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DRUG EVALUATION

Alpelisib for the treatment of *PIK3CA*-mutated, hormone receptor-positive, HER2-negative metastatic breast cancer

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ABSTRACT

Introduction: Two-thirds of advanced breast cancers are hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative (HR+/HER2-). Gene mutations in *PIK3CA*, encoding the PI3K catalytic subunit alpha of phosphatidyl-inositol 3-kinase (PI3K), are a frequent event in this population and are implicated in hormone therapy resistance. Alpelisib is a PI3K-alpha inhibitor and is the first PI3K inhibitor approved, in association with fulvestrant, by the FDA and EMA, based on improved progression-free survival (PFS) versus fulvestrant alone in a randomized phase III trial in HR +/HER2-, *PIK3CA*-mutated tumors following progression on/after HT.

Areas covered: The scientific rationale, preclinical development, pharmacokinetics, and clinical efficacy/safety of alpelisib–fulvestrant are summarized. The role of alpelisib in the clinical setting is discussed, referencing current therapeutic options and clinical challenges associated with alpelisib's safety profile.

Expert opinion: Alpelisib is an option for patients with HR+/HER2-, *PIK3CA*-mutated tumors whose disease progressed during/after aromatase inhibitor treatment. The PFS benefit appears clinically significant over fulvestrant alone, with a 7.9 months, non-significant, improvement in overall survival. Its safety profile requires strict patient selection, mainly based on baseline glycemic status, and close monitoring.

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Metastatic breast cancer; hormonotherapy; phosphatidylinositol 3-kinase; mutation

1. Introduction

Worldwide, breast cancer (BC) remains the leading cause of cancer death and the most common malignancy in women [1]. While frequently diagnosed at a limited stage, once metastatic the disease is considered non-curable, and therapeutic strategies focus on quality of life issues. Two-thirds of advanced BC cases are hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative (HR+/HER2-) [2]. Endocrine therapy, with or without the use of a cyclin-dependent kinase 4 and 6 inhibitor (CDKi), is currently the standard first-line treatment for patients with HR +/HER2- advanced BC [3,4].

However, the effectiveness of treatment is limited by the *de novo* or acquired resistance that occurs in nearly all metastatic BC (mBC) patients [5]. Multiple mechanisms have been suggested to be responsible for hormone therapy (HT) resistance, including activation of various intracellular pathways, mainly the phosphatidyl-inositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) and CDK 4/6/retinoblastoma protein (RB) pathways. The occurrence of mutations in the PI3K catalytic subunit alpha gene (*PIK3CA*), which generally occur in one of the two hotspot regions (exon 9: E545K or E542K, and exon 20: H1047R), is one of the most frequent events in HR+/HER2- mBC (occurring in 30%–40% of cases) [6,7] and has been implicated in HT resistance, resistance to chemotherapy, and shorter survival [3,6,8–11]. Because of the frequency of *PIK3CA* mutations and their role in the oncologic process, PI3K inhibition has been a highly investigated strategy in this subgroup of patients.

First-generation PI3K inhibitors such as buparlisib, pictilisib, and taselisib, which are not specific for particular PI3K isoforms or mutations, have been developed during the last decade [12]. Although they achieved some clinical efficacy, their safety profile – attributable to off-target inhibitions – has limited their development and prompted the evaluation of more specific inhibitors, such as alpelisib.

Here we will discuss the pharmacological profile of alpelisib, review evidence for its pharmacology and clinical use, and examine safety issues and preliminary clinical results outside of the HR+/HER2- metastatic BC setting.

2. Chemistry

Alpelisib is an orally bioavailable small molecule inhibitor of the alpha isoform of PI3K, and thereby inhibits the activation of the PI3K signaling pathway (Box1). Its chemical name is (2S)–N1-{4–Methyl-5–[2–(1,1,1–trifluoro–2–methylpropan–2–yl)pyridin–4–yl]–1,3–thiazol–2–yl}pyrrolidine–1,2 – dicarboxamide, with the molecular formula C19H22F3N5O2S. The molecular weight of

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Article Highlights

- Alpelisib (BYL719) is the first oral PI3K inhibitor to selectively target the class I p110 α-isoform, targeting the mutated and non-mutated forms, with increased activity in cell lines harboring gene alterations in *PIK3CA*.
- Alpelisib plus fulvestrant showed superior progression-free survival over placebo plus fulvestrant in a phase III trial of patients affected by *PIK3CA*-mutated cancer; however, median Overall Survival was not significantly different.
- Data in the post-CDK-inhibitors population are consistent with the pivotal study data; however the phase II nature of the study precludes a formal comparison with the pivotal, randomized study data.
- Safety profile is associated with significant and frequent hyperglycemia, digestive and dermatological toxicities; hyperglycemia being at the same time the most frequent and the more severe toxicity associated with alpelisib- specific p110α inhibition.
- Baseline glycemic status has been identified as a pre-therapeutic factor associated with a risk of developing a hyperglycemic event during alpelisib treatment.
- Alpelisib is an valid option for patients affected by a HR+/HER2-, *PIK3CA*-mutated, tumor who have progressed during or after hormonal therapy; without significantly improving overall survival. Its safety profile means strict selection of patients, mainly based on the baseline glycemic status, and close monitoring are required.

