Phase 1b portion of the ACTION-1 phase 1b/3 trial of RYZ101 in gastroenteropancreatic neuroendocrine tumors progressing after ^{177}Lu somatostatin analog therapy: Safety and efficacy findings

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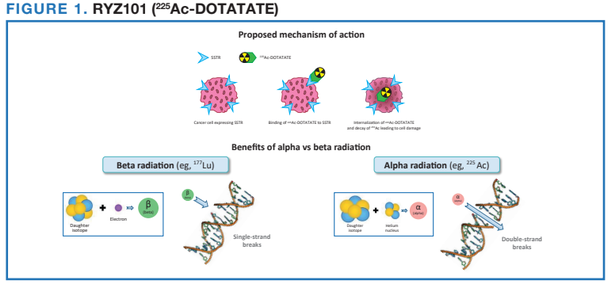
BACKGROUND

- Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a group of biologically and clinically heterogeneous neoplasms arising from neuroendocrine precursor cells in the gastrointestinal tract and pancreas.[1,2]
  - Although GEP-NETs are rare, there has been a consistent increase in their incidence/prevalence globally over the past five decades.[3–6]
  - The three most common primary tumor sites in patients with GEP-NETs are the rectum (28.6%), small intestine (28.1%), and pancreas (16.4%).[7]
- Well-differentiated GEP-NETs are commonly characterized by high-density expression of somatostatin receptors (SSTRs), which can be targeted by radiopharmaceutical therapy (RPT) via radiolabeled somatostatin analogs (SSAs).[1,8–10]
- RYZ101 (^{225}Ac-DOTATATE) is a first-in-class, highly potent, alpha-emitting RPT being developed for the treatment of SSTR2+ solid tumors (**Figure 1**).
- 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)



SSTR, somatostatin receptor.

METHODS

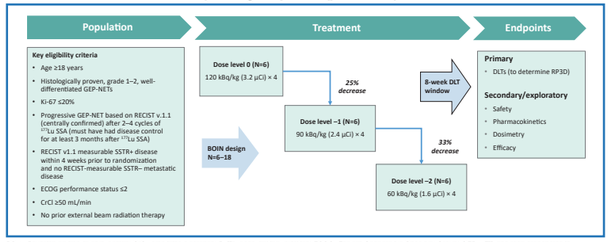
STUDY DESIGN

- Part 1 of ACTION-1 was an uncontrolled dose, de-escalation study based on Bayesian optimal interval design. An escalation boundary of 0.197 and a de-escalation boundary of 0.298 were used based on a target toxicity rate of 25% (**Figure 2**).
- RYZ101 was administered intravenously every 8 weeks for up to four cycles.
- Three dose levels (n=6/level) were possible:
  - level 0 (starting dose), 120 kBq/kg (3.2 µCi/kg)
  - 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 progressed (Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) following two to four cycles of therapy with ^{177}Lu SSA were eligible.
- Patients unresponsive to prior ^{177}Lu SSA (disease control <3 months after ^{177}Lu SSA) were excluded.
- Patients had to have Eastern Cooperative Oncology Group (ECOG) status 0–2 and adequate hematologic and renal function.

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



BOIN, Bayesian optimal interval design; CrCl, creatinine clearance; DLTs, dose-limiting toxicities; ECOG, Eastern Cooperative Oncology Group; GEP-NET, gastroenteropancreatic neuroendocrine tumor; RECIST, Response Evaluation Criteria in Solid Tumors; RP3D, recommended phase 3 dose; SSA, somatostatin analog; SSTR, somatostatin receptor.

TREATMENT

- Patients received one RYZ101 infusion every 8 weeks for up to four cycles.
- 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 using National Cancer Institute Common Terminology Criteria for Adverse Events v5.0.
- Dose de-escalation decisions and safety data review were overseen by a data review committee.

EFFICACY EVALUATIONS

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

RESULTS

STATUS

- As of the December 14, 2023 data cutoff, 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 four planned treatment cycles. Two patients discontinued treatment because of disease progression.

PATIENTS

- The median age was 63 years; 64.7% of patients were male; all had an ECOG performance status of 0 or 1 (58.8% and 41.2%, respectively; **Table 1**).
- The median time since diagnosis at study enrollment 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-19 infection.

TABLE 1. Baseline patient demographics

	RYZ101 120 kBq/kg (N=17)
Median age, years (range)	63.0 (42.0–78.0)
Male/female, %	64.7/35.3
Race, %	
White	82.4
Black or African American	11.8
Unknown	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 Cooperative Oncology 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 four prior 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, gastroenteropancreatic neuroendocrine tumor; PRRT, peptide receptor radionuclide therapy.

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 adverse events (SAEs) were observed in six patients (35.3%), but none were considered treatment-related.
  - Grade ≥3 AEs occurred in nine patients (52.9%). Five patients (29.4%) experienced treatment-related grade ≥3 AEs (**Table 3**).
  - The most common grade ≥3 AEs were anemia and lymphopenia. One patient with reduced creatinine clearance (CrCl) at baseline experienced grade 3 decreased CrCl; another with reduced baseline CrCl developed grade 4 decreased CrCl.
  - No TEAEs or SAEs led to treatment discontinuation.
  - TEAEs leading to dose modification, dose hold, and/or delays occurred in four patients (23.5%).
  - Hematology and renal parameters over time are shown in **Figure 3**.

