FDA Approval Summary: Alpelisib Plus Fulvestrant for Patients with HR-positive, HER2-negative, PIK3CA-mutated, Advanced or Metastatic Breast Cancer

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ABSTRACT

On May 24, 2019, the FDA granted regular approval to alpelisib in combination with fulvestrant for postmenopausal women, and men, with hormone receptor (HR)-positive, HER2-negative, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA)-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen. Approval was based on the SOLAR-1 study, a randomized, double-blind, placebo-controlled trial of alpelisib plus fulvestrant versus placebo plus fulvestrant. The primary endpoint was investigator-assessed progression-free survival (PFS) per RECIST v1.1 in the cohort of trial participants whose tumors had a PIK3CA mutation. The estimated median PFS by investigator assessment in the alpelisib plus fulvestrant arm was 11 months [95% confidence interval (CI), 7.5–14.5] compared with 5.7 months (95% CI, 3.7–7.4) in the placebo plus fulvestrant arm (HR, 0.65; 95% CI, 0.50–0.85; two-sided $P = 0.001$). The median overall survival was not yet reached for the alpelisib plus fulvestrant arm (95% CI, 28.1–NE) and was 26.9 months (95% CI, 21.9–NE) for the fulvestrant control arm. No PFS benefit was observed in trial participants whose tumors did not have a PIK3CA mutation (HR, 0.85; 95% CI, 0.58–1.25). The most common adverse reactions, including laboratory abnormalities, on the alpelisib plus fulvestrant arm were increased glucose, increased creatinine, diarrhea, rash, decreased lymphocyte count, increased gamma glutamyl transferase, nausea, increased alanine aminotransferase, fatigue, decreased hemoglobin, increased lipase, decreased appetite, stomatitis, vomiting, decreased weight, decreased calcium, decreased glucose, prolonged activated partial thromboplastin time, and alopecia.

Introduction

In the United States, breast cancer is the most common cancer in women, with more than 270,000 new cases and 40,000 deaths annually (1). Breast cancer is rare in men, with only 2,600 cases per year (2). Metastatic breast cancer is categorized into different histopathologic subtypes based on expression of hormone receptor [HR, estrogen receptor (ER), and/or progesterone receptor] and HER2. Hormone receptor-positive, HER2-negative breast cancer is the most common subtype in both women and men. The majority of patients with HR-positive, HER2-negative breast cancer are initially diagnosed and treated at an early stage with a combination of surgery with or without radiation and adjuvant endocrine therapy with or without adjuvant chemotherapy. Even after completion of 5 years of adjuvant endocrine therapy, 10%–41% of women will experience distant recurrence by 20 years, depending on tumor diameter, nodal status, and tumor grade (3). Male patients with breast cancer tend to present at a higher stage, likely due to the lack of public awareness and mammographic screening in men. Therefore, there remains an unmet need for further effective therapies for these patients.

Current FDA-approved therapies for patients with HR-positive, HER2-negative advanced or metastatic breast cancer include hormonal-based [aromatase inhibitor (AI) and fulvestrant] therapies in combination with cyclin-dependent kinase (CDK) 4/6 inhibitors (abemaciclib, palbociclib, and ribociclib), everolimus with exemestane, hormonal monotherapy (AI, fulvestrant, and tamoxifen), and chemotherapy (capecitabine, eribulin, ixabepilone, paclitaxel protein-bound, gemcitabine, etc.; ref. 4). Metastatic HR-positive, HER2-negative breast cancer is currently incurable and has a 5-year survival rate of approximately 30% (5). PIK3CA mutations are present in approximately 40% of patients with HR-positive, HER2-negative advanced breast cancer and is a negative prognostic factor that potentially mediates resistance to endocrine therapy (6). Treatment options for all patients, including male patients, remain an area of significant unmet need. This article summarizes the FDA rationale for granting regular approval in May 2019 to alpelisib in combination with fulvestrant for postmenopausal women, and men, with HR-positive, HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer (7).

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Clin Cancer Res 2021;27:1842–9

doi: 10.1158/1078-0432.CCR-20-3652

Chemistry, Manufacturing, and Control

The alpelisib drug substance is a white to almost white powder that is practically insoluble in water. The chemical name of alpelisib is (2*S*)-N^1-[4-Methyl-5-[2-(2,2,2-trifluoro-1,1-dimethylethyl)-4-pyridinyl]-2-thiazolyl]-1,2-pyrrolidinedicarboxamide, with the chemical structure shown in **Fig. 1** (8). The molecular formula for alpelisib is $C_{19}H_{22}F_3N_5O_2S$ with a relative molecular mass of 441.47 g/mol.

