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GENERIC DRUG NAME / COMPOUND NUMBER: Neratinib (HKI-272) / WAY-179272

PROTOCOL NO.: 3144A1-200-WW (B1891037)

PROTOCOL TITLE:

Final Report: A Phase 2 Study of Neratinib (HKI-272) in Subjects With Advanced Non-Small Cell Lung Cancer

Study Centers:

A total of 21 centers; 8 centres in Europe and 13 centres in the United States took part in the study and enrolled subjects.

Study Initiation Date and Final Completion Date:

December 2005 to January 2009

Phase of Development:

Phase 2

Study Objectives:

The primary objective was to determine the overall response rate (ORR) for neratinib in subjects with advanced non-small cell lung cancer (NSCLC).

The secondary objectives were to further evaluate the safety of neratinib, assess additional efficacy endpoints; clinical benefit rate, duration of response, and progression-free survival (PFS), evaluate health outcomes endpoints by administering quality-of-life questionnaires, and evaluate the pharmacokinetics of neratinib.

METHODS

This was an open-label, phase 2, non-randomized, 3-arm study of neratinib 320 mg or 240 mg in subjects with advanced NSCLC. Enrolled subjects were assigned to 1 of 3 treatment arms, on the basis of baseline disease characteristics and prior cancer therapy:

- Treatment Arm A: Subjects who had a solid tumor with an epidermal growth factor receptor (EGFR) mutation demonstrated at Screening and disease progression after ≥12 weeks of erlotinib or gefitinib.

- Treatment Arm B: Subjects who had a solid tumor without an EGFR mutation demonstrated at Screening and disease progression after ≥12 weeks of erlotinib or gefitinib.

- Treatment Arm C: Subjects who had a diagnosis of adenocarcinoma, no prior EGFR tyrosine kinase inhibitor treatment, a ≤20 pack-year smoking history, were currently nonsmokers, and for whom an EGFR mutation was not a requirement.

Subjects participated in the study for approximately 14 months.

RESULTS

Subjects Disposition and Demography:

The study had a planned enrollment of 138 subjects; 46 subjects in each of the 3 treatment arms.

A total of 172 subjects were enrolled in the study and assigned to 1 of the 3 treatment arms in the study; these 172 subjects were considered the intent-to-treat (ITT) population. Five (5) subjects were assigned to treatment but did not receive neratinib. The safety or modified intent-to-treat (mITT) population consisted of 167 subjects. The evaluable population consisted of 158 subjects.

The safety population consisted of 167 subjects with a median age of 60 years (range, 22 to 86 years).

Efficacy Results:

The results suggested that neratinib 240 mg, given as a continual oral daily dose has limited efficacy in subjects with NSCLC.

On the basis of the independent assessment of tumor response, 3 subjects had a best overall response of a partial response (PR). All 3 subjects were enrolled in treatment Arm A. Eighty-one (81) subjects (51.3%) had a best overall response of stable disease. On the basis of the Investigator's assessment of tumor response, 1 subject in treatment Arm B had a best overall response of a CR and 2 subjects in treatment Arm A had a PR. Seventy-six (76) subjects (48.1%) had a best overall response of stable disease.

On the basis of the independent assessment of tumor response for 167 subjects in the mITT population, 4 subjects had a best overall response of a PR (3 subjects in treatment Arm A and 1 subject in treatment Arm C). Eighty-two (82) subjects (49.1%) had a best overall response of stable disease. On the basis of the Investigator's assessment of tumor response for 167 subjects, 1 subject in treatment Arm B had a best overall response of a complete response (CR) and 3 subjects had a best overall response of a PR (2 subjects in treatment Arm A and 1 subject in treatment Arm C). Seventy-seven (77) subjects (46.1%) had a best overall response of stable disease.

On the basis of the independently assessed tumor responses for 158 subjects in the evaluable population, the ORR was 1.9% (90% confidence interval (CI), 0.52%, 4.83%). The ORR for

treatment Arm A was 3.4% (90% CI, 0.94%, 8.58%). On the basis of the Investigator assessed tumor responses for the 158 subjects in the evaluable population, the ORR was 1.9% (90% CI, 0.52%, 4.83%). The ORR for treatment Arm A was 2.3% (90% CI, 0.41%, 6.98%) and the ORR for treatment Arm B was 2.2% (90% CI, 0.11%, 10.11%).

On the basis of the independently assessed tumor responses for 167 subjects in the mITTpopulation, the ORR was 2.4% (90% CI, 0.82%, 5.4%). The ORR for treatment Arm A was 3.3% (90% CI, 0.9%, 8.3%) and the ORR for treatment Arm C was 3.6% (90% CI, 0.18%, 15.85%). On the basis of the Investigator assessed tumor responses for these 167 subjects, the ORR was 2.4% (90% CI, 0.82%, 5.4%). The ORR for treatment Arm A was 2.2% (90% CI, 0.39%, 6.76%), for treatment Arm B was 2.1% (90% CI, 0.11%, 9.51%), and the ORR for treatment Arm C was 3.6% (90% CI, 0.18%, 15.85%).

