United Theranostics

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

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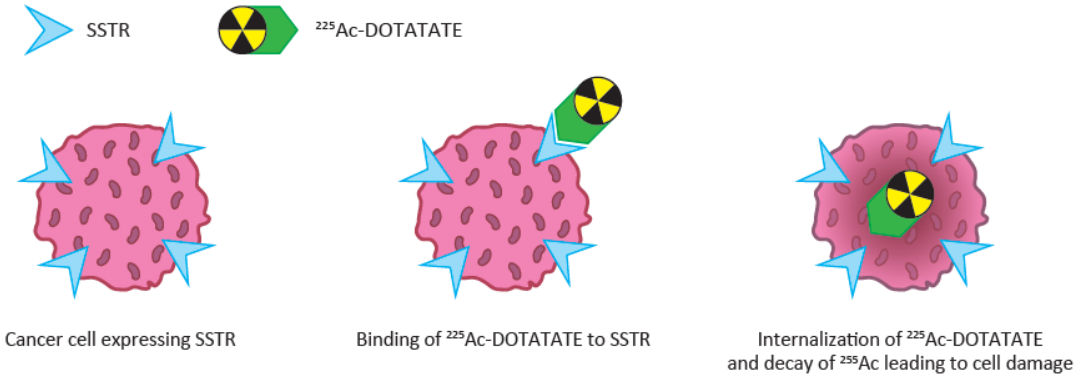
Background

- 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]
- RYZ101 (^{225}Ac-DOTATATE) is a first-in-class, highly potent, alpha-emitting RPT being developed for the treatment of SSTR2+ solid tumors
- ACTION-1 is a phase 1b/3 trial comparing RYZ101 to standard-of-care therapy in patients with gastro-enteropancreatic neuroendocrine tumors (GEP-NETs) that have progressed following ^{177}Lu-labelled somatostatin analogue (SSA) therapy
  - ACTION-1 included a first-of-its-kind dosimetry substudy to determine the feasibility of estimating absorbed radiation doses of RYZ101 to critical organs (primary objective) and tumor lesions (secondary objective)
- We now present the final results of the phase 1b portion of ACTION-1

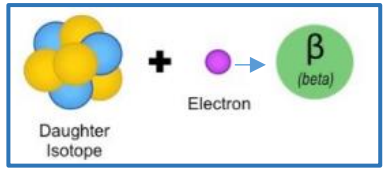
1. Cives M, et al. CA Cancer J Clin 2018;68:471–87; 2. Cives M, et al. J Clin Med 2020;9:3655

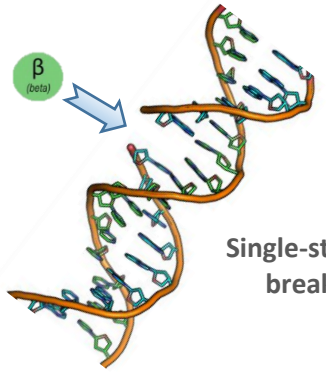
RYZ101 (^{225}Ac-DOTATATE): proposed mechanism of action



