Sapanisertib plus Fulvestrant in Postmenopausal Women with Estrogen Receptor–Positive/HER2-Negative Advanced Breast Cancer after Progression on Aromatase Inhibitor

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ABSTRACT

Purpose: This phase II study investigated daily or weekly sapanisertib (a selective dual inhibitor of mTOR complexes 1 and 2) in combination with fulvestrant.

Patients and Methods: Postmenopausal women with estrogen receptor–positive (ER^+)/HER2-negative ($HER2^-$) advanced or metastatic breast cancer following progression during/after aromatase inhibitor treatment were randomized to receive fulvestrant 500 mg (28-day treatment cycles), fulvestrant plus sapanisertib 4 mg daily, or fulvestrant plus sapanisertib 30 mg weekly, until progressive disease, unacceptable toxicity, consent withdrawal, or study completion.

Results: Among 141 enrolled patients, baseline characteristics were balanced among treatment arms, including prior cyclin-dependent kinase-4/6 (CDK4/6) inhibitor treatment in 33% to 35% of patients. Median progression-free survival (PFS; primary endpoint) was 3.5 months in the single-agent fulvestrant arm, compared with 7.2 months for fulvestrant plus sapanisertib daily [HR, 0.77; 95% confidence interval (CI), 0.47–1.26] and 5.6 months for fulvestrant plus sapanisertib weekly (HR, 0.88; 95% CI, 0.53–1.45). The greatest PFS benefits were seen in patients who had previously received CDK4/6 inhibitors. The most common adverse events were nausea, vomiting, and hyperglycemia, all occurring more frequently in the combination therapy arms. Treatment discontinuation due to adverse events occurred more frequently in the two combination therapy arms than with single-agent fulvestrant (32% and 36% vs. 4%, respectively).

Conclusions: Fulvestrant plus sapanisertib daily/weekly resulted in numerically longer PFS in patients with ER^+/$HER2^-$ advanced or metastatic breast cancer, compared with single-agent fulvestrant. The combination was associated with increased toxicity. Further development of sapanisertib using these dosing schedules in this setting is not supported by these data.

Introduction

Endocrine therapy has been the cornerstone of therapeutic intervention for estrogen receptor–positive (ER^+) breast cancers for several decades, but many patients with metastatic disease have primary resistance to endocrine therapy, and many more who initially respond will ultimately develop secondary resistance (1, 2).

Historically, the basis of treatment for ER^+/HER2-negative ($HER2^-$) advanced breast cancer in postmenopausal women has been sequential endocrine therapy with various agents targeting the estrogen/ER pathway via different mechanisms, including selective ER modulators, aromatase inhibitors, and selective ER downregulators (1). In recent years, treatments targeting other molecular pathways have been explored in a bid to prevent resistance, restore sensitivity to endocrine therapy, or otherwise arrest growth. Targeting the cell cycle survival pathway has proven successful: phase III trials of the cyclin-dependent kinase-4/6 (CDK4/6) inhibitors palbociclib, ribociclib, and abemaciclib demonstrated significant improvements in progression-free survival (PFS), and even overall survival (OS) in some circumstances, when these agents were added to either nonsteroidal

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Translational Relevance

In this randomized phase II study, addition of daily or weekly sapanisertib (a selective dual inhibitor of mTOR complexes 1 and 2) to fulvestrant led to numerical but nonsignificant improvements in progression-free survival (PFS) in postmenopausal women with estrogen receptor–positive (ER^+)/HER2-negative ($HER2^-$) advanced or metastatic breast cancer following progression during/after aromatase inhibitor treatment. Patients with prior cyclin-dependent kinase-4/6 (CDK4/6) inhibitor treatment appeared to derive the greatest PFS benefit from sapanisertib in combination with fulvestrant. Treatment with sapanisertib in combination with fulvestrant was associated with increased toxicity and/or a higher rate of discontinuations due to adverse events compared with fulvestrant alone. These findings support the principle of targeting the PI3K/AKT/mTOR pathway to restore endocrine sensitivity but the toxicity profile of sapanisertib prevents us from recommending it.

aromatase inhibitors, tamoxifen, or fulvestrant in the first- and second-line settings (3–9). The approval of the CDK4/6 inhibitors in combination with aromatase inhibitors or fulvestrant has changed the treatment paradigm (10), but development of resistance to CDK4/6 inhibitors remains an issue and therapies beyond these agents to overcome endocrine resistance are still needed (11).

Cross-talk between ER signaling and the PI3K/AKT/mTOR pathway is strongly implicated in endocrine resistance (12), as well as in resistance to CDK4/6 inhibitors in preclinical models (11). This pathway provides an escape mechanism that allows tumor cells to proliferate under conditions of abrogated ER signaling and/or CDK4/6 inhibition (12, 13). The pathway is also often hyperactivated in breast cancer tumor cells through genetic alterations in various components of the pathway that are present in approximately 30% to 50% of cases (14, 15).

The principle of targeting the PI3K/AKT/mTOR pathway to restore endocrine sensitivity is supported by promising results in clinical trials in the second-line setting of agents targeting different components of the pathway in patients with ER^+/$HER2^-$ breast cancer with resistance to prior endocrine therapy. In the phase III SOLAR-1 trial, the selective PI3Kα inhibitor alpelisib significantly improved PFS when added to fulvestrant compared with fulvestrant plus placebo [median, 11.0 vs. 5.7 months, respectively; HR, 0.65; 95% confidence interval (CI), 0.50–0.85; $P < 0.001$], following prior endocrine therapy in women with ER^+/$HER2^-$ breast cancer harboring *PIK3CA* mutations (16). In the phase III BOLERO-2 trial, addition of the mTOR complex 1 (mTORC1) inhibitor everolimus to exemestane achieved clinically meaningful improved outcomes compared with exemestane plus placebo in patients with ER^+/$HER2^-$ breast cancer that was refractory to nonsteroidal aromatase inhibitors (median PFS, 11.0 vs. 4.1 months, respectively; HR, 0.38; 95% CI, 0.31–0.48; $P < 0.0001$; refs. 17, 18). Benefits of adding everolimus to endocrine therapy in patients with aromatase inhibitor–resistant metastatic breast cancer have also been reported in phase II studies in which everolimus was combined with tamoxifen (19) or fulvestrant (20). However, a possible limitation of targeting mTORC1 is that this inhibits negative feedback that would usually suppress activation of AKT, which can paradoxically increase activity of the PI3K/AKT/mTOR pathway (12, 21, 22). Preclinical studies have shown that inhibition of mTOR via both mTORC1 and mTORC2 protein complexes leads to greater suppression of cancer cell proliferation and migration, compared with selective mTORC1 inhibition, in various malignancies (23–25).

