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Multi-center Phase II Trial of Temsirolimus (TEM) and Bevacizumab (BEV) in Pancreatic Neuroendocrine Tumor (PNET): Results of a Planned Interim Efficacy Analysis

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Background: PNET has long had few effective therapies other than chemotherapy. Recent placebo-controlled phase III trials of the mTOR inhibitor everolimus and the VEGF/ PDGF receptor inhibitor sunitinib noted improved progression-free survival (PFS). However, objective response rates (RR) with these agents are still <10%. Preclinical studies suggest enhanced anti-tumor effects with combined mTOR and VEGF targeted therapy.

Methods: We conducted a phase II trial of the mTOR inhibitor TEM (25 mg IV q week) and the VEGF-A monoclonal antibody BEV (10 mg/kg IV q 2 weeks) in patients (pts) with well or moderately differentiated PNET and progressive disease by RECIST within 7 months of study entry. Co-primary endpoints were RR and 6-month PFS. Planned enrollment is 50 patients, with interim analysis for futility after the first 25 evaluable pts. Pts had no prior mTOR or VEGF targeted agents, ECOG PS 0-1, and adequate hematologic and organ function. Continued octreotide was allowed, but not required. Prior interferon, embolization, and ≤ 2 chemotherapy regimens were allowed.

Results: Confirmed PR was documented in 13 of the first 25 (52%) evaluable patients. 21 of 25 (84%) patients were progression-free at 6 months. Both endpoints exceeded the protocol-defined criteria to continue enrollment. For 36 evaluable patients, the most common grade 3-4 adverse events attributed to therapy were hypertension (14%), leukopenia (11%), lymphopenia (11%), hyperglycemia (11%), mucositis (8%), hypokalemia (8%), and fatigue (8%).

Conclusion: The combination of TEM/BEV has substantial activity in a multi-center phase II trial with RR of 52%, well in excess of single targeted agents in PNET. 6-month PFS was a notable 84% in a population of patients with RECIST criteria progression within 7 months of study entry. Accrual is ongoing.