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ETCTN 10388: A first in human Phase I Trial of Triapine and Lutetium Lu 177 DOTATATE in Well-Differentiated Somatostatin Receptor-Positive Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

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BACKGROUND

Radiation is a potent inducer of DNA double-strand breaks, and ribonucleotide reductase (RNR) is the rate-limiting enzyme in the synthesis and repair of DNA, making RNR-targeted therapy a rationale therapeutic strategy for radiosensitization. ETCTN 10388 (NCT04234568) evaluated safety and efficacy of the combination of lutetium 177 DOTATATE, a beta-emitting radionuclide in combination with triapine, a ribonucleotide reductase (RNR) inhibitor.

METHODS

This study was a multicenter phase 1 dose escalation trial [using the Bayesian optimal interval design (BOIN)] of triapine in combination with fixed dose lutetium Lu 177 DOTATATE for well-differentiated somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumor (GEP-NETs) after the failure of at least one line of prior systemic cancer treatment with an expansion cohort at the recommended phase 2 dose (RP2D). Oral triapine (100mg, 150mg, 200mg) was administered once daily on days 1-14 and Lu-177 DOTATATE [200 mCi] intravenously on day 1 of every 56-day cycle. A total of 4 cycles were administered. Response and adverse effects were assessed per RECIST and CTCAE 5.0, respectively. Exploratory correlative studies included tumor somatic and germline mutation testing, RNA sequencing, pharmacokinetics, deoxynucleosides and circulating cell free DNA analysis. Primary endpoints were safety and RP2D.

RESULTS

Overall, 31 patients were enrolled between 6 sites, 15 in the dose escalation phase and 16 in the dose expansion phase. Adverse events (AE) were assessed in all 31 patients per CTCAE 5.0. One DLT in dose level 1, seven DLTs in dose level 2, and one grade 5 DLT in dose level 3 were observed. The RP2D of the combination is triapine 150 mg QD (dose level 2) on days 1-14 in combination with Lu-177 DOTATATE on day 1 of every 56-day cycle. Detailed safety and adverse event data will be presented at the meeting. There were 28 patients evaluable for efficacy, of which 6 (21%) achieved a partial response.

At 12 months, 6 patients had progressed, while 22 (86%) remained progression free. Median PFS has not been reached. PK data were available for 12 patients enrolled in the dose escalation cohort. The geometric mean (SD) $AUC_{0\text{-}inf}$ was 1159 (1.22) µg/L•h for the 100mg dose level and 1862 (1.76) µg/L•h for the 150 mg dose level, suggesting that exposure increased with dose, and inter-patient variability was as expected for an oral agent.

CONCLUSIONS

The combination of triapine and Lu-177 DOTATATE was safe with preliminary efficacy signals, which will be further evaluated in ETCTN 10558, a randomized phase 2 study that is comparing the effectiveness of triapine and Lu-177 DOTATATE to Lu-177 DOTATATE alone.

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