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PI3K/AKT/mTOR inhibitors for hormone receptor-positive advanced breast cancer

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ABSTRACT

Dysregulation of the phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway plays a pivotal role in the development and progression of various cancers. In hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer, aberrations in this pathway are increasingly recognized as key drivers of resistance to endocrine therapy and cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, the first-line treatments for this disease subtype. Recognizing the urgent need for alternative therapeutic strategies, significant advancements have been made in developing PI3K/AKT/mTOR inhibitors for HR+ advanced/metastatic breast cancer. Among these inhibitors, capivasertib and alpelisib have received approval as targeted therapies for this indication. This review provides a comprehensive summary of the latest developments in PI3K/AKT/mTOR inhibitors for HR+ breast cancer. It also delves into different aspects, including sampling, testing method and timing, of PI3K/AKT/mTOR diagnostic testing. Additionally, the review discusses key considerations for integrating these inhibitors into clinical practice, such as timing and choice of PI3K/AKT/mTOR inhibitors, and management of treatment toxicities. By examining these different aspects, this review aims to provide valuable insights into optimizing the clinical utility of PI3K/AKT/mTOR inhibitors in HR+ advanced breast cancer.

Introduction

Approximately 70% of breast cancers are hormone receptor-positive (HR+) [1–3]. Endocrine therapy (such as aromatase inhibitor or fulvestrant) plus cyclin-dependent kinase 4/6 (CDK4/6) inhibitor (palbociclib, ribociclib or abemaciclib) is currently the standard treatment for HR+/human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer [4,5]. However, treatment resistance remains a major challenge, and optimal management strategies following progression on CDK4/6 inhibitor plus endocrine therapy are much needed [5,6]. Overactivation of the phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway, which occurs in approximately 50% of HR+/HER2- metastatic breast cancer cases, is an important mechanism of both CDK4/6 inhibitor and endocrine therapy resistance [6,7]. Several PI3K/AKT/mTOR inhibitors, including alpelisib and capivasertib, have demonstrated potent efficacy and an acceptable safety profile, and have been approved as second- or subsequent-line therapy for HR+ advanced breast cancer [4,6], and many more are under development. This review summarizes the latest development of PI3K/AKT/mTOR inhibitors for HR+ advanced breast cancer, and further discusses diagnostic testing and other considerations for the use of these inhibitors in clinical practice.

The PI3K/AKT/mTOR pathway

The PI3K/AKT/mTOR pathway is a critical transduction network [8]. PI3Ks are a family of membrane-bound lipid kinases and are directly activated by cell surface receptors, such as receptor tyrosine kinases (RTKs) and G protein-coupled receptors (GPCRs) [9,10]. Upon activation, PI3K mediates the phosphorylation of phosphatidylinositol-4,5-biphosphate (PIP2) to phosphatidylinositol-3,4,5-triphosphate (PIP3) [10,11]. PIP3 then recruits AKT to the plasma membrane, where AKT

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becomes fully activated through phosphorylation by both phosphoinositide-dependent protein kinase 1 (PDK1) and mTOR complex 2 (mTORC2) [10,11]. The fully activated AKT then go on to act on its downstream targets, including activating mTOR complex 1 (mTORC1) (Fig. 1A) [12]. This important pathway mediates many essential cellular processes, including growth, proliferation, metabolism and survival [11].

Role of the PI3K/AKT/mTOR pathway in HR+ Breast cancer

The PI3K/AKT/mTOR pathway is also the most frequently activated signaling pathway in human cancer, and its dysregulation is known to drive cancer development and progression [8]. Glaviano et al. have provided a comprehensive summary of different types of alterations that result in PI3K/AKT/mTOR hyperactivation in cancer [8]. For instance, approximately 30%–40% of estrogen receptor-positive (ER+) breast cancers exhibit activating mutations of *PIK3CA* (encoding for the α isoform of the p110 catalytic subunit of class IA PI3K), which increases p110α activity and promotes excessive cell multiplication and resistance to apoptosis [15]. Other examples include upstream RTK overactivation, loss of function of phosphatase and tensin homolog (PTEN), as well as gain-of-function mutations of AKT genes (Fig. 1B) [8,16].

Of particular interest, hyperactivation of the PI3K/AKT/mTOR pathway has been found to mediate resistance to endocrine therapy and CDK4/6 inhibitors [7,11]. As shown in Fig. 1B, cyclin D, which facilitates cell cycle progression from G1 to S phase through activating CDK4/6, is a downstream target of both PI3K/AKT/mTOR and estrogen receptor signaling [13,14]. Hyperactivation of the PI3K/AKT/mTOR pathway can increase cyclin D level or enhance its activity through post-translational mechanisms [17], potentially attenuating the effect of endocrine therapy or CDK4/6 inhibition. Endocrine-resistant preclinical models of ER+ breast cancer showed elevated phosphorylation levels of PI3K and mTOR substrates, and targeted inhibition of these molecules reduced cell growth and improved response to endocrine therapy [15]. In a recent open-label, multicenter clinical trial, Abu-Khalaf et al. mapped functional activation and signaling architecture of pretreatment tumor tissue biopsies collected from HR+/HER2- metastatic breast cancer patients receiving first-line endocrine therapy plus CDK4/6 inhibitor, and found that patients who had disease progression had increased activation of the PI3K/AKT/mTOR pathway [18]. With the growing evidence of PI3K/AKT/mTOR's participation in HR+ breast cancer, especially treatment resistance, researchers are actively exploring the potential of PI3K/AKT/mTOR inhibitors for patients progressing on first-line treatment.

PI3K/AKT/mTOR INHIBITORS FOR HR+/HER2- BREAST CANCER

Many clinical trials of PI3K/AKT/mTOR inhibitors for patients with HR+ advanced breast cancer have been conducted. The below sections summarize key clinical trial results of these inhibitors as well as other PI3K/AKT/mTOR inhibitors that have entered phase II/III trials (Table 1).

PI3K inhibitors

Alpelisib

Alpelisib is an orally bioavailable, α-selective PI3K inhibitor [41]. In the pivotal randomized, double-blind, placebo-controlled, phase III SOLAR-1 trial enrolling HR+/HER2- advanced breast cancer patients pretreated with endocrine therapy, at a median follow-up of 20 months, alpelisib plus fulvestrant significantly prolonged progression free survival (PFS) compared with placebo plus fulvestrant in the cohort of patients carrying *PIK3CA* mutations (11.0 months vs. 5.7 months, hazard ratio [HR]=0.65, 95% confidence interval [CI] 0.50–0.85, P<0.001) [19]. This led to the approval of alpelisib by the US food and drug administration (FDA) and European Medicines Agency (EMA) to be used in combination with fulvestrant for the treatment of *PIK3CA*-mutated, ER+/HER2- advanced breast cancer among adults whose disease progressed on or after an endocrine-based regimen (US) [42], or among postmenopausal women and men whose disease progressed following endocrine therapy as monotherapy (Europe) [43]. However, final overall results of the SOLAR-1 study did not cross the prespecified efficacy boundary for overall survival (OS), with a median OS of 39.3 months in the alpelisib group and 31.4 months in the placebo group (HR=0.86, 95% CI 0.64–1.15, P=0.15), although the median time to subsequent chemotherapy was longer in the alpelisib group than the placebo group (HR=0.72, 95% CI 0.54–0.95) [41]. The most common grade 3/4 adverse events (AEs) in patients who received alpelisib in the SOLAR-1 study were hyperglycemia (36.6%) and rash (9.9%), and grade 3 diarrhea occurred in 6.7% of patients [19]. Twenty-five percent of patients discontinued study treatment due to AEs [19].

Inavolisib

Inavolisib is a selective inhibitor of PI3Kα, and is currently under evaluation in phase III trials for patients with *PIK3CA*-mutated HR+/HER2- locally advanced or metastatic breast cancer [22]. INAVO120 investigates inavolisib plus palbociclib and fulvestrant versus placebo plus palbociclib and fulvestrant as first-line therapy in such patients who had experienced relapse during or within 12 months after the completion of adjuvant endocrine therapy [22]. Preliminary results of this study showed that at a median follow-up of 21.3 months, compared with the placebo group, the inavolisib group had significantly longer median PFS (15.0 months vs. 7.3 months, HR=0.43, 95% CI 0.32–0.59, P<0.0001) [22]. There was also a risk reduction for OS (HR=0.64, 95% CI 0.43–0.97, P=0.0338), although this did not cross the pre-specified significance boundary (P=0.0098 or HR=0.592) [22]. Safety wise, 88.3% and 82.1% of patients in the inavolisib group and the placebo group, respectively, experienced grade 3–4 AEs, and 6.8% of patients in inavolisib group withdrew from treatment due to AEs (vs. 0.6% in the placebo group) [22]. The most common grade 3–4 AEs in the inavolisib group included neutropenia (80.2%), thrombocytopenia (14.2%), leukopenia (6.8%), anemia (6.2%), hyperglycemia (5.6%), and stomatitis/mucosal inflammation (5.6%) [22]. INAVO121 is an ongoing phase III trial investigating the efficacy and safety of inavolisib plus fulvestrant versus alpelisib plus fulvestrant after progression on CDK4/6 inhibitor [23].

