HORMONE THERAPY IN ADVANCED ER+/HER2-NEGATIVE BREAST CANCER WITH PI3K INHIBITORS:
A REVIEW OF THE LITERATURE

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ABSTRACT
Breast cancer is a heterogenous disease, showing as several different clinical and histologic types. Most of breast cancers express hormone receptors for estrogen and progesterone, which are considered as estrogen receptor-positive and progesterone-receptor-positive, respectively.
Endocrine therapy was the first class of target-directed therapy approved for treating breast cancer and is still very important for the treatment of HR+ breast cancer because of its effectiveness and good toxicity profile. It targets receptor-mediated signaling pathways implicated in cell survival and proliferation, such as those mediated by hormone receptors. Although these approaches have improved the management of advanced breast cancer, many patients either fail to respond to initial therapy (primary or de novo resistance) or eventually become resistant to treatment (secondary or acquired resistance). To expand the use of existing endocrine treatments and their efficiency, new methods are needed. Such new approaches would boost the benefit of existing endocrine therapy by extending time to disease progression, avoiding or overcoming resistance to endocrine treatment, and delaying the use of chemotherapy.
This article will review the central role of the PI3K inhibitors in driving ER+/HER2- breast tumors. Also, schemes to combine pathway inhibitors with endocrine therapy for better patient outcome, and approaches to identify patient populations that would benefit most from inhibition of the PI3K/AKT/mTOR pathway will be assessed.

KEYWORDS: pi3k inhibitors breast cancer, buparlisib belle2, hr+ her2- negative pi3k

Introduction
Breast cancer (BC) is a diverse disease, demonstrating as various clinical and histologic types. About 68-78% of tumors of the breast express estrogen receptor alfa (ER-a), and viewed as ER-positive (ER+) and progesterone receptors; these are regarded as PR-positive (PR+). HR-targeted therapy in such patients is reasonable.
There are different mechanisms which endocrine therapies (ET) obstruct the growth-promoting effects of estrogen. They consist of following broad classes:
1. Selective ER modulators (e.g. tamoxifen), they have dual agonistic/antagonistic effects on ER transcription, based on the tissue;
2. Selective ER downregulators (e.g. fulvestrant), they downregulate expression of the ER;
3. Aromatase inhibitors (AI) (e.g. letrozole, anastrozole, exemestane), they suppress estrogen biosynthesis in post-genic expression.
4. Gonadotropin-Releasing hormone analogs, they suppress estrogen biosynthesis in premenopausal cases. [1]

ET was the first class of target-directed treatment approved for treating BC. [1] This therapy is still of great importance for treating HR+ BC because of its efficiency and good toxicity profile. Targets of this type of treatment include receptor-mediated signaling pathways involved in cell survival and proliferation, for example, those mediated by hormone receptors. Despite improving the therapy of advanced breast cancer (ABC) with such methods, a significant number of women either do not react to initial treatment or at a certain point develop resistance. New approaches considered to expand the use of existing endocrine therapies and their efficiency. Such new methods could boost the advantage of already known ET through extending the period necessary for BC to progress, by avoiding resistance to hormonal treatment, and by making it possible to delay the use of chemotherapy.

The focal point of a high number of preclinical and clinical studies is the possibility of phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR pathway suppression to increase response and expand the duration of ET. [1] Cell proliferation, metabolism, motility, angiogenesis, and survival regulated by a signal transduction cascade known as PI3K/AKT/mTOR pathway. Intense activation of this pathway is involved in the development of ER+ BC and the development of resistance to ET.

The essential role of the PI3K inhibitors (PI3Ki) in driving ER+/HER2- negative BC, will be one of the focal points of this review. Different approaches to recognize cases that could have the most advantage from suppressing the PI3K/AKT/mTOR pathway will be assessed.

**General review of ET methods for advanced HR+/HER2- BC**

Many factors should come into consideration while managing metastatic breast cancer (MBC) to be possible for doctors and patients to select the treatment that will appreciate survival and enhance the quality of life for the patients.

