ACTION-1 phase Ib/3 trial of RYZ101 in somatostatin receptor subtype 2 expressing gastroenteropancreatic neuroendocrine tumors progressing after ^{177}Lu somatostatin analogue therapy: initial safety analysis

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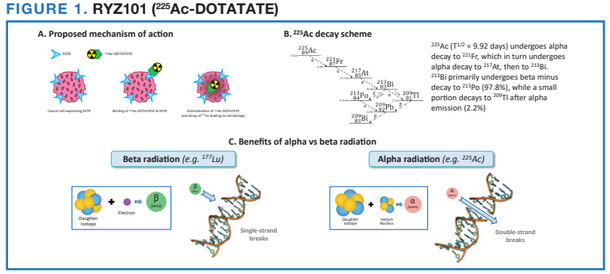
BACKGROUND

- RYZ101 (^{225}Ac-DOTATATE) is a first-in-class, highly potent alpha-emitting radiopharmaceutical therapy being developed for the treatment of somatostatin receptor 2-expressing (SSTR2+) solid tumors (**Figure 1a**):
  - ^{225}Ac has a half life of 9.92 days, and as it decays to stable ^{209}Bi, it generates four short-lived high-energy alpha particles (^{221}Fr, ^{217}At, ^{213}Bi and ^{213}Po) (**Figure 1b**).
  - Alpha-particles have a shorter path length (40–100 µm) and higher linear energy transfer (80–100 keV/µm) than beta-particles, causing more frequent double-strand DNA breaks and potentially improved therapeutic index (**Figure 1c**).
- ACTION-1 (NCT05477576) is a 2-part, global, randomized, controlled, open-label, Phase 1b/3 trial comparing treatment with RYZ101 to standard-of-care therapy in patients with inoperable, advanced, SSTR2+, well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs) that have progressed following prior ^{177}Lu-labelled somatostatin analogue (SSA) therapy:[1]
  - Part 1 (Phase 1b) is designed to determine safety, pharmacokinetics (PK), and recommended Phase 3 dose (RP3D) of RYZ101.
  - Part 2 (Phase 3) will compare the efficacy of RYZ101 at the RP3D with standard of care (SoC) in patients with advanced SSTR2+ GEP-NETs with disease progression following ^{177}Lu-SSA.
- This poster describes preliminary safety results from Part 1 (Phase 1b) of the ACTION-1 trial.

FIGURE 1. RYZ101 (^{225}Ac-DOTATATE)



METHODS

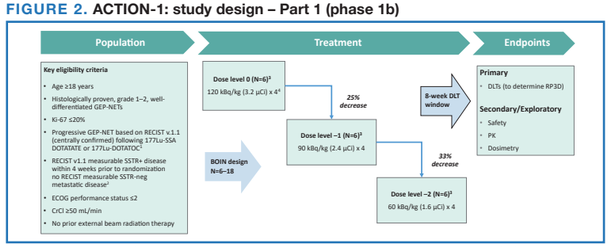
STUDY DESIGN

- Part 1 of ACTION-1 was an uncontrolled dose de-escalation study based on Bayesian optimal interval design (BOIN). An escalation boundary of 0.197 and a de-escalation boundary of 0.298 based on a target toxicity rate of 25% was used (**Figure 2**).
- RYZ101 was administered intravenously every 8 weeks for up to 4 cycles.
- Three dose levels (n=6/level) were possible:
  - 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).
- No dose escalation above the starting dose was permitted.

PATIENTS

- 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 ^{177}Lu-SSA are eligible.
- Patients unresponsive to prior ^{177}Lu-SSA (disease control <3 months after ^{177}Lu-SSA) were excluded.
- ECOG status 0–2 and adequate hematologic and renal function.

FIGURE 2. ACTION-1: study design – Part 1 (phase 1b)



[1]The oldest scan must not be older than 3 years from the date of screening and the most recent scan must not be older than 4 weeks prior to enrollment; [2]SSTR PET imaging must be completed within 12 weeks (84 days inclusive) of enrollment; [3]Concomitant amino acids will be given with each RYZ101 administration for renal protection; [4]Patients will be eligible to receive additional cycles every 8 weeks, up to 4 cycles if they do not experience a DLT or if they recover from a DLT and subsequent treatment is approved by the investigator and Sponsor.
SSTR: Somatostatin receptor; µCi= microcurie; kBq= kilobequerel.

SAFETY EVALUATIONS

- Dose limiting toxicity (DLT) was assessed for 56 days following the first RYZ101 infusion.
- Treatment-emergent adverse events (TEAEs) were graded by NCI-CTCAE v5.0.
- Dose de-escalation decisions and safety data review were overseen by a Data Review Committee.

