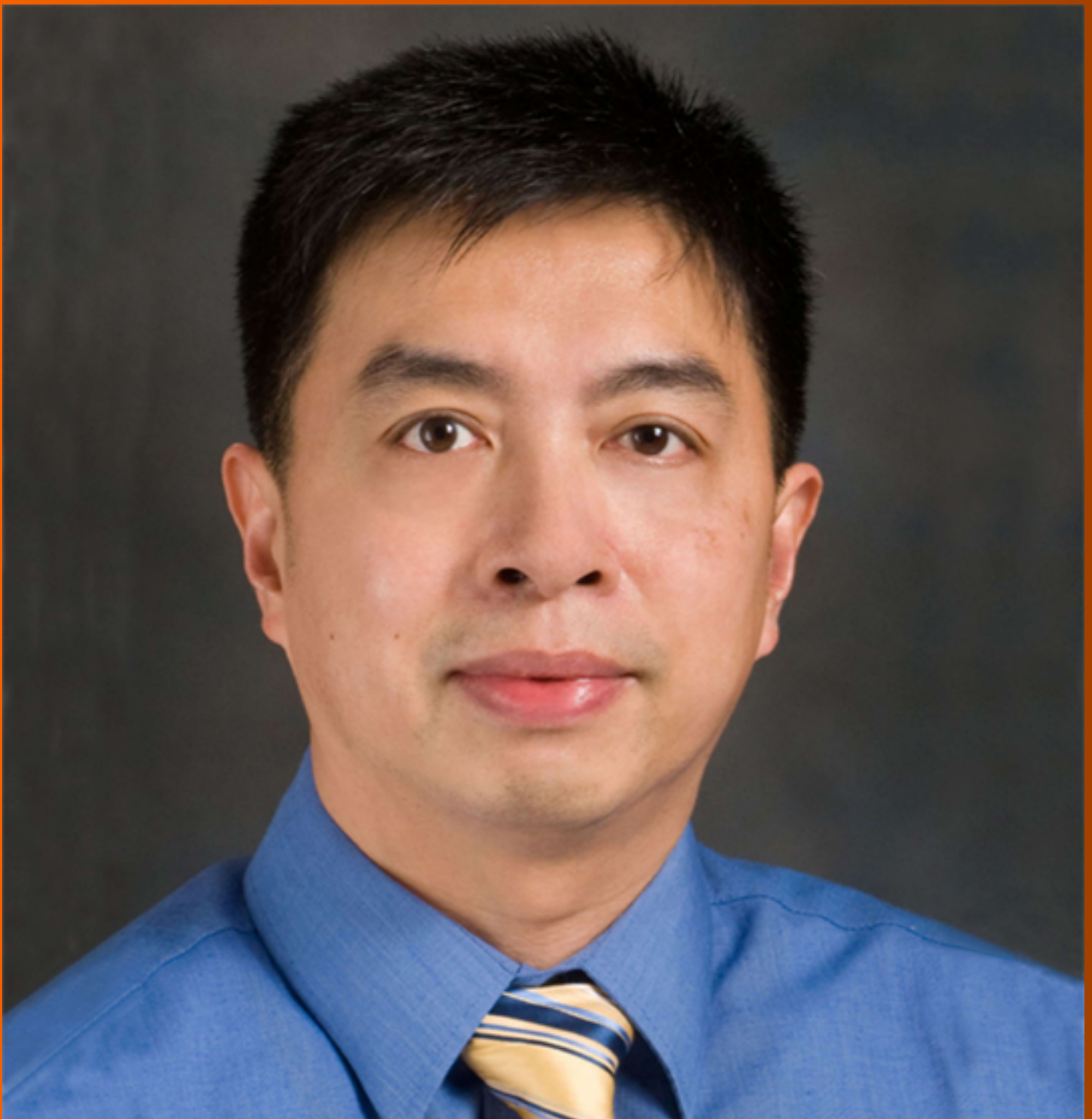


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## Current status of PI3K-mTOR inhibition in hormone-receptor positive, HER2-negative breast cancer

Navid Sobhani, Daniele Generali, Fabrizio Zanconati, Marina Bortul, Bruna Scaggiante

**ORCID number:** Navid Sobhani (0000-0003-1381-0283); Daniele Generali (0000-0003-2480-3855); Fabrizio Zanconati (0000-0001-5357-9579); Marina Bortul (0000-0002-5107-9607); Bruna Scaggiante (0000-0002-8662-138X).