According to internationally approved guidelines, doctors should confirm the histopathological diagnosis of metastases, identify the HR and HER2 status and perform cytological specimens of the most common metastatic sites (bones, viscera, lymph nodes). A comprehension of the tumor biology and the metastatic disease burden is the outcome of such investigations.[2]

Without a doubt, the treatment will be affected by elements associated with the tumor and by elements connected with the individual being treated. Features related to the patient like biological age, menopausal status, patient’s personal preferences, comorbidities, functional status, social and economic characteristics and the availability of treatment are of most relevance.[2]

ET has excellent efficacy and is the most broadly acknowledged therapy regarding toxicity in HR+ ABC.[3] When a quick reaction is needed to manage symptoms or in cases where the BC is confirmed to be clinically aggressive this treatment choice is considered inappropriate.

When discussing options for treating patients with ABC, various problems should come into consideration. First-line ET is a better option in cases with HR+/HER2-negative BC, mainly because of its prominent efficiency and somewhat low toxicity in comparison to cytotoxic chemotherapy.

**Postmenopausal Endocrine therapy**

Options like nonsteroidal and steroidal AI, SERMs, selective estrogen receptor degraders (SERDs), progestins, androgens, and high-dose estrogen come into consideration when choosing endocrine therapy for postmenopausal cases. Treatment with AI, SERDs, or SERMs should be considered for such patients if they have not yet experienced tumor relapse from prior ET or who have not been on ET for a period longer than one year. At the moment, aromatase inhibitors, which lower circulating estradiol levels by obstructing the estrogen produced in peripheral tissues, are a standard first-line treatment (FLT) for postMP with ER-positive BC.

**Palbociclib**

It suppressed the increase of ER+ human breast cancer cells in vitro and re-established sensitivity to tamoxifen in cells with developed resistance. [3] A randomized phase, two trial of palbociclib combined with letrozole came into comparison with letrozole only as an FLT for cases with ER-positive/HER2-negative ABC. One hundred and sixty-five patients who have locally recurrent or MBC was at random prescribed to take this PI3K inhibitor in combination with letrozole or letrozole only; the essential endpoint was progression-free survival (PFS). The combination between palbociclib and letrozole resulted in better PFS in comparison to letrozole only (20.2 vs. 10.2 months; P = 0.0004), with objective response rates (ORRs) of 36% vs. 27%. [3] At the time of the publication, the occurrence of death events in this phase 2 study had been small but it had not been differ statistically between the palbociclib combined with letrozole and the letrozole only arms (37.5 vs. 33.3; P = 0.42). [3] Results like these provide us with evidence that some cases of HR+ BC have a good reaction to palbociclib in combination with AI. FDA gave official approval for the use of palbociclib combined with letrozole as a therapy in postMP with ER-positive/HER2-negative ABC as the First-line ET for their metastatic disease, based on the data provided by such studies.

**Premenopausal patients (preMP)**

Available options for endocrine treatment in premenopausal cases comprise of SERMs, luteinizing hormone-releasing hormone (LH-RH) agonists, surgical oophorectomy, and progestin. In this group the women who experience disease relapse within one year of tamoxifen treatment can be subjected to ovarian ablation, surgical oophorectomy or ovarian suppression with LH-RH agonists as second-line treatment, this therapy is by the latest guidelines. [3] Premenopausal patients who have had an ovarian ablation or inhibition, as a result, become postMP, and should be subjected to the identical therapy protocol as postMPs who develop resistance to endocrine FLT.

**Treatment in endocrine therapy—resistant cases**

Despite the fact that endocrine therapy is very successful in many cases, drug resistance develops; time to progression (TTP) varies (6-11 months) for first-line ET. The primary response to ET
for many HR-positive MBC is not okay, with rates between 20% and 40% depending on the type of treatment and prior exposure. In a significant number of pre- and postmenopausal cases which respond in a good way to initial treatment, further ET may be beneficial.

Protocols for a second- and third-line ET in HR-positive/HER2-negative BCs rely on patient and tumor findings. All women who have experienced ovarian ablation or inhibition and have not taken antiestrogen treatment or have not taken it for one year can be subjected to therapy with AIs, a SERM (e.g., tamoxifen), or an SERD (e.g., fulvestrant). [3]