Buparlisib

Buparlisib was the first pan-PI3K inhibitor to enter global phase III trial for HR+ metastatic breast cancer and achieved modest improvement in PFS compared with placebo in BELLE-2 and BELLE-3 (Table 1) [24,25]. However, it also displayed considerable treatment toxicity. The most common grade 3/4 AEs in the buparlisib group in BELLE-2 were elevated alanine aminotransferase (ALT, 25%), elevated aspartate aminotransferase (AST, 18%), hyperglycemia (15%) and rash (8%); while that in BELLE-3 were elevated ALT (22%), elevated AST (18%), hyperglycemia (12%), hypertension (6%), and fatigue (3%) [24,25]. One treatment-related death (cardiac failure) was observed in BELLE-3 [25].

Pictilisib

Pictilisib is an orally-bioavailable, pan-PI3K inhibitor [26]. There was no significant difference in PFS between the pictilisib group and the placebo group in the phase II FERGI trial (Table 1) [26]. Additionally, grade 3/4 AEs occurred in 61% of patients in the pictilisib group and 28% in the placebo group [26].

Taselisib

Taselisib is an orally-bioavailable, selective inhibitor of class I PI3Kα-, β-, and γ-isoforms [27]. Among *PIK3CA*-mutated patients in the phase III SANDPIPER trial, taselisib achieved modest improvement in investigator-assessed PFS as well as secondary efficacy endpoints [27].

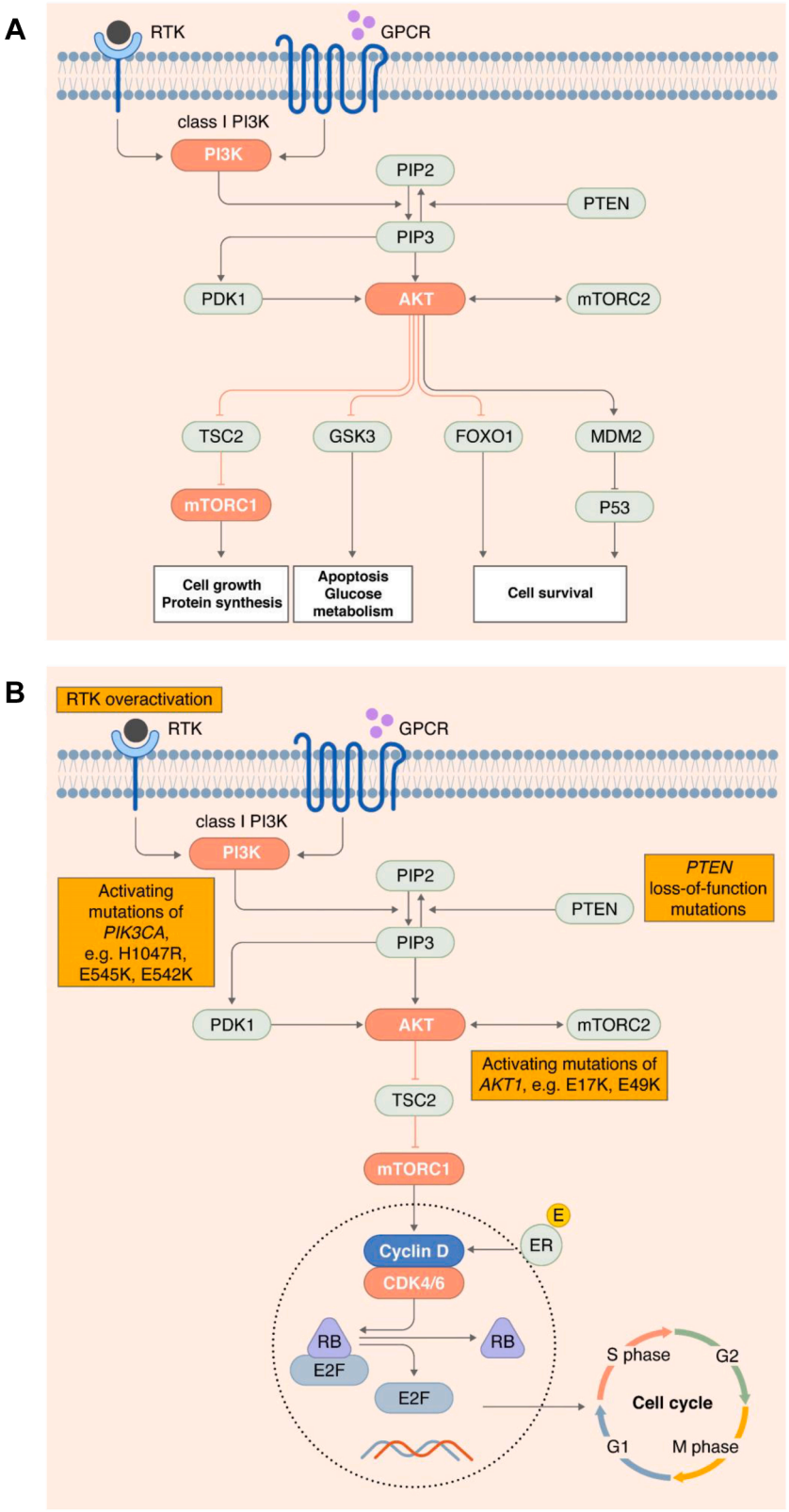

Fig. 1. The PI3K/AKT/mTOR pathway (A) under normal physiological conditions, and (B) its aberrations that contribute to tumorigenesis and progression in cancer [8,12–14]. AKT, protein kinase B; FOXO1, forkhead box protein 1; CDK4/6, cyclin dependent kinase 4/6; E, estradiol; E2F, the E2F family of transcription factors; ER, estrogen receptor; GPCR, G protein coupled receptor; GSK3, glycogen synthase kinase 3; MDM2, mouse double minute 2 homolog; mTORC1, mammalian target of rapamycin complex 1; mTORC2, mammalian target of rapamycin complex 2; PI3K/AKT/mTOR, phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin; PDK1, phosphoinositide-dependent protein kinase 1; PI3K, phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol-4,5-biphosphate; PIP3, phosphatidylinositol-3,4,5-triphosphate; PTEN, phosphatase and tensin homolog; RB, retinoblastoma protein; RTK, receptor tyrosine kinase; TSC2, tuberous sclerosis complex 2.

However, grade ≥3 AEs occurred in 49.5% of patients in the taselisib group (vs. 16.4% in the placebo group), with the most common ones being diarrhea (11.5%) and hyperglycemia (10.8%) [27].

AKT inhibitors

Capivasertib

Capivasertib is a potent and selective inhibitor of all three isoforms of AKT [31]. In the randomized, multicenter, double-blind, phase II FAKTION trial, capivasertib plus fulvestrant achieved significantly longer median PFS compared with placebo plus fulvestrant in female patients with aromatase inhibitor-resistant, ER+/HER2- advanced cancer (10.3 months vs. 4.8 months, HR=0.56, 95% CI 0.38–0.81, P=0.0023) [31], whereas in the previous open-label, phase Ib/II BEECH trial, capivasertib plus paclitaxel did not prolong PFS in patients with ER+/HER2- advanced or metastatic breast cancer compared with placebo plus paclitaxel [28]. The most common grade 3/4 AEs in the FAKTION trial were hypertension (32% in the capivasertib group vs. 25% in the placebo group), diarrhea (14% vs. 4%), and rash (20% vs. 0%). One death from an atypical pulmonary infection (without disease progression) occurred in the capivasertib group and was considered as possibly related to treatment [31].

Subsequently in the pivotal randomized, double-blind, phase III CAPItello-291 trial, capivasertib plus fulvestrant achieved significantly longer PFS than placebo plus fulvestrant (7.2 months vs. 3.6 months, HR=0.60, 95% CI 0.51–0.71, P<0.001) in HR+/HER2- advanced breast cancer patients who had a relapse or disease progression during or after treatment with an aromatase inhibitor, with or without previous CDK4/6 inhibitor therapy [32]. In the subgroup of patients with AKT pathway alterations, the median PFS was 7.3 months in the capivasertib group and 3.1 months in the placebo group (HR=0.50, 95% CI 0.38–0.65, P<0.001) [32]. The most common grade ≥ 3 AEs were rash (12.1% in the capivasertib group vs. 0.3% in the placebo group) and diarrhea (9.3% vs. 0.3%); 13.0% and 2.3% in the capivasertib and placebo group, respectively, discontinued treatment due to AEs [32]. Based on the favorable results observed in CAPItello-291, capivasertib was approved by the US FDA in November 2023 for use in combination with fulvestrant for the treatment of adult patients with HR+/HER- 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 [44]. CAPItello-292, an open-label, randomized phase Ib/III study investigating the triplet combination of capivasertib plus CDK4/6 inhibitor and fulvestrant (vs. a control arm without capivasertib) in CDK4/6 inhibitor-naïve (except for in the adjuvant setting) patients with HR+/HER2- locally advanced, unresectable or metastatic breast cancer is current underway [33].