The film-coated tablets are supplied in blister packs for oral administration with three strengths that contain 50, 150, and 200 mg of alpelisib. These tablets are composed of hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, and sodium starch glycolate, with the film coating consisting of hypromellose, iron oxide black, iron oxide red, macrogol/polyethylene glycol 4000, talc, and titanium dioxide. The tablets are to be stored at 20°C–25°C (68 F–77 F), with excursions permitted between 15°C and 30°C (59°F and 86°F; USP Controlled Room Temperature).

Nonclinical Pharmacology and Toxicology

Alpelisib is a kinase inhibitor with inhibitory activity predominantly against the α-isoform of class I PI3K. Alpelisib showed higher kinase inhibitory activity in cell lines harboring mutations of the catalytic α-subunit of PI3K (PIK3CA) compared with wild-type cell lines. Cell viability assays showed that a higher percentage of PIK3CA-mutant cancer cell lines were sensitive to alpelisib treatment compared with PIK3CA wild-type cell lines tested. In mouse xenograft models of breast cancer, including ER-positive breast cancer models with PIK3CA mutations, single-agent alpelisib showed antitumor activity, and the combination of alpelisib and fulvestrant demonstrated an increase in antitumor activity compared with fulvestrant or alpelisib alone. The observed antitumor activity correlated with inhibition of the PI3K/Akt pathway. In repeat-dose toxicity studies, administration of alpelisib to rats and dogs for up to 3 months resulted in adverse effects in the gastrointestinal (GI) tract, hemolymphoid system, skin, metabolic, and reproductive system. Alpelisib increased blood insulin and glucose levels, which correlated with histopathologic changes in the pancreas (vacuolation or hyperplasia of endocrine cells). The toxicity profile in animals was similar to that in trial participants treated with alpelisib. In embryo-fetal development studies, administration of alpelisib to pregnant rats and rabbits resulted in embryo-fetal mortality, reduced fetal weights, and fetal malformations at ≥0.8 times the human AUC at the recommended clinical dose. On the basis of findings in animals and its mechanism of action, alpelisib can cause fetal harm when administered to a pregnant woman.

Clinical Pharmacology

The proposed alpelisib 300 mg every day dosage was found to be acceptable for approval based on the efficacy results and clinically manageable safety profile demonstrated in the SOLAR-1 trial. Because of treatment-related adverse events (AE), such as hyperglycemia, diarrhea, and rash, 72% of trial participants required at least one dose interruption and 59% required at least one dose reduction. Overall, 21% of trial participants discontinued treatment with alpelisib alone in the alpelisib plus fulvestrant arm. After the second treatment cycle, most trial participants remained on a stable dose with roughly 40%, 30%, and 30% receiving 300, 250, and 200 mg, respectively.

In patients with cancer, alpelisib demonstrated linear pharmacokinetics across the dose range 30–450 mg following a single dose and multiple doses. After approximately three once daily administrations, the exposure of alpelisib reached steady state with an approximately 1.3- to 1.5-fold accumulation ratio. In healthy subjects, both high-fat high-calorie meal and low-fat low-calorie meal boosted alpelisib systemic exposure by 75% compared with fasting condition. Therefore, alpelisib should be taken immediately after food. Alpelisib can be coadministered with acid-reducing agents, given that alpelisib should be taken with food, as alpelisib systemic exposure decreased by 21% with ranitidine in the presence of low-fat low-calorie meal.

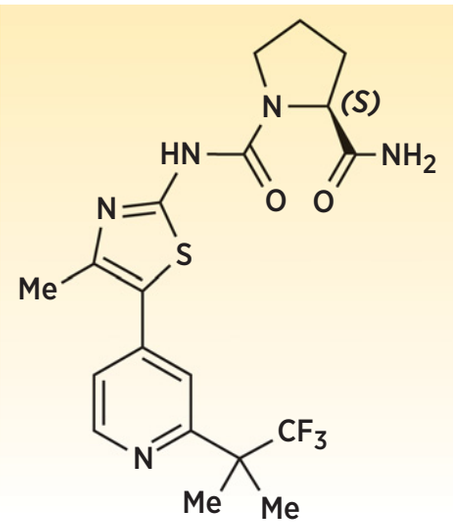

Figure 1.
Chemical structure of alpelisib (8).

