ISSN 2218-4333 (online)

World Journal of *Clinical Oncology*

World J Clin Oncol 2018 December 20; 9(8): 167-207

Published by Baishideng Publishing Group Inc

World Journal of Clinical Oncology

Contents

Continuous Volume 9 Number 8 December 20, 2018

EDITORIAL

MINIREVIEWS

ORIGINAL ARTICLE

Basic Study

CASE REPORT

Contents

World Journal of Clinical Oncology

Volume 9 Number 8 December 20, 2018

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Oncology*, Shiaw-Yih Lin, PhD, Professor, Department of Systems Biology, MD Anderson Cancer Center, the University of Texas, Houston, TX 77054, United States

AIMS AND SCOPE

World Journal of Clinical Oncology (*World J Clin Oncol*, *WJCO*, online ISSN 2218-4333, DOI: 10.5306) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJCO covers a variety of clinical medical topics, including etiology, epidemiology, evidence-based medicine, informatics, diagnostic imaging, endoscopy, tumor recurrence and metastasis, tumor stem cells, radiotherapy, chemotherapy, interventional radiology, palliative therapy, clinical chemotherapy, *etc*. Priority publication will be given to articles concerning diagnosis and treatment of oncology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, *etc*.

We encourage authors to submit their manuscripts to *WJCO*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Clinical Oncology (*WJCO*) is now abstracted and indexed in PubMed, PubMed Central, Scopus, and Emerging Sources Citation Index (Web of Science), China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Ying-Na Bian* **Proofing Editorial Office Director:** *Jin-Lei Wang*

NAME OF JOURNAL
World Journal of Clinical Oncology

ISSN
ISSN 2218-4333 (online)

LAUNCH DATE
November 10, 2010

FREQUENCY
Continuous

EDITORS-IN-CHIEF
Hiten RH Patel

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2218-4333/editorialboard.htm

EDITORIAL OFFICE
Jin-Lei Wang, Director

PUBLICATION DATE
December 20, 2018

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2018 December 20; 9(8): 172-179

DOI: 10.5306/wjco.v9.i8.172

ISSN 2218-4333 (online)

EDITORIAL

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).

Author contributions: Sobhani N proposed and planned the topic of the editorial and wrote the first draft that has been revised and implemented by Generali D and Scaggiante B; Zanconati F and Bortul M further edited the manuscript.

Supported by Ricerca Sanitaria LILT 2015; and Beneficentia Foundation Stiftung, No. BEN2016/16 grants.

Conflict-of-interest statement: None.

Manuscript source: Invited manuscript

Received: July 13, 2018

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

Corresponding author to: Bruna Scaggiante, PhD, Professor, Department of Life Sciences, University of Trieste, Via Giorgeri, 1, Trieste 34127, Italy. bscaggiante@units.it
Telephone: +39-34-59700000

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

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

Peer-review started: July 13, 2018
First decision: October 8, 2018
Revised: October 16, 2018
Accepted: November 26, 2018
Article in press: November 26, 2018
Published online: December 20, 2018

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, PI3Kα, Akt and mTORC1/2 have gained clinical interest. Nevertheless, everolimus 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.

Sobhani N, Generali D, Zanconati F, Bortul M, Scaggiante B. Current status of PI3K-mTOR inhibition in hormone-receptor positive, HER2-negative breast cancer. *World J Clin Oncol* 2018; 9(8): 172-179
URL: https://www.wjgnet.com/2218-4333/full/v9/i8/172.htm
DOI: https://dx.doi.org/10.5306/wjco.v9.i8.172

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[1,2]. 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[3]. In particular, *PIK3CA* is mutated in 20%-40% of BC[4,5], 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_2 into PIP_3, thus activating the phosphatidylinositol signalling bringing to higher cell survival and to inhibition of apoptosis. Predominantly mutations of *PI3KCA* occur around hotspots E542/5 (exon 9) and H1047 (exon 20) at the catalytic subunit[6-9]. Additionally, *AKT* or *PTEN* mutations overrides anti-oestrogen therapies[4,10]. Eventually, PIP_3 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[11]. Targeting PI3K could be capable of restoring ER sensitivity[12]. 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[13]. Of note, recently, Sonnenblick *et al*[14] 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[14].

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[15]. 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+[16].

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 steroideal 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][17]. 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[18]. The BOLERO-6 was a randomized open-labeled study, comparing second line therapies 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 inferred on the evaluation of the capecitabine arm[19]. 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 buparsilib limited the efficacy of the targeted therapy[20]. 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[21]. 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 p110α, 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[22].