This box summarizes key points contained in the article.

alpelisib is 441.47 g/mol. Alpelisib is classified as a Biopharmaceutics Classification System (BCS) Class II compound, according to the criteria in the Food and Drug Administration (FDA) Guidance for Industry (Waiver of *in vivo* bioavailability and bioequivalence studies, FDA 2017b).

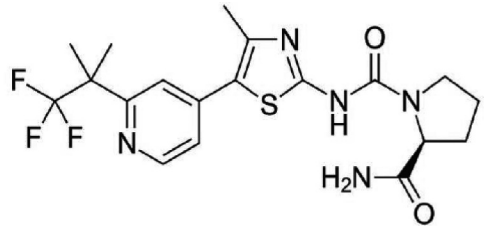
3. Preclinical development and rationale

The PI3K/AKT/mTOR axis regulates critical physiological functions and cellular processes, including cell proliferation, growth, survival, motility, and metabolism. The PI3K/AKT/mTOR pathway is frequently deregulated in BC and involved in tumor growth and secondary endocrine resistance [12]. PI3K inhibition both decreases cellular proliferation and increases cellular death [13]. Small molecule inhibitors of the PI3K pathway include PI3K/mTOR inhibitors, pan-PI3K inhibitors, and isoform-selective PI3K inhibitors like alpelisib. Alpelisib (BYL719; Novartis Pharmaceuticals, Basel, Switzerland) is the first oral PI3K inhibitor to selectively target the class I p110 α-isoform (IC50 = 4.6 nM), and can target the mutated and non-mutated forms (Figure 1). *In vitro*, alpelisib inhibits the proliferation of various cancer cell lines and has increased activity in cell lines harboring gene alterations in *PIK3CA* [14]. *In vivo*, alpelisib shows dose- and time-dependent inhibition of the PI3K/AKT pathway in relevant tumor xenograft models (p110α-mechanistic model and p110α-mutant xenograft models) [14]. Alpeslib has been tested in combination with various drugs (letrozole, exemestane, fulvestrant, CDK4/6 inhibitors, anti-HER2 therapies, mTOR inhibitor) in preclinical settings. Alpelisib–fulvestrant was the only combination that showed a significant synergistic effect *in vitro* and *in vivo* in estrogen receptor (ER)-positive BC xenograft models of acquired resistance to CDK4/6 inhibitors or everolimus [15].

4. Clinical pharmacokinetics

4.1. Absorption: Oral bioavailability of alpelisib is around 68.7% for 300 mg and 50–60% for a 400 mg single dose in healthy subjects, with negligible first-pass metabolism. Alpelisib is quickly absorbed, with a median T_{max} of 2–4 hours (time to reach maximale concentration, Cmax), and plasma concentrations generally decline in a monoexponential manner. In adults who received 300 mg of alpelisib, the non-compartmental geometric mean steady-state for C_{max} was 2900 ng/mL (geometric mean coefficient of variation [CV%], 24.7%) and for $AUC_{0\text{-}24hr}$ was 30700 ng*h/mL (CV%, 31.3%). C_{max} and AUC of alpelisib increased in a dose proportional manner, with a steady-state concentration reached by day 3 [16–18]. The impact of food was characterized; the maximal

Box 1. Drug summary.

Drug name	Alpelisib
Phase	III
Indication reviewed	HR+/HER2- metastatic breast cancer
Pharmacology	PI3K inhibitor
Route of administration	Oral
Chemical structure	
Pivotal trial	SOLAR-1 [28]

