Phase I dose-finding study of golvatinib (E7050), a c-Met and Eph receptor targeted multi-kinase inhibitor, administered orally QD to patients with advanced solid tumors.

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Abstract Disclosures

Abstract:

Background: Golvatinib is a highly potent, small molecule ATP-competitive inhibitor of the c-Met receptor tyrosine kinase and multiple members of the Eph receptor family as well as c-Kit and Ron, based on isolated kinase assays. Golvatinib showed preclinical evidence of anti-tumor activity. This phase 1 study was performed to determine the MTD, safety, PK, PD and preliminary activity of golvatinib. **Methods:** Patients (pts) with advanced solid tumors, ECOG PS 0-1, ≥ 18 years (yrs) and adequate organ function were eligible. Golvatinib was administered orally, once daily (QD), continuously. Blood samples for PK and PD analysis were collected at multiple time-points. Mandatory tumor biopsies for PD analysis were taken pre and post Cycle 1 in an expanded MTD cohort. **Results:** 34 pts (M/F: 21/13; median age 63.5yrs [range 32-78]) were treated at 6 dose levels: 100, 200, 270, 360, 450 and 400 mg. Tumor types were colorectal (n=15), lung (n=4), renal (n=4), esophageal (n=2), melanoma (n=2) and others (n=7). Three DLTs were observed: Gr3 GGT and alkaline phosphatase (n=1; 200mg) and repeated Gr2 (n=1) and Gr3 (n=1) fatigue, both at 450mg. The MTD was determined to be 400 mg QD. Frequently occurring adverse events ([AEs]; all grades) were fatigue: 68% (Gr3: 15%), diarrhea: 65%, nausea: 62%, vomiting: 53%, decreased appetite: 47% (Gr3: 9%), ALT increase: 38% and AST increase: 23%. No Gr4 AEs were observed. Best response was stable disease in 6 pts lasting >84 days. PK showed high variability and plasma concentration increased with dose. The Cmax was reached within a median time of 4 hours. Plasma PD analysis showed an increase in soluble c-Met and Ang 2 levels after golvatinib treatment. Tumor PD analysis in 5 pts at 400 mg demonstrated a baseline elevated MET gene copy number, with c-Met overexpression and post treatment decline in phospho(p)-c-

Met expression in 1 pt; post-treatment decline in p-c-Met in a 2nd pt, and post-treatment decline in p-ERK in a 3rd pt. **Conclusions:** Golvatinib at an MTD of 400 mg QD has manageable toxicity. Preliminary PD analysis demonstrated evidence of c-Met target modulation. Further evaluation will continue in phase 2 combination studies.