TABLE 3. Safety summary

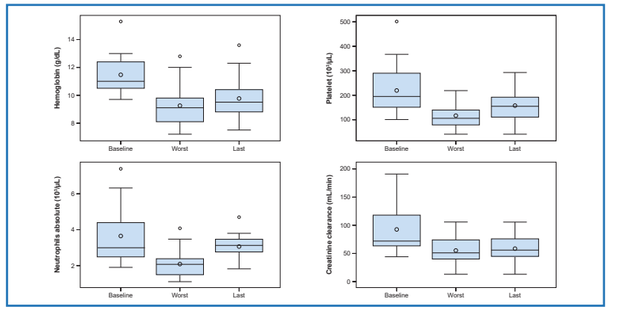
Patients, n (%)	RYZ101 120 kBq/kg (n=17)
Any TEAEs	17 (100.0)
SAEs	6 (35.3)
Treatment-related SAEs	0 (0.0)
Grade ≥3 TEAEs	9 (52.9)
Treatment-related grade ≥3 TEAEs	5 (29.4)
Anemia[a]	3 (17.6)
Lymphocyte count decreased	3 (17.6)
Creatinine clearance decreased[b]	2 (11.8)
Weight decreased	1 (5.9)
Fatal (grade 5) TEAE[c]	1 (5.9)
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; [c]Fatal event was liver failure deemed unrelated to RYZ101 and instead attributed to prior non-alcoholic steatohepatitis and liver cirrhosis.

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)
Anemia	10 (58.8)	Constipation	4 (23.5)
Nausea	10 (58.8)	Vomiting	4 (23.5)
Fatigue	9 (52.9)	White blood cell count decreased	4 (23.5)
Weight decreased	8 (47.1)	Alopecia	3 (17.6)
Creatinine renal clearance decreased	6 (35.3)	Blood creatinine increased	3 (17.6)
Hyperglycemia	6 (35.3)	Diabetes mellitus	3 (17.6)
Lymphocyte count decreased	6 (35.3)	Diarrhea	3 (17.6)
Abdominal pain	5 (29.4)	Dyspnea	3 (17.6)
Blood alkaline phosphatase increased	5 (29.4)	Hypertension	3 (17.6)
Hyponatremia	5 (29.4)	Hypokalemia	3 (17.6)
Platelet count decreased	5 (29.4)		

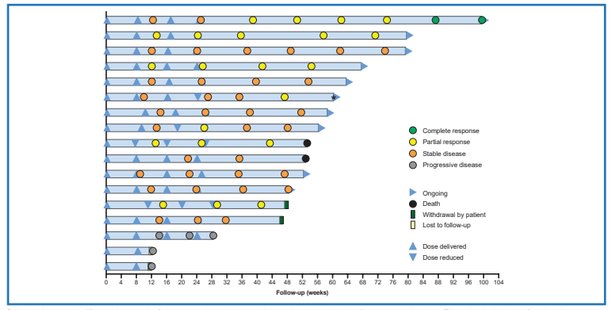
FIGURE 3. Hematology and renal parameters in patients following RYZ101 treatment



EFFICACY

- Efficacy findings are shown in **Table 5** and **Figures 4** and **5**.
  - The confirmed objective response rate was 29.4% (one complete response and four partial responses).
  - One patient had an unconfirmed partial response at the time of data cutoff, which was later confirmed.
  - Seven patients (41.2%) had stable disease, and three (17.6%) had progressive disease.
  - The median duration of response was not estimable (95% CI 9.26 months, not estimable).
  - The median progression-free survival was not estimable (95% CI 12.16 months, not estimable).

FIGURE 4. RYZ101 treatment and duration of follow-up



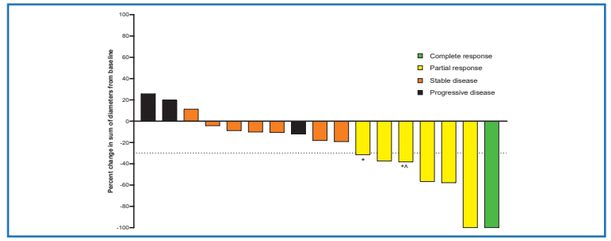
Follow-up time was the difference between the first treatment date and the end of the study, death, or the last disease progression date. *This patient had an unconfirmed partial response at the time of data cut-off that was later confirmed.

TABLE 5. Summary of objective response rate (investigator-assessed) in the efficacy-evaluable population

Response, n (%)	Overall (N=17)
Objective response rate	7 (41.2)
Complete response	1 (5.9)
Partial response	6 (35.3)
Confirmed complete or partial response	5 (29.4)*
Stable disease	7 (41.2)
Progressive disease	3 (17.6)
Disease control rate	14 (82.4)

*One patient had a partial response confirmed after the data cutoff date (Dec 14, 2023); including this confirmed partial response, the confirmed objective response rate would be 35.3% (6 of 17 patients).

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



*Unconfirmed response at time of data cutoff; ^ This partial response was later confirmed after the data cutoff date.
Efficacy evaluable population are those patients 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 anemia (58.8%), nausea (58.8%), fatigue (52.9%), decreased weight (47.1%), decreased creatinine renal clearance, hyperglycemia, and decreased lymphocyte count (35.3% each).
  - The most common grade ≥3 AEs were anemia and lymphopenia. One patient with reduced CrCl at baseline experienced grade 3 decreased CrCl; another with reduced baseline CrCl developed grade 4 decreased CrCl.
  - 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.
  - The confirmed objective response rate was 29.4%, including one complete response and four partial responses.
  - One patient had a partial response confirmed after the data cutoff date (Dec 14, 2023); including this confirmed partial response, the confirmed objective response rate would be 35.3% (6 of 17 patients).
  - A further seven patients (41.2%) had stable disease.
- Part 2 (phase 3) is enrolling and will compare RYZ101 at 10.2 MBq (275 µCi) every 8 weeks for four cycles with standard of care in patients with advanced SSTR2+ GEP-NETs progressing following prior ^{177}Lu-labeled SSAs.

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