HER: Human epidermal growth factor receptor 2; HR: hormone receptor

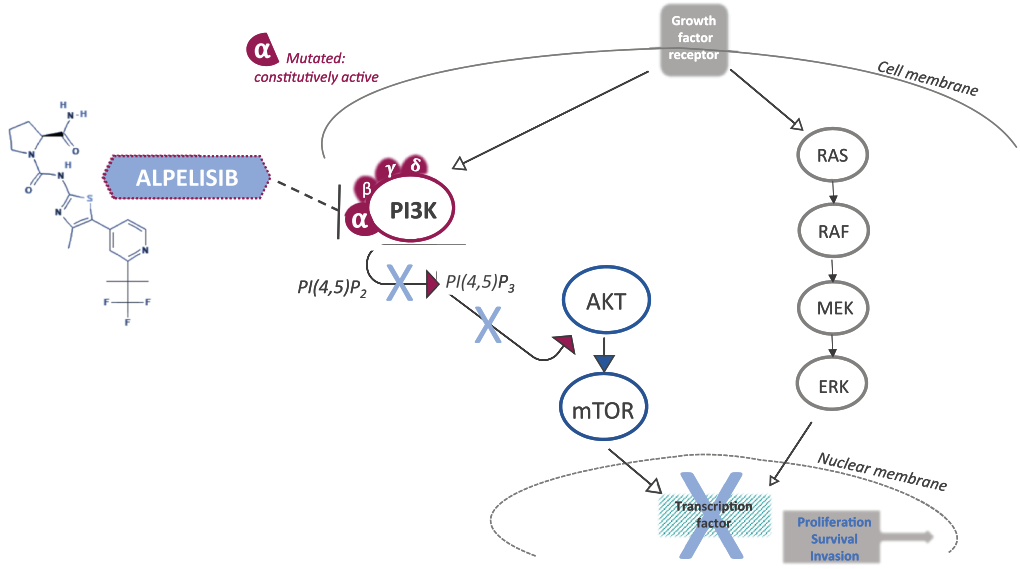


Figure 1. Schematic representation of the PI3K/AKT/mTOR axis and alpelisib pharmacological activity.

absorption effect during a fasted state (high-fat, high-calorie, and low-fat, low-calorie) with increased AUC and C_{max} >70% and >80%, respectively, indicates that alpelisib must be administered after or with food. As do most kinase inhibitors, alpelisib has a pH-dependant solubility profile (greater absorption at a pH between 1 and 6.8). Co-administration of an acid-reducing agent (H2 receptor antagonists, proton-pump inhibitors, and antacids) leads to decreased bioavailability and overall exposure (reduction in AUC of 21%) [18].

4.2. Distribution: The apparent volume of distribution (with intersubject variability expressed as CV%) ranges from 114 to 123 L (41–47% CV) [19]. Plasma protein binding of alpelisib is estimated to be around 89.2%, without significant binding to blood cells. Alpelisib and its major metabolite (BZG791) are distributed rapidly throughout the body. However, these two compounds are not able to cross the blood–brain barrier [18].

4.3. Metabolism and excretion: Alpelisib is a substrate of P-glycoproteins (P-gp) and breast cancer resistance proteins (BCRP) in the intestine and liver. After a single 400 mg oral dose, alpelisib is mainly metabolized by hydrolysis (40% extrahepatic metabolism) and to a lesser extent (around 12%) by liver oxidative metabolism (CYP3A4/5, with negligible UGT1A9 participation). BZG79, also named Alpelisib M4, is the major circulating metabolite in plasma, with a low contribution of pharmacological activity in humans, confirmed by *in vitro* data. Figure 2 illustrates the metabolism and excretion pathways of alpelisib. Thirty eightpercent of the drug is eliminated in an unchanged form via BCRP- and P-gp-mediated mechanisms. Geometric mean apparent total clearance of the drug from

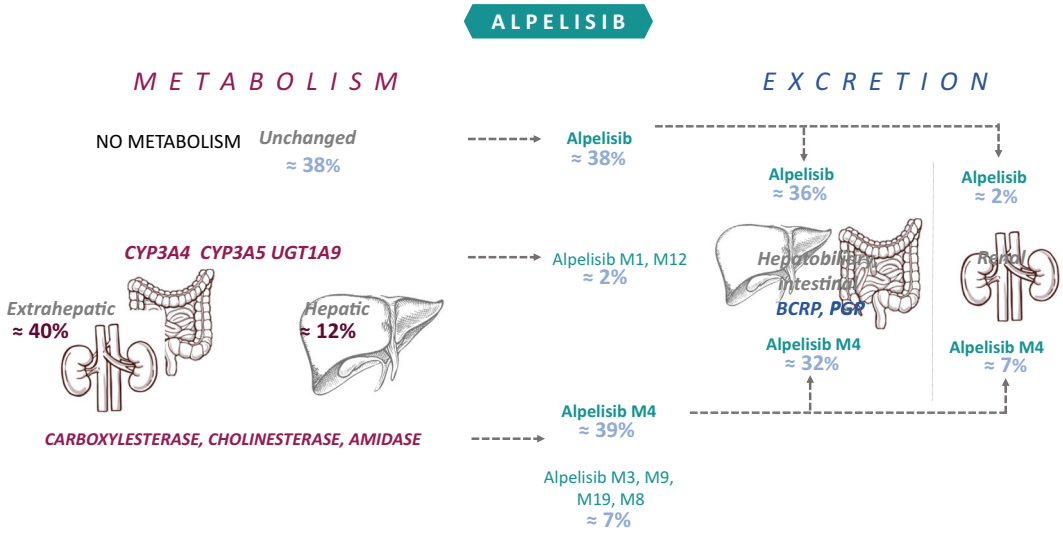


Figure 2. Schematic description of alpelisib elimination pathways.

plasma after oral administration (CL/F) appears to be independent of dose and ranges from 9.39 to 13.6 L/h across dose levels ranging from 30 mg to 450 mg (phase I pooled data). After administration of a single oral dose of 400 mg radiolabeled [14 C] BYL719 in healthy male subjects, most radioactivity was excreted via feces (79.8%), while urinary excretion accounted for 13.1% of the total dose. The terminal half-life is estimated to be is estimated to be ~8–9 hours [16].