Sapanisertib is an investigational, oral, potent, and highly selective adenosine triphosphate–competitive inhibitor of mTOR kinase with dual specificity against mTORC1 and mTORC2 (26, 27). Efficacy of sapanisertib in combination with exemestane or fulvestrant was explored in a phase Ib/II study (28), in which the combinations were well tolerated and exhibited clinical benefit in postmenopausal women with ER^+/$HER2^-$ advanced or metastatic breast cancer, including groups who had shown both resistance and sensitivity to previous everolimus treatment. Based on these data, we hypothesized that dual mTORC1/2 inhibition with sapanisertib may restore sensitivity to endocrine therapies in patients with ER^+/$HER2^-$ metastatic breast cancer. We now report the findings of a phase II, open-label, randomized, three-arm study in which daily or weekly sapanisertib was added to fulvestrant to evaluate whether the combinations improved outcomes, compared with fulvestrant alone, in postmenopausal women with ER^+/$HER2^-$ advanced or metastatic breast cancer that had progressed during or after aromatase inhibitor therapy.

Patients and Methods

Patients

Eligible patients were postmenopausal women with histologic confirmation of ER^+ (≥1% positive stained cells)/$HER2^-$ metastatic or advanced breast cancer that was not amenable to resection or radiotherapy with curative intent, and who had measurable disease or bone lesions. All enrolled patients had experienced disease progression on prior aromatase inhibitor therapy, defined as recurrence during or within 12 months after discontinuation of adjuvant therapy or progression during or within 1 month after the end of therapy in the metastatic setting. Patients were excluded if they had received prior treatment with mTOR inhibitors, PI3K inhibitors, dual PI3K-mTOR inhibitors, AKT inhibitors, or fulvestrant. Prior treatment with CDK4/6 inhibitors was permitted; enrollment was managed to reach a target of approximately 40% of patients with previous exposure to CDK4/6 inhibitors, with enrollment of CDK4/6 inhibitor-naïve patients halted if it exceeded approximately 60% of the study population. Other exclusion criteria included progressive disease (PD) on more than two endocrine therapies or more than one chemotherapy for advanced or metastatic disease, an Eastern Cooperative Oncology Group performance status ≥2, or life-threatening metastatic visceral disease (extensive hepatic involvement or symptomatic pulmonary lymphangitic spread).

All patients provided written informed consent. The study was conducted according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference for Harmonisation E6 Good Clinical Practice Guideline, and all applicable local regulations. The protocol and informed consent form were approved by the relevant Institutional Review Board or Independent Ethics Committee prior to study commencement.

Study design and oversight

This was a phase II, open-label, three-arm, multicenter study (NCT02756364) conducted across 50 study sites in the United States and Spain between July 2016 and November 2019. Patients were randomized 1:1:1 via an interactive response technology (IRT) system to receive: (i) fulvestrant 500 mg intramuscularly every 28 days (with an additional loading dose on day 15 of the first 28-day treatment cycle); (ii) fulvestrant as described plus sapanisertib 4 mg orally daily; or (iii) fulvestrant as described plus sapanisertib 30 mg orally weekly,

administered on days 1, 8, 15, and 22 of each treatment cycle. Patients were stratified according to the presence/absence of visceral metastases, prior sensitivity to endocrine therapy, and previous exposure to CDK4/6 inhibitors. Prior sensitivity to endocrine therapy was defined as ≥24 months of endocrine therapy before recurrence in the adjuvant setting (i.e., in patients who have not received previous endocrine therapy in the metastatic setting) or a response or stabilization for ≥24 weeks of the most recent endocrine therapy for advanced/metastatic disease. Patients were treated until disease progression, discontinuation due to unacceptable toxicity, or withdrawal of consent. Patients who were benefiting from treatment at the end of the study were permitted to continue treatment in a posttrial access program. Patients in the single-agent fulvestrant arm who experienced PD could be rerandomized to sapanisertib daily or weekly plus fulvestrant. This was offered on a compassionate basis and there were no preplanned analyses of efficacy following crossover to combination treatment in these patients.

The primary endpoint was PFS (defined as the time from the date of randomization to the date of first documentation of progression or death due to any cause, whichever occurred first). Secondary efficacy endpoints included: TTP (defined as the time from the date of randomization to the date of first documentation of progression); OS (defined as the time from the date of randomization to the date of death); overall response rate [ORR; the proportion of patients with a complete response (CR) or partial response (PR)]; clinical benefit rate [CBR; the proportion of patients with a CR, PR, or stable disease (SD)]; and CBR ≥6 months (CBR with SD lasting ≥6 months). The proportion of patients with treatment-emergent adverse events (TEAE) was assessed as a safety endpoint. Other endpoints included changes from baseline to end of study in scores on the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the 23-item, breast cancer–specific EORTC QLQ-BR23. Exploratory endpoints included genetic markers or biomarkers in circulating tumor material associated with response or treatment resistance.

Assessments

Response was assessed by investigators according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 based on radiologic tumor evaluations using CT or MRI scans of the chest, abdomen, and pelvis obtained at screening, every other treatment cycle from cycle 2, and at an end-of-treatment (EOT) visit (within 30–40 days of last dose of randomized study drug). Patients entering PFS follow-up after discontinuing treatment for reasons other than PD continued to have scans every 2 to 3 months until PD or starting another anticancer treatment. They were subsequently followed-up every 6 months to monitor OS, as was the case for patients who progressed on study treatment. Safety was evaluated using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Quality of life (QoL) questionnaires (EORTC QLQ-C30 and EORTC QLQ-BR23) were completed before administration of treatment at the start of each 28-day cycle, and at the EOT visit.

Statistical analysis

Assuming an increase in median PFS from 4 months with fulvestrant alone to 8 months with the fulvestrant/sapanisertib combinations (with a target HR of 0.5), a total of 72 PFS events were required to achieve approximately 90% power for each pairwise comparison based on a two-sided log-rank test at a significance level of 10%. With an assumed dropout rate of 10%, it was estimated that 51 patients per treatment arm were required (for a total study population of approximately 153 patients).

The full analysis set (FAS) comprised all patients randomized and the safety analysis set comprised all patients who received at least one dose of study drug. PFS, OS, and TTP were evaluated in the FAS using Kaplan–Meier analysis. For pairwise comparisons of fulvestrant plus sapanisertib daily or weekly versus fulvestrant alone, HRs and 95% CIs were estimated from a stratified Cox regression model with treatment arm and stratification factors as covariates; two-sided P values were generated from a stratified log-rank test and assessed at a 10% significance level. Tumor response (ORR, CBR, and CBR ≥6 months) was analyzed in the safety analysis set and the response-evaluable set (defined as all patients who received at least one dose of study drug, had measurable disease at baseline, and had one postbaseline disease assessment), and compared between treatment arms using a stratified Cochran—Mantel–Haenszel test. For patient-reported outcomes, change from baseline was analyzed using a mixed effects model, including treatment group, visit, treatment-by-visit interaction, and stratification factors as fixed effects, baseline score as a covariate, and intercept as a random effect with autoregressive covariance structure.