**Alternatives for endocrine treatment**

AIs anastrozole and letrozole used for relapsed disease after antiestrogen FLT have proved to be potent because of their better time to progression and overall survival in comparison to megestrol acetate, but these drugs are adequate for FLT. The capabilities of fulvestrant as a second-line treatment in cases with progression after ET displayed in a phase 2 trial. A reaction rate of 14.3%; 20.8% of the women accomplished illness stability for at least six months. However, it was discovered that fulvestrant (250 mg) had the nearly same effectiveness as anastrozole, with a median time to progression of 5.5 months compared to 4.1 months. [4] A phase 3, double-blind, randomized, placebo-controlled study demonstrated that elevated doses of fulvestrant restricted tumor advance with the efficiency of exemestane. However, the CONFIRM phase 3 study showed that using fulvestrant 500 mg in comparison to using fulvestrant 250 mg notably increased progression-free survival (6.5 compared to 5.4 months; \(P = 0.006\)) and overall survival (26.4 months compared to 22.3 months; \(P = 0.02\)). FDA authorization, of high-dose fulvestrant as a second-line therapy for postMPs with the HR-positive metastatic disease, was given way because of the data provided by CONFIRM. [3]

The ways in which resistance to ET developed on a molecular level may be evident before the use of therapy (i.e., primary resistance) or they could become apparent in the course of treatment (i.e., acquired resistance) through a reduction in ER expression or upregulation of “escape pathways”. [5] In women with BC resistant to ET, proof of mutations in the ER has been found. These are considered to cause constitutive activation of the ER and resistance to tamoxifen and AL Receptor tyrosine kinases, such as EGFR, HER2, and insulin-like growth factor 1 receptor (IGF-1R), ER control signaling; pathway downstream of these growth factor receptors, including PI3K/AKT/mTOR and MAPK pathways, could be associated with ER phosphorylation. If there is no endocrine activation, cross-talk between pathways can result in the activation of estrogen-responsive genes related to cell expansion, proliferation, and endurance. This cross-talk is considered to be connected to the appearance of resistance to endocrine treatments. One such example is that, common in breast cancer are mutations in the catalytic subunit domain of PI3K, which can multiply the enzymatic function of PI3K and boost oncogenic transformation. Activating the PI3K signaling involved in the development of resistance to hormones and PI3K suppression decreases ER phosphorylation. The PI3K/AKT/mTOR pathway may activate ER without estrogen, according to the above-stated considerations. [3] Good preclinical results have been achieved by different efforts to overcome resistance to ET by aiming at growth factor receptors.

The phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of the rapamycin (mTOR) pathway is a vital controller of many crucial physiological processes. It is also involved in the malignant alteration of human cancers and their future expansion, metabolism, proliferation, and metastasis. In the past trials have shown that the PI3K/AKT/mTOR pathway often activated in human tumors because of the somatic mutation and amplification of genes encoding crucial elements. Aberrant PI3K/AKT/mTOR signaling activation also confers resistance to frequently used treatments and is an adverse factor for prognosis the progression of a significant number of different tumors. [5]

The PI3K/AKT/mTOR is an essential pathway which downstream the receptors of growth factor tyrosine kinase. It is involved in the regulation of a vast number of biological processes as angiogenesis, proliferation, metabolism, survival, and differentiation. Evidence suggests that changes in the PI3K/AKT/mTOR axis have a crucial and diverse role in cancer pathogenesis and evolution. An evaluation of 3,281 tumors from 12 cancer types of the Cancer Genome Atlas Pan-Cancer effort has shown that parts of the PI3K/AKT/mTOR signaling pathway are one of the most frequently mutated genes in cancer, next to uterine corpus endometrioid, breast, colon, lung, head and neck, and ovarian carcinomas. [5]

PI3K is an intracellular lipid kinase which is an essential part of the function of the cells and cancer evolution. Three classes of PI3Ks, which have varieties in structure and function, exist. The type with the greatest association with diseases in humans is Class Ia; it comprised of a regulatory (p85) and catalytic (p110) subunit. [6] Three genes, PIK3R1, PIK3R2, and PIK3R3, encode the various isoforms of the p85 regulatory subunit, catalytic subunits p110α, p110β, and p110δ produced by PIK3CA, PIK3CB, and PIK3CD.

