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DNA Damage Repair Mutational Status's Effect on Lu-177-DOTATATE in Combination with Olaparib in Metastatic SSTR+ GI Neuroendocrine Tumor: Preliminary Results

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BACKGROUND

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are somatostatin receptor (SSTR) expressing tumors that can be treated with Lu-177-DOTATATE. As ionizing radiation kills tumors via DNA damage, combination therapy with olaparib, a poly-ADP-ribose polymerase inhibitor (PARPi) may enhance Lu-177-DOTATATE's efficacy. In patients with BRCA mutations, PARPi act synergistically with intrinsic DNA-repair deficiencies causing synthetic lethality and is the proposed mechanism underlying PARPi's efficacy in these patients. However, the impact of patient's DDR mutational status on efficacy of this combination in GEP-NETs is unknown.

METHODS

In this standard 3+3 dose escalation, single-center phase 1/2 study (NCT04086485), Lu-177-DOTATATE is given at fixed dose of 200 mCi x 4 cycles with olaparib being escalated from dose level (DL) 1 at 50mg to 100mg (DL2), 200mg (DL3), and 300mg (DL4) bid. Olaparib dosing starts 2 days prior to Lu-177-DOTATATE until 28 days post, for a total of 30 days with each Lu-177-DOTATATE administration. Eligibility includes SSTR+ tumors and progressive disease by RECIST within 36 months of enrollment. Specific DNA-repair mutations such as BRCA are not required for eligibility but the data is collected. The study opened for enrollment in September 2022 and will require up to 33 patients for full accrual.

RESULTS

As of August 2024, 12 patients have been treated on study with 6 having completed therapy and have response data analyzed. Tumor location of origin for these 6 patients include 3 pancreas, 2 mid-gut, and 1 unknown (presumed mid-gut). Of these 6 patients, two have DDR mutations, with one having a pathogenic small nucleotide variation in BRCA2 (pNET) and another with ATM loss. The patient with BRCA2 mutation exhibited exceptional response that is seen after only 1 cycle of therapy, achieved scintigraphic CR in the liver by the second cycle, and achieved radiographic CR in the liver by the end of the 4th cycle. The other 5 patients including the one with ATM loss showed RECIST SD in this same time frame. Post-treatment dosimetry was performed after every cycle of Lu-177-DOTATATE and showed an average cumulative dose of 29.5 Gy to liver lesions in the BRCA2 patient and 48.5 Gy to liver lesions in the other 5 patients.

CONCLUSIONS

Preliminary data suggests that Lu-177-DOTATATE in combination with olaparib is effective in GEP-NET, and may be particularly effective in those with BRCA mutations.

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