On the basis of analysis of specific populations, such as age (21–87 years), sex, race/ethnicity (Japanese or Caucasian), body weight (37–181 kg), mild to moderate renal impairment (CrCl 30–<90 mL/minute based on the Cockcroft-Gault formula), or mild to severe hepatic impairment (Child-Pugh Class A, B, and C), there were no clinically significant differences in the pharmacokinetics of alpelisib that were predicted. As there was no dedicated study in patients with severe renal impairment, (CrCl < 30 mL/minute), the effect on the pharmacokinetics of alpelisib is unknown in this setting.

The metabolism of alpelisib involves primarily chemical and enzymatic hydrolysis with a lesser contribution of CYP3A4. Two postmarketing commitment studies are requested to evaluate the effect of repeated doses of a strong CYP3A4 inducer on the pharmacokinetics of alpelisib, and to evaluate the effect of repeat doses of alpelisib on the single-dose pharmacokinetics of sensitive substrates of CYP2B6, CYP3A4, and CYP2C family enzymes (CYP2C9, CYP2C19, and/or CYP2C8) to determine the magnitude of exposure change for sensitive substrates of the above CYP enzymes.

Clinical Trial Design

SOLAR-1 was a randomized, double-blind, placebo-controlled, international, multicenter study to determine the efficacy and safety of treatment with alpelisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal women, and men, with HR-positive, HER2-negative advanced breast cancer following progression on or after AI treatment. Alpelisib (300 mg) or placebo was administered orally daily

and fulvestrant was administered at a dose of 500 mg via intramuscular injection on days 1 and 15 of cycle 1 and on day 1 of each subsequent cycle, every 28 days. The primary endpoint was progression-free survival (PFS) by investigator assessment per RECIST 1.1. On 9 March 2016 the protocol was amended to limit the primary analysis population to the cohort with a PIK3CA tumor mutation, and PFS in the cohort with wild-type PIK3CA was changed to a secondary proof-of-concept endpoint. Overall survival (OS) for trial participants with a PIK3CA tumor mutation was a key secondary endpoint. Randomization was stratified by the presence of lung and/or liver metastases, and by previous treatment with any CDK 4/6 inhibitor within each of the PIK3CA tumor mutation and PIK3CA wild-type cohorts. The two-sided alpha of 0.05 was split to allocate 0.04 to the PIK3CA tumor mutation cohort and 0.01 to the PIK3CA wild-type cohort, respectively. Cross-over from the placebo plus fulvestrant arm after documented progression was not permitted in the SOLAR-1 study. Trial participants received treatment until radiographic progression or unacceptable toxicity, with tumor assessments performed every 8 weeks for the first 18 months and every 12 weeks thereafter.

Results

Efficacy

A total of 572 trial participants (341 with PIK3CA-mutated tumors and 231 with wild-type tumors) across 33 countries in North and Latin America, Europe, and Asia were randomized between the two arms. Baseline demographics of the intention-to-treat population are shown in **Table 1** and baseline disease characteristics are shown in **Table 2**. Trial participant characteristics were generally similar between the two treatment groups. Of note, among the cohort with a PIK3CA tumor mutation, only nine trial participants randomized to the alpelisib arm and 11 trial participants randomized to the placebo arm had previously received a CDK 4/6 inhibitor. Overall, 60% of trial participants had tumors with a PIK3CA mutation, as determined by tissue-based testing, and were balanced between the control and experimental arm.

In the primary efficacy population of trial participants whose tumors had a PIK3CA mutation, SOLAR-1 demonstrated a statistically significant improvement in PFS for the alpelisib plus fulvestrant arm [HR, 0.65; 95% confidence interval (CI), 0.50–0.85; $P = 0.001$], with a median PFS of 11 months (95% CI, 7.5–14.5), compared with 5.7 months (95% CI, 3.7–7.4) in the placebo plus fulvestrant arm. **Figure 2** shows the Kaplan–Meier curve for PFS in the cohort with PIK3CA tumor mutation.

OS was a key secondary endpoint, and results were immature at the time of the first interim analysis. In the PIK3CA cohort, 92 deaths were reported by the data cut-off date for the regulatory submission to the FDA (23.7% in the alpelisib plus fulvestrant arm and 30.2% in the placebo plus fulvestrant arm), corresponding to a 51.7% information fraction of the targeted 178 events for the final OS analysis. The median OS was not yet reached for the alpelisib plus fulvestrant arm (95% CI, 28.1–NE) and was 26.9 months (95% CI, 21.9–NE) for the fulvestrant control arm.

