Future Oncology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ifon20

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To cite this article: Udhayvir. S. Grewal, Olumide. B. Gbolahan, Amol. M. Takalkar & Daniel. M. Halperin (31 Mar 2025): Alpha radioligand therapy in neuroendocrine neoplasms: current landscape and spotlight on RYZ101, Future Oncology, DOI: 10.1080/14796694.2025.2485650

To link to this article: https://doi.org/10.1080/14796694.2025.2485650

Published online: 31 Mar 2025.

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FUTURE ONCOLOGY
https://doi.org/10.1080/14796694.2025.2485650

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Alpha radioligand therapy in neuroendocrine neoplasms: current landscape and spotlight on RYZ101

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ABSTRACT

The therapeutic landscape for neuroendocrine tumors (NETs) has rapidly evolved over the last three decades with the influx of a myriad of treatment options, such as somatostatin analogs (SSAs), targeted therapies, alkylating chemotherapies, and radioligand therapy (RLT). While the advent and regulatory approval of beta emitting RLT such as 177Lu-DOTATATE has offered a valuable therapeutic option for patients with NETs, there is still very significant room to tap the maximal therapeutic potential of RLT. Alpha RLT agents such as RYZ101 (225Ac-DOTATATE) offer a potential advantage over beta RLT due to more complex double-stranded DNA breaks and targeted cytotoxicity, as well as potential for minimizing off-target side-effects. Existing pre-clinical and clinical data suggest promising safety and efficacy of RYZ101 among patients with NETs. The ongoing phase 1b/3 trial ACTION-1 is poised to compare the safety and efficacy of RYZ101 against standard care therapies in advanced gastroenteropancreatic NETs (Ki67 ≤ 20%), after disease progression of prior 177Lu-SSA therapy. Yet, other alpha RLT agents are currently being investigated in both RLT-naïve as well-pre-treated patient populations. While long-term safety and efficacy data are awaited, alpha RLT agents such as RYZ101 offer a unique opportunity to enhance the therapeutic promise of RLT in NETs.

ARTICLE HISTORY
Received 31 October 2024
Accepted 25 March 2025

KEYWORDS
Neuroendocrine neoplasms; peptide receptor radionuclide therapy; alpha radioligand therapy; somatostatin receptor targeting; ^{225}Ac-DOTATATE; targeted alpha therapy

1. Introduction

Neuroendocrine neoplasms (NENs) are a heterogeneous group of malignancies that are classified according to their site of origin and pathological characteristics such as grade and differentiation. Well-differentiated NENs are termed as neuroendocrine tumors (NETs) and are further sub-classified based on their Ki-67 proliferation index, for example, gastroenteropancreatic NETs (GEPNETs) are classified into grade 1 (Ki-67 < 3%), grade 2 (Ki-67 3–20%), and grade 3 (Ki-67 > 20%) NETs. Poorly differentiated NENs are referred to as neuroendocrine carcinomas (NECs). There has been a rapid evolution in the treatment paradigms for NETs in the last 3 decades which includes the development and use of somatostatin analogs (SSAs), targeted therapies (targeting mTOR or angiogenic pathways), alkylating chemotherapies, and radiopharmaceuticals [1].

