T-1

ACTION-1: A randomized Phase Ib/3 trial of RYZ101 compared with SoC in SSTR+ 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 high-density expression of somatostatin receptors (SSTRs), which can be targeted by radiopharmaceutical therapy (RPT) via radiolabeled somatostatin analogues (SSAs). RYZ101 (^{225}Ac-DOTATATE) is a first-in-class, highly potent alpha-emitting RPT being developed for the treatment of SSTR+ solid tumors. Alpha-particles (such as those emitted by ^{225}Ac) 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) determined the safety, pharmacokinetics, and the recommended Phase 3 dose (RP3D) of RYZ101, 10.2 MBq (275 µCi). Part 2 (Phase 3) will compare RYZ101 at 10.2 MBq (275 µCi) with standard of care (SoC) in patients with advanced SSTR+ GEP-NETs with disease progression following prior ^{177}Lu-labeled SSAs.

METHODS

Adults with grade 1–2, well-differentiated, inoperable, advanced, histologically-proven, SSTR+ GEP-NETs that have progressed (RECIST v1.1) following 2–4 cycles of therapy with ^{177}Lu-SSA are eligible. Patients unresponsive to prior ^{177}Lu-SSA (disease control <6 months after last dose of ^{177}Lu-SSA) are excluded. Patients must have ECOG performance status 0–2 and adequate hematologic and renal function. Phase 1b was an uncontrolled dose de-escalation study and has been completed with no dose-limiting toxicities observed. In Phase 3, patients will be randomized (1:1) to receive RYZ101 at a fixed dose of 10.2 MBq (275 µCi) 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 at time of centrally reviewed progression. Primary endpoint (Phase 3): 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.

RESULTS

Phase 3 is currently enrolling and is planned at ~80 sites in North America, South America, Europe, and Asia.

CONCLUSIONS

Not applicable - the trial is currently in progress.

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