Genomic analysis

Genomic analysis of circulating tumor DNA (ctDNA) was performed for patients who were randomized to fulvestrant or fulvestrant plus sapanisertib 4 mg daily; data for the fulvestrant plus sapanisertib 4 mg daily group were pooled with data from patients who received fulvestrant plus sapanisertib 4 mg daily in a previous phase Ib/II study (28). Plasma samples collected at baseline were analyzed with a custom PlasmaSelect-R next-generation sequencing breast cancer gene panel (Personal Genome Diagnostics, Inc.) designed to evaluate 46 genes and 7 amplifications, as described previously (28). Associations between genetic biomarkers and PFS/OS were analyzed using Cox regression.

Data availability statement

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants' data supporting the results reported in this article, will be made available within 3 months from initial request to researchers who provide a methodologically sound proposal. The data will be provided after its deidentification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

Results

Patients

A total of 141 patients were enrolled and randomized to receive single-agent fulvestrant ($n = 46$), fulvestrant plus sapanisertib daily ($n = 47$), or fulvestrant plus sapanisertib weekly ($n = 48$; **Fig. 1**). One patient in the fulvestrant plus sapanisertib weekly arm was randomized but withdrew before receiving treatment due to symptomatic deterioration; therefore, the safety population comprised 140 patients. The most common reason for discontinuation of treatment in all arms was disease progression, which occurred in 76.1% of patients in the single-agent fulvestrant arm, and 59.6% and 53.2% of patients in the daily and weekly combination treatment arms, respectively. Eighteen patients whose disease progressed on fulvestrant were rerandomized to fulvestrant plus sapanisertib daily or fulvestrant plus sapanisertib weekly (9 to each treatment).

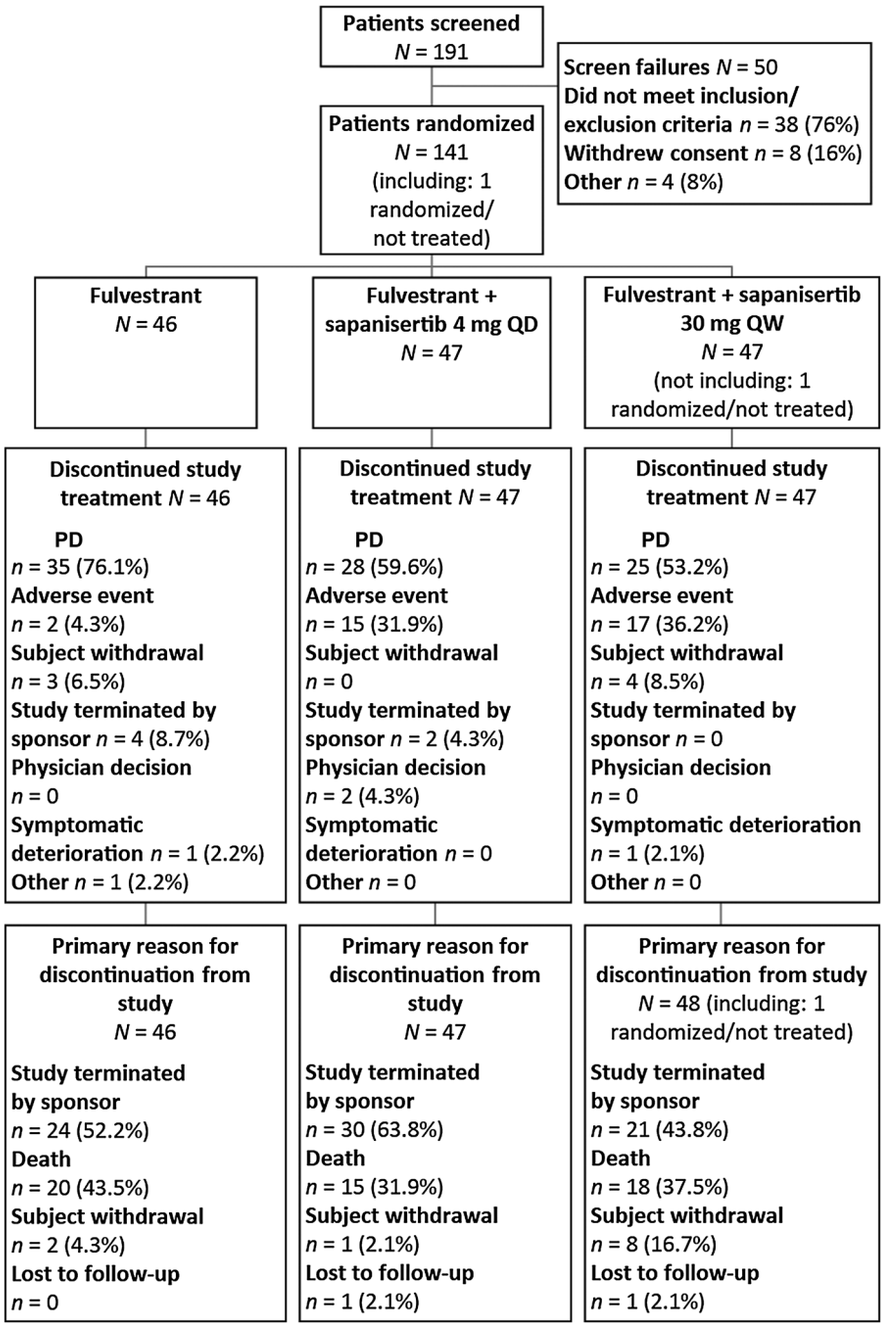


Figure 1.
Patient disposition CONSORT diagram. Eighteen of 35 patients in the single-agent fulvestrant arm who experienced progressive disease were re-randomized to sapanisertib 4 mg daily plus fulvestrant ($n = 9$) or sapanisertib 30 mg weekly plus fulvestrant ($n = 9$). QD, daily; QW, weekly.

Patient baseline demographics and disease characteristics were generally well balanced among study arms (**Table 1**). Across all treatment arms, median age was 58.0 years (range, 33–84); 84.4% of patients had demonstrated sensitivity to prior endocrine therapy and 34.0% had received prior treatment with CDK4/6 inhibitors. Two thirds (64.5%) of patients had visceral metastases.