Peptide receptor radionuclide therapy (PRRT), also referred to as radioligand therapy (RLT), targets somatostatin receptors (SSTR) using SSAs that are labeled with therapeutic radioactive isotopes. One of the earliest radioactive isotopes to be employed as RLT for NETs was Indium-111 (^{111}In). Although the decay of ^{111}In was associated with the release of potentially therapeutic Auger and conversion electrons, clinical activity with agents such as ^{111}In-DTPA(0)]octreotide was modest. There were also concerns for high incidence of myelodysplastic syndrome and acute leukemia with doses higher than 100 GBq [2]. Due to concerns for limited efficacy and high incidence of treatment-related toxicity, drug development efforts were subsequently shifted toward beta emitters such as Yttrium 90 (^{90}Y) and Lutetium 177 (^{177}Lu). The first phase III trial evaluating the safety and efficacy of RLT in NETs was the NETTER-1 trial which included patients with advanced well-differentiated midgut NETs with disease progression on upfront standard dose SSAs. The trial demonstrated a statistically significant improvement in progression-free survival among patients receiving ^{177}Lu-DOTATATE (along with 30 mg octreotide LAR) compared to 60 mg octreotide LAR [HR = 0.21; (95% CI, 0.13–0.33), $p <$ 0.001] [3]. Within the caveats that the analysis was not powered to detect a difference in overall survival and that 36% of patients in the control group subsequently received PRRT post-progression, a trend toward improved overall survival was noted, but this was not statistically significant [HR = 0.84, (95% CI 0.60–1.17), $p = 0.30$] [4]. Based on the results of the NETTER-1 trial and a large single-center analysis on the safety and efficacy of PRRT in GEPNETs and bronchial NETs from Netherlands, the US Food and Drug Administration (USFDA) approved ^{177}Lu-DOTATATE (or Lutathera®) for advanced SSTR-avid GEPNETs in January 2018 [5]. The approval heralded a significant leap forward in offering an effective therapeutic option to patients with advanced GEPNETs. More recently, the NETTER-2 trial demonstrated clinical activity and superior progression free-survival with ^{177}Lu-DOTATATE as first-line therapy in advanced SSTR-avid GEPNETs with Ki67 10–55%. The median progression-free survival was 8.5 months (95% CI 7.7–13.8) in the control group (high-dose octreotide LAR) and 22.8 months (19.4–not estimated) in the ^{177}Lu-DOTATATE group (HR = 0.276 (95% CI 0.18–0.42), $p < 0.0001$) [6].

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Article highlights

- Alpha particle-based radioligand therapy (RLT) is emerging as a potentially promising alternative to beta-emitter RLT, offering higher cytotoxicity due to its greater linear energy transfer (LET) and ability to induce complex DNA damage, including double-stranded breaks.
- Alpha particles have a shorter path length than beta particles, potentially reducing off-target toxicity while maintaining high tumor-killing efficacy.
- ^{225}Ac-DOTATATE (RYZ101) is a novel alpha-emitting RLT targeting somatostatin receptors (SSTRs) and has demonstrated promising preclinical and early clinical results in patients with gastroenteropancreatic neuroendocrine tumors (GEPNETs).
- The ongoing ACTION-1 phase 1b/3 trial is evaluating RYZ101 in patients with well-differentiated GEPNETs who have progressed after 177Lu-DOTATATE, with interim results showing a 29.4% objective response rate and no serious treatment-related adverse events.
- Dosimetry studies indicate that imaging and dose estimation for 225Ac are feasible, which could help optimize treatment delivery and minimize toxicity, although long-term safety data are still needed.
- Additional alpha-emitting RLT agents, such as 212Pb-DOTAMTATE and 212Pb-VMT-α-NET, are under clinical investigation, with early trials showing encouraging efficacy and manageable safety profiles, however long-term efficacy data and final safety analysis are awaited.
- Combining alpha RLT with radiation sensitizers, DNA damage repair inhibitors, or immunotherapy is being explored to enhance efficacy and prolong treatment responses.
- Future studies will determine the optimal role of alpha RLT in neuroendocrine tumor management, its long-term safety, and potential role in the evolving treatment paradigm.

Box 1. Drug summary

RYZ-101 is an alpha radiopharmaceutical currently being investigated for use in progressive gastroenteropancreatic neoplasms with somatostatin receptor-avid disease.

While the USFDA approval and use of ^{177}Lu-DOTATATE offers a very valuable treatment option for patients with advanced NETs, most patients ultimately develop progressive disease within 2–3 years of treatment [7]. Certain sites of metastatic disease (such as peritoneal metastases) may also be associated with suboptimal clinical responses to ^{177}Lu-DOTATATE and higher rates of treatment-related complications [8]. Additionally, long-term toxicities with ^{177}Lu-DOTATATE, particularly therapy-related myeloid neoplasms, remain a critical concern [9]. Therefore, there is a critical need for innovation and further development of safer and more effective agents to maximize the therapeutic potential of RLT for the treatment of NETs.