RESULTS

STUDY STATUS

- As of the 17 February 2023 data cut-off, enrollment was complete and 17 patients had received RYZ101 at 120 kBq/kg (safety set).
- No DLTs occurred and no dose de-escalation steps were implemented.
- One patient discontinued due to disease progression; six patients completed four cycles; 10 patients remain on treatment.

PATIENTS

- Median age was 63 years; 65% of patients were male; all had an ECOG performance status of 0 or 1 (58.8% vs 41.2%; **Table 1**).
- Median time since diagnosis was 5.3 years; the most frequent primary tumor sites were ileum (58.8%) and pancreas (29.4%; **Table 2**).

RYZ101 EXPOSURE

- Two patients had a reduced dose (one patient during cycles 2, 3 and 4; one patient during cycles 2 and 3; **Table 3**).

TABLE 1. Baseline patient demographics

	RYZ101 120 kBq/kg (n=17)
Median age, years (range)	63 (42–78)
Males, n (%)	11 (64.7)
Race, n %	
White	13 (76.5)
Black or African American	2 (11.8)
Unknown	1 (5.9)
Multiple	1 (5.9)
Ethnicity, n (%)	
Hispanic or Latino	2 (11.8)
Not Hispanic or Latino	15 (88.2)
ECOG performance status, n (%)	
0	10 (58.8)
1	7 (41.2)

BMI, body mass index; ECOG, Eastern co-operative group.

TABLE 2. Baseline disease characteristics and prior anticancer therapies

	RYZ101 120 kBq/kg (n=17)
Median duration of GEP-NET, years (range)	5.3 (1.3–19.1)
Primary tumor site, n (%)	
Ileum	10 (58.8)
Pancreas	5 (29.4)
Duodenum	1 (5.9)
Jejenum	1 (5.9)
Median time since diagnosis of metastases, months (range)	61.3 (15.6–229.3)
Functional status, n (%)	
Functional	12 (70.6)
Not-functional	5 (29.4)
Histopathologic grade	
Grade 1	8 (47.1)
Grade 2	9 (52.9)
Patients with prior PRRT, n (%)	17 (100.0)
Patients receiving 2/3/4 PRRT cycles	0/0/17 (100.0)
Median time since prior PRRT to first dose of RYZ101, months (range)	28.7 (1.9–47.3)
Patients receiving ^{177}Lu-DOTATATE/^{177}Lu-DOTATOC, n (%)	17 (100.0)/0

GEP-NET, gastro-enteropancreatic neuroendocrine tumor; PRRT, peptide receptor radionuclide therapy; SD, standard deviation.

TABLE 3. Summary of RYZ101 exposure, including dose reduction and interruption

	RYZ101 120 kBq/kg (n=17)
Total number of cycles, n (%)[a]	
1	1 (5.9)
2	8 (47.1)
3	2 (11.8)
4	6 (35.3)
Median dose received per cycle for all patients, MBq (range)[b]	8.4 (4.1–11.0)
Median starting dose, MBq (range)[b]	8.9 (7.2–11.0)
Number of patients with a dose reduction, n (%)[c]	2 (11.8)
Median reductions per patient, n (range)	2.5 (2.0–3.0)
Number of patients with dose interruption, n (%)	2 (11.8)[d]

[a]Ten patients were still on treatment at the time of data cutoff; [b]The sum of total MBq taken during the total duration of exposure; [c]Patients with dose reduction at any time; [d]One patient due to COVID-19 infection and one patient due to extravasation (infusion was resumed on the same day).

SAFETY

- A summary of the safety findings is shown in **Table 4**:
  - Overall, 15 patients experienced TEAEs (**Table 5**), with 10 patients experiencing TEAEs that were considered treatment related (**Table 6**).
  - Serious AEs (SAEs) were observed in four patients, but none were treatment related.
  - Grade 3 or 4 TEAEs occurred in six patients: lymphopenia (n=4); bile duct stenosis with associated blood bilirubin increase (n=1); creatinine renal clearance decreased (n=1); hyperglycemia (n=1); hypoglycemia (n=1); hypothermia (n=1); jaundice (n=1); skin infection (n=1); and weight decreased (n=1).
  - No TEAEs or SAEs led to treatment discontinuation.
  - TEAE requiring dose reductions occurred in two patients: platelet count decreased (n=2); TEAE requiring study drug interruption occurred in two patients: COVID-19 (n=1); extravasation (n=1).
  - One patient with pre-existing CREST syndrome and renal insufficiency (Grade 2 at baseline) developed Grade 3 creatinine clearance decrease after 4 treatment cycles (deemed unrelated to study treatment by the investigator). The patient also experienced diabetes and weight loss during treatment, which may have contributed to renal toxicity.
- Hematology and renal parameters over time are shown in **Figure 3**.

