

Phase 1 study of ARQ 197, a selective inhibitor of the c-Met RTK in patients with metastatic solid tumors reaches recommended phase 2 dose.

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Abstract: **Background:** ARQ 197 is a selective inhibitor of the c-Met receptor tyrosine kinase, an oncogene implicated in tumor invasiveness, metastasis, cancer cell proliferation, resistance to apoptosis, chemoresistance and angiogenesis. The c-Met RTK is a high-affinity receptor for hepatocyte growth factor (HGF). c-Met and HGF are dysregulated in a broad spectrum of cancers, thus inhibitors of c-Met could be promising targeted agents deserving clinical investigation. **Methods:** A phase 1 dose escalation study in metastatic pts who failed standard therapy was initiated to determine safety, tolerability, RP2D, pharmacokinetics, pharmacodynamics and preliminary antitumor activity of ARQ 197. Cycles consisted of twice-daily oral dosing of ARQ197 for two out of 3 weeks. **Results:** Thirty-eight pts were enrolled with data available for 36 pts (21M/15F; median age 61). Ten cohorts were assessed ranging from 10 to 360 mg/day. ARQ 197 was well tolerated and no DLT was observed. All treated pts achieved plasma drug concentrations significantly above the *in vitro* IC₅₀. Doses through 70 mg b.i.d. revealed C_{max} and AUC_(0-12hr) increased linearly. There was no further increase in systemic exposure in pts treated with 90 through 180 mg b.i.d. There was notable inter-patient variability in C_{max} and AUC_(0-12hr), typical of oral dosing. The effects of cytochrome P450 polymorphism will be discussed. Adverse events (N=29) were generally mild with the most common being: fatigue (24 %), diarrhea (21%), and constipation (21%). Grade 3 or greater events possibly or probably related to ARQ 197 include: elevated ALP (3%), ALT (3%) and AST (3%). Of the 38 pts enrolled, 36 received at least one complete cycle of ARQ 197 with 33 evaluable for efficacy. Two pts achieved a PR (1 confirmed) and 19 had stable disease (SD) 21 10+ to 34+ weeks. **Conclusions:** Based on pharmacokinetic data, a RP2D for ARQ 197 was determined to be 120 mg b.i.d. Higher oral doses did not result in increased systemic exposure to the drug. Eleven pts remain on study and continue to receive ARQ 197 treatment. A favorable adverse event profile and encouraging signs of anti-tumor activity was observed and continuous daily dosing of ARQ 197 is now being explored to better define clinical toxicity and efficacy.

Associated Presentation(s):

- 1. Phase 1 study of ARQ 197, a selective inhibitor of the c-Met RTK in patients with metastatic solid tumors reaches recommended phase 2 dose.**

Meeting: [2007 ASCO Annual Meeting](#)

Presenter: [Agustin Garcia, MD](#)

Session: [Developmental Therapeutics: Molecular Therapeutics](#) (Oral Presentation)



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