On the basis of the independently assessed tumor responses for the 158 subjects in the evaluable population, the median duration of response was 54.1 weeks (90% CI, 17.9, 54.1 weeks), with data censored for 1 subject. On the basis of the Investigator assessed tumor responses for these 158 subjects, the median duration of response was 46 weeks (90% CI, 38.1 weeks, not evaluable), with data censored for 1 subject.

On the basis of the independently assessed tumor responses for the 158 subjects in the evaluable population, the median PFS was 15.3 weeks (90% CI, 14.7, 15.9 weeks), with data censored for 58 subjects. On the basis of the Investigator assessed tumor responses for these 158 subjects, the median PFS was 12.1 weeks (90% CI, 7.9, 14.7 weeks), with data censored for 11 subjects.

On the basis of the independently assessed tumor responses for the 158 subjects in the evaluable population, the median time to tumor progression (TTP) was 15.6 weeks (90% CI, 15.1, 16 weeks), with data censored for 72 subjects. On the basis of the Investigator assessed tumor responses for these 158 subjects, the median TTP was 12.7 weeks (90% CI, 8.1, 15 weeks), with data censored for 17 subjects.

Safety Results:

At least 1 treatment emergent adverse events (TEAE) was reported for 165 subjects (98.8%). The TEAEs of any toxicity grade reported for ≥20% of subjects, regardless of the starting dose of neratinib, were diarrhea (91% of subjects), nausea (55.1%), fatigue (37.1%), vomiting (35.3%), abdominal pain (32.3%), anorexia (32.3%), dyspnea (29.3%), cough (24%), and asthenia (22.2%).

At least 1 grade 3 or higher drug-related TEAE was reported for 61 subjects (36.5%). The grade 3 or higher drug-related TEAEs reported for ≥2% of subjects were diarrhea (28.1% of subjects), vomiting (4.2%); and lymphopenia, anorexia, and dehydration (2.4% each). Subjects who received neratinib 320 mg reported a higher percentage of grade 3 or higher drug-related diarrhea (46.2%) compared with subjects who received neratinib 240 mg (22.7%).

Death was reported for 28 subjects (17%), and 25 subjects died within 28 days after receiving the last dose of neratinib. Disease progression was the reported cause of death for

26 subjects. Pleural effusion, which was considered to be disease related, was reported as the cause of death for 1 subject, and disease-related general health deterioration was reported as the cause of death for 1 subject. All deaths were considered to be disease related.

At least 1 serious adverse event (SAE) was reported for 70 subjects (41.9%). Many of the SAEs were associated with disease progression, metastasis, and death associated with cancer. The SAEs reported for ≥3% of subjects were pleural effusion (12 subjects, 7.2%); general physical health deterioration (11 subjects, 6.6%); NSCLC (disease progression), and dyspnea (8 subjects each, 4.8%); and diarrhea, nausea, vomiting, dehydration, and pneumothorax (5 subjects each, 3%).

Eleven (11) subjects (6.6%) had at least 1 TEAE that led to the discontinuation of treatment and withdrawal from the study. The most commonly reported TEAEs that led to discontinuation of treatment and study withdrawal were diarrhea (4 subjects, 2.4%) and dehydration (2 subjects, 1.2%).

CONCLUSIONS:

The results suggest that neratinib 240 mg, given as a continual oral daily dose has limited efficacy in subjects with NSCLC:

- On the basis of the independent assessment of tumor response for 158 subjects in the evaluable population, 3 subjects had a best overall response of a PR; all 3 subjects were assigned to treatment Arm A, and all had the same G719A/S EGFR mutation.
- On the basis of the independent assessment of tumor response, 81 subjects (51.3%) in the evaluable population had a best overall response of stable disease.
- On the basis of the independently assessed tumor responses for the 158 subjects in the evaluable population, the median PFS was 15.3 weeks (90% CI, 14.7, 15.9 weeks), with data censored for 58 subjects and median TTP was 15.6 weeks (90% CI, 15.1, 16.0 weeks), with data censored for 72 subjects.

Neratinib was reasonably well tolerated:

- Diarrhea was the most commonly reported TEAE of any grade and the most commonly reported grade 3 or higher TEAE. Most reports of diarrhea were considered to be drug related.
- Neratinib 240 mg was better tolerated than neratinib 320 mg with a lower frequency of grade 3 diarrhea and dose reductions reported for the neratinib 240-mg cohort.
- Diarrhea was reversible and generally manageable with antidiarrheal medication, treatment interruption or dose reduction.
- Other commonly reported TEAEs of any grade (≥10% of subjects) were nausea, vomiting, fatigue, and anorexia.

- No clinically important changes in clinical laboratory test results or vital signs measurements were associated with neratinib. No consistent changes in electrocardiogram values were reported.