Ipatasertib

Ipatasertib is another AKT inhibitor that has enter phase II/III trials for HR+ breast cancer [34]. IPATunity130 is a randomized, double-blind, phase III trial of ipatasertib plus paclitaxel versus placebo plus paclitaxel. Cohort B of IPATunity130 included PI3K pathway-mutated HR+/HER2- unresectable locally advanced or metastatic breast cancer patients who were considered inappropriate for endocrine-based therapy [34]. However, ipatasertib did not improve the patients' PFS and objective response rate (ORR) in this study [34]. Currently, two clinical trials of ipatasertib in HR+/HER2- breast cancer patients are ongoing. FINER (NCT04650581) is a randomized, double-blind, phase III trial comparing ipatasertib plus fulvestrant versus placebo plus fulvestrant in patients with ER+/HER2- breast cancer following progression on first-line CDK4/6 inhibitor and aromatase inhibitor treatment [35]. FAIM (NCT04920708) is a multicenter, randomized, open-label superiority phase II trial of the triplet combination of ipatasertib, fulvestrant and CDK4/6 inhibitor in patients with ER+/HER2- metastatic breast cancer [36].

mTOR inhibitors

Everolimus

Everolimus is a sirolimus derivative that inhibits mTOR through allosteric binding to mTORC1 [45]. In the pivotal randomized, double-blind phase III BOLERO-2 trial, everolimus plus exemestane significantly improved the median PFS than placebo plus exemestane post-menopausal women with HR+/HER2- advanced breast cancer with recurrence/progression during or after aromatase inhibitor (investigator review: 7.8 months vs. 3.2 months, HR=0.45, 95% CI 0.31–0.48, P<0.0001; central review: 11.0 months vs. 4.1 months, HR=0.38, 95% CI 0.31–0.48, P<0.0001) [37]. The most common grade 3/4 AEs were stomatitis (8% in the everolimus group vs. <1% in the placebo group), anemia (6% vs. <1%), dyspnea (4% vs. 1%), hyperglycemia (4% vs. <1%), fatigue (4% vs. 1%), and pneumonitis (3% vs. 0%) [45]. Everolimus was approved by the FDA and EMA in 2012 for ER+/HER2- advanced breast cancer after aromatase inhibitor and was the first PI3K/AKT/mTOR inhibitor to be approved for this indication [11].

Dual inhibitors

Gedatolisib

Gedatolisib is a dual inhibitor targeting class I PI3Ks and mTOR [46]. Among HR+/HER2- advanced breast cancer patients in a phase Ib trial, gedatolisib plus palbociclib and endocrine therapy induced an ORR of 85.2% in treatment-naïve patients, 61.5% in previously treated but CDK4/6 inhibitor-naïve patients, and 25.0%–55.6% in previous treated (including CDK4/6 inhibitor) patients [46]. The most common grade 3/4 treatment related AEs were neutropenia (63%), stomatitis (27%), and rash (20%); grade 3/4 hyperglycemia was reported in 6% of patients, and 9% of patients discontinued gedatolisib due to AEs [46]. An open-label, randomized phase III trial (VIKTORIA-1, NCT05501886) evaluating the efficacy and safety of gedatolisib plus fulvestrant with or without palbociclib for the treatment of locally advanced or metastatic HR+/HER2- breast cancer following progression on or after CDK4/6 and aromatase inhibitor therapy is currently ongoing [40].

PI3K/AKT/mTOR inhibitors under phase I investigation

Several PI3K/AKT/mTOR inhibitors that have entered phase I trials are listed in Table 2, and most of them are PI3K inhibitors. Of note, these novel PI3K inhibitors are all PI3Kα-selective [47–50], and STX-478, LOXO-783 and RLY-2608 are mutant-selective [48–50], potentially giving rise to improved tolerability than traditional PI3K inhibitors. Additionally, LOXO-783 is brain-penetrant [50], and may provide additional clinical benefits to patients with brain metastases. Although still under early clinical exploration, these mutant-specific PI3Kα inhibitors demonstrated potent antitumor activity without inducing insulin and/or glucose metabolism dysregulation at the preclinical stage (Table 2) [48,49,51].

Diagnostic testing of PI3K/AKT/mTOR alterations

Accurate and reliable diagnostic testing of PI3K/AKT/mTOR alterations is the foundation of effective targeted treatment with PI3K/AKT/mTOR inhibitors. This section discusses several considerations for diagnostic testing of PI3K/AKT/mTOR alterations, including the sampling site, type of sample, as well as testing method.

Sampling of the metastatic site is important due to tumor heterogeneity

There is heterogeneity in PI3K/AKT/mTOR alterations between primary and metastatic tumors. In the AURORA program, Aftimos et al. performed multi-omics profiling on paired primary tumors and early-course metastases from breast cancer patients (65% of patients were HR+/HER2-), and found that metastases were enriched in mutations in

Table 1
Clinical trials of PI3K/AKT/mTOR inhibitors entering phase II/III investigation for HR+/HER2- locally advanced/metastatic breast cancer.

Trial	Inclusion Marker	Line of therapy	Treatments (n)	Primary endpoints	Approval*
PI3K inhibitors					
SOLAR-1 [19] *Phase III*	*PIK3CA*-mutated	2nd or later	Alpelisib + FUL (169) vs. P + FUL (172)	mPFS: 11.0 vs. 5.7 m (HR=0.65, 95% CI 0.50–0.85, P<0.001)	FDA: 2019 [20] EMA: 2020 [21]
INAVO120 [22] *Phase III*	*PIK3CA*-mutated	1st	Inavolisib + palbociclib + FUL (161) vs. P + palbociclib + FUL (164)	mPFS: 15.0 vs. 7.3 m (HR=0.43, 95% CI 0.32–0.59, P<0.0001) *(ongoing)*	–
INAVO121 [23] *Phase III*	*PIK3CA*-mutated	2nd or 3rd	Inavolisib + FUL vs. P + FUL	PFS *(ongoing)*	
BELLE-2 [24] *Phase III*†	–	2nd or later	Buparlisib + FUL (total: 576; PI3K-activated: 188) vs. P + FUL (total: 571; PI3K-activated: 184)	mPFS (total): 6.9 vs. 5.0 m (HR=0.78, 95% CI 0.67–0.89, P=0.00021) mPFS (PI3K-activated): 6.8 vs. 4.0 m (HR=0.76, 95% CI 0.60–0.97, P=0.014)	–
BELLE-3 [25] *Phase III*†	–	2nd or later	Buparlisib + FUL (289) vs. P + FUL (143)	mPFS: 3.9 vs. 1.8 m (HR=0.67, 95% CI 0.53–0.84, P=0.0003)	
FERGI [26] *Phase II*†	–	2nd or later	Pictilisib (part 1: 89, part 2 [*PIK3CA*-mutated]: 41) vs. P (part 1: 79, part 2: 20)	mPFS (part 1): 6.6 vs. 5.1 m (HR=0.74, 95% CI 0.52–1.06, P=0.096) mPFS (part 2 [*PIK3CA*-mutated]): 5.4 vs. 10.0 m (HR=1.07, 95% CI 0.53–2.18, P=0.84)	–
SANDPIPER [27] *Phase III*†	*PIK3CA*-mutated	2nd or later	Taselisib + FUL (340) vs. P + FUL (176)	mPFS: 7.4 vs. 5.4 m (HR=0.70, 95% CI 0.56–0.89, P=0.0037)	–
AKT inhibitors					
BEECH [28] *Phase Ib/II*	–	2nd or later	Capivasertib (total: 54; *PIK3CA*-mutated: 26) + paclitaxel vs. P + paclitaxel (total: 56; *PIK3CA*-mutated: 25)	mPFS (total): 10.9 vs. 8.4 m (HR=0.80, P=0.308) mPFS (*PIK3CA*-mutated): 10.9 vs. 10.8 m (HR=1.11, P=0.760)	FDA: 2023 [29] EMA: 2024 [30]
FAKTION [31] *Phase II*	–	2nd or later	Capivasertib + FUL (69) vs. P + FUL (71)	mPFS: 10.3 vs. 4.8 m (aHR=0.56, 95% CI 0.38–0.81, P=0.0023)	
CAPItello-291 [32] *Phase III*	–	2nd or later	Capivasertib + FUL (Total: 355; *PIK3CA/AKT1/PTEN*-altered: 155) vs. P + FUL (Total: 353, PI3K/AKT/mTOR altered: 134)	mPFS (total): 7.2 vs. 3.6 m (HR=0.60, 95% CI 0.51–0.71, P<0.001) mPFS (*PIK3CA/AKT1/PTEN*-altered): 7.3 vs. 3.1 m (HR=0.50, 95% CI 0.38–0.65, P<0.001)	
CAPItello-292 [33] *Phase Ib/III*	–	1st	Capivasertib + CDK4/6 inhibitor + FUL vs. CDK4/6 inhibitor + FUL	PFS *(ongoing)*	
IPATunity130 [34] *Phase III*	PI3K/AKT/mTOR altered (cohort B)	2nd or later	Ipatasertib + paclitaxel (146) vs. P + paclitaxel (76)	mPFS: 9.3 vs. 9.3 m (HR=1.0, 95% CI 0.71–1.40)	–
FINER [35] *Phase II*	–	2nd or later	Ipatasertib + FUL vs. P + FUL	PFS *(ongoing)*	
FAIM [36] *Phase II*	–	1st	Ipatasertib + CDK4/6 inhibitor + FUL vs. CDK4/6 inhibitor + FUL	PFS *(ongoing)*	
mTOR inhibitors					
BOLERO-2 [37] *Phase III*	–	2nd or later	Everolimus + exemestane (485) vs. P + exemestane (239)	mPFS: 7.8 vs. 3.2 m (HR=0.45, 95% CI 0.38–0.54, P<0.0001)	FDA: 2012 [38] EMA: 2012 [39]
Dual inhibitors					
VIKTORIA-1 [40] *Phase III*	*PIK3CA*-wildtype vs. *PIK3CA*-mutated	2nd or later	Gedatolisib + FUL +/without palbociclib vs. Alpelisib + FUL	PFS *(ongoing)*	–

*Refers to approval for HR+/HER- advanced/metastatic breast cancer, and only approvals from FDA and EMA are listed here; †There was no further investigation due to poor safety profile and/or limited clinical benefit observed in this trial. aHR, adjusted hazard ratio; AKT, protein kinase B; CDK4/6, cyclin-dependent kinase 4/6; CI: confidence interval; EMA, European Medicines Agency; FDA, US food and drug administration; FUL, fulvestrant; HER2-, human epidermal growth factor receptor 2-negative; HR, hazard ratio; HR+, hormone receptor-positive; mPFS, median progression free survival; m, months; mTOR, mammalian target of rapamycin; P, placebo; PI3K/AKT/mTOR, phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin; PFS, progression free survival; PI3K, phosphatidylinositol 3-kinase.