Benefits of alpha vs beta radiation

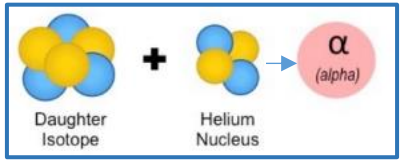
Beta radiation *(eg ^{177}Lu)*

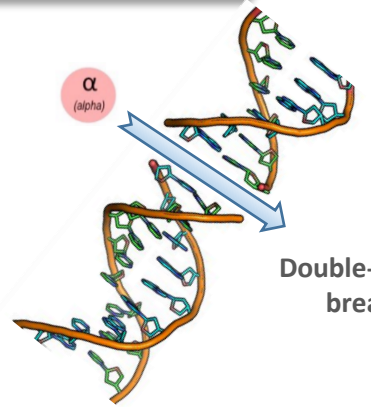




Single-strand breaks

Alpha radiation *(eg ^{225}Ac)*





Double-strand breaks

SSTR, somatostatin receptor

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

Population

Key eligibility criteria

- Age ≥18 years
- Histologically proven, grade 1–2, well-differentiated GEP-NETs
- Ki-67 ≤20%
- Progressive GEP-NET based on RECIST v.1.1 (centrally confirmed) after 2–4 cycles of ^{177}Lu SSA (must have had disease control for ≥3 months after ^{177}Lu SSA)
- RECIST v1.1 measurable SSTR+ disease within 4 weeks prior to randomization and no RECIST measurable, SSTR– metastatic disease
- ECOG performance status ≤2
- CrCl ≥50 mL/min
- No prior external beam radiation therapy, radioembolization or alkylating agents

Treatment

Dose level 0 (n=6)
120 kBq/kg (3.2 µCi) × 4

25% decrease

BOIN design
N=6–18

Dose level –1 (n=6)
90 kBq/kg (2.4 µCi) × 4

33% decrease

Dose level –2 (n=6)
60 kBq/kg (1.6 µCi) × 4

8-week DLT window

