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**GENERIC DRUG NAME / COMPOUND NUMBER:** Neratinib / PF-05208767

**PROTOCOL NO.:** 3144A2-3003 (B1891003)

**PROTOCOL TITLE:**

A Phase 2, Randomized, Open-Label Study of Neratinib Versus Lapatinib Plus Capecitabine for the Treatment of ErbB-2-Positive Locally Advanced or Metastatic Breast Cancer

**Study Centers:**

A total of 159 centers took part in the study, including 53 in the United States, 20 in Japan, 15 in Spain, 9 in Russian Federation, 6 in Hungary, 4 in Australia, 4 in France, 4 in Poland, 4 in Republic of Mexico, 4 in South Africa, 3 in Bulgaria, 3 in Croatia, 3 in Hong Kong, 3 in Italy, 3 in Romania, 3 in Switzerland, 2 in Canada, 2 in Germany, 2 in Serbia, 2 in United Kingdom and 1 each in Austria, Belgium, Czech Republic, Greece, Jordan, Korea, Singapore, Slovenia, Taiwan and Thailand.

**Study Initiation Date and Final Completion Date:**

04 February 2009 and data cutoff date for this interim public disclosure synopsis is 02 September 2011.

**Phase of Development:**

Phase 2

**Study Objective:**

The primary objective of this study was to compare the investigator assessed progression-free survival (PFS) following treatment with single-agent neratinib versus (vs) lapatinib + capecitabine in subjects with erythroblastic leukemia viral oncogene homolog 2 (erbB-2) positive locally advanced or metastatic breast cancer.

**METHODS**

**Study Design:**

This was a Phase 2, randomized, open-label study of neratinib monotherapy vs the combination of lapatinib + capecitabine in subjects with erbB-2 positive locally advanced or metastatic breast cancer. Subjects were randomized in 1:1 ratio to 1 of the 2 arms [Arm A: neratinib (240 mg) and Arm B: lapatinib (1250 mg) + capecitabine (2000 mg/m$^2$)]. Subjects received either neratinib or lapatinib + capecitabine until the occurrence of disease progression, symptomatic deterioration, intolerable toxicity, death, or withdrawal of consent. There was a long-term follow-up phase to the study, which was to conclude after 163 PFS

events had been observed. Study period was 10 months including 1 month for screening and 9 months for treatment. Subjects who had permanently discontinued treatment entered the survival follow-up period until death or until 163 PFS events had been observed, whichever occurred first. This study was to be completed in approximately 27 months, including 18 months for accrual and approximately 9 months for active treatment. The final PFS analysis was to occur after approximately 27 months (when 163 PFS events had occurred) from first subject randomization.

**Number of Subjects (Planned and Analyzed):**

A total of 230 subjects were planned, 349 screened, 233 enrolled and 231 subjects treated. A total of 231 subjects were analyzed for safety and 207 subjects were analyzed for PFS.

**Diagnosis and Main Criteria for Inclusion and Exclusion:**

Female subjects ≥18 years of age with confirmed diagnosis of erbB-2 positive, locally advanced or metastatic breast cancer that was not amenable to curative surgery and/or radiation (Stage 3B, 3C or 4). Subjects also had disease progression on or following a prior trastuzumab-containing treatment regimen, alone or in combination with cytotoxic chemotherapy or hormonal therapy for metastatic or locally advanced disease and prior treatment with a taxane in the neoadjuvant, adjuvant, locally advanced, and/or metastatic disease treatment settings.

Main Exclusion Criteria: Subjects had >2 prior trastuzumab-based regimens for metastatic or locally advanced disease; prior exposure to capecitabine, lapatinib, or other erbB-2 targeted treatments (with the exception of trastuzumab).

**Study Treatment:**

Subjects were to receive either neratinib (six 40 mg tablets orally, once daily with food, preferably in the morning continuously) or lapatinib (five 250 mg tablets orally, once daily, 1 hour before or after breakfast, continuously) + capecitabine (150 mg or 500 mg tablets, for total of 2000 mg/m$^2$ in 2 evenly divided doses orally with water within 30 minutes after a meal. Dose was taken daily for Days 1 to 14 of a 21-day cycle).

**Efficacy Endpoints:**

Efficacy was assessed by performing tumor assessments for all subjects at Screening, and then after every 6 weeks (every 2 cycles) for the first 48 weeks (16 cycles) of the treatment period of the study, and then every 12 to 18 weeks per Investigator discretion after week 48 of the study. Tumor assessments were to continue until progressive disease was documented or a new anticancer therapy was initiated.

**Safety Evaluations:**

Safety was assessed by medical history, vital signs, physical examination, electrocardiograms, left ventricular ejection fraction (multiple gated acquisitions/echocardiograms), and laboratory assessments.

**Statistical Methods:**

Efficacy variables were derived from tumor assessments, death reports or other evaluations during the study.

**RESULTS**

**Subject Disposition and Demography:**

A total of 349 female subjects were screened, of which 233 subjects aged >20 years were randomized to neratinib (117 subjects) and lapatinib + capecitabine (116 subjects) treated groups. Of the 233 subjects, 116 in the neratinib treatment group and 115 in the lapatinib + capecitabine treatment group received allocated treatment. A total of 50 died and 13 were discontinued in the neratinib treatment group. A total of 47 died and 7 were discontinued in lapatinib + capecitabine treatment group.

**Efficacy Results:**

The median PFS was longer on lapatinib + capecitabine (6.83 months, 95% CI, 5.85-8.21) than on neratinib (4.53 months, 95% CI, 3.12-5.65). For the comparison in PFS between treatment groups, the hazard ratio for neratinib was 1.19 (95% CI, 0.89-1.60; p=0.231). Since the upper bound of the 95% CI was larger than 1.15 (the non-inferiority margin) non-inferiority between the neratinib and the lapatinib + capecitabine treatment groups could not be demonstrated for the primary endpoint of PFS.

**Safety Results:**

Serious Adverse Events: Thirty-one (31) subjects in the neratinib treatment group and 25 subjects in the lapatinib + capecitabine treatment group reported 1 or more serious adverse events (SAEs). One (1) or more drug related SAEs were reported for 11 subjects in the neratinib treatment group and for 9 subjects in the lapatinib + capecitabine treatment group.

Adverse Events: A total of 113 subjects in the neratinib treatment group and 114 subjects in the lapatinib + capecitabine treatment group reported treatment-emergent adverse events (TEAEs). A total of 61 subjects in the neratinib treatment group and 58 subjects in the lapatinib + capecitabine treatment group reported Grades 3, 4, or 5 TEAEs.

Discontinuation due to Adverse Events: A total of 27 subjects (7 in the neratinib treatment group and 20 in the lapatinib + capecitabine treatment group) discontinued from the treatment due to adverse events.

Deaths: A total of 97 subjects died; 50 in the neratinib treatment group and 47 in the lapatinib + capecitabine treatment group. Most subjects died due to disease progression.

**CONCLUSION:**

The Investigator assessed PFS following treatment with single-agent neratinib was not found to be non-inferior to the PFS of lapatinib + capecitabine in subjects with erbB-2 positive locally advanced or metastatic breast cancer. This study did not meet its primary objective.