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**Corresponding author to:** Bruna

**Navid Sobhani, Daniele Generali, Fabrizio Zanconati, Marina Bortul,** Department of Medical, Surgical and Health Sciences, University of Trieste, Cattinara Academic Hospital, Trieste 34149, Italy

**Bruna Scaggiante,** Department of Life Sciences, University of Trieste, Trieste 34127, Italy

### Abstract

Breast cancer (BC) is the most common cancer in women and second only to lung cancer in terms of mortality. Among the three different BC subtypes, the oestrogen receptor positive represents nearly 70% of all cases and it is usually treated with anti-oestrogen drugs. However, the majority of hormone receptor positive metastatic BC patients develop resistance to anti-oestrogen treatments. The need for more down-stream therapies brought to the development of therapeutic strategies inhibiting the phosphatidylinositol 3-kinase-mammalian target of rapamycin (mTOR) pathway. Inhibitors of the mTOR have been tested in different clinical trials; everolimus has been Food and Drug Administration approved for the treatment of oestrogen receptor positive/human epidermal growth factor receptor 2 negative BC patients in combination with exemestane in patients who have progressed to anastrozole or letrozole after the encouraging results coming from BOLERO-2 trial. Similar results were obtained by the TAMRAD investigatory study testing tamoxifen in combination with everolimus in advanced BC. This editorial focuses on the results from BOLERO-2, BOLERO 4 and BOLERO-6, which tested the clinical importance of mTOR inhibition. We comment also on the role of phosphatidylinositol 3-kinase-mTOR inhibition as reported in the BELLE-2 and BELLE-3 trials and the future directions for the inhibition of this tumour metabolic axis.

**Key words:** Hormone receptor positive/Her2-negative breast cancer; PI3K; mTOR; TORC1/2; Akt; Everolimus

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**Core tip:** The phosphatidylinositol 3-kinase-mammalian target of rapamycin (PI3K-mTOR) pathway sustains cancer progression and drug resistance. The first Food and Drug Administration approved molecule against this pathway was everolimus, an mTOR inhibitor, to be used in combination with exemestane in hormone receptor positive/human epidermal growth factor receptor 2 negative breast cancers progressing to non-steroidal aromatase inhibitors. Drugs targeting other effectors such as PI3K, PI3K $\alpha$ , Akt and mTORC1/2 have gained clinical interest. Nevertheless, everolimus

Scaggiante, PhD, Professor,  
Department of Life Sciences,  
University of Trieste, Via Giorgeri,  
1, Trieste 34127, Italy.  
[bscaggiante@units.it](mailto:bscaggiante@units.it)  
Telephone: +39-34-5970000

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remains the best option due to the relevant toxicity of the other drugs targeting the PI3K-mTOR pathway. Future directions point towards the development of biomarkers that would identify those patients who would benefit from the PI3K-mTOR inhibitors for improving overall survival.

