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Targeting the PI3K/Akt/mTOR pathway in estrogen-receptor positive HER2 negative advanced breast cancer

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***Abstract*:** Recently many therapeutic classes have emerged in advanced hormone receptor-positive breast cancer, which is the leading cause of cancer death in women. In absence of visceral crisis, treatment relies on endocrine therapy combined with cyclin dependent kinase 4 and 6 inhibitor. Many mechanisms lead to resistance to endocrine therapy, including the activation of intracellular signaling pathways critical for cell survival. Approximately 70% of breast tumors harbor an alteration in the phosphoinositide 3 kinase (PI3K)/Akt pathway, leading to its hyper activation. This pathway is involved in the regulation of growth, proliferation and cell survival as well as in angiogenesis and is consequently a major target in the oncogenesis. An aberrant *PIK3CA* mutation is a common phenomenon in breast cancer and found in approximately 40% of patients with advanced hormone receptor-positive breast cancer. For the moment, the only positive trials showing a progression free survival benefit in this population are BOLERO-2 (2012), SOLAR-1 (2019), which tested everolimus, a mammalian target of rapamycin inhibitor, and alpelisib, a PI3K inhibitor, and led to their marketing authorization. However, many other inhibitors of this pathway are promising; nevertheless their development is actually limited by toxicity, mainly cutaneous (rash), digestive (diarrhea) and endocrine (diabetes).

Keywords: endocrine resistance, HR positive advanced breast cancer, PIK3 mutations, PI3K/Akt/mTOR inhibitor, PI3K/Akt/mTOR pathway

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Introduction

Breast cancer is the most common cancer in women (2.4 million cases) and the leading cause of cancer deaths (520,000 deaths, of which more than 40,000 per year in the US).[1,2] In the metastatic setting, the median overall survival (OS) is around 3 years, regardless of hormonal status or HER2 and the 5-year survival rate is only 25.9%.[3] Metastatic disease remains incurable despite the latest therapeutic advances and recent data suggesting an improvement in OS.[4] The challenge of treatment is to prolong survival and control the symptoms of the disease while respecting the quality of life.

Around 70% of breast cancers are luminal estrogen receptor-positive, HER2-negative (ER+ HER2−) subtype.[5] For this subtype, endocrine therapy (ET) is the core treatment unless there is a visceral crisis or a proof of endocrine resistance. For postmenopausal women, ET includes Selective Estrogen Receptor Modulator (tamoxifen or toremifene), Selective Estrogen Receptor Down-regulator (fulvestrant), non-steroidal aromatase inhibitor (anastrozole and letrozole) and steroidal aromatase inhibitor (exemestane). For pre-menopausal patients, Ovarian Function Suppression (gonadotropin-releasing hormone agonists such as goserelin) or ovarian ablation (with radiation or surgery)[6] is combined with ET of postmenopausal women.

Endocrine resistance and tumor progression eventually occurs after exposure to first line ET,

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with a median time of exposure of 1 year.[7] In addition, the efficacy of ET drops with each subsequent line: clinical benefit rate of fulvestrant or aromatase inhibitor (AI) is 70% *versus* 30% as frontline and second line or above respectively. Endocrine resistance encompasses different situations: primary resistance (progression of disease within the first 6 months of first-line) or secondary resistance (progression disease after 6 months of exposure).

Several mechanisms involved in endocrine resistance have been discovered.[8] Dysregulation of activating signal transduction pathways such as that of the Epidermal Growth Factor Receptor or the Insulin Growth Factor Receptor. Dysregulation of the phosphoinositide 3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway is particularly involved in the case of secondary endocrine resistance like dysregulation of the cell cycle involving the cyclin D/cyclin dependent kinase 4 and 6 (CDK4/6)/Rb pathway.[9]

This led to the strategy of combination therapies associating ET and targeted therapies like PI3K pathway inhibitors or CDK4/6 inhibitors. Palbociclib, a CDK4/6 inhibitor (CDK4/6i), is approved in combination with letrozole or fulvestrant for the treatment of postmenopausal women with advanced HR+ HER2– breast cancer. Pre/peri-menopausal patients received also a luteinizing hormone releasing hormone agonist.

