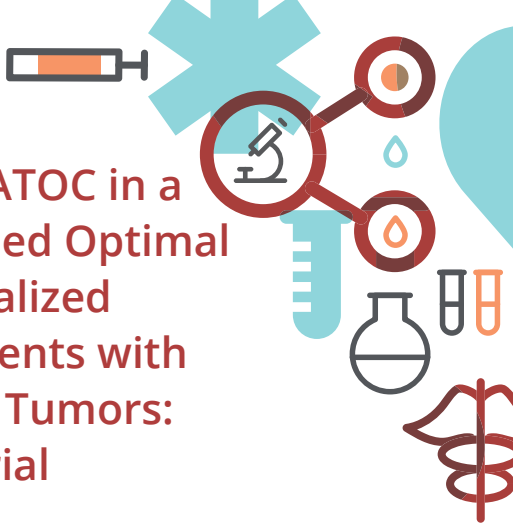

T-5

131I MIBG and 90Y DOTATOC in a Dosimetrically Determined Optimal Combination for Personalized Therapy of Selected Patients with Midgut Neuroendocrine Tumors: A First-In-Man Clinical Trial

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BACKGROUND: Targeted radiomolecular therapy (TRT) is effective for metastatic neuroendocrine tumors (NETs). Delivering sufficient tumor radiation dose remains challenging due to the critical organ dose-limitations. 131I MIBG targets approximately 50-60% of midgut NETs, with bone marrow the critical organ. In contrast, the critical organ for 90Y DOTATOC is the kidney. We previously demonstrated this difference can be exploited by combining these agents into a single treatment regimen to yield higher total tumor radiation dose without exceeding critical organ dose limits.

METHODS: A first-in-man clinical trial was initiated at University of Iowa (NCT03044977) for patients with non-operable progressive NET. Escalation schema employs organ limiting dose cohorts for marrow and kidneys utilizing a standard 3x3 design. Follow-up measures include eGFR, urine protein as well as neutrophil and platelet counts. Tumor targeting and dosimetric evaluation (imaging and blood sampling) were performed prior to therapy using combination administration of 6 mCi of 111In-pentetreotide (as a biodistribution surrogate for 90Y DOTATOC) plus 2.0 mCi of 131I-MIBG. These results were used to determine therapeutic administered activity levels of 90Y DOTATOC plus 131I-MIBG delivered over 2 cycles.

RESULTS: The first dose cohort reported here treated subjects to 1900 cGy kidney and 150 cGy bone marrow. Total administered activities of 90Y DOTATOC and 131I-MIBG are provided (Table 1). Tumor dosimetry estimates from four well defined (CT) liver tumors from subject 1 are shown (Table 1). Dose limiting toxicity has not occurred; thus, dose will be escalated to organ constraints of 2300 cGy kidney and 200 cGy bone marrow.

CONCLUSION: Initial treatment in this first-in-man study demonstrates the feasibility of using forward-planned dosimetry for a phase 1 escalation trial and suggests the safety of combinatorial TRT for neuroendocrine tumor using 90Y DOTATOC and 131I-MIBG for the initial cohort. The trial remains active.

Table 1. Characteristics of calculated administered activity (mCi) and tumor dose (cGy) for the cohort

	90Y DOTATOC (mCi)	131I MIBG (mCi)	Dose limiting toxicity
Subject 1	235	308	0
Subject 2	150	494	0
Subject 3	75	505	0
	single agent 90Y DOTATOC (292 mCi) (kidney limited)	Combined therapy (241 90Y + 338 mCi 131I MIBG)	Increase in radiation dose
Tumor 1	3,795 cGy	5,769 cGy	52%
Tumor 2	7,570 cGy	11,740 cGy	55%
Tumor 3	3,679 cGy	6,416 cGy	74%
Tumor 4	16,352 cGy	21,970 cGy	34%