Endpoints

Primary

- DLTs (to determine RP3D)

Secondary/exploratory

- Safety
- Pharmacokinetics
- Dosimetry
- Efficacy

Dosimetry

- Absorbed doses to target tissues and tumor lesions
- Assessed by SPECT/CT scans

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

Baseline disease characteristics and prior anticancer therapies

	RYZ101 120 kBq/kg (N=17)
Median age, years (range)	63.0 (42.0–78.0)
Male/female, %	64.7/35.3
ECOG performance status, %	
0	58.8
1	41.2
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 4 prior PRRT cycles	100.0
Median time since prior PRRT to first dose of RYZ101, months (range)	28.7 (1.9–47.3)

PRRT, peptide receptor radionuclide therapy

Safety summary

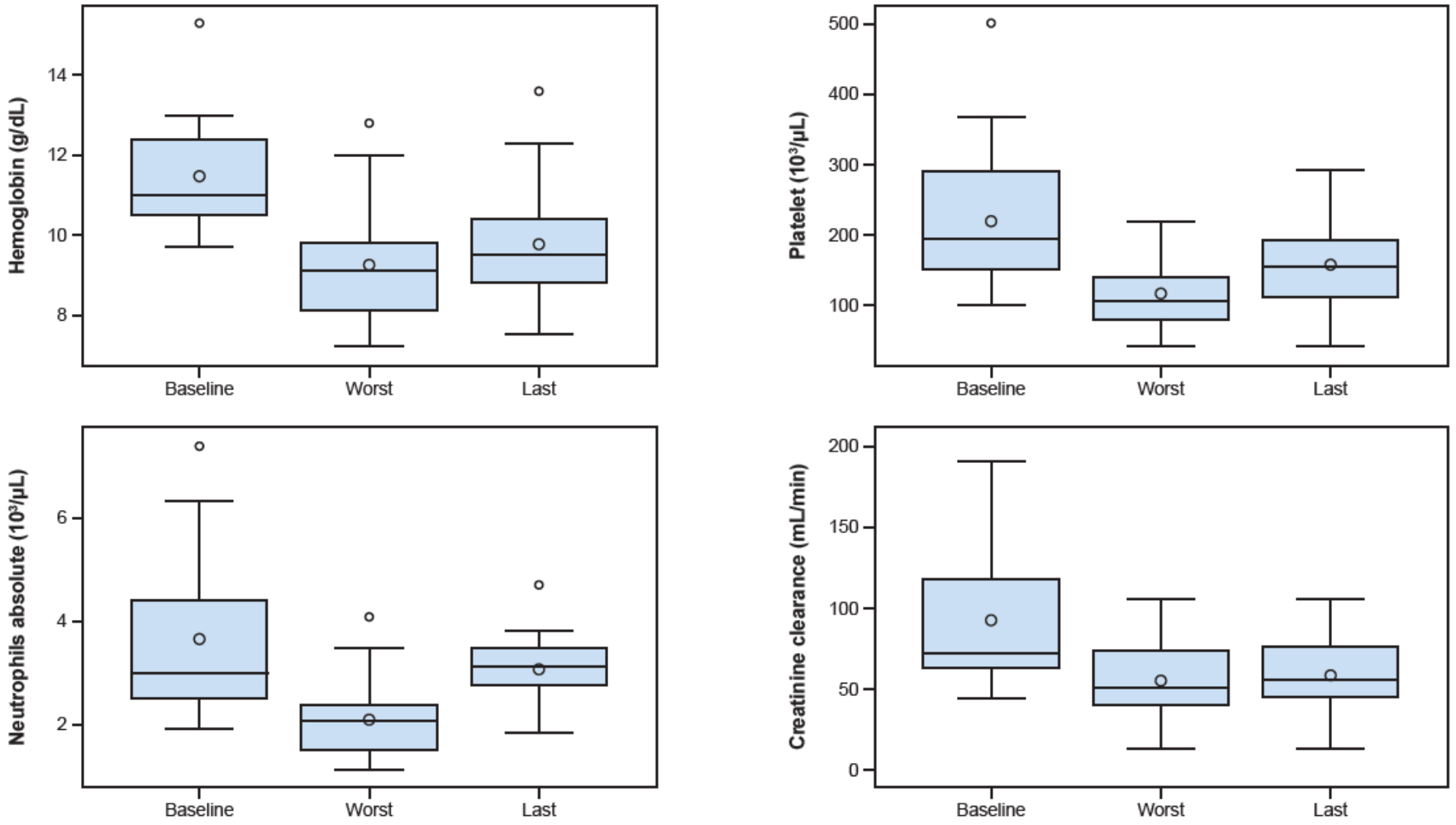
Patients, n (%)	RYZ101 120 kBq/kg (N=17)
Any TEAEs	17 (100.0)
SAEs	6 (35.3)
Treatment-related SAEs	0 (0.0)
Grade ≥3 TEAEs	9 (52.9)
Treatment-related grade ≥3 TEAEs	5 (29.4)
Anemia[a]	3 (17.6)
Lymphocyte count decreased	3 (17.6)
Creatinine clearance decreased[b]	2 (11.8)
Weight decreased	1 (5.9)
Fatal (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