Safety

The assessment of safety was based on a total of 571 trial participants who were treated with at least one dose of study medication (340 with PIK3CA-mutated tumors and 231 with wild-type tumors). There were a high number of dose modifications and discontinuations reported in the SOLAR-1 trial. Dose interruptions occurred in 188 of 284 (66%) of those in the alpelisib plus fulvestrant arm versus 61 of 287 (21%) in the

Table 1. SOLAR-1 demographics, PIK3CA-mutated tumor and wild-type cohorts (7).

	PIK3CA-mutated tumors			PIK3CA wild-type tumors		
	Alpelisib + fulvestrant	**Placebo + fulvestrant**	**All patients**	**Alpelisib + fulvestrant**	**Placebo + fulvestrant**	**All patients**
	n = 169 (%)	*n* = 172 (%)	*n* = 341 (%)	*n* = 115 (%)	*n* = 116 (%)	*n* = 231 (%)
Sex						
Female	168 (99.4)	172 (100)	340 (99.7)	115 (100)	116 (100)	231 (100)
Male	1 (0.6)	0	1 (0.3)	0	0	0
Age (years)						
Median	63	64	63	62	63	62
Range	25–87	38–92	25–92	39–82	32–88	32–88
Age category (years)						
18 to <65	95 (56)	89 (52)	184 (54)	72 (63)	65 (56)	137 (59)
65 to <85	73 (43)	80 (47)	153 (45)	43 (37)	50 (43)	93 (40)
≥85	1 (<1)	3 (2)	4 (1)	0	1 (1)	1 (<1)
Race						
White	117 (69)	109 (63)	226 (66)	82 (71)	69 (60)	151 (65)
Asian	34 (20)	40 (23)	74 (22)	25 (22)	26 (22)	51 (22)
Black or African American	1 (1)	3 (2)	4 (1)	1 (1)	3 (3)	4 (2)
American Indian or Alaska Native	1 (1)	2 (1)	3 (1)	0	2 (2)	2 (1)
Other	8 (5)	10 (6)	18 (5)	1 (1)	7 (6)	8 (4)
Unknown	8 (5)	8 (5)	16 (5)	6 (5)	9 (8)	15 (7)
ECOG						
0	112 (66)	113 (66)	225 (66)	84 (73)	79 (68)	163 (71)
1	56 (33)	58 (34)	114 (33)	30 (26)	37 (32)	67 (29)
Missing	1 (1)	1 (1)	2 (1)	1 (1)	0	1 (<1)

Note: Percentages in the table for each category may not sum to 100% due to rounding.
Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2. Baseline disease characteristics, SOLAR-1 (7).

	PIK3CA-mutant tumors			PIK3CA nonmutant tumors		
	Alpelisib + fulvestrant	Placebo + fulvestrant	All patients	Alpelisib + fulvestrant	Placebo + fulvestrant	All patients
	n = 169 (%)	*n* = 172 (%)	*n* = 341 (%)	*n* = 115 (%)	*n* = 116 (%)	*n* = 231 (%)
Sites of metastases						
Breast	1 (1)	3 (2)	4 (1)	5 (4)	4 (3)	9 (4)
Bone						
Any	131 (78)	121 (70)	252 (74)	79 (69)	89 (77)	168 (73)
Only	42 (25)	35 (20)	77 (23)	26 (23)	23 (20)	49 (21)
Visceral						
Any	93 (55)	100 (58)	193 (57)	66 (57)	74 (64)	140 (61)
Liver	49 (29)	54 (31)	103 (30)	41 (36)	36 (31)	77 (33)
Lung	57 (34)	68 (40)	125 (37)	37 (32)	55 (47)	92 (40)
Number of metastatic sites						
0	0	1 (1)	1 (<1)	0	0	0
1	63 (37)	52 (30)	115 (34)	44 (38)	33 (29)	77 (33)
2	58 (34)	60 (35)	118 (35)	35 (30)	38 (33)	73 (32)
≥3	48 (28)	59 (34)	107 (31)	36 (31)	45 (39)	81 (35)
Prior treatment						
Any CDK 4/6 inhibitor	9 (5)	11 (6)	20 (6)	7 (6)	8 (7)	15 (7)
Tamoxifen	59 (35)	62 (36)	121 (36)	37 (32)	50 (43)	87 (37)
Chemotherapy	101 (60)	107 (62)	208 (61)	78 (68)	72 (62)	150 (65)
Neoadjuvant	25 (15)	29 (17)	54 (16)	20 (17)	23 (20)	43 (19)
Adjuvant	78 (42)	86 (50)	164 (48)	64 (56)	58 (50)	122 (53)
Line of treatment in advanced disease						
First line	88 (52)	89 (52)	177 (52)	72 (63)	61 (53)	133 (58)
Second line	79 (47)	82 (48)	161 (47)	44 (38)	52 (45)	96 (42)
Endocrine status						
Primary resistance	23 (14)	22 (13)	45 (13)	31 (27)	26 (22)	57 (25)
Secondary resistance	120 (71)	127 (74)	247 (72)	66 (57)	65 (56)	131 (57)
Sensitive	20 (12)	19 (11)	39 (11)	16 (14)	20 (17)	36 (16)