PIK3CA, *PTEN* and several other genes [60]. Similarly, another study on paired primary breast tumor and their distant metastases from the same patients (n = 23) found a high discordance rate (47.8%, 11/23) of phosphorylated AKT by immunohistochemistry (IHC) [61]. Given the potentially different expressions of receptors and molecular biomarkers between primary and metastatic tumors, it may be worthwhile to conduct a re-biopsy of metastatic tumor for patients with metastasis [62,63]. Of course, factors such as patient fitness and feasibility of obtaining metastatic biopsy also need to be taken into consideration. If biopsy of the metastatic site is not feasible, the primary tumor sample could also be used. A recent systematic review showed that the discordance rate of *PIK3CA* mutation status between primary and metastatic tumors was less than 10% [64].

Both tissue and liquid biopsies can be used

Tissue biopsy is the gold standard for tumor profiling and is widely used to guide breast cancer therapy [4,65,66]. In recent years, liquid biopsy, in particular circulating tumor DNA (ctDNA), has also emerged as a valuable tool for cancer diagnostics [67,68]. Several large trials of

Table 2
Selected PI3K/AKT/mTOR inhibitors in preclinical and phase I investigation.

Inhibitors	Target	Current evidence	Ongoing trial
TOS-358 [52]	PI3Kα	• Maintained 90% binding at 100 nM six hours after washout, whereas binding of alpelisib at 100 nM was completely lost over the same time frame (TOS-359 is a first-in-class covalent PI3Kα inhibitor) [51,52] • Induced greater tumor regressions than alpelisib and inavolisib in cell-derived xenograft and PDX models [52] • Inhibited PI3Kα potently without inducing significant hyperglycemia [51]	NCT05683418 *Phase I* [47]
STX-478 [48]	Prevalent PI3Kα helical- and kinase-domain mutants	• Efficacious across a panel of PI3Kα-mutant cell-derived xenograft and PDX tumors without inducing insulin resistance [48] • Combination with FUL and/or CDK4/6 inhibitors was well tolerated and induced robust and durable tumor regression in ER+/HER2- xenograft models [48]	NCT05768139 *Phase I/II* [53]
RLY-2608 [49]	PI3Kα mutant	• Inhibited tumor growth in *PIK3CA* mutant xenograft models, with minimal impact on insulin [49] • Elicited objective response in two HR+ advanced breast cancer patients carrying *PIK3CA* mutations in the kinase or helical domain, with no wild type PI3Kα-related toxicities observed [49]	NCT05216432 *Phase I* [54,55]
LOXO-783 [50]	PI3Kα H1047R	• Induced tumor regressions in ER+/HER2-, PI3Kα H1047R-mutant breast cancer models without inducing hyperglycemia [50] • Inhibit tumor growth in brain metastasis models [50]	NCT05307705 *Phase I* [56]
RMC-5552 [57]	mTORC1	• Exhibited antitumor activity in cell line-derived xenograft model with an activating mutation of *PIK3CA* [58]	NCT04774952 *Phase I* [59]

CDK4/6, cyclin-dependent kinase 4/6; ER+, estrogen receptor-positive; FUL, fulvestrant; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; mTORC1, mammalian target of rapamycin complex 1; PI3K/AKT/mTOR, phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin; PDX, patient derived xenograft; PI3Kα, phosphatidylinositol 3-kinase α isoform.

PI3K/AKT/mTOR inhibitors have demonstrated the clinically utility of ctDNA for detecting specific tumor aberrations and informing treatment [69]. For instance, the open-label, multicohort phase II trial plasmaMATCH assigned patients with advanced breast cancer to four different targeted therapies based on mutations identified in ctDNA. This trial found a 93% sensitivity of digital polymerase chain reaction (PCR) ctDNA for mutations identified in tissue sequencing, and the sensitivity increased to 98% if contemporaneous biopsies are used [70]. Cohorts B (patients with *HER2* mutations, treated with neratinib, and fulvestrant if ER+) and C (patients with *AKT1* mutations, treated with capivasertib plus fulvestrant) of this study met or exceeded the target number of responses [70]. In the aforementioned SOLAR-1 trial, alpelisib plus fulvestrant achieved a 35% risk reduction in PFS (HR=0.65, 95% CI 0.50–0.85) among patients with *PIK3CA* mutation as determined by tissue biopsy [19]. A subsequent analysis revealed a 45% risk reduction (HR=0.55, 95% CI 0.39–0.79) among patients with *PIK3CA* mutation as determined by ctDNA [71]. The 2022 update to the American Society of Clinical Oncology (ASCO) guidelines on biomarkers in metastatic breast cancer recommended testing potential candidates for alpelisib treatment for *PIK3CA* mutations using tumor tissue or ctDNA sample; reflex testing on tumor tissue is recommended in case of negative ctDNA results [72]. This recommendation is also endorsed by the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Breast Cancer (NCCN guidelines) [4] (Table 3). Similarly, both tissue and liquid biopsies may be used to detect *AKT1* or *PTEN* alterations [4].

Next-generation sequencing (NGS) may be considered before PCR

Based on the study designs employed in pivotal phase III trials and the results obtained (Table 4), the 2024 NCCN guidelines recommend testing for *PIK3CA* mutations using either PCR or NGS to guide the use of alpelisib; whereas only NGS is recommended to test for *PIK3CA*, *AKT1* activating mutations or *PTEN* alterations to guide the use of capivasertib [4]. NGS is becoming increasingly recommended for molecular testing due to its ability to capture different alterations (single-nucleotide variations, insertion/deletions, copy number alterations) across multiple genes through a single test [31]. Additionally, NGS may be more sensitive than PCR even for a single gene [74,75]. A retrospective analysis of real-world data retrieved from the US Flatiron Health-Foundation Medication clinic-genomic database revealed that compared with the companion diagnostic PCR hotspot test (designed to detect 11 mutations prespecified *PIK3CA* mutations) for alpelisib, NGS was able to capture additional *PIK3CA* mutations outside of the 11 mutations, which accounted for 20% of *PIK3CA*-mutated breast cancer [75]. However, this is not to say that PCR should be replaced with NGS altogether. Colomer et al. noted that it is common for hospitals that do not have their own NGS facility or analytic pipeline to use centralized testing [76]. However, centralized NGS faces several challenges such as astringent sample quality, and delay in turn-around time and clinical decision [76]. Additionally, NGS vendors have limited access to detailed patient information, and at the same time, clinicians do not have access to full NGS data [76]. Furthermore, patient willingness also needs to be considered. As such, while NGS may be preferred due to greater comprehensiveness and sensitivity, both PCR and NGS are valuable in clinical practice.

Other considerations for the use of PI3K/AKT/mTOR inhibitors

Clinical significance of PI3K/AKT/mTOR inhibitors

Patients progressing on endocrine therapy

Endocrine therapy is the cornerstone of HR+ breast cancer treatment [6]. However, the development of endocrine resistance often renders endocrine therapy ineffective as the disease progresses [6]. Of importance, PI3K/AKT/mTOR inhibitors have demonstrated clinical benefits for patients with endocrine resistance. For instance, 85.6% of patients in SOLAR-1 had endocrine-resistant disease at enrollment, and alpelisib plus fulvestrant achieved significantly improved PFS than placebo plus fulvestrant in this cohort of patients [19]. For INAVO120, 34.2% and 65.5% of patients had primary and secondary endocrine resistance, respectively, and both had significantly improved PFS with inavolisib treatment [22]. Similarly, in CAPItello-291, 37.0% and 63.0% of patients had primary and secondary endocrine resistance, respectively, and capivasertib was able to improve the PFS in both groups [32].

Table 3
Guideline recommendations for diagnostic testing for PI3K/AKT/mTOR inhibitors.

