

A Phase II Clinical and Translational Study of MK-2206 in Patients with Metastatic Neuroendocrine Tumors (NETs)

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Background: Up-regulation of the PI3K pathway is associated with poor prognosis in NET cell lines. In patients treated with mTOR inhibitors, up-regulation of AKT may be a key driver in development of resistance. We hypothesized that blockade of AKT would result in eliminating one of the key drivers of tumor growth. We evaluated the safety and efficacy of MK-2206, an orally active, allosteric Akt inhibitor of human Akt1, Akt2, and Akt3 as monotherapy in metastatic progressive NET patients.

Methods: A phase II study was performed in which patients received MK-2206 at a dose of 200 mg PO weekly.

Results: The study was terminated early on the basis of a business decision by the sponsor. 8 patients were treated (6 carcinoid, 2 pNET) female, 25%; median age, 58.5 years, range 25-66. There were no complete or partial responses. 1 patient (atypical thymic carcinoid with brain metastases refractory to all standard therapies including mTOR and VEGF inhibitors) experienced a 17% decrease in tumor size (SD) for over 10 months. Three patients (4/8, 50%) had SD for 12 weeks or longer by RECIST (range 4.2-10.2 months). Grade 3 adverse events thought to be potentially related to MK-2206 were hyperglycemia (3 pts, 37.5%), liver enzyme increase (3 pts, 37.5%) and skin rash (3 pts, 37.5%). There were no serious adverse events (SAEs) related to MK-2206. Next generation sequencing assay of the one tumor shrinkage pre and post therapy failed to identify any pathway mutations (i.e., no PTEN loss, no AKT amplification, and no PI3KCA/AKT mutations).

Conclusion: MK-2206 alone was well tolerated. Although the study was incomplete, evidence of antitumor response in a refractory carcinoid tumor is of interest. Further evaluation of agents targeting AKT and/or PI3K are warranted in NETS. Preclinical studies are ongoing to better define a potential targeted population.