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)		

Hematology and renal parameters following RYZ101 treatment



The horizontal line splitting the box represents the median. Bars indicate the maximum and minimum values. Circles above the upper bar represent outliers Circles within the box represent the mean. These graphs indicate that there were no grade 3 or 4 events in this patient population

Efficacy findings

- The confirmed objective response rate (ORR) was 35.3% (one complete response and five partial responses).
- One patient had an unconfirmed PR at the time of data cut-off, 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 PFS was not estimable (95% CI 12.16 months, not estimable).

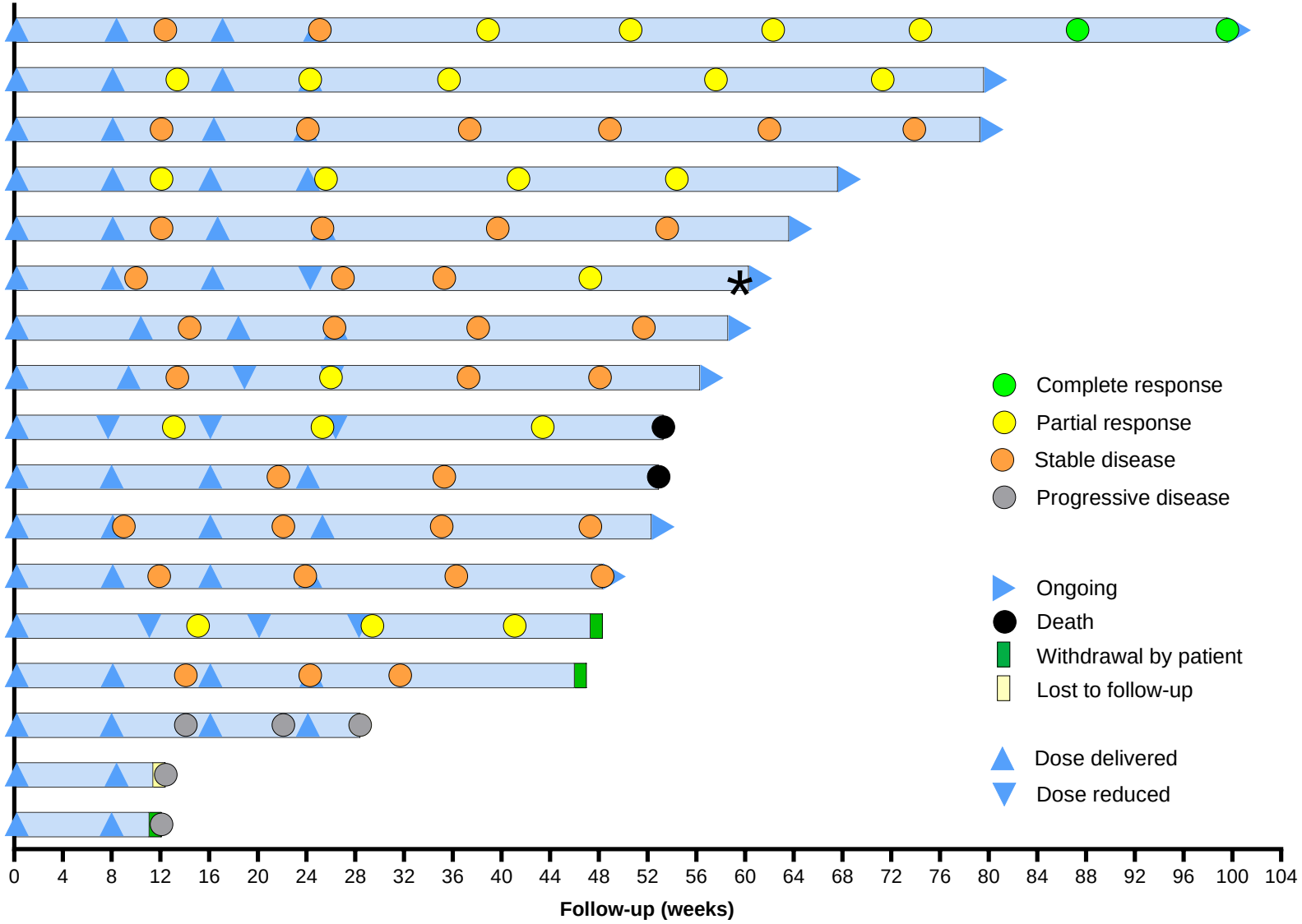
ORR (investigator-assessed) in the efficacy-evaluable population

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)