2. Alpha RLT: the new kid on the block

Alpha RLT comprises the next generation of agents in the RLT pipeline for the treatment of NETs. Theoretically, alpha particle radiation offers several therapeutic advantages over beta particle radiation that have the potential to translate into relatively improved clinical outcomes. Alpha particles have a higher mass and charge compared to beta particles which results in higher linear energy transfer as they traverse through biologic tissue. Consequently, they are more damaging to biologic tissue with greater DNA damage including double stranded DNA breaks (compared to mostly single stranded DNA breaks with beta particles). This more potent DNA damage from alpha particles is difficult to repair and translates into higher cytotoxicity to the targeted cancer cells. Alpha particles also possess a shorter range which can potentially minimize non-target adverse effects associated with RLT [10,11]. However, this can also lead to less effectiveness in the setting of bulky disease. However, in addition to direct cytotoxicity, alpha particles may also induce cell damage due to bystander effect leading to cytotoxicity for cells that may not be physically targeted by the radiopharmaceutical *per se* for various reasons (for example, inaccessible cell or cell surface receptor). This can potentially mitigate the theoretical disadvantage of a lower path length of alpha particles. Oxygen is particularly important for facilitating the biological effects of beta emitter-based RLT by the generation of free radicals in the tumor microenvironment. Therefore, tissue hypoxia significantly impairs the radiosensitivity of tumors. However, high-LET radiation (such as alpha particle radiation) can induce cytotoxic effects even in hypoxic tissues by generating high amounts of reactive oxygen species, giving it an added advantage over beta emitter-based RLT [12,13]. Table 1 summarizes some key differences between alpha and beta particle radiation [14].

Several alpha particle-based radiopharmaceuticals (like Ac-225 and Pb-212) are therefore being investigated in on-going clinical trials among patients with NETs and non-NET malignancies. The current review discusses the development of ^{225}Ac-DOTATATE as a novel alpha RLT or targeted alpha therapy (TAT) for the treatment of patients with NETs.

3. RYZ101 (^{225}Ac-DOTATATE)

RYZ101 is a radiopharmaceutical containing the active drug substance ^{225}Ac-DOTATATE. The long half-life (approximately 10 days) and high alpha emission energy (27.5 MeV) make ^{225}Ac an appealing radioisotope for alpha RLT. As shown in Figure 1, the ^{225}Ac in ^{225}Ac-DOTATATE is bound to a chelator (DOTA) and a somatostatin receptor ligand or SRL (TATE). Upon binding with a SSTR on the neuroendocrine tumor cell surface, the ^{225}Ac-DOTATATE-SSTR complex is internalized into the cell cytoplasm. After internalization, the complex undergoes degradation which leads to the separation of the SRL and SSTR from the complex. Upon release from the complex, ^{225}Ac remains trapped inside the cells and the emitted alpha particle radiation results in double stranded DNA breaks, ultimately causing DNA damage and cell death.

Existing pre-clinical studies of ^{225}Ac-based RLT show promising clinical activity and also allude to potential therapeutic superiority to beta RLT. The initial pre-clinical analysis investigating ^{225}Ac-DOTATOC in mouse tumor xenograft implants noted that the efficacy of ^{225}Ac-DOTATOC was significantly higher than ^{177}Lu-DOTATOC. This was demonstrated by a significantly higher reduction in tumor weight at 14 days with ^{225}Ac-DOTATOC (20 kBq/mouse) compared to ^{177}Lu-DOTATOC (1 MBq/mouse) [15]. Another pre-clinical analysis using small animal models of lung NENs demonstrated

Table 1. Key differences between alpha and beta particle radiation [reference = 30352433].

Variables	Alpha particle radiation	Beta particle radiation
Particle energy	5–9 MeV	50–2,300 keV
Particle path length	40–100 µm	0.05–12 mm
Linear energy transfer	Approx. 80 keV/µm	Approx. 0.2 keV/µm
DNA damage	Double-stranded DNA breaks	Single-stranded DNA breaks
Impact of tissue hypoxia on therapeutic activity	Expected to be less	Expected to be more
Off-target toxicity	Expected to be less	Expected to be more

[Abbreviations: DNA: deoxyribonucleic acid].