First in class, the PALOMA-1/TRIO-18 trial showed that the addition of palbociclib to letrozole significantly prolonged progression-free survival (PFS) as compared with letrozole alone as first line therapy (median PFS 20.2 months *versus* 10.2 months [hazard ratio, 0.49; 95% confidence interval (CI): 0.32–0.75; $p = 0.0004$][10] with no OS benefit in the whole population but a trend towards it in the endocrine sensitive one.[11] Second, MONARCH 2 and MONALEESA 3 demonstrated similar PFS benefit with abemaciclib and ribociclib with a benefit in OS as the first or second line of treatment of postmenopausal patients. In addition, an OS benefit has been shown in premenopausal women with frontline ribociclib in the MONALEESA 7 trial: median OS 40.9 months in the placebo arm *versus* not reached in the ribociclib arm (hazard ratio, 0.71; 95% CI: 0.53–0.84).[12] Based on these studies, international guidelines now recommend a combination of endocrine therapy and a CDK4/6i (palbociclib, ribociclib or abemaciclib) for HR+, HER 2– advanced breast cancer with no sign of visceral crisis from the first line or later if the patient had already had ET for their metastatic disease.[12]

However, resistance to CDK4/6 inhibitors is unavoidable in most patients, prompting the exploration of resistance pathways to these treatments. Among the various possible causes of resistance to CDK4/6is, pathological activation of the PI3K/Akt/mTOR pathway has been demonstrated.[13–15]

The PI3K/Akt/mTOR pathway in estrogen-receptor positive breast cancer

PI3K/Akt/mTOR is one of the major intracellular signaling pathways. The PI3K signaling regulates diverse cellular functions, including cell proliferation, survival, translational regulation of protein synthesis, glucose metabolism, cell migration and angiogenesis.[16] Resistance to different therapeutic classes, including chemotherapy, ET and anti-HER2 therapies, are linked to the constitutive activation of the PI3K pathway.[17] The PI3K/Akt/PTEN/mTOR pathway is activated in approximately >70% of HR+ breast cancers through AKT1 mutation, loss of PTEN or PI3K activator mutation.[18] Discovered in the 1980s, PI3Ks are a family of lipid kinases that phosphorylate the 3′- hydroxyl group of phosphatidylinositols at the level of the plasma membrane.[19] PI3K can be divided into three classes of enzyme isoforms (I–III) according to the coding genes, to their substrate preference and structure.[20] Class I PI3Ks is composed of class IA and class IB. Class IA PI3Ks are heterodimers consisting of two subunits: a catalytic subunit (p110α, p110β, p110δ) is stabilized by dimerization with a regulatory subunit (p85α, p55α, p50α, p85β, p55γ), forming complexes that are activated downstream of receptor tyrosine kinases. The different isoforms of PI3K have various tissue distributions that inform the expected activity and toxicity profile. The α and β isoforms are ubiquitously expressed and regulate a wide range of physiological processes. The γ and δ isoforms, on the other hand, are preferentially expressed in leukocytes and control different aspects of immune responses (in particular in autoimmune toxicities), explaining the interest of their combination with immune checkpoint inhibitors. The central role in this pathway is played by class IA PI3Ks, which phosphorylates phosphatidylinositol-4,5-bisphosphate (PI-4,5-P2) to generate phosphatidylinositol-3 (PIP3),4,5. This subtype is

