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PIQRAY - The First and Only Treatment for Patients with A PIK3CA Mutation in HR+/HER2- Advanced Breast Cancer: A Review

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Abstract**—** *Mutations in the PIK3CA gene in HR-positive or HER2-negative breast cancer patient is one of the most common causes of tumour growth and endocrine treatment resistance. Approximately 40% of the HR-positive or HER2-negative breast cancer patients have PIK3CA mutation worldwide. Alpelisib, a selective oral inhibitor of the class I PI3K catalytic subunit p110α, has shown synergistic antitumor activity with endocrine therapy against ER+/PIK3CA-mutated breast cancer cells.The phosphatidylinositol 3-kinase (PI3K) pathway is frequently activated in patients with estrogen receptor-positive (ER+), endocrine therapy-resistant breast cancers. PIK3CA mutations may lead to hyperactivation of PI3Kα, a key upstream component of the PI3K pathway Inhibiting PI3Kα interrupts AKT-dependent and AKT-independent signaling cascades in the PI3K pathway.PIQRAY and fulvestrant work synergistically to inhibit both the PI3K and ER pathways. in this review we discussed about the pharmacology, pharmacokinetics, pharmacodynamics and detailed clinical study of the piqray(alpelisib) the first and only treatment for the ER+/PIK3CA-mutated breast cancer.*

Keywords**—** *Kinase inhibitor, PIK3CA mutation, hyperactivation of PI3Kα, ER+/PIK3CA-mutated breast cancer.*

I. INTRODUCTION

PIQRAY (alpelisib) is a kinase inhibitor. The chemical name of alpelisib is (2S)-N1-[4-Methyl-5-[2-(2,2,2-trifluoro-1,1-dimethylethyl)-4-pyridinyl]-2-thiazolyl]-1,2-pyrrolidinedicarboxamide. Alpelisib is a white to almost white powder. The molecular formula for alpelisib is C19H22F3N5O2S and the relative molecular mass is 441.47 g/mol. The chemical structure of alpelisib is shown below

PIQRAY film-coated tablets are supplied for oral administration with three strengths that contain 50 mg, 150 mg and 200 mg of alpelisib. The tablets also contain hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, and sodium starch glycolate. The film-coating contains hypromellose, iron oxide black, iron oxide red, macrogol/polyethylene glycol (PEG) 4000, talc, and titanium dioxide.

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II. MECHANISM OF ACTION

Alpelisib is an inhibitor of phosphatidylinositol-3-kinase (PI3K) with inhibitory activity predominantly against PI3Kα. Gain-of-function mutations in the gene encoding the catalytic α-subunit of PI3K (PIK3CA) lead to activation of PI3Kα and Akt-signaling, cellular transformation and the generation of tumors in in vitro and in vivo models.

In breast cancer cell lines, alpelisib inhibited the phosphorylation of PI3K downstream targets, including Akt and showed activity in cell lines harboring a PIK3CA mutation. In vivo, alpelisib inhibited the PI3K/Akt signaling pathway and reduced tumor growth in xenograft models, including models of breast cancer.

PI3K inhibition by alpelisib treatment has been shown to induce an increase in estrogen receptor (ER) transcription in breast cancer cells. The combination of alpelisib and fulvestrant demonstrated increased anti-tumor activity compared to either treatment alone in xenograft models derived from ER-positive, PIK3CA mutated breast cancer cell lines.

III. PHARMACOKINETICS

The pharmacokinetics of alpelisib has been studied in healthy subjects and adult patients with solid tumors. Steady-state alpelisib maximum plasma concentration (Cmax) and AUC increased proportionally over the dose range of 30 mg to 450 mg (0.1 to 1.5 times the approved recommended dosage) under fed conditions. The mean accumulation of alpelisib is 1.3 to 1.5 and steady-state plasma concentrations are reached within 3 days following daily dosage. In adult patients who received PIQRAY 300 mg once daily in the SOLAR-1 trial, population approach derived mean steady-state alpelisib

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[coefficient of variation (CV%)] for Cmax was 2480 (23%) ng/mL and AUC0-24hr was 33224 (21%) ng*h/mL.

Absorption

The median time to reach peak plasma concentration (Tmax) ranged between 2.0 to 4.0 hours .

Effect of food:

A high-fat high-calorie meal (985 calories with 58.1 g of fat) increased alpelisib AUC by 73% and Cmax by 84%, and a low-fat low-calorie meal (334 calories with 8.7 g of fat) increased alpelisib AUC by 77% and Cmax by 145% following a single dose of PIQRAY. No clinically significant differences in alpelisib AUC were observed between low-fat low-calorie and high-fat high-calorie meals.