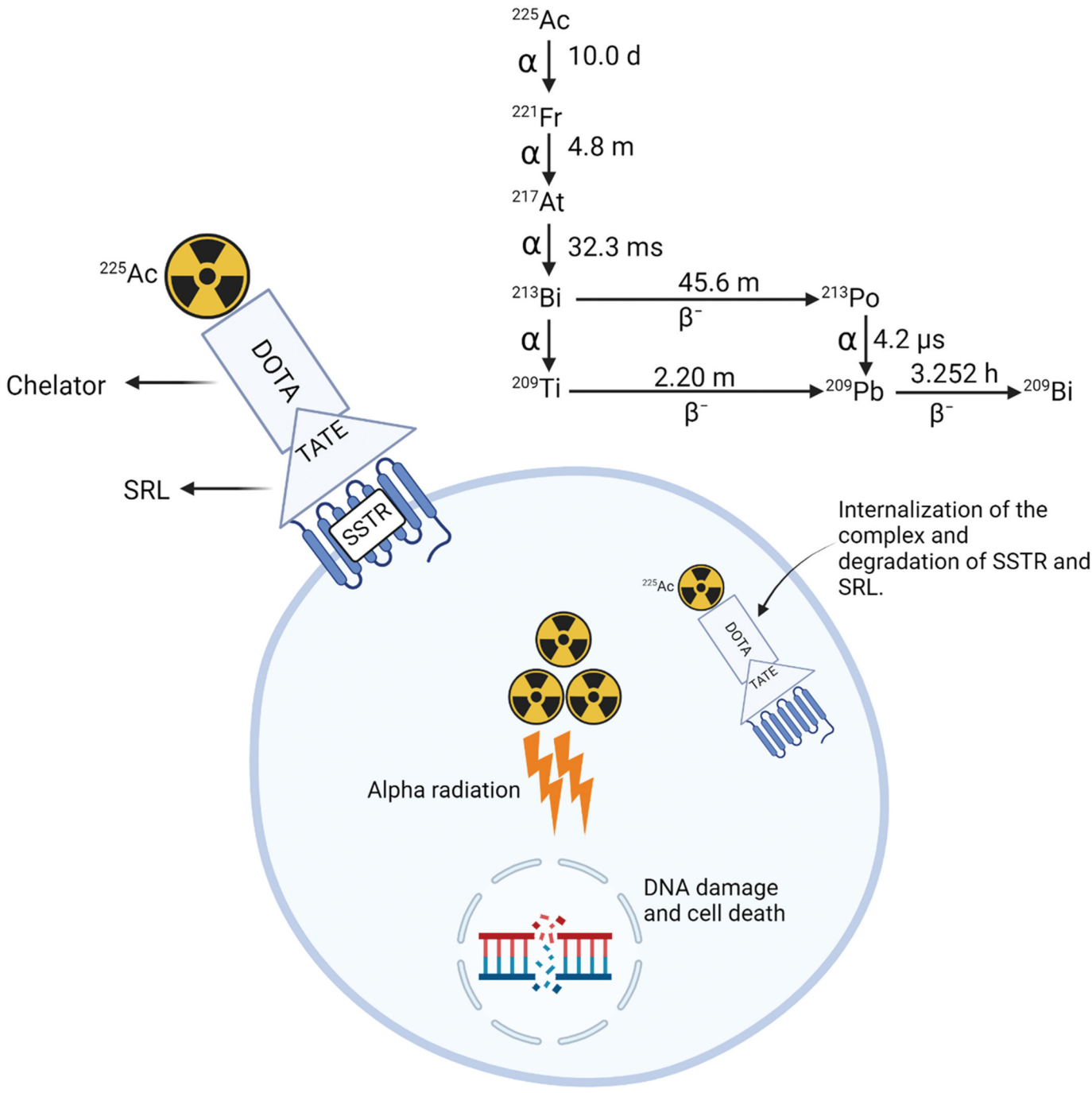

Figure 1. Mechanism of action of RYZ101 (^{225}Ac-DOTATATE).

In ^{225}Ac-DOTATATE, the ^{225}Ac is bound to a chelator (DOTA) and a somatostatin receptor ligand or SRL (TATE). When it binds to a somatostatin receptor (SSTR) on the surface of neuroendocrine tumor cells, the ^{225}Ac-DOTATATE-SSTR complex is internalized into the cytoplasm. Following internalization, the complex undergoes degradation, resulting in the dissociation of the SRL and SSTR from the complex. Once released, ^{225}Ac emits alpha particles, leading to double-stranded deoxyribonucleic acid (DNA) breaks and ultimately DNA damage and cell death. A decay diagram of ^{225}Ac is also shown in the figure.

significant tumor growth delay and time to experimental endpoint with ^{225}Ac-DOTATATE compared to controls [16].