Note: Percentages in the table for each category may not sum to 100% due to rounding.

placebo plus fulvestrant arm. Dose reductions due to AEs occurred in 156 of 284 (55%) versus 13 of 287 (4.5%) of trial participants, respectively. Discontinuations due to AEs were reported in 71 of 284 (25%) versus 13 of 287 (4.5%) of trial participants, respectively (these percentages included discontinuations of either alpelisib or placebo, fulvestrant, or both drugs in each arm). The most frequent adverse reactions resulting in discontinuation of alpelisib were hyperglycemia, rash, diarrhea, and fatigue. While the majority of trial participants were able to continue alpelisib plus fulvestrant with supportive care medications, the high percentage of dose modifications and discontinuations indicates that the alpelisib dose of 300 mg daily was too high for many trial participants. The safety of alpelisib plus fulvestrant in the cohort with PIK3CA tumor mutation did not differ from that of the overall SOLAR-1 population.

Alpelisib plus fulvestrant demonstrated acceptable tolerability for the indicated population with a serious and life-threatening disease. Adverse reactions were common and, except for hyperglycemia and rash, predominantly grade 1–2 in severity. The most common adverse reactions observed in the alpelisib plus fulvestrant arm were hyperglycemia (65%), diarrhea (58%), and rash (52%). Hypersensitivity reactions, severe cutaneous reactions, hyperglycemia, pneumonitis, diarrhea, and embryo-fetal toxicity are labeled as warnings and precautions. Additional common adverse reactions with alpelisib plus fulvestrant ≥20% included diarrhea, nausea, fatigue, anemia, decreased appetite, stomatitis, vomiting, anorexia, and alopecia.

Companion Diagnostic Development

The therascreen PIK3CA RGQ PCR kit was developed as a companion diagnostic (CDx) of 11 defined mutations in the *PIK3CA* gene [exon 7: C420R; exon 9: E542K, E545A, E545D (1635G>T only), E545G, E545K, Q546E, and Q546R; and exon 20: H1047L, H1047R, and H1047Y] using genomic DNA extracted from formalin-fixed, paraffin-embedded tumor tissue or circulating tumor DNA (ctDNA) isolated from plasma (9). The safety and effectiveness of the therascreen PIK3CA RGQ PCR kit were demonstrated through prospectively and retrospectively testing of tissue and plasma specimens from trial participants enrolled in SOLAR-1.

There were 341 trial participants enrolled in the PIK3CA mutation cohort (using tumor tissue) and 231 enrolled in the PIK3CA wild-type cohort. Of the 341 trial participants in the cohort with a PIK3CA mutation, almost all ($n = 336$, 99%) had confirmed PIK3CA mutations in tumor tissue using the FDA-approved therascreen PIK3CA RGQ PCR kit. A total of 317 trial participants with PIK3CA mutations confirmed in tumor tissue had a plasma specimen available for testing, and of these, 177 trial participants (56%) had PIK3CA mutations identified in plasma specimen, and 140 trial participants (44%) did not. The data provide reasonable assurance of safety and effectiveness of the test kit when used in accordance with the indications for use.

Concordance of the plasma results to tumor tissue results was determined using plasma samples collected at baseline from 328 trial participants with therascreen PIK3CA RGQ PCR kit tissue-positive