Data cut-off: Dec 14, 2023

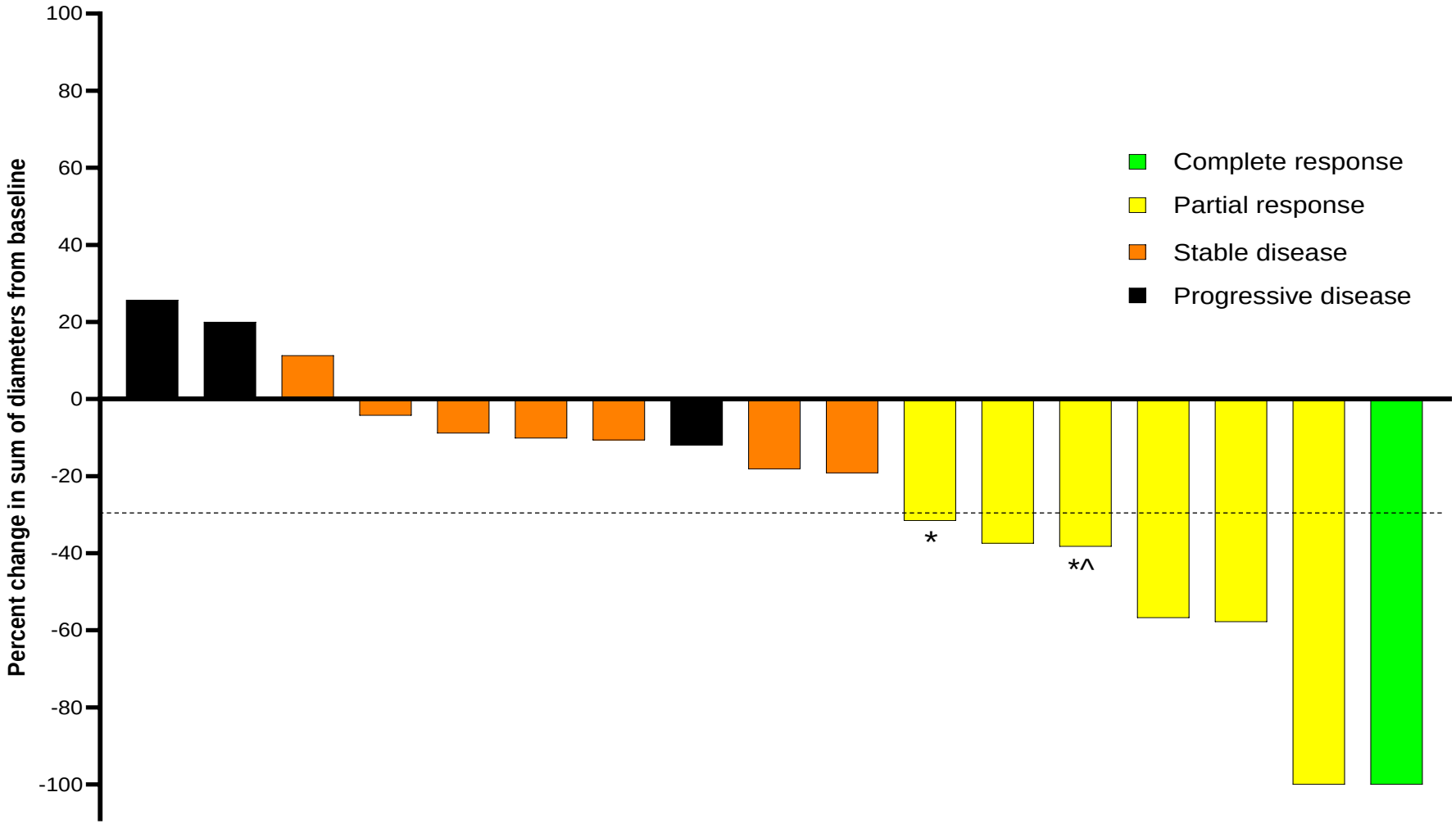
RYZ101 treatment and duration of follow-up:
All patients



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

Data cut-off: Dec 14, 2023

Best percentage change in tumor size:
Efficacy evaluable population (investigator-assessed)



*Unconfirmed response at time of data cut-off. ^This partial response was later confirmed after the cut-off date.
Efficacy evaluable population are those patients who received at least one RYZ101 dose and had at least one efficacy evaluable assessment

Data cut-off: Dec 14, 2023

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 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 ORR was 29.4%, including one complete response and four partial responses
  - One patient had a PR confirmed after the data cutoff date (Dec 14, 2023). By including this confirmed PR, the confirmed ORR would be 35.3% (6 of 17 patients)
- Initial dosimetry data suggest ^{221}Fr and ^{213}Bi can be imaged separately and simultaneously by SPECT/CT and indicate a favorable tumor-to-normal tissue profile, supportive of RYZ101 for treatment of SSTR+ GEP-NETs
- 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

Acknowledgments

- The authors would like to thank all the patients and their caregivers, and all the site investigators and study staff who participated in the study
- The ^{225}Ac used in this research was supplied by multiple sources, including the US Department of Energy Isotope Program managed by the Office of Isotope R&D and Production
- The ACTION-1 study is sponsored by RayzeBio Inc., San Diego, CA. The study sponsor also funded medical writing and layout support for this presentation, which was provided by Miller Medical Communications Ltd