Efficacy

Median (95% CI) PFS was 3.5 (1.9–5.6) months in the single-agent fulvestrant arm, compared with 7.2 (3.9–10.6) and 5.6 (4.1–9.0) months in fulvestrant plus sapanisertib daily and fulvestrant plus sapanisertib weekly arms, respectively (**Fig. 2**). While there was a trend for prolonged PFS with combination treatment versus fulvestrant, it was not statistically significant for either fulvestrant plus sapanisertib daily (HR, 0.77; 95% CI, 0.47–1.26; $P = 0.537$) or fulvestrant plus sapanisertib weekly (HR, 0.88; 95% CI, 0.53–1.45; $P = 0.849$). **Figure 3** shows forest plots of PFS in patient subgroups stratified according to the presence/absence of visceral metastases, sensitivity to prior endocrine therapy, prior treatment with CDK4/6 inhibitors, and demographic variables. The subgroup of patients with a history of CDK4/6 inhibitor treatment ($n = 16$ in each treatment arm) had the greatest improvements in PFS with

Table 1. Patient baseline demographics and disease characteristics in the full analysis set.

	Fulvestrant ($n = 46$)	Fulvestrant + sapanisertib 4 mg daily ($n = 47$)	Fulvestrant + sapanisertib 30 mg weekly ($n = 48$)	Total ($N = 141$)
Median age, years (range)	60.0 (39–80)	59.0 (41–84)	57.0 (33–84)	58.0 (33–84)
Race, *n* (%)				
White	44 (95.7)	45 (95.7)	44 (91.7)	133 (94.3)
African American	1 (2.2)	2 (4.3)	3 (6.3)	6 (4.3)
Other	1 (2.2)	0	1 (2.1)	2 (1.4)
Median time since diagnosis, years (range)	5.91 (0.7–35.4)	5.34 (0.8–27.6)	5.05 (0.7–20.9)	5.27 (0.7–35.4)
Visceral metastases, *n* (%)[a]	30 (65.2)	30 (63.8)	31 (64.6)	91 (64.5)
Prior lines of therapy for advanced or metastatic breast cancer, *n* (%)				
0	9 (19.6)	9 (19.1)	12 (25.0)	30 (21.3)
1	25 (54.3)	28 (59.6)	27 (56.3)	80 (56.7)
2	11 (23.9)	9 (19.1)	9 (18.8)	29 (20.6)
3	1 (2.2)	1 (2.1)	0	2 (1.4)
Previous sensitivity to endocrine therapy, *n* (%)[a]	39 (84.8)	39 (83.0)	41 (85.4)	119 (84.4)
Prior treatment with CDK4/6 inhibitors, *n* (%)[a]	16 (34.8)	16 (34.0)	16 (33.3)	48 (34.0)

[a]Baseline distribution of stratification variables based on original (not corrected) Interactive Response System assignment.

fulvestrant plus sapanisertib daily versus single-agent fulvestrant (HR, 0.34; 95% CI, 0.14–0.82; $P = 0.042$) and fulvestrant plus sapanisertib weekly versus fulvestrant (HR, 0.48; 95% CI, 0.21–1.12; $P = 0.116$).

The majority of PFS events were progression events (1, 1, and 2 patients had events of death in the time-to-event analysis of PFS in the single-agent fulvestrant, fulvestrant plus sapanisertib daily, and fulvestrant plus sapanisertib weekly arms, respectively). TTP results were, therefore, similar to PFS, with median TTP (95% CI) values of 3.5 (1.9–5.6), 7.2 (5.5–10.6), and 5.6 (4.1–9.0) months, respectively.

OS data were immature at the time of database lock, with 43.5%, 31.9%, and 37.5% of patients having died in the single-agent fulvestrant, fulvestrant plus sapanisertib daily, and fulvestrant plus sapanisertib weekly arms, respectively. Median OS was 30.5 months in the fulvestrant arm, not evaluable in the fulvestrant plus sapanisertib daily arm (HR vs. fulvestrant, 0.71; 95% CI, 0.36–1.40; $P = 0.276$), and 34.2 months in the fulvestrant plus sapanisertib weekly arm (HR vs. fulvestrant, 0.89; 95% CI, 0.47–1.68; $P = 0.470$).

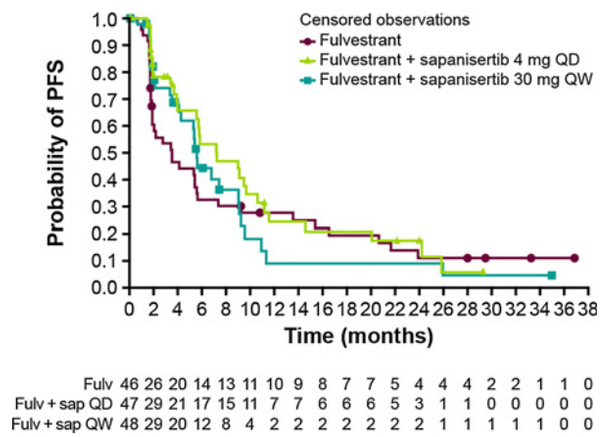


Figure 2.
Kaplan–Meier plot of PFS in patients treated with single-agent fulvestrant, fulvestrant plus sapanisertib 4 mg daily, or fulvestrant plus sapanisertib 30 mg weekly (full analysis set). fulv, fulvestrant; QD, daily; QW, weekly; sap, sapanisertib.

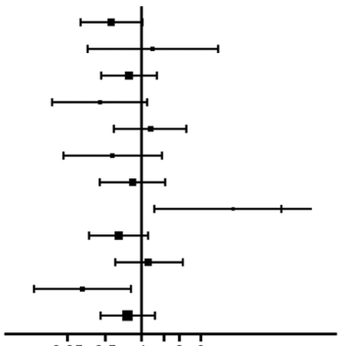
Tumor responses are shown in **Table 2** and Supplementary Fig. S1. The ORR in the safety population was 10.9%, 21.3%, and 12.8% in single-agent fulvestrant, fulvestrant plus sapanisertib daily, and fulvestrant plus sapanisertib weekly arms, respectively. The CBR was 60.9%, 74.5%, and 66.0%, and CBR ≥ 6 months was 32.6%, 48.9%, and 25.5%, respectively. Numerically higher ORR and CBRs in the fulvestrant plus sapanisertib daily arm were not statistically significant compared with fulvestrant alone.