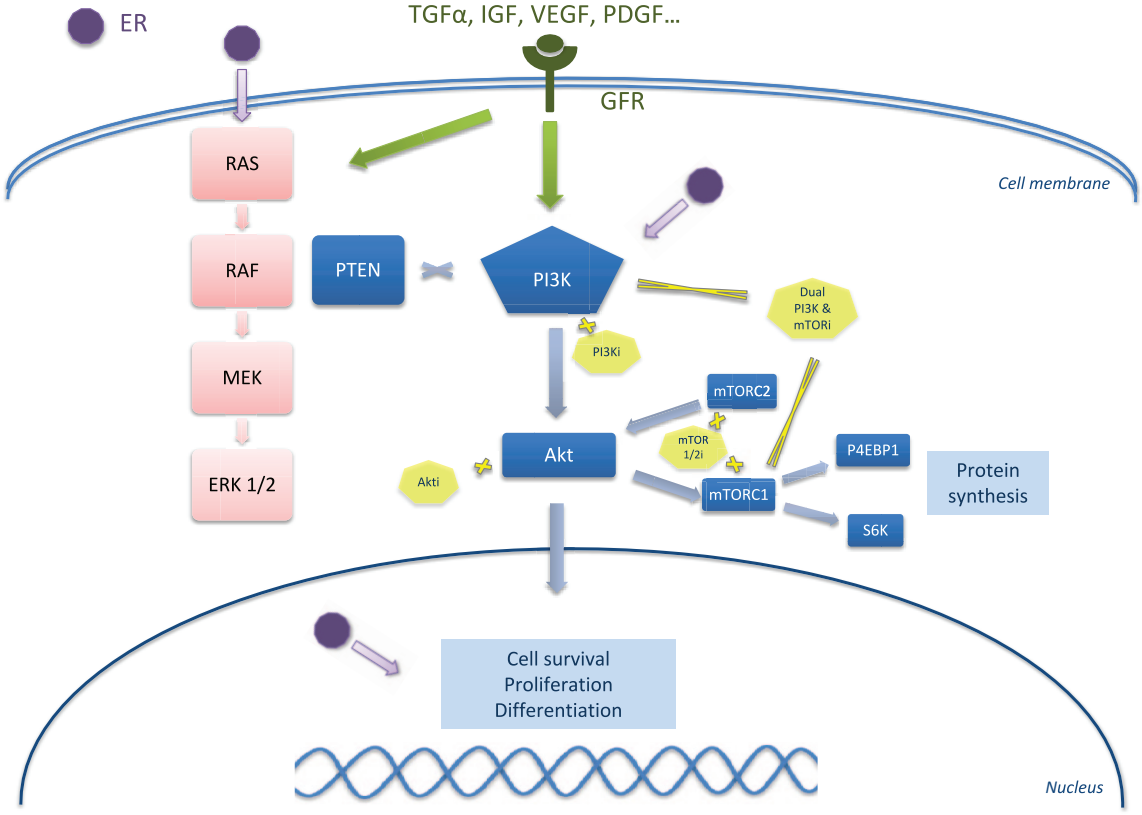

Figure 1. Targeting the PI3K/Akt/mTOR pathway.
Akti, capivasertib, ipatasertib; Dual PI3K & mTORi, dactolisib, samotolisib; mTOR1/2i, everolimus, temsirolimus, ridafarolimus; PI3Ki: alpelisib, buparlisib, pictilisib, tazelisib, pilarlisib.

the type most clearly involved in the development of human cancer.[21] PIP3, which subsequently leads to the phosphorylation of AKT, a serine/threonine kinase with three isoforms (AKT1, AKT2 and AKT3). AKT is a downstream target of the PI3K pathway and plays a major role in the survival, growth, proliferation and metabolism of glucose in cells.[22] Activated AKT induces the activation of the mTOR pathway. mTOR is an atypical serine/threonine protein kinase composed by two distinct protein complexes named mTOR complex 1 (mTORC1) and 2 (mTORC2).[23] mTORC1 is highly sensitive to rapamycin and promotes cell growth and cell cycle progression by inducing anabolic processes and inhibiting catabolic processes, respectively. mTORC2 responds to growth factors and regulates metabolism and cell survival, as well as the cytoskeleton. These two complexes mTORC1 and mTORC2 are downstream and upstream of Akt, respectively.[24] Activation of the PI3K/Akt/mTOR pathway, which promotes cell proliferation and induces inhibition of pro-apoptotic proteins, is an essential element in the control of cell growth and survival.[25]

The signal is turned off by PTEN (Phosphatase and TENsin homolog, deleted on chromosome 10), which is a tumor suppressor gene, by dephosphorylating PIP3 to PI-4,5-P2 inhibiting activation of AKT. The PI3K/Akt/mTOR and estrogen-receptor pathways crosstalk by direct or indirect interaction (Figure 1): signaling through the first activates estrogen independent ER transcriptional activity that promotes cell multiplication. Next to it, activation of the estrogen pathway triggers the synthesis of many components of the PI3K/Akt/mTOR pathway.[13,26]

Hyperactivation of the PI3K pathway can occur through several mechanisms: mutation of PI3K (catalytic domain, or helical), loss of PTEN function (deletion or loss of expression, epigenetics), AKT mutation or by the regulatory function of proteins TSC1/TSC2 (tuberous sclerosis complex). The most frequent mutations observed in *PIK3CA* are clustered in hotspots affecting the helical (exon 9) and kinase (exon 20) domains of the protein.[27] *PIK3CA* mutation frequency varied by subtype of breast cancer: 30–50% of advanced

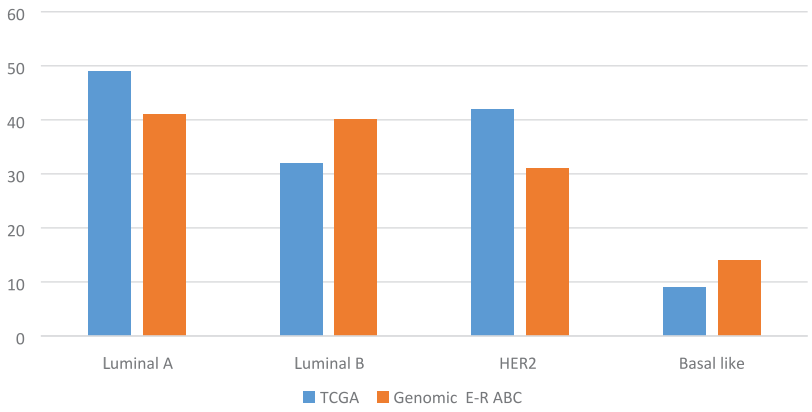

Figure 2. *PIK3CA* mutation frequency by molecular subtype of breast cancer.
Genomic E-R ABC, Genomic Landscape of Endocrine-Resistant Advanced Breast Cancers; TCGA: The Cancer Genome Atlas

