A randomized phase 2 study with exploratory biomarker analysis of ficlatuzumab, a humanized hepatocyte growth factor (HGF) inhibitory monoclonal antibody, in combination with gefitinib versus gefitinib alone in Asian patients with lung adenocarcinoma

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Background: HGF-Met pathway activation has been implicated in solid tumor growth and progression. The current study, which tested fucaltuzumab (formerly SCH 900105) plus gefitinib, is the first clinical trial to directly evaluate the combined inhibition of EGFR and HGF in NSCLC. This study was initially designed to test the combination of gefitinib plus placebo. However, based on preclinical data, the dose of fucaltuzumab was increased, and fucaltuzumab plus gefitinib was included,

Methods: This is a randomized, controlled, phase 2 study in Asian patients with stage IIIB or IV lung adenocarcinoma who have not received prior systemic therapy. Patients were randomized to gefitinib alone or fucaltuzumab plus gefitinib, based on the availability of archived or available tumor tissue for genotyping.

Results: Of 174 randomized patients, 94 were evaluable for ORR and PFS. There was no statistically significant difference in the ORR (primary endpoint) between treatment arms (40% vs. 60%, HR 0.50, 95% CI 0.18-1.35). However, OS was increased in patients treated with fucaltuzumab plus gefitinib compared to gefitinib alone (60% of pts 40 vs. 20% 40, HR 0.79, 95% CI 0.33-1.92). Preliminary OS results suggest that addition of fucaltuzumab to gefitinib may significantly improve survival in a subset of pts with both EGFR-sensitizing mutations and low c-Met.

Statistical Methods

The study was designed to enroll 120 evaluable pts (40 in each arm), with an expected 30% ORR for gefitinib alone. The study is powered to detect an improvement in response rate from 40% to 60% (Hypothesis: ORR gefitinib vs. fucaltuzumab plus gefitinib 0.40 vs. 0.60; Power=80% / α=0.05). We used Fisher’s exact test to compare the ORR between treatment arms. Time-to-event outcomes were analyzed using Kaplan-Meier methodology and compared using log-rank test. Risk factors for response and PFS were analyzed using Cox proportional hazards regression. A subset analysis was performed using censoring and imputation methods. A two-sided 0.05 level was used as the significance level. All analyses were performed using SAS statistical software (Version 9.2). The sample size was computed based on a target of 174 evaluable patients.

Results: The trial included 174 patients, of whom 94 were evaluable for ORR and PFS. There was no statistically significant difference in the ORR (primary endpoint) between treatment arms (40% vs. 60%, HR 0.50, 95% CI 0.18-1.35). However, OS was increased in patients treated with fucaltuzumab plus gefitinib compared to gefitinib alone (60% of pts 40 vs. 20% 40, HR 0.79, 95% CI 0.33-1.92). Preliminary OS results suggest that addition of fucaltuzumab to gefitinib may significantly improve survival in a subset of pts with both EGFR-sensitizing mutations and low c-Met.

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