Safety

Patients received a median of four cycles of single-agent fulvestrant (range, 1–40; mean, 9), five cycles of fulvestrant plus sapanisertib daily (range, 1–33; mean, 8), and four cycles of fulvestrant plus sapanisertib weekly (range, 1–39; mean, 6), resulting in median (mean) treatment exposure lasting 16 (36), 20 (33), and 17 (24) weeks, respectively. Dose modifications, including dose delays, omissions, and reductions, were recorded for 79% and 81% of patients receiving sapanisertib 4 mg daily and 30 mg weekly, respectively. Mean relative dose intensities were 73.9% and 75.0%, respectively, of planned cumulative sapanisertib dosages, while fulvestrant was administered with mean relative dose intensities of 96.9% to 99.6% across single-agent and combination treatment arms. Overall rates of TEAEs are shown in **Table 3**, along with a summary of the most common treatment-related TEAEs (reported by ≥20% of patients in any treatment arm). The most common treatment-related TEAEs occurring more frequently in the combination treatment arms than in the single-agent fulvestrant arm were gastrointestinal TEAEs, including nausea (4.3%, 48.9%, and 83.0% in single-agent fulvestrant, fulvestrant plus sapanisertib daily, and fulvestrant plus sapanisertib weekly arms, respectively), vomiting (4.3%, 31.9%, and 66.0%, respectively), diarrhea (0, 38.3%, and 21.3%, respectively), and stomatitis (2.2%, 34.0%, and 31.9%, respectively). Grade ≥ 3 treatment-related TEAEs occurred in 68.1% and 53.2% of patients in the fulvestrant plus sapanisertib daily and fulvestrant plus sapanisertib weekly arms, respectively, while none of the grade ≥ 3 TEAEs occurring in the fulvestrant-only arm were judged to be treatment-related. The most common grade ≥ 3 treatment-related

A

Subgroup	Fulvestrant Events/*N* (%)		Fulv + sap QD Events/*N* (%)		HR[a] (95% CI)	*P* value[b]
Age <65	27/30	(90.0)	23/32	(71.9)	0.57 (0.32–1.02)	0.134
Age ≥65	11/16	(68.8)	7/15	(46.7)	1.22 (0.37–4.07)	0.915
Race = White	36/44	(81.8)	28/45	(62.2)	0.79 (0.48–1.32)	0.704
Region = North America	21/23	(91.3)	9/13	(69.2)	0.46 (0.19–1.10)	0.269
Region = Europe	17/23	(73.9)	21/34	(61.8)	1.18 (0.61–2.30)	0.456
Visceral metastases absent	11/16	(68.8)	10/17	(58.8)	0.59 (0.24–1.44)	0.343
Visceral metastases present	27/30	(90.0)	20/30	(66.7)	0.85 (0.46–1.57)	0.944
Sensitivity to ET = No	6/7	(85.7)	6/8	(75.0)	5.43 (1.27–23.3)	0.070
Sensitivity to ET = Yes	32/39	(82.1)	24/39	(61.5)	0.66 (0.38–1.13)	0.189
CDK 4/6 = No	23/30	(76.7)	20/31	(64.5)	1.14 (0.61–2.12)	0.476
CDK 4/6 = Yes	15/16	(93.8)	10/16	(62.5)	0.34 (0.14–0.82)	0.042
All	38/46	(82.6)	30/47	(63.8)	0.77 (0.47–1.26)	0.537



B

Subgroup	Fulvestrant Events/*N* (%)		Fulv + sap QW Events/*N* (%)		HR[a] (95% CI)	*P* value[b]
Age <65	27/30	(90.0)	23/34	(67.6)	0.62 (0.35–1.08)	0.273
Age ≥65	11/16	(68.8)	5/14	(35.7)	1.30 (0.37–4.58)	0.961
Race = White	36/44	(81.8)	25/44	(56.8)	0.90 (0.53–1.51)	0.928
Region = North America	21/23	(91.3)	11/15	(73.3)	0.92 (0.43–1.94)	0.852
Region = Europe	17/23	(73.9)	17/33	(51.5)	1.15 (0.57–2.35)	0.495
Visceral metastases absent	11/16	(68.8)	8/17	(47.1)	1.29 (0.51–3.29)	0.645
Visceral metastases present	27/30	(90.0)	20/31	(64.5)	0.82 (0.45–1.49)	0.618
Sensitivity to ET = No	6/7	(85.7)	5/7	(71.4)	0.43 (0.11–1.75)	0.612
Sensitivity to ET = Yes	32/39	(82.1)	23/41	(56.1)	0.98 (0.56–1.71)	0.957
CDK 4/6 = No	23/30	(76.7)	18/32	(56.3)	1.17 (0.62–2.20)	0.364
CDK 4/6 = Yes	15/16	(93.8)	10/16	(62.5)	0.48 (0.21–1.12)	0.116
All	38/46	(82.6)	28/48	(58.3)	0.88 (0.53–1.45)	0.849

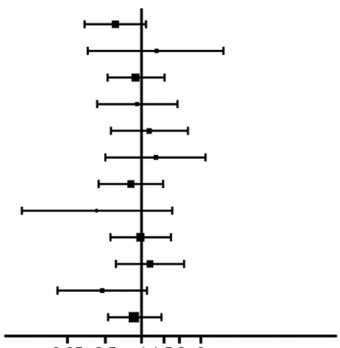


Figure 3.

Forest plot of HRs for PFS in patient subgroups stratified by baseline demographic and clinical characteristics: **A,** Fulvestrant plus sapanisertib 4 mg daily versus single-agent fulvestrant; **B,** Fulvestrant plus sapanisertib 30 mg weekly versus single-agent fulvestrant. ET, endocrine therapy; fulv, fulvestrant; QD, daily; QW, weekly; sap, sapanisertib. [a]HRs obtained using a stratified Cox proportional hazard model. [b]Stratified log-rank *P* value comparing single-agent fulvestrant versus fulvestrant plus sapanisertib in each subgroup.

TEAEs occurring in the sapanisertib arms were vomiting, diarrhea, asthenia, and rash (**Table 3**).

The rate of treatment discontinuation due to TEAEs was higher in the combination treatment arms (31.9% and 36.2%) than in the single-agent fulvestrant arm (4.3%). Three patients died on study (after the first dose and within 30 days of the last dose of study drug): 2 patients in the single-agent fulvestrant arm and 1 in the fulvestrant plus sapanisertib daily arm. All on-study deaths were attributed to underlying disease. No patients who crossed over from single-agent fulvestrant to combination treatment died during the combination treatment phase.

Patient-reported outcomes

There was a high level of compliance with QoL assessments (95%–98%), although the numbers of patients with QoL data declined with successive treatment cycles as patients discontinued treatment. Mean EORTC QLQ-C30 summary scores showed no significant change from baseline in any study arm (Supplementary Fig. S2A). Mean change from baseline in scores on the global health status/QoL subscale showed a trend for deterioration with successive fulvestrant plus sapanisertib daily treatment cycles, while scores remained close to baseline in the single-agent fulvestrant and fulvestrant plus sapanisertib weekly arms (Supplementary Fig. S2B).