Guidelines	Biomarkers	Detection methods	Recommended PI3K/AKT/mTOR inhibitors
NCCN 2024 [4]	*PIK3CA* activating mutation	NGS, PCR (Blood or tumor tissue if blood negative)	Alpelisib
	PIK3CA or *AKT1* activating mutations or *PTEN* alterations	NGS (Blood or tumor tissue if blood negative)	Capivasertib
ASCO 2022 & 2024 [72,73]	*PIK3CA* mutation	Sequencing for targetable mutations through large panel tumor genomic testing in a CLIA-certified laboratory performed on tissue or plasma obtained either at the time of progression or from archival tissue. If no mutation is found in ctDNA, testing in tumor tissue, if available, should be used.	Capivasertib or alpelisib
	AKT1 mutation or *PTEN* inactivation		Capivasertib

ASCO, American Society of Clinical Oncology; CLIA, Clinical Laboratory Improvement Amendments; ctDNA, circulating tumor DNA; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; PI3K/AKT/mTOR, phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin; PCR, polymerase chain reaction

Table 4
Diagnostic testing in select pivotal phase III trials of PI3K/AKT/mTOR inhibitors.

Pivotal studies	Samples	Detection methods	Qualifying mutations*
SOLAR-1† [19,41]	Tumor tissue	PCR by Qiagen *therascreen*® *PIK3CA* RGQ PCR kit	Specified mutations in the C2, helical, and kinase domains of PI3K: C420R, E542K, E545A, E545D (1635G > T only), E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y
INAVO120 [22]	Plasma or tumor tissue	NGS by FoundationOne® Liquid CDx or PredicineCARE assay (in China)	Specified mutations of *PIK3CA*
CAPItello-291 [32]	Tumor tissue	NGS by FoundationOne® CDx assay or OncoScreen Plus (in China)	Specified activating mutations in *PIK3CA* and *AKT1* and inactivating alterations in *PTEN* genes
IPATunity [34]	Tumor tissue	NGS by Foundation Medicine Clinical Trial Assay	Specified *PIK3CA*/*AKT1*/*PTEN* alterations, such as *AKT1* missense mutations resulting in E17, L52 or Q79 substitution

*Examples of specific mutations are included here if reported in the study publications; †Plasma samples and NGS were also used in SOLAR-1, but only for exploratory analysis. NGS, next-generation sequencing; PI3K/AKT/mTOR, phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin; PCR, polymerase chain reaction

Patients progressing on CDK4/6 inhibitor

The advancements of CDK4/6 inhibitors in the recent decade have greatly transformed the treatment for advanced/metastatic HR+ breast cancer [77–83]. Ribociclib, abemaciclib or palbociclib in combination with endocrine therapy is currently the recommended first-line treatment for HR+/HER2- advanced/metastatic breast cancer [4]. However, most patients eventually also develop resistance to CDK4/6 inhibitors [2,11,84,85], and patients progressing on CDK4/6 inhibitors typically have poor prognosis, especially for those carrying PI3K/AKT/mTOR mutations. Approximately 70% of patients in the global CAPItello-291 trial had previously received a CDK4/6 inhibitor, and the median PFS of these CDK4/6 inhibitor-experienced patients (capivasertib arm, 5.5 months; placebo arm, 2.6 months) were much shorter than those without prior CDK4/6 exposure (capivasertib arm: 10.9 months, placebo arm: 7.2 months) [32]. While rechallenging with a CDK4/6 inhibitor after disease progression on a prior CDK4/6 inhibitor may be efficacious for some patients [86–89], it is of limited efficacy in patients with PI3K/AKT/mTOR mutations. In the phase II MAINTAIN trial, rechallenging with ribociclib significantly improved PFS in CDK4/6 inhibitor-experienced patients who did not have *PIK3CA* mutation than placebo (median PFS: 6.11 months vs. 2.79 months, HR=0.39, 95% CI 0.22–0.71), but not in those with *PIK3CA* mutation (median PFS: 2.56 months vs. 2.74 months, HR=1.02, 95% CI 0.39–2.68) [90]. Similarly, in the phase III postMONARCH trial, although rechallenging with abemaciclib achieved clinical benefits in patients previously treated with CDK4/6 inhibitors, those with *PIK3CA/AKT1/PTEN* mutations experienced smaller risk reductions for PFS than other subgroups [91]. Such results highlight the poor prognosis of CDK4/6 inhibitor-treated patients carrying PI3K/AKT/mTOR mutations, and the need for more effective treatment for these patients.

Importantly, as demonstrated in CAPItello-291, capivasertib plus fulvestrant was able to extend the patients' PFS regardless of previous history of CDK4/6 inhibitor treatment or the existence of PI3K/AKT/mTOR alterations [32]. Specifically, the hazard ratio of capivasertib plus fulvestrant versus placebo plus fulvestrant was 0.49 (95% CI 0.36–0.66) for *PIK3CA/AKT1/PTEN*-mutated, CDK4/6 inhibitor-treated patients [32]. Taken together, these results demonstrate that importance of PI3K/AKT/mTOR inhibitors for HR+ advanced breast cancer patients progressing on CDK4/6 inhibitors. These inhibitors represent a valuable addition to the armamentarium of precision medicine for HR+ breast cancer. On a related note, other than patients with rapidly progressing disease, the ongoing CAPItello-292 trial also recruits patients who have received CDK4/6 inhibitors in the adjuvant setting [33]. Future results of CAPItello-292 will help inform the clinical benefits of capivasertib plus CDK4/6 inhibitor and fulvestrant for these patients.

Choice of PI3K/AKT/mTOR inhibitors in the second line setting

Alpelisib, capivasertib, and everolimus have demonstrated clinical benefits in pivotal phase III trials [19,32,37], and are recommended as second- or subsequent-line therapies for HR+/HER2- advanced breast cancer [4]. Treatment efficacy, safety and patient characteristics need to be considered when choosing a suitable PI3K/AKT/mTOR inhibitor. In terms of mechanism, everolimus only inhibits mTORC1 and its downstream target, and is unable to act on other downstream effectors of PI3K and AKT, such as forkhead box protein 1, glycogen synthase kinase 3, mouse double minute 2 homolog, and tuberous sclerosis complex 2 (Fig. 1A). Before the approval of capivasertib and its recent endorsement by major guidelines [4,73], alpelisib was generally considered ahead of everolimus (biomarker un-selected) for patients carrying *PIK3CA* mutations due to improved response rate, lower rates of pneumonitis and stomatitis, and the concept of precision medicine [11].

With the introduction of capivasertib, which is indicated for patients with *PIK3CA* or *AKT1* activating mutations or *PTEN* alterations, patients with *AKT1* and/or *PTEN* alterations can now receive second-line treatment with capivasertib, and patients carrying only *PIK3CA* mutation

Table 5
AEs observed in pivotal phase III trials of key PI3K/AKT/mTOR inhibitors.

Clinical Trials	SOLAR-1 [19]	INAVO120 [22]	CAPItello-291 [32]	BOLERO-2 [37]
Treatment	Alpelisib + FUL	Inavolisib + palbociclib + FUL	Capivasertib + FUL	Everolimus + exemestane
Number of patients	284*	162	355	482
Grade ≥3 AEs, n (%)	216 (76.1)	149 (92.0)	152 (42.8)	50%
AEs leading to dose modification or treatment interruption, n (%)	125 (74.0)	134 (82.7)	• Dose interruption: 124 (34.9) • Dose reduction: 70 (19.7)	62.4%
AEs leading to discontinuation, n (%)	71 (25.0)	11 (6.8)	46 (13.0)	26.3%
Most common AEs, all grade (grade ≥3), %	• Hyperglycemia 63.7 (36.6) • Diarrhea 57.7 (6.7) • Nausea 44.7 (2.5) • Rash 35.6 (9.9) • Decreased appetite 35.6 (0.7)	• Neutropenia 88.9 (80.2) • Hyperglycemia 58.5 (5.6) • Stomatitis/mucosal inflammation 51.2 (5.6) • Thrombocytopenia 48.1 (14.2) • Diarrhea 48.1 (3.7)	• Diarrhea 72.4 (9.3) • Rash 38.0 (12.1) • Nausea 34.6 (0.8) • Fatigue 20.8 (0.6) • Vomiting 20.6 (1.7)	• Stomatitis 59 (8) • Rash 39 (1) • Fatigue 37 (<5) • Diarrhea 34 (<3) • Nausea 31 (<2)

* Including patients who received alpelisib plus fulvestrant from the overall population (including the *PIK3CA*-mutated cohort). AE, adverse event; FUL, fulvestrant; PI3K/AKT/mTOR, phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin.

could choose either capivasertib or alpelisib [11]. A recent indirect treatment comparison study provided preliminary evidence that capivasertib plus fulvestrant may be more efficacious than alpelisib plus fulvestrant for *PIK3CA*-altered, HR+ advanced breast cancer after disease progression following endocrine therapy [92]. This may be because the effect of PI3K inhibition is mediated through downstream AKT signaling. Besides, the effect of PI3K inhibition may be affected by changes in PTEN activity. PTEN antagonizes the function of PI3K and acts as a negative regulator of the PI3K/AKT/mTOR pathway (Fig. 1A). Recent research has demonstrated that pharmacological inhibition of the PI3K/AKT/mTOR pathway may reduce PTEN, contributing to the rebound in pathway activity in tumors treated with PI3K inhibitors and limiting their efficacy [93].

