444PD | PHASE I DOSE-ESCALATION STUDY OF ORAL SELECTIVE C-MET INHIBITOR EMD 1214063 IN PATIENTS WITH ADVANCED SOLID TUMORS

G.S. Falchook[1], D.S. Hong[1], H.M. Amin[1], S. Fu[1], S.A. Piha-Paul[1], M.B. Klevesath[2], V. Jego[3], A. Johne[2], S. Stinchi[4], R. Kurzrock[1]

[1]Houston, TX/US, [2]Darmstadt/DE, [3]Geneva/CH, [4]Colleretto Giacosa/IT

Purpose

The cell surface receptor tyrosine kinase c-Met and its ligand, hepatocyte growth factor (HGF), mediate cell migration, survival and proliferation. EMD 1214063 is a highly selective, reversible and ATP-competitive c-Met inhibitor that causes growth inhibition and regression of HGF-dependent and HGF-independent tumors in pre-clinical models.

Methods

This is a first-in-man dose-escalation study to establish the MTD of EMD 1214063. Eligible pts had advanced solid tumors not amenable to standard therapy. Following a 3 + 3 dose escalation scheme, pts were treated with once-daily oral EMD 1214063 according to two 21-day-cycle schedules, either days 1-14 followed by a 7-day rest (regimen 1, [R1]), or continuous 3 times weekly (regimen 2, [R2]). An optimised formulation was introduced in August 2011. Pd markers were evaluated in paired tumor biopsies using immunohistochemistry (IHC) and a Luminex based assay.

Results

Until 3 November 2011, 50 pts had been treated; 27 in R1 and 23 in R2. The dose was escalated from 30 mg/day to 230 mg/day in R1 and to 115 mg/day in R2 with the initial formulation. For the optimised formulation, data are available for 30 mg and 60 mg/day for R1, and for 60 mg/day in R2. Cmax and AUC increased with dose. The optimised formulation showed higher oral bioavailability. Two DLTs were reported, a G4 lipase and G3 amylase elevation in 1 pt in R1 at 115 mg/day, and a G3 lipase elevation in R2 at 115 mg/day. No treatment-related SAEs were observed. Treatment-related AEs of ≥G2 included nausea (n = 1), vomiting (n = 1), decreased appetite (n = 2), diarrhea (n = 1), and fatigue (n = 1) in R1, and neutropenia (n = 1) and fatigue (n = 1) in R2. Forty-four patients (88%) had no drug-related AE >G1. Analysis of pre- and on-treatment biopsies showed decreased phospho-c-Met staining intensity under treatment on IHC and >80% reduction in phospho-c-Met levels on the Luminex assay. Preliminary anti-tumor activity included an unconfirmed PR in 1 pt and SD ≥4 months in 7 pts. One pt with sarcomatoid bladder cancer and multiple MET copies due to polysomy of Chr 7 achieved SD for 12+ months.

Conclusion

The MTD has not yet been reached and dose escalation of EMD 1214063 continues. Updated results will be presented.

Disclosure

G.S. Falchook: Has a consultant/advisory relationship with EMS Serono, received research funding of EMD Serono, received travel reimbursement from EMD Serono.

H.M. Amin: Received research funding of EMD Serono

M.B. Klevesath: Merck KGaA employee

V. Jego: Merck Serono employee

A. Johne: Merck Serono employee

S. Stinchi: Merck Serono employee

R. Kurzrock: Received research funding of EMD Serono and Merck KGaA

All other authors have declared no conflicts of interest.

Session Info: Poster Discussion, [] Developmental therapeutics
Day/Date: Sunday, September 30, 2012
Session Time: 1:00 PM - 2:00 PM
Room: Hall H