There were no apparent differences between treatment arms in scores on most functional subscales, although social functioning scores declined in the combination treatment arms relative to single-agent fulvestrant (Supplementary Fig. S2C). The impact of side effects was revealed by increased (worsened) scores on the nausea and vomiting, appetite loss, and diarrhea EORTC QLQ-C30 symptom subscales in the combination treatment arms relative to single-agent fulvestrant (Supplementary Fig. S2D–S2F). Patients in the combination treatment arms also had higher (worse) mean scores on the EORTC QLQ-BR23 systemic side effects subscale (Supplementary Fig. S2G).

Biomarkers

Genomic analysis of ctDNA incorporated data from 22 patients in the single-agent fulvestrant arm who did not cross over to combination treatment, and 31 patients in the fulvestrant plus sapanisertib daily

Table 2. Treatment response in the safety analysis set and response-evaluable set.

Patients, *n* (%) Safety population[a]	Fulvestrant *n* = 46	Fulvestrant + sapanisertib 4 mg daily *n* = 47	Fulvestrant + sapanisertib 30 mg weekly *n* = 47
CR	0	2 (4.3)	0
PR	5 (10.9)	8 (17.0)	6 (12.8)
SD	23 (50.0)	25 (53.2)	25 (53.2)
SD ≥6 months	10 (21.7)	13 (27.7)	6 (12.8)
PD	18 (39.1)	10 (21.3)	11 (23.4)
No postbaseline response assessment	0	2 (4.3)	5 (10.6)
ORR (CR + PR)	5 (10.9)	10 (21.3)	6 (12.8)
OR (95% CI) vs. fulvestrant	—	2.23 (0.68–7.29)	1.22 (0.34–4.39)
CBR	28 (60.9)	35 (74.5)	31 (66.0)
OR (95% CI) vs. fulvestrant	—	2.56 (0.94–6.94)	1.75 (0.69–4.44)
CBR ≥ 6 months	15 (32.6)	23 (48.9)	12 (25.5)
OR (95% CI) vs. fulvestrant	—	2.15 (0.86–5.37)	0.69 (0.28–1.70)
Response-evaluable population[b]	***n* = 46**	***n* = 45**	***n* = 42**
ORR (CR + PR)	5 (10.9)	10 (22.2)	6 (14.3)

[a]Patients who received at least one dose of study drug.
[b]Patients who received at least one dose of study drug, had measurable disease or bone lesions [lytic or mixed (lytic plus sclerotic)] in the absence of measurable disease at baseline, and had one postbaseline disease assessment.

arm, who were pooled with 15 patients who received fulvestrant plus sapanisertib 4 mg daily in a previous study (28). Cox regression analyses showed that baseline *TP53* mutations were associated with worse PFS and OS outcomes compared with wild-type (WT) tumors (Supplementary Fig. S3). Additionally, the impact of *TP53* mutations on PFS was greater in patients treated with single-agent fulvestrant compared with sapanisertib 4 mg daily (Supplementary Fig. S3A). Similar associations were seen for *AKT1* mutations and PFS (Supplementary Fig. S3A), and *MTOR* mutations and OS (Supplementary Fig. S3B).

Table 3. Summary of TEAEs in the safety analysis set.

	Fulvestrant (*n* = 46)		Fulvestrant + sapanisertib 4 mg daily (*n* = 47)		Fulvestrant + sapanisertib 30 mg weekly (*n* = 47)	
Safety population, *n* (%)	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**
TEAEs	41 (89.1)	14 (30.4)	47 (100.0)	35 (74.5)	47 (100.0)	31 (66.0)
Treatment-related TEAEs	19 (41.3)	0	46 (97.9)	32 (68.1)	46 (97.9)	25 (53.2)
SAEs	8 (17.4)	—	13 (27.7)	—	8 (17.0)	—
Treatment-related SAEs	0	—	8 (17.0)	—	1 (2.1)	—
TEAEs leading to treatment discontinuation	2 (4.3)	—	15 (31.9)	—	17 (36.2)	—
Most common treatment-related TEAEs (occurring at any grade in ≥20% of patients in any study arm or grade ≥3 in ≥2% of patients overall)						
Gastrointestinal						
Nausea	2 (4.3)	0	23 (48.9)	0	39 (83.0)	4 (8.5)
Vomiting	2 (4.3)	0	15 (31.9)	2 (4.3)	31 (66.0)	7 (14.9)
Diarrhea	0	0	18 (38.3)	5 (10.6)	10 (21.3)	2 (4.3)
Stomatitis	1 (2.2)	0	16 (34.0)	4 (8.5)	15 (31.9)	2 (4.3)
Dry mouth	1 (2.2)	0	10 (21.3)	0	2 (4.3)	0
Metabolism and nutrition disorders						
Hyperglycemia	0	0	26 (55.3)	3 (6.4)	26 (55.3)	1 (2.1)
Decreased appetite	1 (2.2)	0	11 (23.4)	1 (2.1)	17 (36.2)	0
General disorders						
Asthenia	4 (8.7)	0	12 (25.5)	4 (8.5)	20 (42.6)	3 (6.4)
Fatigue	5 (10.9)	0	17 (36.2)	1 (2.1)	10 (21.3)	5 (10.6)
Headache	6 (13.0)	0	3 (6.4)	0	8 (17.0)	1 (2.1)
Skin and subcutaneous tissue disorders						
Pruritis	0	0	13 (27.7)	2 (4.3)	7 (14.9)	1 (2.1)
Rash	0	0	13 (27.7)	7 (14.9)	6 (12.8)	1 (2.1)
Investigations						
Weight decreased	0	0	6 (12.8)	2 (4.3)	5 (10.6)	1 (2.1)
Increased γ-glutamyltransferase	0	0	3 (6.4)	3 (6.4)	2 (4.3)	1 (2.1)

Abbreviation: SAE, serious adverse event.

Discussion

This phase II study investigated the efficacy and safety of the combination of fulvestrant plus sapanisertib, a strategy to simultaneously inhibit the estrogen/ER and PI3K/AKT/mTOR pathways, in patients with $ER^+/HER2^-$ advanced breast cancer who had received prior endocrine treatment. The patient population comprised postmenopausal women with a history of resistance to aromatase inhibitor treatment; the majority had acquired resistance to endocrine therapy and approximately one third of patients had previously been treated with CDK4/6 inhibitors.

PFS was numerically longer with both sapanisertib plus fulvestrant combination regimens than with fulvestrant alone; however, the treatment differences did not reach statistical significance, so the primary study endpoint was not met. The clear trend for prolonged PFS, coupled with numerical increases in ORR and CBR in the combination arms, suggest a modest clinical benefit of adding sapanisertib to fulvestrant. Limited interpretation can be made based on the OS results, as the data were immature at the time of data cutoff.

