Efficacy of Rociletinib (CO-1686) in Plasma-genotyped T790M-positive Non-small-cell Lung Carcinoma Patients

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Background. Rociletinib (CO-1686) is an oral irreversible inhibitor of mutant epidermal growth factor receptor (EGFR), including the T790M variant. Rociletinib was initially studied in single-arm trials in patients with mutant EGFR non-small-cell lung carcinoma (NSCLC) and acquired resistance to tyrosine kinase inhibitor (TKI) therapies. Here, we present the results of the patient subset with T790M detected by plasma genotyping, focusing on the treatment group who received the recommended dose of 500 mg rociletinib twice daily (bid).

Methods. The overall phase 1/2 open-label study enrolled patients with advanced or recurrent EGFR-mutant NSCLC, who previously received EGFR-targeting therapy. Phase 2 only included patients with disease progression under EGFR-targeting treatment and biopsy-proven T790M mutation at study entry. Brain metastases were allowed. Plasma *EGFR* status was assessed by BEAMing (Sysmex Inostics), a quantitative test using emulsion polymerase chain reaction followed by flow cytometry. In phase 2, patients received rociletinib hydrobromide at 500/625/750/1000 mg bid. Key outcomes were safety, tolerability, pharmacokinetic profile, and objective response rate (ORR).

Results. Overall, 456 patients (500 mg group: n=119) were included in phase 2, 84% at US-sites. Median age was 63 years, 66% female, 28% Eastern cooperative oncology group performance status 0, with a median of two prior therapies (82% immediate prior TKI). Best response data were available for 243 (500 mg group: n=48) and 147 (500 mg group: n=30) patients with tissue and plasma genotyping, respectively. Among 500 mg receivers, ORR was 60% (all doses: 53%) and 57% (all doses: 53%) for tissue and plasma genotyping, respectively, and the disease control rate was 90% (all doses: 85%), and 80% (all doses: 82%) among patients with tissue- and plasma-confirmed T790M positivity, respectively. The median progression-free survival was 8 months in all 500-mg or 625-mg receivers (n=270), 10.3 months among those without brain metastases. Treatment-related all-grade adverse events (AEs) in ≥15% patients in the 500 mg group included hyperglycemia (35%, n=42), diarrhea (33%, n=39), nausea (19%, n=23), and decreased appetite (15%, n=18); 2.5% patients discontinued treatment because of an AE. Grade 3/4 hyperglycemia developed in 20% (n=17%) of 500 mg receivers and was readily managed with oral therapeutics. Among patients with T790M negativity, ORR was 37% (n=13/35). No resistance mechanism could be established in this study.

Conclusions. At the recommended dose of 500 mg bid, rociletinib was well-tolerated and showed good response rates in patients with mutant EGFR NSCLC. Plasma genotyping may be a viable alternative to tissue biopsies for T790M detection. Further studies are underway to establish the efficacy of rociletinib and benchmark it against other therapies.