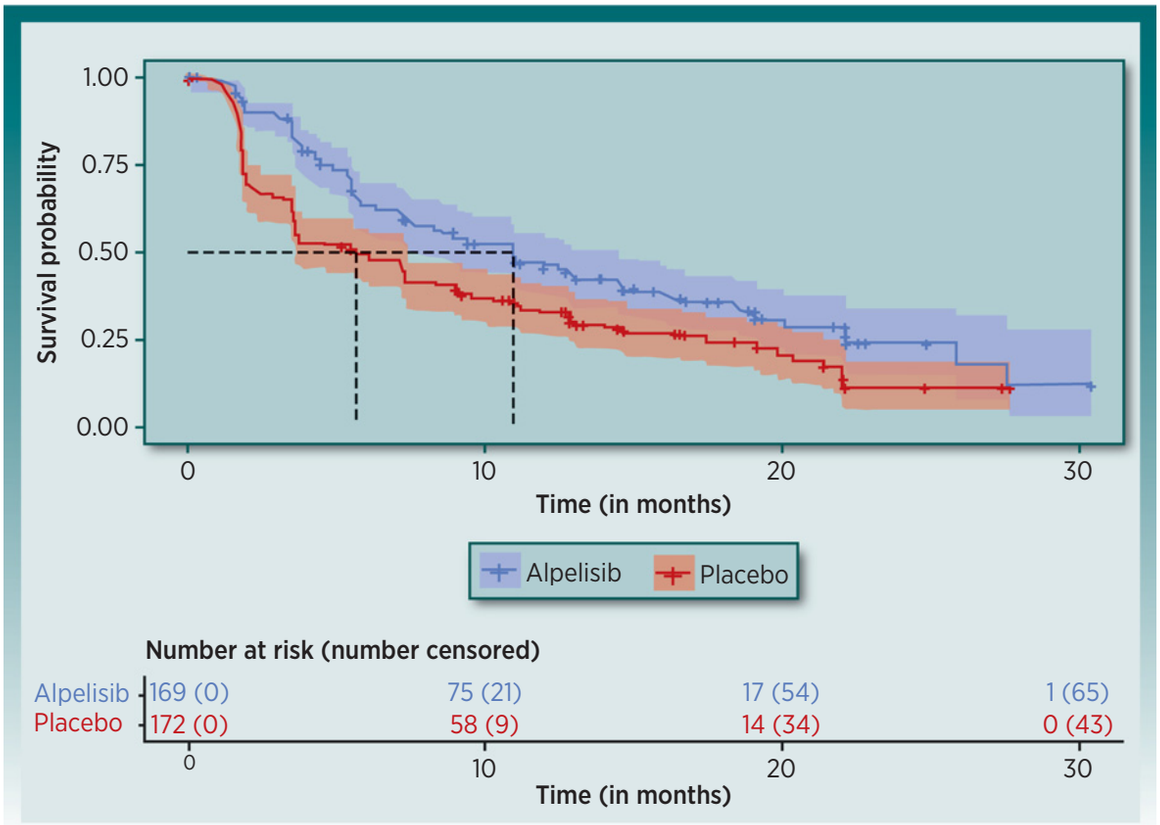

Figure 2.
Kaplan–Meier plot of PFS in SOLAR-1 (per investigator assessment of patients with a PIK3CA tumor mutation; ref. 7).

results and 215 trial participants with therascreen PIK3CA RGQ PCR kit tissue-negative results. The positive percent agreement (PPA) of the plasma test for 11 mutations compared with the tissue test was 179 of 328 (54.6%) in the concordance analysis, which may be due to low tumor shedding into the blood. Notably, five of the 11 mutations targeted by the therascreen PIK3CA RGQ PCR kit (H1047Y, Q546R, Q546E, E545D, and E545A) were not detected when testing plasma from trial participants enrolled in SOLAR-1 whose tissue was also tested. The negative percent agreement was 97.2% (209/215). Taking into consideration the convenience of plasma testing, as well as the risk of false-negative results in plasma and the low PPA between the plasma and tissue, the approved product labeling recommends a reflex approach, with plasma testing to be followed by tissue testing for those in whom plasma is negative for PIK3CA mutation.

Patient-Reported Outcomes

In this trial, the European Organization for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30) was collected at baseline and every second cycle until the end of treatment. This patient-reported outcome (PRO) measure captures functioning, symptoms, and overall quality of life (Qol). The completion rates were >95% at baseline and >84% for assessments on both arms during the first 12 months of therapy regardless of treatment arm. Prespecified clinical outcome assessment (COA) and PRO analyses were exploratory without any control of type I error and included time to 10% deterioration in the global health status/Qol scale score of the EORTC QLQ-C30 instrument and change from baseline in the GHS/Qol scale score of the EORTC QLQ-C30.

For trial participants who remained on therapy, patient responses to both physical and role functioning scales were not indicative of large decrements for either treatment arm. The descriptive distributions of trial participants reporting key GI side effects that were captured using PRO measures reveal a similar pattern to what was reported in the adverse reaction table, that is, more trial participants in the alpelisib arm experienced worsening diarrhea, nausea, and vomiting.