Distribution:

The mean (% CV) apparent volume of distribution of alpelisib at steady-state is predicted to be 114 L (46%). Protein binding of alpelisib is 89% and is independent of concentration.

Metabolism:

Alpelisib is primarily metabolized by chemical and enzymatic hydrolysis to form its metabolite BZG791 and to a lesser extent by CYP3A4, in vitro.

Excretion:

Following a single oral dose of 400 mg radiolabeled alpelisib under fasted condition, 81% of the administered dose was recovered in feces (36% unchanged, 32% BZG791) and 14% (2% unchanged, 7.1% BZG791) in urine. CYP3A4-mediated metabolites (12%) and glucuronides amounted to approximately 15% of the dose.

IV. Adverse Effects

Severe hypersensitivity

Severe hypersensitivity reactions, including anaphylaxis and anaphylactic shock, were reported in patients treated with PIQRAY. Severe hypersensitivity reactions were manifested by symptoms including, but not limited to, dyspnea, flushing, rash, fever, or tachycardia. The incidence of grade 3 and 4 hypersensitivity reactions was 0.7%. Advise patients of the signs and symptoms of severe hypersensitivity reactions. Permanently discontinue PIQRAY in the event of severe hypersensitivity.

Severe cutaneous reactions, including Stevens-Johnson syndrome (SJS) and erythema multiforme (EM) were reported in patients treated with PIQRAY. SJS and EM were reported in 0.4% and 1.1% of patients, respectively.

Hyperglycemia

Severe hyperglycemia, including ketoacidosis, has been reported in patients treated with PIQRAY. Hyperglycemia was reported in 65% of patients treated with PIQRAY. Grade 3 (FPG >250-500 mg/dL) and Grade 4 (FPG >500 mg/dL) hyperglycemia was reported in 33% and 3.9% of patients, respectively. Ketoacidosis was reported in 0.7% of patients (n=2) treated with PIQRAY.

Pneumonitis

Severe pneumonitis, including acute interstitial pneumonitis and interstitial lung disease, has been reported in patients treated with PIQRAY. Pneumonitis was reported in 1.8% of patients treated with PIQRAY.

Diarrhea

Severe diarrhea, including dehydration and acute kidney injury, occurred in patients treated with PIQRAY. Most patients (58%) experienced diarrhea during treatment with PIQRAY. Grade 3 diarrhea occurred in 7% (n=19) of patients. Based on the severity of the diarrhea, PIQRAY may require dose interruption, reduction, or discontinuation. Advise patients to start antidiarrheal treatment, increase oral fluids, and notify their health care provider if diarrhea occurs while taking PIQRAY.

Embryo-Fetal Toxicity

Based on findings in animals and its mechanism of action, PIQRAY can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with PIQRAY and for 1 week after the last dose. Advise male patients with female partners of reproductive potential to use condoms and effective contraception during treatment with PIQRAY and for 1 week after the last dose. Refer to the Full Prescribing Information of fulvestrant for pregnancy and contraception information

The most common adverse reactions (all grades, incidence ≥20%)

It includes diarrhea (58%), rash (52%), nausea (45%), fatigue (42%), decreased appetite (36%), stomatitis (30%), vomiting (27%), weight decreased (27%), and alopecia (20%). The most common grade 3/4 adverse reactions (incidence ≥2%) were rash (20%), diarrhea (7%), fatigue (5%), weight decreased (3.9%), nausea (2.5%), stomatitis (2.5%), and mucosal inflammation (2.1%).

The most common laboratory abnormalities (all grades, incidence ≥20%)

Were glucose increased (79%), creatinine increased (67%), lymphocyte count decreased (52%), gamma glutamyl transferase (GGT) increased (52%), alanine aminotransferase (ALT) increased (44%), hemoglobin decreased (42%), lipase increased (42%), calcium decreased (27%), glucose decreased (26%), and activated partial thromboplastin time (aPTT) prolonged (21%). The most common grade 3/4 laboratory abnormalities (incidence ≥5%) were glucose increased (39%), GGT increased (11%), lymphocyte count decreased (8%), and lipase increased (7%), and potassium decreased (6%).

V. Clinical Studies

SOLAR-1 (NCT02437318) was a randomized, double-blind, placebo-controlled trial of PIQRAY plus fulvestrant versus placebo plus fulvestrant in 572 patients with HR-positive, HER2-negative, advanced or metastatic breast cancer

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whose disease had progressed or recurred on or after an aromatase inhibitor-based treatment (with or without CDK4/6 combination). Patients were excluded if they had inflammatory breast cancer, diabetes mellitus Type 1 or uncontrolled Type 2, or pneumonitis. Randomization was stratified by presence of lung and/or liver metastasis and previous treatment with CDK4/6 inhibitor(s). Overall, 60% of enrolled patients had tumors with one or more PIK3CA mutations in tissue, 50% had liver/lung metastases, and 6% had previously been treated with a CDK4/6 inhibitor.