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## INTRODUCTION

With the introduction of molecular technologies, breast cancer (BC) has been divided into four main subtypes: luminal A, luminal B, human epidermal growth factor receptor 2 (HER2), or triple negative. The luminal variants, due to the hormone receptor positive (HR+) expression, have a generally favourable prognosis in the non-metastatic setting. Some of the most commonly used drugs for the treatment of HR+ disease have been anti-oestrogen therapies, *e.g.* tamoxifen and aromatase inhibitors (AI) - such as anastrozole or letrozole or exemestane. In BC survivors, metastatic breast cancer (MBC) is a treatable but still incurable disease. The majority of HR+ MBCs develop resistance to anti-oestrogen treatments<sup>[1,2]</sup>. Cancer driver mutations and/or constitutive activation in the key signalling pathway genes of phosphatidylinositol 3-kinase-mammalian target of rapamycin (PI3K-mTOR) cascade are capable of overriding anti-oestrogen treatments in BC cells<sup>[3]</sup>. In particular, *PIK3CA* is mutated in 20%-40% of BC<sup>[4,5]</sup>, representing therefore an interesting target for therapies. For these reasons, inhibitors of the PI3K-mTOR pathway was pursued in clinical development until one of them, an mTOR inhibitor-a derivative of rapamycin - named everolimus, reached Food and Drug Administration (FDA) approval for the treatment of the disease in 2012, in combination with exemestane, for second line treatment of HR+/HER2- BCs that have previously regressed to anastrozole or letrozole treatment.

This commentary is focused on the outcomes coming from the most important clinical trials, testing everolimus in combination with other drugs: TAMRAD (Tamoxifen Plus Everolimus), BOLERO-2 (OraL Everolimus-2), BOLERO-4, BOLERO-6, BELLE-2 and BELLE-3. Future directions and perspectives testing therapeutical combinations targeting different effectors are also discussed.

## PI3K-mTOR PATHWAY

PI3K-mTOR signaling events play an important role in the modulation of cell survival, proliferation, motility and apoptosis: activation of PI3K phosphorylates Akt, shifting thereby the protein in the activated form that localizes in the plasma membrane. Subsequently a cascade of downstream events are activated, including the inhibition of p27 and the increase of the transcription factor CREB levels and, consequently, of the cell cycle promoter cyclin A, leading to mTOR activation that promotes the expression of genes related to cell proliferation. The aberrant activation of the PI3K-mTOR pathway sustains cancer cell survival and proliferation and also contributes to anti-oestrogen treatment resistance.

*PIK3CA* mutations constitutively activate the PI3K signal transduction pathway, which ultimately leads to the phosphorylation of PIP<sub>2</sub> into PIP<sub>3</sub>, thus activating the phosphatidylinositol signalling bringing to higher cell survival and to inhibition of apoptosis. Predominantly mutations of *PIK3CA* occur around hotspots E542/5 (exon 9) and H1047 (exon 20) at the catalytic subunit<sup>[6-9]</sup>. Additionally, *AKT* or *PTEN* mutations overrides anti-oestrogen therapies<sup>[4,10]</sup>. Eventually, PIP<sub>3</sub> phosphorylates Akt (pAkt is the active form), which then activates the mTOR.

Of note, PI3K activation has been shown to cause a decrease in ER levels and therefore a lesser degree of response to anti-oestrogen therapies<sup>[11]</sup>. Targeting PI3K could be capable of restoring ER sensitivity<sup>[12]</sup>. Therefore, PI3K-mTOR pathway inhibition plus endocrine therapies represent an interesting strategy to pursue. There is a link between ER and mTORC1: mTORC1 can phosphorylate ER at S167 through

p70S6K or it can also phosphorylate ER at S104/S106, thus resulting in ER activation<sup>[13]</sup>. Of note, recently, Sonnenblick *et al.*<sup>[14]</sup> discovered a gene signature related to the phosphorylation of Akt (pAkt) and mTOR (p-mTOR) in early ER+ BC. Analyzing gene expression and proteomic data collected from over 7000 early BC, they found pAkt correlated to luminal A and a good prognosis, whereas p-mTOR was found in worse prognosis luminal B cases. Interestingly, the signatures of pAkt and p-mTOR correlated to *PI3KCA* mutations positively and negatively, respectively. The authors underlined the different role at the molecular level of pAkt and p-mTOR effectors in early luminal BC, a matter that further contributes to the heterogeneity of the disease<sup>[14]</sup>.

