Phase Ib portion of the ACTION-1 phase Ib/3 trial of RYZ101 in gastroenteropancreatic neuroendocrine tumors (GEP-NET) progressing after ^{177}Lu somatostatin analogue (SSA) therapy: preliminary safety and efficacy

[1]Jonathan Strosberg; [2]Gary Ulaner; [3]Daniel Halperin; [4]Samuel Mehr; [5]Daneng Li; [6]Heloisa Soares; [7]Lowell Anthony; [8]Sandy Kotiah; [9]Heather Jacene; [10]Pamela L. Kunz; [11]Denis Ferreira; [11]Joanne Li; [11]Kimberly Ma; [11]Jessica Rearden; [11]Susan Moran; [12]Thomas Hope; [13]Simron Singh; [14]Michael Morris

[1]Moffitt Cancer Center, Tampa, FL; [2]Hoag Family Cancer Institute, Newport Beach, CA; [3]MD Anderson Cancer Center, Houston, TX; [4]Nebraska Cancer Specialists, Omaha, NE; [5]City of Hope Comprehensive Cancer Center, Duarte, CA; [6]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; [7]University of Kentucky Markey Cancer Center, Lexington, KY; [8]Mercy Medical Center, Baltimore, MD; [9]Dana Farber Cancer Institute, Boston, MA; [10]Yale Cancer Center, New Haven, CT; [11]RayzeBio, San Diego, CA; [12]University of California San Francisco, CA; [13]University of Toronto, Odette Cancer Center at Sunnybrook Health Sciences Center, Toronto, ON, Canada; [14]Advanced Molecular Imaging and Therapy, Glen Burnie, MD, USA

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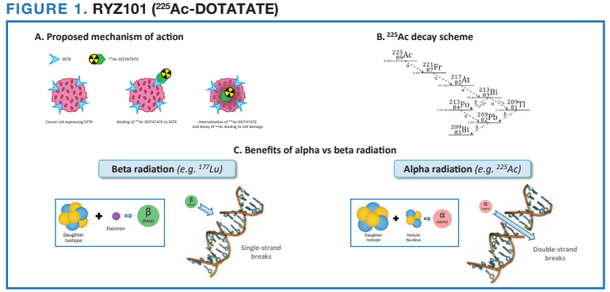
BACKGROUND

- RYZ101 (^{225}Ac-DOTATATE) is a first-in-class, highly potent alpha-emitting radiopharmaceutical therapy being developed for 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 (as emitted by ^{177}Lu or ^{90}Y), causing more frequent double-strand DNA breaks and potentially improved therapeutic index (**Figure 1c**).
- ACTION-1 (NCT05477576) is a two-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) and initial efficacy 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 the latest safety and initial efficacy findings from Part 1 (Phase 1b) of the ACTION-1 trial.

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



METHODS

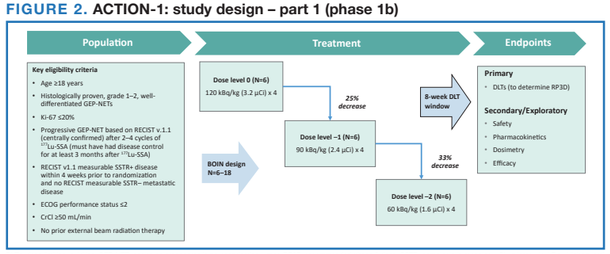
STUDY DESIGN

- 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)



DLTs, dose-limiting toxicities; GEP-NET, gastro-enteropancreatic neuroendocrine tumor; RP3D, recommended phase 3 dose; SSTR: somatostatin receptor; µCi= microcurie; kBq= kilobequerel

TREATMENT

- Patients received one RYZ101 infusion every 8 weeks for up to 4 cycles.
- Amino acids containing lysine and arginine were co-infused with each RYZ101 administration for renal protection.

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.

EFFICACY EVALUATIONS

- Tumor response was assessed locally by RECIST v1.1.