ER+ HER2− breast cancers have an activating *PIK3CA* mutation; however, *PIK3CA* is mutated less frequently in ER-negative breast cancers, except for androgen receptor-positive, triple-negative breast cancers (Figure 2).[28,29] The clinical development of pan-Class I PI3K inhibitors including buparlisib (BKM120),[30] pilaralisib (XL147)[31] and pictilisib (GDC-0941)[32] has been limited by major toxicities and modest clinical efficacy. The clinical development of these agents has been stopped.[33] Isoform-specific inhibitors have allowed these treatments to be given at higher active doses with fewer side effects.[34] Thus far, the most successful PI3K inhibitor clinically is alpelisib, which selectively inhibits p110α at least 50 times more than other isoforms.[35]

Pivotal clinical trials targeting the PI3K/Akt/mTOR pathway in estrogen-receptor positive breast cancer

Targeting the PI3K/Akt/mTOR pathway involves mTOR inhibitors, PI3K inhibitors, AKT inhibitors or dual mTOR/PI3K inhibitors (Table 1).[36–52] Here we detail the phase I to III trials targeting each class with their clinical outcomes and toxicity profile.

mTOR inhibition. The HORIZON study was designed to study the benefit of the addition of temsirolimus, a selective mTORC1 inhibitor, to letrozole in postmenopausal women with HR-positive locally advanced or metastatic breast cancer with no prior exposure to AIs for unresectable or metastatic disease.[53] Patients were eligible if their disease did not relapse during the first year following the completion of adjuvant ET. PFS was comparable in both groups (hazard ratio, 0.90; 95% CI: 0.76–1.07; $p=0.25$) with no improvement in the temsirolimus group. The same results were observed for OS. In addition, PFS was similar in patients with or without prior adjuvant endocrine therapy (hazard ratio, 0.84; 95% CI: 0.66–1.08; hazard ratio, 0.87; 95% CI: 0.69–1.11, respectively). The authors report also a slight but significant benefit of the combination in patients younger than 65 years (median PFS, 9.0 *versus* 5.6 months; hazard ratio, 0.75; 95% CI: 0.60–0.93; $p=0.009$). This drug led to a significant increase in grade 3 and 4 adverse events with temsirolimus (37% *versus* 24%), including hyperglycemia, diarrhea, mucositis/stomatitis and hyperlipidemia.

The clinical benefit of everolimus, a rapamycin derivative that inhibits specifically mTORC1, was proven in the randomized phase III, placebo controlled BOLERO-2 trial.[54] A total of 724 patients with HR-positive locally advanced or metastatic breast cancer that relapsed or progressed while receiving previous therapy with a non-steroidal AI in the adjuvant setting or to treat advanced disease (or both) were included. Primary endpoint was PFS with a significant benefit for the everolimus arm: hazard ratio 0.43; 95% CI: 0.35–0.54; $p<0.001$. Median PFS survival was 10.6 *versus* 4.1 months, according to central assessment (hazard ratio 0.36; 95% CI: 0.27–0.47; $p<0.001$). OS was similar in both groups: 31.0 (everolimus group) *versus* 26.6 months (placebo group) (hazard ratio, 0.89; 95% CI: 0.73–1.10; $p=0.14$).[55]

PI3K inhibition. The hypothesis of the BELLE-3 trial was that resistance to mTOR inhibitors is

Table 1. Summary of phases I–II–III trials with PI3K_AKT inhibitors in HR positive advanced breast cancer.