## CLINICAL TRIALS

The discovery of everolimus led to the hypothesis of synergism in co-targeting two different pathways in HR+/HER2- advanced BC patients: the mTOR and the HRs pathways. Such hypothesis has been tested in several clinical trials.

The TAMRAD trial was a phase 2, randomized clinical trial that tested the combination of everolimus with tamoxifen in postmenopausal women with MBC and resistance to AI. Besides proving to be a safe approach, it demonstrated that the combination of these treatments was capable of increasing the clinical benefit rate (CBR) from 42% with tamoxifen to 61% with the combination. The time to progression increased from 4.5 mo in patients receiving only tamoxifen to 8.6 mo in patients receiving both tamoxifen and everolimus. The death risk was reduced by 55% after treating patients with tamoxifen plus everolimus in comparison to tamoxifen alone<sup>[15]</sup>. Interestingly, the combination was efficient in patients who responded to AIs but subsequently became resistant to AIs. Contrarily, the combination was not effective in *de novo* treated MBC HR+<sup>[16]</sup>.

The BOLERO-2 trial was a phase 3, randomized, double-blinded, multicentre clinical trial that recruited 724 HR+ MBC patients. This trial evaluated everolimus with the steroidal AI as exemestane compared to exemestane and placebo. Patients who were enrolled in this clinical trial had previously received AI anastrozole or letrozole. This clinical trial showed an improved progression free survival (PFS) of 11 mo in the exemestane + everolimus arm compared to the 4.1 mo placebo + exemestane ones [ $P < 0.0001$ ; hazard ratio = 0.38; 95% confidence interval (CI): 0.31-0.48]<sup>[17]</sup>. This shows that the combination of everolimus with exemestane doubled up the PFS time versus placebo plus exemestane alone; these results led to the FDA approval of everolimus with exemestane in the treatment of HR+ MBC patients who did not respond to letrozole nor anastrozole treatments.

Recent studies further tested everolimus in combination with other therapies as first line in HR+ BC patients. The BOLERO-4 (NCT01698918) and BOLERO-6 (NCT01783444) tested everolimus with different combinations of drugs. BOLERO-4 was a single arm, open labeled phase 2 study evaluating in 202 ER+, HER2- advanced BC patients the PFS of first line everolimus + letrozole and in a quarter of them whose disease progressed, everolimus + exemestane as second line. This study demonstrated the efficacy of everolimus + letrozole with a median PFS of 22 mo, whereas the second line everolimus + exemestane, which was used in some of the progressed patients, gave limited results with a median PFS of only 3.7 mo<sup>[18]</sup>. The BOLERO-6 was a randomized open-labeled study, comparing second line everolimus + exemestane against everolimus or capecitabine alone in 309 AI-resistant ER+, HER2-MBC patients. Consistent with the BOLERO-2 study, robust evidence of superiority in median PFS was registered for everolimus + exemestane versus everolimus alone but surprisingly not versus capecitabine alone. However, the authors pointed out that there were some limits to the study, such as censored data and baseline imbalance in Kaplan Meyer curves, that could have interfered on the evaluation of the capecitabine arm<sup>[19]</sup>. Thus, the combination of everolimus + exemestane was confirmed to benefit these patients, whereas the superiority/equivalence/inferiority of capecitabine needs further clinical evaluation.

Inhibition of PI3K has been also investigated as an alternative strategy in targeted therapies of the mTOR pathway. As an example, buparlisib (BKM120), which is a PI3K inhibitor, has been tested in combination with fulvestrant in patients progressing AIs (BELLE-2, NCT01610284) and in patients progressing mTOR inhibition (BELLE-3, NCT01633060).

