ACTION-1: A Randomized Phase Ib/3 trial of RYZ101 Compared with SoC in SSTR2+ Well-Differentiated GEP-NET with Progression Following Lu-177 SSA

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BACKGROUND
Well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are commonly characterized by overexpression of somatostatin receptor subtype 2 (SSTR2), which can be targeted by radiopharmaceutical therapy (RPT) via radiolabeled somatostatin analogues (SSAs). RYZ101 (Ac-225 DOTATATE) is a first-in-class, highly potent alpha-emitting RPT being developed for the treatment of SSTR2+ solid tumors. Alpha-particles (such as emitted by Actinium-225) have a shorter path length (40–100 μm) and higher linear energy transfer (80–100 keV/μm) than beta-particles, potentially allowing for higher cancer cell kill rates and less damage to healthy tissues. ACTION-1 is a 2-part, global, randomized, controlled, open-label, Phase 1b/3 trial of RYZ101. Part 1 (Phase 1b) will determine the safety, pharmacokinetics, and recommended Phase 3 dose (RP3D) of RYZ101. Part 2 (Phase 3) will compare RYZ101 at the RP3D with investigator’s choice SoC (everolimus, sunitinib, or high-dose long-acting SSA); crossover to RYZ101 is permitted.

METHODS
Adults with grade 1–2, well-differentiated, inoperable, advanced SSTR2+ GEP-NETs that have progressed (RECIST v1.1) following 2–4 cycles of therapy with Lu-177 SSA are eligible. Patients unresponsive to prior Lu-177 SSA (disease control <3 months after last dose of Lu-177 SSA) are excluded. Patients must have an ECOG status 0–2 and adequate hematologic and renal function. Part 1 is an uncontrolled dose de-escalation study based on Bayesian optimal interval design (de-escalation will occur if DLT incidence estimated >25%). RYZ101 is administered intravenously every 8 weeks for up to 4 cycles. Dose levels (n=6/level) planned: Level 0 (starting dose), 120 kBq/kg (3.2 μCi/kg); if necessary, Level –1, 90 kBq/kg (2.4 μCi/kg); Level –2, 60 kBq/kg (1.6 μCi/kg). In Part 2, ~210 patients will be randomized (1:1) to receive RYZ101 RP3D every 8 weeks for up to 4 cycles or investigator’s choice SoC (everolimus, sunitinib, or high-dose long-acting SSA); crossover to RYZ101 is permitted.
Primary endpoint: progression-free survival (PFS) by blinded independent central review (BICR) using RECIST v1.1. Secondary endpoints: overall survival; objective response rate and best overall response (BICR and investigator assessment); duration of response; disease control rate; PFS (investigator assessment); safety. Exploratory endpoints: PFS after first subsequent anticancer therapy; biomarkers; health-related quality of life. Pharmacokinetic / electrocardiogram (n=30) and dosimetry (n~8) sub-studies will be performed at select sites.

RESULTS
ACTION-1 Part 1 is currently enrolling patients at ~10 US sites. Part 2 will commence after Part 1 at ~60 sites in North America, South America, Europe, and Asia.

CONCLUSIONS
No conclusions; TiP abstract.

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