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An Open-label, Phase II Study Evaluating the Safety and Efficacy of PTK787/ZK222584 in Patients with Metastatic Neuroendocrine Tumors that Have Evidence of Progressive Disease or an Increase in Disease Related Syndrome Symptoms

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Background: Vatalanib inhibits endothelial growth factor receptor (VEGFR) by binding to the intracellular kinase domain of all 3 VEGFRs. Neuroendocrine tumors (NETs) express VEGF receptors. Inhibiting VEGF with bevacizumab, sorafenib, and sunitinib reduced time to progression or tumor size in some NET patients (pts). To determine vatalanib's tolerability and efficacy in NET pts, a trial was performed.

Methods: Eligibility criteria included NET pts with biopsy-proven metastatic disease and rising biomarkers on somatostatin analog therapy. Eligible pts had measurable lesions, a KPS > 60%, and normal hematologic, renal, and hepatic functions. A stable octreotide LAR dose, not exceeding 30 mg monthly, was required. Initial total daily dosing of vatalanib was 1,250mg. Biochemical responses within a 90 day interval were the primary response criteria. Secondary endpoints included radiographic/scintigraphic scan changes and safety.

Results: Twenty-four pts (12 males) were enrolled between 5/20/05 to 5/28/09. The median age (range) was 60.4 (25-74). Eighteen pts were evaluable for efficacy and safety. Four pts continue on therapy. One pt withdrew consent; 2 pts died of disease prior to first cycle initiation; 1 pt was allergic to vatalanib. Six pts required a 10-28 day discontinuation for rising SGOT/SGPT, alkaline phosphatase, G2 proteinuria, G2 headache, and G3 nausea/vomiting. Resumption of vatalanib at 1,000mg daily was well tolerated in 2 pts and 750mg in another. One pt developed carcinoid crisis with fever, flushing, and rising 5HIAA. Grade 1 nausea occurred in 15 pts with antiemetics required for 4 pts. A partial (> 50% decrease) biochemical response occurred in 4 pts. The observed radiographic and scintigraphic responses in 16 pts have shown progressive disease in 6 and stable/minimal response in 10 pts. Accrual continues.

Conclusions: Vatalanib is well tolerated in most pts and results in a 24% biochemical partial response rate in NET pts with rising biochemical markers on somatostatin analog therapy.