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)[23]. 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[24]. 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-β 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	PI3Kα
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 ± BKM120 (AIs refractory pts)	PFS	PI3K
BELLE-3; NCT01633060	3	04.06.2012	Fulvestrant ± 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 ± 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	PI3Kα
NCT01805271	3	06.03.2013	Everolimus + placebo	DFS	mTOR
CLEE011X2107; NCT01872260	1b/2	07.06.2013	Letrozole + ribociclib + alpesilib	DLT	PI3K
INPRES; NCT01948960	4	24.09.2013	Everolimus	AUC correlation with age and/or obesity	mTOR
NCT01992952	1/2	25.11.2013	Fulvestrant ± 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 + anastrazole *vs* LY2835219 + tamoxifen *vs* LY2835219 + letrozole *vs* LY3023414 + LY2835219 + fulvestrant	Safety	mTOR
NCT02058381	1b	10.02.2014	BYL719 + BKM120	MTD	PI3Kα + 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 *vs* 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 *vs* placebo + fulvestrant	PFS	PI3K
FEVEX; NCT02404051	3	31.03.2015	Everolimus + exemestane *vs* 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	PI3Kα
SOLAR-1; NCT02437318	3	07.05.2015	Fulvestrant ± alpelisib (AIs refractory pts)	PFS	PI3K
NCT02506556	2	23.07.2015	BYl719	ORR	PI3Kα
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 *vs* 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 ± 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	PI3Kα
NCT03377101	2	19.12.2017	Fulvestrant + palbociclib ± 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.

REFERENCES

1 **Buzdar AU**. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the

international letrozole breast cancer group. *J Clin Oncol* 2004; **22**: 3199-3200; author reply 3200-3201 [PMID: 15284276 DOI: 10.1200/JCO.2004.99.058]
2 **Dalmau E**, Armengol-Alonso A, Muñoz M, Seguí-Palmer MÁ. Current status of hormone therapy in patients with hormone receptor positive (HR+) advanced breast cancer. *Breast* 2014; **23**: 710-720 [PMID: 25311296 DOI: 10.1016/j.breast.2014.09.006]
3 **Osborne CK**, Schiff R. Mechanisms of endocrine resistance in breast cancer. *Annu Rev Med* 2011; **62**: 233-247 [PMID: 20887199 DOI: 10.1146/annurev-med-070909-182917]
4 **Stemke-Hale K**, Gonzalez-Angulo AM, Lluch A, Neve RM, Kuo WL, Davies M, Carey M, Hu Z, Guan Y, Sahin A. An integrative genomic and proteomic analysis of PIK3CA, PTEN, and AKT mutations in breast cancer. *Cancer Res* 2008; **68**: 6084-6091 [PMID: 18676830 DOI: 10.1158/0008-5472.CAN-07-6854]
5 **Saal LH**, Holm K, Maurer M, Memeo L, Su T, Wang X, Yu JS, Malmström PO, Mansukhani M, Enoksson J. PIK3CA mutations correlate with hormone receptors, node metastasis, and ERBB2, and are mutually exclusive with PTEN loss in human breast carcinoma. *Cancer Res* 2005; **65**: 2554-2559 [PMID: 15805248 DOI: 10.1158/0008-5472-CAN-04-3913]
6 **Paplomata E**, O'Regan R. The PI3K/AKT/mTOR pathway in breast cancer: targets, trials and biomarkers. *Ther Adv Med Oncol* 2014; **6**: 154-166 [PMID: 25057302 DOI: 10.1177/1758834014530023]
7 **deGraffenried LA**, Friedrichs WE, Russell DH, Donzis EJ, Middleton AK, Silva JM, Roth RA, Hidalgo M. Inhibition of mTOR activity restores tamoxifen response in breast cancer cells with aberrant Akt Activity. *Clin Cancer Res* 2004; **10**: 8059-8067 [PMID: 15585641 DOI: 10.1158/1078-0432.CCR-04-0035]
8 **Bhattacharvva GS**, Biswas J, Singh JK, Singh M, Govindbabu K, Ranade AA, Malhotra H, Parikh PM, Shahid T, Basu S. Reversal of Tamoxifen Resistance (Hormone Resistance) by Addition of Sirolimus (mTOR Inhibitor) in Metastatic Breast Cancer. *Eur J Cancer* 2011; **47**: 9 [DOI: 10.1016/S0959-8049(11)70115-0]
9 **Generali D**, Fox SB, Brizzi MP, Allevi G, Bonardi S, Aguggini S, Milani M, Bersiga A, Campo L, Dionisio R. Down-regulation of phosphatidylinositol 3'-kinase/AKT/molecular target of rapamycin metabolic pathway by primary letrozole-based therapy in human breast cancer. *Clin Cancer Res* 2008; **14**: 2673-2680 [PMID: 18451231 DOI: 10.1158/1078-0432.CCR-07-1046]
10 **Creighton CJ**, Fu X, Hennessy BT, Casa AJ, Zhang Y, Gonzalez-Angulo AM, Lluch A, Gray JW, Brown PH, Hilsenbeck SG. Proteomic and transcriptomic profiling reveals a link between the PI3K pathway and lower estrogen-receptor (ER) levels and activity in ER+ breast cancer. *Breast Cancer Res* 2010; **12**: R40 [PMID: 20569503 DOI: 10.1186/bcr2594]
