FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Oncologic Drugs Advisory Committee (ODAC) Meeting
FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503)
10903 New Hampshire Avenue, Silver Spring, Maryland 20993
May 24, 2017

DRAFT QUESTIONS

NDA 208051

Neratinib maleate tablets

Applicant: Puma Biotechnology, Inc.

PROPOSED INDICATION: As a single agent for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab-based therapy.

Neratinib is a kinase inhibitor that irreversibly binds to epidermal growth factor receptors (EGFR), Human Epidermal Growth Factor Receptor 2 (HER2), and HER4.

EFFICACY

The efficacy of neratinib is based on the results of Study 3004, a multicenter, randomized, double-blind, placebo-controlled trial of one year of neratinib versus placebo in women with early stage HER2-positive breast cancer after adjuvant treatment with trastuzumab. A total of 2840 patients were randomized 1:1 to receive either neratinib (n=1420) or placebo (n=1420). The primary endpoint of the study was invasive disease-free survival (iDFS) within 2 years and 28 days.

- The primary analysis demonstrated a statistically significant stratified hazard ratio of 0.66 (0.49, 0.90) observed with an estimated 2.3% absolute difference in iDFS at two years (94.2% on the neratinib arm vs. 91.9% on the placebo arm).
- There may be a difference in the magnitude of benefit based on hormone receptor status [HR-positive HR=0.49 (0.31, 0.75), HR-negative HR=0.93 (0.60, 1.43)], however this is an exploratory subgroup analysis.

Throughout the conduct of the trial, there were multiple amendments to the protocol, and multiple changes of sponsor control. Effects of major amendments included:

1. Study population enriched with high-risk patients
2. Study follow-up time shortened from 5 years to 2 years; analysis changed from event-driven to time-driven
3. Reconsent process introduced to extend follow-up to 5 years post randomization

DRAFT QUESTIONS (cont.)

SAFETY

Safety data were evaluated in 1408 patients who received neratinib in Study 3004.

- Diarrhea was the most frequently reported adverse reaction in the neratinib arm with an overall incidence of 95% and 40% of patients experiencing at least one episode of Grade 3 diarrhea.
- Twenty eight percent of patients discontinued neratinib due to an adverse event (AE), and the most common AE leading to discontinuation was diarrhea.
- Other common adverse reactions observed in 10% or more of patients taking neratinib were nausea, abdominal pain, fatigue, vomiting, rash, stomatitis, decreased appetite, and muscle spasms.

Results from an ongoing Phase 2 study (PUMA-NER-6201, also referred to as Study 6201) suggest that antidiarrheal prophylaxis decreases the incidence and severity of diarrhea in patients treated with neratinib in the extended adjuvant setting.

QUESTION

1. **VOTE:** Given the totality of evidence, is the risk-benefit profile of neratinib sufficient to support treatment in the proposed population?
    a. Please discuss if there is a subpopulation with a more favorable risk-benefit profile.