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ETCTN 10450: A phase I trial of peposertib and lutetium 177 DOTATATE in well-differentiated somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

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BACKGROUND

Radiolabeled somatostatin analogs provide a means of delivering targeted radiation with a high therapeutic index to NETs that express somatostatin receptors (SSTRs). We hypothesize that the addition of an effective radiation sensitizer could help improve the antitumor activity of Lutathera.

Radiation is a potent inducer of DNA damage. The primary repair mechanism of radiation-induced double-stranded breaks (DSBs) is the nonhomologous end-joining (NHEJ) pathway, in which the DNA-PK (Deoxyribonucleic acid protein kinase) complex plays a pivotal role. Upregulation of DNA-PK promotes the repair of DSBs leading to tumor radio-resistance preclinically and clinically. Thus, DNA-PK is an important molecular target for inhibiting DSB repair and enhancing the cytotoxicity of radiation. Peposertib is a selective inhibitor of DNA-PK that targets tumor cell DNA damage repair and survival by blocking NHEJ.

METHODS

This is an investigator-initiated, NCI-sponsored, multicenter phase 1 trial of peposertib and Lutetium 177 DOTATATE in well-differentiated somatostatin receptor-positive GEP-NETs after the failure of at least one line of prior systemic treatment. Peposertib was administered orally from D1-21 with each dose of PRRT. The primary endpoint is to evaluate recommended phase II dose (RP2D) with the help of BOIN design. Secondary endpoints are to evaluate the safety, pharmacokinetics, and clinical activity (ORR and PFS). We are also evaluating Lu-177 DOTATATE dosimetry in collaboration with NIH IROC.

RESULTS

13 patients were treated in the dose escalation phase. A total of three dose-limiting toxicities were noted. One patient had transient grade 3 elevation of ALT on dose level 2, and two patients developed anaphylactic reactions on dose level 3. These patients came off Peposertib per protocol but continued Lutathera (PRRT).

Peposertib PK parameter values observed in this trial were comparable to previous reports. The peposertib exposure in our four patients dosed at 150 mg BID was C_{max} 572 (1.92) µg/L, and AUC 2744 (2.01) µg/L•h, while previously reported values are 610 µg/L, and 2960 µg/L•h, respectively. Similarly, dose-normalized C_{max}, T_{max}, and apparent clearance (38-55 L/h vs 30-60 L/h) were comparable. In PBMC's, the IC_{50} for DNA-PK was reported to be around 200 ng/mL, a value exceeding in all patients at 100 mg (the MTD) and 150 mg BID, though the plasma C_{min} fell below this IC_{50} in most patients. The limited dose range evaluated in our trial, combined with the high between-patient variability precluded a definitive assessment of dose linearity by either absolute exposure or metabolic ratio.

CONCLUSIONS

Based on DLT data, PK data, and concern for anaphylaxis with dose level 3, dose level 2 (100 mg PO BID, Days 1-21) was assigned as RP2D. The expansion cohort for additional safety analysis and dosimetry sub-study is now open for enrollment at 6 sites within the US.

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