First-in-human study of AMG 208, an oral MET inhibitor, in adult patients (pts) with advanced solid tumors.

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Abstract Disclosures

Abstract:

Background: AMG 208 is a small molecule MET inhibitor that suppresses proliferation and induces apoptosis in human tumor xenografts. This first-in-human study evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of AMG 208. We report data from the dose escalation part of the study. **Methods:** Key eligibility criteria: ≥ 18 yr, advanced solid tumors, ECOG ≤ 2, and evaluable/measurable disease. Using a modified Fibonacci design, 3–9 pts were enrolled into 1 of 7 sequential dose cohorts (25, 50, 100, 150, 200, 300, and 400 mg) of AMG 208. Pts received AMG 208 orally on days 1 and 4–28 once daily. If no dose limiting toxicity (DLT) was seen on days 1–28, pts received AMG 208 once daily starting at day 36 provided pts showed no evident disease progression. In cohorts 1–3, a standard 3+3 design was followed. In cohorts 4–7, a modified 3+3+3 design was followed. **Results:** As of July 16 2012, 54 pts (25 mg [n=6], 50 mg [n=4], 100 mg [n=4], 150 mg [n=3], 200 mg [n=16], 300 mg [n=10], and 400 mg [n =11]) had received ≥ 1 dose of AMG 208. 67% were men; 19% had prostate cancer (PC). Median (range) age: 61 (39–80) yr. ECOG 0/1: 52%/48%. 6 DLTs were seen: a grade (G) 3 increased AST (200 mg), a G3 thrombocytopenia (200 mg), a G4 acute myocardial infarction (300 mg), a G3 prolonged QT (300 mg), and two G3 hypertensions (400 mg). The maximum tolerated dose was not reached. 83% of pts had tx-related adverse events (AE). Tx-related AE occurring in > 10 pts: fatigue (n=24), nausea (n=18), hypertension (n=12), and diarrhea (n=11). 24% of pts had grade ≥ 3 tx-related AE. AMG 208 was orally bioavailable with a 30–35 hr mean half-life in plasma. Exposure increased linearly with dose; accumulation at day 28 was 2.7-fold across cohorts. Of the 42 pts with available tumor response data for site reads, 1 had complete response on bone scan (PC 300 mg) while 2 had partial responses (PR; PC 400 mg and kidney cancer 200 mg; both had -33% tumor shrinkage), and 29 had stable disease (SD); 1 other PC pt had PR after data cutoff. Of the 35 pts with available tumor response data for central reads, 26 had SD. FLT and biomarker data will be presented. **Conclusions:** AMG 208 up to 400 mg daily had manageable toxicities and showed evidence of antitumor activity, especially in prostate cancer. Clinical trial information: **NCT00813384**.