5. Drug–drug interaction

No clinical drug–drug interaction studies of alpelisib have been reported in healthy volunteers. Drug metabolism and PK studies have evaluated alpelisib and its metabolite BZG791 as causative agents of interactions [16,18].

5.1. Effect of alpelisib on metabolic enzymes and transporters

Interactions with metabolic enzymes (liver and intestine studies):

In vitro studies suggest that alpelisib weakly and reversibly inhibits the CYP450 enzymes CYP2C8, CYP2C9, and CYP2C19 [18]. The clinical significance is unknown but cannot be excluded in the case of CYP2C9. Alpelisib seemed to be a time-dependent inhibitor and/or inducer of CYP3A4/5. *In vitro* studies suggest that alpelisib mediates a weak inhibition of sulfotransferase SULT (SULT1A1, 1E1, and 2A1) without meaningful clinical impact [18].

Interactions with transporter proteins (P-gp and BCRP in liver and intestine studies and organic anion and cation transporters (OATP and OCT) in liver only):

In vitro studies suggest that alpelisib mediates a weak and reversible inhibition of OATP1B1, OATP1B3, and OCT1; the clinical significance is unknown. At a therapeutic dose, alpelisib is not expected to inhibit efflux transporters (P-gp and BCRP) [18].

5.2. Interactions of alpelisib with strong CYP inducers/inhibitors

Strong inducers of CYP3A4 could reduce the effectiveness of alpelisib. However, physiologically based PK (PBPK) modeling suggests that the PK of alpelisib will not be significantly altered when the drug is given in combination with CYP3A4 inhibitors. In the absence of clinical drug-drug interaction data, it seems logical to avoid co-administration of alpelisib with strong CYP3A4 inducers. Hence, in the absence of clinical data, co-administration of CYP3A4 and BCRP inhibitors is not recommended.

5.3. Everolimus or fulvestrant and alpelisib

No clinically relevant drug–drug interactions between alpelisib and everolimus or fulvestrant have been identified in a clinical setting [20]. Consequently no dose adjustments are required when alpelisib and fulvestrant or everolimus are administered in combination [21].

5.4. Specific populations

Hepatic impairment: Overall, moderately and severely impaired hepatic function had limited impact on the PK of alpelisib and therefore no dose adjustment is required [18].

Renal impairment: Based on population PK analysis with a creatinine clearance (CLcr) of 30 to <90 mL/min (based on the Cockcroft–Gault formula), no dose adjustment is necessary in patients with mild to moderate renal impairment. The effect of severe renal impairment (CLcr <30 mL/min) on the PK of alpelisib is unknown [18].

Alpelisib in a Japanese population: Non-compartmental analysis revealed no significant differences between a Japanese population and a white population [22].

6. Pharmacokinetic/pharmacodynamic evaluation (exposure-efficacy)

PK/PD model simulations, in the dose range of 100–400 mg once daily, confirmed the concentration–effect relationship [19]. Exposure-efficacy analyses conducted based on data from the SOLAR-1 phase III trial revealed that a higher median exposure or dose intensity of alpelisib, in combination with fulvestrant, led to a greater treatment benefit in participants with *PIK3CA* mutations, supporting the use of the 300-mg dose [23].

7. Clinical efficacy and safety

Clinical studies evaluating alpelisib in breast cancer patients are summarized in Table 1. The first-in-human phase Ia study evaluating alpelisib monotherapy included 134 patients with *PIK3CA*-altered advanced solid tumors, including 36 BCs [24]. The maximum tolerated doses were 400 mg once daily and 150 mg twice daily. Dose-limiting toxicities were hyperglycemia (n = 6), nausea (n = 2), and hyperglycemia and hypophosphatemia (n = 1). The most frequent adverse events (AEs) of all grades were hyperglycemia (51.5%), nausea (50.0%), skin toxicities (42.5%), and diarrhea (40.3%). The frequency of AEs tended to increase with the duration of treatment. Fifty-one (38.1%) patients required a dose reduction and 63 (47.0%) a dose interruption due to AEs. The objective response rate (ORR) was 6% among a population of 115 evaluable patients (partial response in one case of BC). Disease control rate was 60.9% and clinical benefit rate (response or stability for more than 24 weeks) was 17.4% in patients with ER+/HER2- BC. Median PFS was 5.5 months.

