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ACTION-1 phase Ib/3 trial of RYZ101 in gastroenteropancreatic neuroendocrine tumors progressing after ¹⁷⁷Lu somatostatin analogue therapy: Phase 1b safety/efficacy

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BACKGROUND

RYZ101 (²²⁵Ac-DOTATATE) is an alpha-emitting radiopharmaceutical in development for SSTR2+ solid tumors. Alpha-particles have a shorter path length/higher linear energy transfer than beta-particles, causing more frequent double-strand DNA breaks and potentially improved therapeutic index. ACTION-1 (NCT05477576) is a 2-part, global, randomized, controlled, open-label, phase 1b/3 trial of RYZ101 in advanced, well-differentiated SSTR+ gastroenteropancreatic neuroendocrine tumors (GEP-NETs) progressing after ¹⁷⁷Lu somatostatin analogue (SSA) therapy. Herein, we report updated results from the phase 1b portion of the trial.

METHODS

The phase 1b portion of the trial had a dose de-escalation/Bayesian optimal interval design with boundaries based on a dose-limiting toxicity (DLT) rate of 25%. Patients received RYZ101 IV every 8 weeks for 4 cycles. Planned dose levels (n=6/level): Level 0 (starting dose) 120 kBq/kg; Level -1 90 kBq/kg; Level -2 60 kBq/kg. DLT was assessed for 56 days after the first RYZ101 dose. Treatment-emergent adverse events (TEAEs) were graded by NCI-CTCAE v5.0. Dose de-escalation decisions/safety data were overseen by a Data Review Committee. Tumor response was assessed locally by RECIST v1.1.

RESULTS

17 patients have received at least one dose of RYZ101 at 120 kBq/kg (4 doses: 15 patients; 2 doses: 2 patients; median 8.3 MBq). Baseline characteristics: median age 63 years; male (n=11); ECOG PS 0/1 (n=10/7); primary tumor site GI/pancreas (n=12/5). As of 30 June 2023, the most frequent TEAEs were nausea (58.8%) and fatigue (52.9%). Serious adverse events (SAEs) were observed in 6 patients (none were treatment related); grade ≥3 AEs occurred in 9 patients (5 were treatment related). No AEs led to treatment discontinuation. 4 patients had TEAEs leading to dose modification, dose hold, and/or delays. The confirmed objective response rate was 29.4% (n=5; all partial responses); 1 patient

had an unconfirmed partial response. 8 patients (47.1%) had stable disease and 3 patients (17.6%) had progressive disease. Updated safety and efficacy data, including duration of response and progression-free survival, will be presented.

CONCLUSIONS

RYZ101 was well tolerated and a fixed dose of 10.2 MBq was declared the recommended phase 3 dose. Initial data suggest promising efficacy. Longer-term safety and efficacy data will be presented. Part 2 (phase 3) is enrolling and will compare RYZ101 at 10.2 MBq every 8 weeks for 4 cycles with standard of care in patients with advanced SSTR2+ GEP-NETs progressing following prior ¹⁷⁷Lu-labeled SSAs.

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