The overall review of the PRO results by the FDA did not identify a large decrement in symptoms or function that would materially alter the net favorable risk-benefit determination. Therefore, no information on PROs was included in the U.S. prescribing information for alpelisib.

Regulatory Insights

This is the first FDA approval for treatment of patients with PIK3CA-mutated advanced or metastatic breast cancer (10). The SOLAR-1 trial met its primary endpoint in the intended use population of patients with HR-positive, HER2-negative PIK3CA-mutated tumor advanced or metastatic breast cancer. Superior efficacy was not demonstrated for alpelisib plus fulvestrant in the PIK3CA wild-type cohort, and, therefore, use of alpelisib plus fulvestrant was limited to

Table 3. FDA risk-benefit analysis, SOLAR-1 (7).

Dimension	Evidence and uncertainties	Conclusions and reasons
Analysis of condition	Breast cancer is the most common cancer in women, with more than 260,000 new cases and 40,000 deaths annually. Breast cancer is rare in men, and limited data are available from clinical trials on its treatment. Advanced or metastatic breast cancer is incurable.	Advanced or metastatic breast cancer is a serious and life-threatening condition with ongoing unmet medical need in both female and male patients.
Current treatment options	Metastatic breast cancer is not currently curable. Treatment goals are palliative in nature and include delay of disease progression, prolongation of survival, and reduction of cancer-related symptoms. FDA-approved therapies for patients with HR-positive, HER2-negative advanced or metastatic breast cancer include endocrine therapy (AI and fulvestrant) in combination with CDK 4/6 inhibitors (abemaciclib, palbociclib, and ribociclib), everolimus with exemestane, endocrine monotherapy (AI, fulvestrant, and tamoxifen), and chemotherapy (multiple agents including taxanes, capecitabine, eribulin, vinorelbine, ixabepilone, and gemcitabine).	All currently available treatment options are palliative. There is an unmet medical need to improve outcomes of female and male patients with HR-positive, HER2-negative advanced or metastatic breast cancer.
Benefit	SOLAR-1 enrolled 572 postmenopausal women and men with HR-positive, HER2-negative advanced or metastatic breast cancer whose disease had progressed or recurred on or after an AI, with or without a CDK 4/6 inhibitor.	The SOLAR-1 trial met its primary endpoint with a statistically significant and clinically meaningful improvement in PFS. This is also the first drug approved specifically for the treatment of patients with PIK3CA-mutated tumor, advanced breast cancer, which represents a new molecular subset in breast cancer.
	In patients whose tumors had a PIK3CA tumor mutation, the estimated median PFS by investigator assessment in the alpelisib plus fulvestrant arm was 11 months (95% CI, 7.5–14.5) compared with 5.7 months (95% CI, 3.7–7.4) in the placebo plus fulvestrant arm (HR, 0.65; 95% CI, 0.50–0.85; two-sided $P = 0.001$). The overall response rate in patients with a PIK3CA tumor mutation, measurable disease at baseline, and confirmed response was higher in the alpelisib plus fulvestrant arm (36% vs. 16%).	The CDx test therascreen PIK3CA RGQ PCR Kit (QIAGEN Manchester, Ltd.) will be used to select patients who have PIK3CA mutations in tumor tissue specimens and/or in ctDNA isolated from plasma specimens. If the test is negative for PIK3CA mutations in plasma, tumor tissue should be tested.
Risk and risk management	Adverse reactions were common and, except for hyperglycemia and rash, predominantly grade 1–2 in severity. The majority of adverse reactions were managed with dose reductions, temporary treatment discontinuations, supportive care treatments, and/or standard therapy, but 21% of patients discontinued alpelisib due to AEs. Severe hypersensitivity, severe cutaneous reactions, hyperglycemia, pneumonitis, diarrhea, and embryo-fetal toxicity are labeled as warnings and precautions. The most common adverse reactions on the alpelisib plus fulvestrant arm were increased glucose (79%), increased creatinine (67%), diarrhea (58%), rash (52%), lymphocyte count decreased (52%), increased gamma glutamyl transferase (52%), nausea (45%), increased alanine aminotransferase (44%), increased lipase (42%), and fatigue (42%). Serious adverse reactions occurred in 35% of patients who received alpelisib plus fulvestrant, including hyperglycemia, rash, diarrhea, acute kidney injury, abdominal pain, and anemia. 21% of patients permanently discontinued alpelisib alone due to adverse reactions, and 4.6% permanently discontinued both alpelisib and fulvestrant.	Alpelisib plus fulvestrant can be used safely with appropriate labeling. No Risk Evaluation and Mitigation Strategies (REMS) is indicated.

the PIK3CA-mutated population, as reflected in the indication for which regular approval was granted.