A phase Ib study evaluated the alpelisib–letrozole combination in 26 patients with ER+/HER2- mBC (whether *PIK3CA*-mutated or not) [25]. The maximum tolerated dose was 300 mg daily. The most frequent AEs were gastrointestinal disorders (73%), hyperglycemia (62%), fatigue (54%), and rash (42%). Seven of 16 patients with a *PIK3CA*-mutated tumor had a clinical benefit (lack of progression) longer than 6 months and six had a clinical benefit longer than 12 months.

Another phase Ib study evaluated the alpelisib–fulvestrant combination in 87 patients with metastatic ER+/HER2- BC,

Table 1. Clinical trials evaluating alpelisib.

Reference	Study phase	Population	Efficacy in HR+/HER2- *PIK3CA*-mutated breast cancer	Safety
[24]	Ia Monotherapy	*PIK3CA*-mutated advanced solid tumors, n = 134 Breast cancer cases, n = 36/134	DCR = 60.9% CBR = 17.4% PFS = 5.5 months	Hyperglycemia (52%) Nausea (50%) Skin toxicities (43%) Diarrhea (40%)
[25]	Ib Alpelisib + letrozole	ER+/HER2- metastatic breast cancer, n = 26 *PIK3CA*-mutated tumors, n = 16/26	DCR = 63% CBR = 44%	Gastrointestinal disorders (73%) Hyperglycemia (62%) Fatigue (54%) Rash (42%)
[20]	Ib Alpelisib + fulvestrant	ER+ metastatic breast cancer, postmenopausal, n = 87 HER2+, n = 3/87 *PIK3CA*-mutated tumors, n = 52/87	PFS = 9.1 months (95%CI, 6.6 to 14.6)	Diarrhea (60%) Nausea (53%) Hyperglycemia (51%)
[26]	Ib Alpelisib + tamoxifen + goserelin	HR+, HER2- metastatic breast cancer, premenopausal, n = 16 *PIK3CA*-mutated tumors, n = 5/16	PFS = 25.2 months (95%CI, 2.7 to 36.3) ORR = 50% CBR = 56%	Rash (43.8%) Decreased appetite (56.3%) Stomatitis (37.5%) Nausea (37.5%) Hyperglycemia (31.3%)
[28]	III Randomization to alpelisib plus fulvestrant or placebo plus fulvestrant	HR+/HER2- advanced breast cancer with previous endocrine therapy postmenopausal, n = 572 *PIK3CA*-mutated tumors, n = 341/572	PFS = 11.0 months (95%CI, 7.5 to 14.5) Overall response = 26.6% Clinical benefit = 61.5%	Hyperglycemia (63.7%) Diarrhea (57.7%) Nausea (44.7%) Decreased appetite (35.6%) Rash (35.6%), maculopapular rash (14.1%)
[27]	II Alpelisib + fulvestrant	ER+/HER2-/*PIK3CA*-mutated, previously treated with CDK4/6 inhibitor, previously treated with AI, n = 127	Patients alive without disease progression at 6 months = 50.4% (95% CI, 41.2 to 59.6) PFS = 7.3 months (95%CI, 5.6 to 8.3)	Diarrhea (60%) Hyperglycemia (58%), Nausea (46%) Fatigue (29%) Decreased appetite (28%) Rash (28%)

AI: Aromatase inhibitor; CBR: clinical benefit rate; DCR: disease control rate; PFS: progression-free survival

including 52 patients with *PIK3CA*-mutated tumors [20]. The most frequent all-grade AEs were diarrhea (60%), nausea (53%), and hyperglycemia (51%). The recommended phase II dose was 300 mg once daily. Median PFS was 9.1 months (95% CI, 6.6–14.6 months), with an ORR of 29% (95%CI, 17%–43%), in the patients with *PIK3CA*-mutated tumors and 4.7 months (95%CI, 1.9–5.6 months), without objective responses, in the wild-type group. In this study, 86 of the 87 patients had at least one AE. The most frequent AEs were diarrhea (59.8%), nausea (52.9%), hyperglycemia (50.6%), decreased appetite (44.8%), fatigue (41.4%), vomiting (34.5%), stomatitis (28.7%), dysgeusia or maculopapular rash (21.8% each), and cough (20.7%). Alpelisib-related grade 3 or 4 AEs were reported in more than 69% of patients (hyperglycemia [21.8%], maculopapular rash [12.6%], rash (8.0%), and increased aspartate aminotransferase (AST) [5.7%]).

A study evaluated the alpelisib-tamoxifen-goserelin association in 16 HR+/HER2- MBC premenopausal Asian patients, including 5 patients with *PIK3CA*-mutated tumors [26]. The recommended phase II dose was 350 mg once daily, with a classical safety profile. Median PFS was 25.2 months (95% CI, 2.7 to 36.3), with an overall response rate of 50% and a clinical benefit rate of 56%.

