O – 011 Assessment of tumor response, AFP response, and time to progression in the phase 3 CELESTIAL trial of cabozantinib versus placebo in advanced hepatocellular carcinoma (HCC)

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Introduction: Cabozantinib inhibits tyrosine kinases including MET, vascular endothelial growth factor receptors, and AXL. In the CELESTIAL trial (NCT01908426), cabozantinib improved overall survival and progression-free survival compared with placebo in patients with previously treated advanced HCC. The study met the primary end point, with a median overall survival of 10.2 months with cabozantinib versus 8.0 months with placebo (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.63–0.92; P = 0.0049). Median progression-free survival was 5.2 months with cabozantinib versus 1.9 months with placebo (HR, 0.44; 95% CI, 0.36–0.52; P < 0.0001), and the objective response rate was 4% with cabozantinib versus 0.4% with placebo (P = 0.0086) per Response Evaluation Criteria in Solid Tumors v1.1. Here, we report a secondary analysis of tumor response including the best percentage change at any timepoint in tumor target lesion size, the best percentage change at any timepoint in serum alpha-fetoprotein (AFP) levels, and time to progression (TTP).

Methods: A total of 707 patients, stratified by disease etiology, geographic region, and extent of disease, were randomized 2:1 to receive cabozantinib 60 mg once daily (n = 470) or placebo (n = 237). Eligible patients had a pathologic diagnosis of HCC, Child-Pugh score A, and an Eastern Cooperative Oncology Group performance status ≤1. Patients must have received prior sorafenib and were allowed up to 2 lines of prior systemic therapy for HCC. Change in the sum of target lesion diameters (SOD) from baseline was determined every 8 weeks by the investigator. Best percentage change in SOD was defined as the maximum reduction in SOD at any postbaseline timepoint. Serum AFP levels were measured centrally at baseline and every 8 weeks on the same schedule as tumor assessments. TTP was defined as the time from randomization to radiological progression or clinical deterioration and was determined retrospectively.

Results: Based on the intention-to-treat population, 222 of 470 patients (47%) in the cabozantinib arm and 27 of 237 patients (11%) in the placebo arm had any postbaseline reduction in SOD as a best response. Thirty-nine of 470 patients (8%) in the cabozantinib arm and 3 of 237 patients (1%) in the placebo arm had at least 1 postbaseline tumor assessment with a ≥ 30% reduction in SOD. The percentages of patients in the cabozantinib arm with a ≥ 30% reduction in postbaseline SOD were 9% (n = 26/278) and 7% (n = 13/192) among those with a baseline AFP level <400 ng/mL versus ≥400 ng/mL, respectively. Overall, 109 of 470 patients (23%) in the cabozantinib arm and 13 of 237 (5%) in the placebo arm had a ≥ 50% postbaseline decrease in serum AFP levels. Median TTP was 5.4 months with cabozantinib versus 1.9 months with placebo (HR, 0.41; 95% CI, 0.34–0.49).

Conclusion: Cabozantinib is associated with improved TTP, higher rates of target lesion regression, and AFP response compared with placebo in patients with previously treated advanced HCC.