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Multi-center NCI-sponsored phase 1 study of triapine in combination with ¹⁷⁷Lu-dotatate in patients with progressive well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs)

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BACKGROUND

¹⁷⁷Lu-Dotatate is an FDA-approved somatostatin receptor-targeted radiopharmaceutical shown to improve progression-free survival (PFS) in patients with progressive well-differentiated neuroendocrine tumors (NETs). Benchmark NETTER-1 trial established a median PFS of 28.4 months and an objective response rate (ORR) of 14% for Lu-177 dotatate. Triapine, an oral ribonucleotide reductase inhibitor, is a potent radiation sensitizer. This phase 1 study evaluated the safety and efficacy of combining triapine with ¹⁷⁷Lu-Dotatate in patients with progressive NETs.

METHODS

ETCTN 10388 is a multi-center, investigator-initiated, NCI-sponsored phase 1 trial conducted at six academic institutions in the United States. Eligible patients had metastatic, progressive, well-differentiated GEP-NETs and had progressed on at least one prior line of therapy. The study included a dose-escalation phase (Part A, n=15) utilizing a Bayesian Optimal Interval (BOIN) design, followed by a dose-expansion phase (Part B, n=16). All patients received ¹⁷⁷Lu-Dotatate 200 mCi on Day 1 of each 8-week cycle, along with oral triapine (50–200 mg) on Days 1–14, for a total of four cycles.

RESULTS

Thirty-one patients received study treatment. The most common treatment-related adverse events were anemia (94%), lymphopenia (88%), and thrombocytopenia (81%), which were largely transient and resolved within two weeks without impacting treatment continuity. Dose-limiting toxicities (DLTs) were observed in nine patients across dose levels. Based on integrated safety and pharmacokinetic data, the recommended phase 2 dose (RP2D) of triapine was established at 150 mg. Among 28 patients evaluable for efficacy, the confirmed ORR was 21.4%, and the median PFS was 38.03 months. In the RP2D cohort, median PFS has not yet been reached and may exceed 40 months.

CONCLUSIONS

Triapine in combination with ¹⁷⁷Lu-Dotatate was well tolerated and demonstrated encouraging signs of clinical activity in patients with progressive well-differentiated GEP-NETs. The ¹⁷⁷Lu-Dotatate (200

mCi) plus triapine (150 mg) regimen has been selected for further evaluation. A randomized phase 2 trial (ETCTN 10558) comparing the combination to standard ^{177}Lu -Dotatate monotherapy is currently enrolling at 14 sites across the United States.

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