The BYLieve study is a phase II study which evaluated the alpelisib–fulvestrant or alpelisib–letrozole combinations in patients with HR+/HER2-, *PIK3CA*-mutated advanced BC who progressed after prior therapy that included a CDKi. This recent study, initiated after the release of the SOLAR-1 data (see below), aimed to evaluate the safety profile and (indirectly) efficacy in a more diverse population of patients than that included in SOLAR-1 (see below). The results for the cohort of 127 patient pretreated with CDKi and aromatase inhibitors were presented during the American Society of Clinical Oncology (ASCO) 2020 Annual Meeting [27]. Patients received alpelisib and fulvestrant following progression during/after treatment with an aromatase inhibitor–CDKi combination. Median follow-up was 11.7 months. The proportion of patients without disease progression at 6 months was 50.4% (95% CI, 41.2–59.6), with a median PFS of 7.3 months (95%CI, 5.6–8.3). The AE profile was consistent with previous reports; AEs included diarrhea (60%), hyperglycemia (58%), nausea (46%), fatigue (29%), decreased appetite (28%), and rash (28%). Twenty-three patients (18.1%) stopped alpelisib because of AEs.

The pivotal SOLAR-1 study was a phase III, double-blind, randomized, multicentric study that compared alpelisib (300 mg once daily) plus fulvestrant with placebo plus fulvestrant [28]. It included 572 patients, including 341 patients with *PIK3CA*-mutated cancer. The study included men or postmenopausal women with HR+/HER2- mBC who had already been treated with an aromatase inhibitor. Patients who had received chemotherapy, fulvestrant, or any PI3K, AKT, or mTOR inhibitor, were excluded. Less than 7% of the population had been previously treated with a CDKi.

Median follow-up was 20.0 months (10.7–33.3). In the *PIK3CA*-mutated cohort, median PFS was 11.0 months (95% CI, 7.5 to 14.5) in the alpelisib–fulvestrant group and 5.7 months (95% CI, 3.7 to 7.4) in the placebo–fulvestrant group (HR = 0.65; 95%CI, 0.50 to 0.85; $p < 0.001$). Overall response was 26.6% in the alpelisib–fulvestrant arm and

12.8% in the placebo–fulvestrant arm. Regarding OS, median OS (95% confidence interval [CI]) was 39.3 months (34.1–44.9) in the alpelisib-fulvestrant group and 31.4 months (26.8–41.3) in the placebo-fulvestrant group (hazard ratio [HR] = 0.86 [95% CI, 0.64–1.15; P = 0.15]) [29].

In the cohort without identified *PIK3CA*-mutated cancer, median PFS was 7.4 months (95%CI, 5.4 to 9.3) in the alpelisib–fulvestrant group compared to 5.6 months (95%CI, 3.9 to 9.1) in the placebo–fulvestrant group (HR = 0.85; 95%CI, 0.58 to 1.2). Therefore, there was no significant difference between placebo and alpelisib in this cohort.

Analysis of the safety data showed that 99.3% of patients in the alpelisib–fulvestrant group presented with at least one AE of any grade compared to 92% in the placebo–fulvestrant group.

The most frequently reported AEs in the alpelisib–fulvestrant group were consistent with those described during earlier phase studies, and included mainly hyperglycemia (63.7%), diarrhea (57.7%), nausea (44.7%), decreased appetite (35.6%), rash (35.6%), and maculopapular rash (14.1%). The most frequent grade 3–4 AEs affecting at least 5% of the patients were hyperglycemia (36.6%), rash (9.9%), maculopapular rash (8.8%), and diarrhea (6.7%). Serious AEs occurred in 99 patients (34.9%) receiving alpelisib–fulvestrant and 48 (16.7%) receiving placebo–fulvestrant. Alpelisib was stopped in 71 patients (25%) due to AEs and placebo was stopped in 12 patients (4.2%).

The toxicity profile of alpelisib appears to be associated with specific p110α inhibition, mainly represented by hyperglycemia, rash, and diarrhea. This safety profile has previously been described for bulparisib, a pan-PI3K inhibitor, with a clear correlation between side effects and pharmacological activity [30].

The time course of the most frequent side effects is clearly defined, with early risk of hyperglycemia (median time to onset of grade 3/4 hyperglycemia of 15 days) and rash (median time to onset of 13 days). Digestive toxicity appears to be a later event, with a median time to onset of 139 days for diarrhea. Guidelines have been published to help manage these toxicities [23]. These recommendations focus on identifying risk factors for the development of side effects, early identification of these events, and guidelines for early intervention (for example, metformin for hyperglycemia or topical steroid for rash) or dose adjustment if indicated. These recommendations were introduced by an amendment during the recruitment of patients to SOLAR-1; they led to a significant decrease in the rate of discontinuation due to side effects, and more specifically due to hyperglycemia.