Class	SMI	Study	NCT	Phase and trial design	Population number	Patient population	Treatment	PFS (months)	OS (months)	ORR	Toxicity (Grade 3 and Grade 4 AEs) in experimental arm
PI3K p110α isoform	**Alpelisib (BYL719)**	SOLAR-1[36]	NCT02437318	III randomized, double-blind placebo-controlled, multicenter	*N* = 572 Cohort *PIK3CA*-mut: *n* = 341 Cohort *PIK3CA*-WT *n* = 231	Postmenopausal ER+, HER2– ABC progressing after prior ET	Alpelisib (300 mg/d) or placebo + fulvestrant*	Alpelisib: 11 Control: 5.7 HaR = 0.65, $p < 0.0001$	N/A	Alpelisib+ fulvestrant: 26.6% Placebo+ fulvestrant: 12.8%	Hyperglycemia 36.6% Rash 9.9% Diarrhea 6.7%
		Mayer *et al.*[37]	NCT01791478	Ib open-label study	*N* = 26 Cohort *PIK3CA*-mut: *n* = 16 Cohort *PIK3CA*-WT *n* = 10	Postmenopausal ER+, HER2– ABC progressing on/ after prior ET	Alpelisib (300 mg/d) + letrozole (2,5 mg/d)	N/A	N/A	*PIK3CA*-mut. 25% *PIK3CA*-WT 10%	Diarrhea 10% Hyperglycemia 10% AST/ALT elevation 5%
		Juric *et al.*[38]	NCT01219699	Ib open-label study	*N* = 87 Cohort *PIK3CA*-mut: *n* = 49 Cohort *PIK3CA*-WT *n* = 32 UK status *n* = 6	Postmenopausal ER+, HER2– ABC progressing on/ after prior ET	Alpelisib (starting at 300 mg/d) + fulvestrant*	*PIK3CA*-mut., 9.1 *PIK3CA*-WT, 4.7	N/A	*PIK3CA*-mut. 29% *PIK3CA*-WT 0%	Hyperglycemia 22% Maculopapular rash 13% Rash 8%
		Rugo *et al.*[39]	NCT02437318	II open-label non-comparative study	*N* = 100 Fulvestrant cohort *n* = 64 Letrozole cohort *n* = 36	Men and women with *PIK3CA*-mut. ER+, HER2– ABC progressing on/ after CDKi + ET	Alpelisib (300 mg/d) + fulvestrant* or Alpelisib + letrozole (2.5 mg/d)	N/A	N/A	20% fulvestrant and 18% letrozole	Hyperglycemia 38.1% (fulvestrant) and 27.8% (letrozole) Rash 4.8% (fulvestrant) and 27.8% (letrozole)
		Sharma *et al.*[40]	NCT02379247	I/II	*N* = 43 Cohort *PIK3CA*-mut.: *n* = 19 Cohort *PIK3CA*-WT: *n* = 23	HER2– ABC, after one line of CT, ER+ or not	Alpelisib (250 mg, 300 mg, 350 mg/d) + nab-paclitaxel (100 mg/m^2 d 1, 8, 15 every 28 d)	*PIK3CA*-mut., 13 *PIK3CA*-WT, 7 HaR = 0.39, $p = 0.03$	N/A	57%	Neutropenia 31% Hyperglycemia 29% Anemia 12% Diarrhea 7%
		Juric *et al.*[41]	NCT01872260	Ib/II three-arm study	*N* = 98 Arm LEE+LET: *n* = 41 Arm BYL+LET: *n* = 21 Arm LEE+BYL+LET: *n* = 36	Postmenopausal women with ER+, HER2– ABC	Letrozole (2.5 mg/d) + escalating doses of LEE qd [(300–500 mg) 3-wks-on/1-wk-off)] or BYL (200–250 mg)	N/A	N/A	16/27 evaluable patients	Nausea 6% Hyperglycemia 17% Neutropenia 22% Fatigue 11%)
Pan-PI3K inhibitors	**Buparlisib (BKM120)**	BELLE-2[43]	NCT01610284	III randomized, double-blind, placebo-controlled, multicenter study	*N* = 1147 Buparlisib+ fulvestrant: *n* = 576 Placebo + fulvestrant: *n* = 571	HER2– ER+ ABC progressing on/ after prior ET and after up to one line of CT	Fulvestrant* ± buparlisib (100 mg/d)	Buparlisib: 6·9 Placebo: 5 HaR = 0·78, $p = 0·00021$	N/A	Buparlisib: 11.8% Placebo: 7.7%	Increased ALT 25% Increased AST 18% Hyperglycemia 15% Rash 8%)

(Continued)

Table 1. (Continued)