Initial results of clinical efficacy and safety of ^{225}Ac-DOTATATE were reported in a prospective analysis of 32 patients with metastatic GEP-NETs with stable or progressive disease after prior treatment with ^{177}Lu-DOTATATE therapy. Of 24 patients with data available for response assessment, 15 patients had partial response, while 9 patients had stable disease. Additionally, no concerning safety signals emerged with a median follow-up of 8 months, highlighting the potential of ^{225}Ac-DOTATATE as a promising treatment option among patients with GEP-NETs with stable or refractory disease to prior ^{177}Lu-DOTATATE therapy [17]. The group subsequently reported follow-up data in a cohort of 91 patients with metastatic GEP-NETs that included both RLT-naïve and pre-treated patients who had received a median of four cycles of ^{225}Ac-DOTATATE with capecitabine. At a median follow-up of 24 months, the progression-free and overall survival rates were 67.5% and 70.8%, respectively. A total of 79 patients had data available for radiographic response assessment, of which two patients had complete response (2.5%), 38 (48%) had a partial response, 23 (29%) had stable disease while 16 (20.2%) had progressive disease. No concerning safety signals were noted in the analysis [18]. Another report of a pilot study which included nine consecutive patients with histologically proven metastatic paragangliomas who received ^{225}Ac-DOTATATE concomitantly with capecitabine, at 8-weekly intervals up to a cumulative activity of ~74 MBq. The analysis recorded a partial response in 50%, stable disease in 37.5%, and progressive disease in 12.5% patients, corresponding to a disease control rate of 87.5%. Benefit was also noted among patients with disease refractory to prior ^{177}Lu-DOTATATE therapy (disease control rate of 66.6%). Additionally, no concerning safety signals were recorded [19].

4. ACTION-1 (phase 1b/3 randomized clinical trial)

4.1. Study design and inclusion criteria

ACTION1 (NCT05477576) is an on-going 2-part, global, randomized, controlled, open-label, phase 1b/3 trial of RYZ101 in patients with advanced, well-differentiated GEPNETs with disease progression on prior ^{177}Lu-SSA therapy. The trial includes patients with histologically proven well-differentiated grade 1–2 GEP NETs with a Ki67 ≤ 20%. Patients are mandated to have progressive disease (confirmed per central review) per RECIST v1.1 after prior treatment with ^{177}Lu-SSA therapy. Only patients with RECIST v1.1 measurable SSTR-avid disease and no RECIST v1.1 measurable SSTR-negative metastatic disease are included. Patients are also required to have adequate renal and hematologic function prior to accrual. Patients who have received prior radioembolization and select clinically significant co-morbidities (such as resistant hypertension, heart failure, uncontrolled diabetes, and liver cirrhosis) are excluded.

The safety, pharmacokinetics (PK), and recommended Phase 3 dose (RP3D) of RYZ101 were determined in part 1 (phase 1b), at 10.2 MBq (or 275 uCi) RYZ101 infusions every 8 weeks for a total of 4 intravenous infusions. In part 2, using a 1:1 randomization design, patients are being randomized to receive either RYZ101 (at RP3D) or investigator's choice of standard of care (SOC) therapies. All patients in the RYZ arm are also receiving renal protection with customized amino acid co-infusion (L-arginine and L-lysine) with each RYZ101 infusion. The investigator's choice SOC therapies include everolimus, sunitinib, or high-dose SSAs (octreotide LAR or Lanreotide). Radiographic surveillance is performed with computed tomography (CT) or magnetic resonance imaging (MRI) scans every 12 weeks while on study. Crossover is allowed upon centrally confirmed progressive disease on the control arm (SOC therapies) (Figure 2).