Safety wise, the safety profile of capivasertib is generally considered as more favorable than alpelisib (Table 5) [4,11,92]. Although PI3K inhibitors demonstrate potent antitumor activity, their clinical application is often limited by frequent and severe AEs [24–27,94]. As different isoforms of PI3K are involved in multiple physiological functions, such as glucose metabolism, inflammation and immunity, it is not surprising that pan-PI3K inhibitors, such as buparlisib and pictilisib, have significant safety concerns [24–26,94,95]. Even with isoform-selective inhibitors, traditional inhibitors including the approved alpelisib inhibit both wild-type and mutant PI3Ks with comparable potency, resulting in considerable on-target toxicity (especially hyperglycemia as inhibiting wild type PI3Kα causes acute insulin resistance) [48,95]. In SOLAR-1, hyperglycemia occurred in 63.7% of patients receiving alpelisib plus fulvestrant, whereas only 16.3% of patients receiving capivasertib plus fulvestrant in CAPItello-291 experienced hyperglycemia; similarly, grade 3/4 hyperglycemia occurred in a much higher proportion of patients in SOLAR-1 than in CAPItello-291 (36.6% vs. 2.3%) [19,32]. Diarrhea was the only AE that seemed to occur at a higher incidence in CAPItello-291 than SOLAR-1 (Table 5). Considering both efficacy and safety, capivasertib may be the preferred choice of PI3K/AKT/mTOR inhibitor for patients with PI3K/AKT/mTOR alterations, including those with *PIK3CA* mutations.

Management of hyperglycemia and other AEs

Besides choosing a PI3K/AKT/mTOR inhibitor with less safety concerns, prevention, early identification, and appropriate intervention of AEs may be taken to help manage the potential toxicities of PI3K/AKT/mTOR inhibitors [96]. In SOLAR-1, the median time to onset of grade ≥3 hyperglycemia, rash and diarrhea were 15, 13 and 139 days, respectively [96]. Of the 187 patients experiencing any-grade hyperglycemia in the alpelisib cohort, 163 received anti-diabetic medications. Metformin alone or in combination with other antidiabetic agents was used by most patients (87.1%), and 47% of patients required three or more medications to manage hyperglycemia [96]. If ill-managed, severe hyperglycemia may be associated with hyperglycemic hyperosmolar non-ketotic syndrome or ketoacidosis [20]. Fatal cases of ketoacidosis have occurred in the post-marketing use of alpelisib [20]. Although the risk of severe hyperglycemia is much lower for capivasertib, pre-treatment testing and on-treatment monitoring of blood glucose are recommended for both alpelisib and capivasertib [20,29]. Preventive measures and intervention for other AEs of special interest should also be taken where necessary. As observed in SOLAR-1 and CAPItello-291, steroids (including prednisone, dexamethasone, prednisolone, or hydrocortisone) and antihistamines (including fexofenadine, desloratadine, hydroxyzine, or loratadine) could be used to manage rash [96,97]. Prophylactic anti-rash medication could also be used to lower the incidence and severity of rash [96]. Antipropulsives (mostly loperamide) were commonly received by patients as supportive medication to manage diarrhea. Treatment modification or discontinuation may be warranted depending on the severity of AEs [20,29,98].

Conclusions

In sum, the recent advancements in PI3K/AKT/mTOR inhibitors represent a significant stride forward in the management of HR+/HER2- advanced breast cancer, offering promising treatment options for the large proportion of patients progressing on first-line aromatase inhibitor plus CDK4/6 inhibitor treatment. Of particular interest, AKT inhibitors including capivasertib, with their potent antitumor efficacy and favorable safety profiles, represent a significant addition to the armamentarium of precision medicine in oncology. By leveraging molecular biomarkers and genomic profiling, clinicians can now identify individuals most likely to benefit from PI3K/AKT/mTOR inhibition (such as those presenting with co-mutations), thereby optimizing treatment selection and improving overall survival rates. This individualized approach not only enhances treatment efficacy but also mitigates unnecessary toxicities, thereby enhancing patients' quality of life. As we continue to unravel the complexities of cancer biology and refine our understanding of molecular subtypes, PI3K/AKT/mTOR inhibitors stand as a beacon of progress, driving us towards more effective, personalized, and patient-centered care.

CRediT authorship contribution statement

Chunfang Hao: Conceptualization, Data curation, Writing – original draft. **Yunchu Wei:** Conceptualization, Data curation, Writing – original draft. **Wenjing Meng:** Data curation, Writing – review & editing. **Jie Zhang:** Data curation, Writing – review & editing. **Xiaonan Yang:** Data curation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] McAndrew NP, Finn RS. Clinical review on the management of hormone receptor-positive metastatic breast cancer. JCO Oncol Pract 2022;18:319–27.
[2] Mittal A, Molto Valiente C, Tamimi F, Schlam I, Sammons S, Tolaney SM, et al. Filling the gap after CDK4/6 inhibitors: Novel endocrine and biologic treatment options for metastatic hormone receptor positive breast cancer. Cancers (Basel) 2023;15:2015.
[3] Giaquinto AN, Sung H, Miller KD, Kramer JL, Newman LA, Minihan A, et al. Breast cancer statistics, 2022. CA Cancer J Clin 2022;72:524–41.
[4] National Comprehensive Cancer Network. Breast cancer, version 2.2024. NCCN Clinical Practice Guidelines in Oncology 2024.
[5] Ma J, Chan JJ, Toh CH, Yap YS. Emerging systemic therapy options beyond CDK4/6 inhibitors for hormone receptor-positive HER2-negative advanced breast cancer. npj Breast Cancer 2023;9:74.
[6] Raheem F, Karikalan SA, Batalini F, El Masry A, Mina L. Metastatic ER+ breast cancer: Mechanisms of resistance and future therapeutic approaches. Int J Mol Sci 2023;24:16198.
[7] Papadimitriou MC, Pazaiti A, Iliakopoulos K, Markouli M, Michalaki V, Papadimitriou CA. Resistance to CDK4/6 inhibition: Mechanisms and strategies to overcome a therapeutic problem in the treatment of hormone receptor-positive metastatic breast cancer. Biochim Biophys Acta Mol Cell Res 2022;1869:119346.
[8] Glaviano A, Foo ASC, Lam HY, Yap KCH, Jacot W, Jones RH, et al. PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer. Mol Cancer 2023;22:138.
[9] du Rusquec P, Blonz C, Frenel JS, Campone M. Targeting the PI3K/Akt/mTOR pathway in estrogen-receptor positive HER2 negative advanced breast cancer. Ther Adv Med Oncol 2020;12.
[10] Miricescu D, Totan A, Stanescu-Spinu I-I, Badoiu SC, Stefani C, Greabu M. PI3K/AKT/mTOR signaling pathway in breast cancer: From molecular lands cape to clinical aspects. Int J Mol Sci 2020;22:173.
[11] Browne IM, André F, Chandarlapaty S, Carey LA, Turner NC. Optimal targeting of PI3K-AKT and mTOR in advanced oestrogen receptor-positive breast cancer. Lancet Oncol 2024;25:e139–51.
[12] Zhu K, Wu Y, He P, Fan Y, Zhong X, Zheng H, et al. PI3K/AKT/mTOR-targeted therapy for breast cancer. Cells 2022;11:2508.
[13] Wang X, Zhao S, Xin Q, Zhang Y, Wang K, Li M. Recent progress of CDK4/6 inhibitors' current practice in breast cancer. Cancer Gene Ther 2024.
[14] Zhang C, Zhou F, Zou J, Fang Y, Liu Y, Li L, et al. Clinical considerations of CDK4/6 inhibitors in HER2 positive breast cancer. Frontiers. Oncology 2024;13.
[15] Alves CL, Ehmsen S, Terp MG, Portman N, Tuttolomondo M, Gammelgaard OL, et al. Co-targeting CDK4/6 and AKT with endocrine therapy prevents progression in CDK4/6 inhibitor and endocrine therapy-resistant breast cancer. Nat Commun 2021;12:5112.
[16] Wylaź M, Kaczmarska A, Pajor D, Hryniewicki M, Gil D, Dulińska-Litewka J. Exploring the role of PI3K/AKT/mTOR inhibitors in hormone-related cancers: A focus on breast and prostate cancer. Biomed Pharmacother 2023;168:115676.
[17] Watt AC, Goel S. Cellular mechanisms underlying response and resistance to CDK4/6 inhibitors in the treatment of hormone receptor-positive breast cancer. Breast Cancer Res 2022;24:17.
[18] Abu-Khalaf MM, Alex Hodge K, Hatzis C, Baldelli E, El Gazzah E, Valdes F, et al. AKT/mTOR signaling modulates resistance to endocrine therapy and CDK4/6 inhibition in metastatic breast cancers. NPJ Precis Oncol 2023;7:18.
[19] André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, et al. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. N Engl J Med 2019;380:1929–40.
[20] Novartis. PIQRAY®(alpelisib) prescribing information. 2019.
[21] European Medicines Agency. Piqray (alpelisib) An overview of Piqray and why it is authorised in the EU. EMA/298596/2020. 2020.
[22] Turner NC, Im SA, Saura C, Juric D, Loibl S, Kalinsky K, et al. Inavolisib-Based Therapy in PIK3CA-Mutated Advanced Breast Cancer. N Engl J Med 2024;391:1584–96.
[23] Juric D, Kalinsky K, Im S-A, Ciruelos EM, Bianchini G, Barrios CH, et al. INAVO121: Phase III study of inavolisib (INAVO) + fulvestrant (FUL) vs. alpelisib (ALP) + FUL in patients (pts) with hormone receptor-positive, HER2-negative (HR+, HER2–) PIK3CA-mutated (mut) locally advanced or metastatic breast cancer (LA/mBC). J Clin Oncol 2023;41.
[24] Baselga J, Im SA, Iwata H, Cortés J, De Laurentiis M, Jiang Z, et al. Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2017;18:904–16.
[25] Di Leo A, Johnston S, Lee KS, Ciruelos E, Lønning PE, Janni W, et al. Buparlisib plus fulvestrant in postmenopausal women with hormone-receptor-positive, HER2-negative, advanced breast cancer progressing on or after mTOR inhibition (BELLE-3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2018;19:87–100.
[26] Krop IE, Mayer IA, Ganju V, Dickler M, Johnston S, Morales S, et al. Pictilisib for oestrogen receptor-positive, aromatase inhibitor-resistant, advanced or metastatic breast cancer (FERGI): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol 2016;17:811–21.
[27] Dent S, Cortés J, Im YH, Diéras V, Harbeck N, Krop IE, et al. Phase III randomized study of taselisib or placebo with fulvestrant in estrogen receptor-positive, PIK3CA-mutant, HER2-negative, advanced breast cancer: the SANDPIPER trial. Ann Oncol 2021;32:197–207.
[28] Turner NC, Alarcón E, Armstrong AC, Philco M, López Chuken YA, Sablin MP, 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;30:774–80.
[29] AstraZeneca. TRUQAP™ (capivasertib) prescription information. 2023.
[30] European Medicines Agency. Truqap capivasertib. EMA/151857/2024. 2024.
[31] Howell SJ, Casbard A, Carucci M, Ingarfield K, Butler R, Morgan S, 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;23:851–64.
[32] Turner NC, Oliveira M, Howell SJ, Dalenc F, Cortes J, Moreno HLG, et al. Capivasertib in hormone receptor–positive advanced breast cancer. N Engl J Med 2023;388:2058–70.
[33] ClinicalTrial.gov. Capivasertib + CDK4/6i + fulvestrant for advanced/metastatic HR+/HER2- breast cancer (CAPItello-292) 2024. https://www.clinicaltrials.gov/study/NCT04862663. Accessed April 18, 2024.
[34] Turner N, Dent RA, O'Shaughnessy J, Kim SB, Isakoff SJ, Barrios C, et al. Ipatasertib plus paclitaxel for PIK3CA/AKT1/PTEN-altered hormone receptor-positive HER2-negative advanced breast cancer: primary results from cohort B of the IPATunity130 randomized phase 3 trial. Breast Cancer Res Treat 2022;191:565–76.
[35] ClinicalTrial.gov. Fulvestrant and ipatasertib for advanced HER-2 negative and estrogen receptor positive (ER+) breast cancer following progression on first line CDK 4/6 inhibitor and aromatase inhibitor (FINER). 2024. https://www.clinicaltrials.gov/study/NCT04650581. Accessed April 18, 2024.
[36] ClinicalTrial.gov. Fulvestrant, ipatasertib and CDK4/6 inhibition in metastatic ER+/HER2- breast cancer patients without ctDNA suppression (FAIM). 2023. https://www.clinicaltrials.gov/study/NCT04920708. Accessed April 18, 2024.
[37] Yardley DA, Noguchi S, Pritchard KI, Burris 3rd HA, Baselga J, Gnant M, et al. Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. Adv Ther 2013;30:870–84.
[38] Novartis. AFINITOR®(everolimus) prescribing information. 2012.
[39] European Medicines Agency. Afinitor everolimus. EMA/CHMP/402772/2012. 2012.
[40] ClinicalTrial.gov. Gedatolisib plus fulvestrant with or without palbociclib vs standard-of-care for the treatment of patients with advanced or metastatic HR+/HER2- breast cancer (VIKTORIA-1). 2023. https://clinicaltrials.gov/study/NCT05501886. Accessed April 18, 2024.
[41] André F, Ciruelos EM, Juric D, Loibl S, Campone M, Mayer IA, et al. Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: final overall survival results from SOLAR-1. Ann Oncol 2021;32:208–17.
[42] U.S. Food and Drug Administration. FULL PRESCRIBING INFORMATION FOR PIQRAY. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/212526s009lbl.pdf. Accessed 14 November 2024.
[43] European Medicines Agency. Piqray : EPAR - Product information. https://www.ema.europa.eu/en/documents/product-information/piqray-epar-product-information_en.pdf. Accessed 14 November 2024.
[44] Shirley M. Capivasertib: First approval. Drugs 2024;84:337–346.
[45] Baselga J, Campone M, Piccart M, Burris 3rd HA, Rugo HS, Sahmoud T, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 2012;366:520–9.