Activation of the PI3K can be instigated by Somatic mutations frequently found on PIK3CA and PIK3CB in cancer cells. This process can also be induced by extracellular stimuli, through receptor tyrosine kinases (RTK) or by stimulation from activated Ras, a component with a crucial part in the evolution of CRC. Once p85 is bound to phosphatidylserine residues found in the intracellular part of RTK, the suppressive effect of p85 to p110 is shown, and PI3K is activated. PI3K phosphorylates phosphatidylinositol 4,5 biphosphate (PIP2) to phosphatidylinositol 3,4,5 triphosphate (PIP3) and later the accumulation of PIP3 at the membrane leads to the recruitment of AKT and its following phosphorylation by PDK1 and mTORC2. [6,7,8]

Some of the paths by which activated AKT promotes cell growth, and survival are:

- suppression of proapoptotic proteins of the bcl-2 family,
- increased degradation of p53 (a pro-apoptotic molecule), through elevated cytoplasmic availability of mdm2
- increased transcription of antiapoptotic genes by affecting the transcription factor NF-KB. [6]

Activated AKT also has the capability to stimulating the mammalian target of the rapamycin (mTOR) group of proteins, which leads to the enhanced synthesis of proteins by activating mTORC1 and mTORC2. Phosphatase and tensin homolog protein (PTEN), a tumor suppressor molecule, which dephosphorylates PIP3 to PIP2, is a vital down-regulator of the PI3K pathway. Truncated proteins are in most cases the reason for the low activity of PTEN. These proteins are a product of somatic mutations – or epigenetic silencing frequently by promoter hypermethylation. To activate PI3K, cells with low PTEN rely on PIK3CB and its product p110δ this gives the basis for developing a targeted treatment against PIK3CB in cases with PTEN.
downregulated breast cancers.[6]

New molecules which disrupt signaling from parts of the PI3K are at the moment evaluated in a significant number of clinical trials. Four types of molecules are currently under development: (I) PI3K inhibitors, (II) dual inhibitors of PI3K and mTOR, (III) AKT inhibitors and (IV) mTOR inhibitors. In this article, we show drugs that use the PI3K axis, with a focal point on women with ER+/HER2-negative BC and comprehending possible toxicities related to drugs.[6]

Suppressors of PI3K can be grouped into isoform specific and pan-inhibitors of class Ia PI3Ks in cancer. Cytostatic effects with arrest after the G1 period in vitro and good anti-cancer results in vivo are primarily shown by these compounds. BKM120 (buparlisib) is a pan-Class I PI3K inhibitor.[6]

Conversion of PI2P to PI3P can be promoted by activating PI3K by receptor tyrosine kinases. PTEN dephosphorylates PI3P, resulting in negative regulation of PI3K signaling.

The Role of PI3K/AKT/mTOR in BC

Genetic alterations, such as somatic mutations and gains and losses of genes can influence the PI3K/AKT/mTOR pathway in various robust and hematological tumors. The PI3K pathway can be triggered by direct upstream signs and can be intrinsically activated by a gain of functional mutations or amplifications in PIK3CA (p110 subunit), mutations in PIK3R (p85 subunit), and mutations or amplifications in one of the AKT isoforms or loss of PTEN. The process of losing PTEN through inactivating mutations, because of copy number loss or homozygous deletions, corresponds to chemotherapy resistance and lowered survival of human patients.[5]

Related to lymph node metastases and overexpression of ER, PR, and HER2 in primary breast cancer are PIK3CA mutations. A minor response to trastuzumab and lapatinib associated with PIK3CA mutant cancers but not PIK3CA wild-type cancers with fulvestrant had good tolerance and displayed antitumor properties (7 cases had a partial reaction whereas 7 had a period of stable disease of more than six months). [3]

Alpelisib (BYL719), a drug taken orally has revealed in vitro anti-cancer activity, selectively aiming at the isoform of class I PI3K. In a phase 1 trial of 34 cases with ER-positive ABC who have a registered progression on the standard treatment protocol, alpelisib combined with fulvestrant showed a partial reaction rate of 9%, a stable disease rate of 29%, a median progression free survival rate of 9%, a stable disease rate of 29%, a median progression free survival rate of 176 days, and an excellent safety profile. Patients with PIK3CA mutant cancers but not PIK3CA wild-type cancers were the only ones who showed a partial response. Initial clinical data suggests that combining alpelisib and an AI(letrozole or exemestane) has good tolerance and clinical potency. An ongoing phase 2 study will evaluate alpelisib combined with tamoxifen and goserelin in preMPS with HR-positive ABC(NCT012058381). Pictilisib (GDC-0941) and taselisib (GDC-0032) are dominant suppressors of class I PI3Ks that are making their way through early-phase assessment at the moment. The phase 2 FERGI study assessed pictilisib combined with fulvestrant in postMP with ER-positive ABC, HER2-negative BC who, after AI therapy, developed disease progression. The inclusion of pictilisib to fulvestrant did not result in better progression free survival (6.6 vs. 5.1 months). There is no matter whether tumors were PI3K mutant or wild-type, outcomes were nearly the same. [3]
An exploratory study displayed that a group of women with both ER-positive and progesterone receptor–positive disease (about 70%) had notably increased progression-free survival with the combination therapy: 7.4 compared to 3.7 months (P = .002). Another clinical assessment of pictilisib in combination with paclitaxel, with the inclusion of or without the addition bevacizumab or trastuzumab, found that the combination had good tolerance and initial antitumor activity. Initial data from a phase 1b dose escalation trial of taselisib in combination with letrozole in 28 patients with HR-positive ABC shows that combining these drugs has a good tolerance, with an overall reaction rate of 38% in cases with PIK3CA mutant tumors.[20] At the moment, some trials are carried out to evaluate the results of combining taselisib with ET (NCT01296555) and with docetaxel or paclitaxel (NCT01862081).[3,21,22]

