T-6

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

Thomas Hope[1], Samuel Mehr[2], Michael Morris[3], Daneng Li[4], Daniel Halperin, MD[5], Jonathan Strosberg[6], Heloisa Soares[7], Heather Jacene[8], Marianne Pavel[9], Pamela L. Kunz[10], Denis Ferreira[11], Joanne Li[11], Kimberly Ma[11], Jessica Rearden[11], Susan Moran[11], Simron Singh[12].

[1]University of California San Francisco, CA; [2]Nebraska Cancer Specialists, Omaha, NE; [3]Advanced Molecular Imaging and Therapy, Glen Burnie, MD; [4]City of Hope Comprehensive Cancer Center, Duarte, CA; [5]Anderson Cancer Center, Houston, TX; [6]Moffitt Cancer Center, Tampa, FL; [7]Huntsman Cancer Hospital, University of Utah, Salt Lake City, UT; [8]Dana Farber Cancer Institute, Boston, MA; [9]Friedrich-Alexander University, Erlangen, Germany; [10]Yale University, New Haven, CT; [11]RayzeBio, San Diego, CA; [12]University of Toronto, Odette Cancer Center at Sunnybrook Health Sciences Center, Toronto, ON, Canada.

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 standard of care (SoC) in patients with advanced SSTR2+ GEP-NETs with disease progression following prior Lu-177-labeled SSAs.

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.

ABSTRACT ID 21414