Class	SMI	Study	NCT	Phase and trial design	Population number	Patient population	Treatment	PFS (months)	OS (months)	ORR	Toxicity (Grade 3 and Grade 4 AEs) in experimental arm
		BELLE-3[42]	NCT01633060	III randomized, double-blind, placebo-controlled, multicenter study	*N* = 432 Buparlisib: *n* = 289 Placebo: *n* = 143	HER2– ER+ ABC progressing on/after prior ET and mTOR inhibitors	Fulvestrant (500 mg) ± buparlisib (100 mg/d)	Buparlisib: 3.9 Placebo: 1.8 HaR = 0·67, *p* = 0.003	N/A	Buparlisib: 8% Placebo: 2%	Increased ALT 22% Increased AST 18% Hyperglycemia 12% Hypertension 16% Fatigue 3%
		BELLE-4[44]	NCT01572727	II/III randomized, double-blind, placebo-controlled, multicenter study	*N* = 416 Buparlisib: *n* = 209 Placebo: *n* = 207	HER2– ABC, ER+ (73%) or not, no prior CT for ABC; prior ET allowed	Paclitaxel (80 mg/m^2 per wk) in 28-day ± buparlisib (100 mg/d)	Buparlisib + paclitaxel: 8.0 Placebo + paclitaxel: 9.2 HaR = 1·18	N/A	Buparlisib + paclitaxel: 22.6% Placebo + paclitaxel: 27.1%	Neutropenia 14.9% Hyperglycemia 8.9% Rash 7.9% Increased ALT 6.9% Fatigue 5.9% Diarrhea 5.4% Alopecia 5.0%
PI3K p110α isoform	**Taselisib (GDC-0032)**	SANDPIPER[45]	NCT02340221	III randomized, double-blind, placebo-controlled, multicenter study	*N* = 516 Taselisib: *n* = 340 Placebo: *n* = 176	Postmenopausal women with ER+, HER2– ABC progressing on/after prior ET	Fulvestrant* ± taselisib (4 mg/qd)	Taselisib: 7.4 Placebo: 5.4 HaR = 0·7, *p* = 0.0037	N/A	Taselisib: 28% Placebo: 11.9%	Diarrhea 12% Hyperglycemia 10% Colitis 3% Stomatitis 2%
		Dickler *et al.*[46]	NCT01296555	II open-label	*N* = 60 Cohort *PIK3CA*-mutation: *n* = 20 Cohort *PIK3CA*-WT: *n* = 27 UK status: *n* = 13	Postmenopausal women with ER+, HER2– ABC, progressing after ⩾1 ET line	Fulvestrant* + taselisib (6 mg/d)	*IK3CA*-mut., 7.6 *PIK3CA*-WT, 5.4 UK status, 5.3	*PIK3CA*-mut., 19.2 *PIK3CA*-WT, 27 UK status, N/A	*PIK3CA*-mut.: 38.5% *PIK3CA*-WT: 14.3% UK status: 20%	Colitis 13.3% Diarrhea 11.7% Hyperglycemia 6.7%
		Saura *et al.*[47]	NCT01296555	Ib dose escalation study	*N* = 28	ER+, ABC, postmenopausal women progressing after ⩾1 ET line	Letrozole (2.5 mg) + taselisib (6–9 mg/d)	N/A	N/A	*PIK3CA*-mut.: 38% *PIK3CA*-WT: 9%	Diarrhea 14% Hyperglycemia 7% Mucosal inflammation 7%
		PIPA[48]	NCT02389842	Ib/II three-arm study	*N* = 24	ER+, HER2– ABC, with *PIK3CA*-mut., progressing after ⩾1 ET line	Taselisib (2 mg/d) + fulvestrant* + palbociclib (125 mg/d on a 3/1 scheme)	7.9	N/A	33%	Neutropenia 57% Rash 11%

(Continued)

Table 1. (Continued)