At the moment, various active, not recruiting, and recruiting clinical studies are carried out in all the biological subsets of BC, such as combining with buparlisib with ET, antiHER2 molecules, poly (ADP-ribose) polymerase (PARP) suppressors, and chemotherapy. Two large phase III trials (BELLE-2 and BELLE-3) (NCT01610284, NCT01633060) are evaluating the combination of buparlisib and fulvestrant in postMPS with hormone receptor-positive/HER2-negative BC after unsuccessful treatment with AI alone or AI in combination with mTOR inhibitor. A different clinical trial which is underway is BELLE-4, a placebo-controlled phase II study of buparlisib combined with paclitaxel prescribed as FLT of HER2-negative metastatic BC (NCT01572727). Buparlisib is also the subject of a phase II trial of paclitaxel combined with trastuzumab in HER2- overexpressing BC (NCT01816594).[5,8,24]

The use of isoform-specific PIs is just one of the approaches to attain notable pathway suppression clinically with favorable adverse effect outline. Every isoform has a is involved in a specific way in normal physiological processes and disease. PI3K catalytic subunit p110-alfa is for the most part accountable for mediating growth factor signaling from receptor tyrosine kinases and is a commonly genetic driver (PIK3CA mutations) in a significant number of cancers. However, also, p110-alfa is inessential for PI3K pathway activation in tumors without PTEN. In such cases, the cells rely significantly on p110-beta to trigger the pathway. Preclinical trials reveal that p110-beta-selective suppressors had a remarkably better potency in cell lines with PTEN null than in those with PTEN intact, although, some PTEN-intact cell lines showed sensitivity and some cell lines lacking PTEN displayed resistance. [5]
Dual mTOR/PI3K inhibitors

A scientist has explored to shed light on strategies to overcome the limitations by concomitantly targeting two molecules in the PI3K/AKT/mTOR pathway, PI3K, and mTOR, whereas the resistance mTOR inhibitors cloud arise via feedback PI3K activation. The finding of new suppressors titled dual PI3K-mTOR inhibitors such as NVP-BEZ235, XL765, BGT226, PI-103, PF-04691502, PKI-587, and GDC-0980 has been encouraged by this knowledge. In comparison to other classes of PI3K pathway suppressors, dual PI3KmTOR inhibitors have the advantage of suppressing all PI3K catalytic isoforms, mTORC1, and mTORC2. These suppressors could successfully turn off this route as a whole and reveal the best efficacy in feedback suppression frequently seen with mTORC1 inhibitors. Whether dual PI3K-mTOR inhibitors will have enough tolerance at doses that suppress all p110 isoforms and mTOR is still not entirely satisfied.[5, 16, 23]

The possible clinical significance of the dual PI3K/mTOR inhibitors showed by their remarkable suppression of cell expansion and the induction of apoptosis or autophagy in different types of tumor cells. These suppressors have displayed potent activity in xenograft models of BC, pancreatic cancer, melanoma, multiple myeloma, and RCC.[5]

Reasons for PI3K/AKT/mTOR pathway suppression after the development of resistance to ET

Studies assessing PI3K/AKT/mTOR pathway inhibitors administered after resistance to ET developed aimed at the first-generation mTOR inhibitors everolimus and temsirolimus. Two famous trials in the advanced setting, BOLERO-2, and TAMRAD, have assessed everolimus in women who have experienced progression after AI therapy. [1,2]

