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**Abstract**

## **First in human phase I study of MK-2461, a small molecule inhibitor of c-Met, for patients with advanced solid tumors**

**L. H. Camacho, S. L. Moulder, P. M. LoRusso, G. R. Blumenschein, P. J. Bristow, R. Kurzrock, S. Fu, K. Schlienger and D. A. Bergstrom**

University of Texas M. D. Anderson Cancer Center, Houston, TX; Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, MI; Merck Research Laboratories, Upper Gwynedd, PA

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**Background:** MK-2461 is a potent small molecule inhibitor of c-Met, a receptor tyrosine kinase involved in tumor cell proliferation and motility. Over-expression of c-Met or Met gene amplification has been associated with poorer prognosis in several tumor types. **Methods:** Multicenter, open-label, phase I dose escalation study in patients with advanced solid tumors refractory to standard therapy. Drug was administered by mouth daily or twice daily (BID) for 28 days followed by a 14 day rest period during cycle 1. Patients received continuous dosing subsequently for 28-day cycles. Maximum tolerated dose (MTD) was determined using a standard 3+3 dosing design. PK analyses were performed on days 1 and 28 of cycle 1. **Results:** Fourteen patients (10 M/ 4 F), mean age 54 (range 19–76), have received 31 cycles (range 1–6). Dose levels tested include 60mg daily, 60mg BID, 120mg BID, and 180 mg BID. Toxicity data are available for 11 patients treated at the 60mg daily-120mg BID dosing cohorts. Ten patients (91%) have not experienced > Grade 1 drug-related toxicity. Dose limiting toxicity has not been reached and no objective antitumor responses have been observed. One patient with mucinous carcinoma of the appendix had stable disease for 6 cycles. Common drug related toxicities are outlined in

the table below. Four patients experienced serious adverse experiences that were considered not related to MK-2461. PK analysis revealed a rapid T<sub>max</sub> (1–3 hr) across all dosing cohorts with a terminal half life of 6.3 hr following the final day of dosing for the QD dosing cohort. **Conclusions:** Twice daily administration of MK-2461 at the doses tested is well tolerated. Terminal t<sub>1/2</sub> suggests acceptable drug plasma concentrations expected at BID dosing. Dose escalation continues.