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A Phase I Trial of Triapine and Lutetium Lu 177 Dotatate in Combination for Well-Differentiated Somatostatin Receptor-Positive Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

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BACKGROUND: Radiolabeled somatostatin analogue Lutetium Lu 177 Dotatate (Lutathera) has been FDA approved for use in SSTR positive gastroenteropancreatic neuroendocrine tumors (GEPNETS) in the US based on NETTER-1 Phase III trial. Despite favorable PFS, and safety profile, the drug has limited cytoreductive capability. NETTER-1 reported 18% ORR. PRRT also doesn't seem to be very effective in treating peritoneal disease. We hypothesize that addition of an effective radiation sensitizer can help improve antitumor activity of Lutathera. Triapine is a ribonucleotide reductase (RNR) inhibitor. RNR is the rate-limiting enzyme in the synthesis and repair of DNA, and it is directly involved in the cellular response to radiation, making RNR-targeted therapy to enhance radiation treatment a rational therapeutic strategy. RNR is the only enzyme responsible for conversion of ribonucleoside diphosphate to

deoxyribonucleotide diphosphate (dNDP), the key building blocks for DNA synthesis. This study will test the hypothesis that triapine is an effective radiation sensitizer which can be safely combined with peptide receptor radionuclide therapy and can improve antitumor activity of Lutetium Lu 177 Dotatate.

Methods: This study is an investigator initiated, NCI sponsored, multicenter phase 1 trial of combination triapine and Lutetium Lu 177 Dotatate in GEP-NET patients. A total of 29 patients will be enrolled in the dose escalation (BOIN design) and dose expansion cohorts. The study will be open through the entire ETCTN. Patients will be treated with 177 lutetium dotatate in combination with Triapine. Triapene will be administered orally from D1-14 with each dose of PRRT. Primary endpoint is to evaluate RP2D. Secondary endpoints are looking into clinical activity (ORR, PFS). We are also evaluating NETEST, a novel blood based predicting as well as prognosticating test. In addition, the study will evaluate baseline somatostatin receptor density, somatic tumor mutations and germline mutations and correlate with clinical outcome.

RESULTS: Currently enrolling. NCT04234568

CONCLUSION: In progress

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