T-2:

A Phase 1 Study of Fosbretabulin in Combination with Everolimus in Neuroendocrine Tumors (Grades 1-3) That Have Progressed After At Least One Prior Regimen for Metastatic Disease

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BACKGROUND: Gastroenteropancreatic neuroendocrine tumors (GEPNETs) are rare tumors with limited treatment options. Recent SEER database analysis shows consistent surge in incidence of GEPNETs. Current approved systemic treatment for metastatic disease is limited to somatostatin analogs, everolimus, sunitinib for G-1 and G-2 GEPNETs. G-3 NETs are treated with platinum based IV chemotherapy. Limited treatment options exist for progressive disease. Fosbretabulin is a synthetic, water-soluble, phosphorylated prodrug of the natural product Combretastatin A4 (CA4P), which was originally isolated from the bark of the South African bush willow, Combretum caffrum. Fosbretabulin is the lead compound in a class of agents termed vascular disrupting agents (VDAs) and has shown activity as single agent in ovarian cancers and GEPNETs. Rationale: The vasoconstrictive effect of fosbretabulin is potent, though short-lived (4-8 hours), with no cumulative adverse effect. Everolimus inhibits angiogenesis, slows tumor growth and has a prolonged half-life (30 hours). Combining these two agents with distinctly different mechanisms of action may improve tumor control without additional toxicities, and has the potential of reducing drug resistance.

METHODS: This is an investigator initiated, single center, open label, phase I study involving grade I-III gastroenteropancreatic neuroendocrine tumors, consisting of a dose escalation Part A followed by an expansion cohort Part B. Primary Objective is to establish the maximum tolerated dose of the combination of everolimus and fosbretabulin in neuroendocrine tumors (Grades 1-3) that have progressed after at least one prior regimen for metastatic disease. Secondary objectives include evaluation of safety profile of the combination and to observe and record anti-tumor activity. Patients will be treated with daily oral everolimus. Fosbretabulin will be administered IV either q3 weekly or q weekly based on partial order continuous reassessment model (PO CRM).

RESULTS: Trial in progress. ClinicalTrials.gov Identifier: NCT03014297

CONCLUSION: 50% accrual completed