RESULTS

STATUS

- As of the 30 June 2023 data cut-off, enrollment was complete, and 17 patients had received RYZ101 at the starting dose level of 120 kBq/kg (safety data set).
- No DLTs occurred and no dose de-escalation steps were implemented.
- Fifteen patients completed all 4 planned treatment cycles. Two patients discontinued treatment due to disease progression.

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 the ileum (58.8%) and pancreas (29.4%; **Table 2**).

RYZ101 EXPOSURE

- Four patients required dose reductions during treatment (three due to grade 2 thrombocytopenia and one patient due to grade 3 anemia). One patient had a dose interruption due to extravasation, although infusion was resumed on the same day. One other patient had a dose delay due to COVID infection.

TABLE 1. Baseline patient demographics

	RYZ101 120 kBq/kg (n=17)
Median age, years (range)	63 (42–78)
Male / female, %	64.7 / 35.3
Race, %	
White	76.5
Black or African American	11.8
Unknown	5.9
Multiple	5.9
Ethnicity, %	
Hispanic or Latino	11.8
Not Hispanic or Latino	88.2
ECOG performance status, %	
0	58.8
1	41.2

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, %	
Ileum	58.8
Pancreas	29.4
Duodenum	5.9
Jejunum	5.9
Functional status, %	
Functional	70.6
Not-functional	29.4
Histopathologic grade, %	
Grade 1	47.1
Grade 2	52.9
Patients with prior PRRT, n%	100.0
Patients receiving 2/3/4 PRRT cycles	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, %	100.0/0

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

SAFETY

- A summary of safety findings is shown in **Table 3**:
  - All patients experienced TEAEs. The most frequent TEAEs are shown in **Table 4**.
  - Serious AEs (SAEs) were observed in six patients, but none were considered treatment related.
  - Grade ≥3 AEs occurred in nine patients. Five patients experienced treatment-related grade ≥3 AEs (**Table 3**).
  - No TEAEs or SAEs led to treatment discontinuation.
  - TEAEs leading to dose modification, dose hold, and/or delays occurred in four patients.
  - Hematology and renal parameters over time are shown in **Figure 3**.

TABLE 3. Safety summary

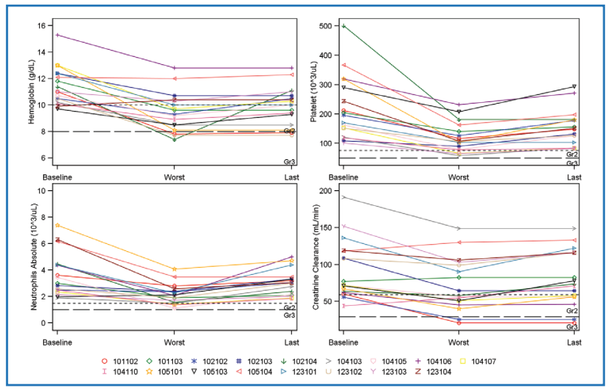
Patients, n (%)	RYZ101 120 kBq/kg (n=17)
Any TEAEs	17 (100.0)
SAEs	6 (35.3)
Treatment-related SAEs	0 (0.0)
Grade ≥3 TEAEs	9 (52.9)
Treatment-related Grade ≥3 TEAEs	5 (29.4)
Anemia[a]	3 (17.6)
Lymphocyte count decreased	3 (17.6)
Creatinine clearance decreased[b]	2 (11.8)
Weight decreased	1 (5.9)
Fatal (Grade 5) TEAEs	0 (0.0)
TEAEs leading to treatment discontinuation	0 (0.0)
TEAEs leading to dose modification, dose hold, and/or delay	4 (23.5)

SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]Includes the terms hemoglobin decreased and anemia; [b]Includes the terms chronic kidney disease and creatinine renal clearance decreased.

