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Phase Ib trial of cabozantinib (Cabometyx®) combined with Lu-177 DOTATATE radioligand therapy in patients with advanced, somatostatin receptor positive NETs.

Hagen F Kennecke MD, MHA, FRCPC[1], Lena Yamasaki, RN[1], Anup Kasi, MD, MPH[2], Katherine Herz[1], Erik S Mittra, MD[3].

[1]Providence Cancer Institute, Portland, OR; [2]University of Kansas Medical Center, KS; [3]Oregon Health Sciences University, Portland, OR.

BACKGROUND

Combination peptide receptor radionuclide therapy (PRRT) with the multikinase inhibitor cabozantinib may result in enhanced tumor response and improved intratumoral delivery of Lu-177 DOTATATE by normalization of tumor vasculature through VEGFR inhibition.

METHODS

In a phase Ib trial, patients with advanced somatostatin receptor (SSTR) positive, G1-3 neuroendocrine tumors (NETs) with a Krenning score of >2 are treated with 4 x 8 week cycles of Lu-177 DOTATATE 7.4 *GBq (200 mCi) intravenously* in combination with escalating doses of oral cabozantinib daily, starting 14 days prior to Lutathera®. Single-agent cabozantinib is continued to progression after completion of PRRT. The primary study endpoint is maximal tolerated dose (MTD) of cabozantinib and the secondary endpoint is radiographic objective response rate by RECIST criteria.

RESULTS

The single-institution study was activated December 2022 and a total of 6 patients have been enrolled of which 3 entered the first dose cohort of cabozantinib 20mg daily. All 3 patients have well-differentiated, Grade 3 NETs of pancreatic (2) or unknown primary (1) origin. No dose limiting toxicities were identified during cycle 1 and no serious adverse events (SAEs) were reported. Hypocalcemia was the only grade 3 toxicity during cycle 1 reported in 1 of 3 patients. Initial imaging after cycle 2 of therapy documented a RECIST partial response in both patients with pNETs and stable disease in the patient with unknown primary NET. After review of the complete dose cohort 1, cycle 1 adverse event data, on May 15, 2023, the Data Safety Monitoring Committee approved dose escalation to level 2 with cabozantinib 20mg alternating with 40mg daily and 3 further patients were subsequently enrolled.

CONCLUSIONS

Cabozantinib 20mg daily starting 14 days prior to standard doses of Lu-177 PRRT had no dose limiting toxicities during cycle 1 allowing dose escalation to 20mg/40mg alternate daily dosing. Preliminary efficacy signals with initial response are promising. Updated safety and efficacy information will be reported for the first 6 patients enrolled.

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