Buparlisib has been tested in 1147 patients as second line in the randomized, double-blinded BELLE-2 clinical trial, alone or in combination with fulvestrant. It was clear that the combination with the PI3K inhibitor had slightly increased PFS compared to fulvestrant alone, with the exception of *PI3KCA* mutated patients who

improved the PFS of about 4 mo. Of note, the serious toxicity of buparlisib limited the efficacy of the targeted therapy<sup>[20]</sup>. BELLE-3 was a randomized double-blinded phase 2 trial enrolling 432 patients who progressed AIs to evaluate PFS in buparlisib + fulvestrant arm compared to fulvestrant + placebo. The combination with buparlisib improved the PFS of only 2 mo while showing a high toxicity profile that hampered the clinical benefit<sup>[21]</sup>. Finally, an exploratory strategy is aiming for the simultaneous inhibition of PI3K and mTOR by alpelisib (BYL719) and everolimus, respectively. The safety of the combination of alpelisib and everolimus alone or everolimus + exemestane has been tested in a Phase 1 trial in various solid tumours, including BC (NCT02077933).

Worth of note is the combination of letrozole and alpelisib, a selective oral inhibitor of the class I PI3K catalytic subunit p110 $\alpha$ , which has shown synergistic antitumour activity with endocrine therapy against ER+/PIK3CA-mutated BC cells. The combination was safe with reversible toxicities. Clinical activity was observed independently of PIK3CA mutation status, although clinical benefit was seen in a higher proportion of patients with PIK3CA-mutated tumours. Phase 2 and 3 trials of alpelisib and endocrine therapy in patients with ER+ BC are ongoing<sup>[22]</sup>.

## PERSPECTIVE

In addition to the previous therapies targeting mTOR, other research groups sought to investigate alternative strategies targeting molecules belonging to the mTOR complex or other effectors of the PI3K-mTOR pathway. An investigatory strategy consists in the use of sapanisertib (TAK228) for TORC1/2 inhibition by targeting mTOR kinase. TORC1/2 are complexes of proteins that regulate many vital cellular processes and proliferation. This drug has been tested in the neoadjuvant setting with tamoxifen (NCT02988986) or letrozole (NCT02619669) in the treatment of HR+ BC patients. AZD5363 is a specific Akt inhibitor, which has been tested either as a monotherapy (NCT01226316) or as a combination with fulvestrant in HR+ MBC patients who progressed AIs (NCT01992952). **Table 1** summarizes all the clinical trials testing PI3K-mTOR pathway inhibitors. In our opinion, there is a need for predictors of the efficacy of such inhibitors: a pooled analysis for overall survival, disease free survival and PFS meta-analysis using clinical studies investigating the prognostic role of PI3KCA mutations in BC, proved that mutations of this gene are predictive of a worse clinical survival outcome for the patients (HR = 1.67, 95%CI: 1.15-2.43;  $P = 0.007$ )<sup>[23]</sup>. Unfortunately, there was not enough clinical evidence to prove that PI3KCA mutations could be predictive for therapy-efficacy and further clinical trials investigating the role of such mutations could be precious for guiding clinicians to choose those patients who would benefit from PI3K-mTOR inhibition treatment.

In conclusion, the inhibition of the PI3K-mTOR pathway remains one of the major goals for the treatment of HR+ advanced BC patients. It is known that targeting more upstream effectors, such as PI3K, which proved to be very promising based on *in vitro* evidence, lead to major side effects in clinical studies, limiting the clinical development of this type of drugs. This class of inhibitors, however, seems to be beneficial for patients harboring PI3KCA mutations, thus producing less toxicity.

