FDA approves inavolisib with palbociclib and fulvestrant for endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative, advanced breast cancer

On October 10, 2024, the Food and Drug Administration approved inavolisib (Itovebi, Genentech, Inc.) with palbociclib and fulvestrant for adults with endocrine-resistant, PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth-factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy.

FDA also approved the FoundationOne Liquid CDx assay as a companion diagnostic device to identify patients with breast cancer for treatment with inavolisib with palbociclib and fulvestrant.

Full prescribing information for Itovebi will be posted on Drugs@FDA (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm).

Efficacy and Safety

Efficacy was evaluated in INAVO120 (NCT04191499), a randomized, double-blind, placebo-controlled, multicenter trial in 325 patients with endocrine-resistant, PIK3CA-mutated HR-positive, HER2-negative locally advanced or metastatic breast cancer whose disease progressed during or within 12 months of completing adjuvant endocrine therapy and who had not received prior systemic therapy for locally advanced or metastatic disease. Primary endocrine resistance was defined as relapse while on the first 2 years of adjuvant endocrine therapy (ET) and secondary endocrine resistance was defined as relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET.

Patients were randomized 1:1 to either inavolisib 9 mg or placebo orally once daily, with palbociclib 125 mg orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a cycle of 28 days, and 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 disease progression or unacceptable toxicity. Randomization was stratified by presence of visceral disease (yes or no), endocrine resistance (primary or secondary), and geographic region (North America/Western Europe, Asia, other).

The major efficacy outcome measure was investigator-assessed progression-free survival (PFS) per RECIST version 1.1. Additional efficacy outcome measures included overall survival (OS), investigator-assessed objective response rate (ORR), and duration of response (DOR). Median PFS was 15.0 months (95% CI: 11.3, 20.5) in the inavolisib +

palbociclib + fulvestrant arm and 7.3 months (95% CI: 5.6, 9.3) in the placebo + palbociclib + fulvestrant arm (Hazard ratio 0.43 [95% CI: 0.32, 0.59] p-value <0.0001). ORR was 58% (95% CI: 50, 66) in the inavolisib + palbociclib + fulvestrant arm and 25% (95% CI: 19, 32) in the placebo + palbociclib + fulvestrant arm. Median DOR was 18.4 months (95% CI: 10.4, 22.2) and 9.6 months (95% CI: 7.4, 16.6), respectively. Interim analysis of overall survival based on 63% information fraction did not reach statistical significance but was supportive of the overall benefit risk assessment with a HR of 0.64 (95% CI: 0.43, 0.97).

The most common adverse reactions (≥20%), including laboratory abnormalities, were decreased neutrophils, decreased hemoglobin, increased fasting glucose, decreased platelets, decreased lymphocytes, stomatitis, diarrhea, decreased calcium, fatigue, decreased potassium, increased creatinine, increased ALT, nausea, decreased sodium, decreased magnesium, rash, decreased appetite, COVID-19 infection, and headache.

The recommended inavolisib dose is 9 mg taken orally once daily, with or without food, until disease progression or unacceptable toxicity. Refer to the prescribing information for palbociclib and fulvestrant dosing information.

This review was conducted under Project Orbis (https://www.fda.gov/about-fda/oncology-center-excellence/project-orbis), an initiative of the FDA Oncology Center of Excellence. Project Orbis provides a framework for concurrent submission and review of oncology drugs among international partners. For this review, FDA collaborated with the Australian Therapeutic Goods Administration (TGA), Health Canada, and Switzerland's Swissmedic. The application reviews are ongoing at the other regulatory agencies.

Expedited Programs

This review used the Assessment Aid (https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid), a voluntary submission from the applicant to facilitate the FDA's assessment. The FDA approved this application 7 weeks ahead of the FDA goal date.

This application was granted priority review and breakthrough designation. FDA expedited programs are described in the Guidance for Industry: Expedited Programs for Serious Conditions-Drugs and Biologics (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics).

Healthcare professionals should report all serious adverse events suspected to be associated with the use of any medicine and device to FDA's MedWatch Reporting System (https://www.accessdata.fda.gov/scripts/medwatch/index.cfm) or by calling 1-800-FDA-1088.

For assistance with single-patient INDs for investigational oncology products, healthcare professionals may contact OCE's Project Facilitate (https://www.fda.gov/about-fda/oncology-center-excellence/project-facilitate) at 240-402-0004 or email

OncProjectFacilitate@fda.hhs.gov (mailto:OncProjectFacilitate@fda.hhs.gov).

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