The current standard of care for first-line treatment of postmenopausal women with HR-positive, HER2-negative metastatic breast cancer in the United States is a combination of endocrine therapy and a CDK 4/6 inhibitor, irrespective of PIK3CA mutation status. Only 6% of trial participants on the SOLAR-1 trial had previously received an AI plus CDK 4/6 inhibitor combination and no trial participants had previously received fulvestrant plus a CDK 4/6 inhibitor. The drug company noted that some trial participants with metastatic disease previously treated with a CDK 4/6 inhibitor had been enrolled in SOLAR-1, and that the PFS

results in this subset similarly favored the alpelisib plus fulvestrant arm (HR, 0.48; 95% CI, 0.17–1.36). This observation was based on a very small sample size of 20 trial participants, of whom only nine were treated with alpelisib plus fulvestrant, with correspondingly wide CIs. However, activation of PI3K signaling is a known mechanism of resistance in patients whose tumors have progressed on CDK 4/6 inhibitors, and, therefore, a strategy of combining endocrine therapy plus a PI3K inhibitor after progression on CDK 4/6 inhibitor–based regimens is a possible approach (11, 12).

At the American Society for Clinical Oncology Annual Meeting in 2020, results were presented from a cohort of the BYLieve study, a multicohort phase II study with a cohort of patients with PIK3CA-mutated, HR-positive, HER2-negative advanced breast cancer treated with alpelisib plus fulvestrant who previously received CDK 4/6 inhibitor and AI as immediate prior treatment (13). The primary endpoint of the proportion of patients alive without progression of disease at 6 months was met in this cohort at 50.4% (95% CI, 41.2–59.6). These data are supportive of the use of alpelisib plus fulvestrant in the post-CDK4/6 inhibitor setting and support the findings seen in the SOLAR-1 study.

As breast cancer in men is rare, male patients have historically been excluded from clinical trials and their clinical management is often based on extrapolation of data from female patients enrolled in trials. The FDA has encouraged the inclusion of male patients in breast cancer trials and has released a guidance on this topic, which, in part, details that even when male enrollment is limited, it may be possible to extrapolate findings in cases when no difference between males and females is anticipated on the basis of the mechanism of action of the drug (14). Male patients were eligible and included in the SOLAR-1 study, and the current indication for alpelisib includes men.

Premenopausal patients were neither eligible for nor enrolled in the SOLAR-1 trial, and, therefore, the indication granted only included postmenopausal women. However, similar to male patients, in the clinical setting, data in postmenopausal patients are typically extrapolated to the treatment of premenopausal patients in combination with ovarian suppression. FDA encourages the inclusion of premenopausal and postmenopausal patients into future clinical trials to increase the data and knowledge regarding the use of drugs for this important group of patients.

Alpelisib is the first new molecular entity reviewed using the Real Time Oncology Review (RTOR) program, which allows the FDA to begin analyzing key efficacy and safety datasets prior to the official submission of an application, aiding the review team to begin their analysis and communicate with the submitting drug company (referred to as the applicant) earlier on for important review issues prior to the official filing of the application (15, 16). This new drug application also utilized the Assessment Aid (AAid), a multidisciplinary review template that is a voluntary submission from the applicant with the goal to focus the FDA's written review on critical thinking and analysis and decrease the time spent on repeating data already presented by the applicant (17). Both the RTOR and AAid are initiatives by the Oncology Center of Excellence intended to streamline the FDA's review process that may lead to patients' early access to therapies that serve unmet needs in oncology. Using these programs, this application was approved on May 24, 2019, approximately 3 months ahead of the Prescription Drug User Fee Act VI deadline of 18 August 2019.

Conclusions

In summary, the addition of alpelisib to fulvestrant demonstrates a favorable benefit-risk profile (**Table 3**) for the treatment of postmenopausal women and men with hormone receptor-positive, HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer. The safety profile of alpelisib plus fulvestrant showed acceptable tolerability for this population of patients with a life-threatening disease. Therefore, the results from the SOLAR-1 study supported a regular approval for this indication.

Authors' Disclosures

Y. Gong has left the FDA and started working at BeiGene in August 2020 (work on the article was done during employment at the FDA). No disclosures were reported by the other authors.

Disclaimer

The Editor handling the peer review and decision-making process for this article has no relevant employment associations to disclose.

Received September 16, 2020; revised October 19, 2020; accepted November 5, 2020; published first November 9, 2020.

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