Class	SMI	Study	NCT	Phase and trial design	Population number	Patient population	Treatment	PFS (months)	OS (months)	ORR	Toxicity (Grade 3 and Grade 4 AEs) in experimental arm
Pan- PI3K inhibitors	**Pictilisib (GDC-0941)**	PEGGY[49]	NCT01740336	II randomized, placebo-controlled	*N* = 183 Pictilisib: *n* = 91 Placebo: *n* = 92	ER+, HER2– ABC, first-/second-line CT	Paclitaxel (90 mg/m^2 weekly for 3 weeks in every 28 d) + 260 mg pictilisib or placebo (daily on days 1–5 every week)	Pictilisib: 8.2 Placebo: 7.8 HaR = 0·95, *p* = 0.83	N/A	Pictilisib: 22% Placebo: 19.6%	67% Neutropenia> peripheral neuropathy> anemia> diarrhea
		FERGI[50]	NCT01437566	II randomized, double-blind, placebo-controlled, multicenter study	Part 1: *n* = 168 Part 2: *n* = 61	HER2– ER+ ABC progressing after ET and only *PIK3CA*-mut. for Part 2	Fulvestrant* ± pictilisib (340 mg/d in Part 1 or 260 mg/d in Part 2)	Part 1: Pictilisib: 6.6 Placebo: 5.1 HaR = 0·74, *p* = 0.096 Part 2: Pictilisib: 5.4 Placebo: 10 HaR = 1·07, *p* = 0.84	N/A	Part 1: Pictilisib: 7.9% Placebo: 6.3% Part 2: Pictilisib: 7.3% Placebo: 5% HaR = 1·07, *p* = 0.84	Part 1/Part 2 Maculopapular rash 9% Diarrhea 8% increased ALT 5% Fatigue 8%
Pan-Akt inhibitors	**Capivasertib (AZD5363)**	FAKTION[51]	NCT01992952	II randomized, double-blind, placebo-controlled, multicenter study	*N* = 140 Capivasertib: *n* = 69 Placebo: *n* = 71	Postmenopausal ER+, HER2– ABC progressing on/after prior ET	Fulvestrant* ± capivasertib [(400 mg t/d) 4-d-on/3-d-off]	Capivasertib: 10.3 Placebo: 4.8 HaR = 0·58, *p* = 0·0018	Capivasertib: 26.0 Placebo: 20.0 HaR = 0·59, *p* = 0·071	Capivasertib: 29% Placebo: 8%	Hypertension 32% Diarrhea 14% Rash 20% Infection 6%)
		BEECH[52]	NCT01625286	Ib (Part A) open label; II (Part B) randomized, placebo-controlled, double-blind	*N* = 148 Part A: *n* = 38 Part B: *n* = 110	ER+ HER2– ABC, no prior CT, *PIK3CA*-mut. or not	Part A: paclitaxel 90 mg/m^2 (d 1, 8 and 15 of a 28-d cycle) + escalating doses of capivasertib Part B: paclitaxel ± capivasertib (400 mg b.i.d. 4 d on/3 d off)	Capivasertib: 10.9 Placebo: 8.4 HaR = 0·80, *p* = 0·308	N/A	Part A: 10.5% Part B: Placebo: 57% Capivasertib: 59%	Diarrhea 10% Hyperglycemia 10% AST/ALT elevation 5%

*Fulvestrant 500 mg by IM injection at cycle 1, days 1 and 15, and then on day 1 of each subsequent 28-day cycle.
ABC, advanced breast cancer; AI, aromatase inhibitor; CT, chemotherapy; d, day; ER+, estrogen receptor positive; ET, endocrine therapy; HER2–, HER2 negative; HaR, hazard ratio; LET, letrozole; N/A, not applicable; NCT, Clinical Trials.gov identifier; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; *PIK3CA*-mut., mutation in the *PIK3CA* gene; SMI, small molecule inhibitor; wk, week; WT, wild-type.

potentially due to a feedback activation of the PI3K/Akt/mTOR pathway. Buparlisib is a pan-Class I PI3K inhibitor. The trial included patients who progressed on or after ET combined with mTOR inhibitors. Median PFS was low in both groups but significantly longer in the buparlisib plus fulvestrant *versus* placebo plus fulvestrant group: 3.9 *versus* 1.8 months (hazard ratio 0.67, 95% CI: 0.53–0.84, one-sided $p = 0.00030$), respectively.[42] However, it was decided by the trial sponsor that development of the safety profile of buparlisib was inadequate with further investigations and the sponsor stopped its development, in particular due to psychiatric side effects of depression and anxiety. Subgroup analyses showed a greater benefit in the population with *PIK3CA* mutation in the ctDNA: hazard ratio 0.46 (95% CI: 0.29–0.73); $p = 0.00031$ *versus* hazard ratio 0.73 (95% CI: 0.53–1.00); $p = 0.026$. These results support future trials testing α-selective PI3K inhibitors in combination with ET in patients with *PIK3CA* mutations.

In the SOLAR-1 trial all patients had received AI during adjuvant therapy or advanced disease and were considered endocrine-resistant as they relapsed during ET or within the 12 months following its completion. Patients were included in two cohorts based on *PIK3CA* mutation and were randomized to receive fulvestrant plus alpelisib or placebo. Primary end-point was the PFS in the *PIK3CA*-mutated patient group. In total, 341 of the 572 patients (59%) with HR-positive HER2 negative advanced breast cancer included in the SOLAR-1 trial had confirmed *PIK3CA* mutation.[36] After a median follow-up of 20 months, median PFS was almost doubled in the alpelisib plus fulvestrant group: 11.0 *versus* 5.7 months (hazard ratio 0.65; 95% CI: 0.50–0.85; $p < 0.001$). Overall response (26.6% *versus* 12.8%) and clinical response (61.5% *versus* 45.3%) rates were also greater in the combination group. In the cohort of patients without *PIK3CA*-mutated cancer at the final efficacy analysis the median PFS was 7.4 months in the alpelisib–fulvestrant group and 5.6 months in the placebo–fulvestrant group (hazard ratio 0.85; 95% CI: 0.58–1.25), confirming a lack of benefit in patients without a tumor harboring *PIK3CA* mutation.