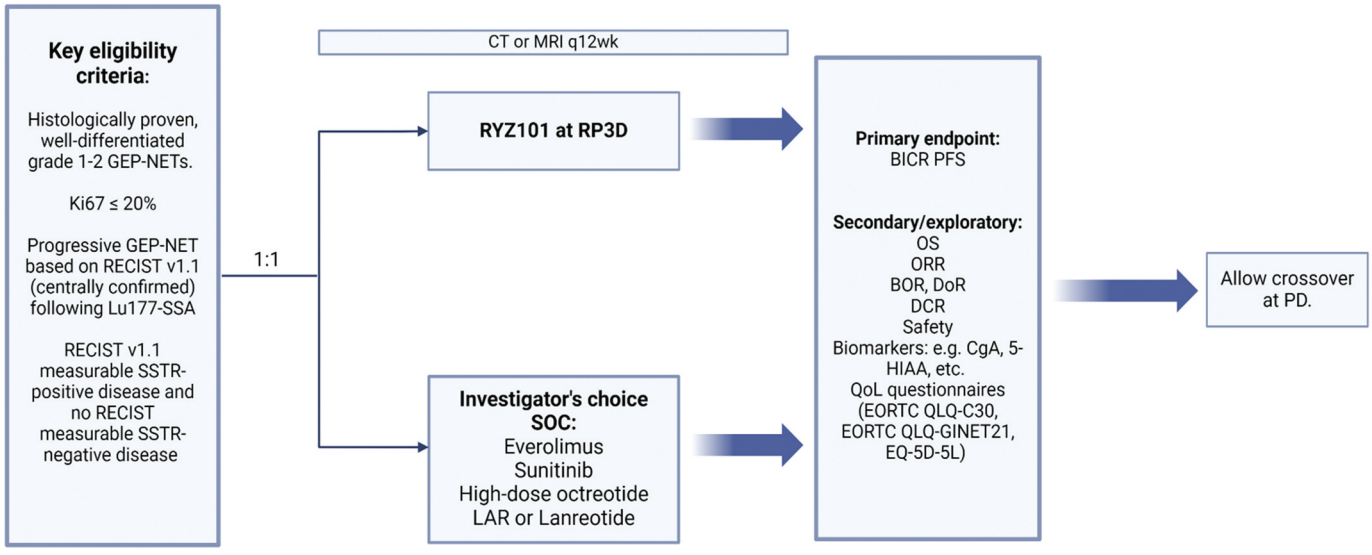

Figure 2. Study design of ACTION-1, an on-going 2-part, global, randomized, controlled, open-label, phase 1b/3 trial of RYZ101 (versus standard of care) in patients with advanced, well-differentiated GEPNETs (Ki67 ≤ 20%) with disease progression on prior ^{177}Lu-SSA therapy.

[Key abbreviations: BICR: blinded independent central review; BOR: best overall response, CgA: chromogranin A; CT: computed tomography, DoR: duration of response; DCR: disease control rate; EORTC: European Organization for Research and Treatment of Cancer; 5-HIAA: 5-hydroxyindoleacetic acid; GEPNETs: gastroenteropancreatic neuroendocrine tumors, OS: overall survival; PD: progressive disease; PFS: progression-free survival; QLQ: quality of life questionnaire; RECIST: response evaluation criteria in solid tumors; RP3D: recommended phase 3 dose; SOC: standard of care; SSA: somatostatin analog; SSTR: somatostatin receptor].

4.2. Study endpoints

The primary endpoint of the study is progression-free survival (PFS) as assessed by blinded independent central review (BICR). The secondary/exploratory endpoints include overall survival (OS), overall response rate (ORR), best overall response (BOR), duration of response (DoR), disease control rate (DCR) and safety. Data on key biomarkers such as chromogranin A (CgA) and 5-hydroxyindolacetic acid (5-HIAA) will also be collected as an exploratory endpoint. Quality of life (QoL) data will be captured using standardized questionnaires such as EORTC QLQ-C30, EORTC QLQ-GINET21, and EQ-5D-5 L (Figure 2).