Currently, everolimus remains the best option in the clinical setting in combinational therapies for HR+ BC patients. Moreover, several studies are directed to explore the clinical benefits of everolimus in combination with other drugs, as illustrated in **Table 1**. Of note, 10%-15% of patients are intrinsically resistant to everolimus treatment<sup>[24]</sup>. For this reason, dual inhibition of the pathway by targeting mTORC1/2 proteins have been tested (**Table 1**), and some phase 1 studies are exploring new PI3K inhibitors, such as gedatolisib (NCT02626507) in neoadjuvant setting for ER+, HER2- BC patients. CUDC-907, an histone deacetylase and PI3K inhibitor (NCT02307240), and AZD8186, a PI3K- $\beta$  inhibitor (NCT03218826), have been tested in advanced solid tumours, including BC. Having biomarkers from the metastatic setting to predict the responsiveness/resistance to anti-PI3K/mTOR/Akt drugs are thus an urgent task, and many efforts in this direction are expected. Finally, with the advancement of immune-therapy, trials testing the combination of immune-therapy with everolimus are warranted.

**Table 1 Clinical trials inhibiting PI3K-mTOR pathway in HR+, HER2- breast cancer patients**

Clinical trial identifier	Phase	Year	Administered drug(s) (target)	Primary endpoint	Target/s of the PI3K-mTOR pathway
NCT00699491	1/2	18.06.2008	Cixutumumab + temsirolimus	ORR	mTOR
Bolero 2; NCT00863655 [16]	3	18.03.2009	Everolimus + exemestane or placebo + exemestane	PFS	mTOR
NCT00876395	3	06.04.2009	Everolimus + placebo	PFS	mTOR
NCT01219699	1	13.10.2010	BYL719 + fulvestrant	MTD	PI3K $\alpha$
NCT01283789	2	26.01.2011	Everolimus + lapatinib	ORR	mTOR
TAMRAD; NCT01298713 [14]	2	18.02.2011	Everolimus + tamoxifen	CBR	mTOR
BELLE-2; NCT01610284	3	04.06.2012	Fulvestrant $\pm$ BKM120 (AIs refractory pts)	PFS	PI3K
BELLE-3; NCT01633060	3	04.06.2012	Fulvestrant $\pm$ BKM120 (Pts previously on mTOR inhibitors)	PFS	PI3K
NCT01627067	2	25.06.2012	Everolimus + exemestane + metformin	PFS	mTOR
NCT01674140	3	28.08.2012	Everolimus + standard adjuvant endocrine therapy (tamoxifen citrate, goserelin acetate, leuprolide acetate, anastrozole, letrozole, or exemestane)	Invasive DFS	mTOR
Bolero 4; NCT01698918	2	03.10.2012	Everolimus + letrozole	PFS	mTOR
NCT01776008	2	25.01.2013	everolimus + exemestane; MK2206 + anastrozole $\pm$ goserelin acetate	CRR	Akt
NCT01783444; Bolero-6	2	05.02.2013	Everolimus or capecitabine or everolimus + exemestane	PFS	mTOR
NCT01791478	1	15.02.2013	BYL719 + letrozole	DLT	PI3K $\alpha$
NCT01805271	3	06.03.2013	Everolimus + placebo	DFS	mTOR
CLEE011X2107; NCT01872260	1b/2	07.06.2013	Letrozole + ribociclib + alpelisib	DLT	PI3K
INPRES; NCT01948960	4	24.09.2013	Everolimus	AUC correlation with age and/or obesity	mTOR
NCT01992952	1/2	25.11.2013	Fulvestrant $\pm$ AZD5363 or placebo	MTD	Akt
PEARL; NCT02028364	2	07.01.2014	Everolimus + exemestane	PFS and response by PET	mTOR
NCT02035813	2	14.01.2014	Everolimus + eribulin	PFS	mTOR
NCT02049957	1b/2	30.01.2014	MLN0128 + exemestane vs MLN0128 + fulvestrant	Participant with AE and Clinical Benefit Rate	mTORC1/2
NCT02057133	1b	06.02.2014	LY2835219 + exemestane + everolimus vs exemestane + everolimus vs LY2835219 + trastuzumab vs LY2835219 + anastrozole vs LY2835219 + tamoxifen vs LY2835219 + letrozole vs LY3023414 + LY2835219 + fulvestrant	Safety	mTOR
NCT02058381	1b	10.02.2014	BYL719 + BKM120	MTD	PI3K $\alpha$ + PI3K
NCT02077933	1	04.03.2014	Alpelisib + everolimus + exemestane	DLT and MTD	PI3K + mTOR