AKT inhibition. Similarly, the addition of the investigational AKT 1-3 isoform inhibitor capivasertib to fulvestrant significantly extended PFS for endocrine resistant HR-positive HER2-negative advanced breast cancer patients in the FAKTION phase II study: PFS was 10.3 months for capivasertib compared with 4.8 months for placebo (hazard ratio, 0.57; 95% CI: 0.39–0.84; one-sided $p = 0.0017$; two-sided 0.0035).[51] However, this benefit of capivasertib over placebo was not consistent with the BEECH trial.[52] In this last, patients were also considered resistant to ET and received capivasertib or placebo, in combination with weekly paclitaxel and no ET. Capivasertib was well tolerated. Median PFS in the overall population was 10.9 months with capivasertib *versus* 8.4 months with placebo (hazard ratio 0.80; 80% CI 0.60–1.06; $p = 0.308$). The result was not better in the subgroup of *PIK3CA* mutated patients.

Ipatasertib, another AKT inhibitor, was tested with paclitaxel *versus* placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer in the LOTUS trial: a multicenter, randomized, double-blind, placebo-controlled, phase II trial.[56] PFS was longer in patients who received ipatasertib than in those who received placebo: 6.2 *versus* 4.9 months (hazard ratio 0.60, 95% CI: 0.37–0.98; $p = 0.037$), supporting the combination of targeted therapy with chemotherapy. A similar combination will be tested in the IPATunity130 trial: a pivotal randomized phase III trial evaluating ipatasertib + paclitaxel for PIK3CA/AKT1/PTEN-altered advanced breast cancer with both triple-negative and hormone receptor-positive HER2-negative (HR+/HER2–).[57]

Profile of tolerance and management of side effects

These new treatments have frequent but reversible side effects including hyperglycemia, rash, stomatitis, diarrhea, nausea and fatigue. In the different studies, targeting selectively the PI3Kα isoform decreased the side effects compared with pan-Class I inhibitors. Therefore, in the SOLAR-1 trial evaluating alpelisib (BYL719), an α-specific PI3K inhibitor combined with fulvestrant, the most common grade 3 or 4 adverse events of special interest were hyperglycemia (high blood sugar), rash and diarrhea.[58] This toxic profile is similar to other PI3K inhibitors.

Hyperglycemia is a known effect of PI3K pathway inhibitors and is considered an on-target effect. It results partially from the induction of a fasting metabolic state characterized by reduced glucose utilization in favor of fatty acids for energy production.

In addition, glucose transport capacity, glycolysis and glycogen synthesis are decreased.[59] High blood sugar occurs early around the 15th day in 63.7% of the patients with alpelisib–fulvestrant, leading to an early stopping of the drug in 6.3% of patients. Grade 3 [fasting plasma glucose (FPG) >250–500 mg/dL] and Grade 4 (FPG >500 mg/dL) hyperglycemia were reported in 33% and 3.9% of patients, respectively. Metformin is usually given to manage hyperglycemia in people taking alpelisib–fulvestrant. Hyperosmolar and ketoacidotic states are rare but can occur in patients with pre-existing diabetes.[60]

Skin toxicity (including (including rash, follicular rash, generalized rash and maculopapular rash) also occurs mostly after 2 weeks of exposure to alpelisib, in around 53.9% of patients (Grade 3/4 in 20.1%). This toxicity was mostly treated with local and/or systemic corticosteroids. Use of anti-rash drugs (antihistamines) prior to the onset of the skin toxicity was associated with a decreased frequency of skin damage (26.7% *versus* 53.9%). Regarding diarrhea, it occurs later, with a median onset time of 139 days (about 5 months). It was reported in 57.7% (Grade 3/4 in 6.7%). The most commonly used treatments were antipropulsives. Gastrointestinal adverse effects such as diarrhea are regular with metformin. However, in people taking alpelisib with fulvestrant, prescribing metformin did not increase diarrhea. In the case of adverse events requiring a reduction in dose, the dose of alpelisib should be reduced first to 250 mg once daily and then to 200 mg. If dose reduction below 200 mg/day is required, alpelisib should be discontinued.[61] The most common side effects that led to stopping taking alpelisib and fulvestrant were hyperglycemia (6.3% of patients) and rash (3.2% of patients).[36]

Conclusion

To date, the frontline reference treatment for advanced or metastatic HR+ HER2 negative breast cancer is a combination of ET with a CDK4/6i. At progression, targeting the PI3K/Akt/mTOR pathway seems with alpelisib and ET has proven a significant PFS benefit. Management of toxicity, including diarrhea and hyperglycemia, is critical as it may lead to the early cessation of the drug in the case of insufficient management. This will probably limit explorations combining hormone therapy, CDK4/6i and PI3K/Akt/mTOR inhibitor.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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