4.3. Interim safety and efficacy data (phase 1b)

As discussed before, the safety, PK, and RP3D of RYZ101 were assessed in part 1 (phase 1b) of the trial. Using a dose de-escalation trial utilizing a Bayesian optimal interval design, 120 kBq/kg (or 3.2 uCi/kg) was declared RP3D. No treatment related serious adverse events (SAEs) were noted in the initial interim safety analysis [20]. An updated safety analysis was reported for 17 patients who had received at least one dose of RYZ101 at 120 kBq/kg. The most common treatment-emergent AEs were nausea (58.8%) and fatigue (52.9%) and no serious treatment-related AEs were noted. While no AEs led to treatment discontinuation, four patients had treatment-emergent AEs requiring dose modification, dose hold, and/or delays. In the interim efficacy analysis, the confirmed objective response rate was 29.4% (all partial responses); stable disease and progressive disease were noted in eight (47.1%) and four patients (17.6%) [21]. The trial is currently actively enrolling patients in part 2 (phase 3) with 10.2 MBq (or 275 uCi) RYZ101 infusions every 8 weeks for a total of 4 i.v. infusions.

4.4. Interim dosimetry analysis

As part of phase 1b of the ACTION-1 trial, a dosimetry analysis was conducted to determine the feasibility of obtaining imaging data with ^{225}Ac to estimate RYZ101 absorbed doses to critical organs (primary objective) and to tumors (secondary objective). Dosimetry calculations were performed using SPECT/CT images acquired for both Cycle 1 and Cycle 4 at 4 ± 1 h, 24 ± 2 h and 168 ± 24 h post-infusion. Based on the dosimetry results for the first cycle of four patients, it appears feasible to image and obtain quantitative information appropriate for dosimetry of ^{225}Ac. It appears feasible to image ^{221}Fr (the first daughter as the surrogate of ^{225}Ac), and also image ^{213}Bi (the grand-grand-daughter of ^{225}Ac) directly and simultaneously per this interim dosimetry analysis [22]. Final results of the dosimetry sub-study are currently awaited.

5. Additional alpha RLT agents in the pipeline

There are several other alpha RLT agents in the therapeutic pipeline for NETs. Notably, ^{212}Pb-DOTAMTATE is being investigated in an on-going phase 2 multi-center clinical trial including patients with SSTR+ advanced NETs who are both RLT-naïve (cohort 1) or pre-treated (cohort 2). The trial aims to assess objective response rate per RECIST v1.1 as the primary endpoint and progression-free survival, overall survival, and quality of life as key secondary endpoints [NCT05153772]. A recent interim analysis of cohort 1 of the trial (phase 2) showed an encouraging ORR of 47.2% (95% CI 32.0%–63.0%). While no concerning hematologic or renal adverse events emerged, the incidence of any-grade dysphagia was 42%, and grade 3 or 4 dysphagia was reported in 1 patient (3%). Lymphocytopenia was noted to be the cause of 59% grade 3 and 4 adverse events reported in subjects in cohort 1. Concerningly, 4 fatal adverse events were reported: death/progressive disease ($n = 2$), carcinoid syndrome ($n = 1$), and sepsis ($n = 1$) [23]. ^{212}Pb-VMT-α-NET is another novel Pb-specific SSTR (subtype 2) targeting agent with a unique polyethylene linker and has been shown to have rapid tumor accumulation with fast renal excretion (and therefore potential for low nephrotoxicity) [24]. ^{212}Pb-VMT-α-NET is being investigated in two separate ongoing trials for patients with NETs who are pre-treated with beta RLT [NCT] or are RLT-naïve [NCT06148636]. Another agent with preliminary evidence of safety and efficacy, ^{213}Bi-DOTATOC, is not currently being investigated in on-going clinical trials [25]. Table 2 summarizes on-going clinical trials with these novel RLT agents.

Table 2. On-going clinical trials with other novel alpha radioligand therapeutic agents.

