RYZ101 (^{225}Ac-DOTATATE) ± pembrolizumab in estrogen receptor-positive, human epidermal growth factor receptor 2-negative, locally advanced and unresectable or metastatic breast cancer progressing after prior therapy: the Phase 1b/2 TRACY-1 study

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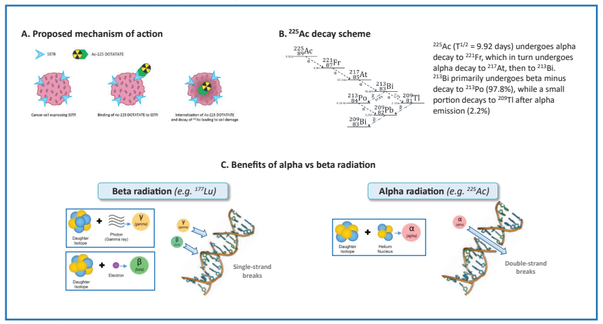
BACKGROUND

- Breast cancer is the most common malignancy in women, with ~80% of breast cancers expressing estrogen receptors (ERs).[1,2]
- Endocrine-based therapies are the first-line treatment for most ER+, human epidermal growth factor receptor 2 (HER2) negative, unresectable and locally advanced or metastatic breast cancer; however, once endocrine therapies are exhausted, treatment mainly comprises cytotoxic agents, with increasingly short durability of response for each subsequent line.
- Clinical positron emission tomography (PET) imaging has reported somatostatin receptor (SSTR) expression in breast cancers.[3]
- In a phase 2 DOTATATE PET/CT imaging study, 30% of patients with metastatic ER+ breast cancer showed strong SSTR2 expression.[4]
- RYZ101 (^{225}Ac-DOTATATE) is a first-in-class, highly potent alpha-emitting radiopharmaceutical therapy (RPT) being developed for SSTR2+ solid tumors (**Figure 1**):
  - In an emergency investigational new drug use case, SSTR2-targeted therapy with ^{225}Ac-DOTATATE resulted in a near complete response in a heavily pretreated participant with metastatic ER+ breast cancer and strong positivity on SSTR-PET imaging.[4]
- This poster describes the study design of TRACY-1 (NCT06590857), a global, multicenter, open-label, three-part Phase 1b/2 study of RYZ101± pembrolizumab in ER+, human epidermal growth factor receptor 2-negative, locally advanced and unresectable or metastatic breast cancer.

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



SSTR, somatostatin receptor.

METHODS

PATIENTS

- Adults with ER+, HER2-negative, unresectable or metastatic breast cancer who are endocrine-refractory and have received prior chemotherapy and antibody–drug conjugates (ADCs).
- Documented positivity on protocol-specified SSTR-PET imaging, during screening or optional prescreening.
- Patients who have received prior RPT, including radioembolization, or prior therapy with an anti-programmed cell death protein 1, anti-programmed cell death-ligand 1, or anti-programmed cell death-ligand 2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor are excluded.
- ECOG status ≤2 and adequate hematologic, renal, and hepatic function.
- Key inclusion and exclusion criteria are shown in **Table 1**.

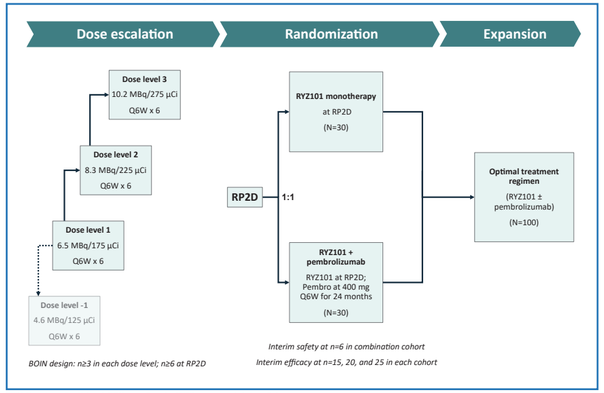
STUDY DESIGN

- TRACY-1 is a three-part, global, multicenter, open-label, Phase 1b/2 trial of RYZ101 alone or in combination with pembrolizumab in patients with refractory ER+, HER2-negative advanced breast cancer:
  - Dose escalation will determine the recommended phase 2 dose (RP2D) of RYZ101.
  - Randomization will determine the optimal treatment regimen of RYZ101, alone or in combination with pembrolizumab.
  - Expansion will determine the efficacy of RYZ101 at the optimal treatment regimen.