Indeed, baseline glycemic status has been identified as a pre-therapeutic factor associated with a risk of developing a hyperglycemic event during alpelisib treatment. In SOLAR-1, baseline glycemic status was defined as normal (fasting plasma glucose [FPG] <5.6 mmol/L or 100 mg/dL and HbA1c, <5.7%, 40% of patients), prediabetic (FPG, 5.6 to <7.0 mmol/L or 100 mg/dL to <126 mg/dL and/or HbA1c, 5.7 to <6.5%, 56% of patients), or diabetic (FPG, ≥7.0 mmol/L or 136 mg/dL and/or HbA1c, ≥6.5%, 4% of patients). Seventy-four percent of the prediabetic patients treated with alpelisib experienced hyperglycemia during the study (grade 3, 43.4%; grade 4, 5.0%) compared with 52% of patients with normal baseline glycemic status (grade 3, 16.8%; grade 4, 1.8%). While no difference in PFS was reported between these two groups, particular attention must be paid to the safety profile and the high risk of serious hyperglycemia in the prediabetic and diabetic groups. Metformin appears to be a safe and effective medication for low-grade hyperglycemia. However, some patients needed transient insulin use. All patients who developed hyperglycemia returned to grade 0 or 1 hyperglycemia after alpelisib was discontinued.

Analysis of cutaneous side effects showed that prophylactic anti-rash use of anti-histaminic drugs was associated with a lower incidence of rash: 38.3% of patients receiving prophylactic anti-histaminic drugs developed a rash compared to 58.0% of patients who did not receive premedication. These results need to be considered with caution, as this strategy was implemented locally during the study and was not implemented as a generalized modification of supportive care.

8. Regulatory status

On 24 May 2019, alpelisib was approved by the United States FDA in combination with fulvestrant for the treatment of postmenopausal women, and men, with HR-positive, HER2-negative, *PIK3CA*-mutated, advanced or metastatic BC as detected by an FDA-approved test following progression on or after an endocrine-based regimen. The European Medicines Agency (EMA) approved alpelisib on 27 July 2020, in combination with fulvestrant for the treatment of postmenopausal women, and men, with HR-positive, HER2-negative, locally advanced or metastatic BC with a *PIK3CA* mutation after disease progression following endocrine therapy as monotherapy. In Europe, alpelisib is also available for CLOVES syndrome under a temporary use authorization.

9. Clinical results outside of HR+/HER2- metastatic breast cancer

Preclinical data raise the scientific interest in combining alpelisib with various anticancer agents, and the PI3K pathway is also implicated in resistance to anti-HER2 therapies and in the prognosis of triple-negative BC, but clinical data remains scarce outside of the HR+/HER2- mBC setting.

The phase II randomized study NEO-ORB evaluated the combination of letrozole–alpelisib in the neoadjuvant setting in early HR+/HER2- BC [31]. A total of 257 patients received letrozole plus placebo or alpelisib 300 mg daily for 24 weeks. The ORR was 43% in the alpelisib group versus 45% in the placebo group for patients with *PIK3CA*-mutated tumors (n = 164) and 63% versus 61% for patients with non-mutated tumors. Therefore, the addition of alpelisib did not appear to increase the response rate. The safety profile was concordant with that reported in SOLAR-1. Additional investigations are needed to understand if this lack of efficacy was linked to differential impacts of the PI3K pathway during disease progression or if the primary endpoint (objective response) of the study was the most relevant.

In a HER2+ mBC population, a phase I study evaluated alpelisib in combination with trastuzumab emtansine after disease progression during or after treatment with trastuzumab and taxanes, without considering the *PIK3CA* mutation status of patients [32]. Among the 14 patients evaluable, the ORR was 43%. No specific additional safety profile was reported. Considering the impact that the presence of *PIK3CA* activating mutations has on alpelisib activity, future studies will need to incorporate this parameter into their design.

Lastly, a phase Ib trial evaluated the possibility of combining alpelisib and paclitaxel in patients with advanced solid tumors. The study was stopped early, before the dose-expansion phase, due to toxicity [33].

10. Conclusion

Alpelisib is an option for patients with HR+/HER2-, *PIK3CA*-mutated tumors whose disease progressed during/after aromatase inhibitor treatment. In patients with HR+/HER2-, *PIK3CA*-mutated mBC progressing after first-line endocrine therapy, alpelisib in combination with fulvestrant prolongs PFS compared with fulvestrant alone, with a non-significant 7.9 months increase in median OS. Considering the lack of significant OS increase and the safety profile of this drug, special attention must be given to patient selection in order to reduce frequent and serious side effects, especially hyperglycemia. Alpelisib use must be considered with caution and closely monitored, particularly in the prediabetic population. Prophylactic anti-rash treatment based on anti-histaminic drugs could reduce the impact of this side effect on quality of life.