BOLERO-2 examined everolimus combined with exemestane the following progression on an AI. BOLERO-2 was a randomized Phase III trial of 724 postMPs with HR+/HER2-negative (HER2) metastatic BC, who have experienced progression after therapy with non-steroidal AIs (letrozole or anastrozole; progression during or within 12 months of treatment). Combining everolimus and exemestane notably extended PFS (7.8 versus 3.2 months) and reaction rate in comparison to exemestane only, according to the acquired data. A group evaluation of BOLERO-2 cases on FLT for ABC (137 patients; 21%) showed that combining everolimus and exemestane increased two times progression-free survival in comparison to exemestane only (11.5 versus 4.1 months), these results support this therapy as an FLT for ABC after recurrence during or after adjuvant ET.[1, 9, 22]

TAMRAD evaluated everolimus combined with tamoxifen after a progression of the disease on an AI. This was a randomized Phase II trial in postMPs with HR+/HER2 aromatase inhibitor-resistant metastatic BC in a small-scale group of cases (111 patients). Adding everolimus to tamoxifen notably raised clinical advantage rate (61% versus 42%), lengthened the time to progression (8.6 compared to 4.5 months), and increased overall survival (70% compared to 46%) compared with tamoxifen alone, according to the results. In women with secondary endocrine resistance, combining these drugs can be particularly beneficial because such patients experience relapse after a period of more than six months after stopping adjuvant AI therapy or are reacting to AIs for six months or more in the metastatic setting.[1,4,17]

The data provided indicates that PI3K/AKT/mTOR pathway inhibitors have the capability to increase the efficiency of already significantly in used ETs in next lines of treatment after endocrine resistance has occurred. FDA authorized everolimus combined with exemestane for treating of HR+ BC after progression on letrozole or anastrozole in July 2012, by the data provided by the BOLERO-2 trial. [1] The reason the combination of ET with PI3K/AKT/mTOR pathway inhibition before endocrine resistance has occurred. There is data indicating that combining ER and PI3K/AKT/mTOR pathway suppression could have a significant effect in new lines of treatment before endocrine resistance has occurred.[1]

The clinical use of PI3K/AKT/mTOR pathway inhibition combined with ET is also the subject of assessment as a first-line treatment. Studies indicate that entire suppression of mTOR signaling could be an efficient way to counter the development of endocrine resistance. RAD2222 a randomized Phase II study evaluated letrozole combined with everolimus in 270 postMPs with treatment-naïve ER+ early-stage BC [18]. Combining neoadjuvant letrozole and everolimus for 4 months resulted in a growth in response rate in comparison to letrozole only (68% versus 59%) and an antiproliferative reaction (as measured by a reduction in Ki67 levels) was seen in a notably higher proportion of women in the combination group than in the letrozole only group (57% versus 30%). [1]

However, HORIZON, a big, randomized Phase III study of letrozole in combination with or without temsirolimus for FLT of ABC, was stopped in 2006 because of low efficiency. It believed that the cause of this was the insufficient suppression of mTOR signaling because of an intermittent dosing protocol for temsirolimus compared to continuous daily dosing protocol for everolimus. Although combining temsirolimus and letrozole is connected with an increased occurrence of toxicity than letrozole only, the frequency of adverse events in the combination arm of the HORIZON trial was decreased in comparison to those stated in trials with continuous daily everolimus, giving a further basis for incomplete pathway activation.[1,11]

Given the right preclinical results, a bigger number of trials are required to explain the advantage of the first-line combination of ET and PI3K/AKT/ mTOR pathway suppression altogether. UNIRAD and SWOG/NSABP S1207 Phase III randomized trials in cases with early ER+, HER2 BC at high risk of relapse are assessing the role of everolimus combined with ET in the adjuvant setting, and could supply the basis for using these drugs in cases in which secondary endocrine resistance has not yet occurred. BOLERO-4, single-arm, Phase II clinical trial in postMPs with ER+ metastatic BC (NCT01698918), which has not still concluded, will investigate the effect on progression-free survival of everolimus therapy as an FLT and further. Women who have not yet treated for metastatic disease will receive everolimus in combination with letrozole as FLT, succeeded by everolimus in combination with exemestane when disease advance established. This trial will provide the necessary information to decide which lines of treatment are most suitable for the inclusion of PI3K/AKT/mTOR pathway suppression to ET, and also evaluate the prospective advantage of PI3K/AKT/mTOR inhibition in all lines of therapy, as a centerpiece of ET.[1]