NCT02123823	1b	28.04.2014	BI 836845 + everolimus + exemestane	PFS, MTD and DLT	mTOR
NCT02216786	2	15.08.2014	Everolimus + fulvestrant <i>vs</i> AZD2014 + fulvestrant	PFS	mTOR + mTORC1/2
NCT02236572	2	10.09.2014	Everolimus + aromatase inhibitor	Preoperative Endocrine Prognostic Index	mTOR
NCT02269670	2	21.10.2014	Everolimus + endocrine therapy (anastrozole, letrozole, tamoxifen citrate, fulvestrant or megestrol acetate)	PFS and ORR	mTOR
NCT02285179	1/2	16.11.2014	Taselisib + tamoxifen	MTD	PI3K
NCT02291913	2	17.11.2014	Everolimus + anti-estrogen therapy (exemestane, tamoxifen, fulvestrant, anastrozole, letrozole, toremifine )	PFS	mTOR
Sandpiper NCT02340221	3	16.01.2015	Taselisib + fulvestrant <i>vs</i> placebo + fulvestrant	PFS	PI3K
FEVEX; NCT02404051	3	31.03.2015	Everolimus + exemestane <i>vs</i> everolimus + exemestane (at progression fulvestrant)	PFS	mTOR
NCT02404844	2	01.04.2015	BKM120 + tamoxifen	PFS	PI3K
NCT02379247		04.05.2015	BYL719 + Nab-paclitaxel	DLT , ORR for Phase II	PI3K $\alpha$
SOLAR-1; NCT02437318	3	07.05.2015	Fulvestrant $\pm$ alpelisib (AIs refractory pts)	PFS	PI3K
NCT02506556	2	23.07.2015	BYI719	ORR	PI3K $\alpha$
NCT02511639	3	30.07.2015	Everolimus + aromatase inhibitors	PFS	mTOR
NCT02520063	1/2	11.08.2015	Letrozole + everolimus + TRC105	MTD	mTOR
NCT02619669	1	02.12.2015	Sapanisertib + letrozole	TAE	mTORC1/2
TRINITI-1; NCT02732119	1/2	08.04.2016	Everolimus + ribociclib + exemestane	MTD	mTOR
NCT02742051	2	18.04.2016	Everolimus + letrozole <i>vs</i> neoadjuvant+ fluorouracil, epirubicin + cyclophosphamide (FEC)	ORR	mTOR
NCT02871791	2	18.08.2016	Everolimus + exemestane	DLT	mTOR
NCT02988986	2	12.12.2016	Sapanisertib + tamoxifen	Change in Ki67 expression	mTORC1/2
CLEVER; NCT03032406	2	26.01.2017	Everolimus $\pm$ hydroxychloroquine	AE	mTOR
NCT03056755	2	17.02.2017	Alpelisib + fulvestrant + letrozole (AIs and CDK4/6 refractory pts)	DFS	PI3K
NCT03128619	1/2	25.04.2017	Copanlisib + letrozole + palbociclib	MTD	PI3K
EVEREXES; NCT03176238	3	05.06.2017	Everolimus + exemestane	AE	mTOR
NCT03207529	1	02.07.2017	BYL719 + enzalutamide	MTD	PI3K $\alpha$
NCT03377101	2	19.12.2017	Fulvestrant + palbociclib $\pm$ copanlisib	DLT	PI3K

DLT: Dose limiting toxicity; PFS: Progression free survival; DFS: Disease free survival; MTD: Maximum tolerated dose; AE: Adverse events; CBR: Clinical benefit rate; ORR: Overall response rate; CRR: Clinical response rate; PI3K-mTOR: Phosphatidylinositol 3-kinase-mammalian target of rapamycin.

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