TABLE 4. Most frequent AEs (occurring in >2 patients)

Patients, n (%)	RYZ101 120 kBq/kg (n=17)	Patients, n (%)	RYZ101 120 kBq/kg (n=17)
Nausea	10 (58.8)	Creatinine renal clearance decreased	4 (23.5)
Fatigue	9 (52.9)	Hyponatremia	4 (23.5)
Hyperglycemia	8 (47.1)	Vomiting	4 (23.5)
Weight decreased	8 (47.1)	White blood cell count decreased	4 (23.5)
Anemia	6 (35.3)	Blood alkaline phosphatase increased	3 (17.6)
Lymphocyte count decreased	6 (35.3)	Diarrhea	3 (17.6)
Abdominal pain	5 (29.4)	Dyspnea	3 (17.6)
Platelet count decreased	5 (29.4)	Hypokalemia	3 (17.6)
Constipation	4 (23.5)		

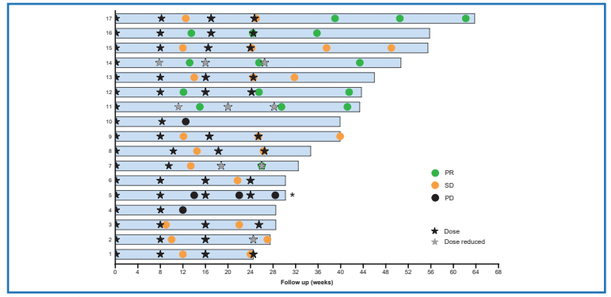
FIGURE 3. Hematology and renal parameters in patients following RYZ101 treatment



EFFICACY

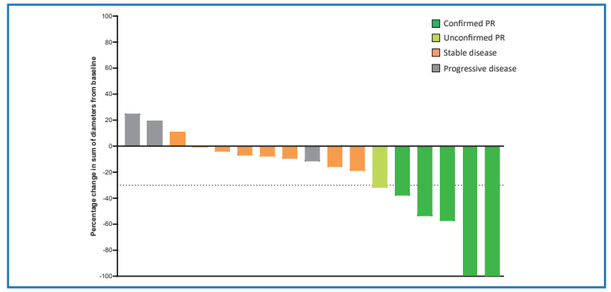
- Efficacy findings are shown in **Figures 4 and 5**:
  - The confirmed objective response rate (ORR) was 29.4% (n=5, all partial responses).
  - One patient had an unconfirmed PR.
  - Eight patients (47.1%) had stable disease, and three (17.6%) had progressive disease.

FIGURE 4. RYZ101 treatment and duration of follow-up



*This patient was initially thought to have pseudo-progression but was permitted to continue treatment by the investigator.

FIGURE 5. Best percentage change in tumor size (investigator-assessed)



Efficacy evaluable population are those subjects who received at least one RYZ101 dose and had at least one efficacy evaluable assessment.

CONCLUSIONS

- The AEs observed with RYZ101 in patients with GEP-NETs that progressed after prior ^{177}Lu-labeled SSAs are consistent with its mechanism of action, concomitant amino acid administration, and the disease under study.
  - The most common AEs were nausea (58.8%), fatigue (52.9%), hyperglycemia (47.1%), decreased weight (47.1%), anemia and lymphocyte count decrease (35.3% each).
  - The most common grade ≥3 AEs were anemia and lymphopenia. Two patients with reduced creatinine clearance at baseline experienced shifts to grade 3 decreased creatinine clearance.
  - There were no DLTs, no RYZ101-related SAEs, and no AEs leading to study drug discontinuation.
- Initial data suggest promising efficacy of RYZ101 in this setting:
  - Confirmed ORR was 29.4%, with all five patients having a confirmed PR.
  - A further eight patients (47.1%) had SD.
- Part 2 (phase 3) is enrolling and will compare RYZ101 at 10.2 MBq q8w for 4 cycles with standard of care in patients with advanced SSTR2+ GEP-NETs progressing following prior ^{177}Lu-labeled SSAs.

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REFERENCES

1. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT05477576. Accessed April 26, 2023.