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Phase I Study of Fulvestrant in Combination with 177Lu-DOTATATE for Advanced Pancreatic Neuroendocrine Tumors

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BACKGROUND

Peptide receptor radionuclide therapy (PRRT) using ^{177}Lu-DOTATATE prolongs progression-free survival (PFS) in patients with advanced well-differentiated pancreatic neuroendocrine tumors (pNETs) expressing somatostatin receptors, but further improvement in efficacy is needed. Preclinical data has shown that estrogen receptor alpha (*ESR1*) inhibition with Fulvestrant, an *ESR1* antagonist, radiosensitizes pNET cells. We conducted a study to evaluate the safety and preliminary efficacy of Fulvestrant in combination with ^{177}Lu-DOTATATE for advanced metastatic pNETs (NCT06663072).

METHODS

This is an investigator-initiated phase I study of Fulvestrant in combination with ^{177}Lu-DOTATATE for patients with well-differentiated pNETs. A total of 19 patients (pts) will be enrolled in Stage 1 (safety run-in, 6 pts) and Stage 2 (dose-expansion, 13 pts). PRRT with ^{177}Lu-DOTATATE was administered at 7.4 GBq (200 mCi) IV every 8 weeks for a total of 4 cycles. Fulvestrant was administered at 500mg IM on Cycle 1 days 1, 15, and 29, then every 4 weeks thereafter, for a total of 9 doses. The primary endpoint is to assess the safety and preliminary efficacy of Fulvestrant in combination with ^{177}Lu-DOTATATE for advanced pNETs based on objective response rate (ORR) assessed by RECIST v1.1. Post-therapy ^{68}Ga-DOTATATE PET/CT scans were performed following completion of cycle 4, and PET responses were assessed by PERCIST v1.0. Tumor volumes and associated statistics were quantified from PET images using MIM Software version 7.4.4.

RESULTS

At the time of data cutoff, 6 patients were enrolled in Stage 1 (safety run-in). Four patients completed all 4 cycles, and two patients completed cycle 2 only. All patients received Fulvestrant and ^{177}Lu-DOTATATE per protocol. There were no serious adverse events (SAEs) or AEs that led to dose reduction/interruption or treatment discontinuation. All reported adverse events (AEs) were Grade 1 or 2 with the majority (97%, 116/119) being Grade 1. Most common AEs were nausea, vomiting, diarrhea, fatigue, flushing, and

leukopenia. No patients experienced grade ≥3 AEs. ORR was 50% with partial response (PR) in 50% (3/6) and stable disease in 50% (3/6) of patients. Partial metabolic response (PMR) was observed in 100% (4/4) of PET response evaluable patients, with a mean tumor volume reduction of -56.5% (range -38.6%, -92.8%).

CONCLUSIONS

Fulvestrant in combination with ^{177}Lu-DOTATATE is safe and shows preliminary efficacy in advanced PNET patients with an ORR of 50%. Enrollment is currently underway in Stage 2 (dose-expansion) of our study.

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