TABLE 4. Summary of safety

Patients, n (%)	RYZ101 120 kBq/kg (n=17)
Any TEAE	15 (88.2)
SAE	4 (23.5)
Treatment-related TEAE	10 (58.8)
Treatment-related SAE	0
Treatment-related Grade 3* TEAE	3 (17.6)
Lymphocyte count decreased	2 (11.8)
Weight decreased	1 (5.9)
Fatal TEAE	0
TEAEs leading to treatment discontinuation	0
TEAEs leading to dose modification, dose hold, and/or delay	3 (17.6)

SAE, serious adverse event; TEAE, treatment-emergent adverse event.
*There were no treatment-related Grade 4 TEAEs.

TABLE 5. Most common TEAEs in >1 patient

Patients, n (%)	RYZ101 120 kBq/kg (n=17)	Patients, n (%)	RYZ101 120 kBq/kg (n=17)
Fatigue	8 (47.1)	**Hyponatremia**	3 (17.6)
Nausea	7 (41.2)	**Vomiting**	3 (17.6)
Weight decreased	7 (41.2)	**White blood cell count decreased**	3 (17.6)
Hyperglycemia	6 (35.3)	**Alopecia**	2 (11.8)
Anemia	5 (29.4)	**Back pain**	2 (11.8)
Lymphopenia	5 (29.4)	**Blood alkaline phosphatase increased**	2 (11.8)
Abdominal pain	4 (23.5)	**Blood bilirubin increased**	2 (11.8)
Thrombocytopenia	4 (23.5)	**COVID-19**	2 (11.8)
Constipation	3 (17.6)	**Dyspnea**	2 (11.8)
Diarrhea	3 (17.6)	**Neutropenia**	2 (11.8)
Hypokalemia	3 (17.6)	**Pyrexia**	2 (11.8)

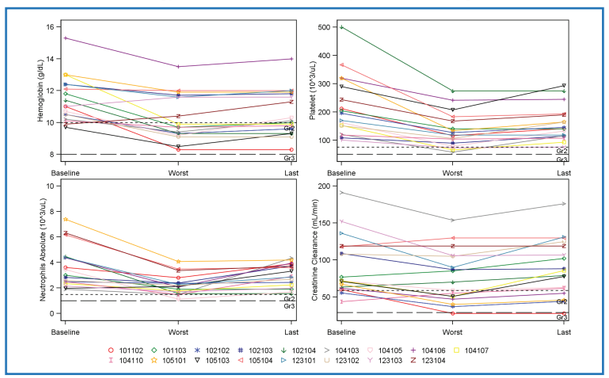
TEAE, treatment-emergent adverse event.

TABLE 6. Summary of treatment-related TEAEs in >1 patient

Patients, n (%)	RYZ101 120 kBq/kg (n=17)
Any treatment-related TEAE	10 (58.8)
Fatigue	7 (41.2)
Nausea	4 (23.5)
Lymphocyte count decreased	3 (17.6)
Vomiting	3 (17.6)
Alopecia	2 (11.8)
Anemia	2 (11.8)
Constipation	2 (11.8)
Weight decreased	2 (11.8)
White blood cell count decreased	2 (11.8)

TEAE, treatment-emergent adverse event.

FIGURE 3. Hematology and renal parameters in patients following RYZ101 treatment



CONCLUSIONS

- The AEs observed with RYZ101 in patients with GEP-NETs that progressed after prior ^{177}Lu-labeled SSAs are consistent with the mechanism of action and concomitant amino acid administration and the disease under study.
- The most common (≥20%) AEs were fatigue (47.1%), nausea (41.2%), weight loss (41.2%), hyperglycemia (35.3%), anemia (29.4%), lymphopenia (29.4%), and abdominal pain (23.5%).
- The most common grade 3 or 4 AE was lymphopenia, but clinical significance is doubtful given the absence of opportunistic infections.
- There were no DLTs, no RYZ101-related SAEs, and no AEs leading to study drug discontinuation.
- The most important identified risk related to RYZ101 was hematologic toxicity (especially thrombocytopenia). This can be managed with routine laboratory monitoring, dose delay or reduction, and supportive therapies.
- RYZ101 was well tolerated at 120 kBq/kg (max dose: 10.2 MBq), which was declared the RP3D. As the data do not suggest an influence of body mass with exposure levels or safety findings, the dose to be used in the Phase 3 study is a flat dose of 10.2 MBq every 8 weeks for 4 cycles.
- Part 2 (Phase 3) is open for enrollment and will compare RYZ101 at the RP3D with standard of care in patients with advanced SSTR2+ GEP-NETs with disease progression following prior ^{177}Lu-labeled SSAs.

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