STUDY AIMS

- The aims of the study are to determine the RP2D, the optimal treatment regimen, and to evaluate preliminary efficacy of RYZ101 alone and in combination with pembrolizumab in ER+, HER2–, locally advanced and unresectable or metastatic breast cancer.
- The design, objectives and corresponding endpoints of the study are provided in **Figure 2**, and **Tables 2 & 3**.

FIGURE 2. TRACY-1 study design



BOIN, Bayesian optimal interval; Q6W, every 6 weeks; RP2D, recommended phase 2 dose.

TABLE 1. Key inclusion/exclusion criteria

Key inclusion criteria
1. Adult patients with histologically proven, unresectable or metastatic breast cancer
2. ER-positive, PR-any, HER2-negative (defined as IHC score of 0 or 1, or IHC score of 2 with negative ISH)
3. Refractory to and no further benefit expected from endocrine therapy
4. Received 2–4 prior lines of chemo/ADC in the unresectable/metastatic setting with at least one being an ADC
5. At least one RECIST-measurable lesion and at least 80% of RECIST-measurable lesions positive on SSTR-PET scan (lesion SUV_{max} > liver SUV_{mean})
6. ECOG performance status ≤2
7. CrCl ≥ 60 mL/min
8. Hgb ≥8 g/dL; ANC ≥1K; PLT ≥ 100K

Key exclusion criteria
1. Hypersensitivity or allergy to pembrolizumab or any of its components, or to ^{225}Ac, ^{68}Ga, ^{64}Cu, octreotate, or any of the excipients of DOTATATE imaging agents
2. Prior radiopharmaceutical therapy, including radioembolization
3. Has received prior therapy with an anti-programmed cell death protein 1, anti-programmed cell death-ligand 1, or anti-programmed cell death-ligand 2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., cytotoxic T-lymphocyte-associated protein 4, OX 40, CD137)
4. Cytotoxic chemotherapy, targeted agents, immunotherapy, antibody, retinoid, or anticancer hormonal treatment within 4 weeks prior to the first dose of study treatment
5. External-beam radiotherapy, major surgery, and other invasive procedures within 6 weeks prior to the first dose of study treatment
6. Diagnosis of immunodeficiency; active autoimmune disease requiring systemic treatment in the past 2 years; receiving chronic systemic steroid therapy or any other immunosuppressive therapy within 14 days prior to the first dose of study treatment

ADC, antibody drug conjugate; ANC, absolute neutrophil count; CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HER-2, human epidermal growth factor receptor 2; Hgb, hemoglobin; IHC, immunohistochemistry; ISH, in situ hybridization; PET, positron emission tomography; PLT, platelets; PR, progesterone receptor; RECIST, response evaluation criteria in solid tumors; SSTR, somatostatin receptor; SUV, standard uptake value.

TABLE 2. Primary objectives and endpoints

Study part	Objectives	Endpoints
Dose escalation	To determine the RP2D of RYZ101	Incidence rate of DLTs during the first 6 weeks of RYZ101 treatment
Randomization	To determine the optimal treatment regimen of RYZ101, alone or in combination with pembrolizumab	DRR, defined as rate of patients achieving a CR or PR for at least 6 months, as determined by the Investigator using RECIST v1.1
Expansion	To determine the optimal treatment regimen in terms of ORR by BICR	ORR, defined as rate of patients achieving a CR or PR as determined by BICR using RECIST v1.1

BICR, blinded independent central review; CR, complete response; DLT, dose-limiting toxicity; DRR, durable response rate; ORR, objective response rate; PR, partial response; RECIST v1.1, response evaluation criteria in solid tumors version 1.1; RP2D, recommended phase 2 dose.

TABLE 3. Secondary and exploratory objectives and endpoints

Objectives		Endpoints
Secondary	• To further evaluate the efficacy of RYZ101 alone and in combination with pembrolizumab	• ORR, DOR, DCR, CBR, BOR, PFS, OS
	• To characterize the safety and tolerability of RYZ101 administered every 6 weeks for up to 6 cycles, alone and in combination with pembrolizumab	• Incidence and severity of AEs by NCI-CTCAE v5.0, including SAEs, laboratory changes, ECG changes, dose delays, dose reductions and other safety findings
	Expansion only: • To further evaluate the efficacy of RYZ101 at the optimal treatment regimen in terms of other efficacy endpoints as assessed by BICR in subjects with refractory ER+, HER2-negative ABC	• DOR, DCR, CBR, BOR, PFS
Exploratory	• To determine the prevalence of subjects with refractory ER+, HER2-negative breast cancer that would be candidates for treatment with RYZ101 as determined by SSTR-PET	• SUV values obtained with SSTR-PET imaging and their correlation with baseline characteristics and efficacy results.
	• To determine the association between uptake of SSTR-PET imaging agents in tumors and clinical efficacy following treatment with RYZ101 in subjects with SSTR+ breast cancer	• Association between uptake of SSTR-PET imaging agents (including but not limited to BICR of SUV_{mean}, SUV_{max} and SUV_{peak} of tumors; tracer avid volume of disease with segmentation; tumor to normal organ tracer uptake ratios) and clinical efficacy (including BICR of percent change in the sum of the longest diameter of SSTR+ lesions, ORR per RECIST v1.1, and DOR)
	• Evaluate blood and tumor tissue biomarkers and their association with the efficacy of RYZ101	• DNA, RNA, or protein markers and their correlation with response rate or other clinical endpoints

