2506^ **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Phase I study of oral selective c-Met inhibitor EMD 1214063 in pts with advanced solid tumors.

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Background: To perform the first-in-human study of EMD 1214063, a highly selective, reversible, ATP-competitive c-Met inhibitor that causes growth inhibition and regression of hepatocyte growth factor-dependent and -independent tumors in preclinical models. **Methods:** Primary objective of this dose-escalation study (3+3 design) was to establish the EMD 1214063 MTD (NCT01014936). Secondary endpoints included safety, PK, antitumor effect, and pharmacodynamics (Pd). Eligible pts had advanced solid tumors not amenable to standard therapy. Pts received once daily (QD) oral EMD 1214063 on 1 of 3 regimens (all 21-d cycles): d 1–14 followed by 7-d rest (R1), continuous 3 times weekly (R2), or d 1–21 (R3). An optimized formulation (OF) was introduced in Aug 2011. **Results:** 100 pts were treated (R1:42; R2:41; R3:17). On the initial formulation, doses were escalated from 30–230 mg/d in R1, and 30–115 mg/d in R2. OF data are available for 30–400 mg/d in R1, 60–175 mg/d in R2, and up to 500 mg/d in R3. C_{max} and AUC increased with dose; OF showed higher bioavailability. 4 pts experienced DLTs: G4 lipase and G3 amylase increase (R1; 115 mg/d), G3 lipase increase (R2; 60 and 115 mg/d), and G3 nausea and vomiting (R2; 130 mg/d OF). Other G3 drug-related AEs included G3 peripheral edema (1 pt in R3, 300 mg/d OF). G2 drug-related AEs (R1-3) included fatigue (n=8), lipase increase (n=3), nausea (n=2), decreased appetite (n=2), vomiting (n=2), and neutropenia (n=2). 80% pts had no drug-related AE >G1. Pre- and on-treatment tumor biopsies showed inhibition of phospho-c-Met levels in 13/15 evaluable pts. 2 unconfirmed partial responses were observed (NPC and NSCLC). SD >4 mo was observed in 15 pts. 1 pt with sarcomatoid bladder cancer and multiple MET copies due to Chr 7 polysomy had SD for >32 mo. PK/Pd analysis suggested that 500 mg QD was sufficient for target inhibition, consistent with preclinical models. In the 500 mg QD cohort, which was expanded to 12 pts, no DLTs were observed. 500 mg QD was confirmed as the recommended phase 2 dose (RP2D). A formal MTD was not identified despite dose escalation beyond 500 mg. Dose escalation above 1000 mg is not anticipated. **Conclusions:** EMD 1214063 was safe and demonstrated antitumor activity. 500 mg QD was determined as the RP2D. Clinical trial information: NCT01014936.