RLT agents	Phase	Target Accrual	Study Population	Primary endpoints	Secondary endpoints	ClinicalTrials.gov ID
^{212}Pb-DOTAMTATE	Phase 2, multi-center.	69	Histologically confirmed NETs and positive somatostatin analog imaging, with either no prior PRRT (PRRT naive) or prior history of PRRT (previous PRRT).	Objective response rate per RECIST v1.1 and treatment-related adverse events.	PFS, OS, TTP and QoL.	NCT05153772
[^{212}Pb] VMT-α-NET	Phase 1/2, multi-center, open-label	280	Histologically confirmed unresectable or advanced SSTR2-avid NETs who have not received prior PRRT.	Safety analysis (DLTs).	ORR, DoR, PFS, OS and biodistribution.	NCT05636618
[^{212}Pb] VMT-α-NET	Phase 1, single-center	24	Pathologically confirmed advanced well-differentiated WHO grade 1 or 2 NETs who have received prior PRRT.	Determine the recommended phase 2 dose [^{212}Pb] VMT-α-NET.	ORR and maximum tolerated radiation dose for kidneys.	NCT06148636

[Abbreviations: DLTs: dose-limiting toxicities; DoR: duration of response; NETs: neuroendocrine tumors; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PRRT: peptide receptor radionuclide therapy; QoL: quality of life; RECIST: response evaluation criteria in solid tumors, SSTR: somatostatin receptor; TTP: time to progression.].

6. Conclusion

While still investigational and not yet a component of standard care, the advent of alpha RLT agents may represent a significant advancement in the therapeutic landscape for NETs, particularly with the potential to improve upon the therapeutic efficacy of conventional beta RLT such as ^{177}Lu-DOTATATE. Unique characteristics such as higher LET and ability to induce complex DNA damage (double-stranded breaks) position RYZ101 (and other alpha RLT agents) as a promising candidate for relatively superior therapeutic efficacy compared to beta RLT. Preliminary clinical data from ongoing trials, such as ACTION-1, indicate a favorable safety profile and encouraging objective response rates. However, safety and efficacy data with long-term follow-up will be crucial to introduce RYZ101 as an addition to the paradigm of standard therapies for GEPNETs. Yet other novel alpha RLT is being evaluated in patients with RLT-naïve as well as RLT pre-treated disease. Ongoing and future studies will help us understand if and how alpha-emitting RLT will fit into the landscape of options for SSTR-expressing NENs. Additionally, the availability of ^{225}Ac-DOTATATE will diversify the arsenal of RLT and prevent potential issues with supply chain shortage (as ^{177}Lu is also widely used in other malignancies such as hormone-resistant prostate cancer).

Despite these encouraging results, it is imperative to carefully evaluate the clinical safety of these agents with more long-term follow-up. Longer follow-up will also be paramount to demonstrate the durability of therapeutic responses with alpha RLT agents such as RYZ101. Further results from the dosimetry sub-study would be key to investigate the possibility of minimizing radiation exposure as well as the potential use of RYZ101 in patients with certain co-morbidities (such as underlying chronic kidney disease). Several ongoing trials are evaluating the safety and feasibility of combining beta emitter RLT such as ^{177}Lu-DOTATATE with other agents such as the ribonucleotide reductase inhibitor Triapine (NCT05724108), DNA-dependent protein kinase inhibitor Peposertib (NCT04086485), poly-ADP-ribose polymerase inhibitor Olaparib (NCT03457948) and others. The rationale behind combining these agents with RLT is to further accentuate DNA damage and amplify the therapeutic efficacy of RLT. RLT's ability to induce DNA damage and subsequently activate the immune system through neoantigen exposure is also being leveraged to study the safety and efficacy of combination of immune checkpoint inhibitors with beta RLT (NCT03457948). Similarly, there is also potential to investigate the safety and efficacy of RYZ101 (and other novel RLT agents) in combination with radiation sensitizing agents to further optimize its therapeutic index, or immune checkpoint inhibitors to encourage even more durable oncologic control. Many on-going clinical trials are aiming at expanding the indication for use of ^{177}Lu-DOTATATE to less common NENs such as advanced bronchopulmonary NETs [NCT04665739], advanced Merkel cell carcinoma [NCT05583708], advanced pheochromocytoma and paraganglioma [NCT03206060], etc. Similarly, there is also potential to study alpha RLT for use in NENs of relatively uncommon sites of origin. Assuming that RYZ101 becomes a part of our standard arsenal, such additional studies will be critical to understand and maximize its role in the management of patients suffering with NENs.

Author contributions

Udhayvir Singh Grewal, Olumide B Gbolahan, Amol M Takalkar, Daniel M Halperin: Conceptualized, Wrote and Reviewed the final draft.

Disclosure statement

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Funding

This article was not funded.

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