Overall, the results of this study were consistent with the findings of a phase II study with another dual mTORC1/2 inhibitor vistusertib, also administered in combination with fulvestrant in a similar patient population (the MANTA trial; ref. 29). That study failed to demonstrate a significant benefit of adding daily or intermittent vistusertib to fulvestrant compared with fulvestrant alone, with only a modest numerical improvement in PFS (median, 7.6–8.0 months vs. 5.4 months, respectively) that was significantly lower than that seen with fulvestrant plus everolimus (median, 12.3 months).

The safety profile of sapanisertib was consistent with the mTORC1/2 inhibitor mechanism of action and no new safety signals were detected (28, 30, 31). However, the sapanisertib plus fulvestrant combinations had increased toxicity, including a higher incidence of gastrointestinal and dermatologic side effects, leading to more treatment discontinuations due to TEAEs compared with single-agent fulvestrant. A similar side-effect profile was seen with vistusertib in combination with fulvestrant in the MANTA study (29). That study also investigated daily and intermittent dosing regimens, and found that intermittent dosing reduced the incidence of rash and stomatitis, but that this came at the cost of higher rates of nausea and vomiting (29). That finding is consistent with observations in the present study, in which the safety data did not clearly indicate whether sapanisertib daily or weekly dosing was optimal. With each regimen, efficacy may have been tempered by suboptimal dosing (mean relative dose intensities of approximately 75% with each sapanisertib regimen).

Patient-reported outcomes suggested a negative impact of sapanisertib daily on QoL, based on the deterioration in mean global health status/QoL score in this arm that was not seen with fulvestrant alone or sapanisertib weekly. This observation was surprising given the high rates of nausea and vomiting in the sapanisertib weekly group, and we speculate that the difference between the two combination treatment regimens, in terms of QoL impact, may relate to the dropout of patients who experienced the worst side effects in the weekly dosing arm (who had worse mean scores on several symptom subscales including diarrhea/vomiting, and a faster attrition rate over successive treatment cycles; Supplementary Fig. S2) leaving a subgroup of patients who tolerated treatment relatively well. Patients in the sapanisertib daily arm remained on treatment for a median of 20 weeks (mean, 33 weeks) compared with 17 (24) weeks in the weekly arm and 16 (36) weeks in the single-agent fulvestrant arm.

CDK4/6 inhibitors have advanced the treatment of ER^+ breast cancer in recent years (10), but long-term success continues to be limited by acquired resistance (11). Optimal sequencing of endocrine therapy, CDK4/6 inhibitors, and other targeted therapies is yet to be determined (10). In this study, patients with a history of prior CDK4/6 inhibitor treatment appeared to derive greater PFS benefit from the addition of sapanisertib to fulvestrant than CDK4/6 inhibitor-naïve patients. Although this observation was based on a small subgroup of patients ($n = 16$ in each treatment arm), the findings suggest that further investigation of the interactions between pathways is warranted. Preclinical studies suggest that targeting the PI3K/AKT/mTOR pathway can overcome resistance to CDK4/6 inhibitors (32) and that triple therapy targeting ER, CDK4/6, and PI3K/AKT/mTOR could prevent the onset of resistance to endocrine plus CDK4/6 inhibitor therapy; although the additional toxicity seen with dual combination therapy compared with single-agent treatment indicates that optimizing tolerability of triple therapy would be a challenge. A phase I/II study of ribociclib, everolimus, and exemestane in postmenopausal women with ER^+/HER2– advanced breast cancer who had progressed on prior CDK4/6 inhibitor therapy demonstrated clinical benefit and tolerability (33), and a phase II/III study of inavolisib, palbociclib, and fulvestrant versus placebo, palbociclib, and fulvestrant in patients with *PIK3CA*-mutated, $ER^+/HER2^-$ locally advanced or metastatic breast cancer is currently ongoing (NCT04191499).

Sapanisertib targets the PI3K/AKT/mTOR pathway, and genomic analysis in this study showed that patients with mutations in components of this pathway, including *AKT1* and *MTOR* mutations, exhibited increased sensitivity to sapanisertib treatment. This was evidenced by a more pronounced treatment effect of fulvestrant plus sapanisertib versus single-agent fulvestrant on PFS in patients with *AKT1*-mutated tumors than in those with WT tumors, and a similar effect on OS in patients with *MTOR* mutations. This result is consistent with the findings from a previous study of sapanisertib in combination with fulvestrant or exemestane, in which a positive association between *AKT1* mutation status and best treatment response was observed (28). *TP53* mutations were also associated with relative improvements in PFS and OS with fulvestrant plus sapanisertib versus fulvestrant alone, although *TP53* mutations are common in many tumor types and may be a marker for underlying tumor biology rather than being directly implicated in PI3K/AKT/mTOR pathway dysfunction.

The efficacy and safety findings from this study, in which a modest clinical benefit of adding sapanisertib to fulvestrant was accompanied by significant additional toxicity, do not suggest a favorable risk–benefit profile for this combination in the overall study population. Future research should focus on the role of mTOR inhibition in relation to other strategies, such as CDK4/6 inhibition, with a view to optimizing treatment benefits, since patients with a history of CDK4/6 inhibitor treatment appeared to derive the greatest benefit from mTOR inhibition with sapanisertib. The results of the genomic analyses also support a strategy of targeted treatment based on genetic markers, to identify patients who are likely to benefit most from such treatment, especially those with mutations in the genes encoding proteins in the PI3K/AKT/mTOR pathway.

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Authors' Contributions

J.Á. García-Sáenz: Formal analysis, supervision, validation, investigation, visualization, writing–original draft, writing–review and editing. **N. Martínez-Jáñez:** Writing–review and editing. **R. Cubedo:** Resources, investigation, writing–review and editing. **Y. Jerez:** Conceptualization, writing–review and editing. **A. Lahuerta:** Investigation, writing–review and editing. **S. González-Santiago:** Investigation, writing–review and editing. **N. Ferrer:** Writing–review and editing. **M. Ramos:** Validation, investigation. **J.L. Alonso-Romero:** Validation, investigation, writing–review and editing. **A. Antón:** Supervision, validation, investigation, writing–original draft, writing–review and editing. **E. Carrasco:** Supervision, investigation, project administration, writing–review and editing. **J. Chen:** Formal analysis, writing–review and editing. **R. Neuwirth:** Formal analysis. **K. Galinsky:** Formal analysis, visualization. **S. Vincent:** Data curation, writing–review and editing. **E.J. Leonard:** Data curation, supervision, methodology, writing–review and editing. **D. Slamon:** Conceptualization, supervision, investigation, writing–review and editing, conceptualization based on the initial preclinical concept and data generated regarding triple therapy with hormonal blockade + cdk4/6 inhibition + pi3k inhibition (26).

