38. Smyth LM, Batist G, Meric-Bernstam F, et al. Selective AKT kinase inhibitor Capivasertib in combination with Fulvestrant in PTEN-mutant ER-positive metastatic breast cancer. *NPJ Breast Cancer* 2021; 7: 44.
39. Turner NC, Alarcón E, Armstrong AC, et al. BEECH: a dose-finding run-in followed by a randomised phase II study assessing the efficacy of AKT inhibitor Capivasertib (AZD5363) combined with paclitaxel in patients with estrogen receptor-positive advanced or metastatic breast cancer, and in a PIK3CA mutant sub-population. *Ann Oncol* 2019; 30(5): 774–780.
40. Jones RH, Casbard A, Carucci M, et al. Fulvestrant plus Capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive breast cancer (FAKTION): a multicentre, randomised, controlled, phase 2 trial. *Lancet Oncol* 2020; 21(3): 345–357.
41. Howell SJ, Casbard A, Carucci M, et al. Fulvestrant plus Capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive, HER2-negative breast cancer (FAKTION): overall survival, updated progression-free survival, and expanded biomarker analysis from a randomised, phase 2 trial. *Lancet Oncol* 2022; 23(7): 851–864.
42. Turner NC, Oliveira M, Howell SJ, et al. Capivasertib in hormone receptor-positive advanced breast cancer. *N Engl J Med* 2023; 388(22): 2058–2070.
43. NICE-1 Recommendations. Capivasertib with Fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment. *NICE Guidance*, https://www.nice.org.uk/guidance/ta1063/chapter/1-Recommendations (2025, accessed 22 May 2025).
44. Schmid P, Abraham J, Chan S, et al. Capivasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer: the PAKT trial. *J Clin Oncol* 2020; 38(5): 423–433.
45. Burstein HJ, DeMichele A, Fallowfield L, et al.; Biomarker Testing and Endocrine and Targeted Therapy in Metastatic Breast Cancer Expert Panels. Endocrine and targeted therapy for hormone receptor-positive, human epidermal growth factor receptor 2–negative metastatic breast cancer – Capivasertib-Fulvestrant: ASCO rapid recommendation update. *J Clin Oncol* 2024; 42(12): 1450–1453.

Visit Sage journals online
journals.sagepub.com/home/tam

Sage journals