There were 341 patients enrolled by tumor tissue in the cohort with a PIK3CA mutation and 231 enrolled in the cohort without a PIK3CA mutation. Of the 341 patients in the cohort with a PIK3CA mutation, 336 (99%) patients had one or more PIK3CA mutations confirmed in tumor tissue using the FDA-approved therascreen® PIK3CA RGQ PCR Kit. Out of the 336 patients with PIK3CA mutations confirmed in tumor tissue, 19 patients had no plasma specimen available for testing with the FDA-approved therascreen® PIK3CA RGQ PCR Kit. Of the remaining 317 patients with PIK3CA mutations confirmed in tumor tissue, 177 patients (56%) had PIK3CA mutations identified in plasma specimen, and 140 patients (44%) did not have PIK3CA mutations identified in plasma specimen.

Patients received either PIQRAY (300 mg) or placebo orally once daily on a continuous basis, plus fulvestrant (500 mg) administered intramuscularly on Cycle 1, Days 1 and 15, and then on Day 1 of every 28-day cycle. Patients received treatment until radiographic disease progression or unacceptable toxicity. Tumor assessments were performed every 8 weeks for the first 18 months and every 12 weeks thereafter.

Patient demographics for those with PIK3CA-mutated tumors were generally representative of the broader study population. The median duration of exposure to PIQRAY plus fulvestrant was 8.2 months with 59% of patients exposed for > 6 months.

The majority of patients (98%) received prior hormonal therapy as the last treatment (48% metastatic setting, 52% adjuvant setting). Primary endocrine resistance, defined as relapsed within 24 months on adjuvant endocrine therapy or progression within 6 months on endocrine therapy for advanced disease, was observed in 13% of patients and secondary endocrine resistance, defined as relapsed after 24 months on adjuvant endocrine therapy, relapsed within 12 months of the end of adjuvant endocrine therapy, or progression after 6 months on endocrine therapy for advanced disease, was observed in 72% of patients.

The major efficacy outcome was investigator-assessed progression-free survival (PFS) in the cohort with a PIK3CA mutation per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Additional efficacy outcome measures were overall response rate (ORR) and overall survival (OS) in the cohort with a PIK3CA mutation.

Efficacy results for the cohort with a PIK3CA mutation in tumor tissue are presented in Table 8 and Figure 1. PFS results for the cohort with a PIK3CA mutation by investigator assessment were supported by consistent results from a blinded independent review committee (BIRC) assessment. Consistent results were seen in patients with tissue or plasma PIK3CA mutations. At the time of final PFS analysis, 27% (92/341) of patients had died, and overall survival follow-up was immature.

No PFS benefit was observed in patients whose tumors did not have a PIK3CA tissue mutation (HR = 0.85; 95% CI: 0.58, 1.25).

See the following table 1. Efficacy Results in SOLAR-1 (Per Investigator Assessment of Patients with a PIK3CA Tumor Mutation)

TABLE 1. Efficacy Results in SOLAR-1 (Per Investigator Assessment of Patients with a PIK3CA Tumor Mutation)

Progression free survival	N =169	N=172
Number of PFS events – n (%)	103 (61)	129 (75)
Median PFS months (95% CI)	11.0 (7.5, 14.5)	5.7 (3.7, 7.4)
Hazard ratio (95% CI 0.65 (0.50, 0.85)		
p- value 0.0013		
Overall Response Rate	N = 126	N = 136
ORR2 (95% CI)	35.7 (27.4, 44.7)	16.2 (10.4, 23.5)

1 Both log-rank test and Cox proportional hazards model are stratified by prior CDK4/6 inhibitor usage and presence of lung/liver metastases. P-value was compared to prespecified Haybittle-Peto stopping boundary (two-sided $p \leq 0.0398$).
2 ORR = percentage of patients with confirmed Complete Response or Partial Response with measurable disease at baseline

VI. Conclusion

In HR-positive or HER2-negative breast cancer patients with PIK3CA mutation PIQRAY and fulvestrant work synergistically to inhibit both the PI3K and ER pathways. Mutations in the PIK3CA gene in HR-positive or HER2-negative breast cancer patient is one of the most common causes of tumour growth and endocrine treatment resistance in this case Piqray is the only treatment to overcome the conditions where other treatments are not suitable.

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