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Recombinant Human Alpha-1-Microglobulin - RMC-035: An Organ Protective Agent During 177Lu-DOTATATE Treatment of Neuroendocrine Tumors

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BACKGROUND: Lutathera (177Lu-DOTATATE) was recently the first pharmaceutical product to be granted market authorization in USA and Europe for treatment of neuroendocrine Importantly, in a recent study by Garske-Román et al (EJNMMI, 2018) showed that patients in whom the absorbed dose to the kidneys reached 23 Gy had a longer overall survival than those in whom it did not. Furthermore, Puszkiel et al (Clin Pharmacokinet, 2018) showed that amino acids, used to prevent nephrotoxic effects of 177Lu-DOTATATE, is associated with increased hematologic toxicity. Together, these findings raise the question of renal and hematologic protection beyond current practice.

METHODS: Evaluation of renal and hematologic protection of the radioprotector RMC-035, a pharmaceutical drug candidate of human alpha-1-microglobulin, was studied in a mouse model of 177Lu-DOTATATE radiation therapy. Balb/c mice were exposed to 177Lu-DOTATATE with or without the simultaneous administration of RMC-035.

RESULTS: We found renal and hematologic protective effects of RMC-035 on both short- and long-term damage observed following 177Lu-DOTATATE exposure in BALB/c mice. This included reduced formation of renal DNA double-

strand breaks, induction of apoptosis and stress-response related genes, kidney lesions, glomerular loss and proteinuria. Furthermore, co-administration of RMC-035 resulted in an increased percentage of viable platelets and reticulocytes as compared to 177Lu-DOTATATE only. In addition, long-term follow-up showed prolonged survival following RMC-035 treatment.

CONCLUSION: This study demonstrates that RMC-035 effectively inhibits radiation-induced renal and hematologic damage. The findings suggest that RMC-035 may be used as a radioprotector during clinical 177Lu-DOTATATE treatment. Encouraged by these findings, a clinical development program will be initiated to evaluate RMC-035 as an organ protecting agent during 177Lu-DOTATATE treatment, to enable more aggressive antitumor treatment, either by increasing the dose given at each cycle, by increasing the number of treatment cycles or by reducing the time interval between cycles.