PI3K/AKT/mTOR pathway modifications used for predicting clinical outcome and reaction to therapy. PI3K modifications are still not confirmed as markers for patient outcome. Genetic changes in the PI3K/AKT/mTOR pathway are inconsistently
corresponding with patient outcome after ET; many trials recognize that PIK3CA mutations can be used in the prediction of better results, poorer outcomes, or having no association with the outcome at all. PIK3CA mutations have proven to be a variable for prognosis within the HER2+ group in the CLEOPATRA study. This study found that PIK3 mutations corresponded to poorer outcomes separately from the therapy administered. It is unclear whether there is a connection between the reaction to ET and modifications in other parts of the PI3K/AKT/mTOR pathway. There have been better results in the evaluation of the PI3K/AKT/mTOR pathway changes as used to predict the response to channel suppression. Using in vivo xenograft models and breast cancer cell lines, a correlation has been found between the mutation in PIK3CA and sensitivity to pictilisib. In cells with PIK3CA mutation and PTEN loss, apoptosis induced by buparlisib, everolimus, or the dual PI3K/mTOR inhibitor BGT226, was at its highest level. [1]

Next-generation sequencing revealed that cases who had minimal genetic variations in the PI3K/ AKT/mTOR or FGFR pathways, or CCND1, profited the most from everolimus therapy, in the BOLERO-2 trial. This showed the practicality of large-scale genomic sequencing for patients with these types of studies, and the importance of PI3K/AKT/mTOR pathway modifications used to predict sensitivity to everolimus. In the future, it will be valuable to distinguish women who will profit the most from PI3K/AKT/mTOR pathway suppression this will allow optimization of the therapeutic index with lower toxicity for the women receiving therapy. Because of this, PI3K/AKT/mTOR pathway modifications are examined as possible biomarkers for reaction to the treatment administered in some upcoming and already under way clinical evaluations of pathway inhibitors, BELLE-2 and FERG1 trials take into account exploratory biomarker assessments. These biomarker trials will distinguish modifications in molecular tumor profiles in search for possible relation to the clinical reaction and disease evolution, resistance to the previous ET, and response to study treatment. Furthermore, large-scale genomic datasets such as the Cancer Cell Line Encyclopedia and the Genomics of Drug Sensitivity in Cancer Project are compilations of sequencing information, incorporating gene expression, and pharmacologic profiles for a high number of anticancer molecules, from a great variety of human cancer cell lines, which can at a certain point in the future be helpful in the recognition of biomarkers in the prediction of drug sensitivity and aiding in patient selection for upcoming clinical trials. [1]

The BOLERO-2 study demonstrated that, despite the real effects of everolimus in combination with exemestane, two crucial regulatory feedback loops may enable cell-cycle progression independent of mTOR activity and in the end may restrict the effectiveness of the current generation of mTOR inhibitors. A negative feedback loop in the PI3K/AKT/mTOR pathway has made possible for mTOR-activated kinase S6K1 to phosphorylate and destabilize the IRS1 and IRS2 proteins in insulin-like growth factor (IGF) responsive cells, resulting in increased activation of IGF-1-dependent AKT activity. A positive feedback loop with the mTORC2 complex could be activated by growth factors and activated phosphorylated AKT also exists in the PI3K/AKT/mTOR pathway. A variety of other molecules that aim at PI3K/AKT/mTOR pathway upstream of mTOR assessed at the moment in clinical trials of HR+ advanced breast cancer, such as pan-PI3K or isoform-specific PI3K inhibitors, dual PI3K/mTOR inhibitors, and AKT inhibitors. A phase 3, randomized trial of the pan-PI3K inhibitor BKM120 (buparlisib) combined with fulvestrant in HR+ advanced BC that progressed on or after previous AI treatment (Buparlisib Breast Cancer Clinical Evaluation [BELLE]-2) is recruiting patients at the moment; the group of patients in BELLE-2 is nearly the same as that in BOLERO-2 and will be prospectively stratified based on PI3K pathway activation status. Based on the likely increased use of everolimus in combination with exemestane as second-line therapy for HR+ ABC, a second phase 3 trial will assess BKM120 combined with fulvestrant in cases with disease evolution on or after mTOR inhibitor therapy (BELLE-3). [17]