11. Expert opinion

While PI3K pathway activation has long been recognized as an important biological event in BC, PI3K targeting has remained an elusive goal for a decade.

Everolimus targets a downstream protein of the pathway, and while it was validated in clinical practice following the publication of the BOLERO-2 trial in 2012, it is associated with significant toxicity [34]. However, the search for a direct inhibitor of PI3K, while appealing, has been hampered by toxicity concerns related to the involvement of this protein in multiple signaling pathways, from glycemic regulation to immunity, and even to psychiatry, as illustrated by the risk of depression associated with buparlisib [35]. Buparlisib, and more recently taselisib, showed a significant prolongation of PFS compared to placebo; however, their clinical development stopped after the phase III, due to an unfavorable balance between a modest improvement in PFS and a complex safety profile, without definitive evidence of an overall survival advantage [36].

Following the publication of the SOLAR-1 study, alpelisib was the first PI3K inhibitor to reach clinical approval. It is a proven option, after progression during/after treatment with an aromatase inhibitor, for patients with HR+/HER2-, *PIK3CA*-mutated tumors who are eligible for a new line of endocrine therapy. The PFS benefit appears clinically significant over fulvestrant alone. However, the study failed at demonstrating a significant advantage in OS of this association, despite a 7.9 months increase in OS, supporting the activity of alpelisib in this setting.

However, to date, many questions remain regarding its definitive place in the HR+/HER2- therapeutic strategy.

First of all, the first-line standard of care for patients affected by a HR+/HER2- tumor has, over recent years, moved to combination therapy that includes a CDKi. Few patients included in SOLAR-1 received such a combination before enrollment, precluding a solid evaluation of the safety and efficacy of alpelisib–fulvestrant after first-line treatment with an aromatase inhibitor–CDKi combination [28]. The recent results from the BYLieve trial are reassuring regarding the safety issue; however, no definitive conclusion could be issued regarding the efficacy, as this is a non-randomized phase II trial [27]. The indication for alpelisib after first-line HT without CDKi is weakened by the demonstration of an overall survival advantage of fulvestrant–CDKi in this setting, which also has a safety profile that appears more manageable [37,38]. Thus, strategic trials that evaluate the best sequence of treatments are required to better define the role of alpelisib in this population.

Another issue is the relative place of alpelisib and everolimus in the global treatment strategy. Indeed, both compounds failed to demonstrate an overall survival advantage to date, but everolimus avoids the need to identify *PIK3CA* mutations, thus allowing the treatment of the whole cohort of patients. Both side effect profiles are affected by significant toxicities, but everolimus appears to be better tolerated in terms of hyperglycemia.

Finally, alpelisib's toxicity profile is a significant pitfall. Targeting the alpha isoform of PI3K certainly allows avoidance of the psychiatric effects that are reported with buparlisib and some of the colitis that is reported with taselisib [35,36]. However, hyperglycemia seems to occur even more frequently with alpelisib than with its predecessors. Very strict selection of the patient population appears mandatory. Indeed, in SOLAR-1 [28], with a population selected for a clinical research study, 60% of the population was classified as diabetic or prediabetic based on their fasting blood glucose and HbA1c levels. In view of the incidence and severity of this side effect, validated strategies evaluating prophylactic treatment or early management are necessary. Otherwise, it may seem prudent, in the absence of additional data, not to prescribe this compound in this high-risk population in the absence of a demonstrated superiority over its comparators, everolimus and CDKi.

Beyond strategy and comparison studies, one way forward could be the development of innovative combinations. Preclinical studies highlighted the synergistic effect of the alpelisib–ribociclib combination in non-keratinizing nasopharyngeal carcinoma [39]. Indeed, in ER-positive xenograft models, the authors revealed the greater impact of an alpelisib and fulvestrant and ribociclib triple combination that was able to

induce tumor regression, while the fulvestrant–ribociclib doublet induced only tumor stabilization. This combination has been tested in a phase I/II study (NCT02088684). While the phase I part of the study has been completed, the study did not move to phase II. At the same time, Tolaney *et al*. recently published the results of a phase Ib study in which they failed to find a recommended dose for the ribociclib – fulvestrant – alpelisib, due to early, unexpected, toxicity, especially rashes clinically incompatible with long-term dosing [40]. Future studies must address the question of the possible differences in toxicity profiles associated with the combination of alpelisib with a given CDK4/6 inhibitor.

Overall, alpelisib is an valid option for patients affected by a HR+/HER2-, *PIK3CA*-mutated, tumor who have progressed during or after hormonal therapy; however without significantly improving overall survival. Its safety profile means strict selection of patients, mainly based on the baseline glycemic status, and close monitoring are required. Strategic trials that evaluate the best sequence of treatments are awaited in order to better define the role of alpelisib in this population.

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