[46] Layman RM, Han HS, Rugo HS, Stringer-Reasor EM, Specht JM, Dees EC, et al. Gedatolisib in combination with palbociclib and endocrine therapy in women with hormone receptor-positive, HER2-negative advanced breast cancer: results from the dose expansion groups of an open-label, phase 1b study. Lancet Oncol 2024;25:474–87.
[47] ClinicalTrial.gov. A study to evaluate the safety and tolerability of TOS-358 in adults with select solid tumors. 2024. https://clinicaltrials.gov/study/NCT05683418. Accessed April 18, 2024.
[48] Buckbinder L, St Jean DJ, Jr., Tieu T, Ladd B, Hilbert B, Wang W,, et al. STX-478, a mutant-selective, allosteric PI3Kα inhibitor spares metabolic dysfunction and improves therapeutic response in PI3Kα-mutant xenografts. Cancer Discov 2023;13:2432–47.
[49] Varkaris A, Pazolli E, Gunaydin H, Wang Q, Pierce L, Boezio AA, et al. Discovery and clinical proof-of-concept of RLY-2608, a first-in-class mutant-selective allosteric PI3Kα inhibitor that decouples antitumor activity from hyperinsulinemia. Cancer Discov 2024;14:240–57.
[50] Puca L, Dowless MS, Perez-Ferreiro CM, Ortiz-Ruiz MJ, Donoho GP, Capen A, et al. LOXO-783: A potent, highly mutant selective and brain-penetrant allosteric PI3Kα H1047R inhibitor in combination with standard of care (SOC) treatments in preclinical PI3Kα H1047R-mutant breast cancer models. Cancer Res 2023;83.
[51] MacDougall JR, Bradley J, Mak R, Dhawan N, Chen W. TOS-358, a first-in-class covalent PI3Kα inhibitor, demonstrates superior efficacy and does not induce significant hyperglycemia at efficacious doses in multiple animal models. Cancer Res 2023;83:4946.
[52] MacDougall J, Bradley J, Bader S, Blair J, Dhawan N, Chen W. Preclinical characterization of TOS-358, a potent and selective covalent inhibitor of wild-type and mutant PI3Kα; with superior anticancer activity. Eur J Cancer 2022;174:S38.
[53] ClinicalTrial.gov. First-in-human study of STX-478 as monotherapy and in combination with other antineoplastic agents in participants with advanced solid tumors. 2024. https://www.clinicaltrials.gov/study/NCT05768139. Accessed April 18, 2024.
[54] ClinicalTrial.gov. First-in-human study of mutant-selective PI3Kα inhibitor, RLY-2608, as a single agent in advanced solid tumor patients and in combination with fulvestrant in patients with advanced breast cancer. 2023. https://clinicaltrials.gov/study/NCT05216432. Accessed April 18, 2024.
[55] Perez CA, Henry JT, Varkaris A, Subbiah V, Spira AI, Schmidt O, et al. First-in-human global multi-center study of RLY-2608, a pan-mutant and isoform-selective PI3Kα inhibitor, as a single agent in patients with advanced solid tumors and in combination with fulvestrant in patients with advanced breast cancer. J Clin Oncol 2022;40.
[56] ClinicalTrial.gov. A study of LOXO-783 in patients with breast cancer/other solid tumors (PIKASSO-01). 2024. https://classic.clinicaltrials.gov/ct2/show/NCT05307705. Accessed April 18, 2024.
[57] Schram AM, Naqash AR, Haura EB, Riess JW, Ulahannan SV, Ou S-H-I, et al. First-in-human phase 1/1b trial of the first-in-class bi-steric mTORC1-selective inhibitor RMC-5552 in patients with advanced solid tumors. Mol Cancer Ther 2023;22:C020.
[58] Burnett GL, Yang YC, Aggen JB, Pitzen J, Gliedt MK, Semko CM, et al. Discovery of RMC-5552, a selective bi-steric inhibitor of mTORC1, for the treatment of mTORC1-activated tumors. J Med Chem 2023;66:149–69.
[59] ClinicalTrial.gov. Dose escalation of RMC-5552 monotherapy in relapsed/refractory solid tumors. 2014. https://www.clinicaltrials.gov/study/NCT04774952. Accessed April 18, 2024.
[60] Aftimos P, Oliveira M, Irrthum A, Fumagalli D, Sotiriou C, Gal-Yam EN, et al. Genomic and transcriptomic analyses of breast cancer primaries and matched metastases in AURORA, the Breast International Group (BIG) molecular screening initiative. Cancer Discov 2021;11:2796–811.
[61] Akcakanat A, Sahin A, Shaye AN, Velasco MA, Meric-Bernstam F. Comparison of Akt/mTOR signaling in primary breast tumors and matched distant metastases. Cancer 2008;112:2352–8.
[62] Lv H, Niu L, Zhang M, Zeng H, Zhao S, Yan M. Diagnostic diversity and heterogeneity of tumors: a real-world study of metastasis re-biopsy in advanced breast cancer. Chin Med J (Engl) 2022;135:2076–82.
[63] Grinda T, Joyon N, Lusque A, Lefèvre S, Arnould L, Penault-Llorca F, et al. Phenotypic discordance between primary and metastatic breast cancer in the large-scale real-life multicenter French ESME cohort. npj Breast Cancer 2021;7:41.
[64] Rosin J, Svegrup E, Valachis A, Zerdes I. Discordance of PIK3CA mutational status between primary and metastatic breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat 2023;201:161–9.
[65] Armakolas A, Kotsari M, Koskinas J. Liquid Biopsies, Novel Approaches and Future Directions. Cancers (Basel) 2023;15.
[66] Freitas AJA, Causin RL, Varuzza MB, Calfa S, Hidalgo Filho CMT, Komoto TT, et al. Liquid biopsy as a tool for the diagnosis, treatment, and monitoring of breast cancer. Int J Mol Sci 2022;23:9952.
[67] Fuentes-Antrás J, Martínez-Rodríguez A, Guevara-Hoyer K, López-Cade I, Lorca V, Pascual A, et al. Real-world use of highly sensitive liquid biopsy monitoring in metastatic breast cancer patients treated with endocrine agents after exposure to aromatase inhibitors. Int J Mol Sci 2023;24:11419.
[68] Vollbrecht C, Hoffmann I, Lehmann A, Merkelbach-Bruse S, Fassunke J, Wagener-Ryczek S, et al. Proficiency testing of PIK3CA mutations in HR+/HER2-breast cancer on liquid biopsy and tissue. Virchows Arch 2023;482:697–706.
[69] Amato O, Giannopoulou N, Ignatiadis M. Circulating tumor DNA validity and potential uses in metastatic breast cancer. npj Breast Cancer 2024;10:21.
[70] Turner NC, Kingston B, Kilburn LS, Kernaghan S, Wardley AM, Macpherson IR, et al. Circulating tumour DNA analysis to direct therapy in advanced breast cancer (plasmaMATCH): a multicentre, multicohort, phase 2a, platform trial. Lancet Oncol 2020;21:1296–308.
[71] Juric D, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo H, et al. Alpelisib + fulvestrant for advanced breast cancer: Subgroup analyses from the phase III SOLAR-1 trial. Cancer Res 2019;79.
[72] Henry NL, Somerfield MR, Dayao Z, Elias A, Kalinsky K, McShane LM, et al. Biomarkers for systemic therapy in metastatic breast cancer: ASCO guideline update. J Clin Oncol 2022;40:3205–21.
[73] Burstein HJ, DeMichele A, Fallowfield L, Somerfield MR, Henry NL, Henry NL, et al. 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;42:1450–3.
[74] Venetis K, Pepe F, Sajjadi E, Bonizzi G, Ivanova M, Vacirca D, et al. Comparison of next-generation sequencing and real-time PCR for PIK3CA testing in hormone receptor-positive/HER2-negative breast cancer on metastatic and matched primary tumor samples. Cancer Res 2023;83.
[75] Rugo HS, Raskina K, Schrock AB, Madison RW, Graf RP, Sokol ES, et al. Biology and targetability of the extended spectrum of PIK3CA mutations detected in breast carcinoma. Clin Cancer Res 2023;29:1056–67.
[76] Colomer R, Miranda J, Romero-Laorden N, Hornedo J, González-Cortijo L, Mouron S, et al. Usefulness and real-world outcomes of next generation sequencing testing in patients with cancer: An observational study on the impact of selection based on clinical judgement. eClinicalMedicine 2023;60:102029.
[77] Morrison L, Loibl S, Turner NC. The CDK4/6 inhibitor revolution - a game-changing era for breast cancer treatment. Nat Rev Clin Oncol 2024;21:89–105.
[78] Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol 2015;16:25–35.
[79] Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med 2016;375:1925–36.
[80] Goetz MP, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J, et al. MONARCH 3: Abemaciclib as initial therapy for advanced breast cancer. J Clin Oncol 2017;35:3638–46.
[81] Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. N Engl J Med 2016;375:1738–48.
[82] Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. Ann Oncol 2018;29:1541–7.
[83] Im SA, Lu YS, Bardia A, Harbeck N, Colleoni M, Franke F, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. N Engl J Med 2019;381:307–16.
[84] Lee JS, Hackbart H, Cui X, Yuan Y. CDK4/6 inhibitor resistance in hormone receptor-positive metastatic breast cancer: Translational research, clinical trials, and future directions. Int J Mol Sci 2023;24:11791.
[85] Zhou FH, Downton T, Freelander A, Hurwitz J, Caldon CE, Lim E. CDK4/6 inhibitor resistance in estrogen receptor positive breast cancer, a 2023 perspective. Front Cell Dev Biol 2023;11.
[86] Albanell J, Pérez-García JM, Gil-Gil M, Curigliano G, Ruíz-Borrego M, Comerma L, et al. Palbociclib Rechallenge for Hormone Receptor-Positive/HER-Negative Advanced Breast Cancer: Findings from the Phase II BioPER Trial. Clin Cancer Res 2023;29:67–80.
[87] de Luna Aguilar AM, Fuentes JDB, Ortega Anselmi J, Olalla Inoa J, Flores Navarro P, Lopez de Sá A, et al. Clinical Experience with Abemaciclib in Patients Previously Treated with Another CDK 4/6 Inhibitor in a Tertiary Hospital: A Case Series Study. Cancers (Basel) 2023;15.
[88] Ozawa Y, Fujimiya T, Shimada A, Okazawa A, Kusano J, Yamamoto R, et al. Successful continuance of CDK4/6 inhibitor treatment with palbociclib after abemaciclib-induced hepatotoxicity in breast cancer: a case report. Anticancer Drugs 2024;35:89–92.
[89] Stanciu IM, Pirlog CF, Anghel AW, Parosanu AI, Olaru CM, Orlov-Slavu C, et al. Does the Rechallenge with Another CDK 4/6 Inhibitor in Breast Cancer Work? A Case Report and Literature Review Medicina (Kaunas) 2023;59.
[90] Kalinsky K, Accordino MK, Chiuzan C, Mundi PS, Sakach E, Sathe C, et al. Randomized Phase II Trial of Endocrine Therapy With or Without Ribociclib After Progression on Cyclin-Dependent Kinase 4/6 Inhibition in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: MAINTAIN Trial. J Clin Oncol 2023;41:4004–13.
[91] Kalinsky K, Bianchini G, Hamilton EP, Graff SL, Park KH, Jeselsohn R, et al. Abemaciclib plus fulvestrant vs fulvestrant alone for HR+, HER2- advanced breast cancer following progression on a prior CDK4/6 inhibitor plus endocrine therapy: Primary outcome of the phase 3 postMONARCH trial. J Clin Oncol 2024;42.
[92] de Wilt E, Hettle R, Liljas B. CO172 Indirect Treatment Comparison of Efficacy and Safety of Capivasertib-Fulvestrant Versus Alpelisib-Fulvestrant for PIK3CA-Altered, HR-Positive, Advanced Breast Cancer after Disease Progression Following Endocrine-Based Therapy. Value Health 2024;27:S49–50.