Many factors come into consideration in the process of proposing a PI clinical study for a given case like toxicity, suppression level, practicality in the combination with other treatments, the molecular structure of the tumor, and others. In early clinical development are a significant number of PIs which results in limited clinical knowledge about these agents to compare efficacy and toxicity between the various types of PI3K pathway suppressors. PIs affiliated with a high number of drug-related toxicities, such as fatigue, nausea, and diarrhea. Hyperglycemia is a common on-target effect that is predictably given the crucial role of the PI3K/AKT/mTOR pathway in insulin signaling. This fact led to the exclusion of patients with diabetes from clinical studies with such molecules. Infrequent cardiac effects associated with pictilisib. Mood changes are a commonly documented adverse event with buparlisib, which has resulted in the non-inclusion of patients with a previous or current mood disorder from the clinical trials of buparlisib. This toxic effect may arise because of the capability of buparlisib to pass through the barrier between the blood and the brain; that is why it considered that buparlisib could be beneficial for treating brain metastases. Isoform-specific PIs could be better than pan-Pis regarding safety and efficacy gave the roles of each isoform in both fundamental physiologic and pathologic cellular processes. [1]

Establishing the correct treatment order, especially in cases with drug resistance, can be hard because of the various accessible options for treating metastatic breast cancer. Another difficulty could arise from the desire to practice precision medicine, which means to adjust the treatment to the specific needs of every patient. There have been a significant number of breakthroughs in the management of cases with HR-positive BC. Despite being more efficient as FLT, therapy with AI anastrozole or letrozole has also shown great efficiency after antiestrogen FLT in cases with relapsed BC.

According to the CONFIRM study, a better alternative for treating postMPS with the HR-positive metastatic BC could be the ER antagonist fulvestrant at an elevated dose of 500 mg. Because all cases who receive ET will, in the end, become resistant, compounds that re-establish sensitivity is of great significance for the treatment of metastatic BC. Sadly, the use of therapeutic molecules that aim at growth factor receptors (i.e., the dual EGFR/HER2 tyrosine kinase inhibitor lapatinib, the EGFR inhibitor gefitinib, and the farnesyltransferase inhibitor tipifarnib) to overwhelm resistance to ET have not shown clinical advantages, despite preclinical proof of activity, however, the blockade of the PI3K/AKT/mTOR pathway has had success in overwhelming this, and the BELLE-2, BELLE-3 and BELLE-4 trials showed the efficiency of the PI3K inhibitor buparlisib combined with fulvestrant (BELLE-2 and BELLE-3 trials) and with paclitaxel (BELLE-4 trial) for treating postMPS with relapsed BC after first-line ET. In women with three consecutive endocrine

therapy failures, three following chemotherapy regimens could be a viable option; these women should begin on single FLT with chemotherapy due to its lesser toxicity than the combination treatment. Despite the advances in outcomes seen in previous clinical studies with therapies already in use, a high number of patients will in the end relapse. This shows that there is a great need for more therapeutic compounds which enable women to overwhelm resistance to hormone therapy. To shed light on how to conquer and understand the better clinical resistance to existing agents, there is a huge need for more translational studies. Different approaches are being investigated as FLTIs. Using elevated-dose fulvestrant as single-agent treatment has more efficiency than using anastrozole, but combining elevated-dose fulvestrant and anastrozole has revealed contradictory data. Small-scale studies have shown the efficiency of FLT with everolimus combined with letrozole or with exemestane. As second-line therapy, everolimus or palbociclib combined with other ETs, such as letrozole, tamoxifen, or fulvestrant, could be especially useful for patients who have been previously heavily treated. Despite the fact that further assessment is needed, buparlisib, alpelisib, pictilisib, and taselisib, which PIs, combined with fulvestrant or other ETs have also revealed new proof of clinical potency in women with ABC. More under way phase 3 trials (e.g. BELLE 3 trial) of these compounds could help to explain better the part they play in the management of ABC. [3]

Due to the fast evolving available treatments for BC, the real problem is not only the small development of more therapies but also ensuring that doctors and patients keep up to date with the new alternatives for treating BC and choose treatment accordingly. That is why future investigation with a focal point on the molecular assessment of newly diagnosed and recurrent tumors is needed, as are host factors (e.g., pharmacogenomics, genomic mutational alterations, modulation of the immune system) to improve the efficiency of patient management.

**Authors’ Statements**

**Competing Interests**

Ivan Inkov has received a research grant from Novartis Pharmaceuticals.

**References**


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