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References

1. Pritchard KI, Gelmon KA, Rayson D, Provencher L, Webster M, McLeod D, et al. Endocrine therapy for postmenopausal women with hormone receptor-positive her2-negative advanced breast cancer after progression or recurrence on non-steroidal aromatase inhibitor therapy: a Canadian consensus statement. Curr Oncol 2013;20:48–61.
2. Castrellon AB. Novel strategies to improve the endocrine therapy of breast cancer. Oncol Rev 2017;11:323.
3. 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.
4. 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; 29:1541–47.
5. Johnston S, Martin M, Di Leo A, Im SA, Awada A, Forrester T, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. NPJ Breast Cancer 2019;5:5.
6. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. N Engl J Med 2020;382:514–24.
7. Sledge GW Jr, Toi M, Neven P, Sohn J, Inoue K, Pivot X, et al. The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor-positive, ERBB2-negative breast cancer that progressed on endocrine therapy-MONARCH 2: a randomized clinical trial. JAMA Oncol 2019;6:116–24.
8. 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.
9. Tripathy D, Im SA, Colleoni M, Franke F, Bardia A, Harbeck N, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol 2018;19:904–15.
10. Shah M, Nunes MR, Stearns V. CDK4/6 inhibitors: game changers in the management of hormone receptor–positive advanced breast cancer? Oncology 2018;32:216–22.
11. Pandey K, An HJ, Kim SK, Lee SA, Kim S, Lim SM, et al. Molecular mechanisms of resistance to CDK4/6 inhibitors in breast cancer: a review. Int J Cancer 2019; 145:1179–88.
12. Hasson SP, Rubinek T, Ryvo L, Wolf I. Endocrine resistance in breast cancer: focus on the phosphatidylinositol 3-kinase/akt/mammalian target of rapamycin signaling pathway. Breast Care 2013;8:248–55.
13. Jansen VM, Bhola NE, Bauer JA, Formisano L, Lee KM, Hutchinson KE, et al. Kinome-wide RNA interference screen reveals a role for PDK1 in acquired resistance to CDK4/6 inhibition in ER-positive breast cancer. Cancer Res 2017; 77:2488–99.
14. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature 2012;490:61–70.
15. 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;12:1758835920940939.
16. 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.
17. Baselga J, Campone M, Piccart M, Burris HA III, Rugo HS, Sahmoud T, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 2012;366:520–9.
18. Yardley DA, Noguchi S, Pritchard KI, Burris HA 3rd, 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.
19. Bachelot T, Bourgier C, Cropet C, Ray-Coquard I, Ferrero JM, Freyer G, et al. Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO study. J Clin Oncol 2012;30:2718–24.
20. Massarweh S, Romond E, Black EP, Van Meter E, Shelton B, Kadamyan-Melkumian V, et al. A phase II study of combined fulvestrant and everolimus in patients with metastatic estrogen receptor (ER)-positive breast cancer after aromatase inhibitor (AI) failure. Breast Cancer Res Treat 2014;143:325–32.

21. O'Reilly KE, Rojo F, She QB, Solit D, Mills GB, Smith D, et al. mTOR inhibition induces upstream receptor tyrosine kinase signaling and activates Akt. Cancer Res 2006;66:1500–8.
22. Rodrik-Outmezguine VS, Chandarlapaty S, Pagano NC, Poulikakos PI, Scaltriti M, Moskatel E, et al. mTOR kinase inhibition causes feedback-dependent biphasic regulation of AKT signaling. Cancer Discov 2011;1:248–59.
23. Zhang X, Wang X, Xu T, Zhong S, Shen Z. Targeting of mTORC2 may have advantages over selective targeting of mTORC1 in the treatment of malignant pheochromocytoma. Tumor Biology 2015;36:5273–81.
24. Jhanwar-Uniyal M, Gillick JL, Neil J, Tobias M, Thwing ZE, Murali R. Distinct signaling mechanisms of mTORC1 and mTORC2 in glioblastoma multiforme: A tale of two complexes. Advances in Biological Regulation 2015;57:64–74.
25. Zhipeng Z, Juan C, Jun Y, Xiaochun B. Targeted inhibition of Rictor/mTORC2 in cancer treatment: a new era after rapamycin. Curr Cancer Drug Targets 2016;16:288–304.
26. Gokmen-Polar Y, Liu Y, Toroni RA, Sanders KL, Mehta R, Badve S, et al. Investigational drug MLN0128, a novel TORC1/2 inhibitor, demonstrates potent oral antitumor activity in human breast cancer xenograft models. Breast Cancer Res Treat 2012;136:673–82.
27. Zeng Z, Wang RY, Qiu YH, Mak DH, Coombes K, Yoo SY, et al. MLN0128, a novel mTOR kinase inhibitor, disrupts survival signaling and triggers apoptosis in AML and AML stem/progenitor cells. Oncotarget 2016;7:55083–97.
28. Lim B, Potter DA, Salkeni MA, Silverman P, Haddad TC, Forget F, et al. Sapanisertib plus exemestane or fulvestrant in women with hormone receptor-positive/HER2-negative advanced or metastatic breast cancer. Clin Cancer Res 2021;27:3329–38.
29. Schmid P, Zaiss M, Harper-Wynne C, Ferreira M, Dubey S, Chan S, et al. Fulvestrant plus vistusertib vs fulvestrant plus everolimus vs fulvestrant alone for women with hormone receptor-positive metastatic breast cancer: the MANTA phase 2 randomized clinical trial. JAMA Oncol 2019;5:1556–63.
30. Ghobrial IM, Siegel DS, Vij R, Berdeja JG, Richardson PG, Neuwirth R, et al. TAK-228 (formerly MLN0128), an investigational oral dual TORC1/2 inhibitor: a phase I dose escalation study in patients with relapsed or refractory multiple myeloma, non-Hodgkin lymphoma, or Waldenstrom's macroglobulinemia. Am J Hematol 2016;91:400–5.
31. Moore KN, Bauer TM, Falchook GS, Chowdhury S, Patel C, Neuwirth R, et al. Phase I study of the investigational oral mTORC1/2 inhibitor sapanisertib (TAK-228): tolerability and food effects of a milled formulation in patients with advanced solid tumours. ESMO Open 2018;3:e000291.
32. O'Brien NA, McDermott MSJ, Conklin D, Luo T, Ayala R, Salgar S, et al. Targeting activated PI3K/mTOR signaling overcomes acquired resistance to CDK4/6-based therapies in preclinical models of hormone receptor-positive breast cancer. Breast Cancer Res 2020;22:89.
33. Bardia A, Hurvitz SA, DeMichele A, Clark AS, Zelnak AB, Yardley DA, et al. Triplet therapy (continuous ribociclib, everolimus, exemestane) in HR+/HER2− advanced breast cancer postprogression on a CDK4/6 inhibitor (TRINITI-1): efficacy, safety, and biomarker results. J Clin Oncol 2019;37:1016–16.