[93] Mukherjee R, Vanaja KG, Boyer JA, Gadal S, Solomon H, Chandarlapaty S, et al. Regulation of PTEN translation by PI3K signaling maintains pathway homeostasis. Mol Cell 2021;81:708–823.
[94] Yu M, Chen J, Xu Z, Yang B, He Q, Luo P, et al. Development and safety of PI3K inhibitors in cancer. Arch Toxicol 2023;97:635–50.
[95] Belli C, Repetto M, Anand S, Porta C, Subbiah V, Curigliano G. The emerging role of PI3K inhibitors for solid tumour treatment and beyond. Br J Cancer 2023;128: 2150–62.
[96] Rugo HS, André F, Yamashita T, Cerda H, Toledano I, Stemmer SM, et al. Time course and management of key adverse events during the randomized phase III SOLAR-1 study of PI3K inhibitor alpelisib plus fulvestrant in patients with HR-positive advanced breast cancer. Ann Oncol 2020;31:1001–10.
[97] Rugo HS, Oliveira M, Howell SJ, Dalenc F, Cortes J, Gomez HL, et al. Capivasertib (C) and fulvestrant (F) for patients (pts) with aromatase inhibitor (AI)-resistant HR +/HER2– advanced breast cancer (ABC): Characterization and management of common adverse events (AEs) from the phase 3 CAPItello-291 trial. J Clin Oncol 2023;41.
[98] Novartis. AFINITOR®(everolimus) prescribing information. 2022.