11 **Fu X**, Osborne CK, Schiff R. Biology and therapeutic potential of PI3K signaling in ER+/HER2-negative breast cancer. *Breast* 2013; **22** Suppl 2: S12-S18 [PMID: 24011769 DOI: 10.1016/j.breast.2013.08.001]
12 **Corona SP**, Sobhani N, Ianza A, Roviello G, Mustacchi G, Bortul M, Zanconati F, Generali D. Advances in systemic therapy for metastatic breast cancer: future perspectives. *Med Oncol* 2017; **34**: 119 [PMID: 28526922 DOI: 10.1007/s12032-017-0975-5]
13 **Alayev A**, Salamon RS, Berger SM, Schwartz NS, Cuesta R, Snyder RB, Holz MK. mTORC1 directly phosphorylates and activates ERα upon estrogen stimulation. *Oncogene* 2016; **35**: 3535-3543 [PMID: 26522726 DOI: 10.1038/onc.2015.414]
14 **Sonnenblick A**, Brohée S, Pondé N, Venet D, Sotiriou C. Dissecting the Akt/mTOR pathway in estrogen receptor positive breast cancers identifies phosphorylated Akt signature to be associated with luminal A and good prognosis in contrast to phosphorylated mTOR. *The Breast* 2017; **32**: S103 [DOI: 10.1016/S0960-9776(17)30328-4]
15 **Bachelot T**, Bourgier C, Cropet C, Ray-Coquard I, Ferrero JM, Freyer G, Abadie-Lacourtoisie S, Eymard JC, Debled M, Spaëth D. 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**: 2718-2724 [PMID: 22565002 DOI: 10.1200/JCO.2011.39.0708]
16 **Tomii K**, Tsukuda K, Toyooka S, Dote H, Hanafusa T, Asano H, Naitou M, Doihara H, Kisimoto T, Katayama H. Aberrant promoter methylation of insulin-like growth factor binding protein-3 gene in human cancers. *Int J Cancer* 2007; **120**: 566-573 [PMID: 17096329 DOI: 10.1002/ijc.22341]
17 **Yardley DA**, Noguchi S, Pritchard KI, Burris HA 3rd, Baselga J, Gnant M, Hortobagyi GN, Campone M, Pistilli B, Piccart M, Melichar B, Petrakova K, Arena FP, Erdkamp F, Harb WA, Feng W, Cahana A, Taran T, Lebwohl D, Rugo HS. Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. *Adv Ther* 2013; **30**: 870-884 [PMID: 24158787 DOI: 10.1007/s12325-013-0060-1]
18 **Royce M**, Bachelot T, Villanueva C, Özgüroglu M, Azevedo SJ, Cruz FM, Debled M, Hegg R, Toyama T, Falkson C. Everolimus Plus Endocrine Therapy for Postmenopausal Women With Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: A Clinical Trial. *JAMA Oncol* 2018; **4**: 977-984 [PMID: 29566104 DOI: 10.1001/jamaoncol.2018.0060]
19 **Jerusalem G**, de Boer RH, Hurvitz S, Yardley DA, Kovalenko E, Ejlertsen B, Blau S, Özgüroglu M, Landherr L, Ewertz M. Everolimus Plus Exemestane vs Everolimus or Capecitabine Monotherapy for Estrogen Receptor-Positive, HER2-Negative Advanced Breast Cancer: The BOLERO-6 Randomized Clinical Trial. *JAMA Oncol* 2018; **4**: 1367-1374 [PMID: 29862411 DOI: 10.1001/jamaoncol.2018.2262]
20 **Baselga J**, Im SA, Iwata H, Cortés J, De Laurentiis M, Jiang Z, Arteaga CL, Jonat W, Clemons M, Ito Y. 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**: 904-916 [PMID: 28576675 DOI: 10.1016/S1470-2045(17)30376-5]
21 **Di Leo A**, Johnston S, Lee KS, Ciruelos E, Lønning PE, Janni W, O'Regan R, Mouret-Reynier MA, Kalev D, Egle D. 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 [PMID: 29223745 DOI: 10.1016/S1470-2045(17)30688-5]
22 **Mayer IA**, Abramson VG, Formisano L, Balko JM, Estrada MV, Sanders ME, Juric D, Solit D,

Berger MF, Won HH. A Phase Ib Study of Alpelisib (BYL719), a PI3Kα-Specific Inhibitor, with Letrozole in ER+/HER2- Metastatic Breast Cancer. *Clin Cancer Res* 2017; **23**: 26-34 [PMID: 27126994 DOI: 10.1158/1078-0432.CCR-16-0134]

23 **Sobhani N**, Roviello G, Corona SP, Scaltriti M, Ianza A, Bortul M, Zanconati F, Generali D. The prognostic value of PI3K mutational status in breast cancer: A meta-analysis. *J Cell Biochem* 2018; **119**: 4287-4292 [PMID: 29345357 DOI: 10.1002/jcb.26687]

24 **Beaver JA**, Park BH. The BOLERO-2 trial: the addition of everolimus to exemestane in the treatment of postmenopausal hormone receptor-positive advanced breast cancer. *Future Oncol* 2012; **8**: 651-657 [PMID: 22764762 DOI: 10.2217/fon.12.49]

P- Reviewer: Huo Q, Kim HS, Kok VC, Morelli F
S- Editor: Ji FF **L- Editor:** Filipodia **E- Editor:** Bian YN

Published By Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk:https://www.f6publishing.com/helpdesk
https://www.wjgnet.com