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ETCTN 10388: a Phase 1 Trial of Triapine and Lutetium 177 Dotatate in Well-differentiated Somatostatin Receptor-positive Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

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BACKGROUND: Radiolabeled somatostatin analogues provide a means of delivering targeted radiation with a high therapeutic index to NETs that express somatostatin receptors (SSTRs). Radiolabeled somatostatin analogue Lutetium Lu 177 Dotatate (Lutathera) is a beta-emitting radionuclide, FDA approved for use in SSTR positive gastroenteropancreatic neuroendocrine tumors (GEPNETS) in the US based on the NETTER-1 Phase III trial. Despite favorable PFS and safety profile, the drug has limited cytoreductive capability with a 17% ORR. Peptide receptor radionuclide therapy (PRRT) also doesn't seem to be very effective in treating peritoneal disease. We hypothesize that addition of an effective radiation sensitizer could help improve antitumor activity of Lutathera.

METHODS: This study is an investigator initiated, NCI sponsored, multicenter phase 1 trial of triapine and Lutathera in GEP-NET patients after the failure of at least one line of prior systemic treatment. A total of 29 patients are being enrolled in the dose escalation with help of Bayesian optimal interval design (BOIN) and dose expansion cohorts. Patients are being treated with 177 lutetium dotatate in combination with triapine. Triapine will be administered orally from D1-14 with each dose of PRRT [200 mCi]. Primary endpoint is to evaluate

recommended phase II dose (RP2D). Secondary endpoints are to evaluate safety, pharmacokinetics, and clinical activity (ORR and PFS).

RESULTS: Trial is currently enrolling patients. NCT04234568

CONCLUSION: Ribonucleotide reductase (RNR) is the only enzyme responsible for conversion of ribonucleoside diphosphate to deoxyribonucleotide diphosphate (dNDP), the key building blocks for DNA synthesis. Radiation is a potent inducer of DNA double-strand breaks (DSBs), and RNR is the rate-limiting enzyme in the repair of DNA in this setting. Triapine is an inhibitor of RNR. This study will test the hypothesis that radiation sensitizer triapine can be safely combined with peptide receptor radionuclide therapy and ultimately may improve antitumor activity of Lutathera.

ABSTRACT ID: 196