ABC, advanced breast cancer; AE, adverse event; BICR, blinded independent central review; BOR, best overall response; CBR, clinical benefit rate; CTCAE v5.0, Common Terminology Criteria for Adverse Events, version 5.0; DCR, disease control rate; DOR, duration of response; ER+, estrogen receptor-positive; ECG-electrocardiogram; HER2, human epidermal growth factor receptor 2; NCI, National Cancer Institute; ORR, objective response rate; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; RECIST v1.1, response evaluation criteria in solid tumors version 1.1; SAE, serious adverse event; SSTR, somatostatin receptor; SUV, standard uptake value

TREATMENT

- RYZ101 is administered via intravenous infusion every 6 weeks (Q6W) for up to 6 cycles.
- Dose escalation will be guided using the Bayesian optimal interval design (BOIN).
  - RYZ101 will be administered at increasing dose levels beginning at Dose Level 1 (6.5 MBq). Dose level -1 (4.6 MBq) may be explored if triggered by Dose Limiting Toxicities (DLTs) at the starting dose.
  - Once ≥3 patients become DLT-evaluable (received one dose and was observed for the DLT period of 6 weeks or has experienced a DLT), the Data Review Committee (DRC) will decide between: dose escalation; dose de-escalation; extension of current dose level; RP2D determination; termination of dose escalation. The decision will be made based on the occurrence of DLTs at the current cohort as well as any possible safety signals observed in all patients treated in the study.
- During Randomization, ~60 patients will be randomized 1:1 to receive RYZ101 (at the RP2D) as monotherapy or in combination with pembrolizumab.
  - Patients in the combination arm will continue to receive pembrolizumab Q6W (after the completion of 6 cycles of RYZ101) for up to 2 years after the first dose or until progression.
  - Interim efficacy analyses will be conducted at 15, 20, and 25 patients enrolled in each cohort.
  - An interim safety analysis will be conducted following treatment of 6 DLT-evaluable patients in the combination arm (same criteria as in dose escalation); the DRC will convene to evaluate the safety of the combination treatment before proceeding.
- During Expansion, patients will be sequentially enrolled to receive RYZ101 at the optimal treatment regimen defined during randomization.

STATISTICAL ANALYSIS

Randomization:

- There will be no formal statistical comparison between the treatment arms. The hypothesis testing will be conducted within each cohort:
  - H_0 is defined as: DRR for either cohort ≤20% (non-promising treatment effect).
  - H_1 is defined as: DRR for either cohort ≥50% (promising treatment effect).
- The primary efficacy endpoint DRR will be monitored using the Bayesian optimal phase 2 (BOP2) design. Interim analysis will be performed during randomization. The stopping criteria for each cohort are non-binding.

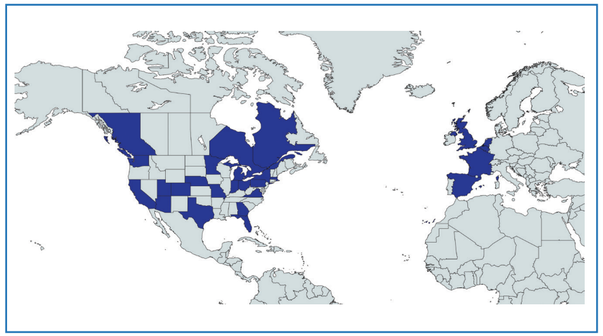
Number of efficacy-evaluable subjects per cohort	Stop if subjects with durable responses per cohort ≤
15	3
20	4
25	6

Expansion:

- The dose expansion will test the null hypothesis that the ORR is ≤21% against the alternative hypothesis that is ≥50%. The sample size is estimated at 100 subjects, with at least 90% power and 1-sided alpha=0.025.

CURRENT STATUS

- TRACY-1 will recruit patients in Belgium, Canada, France, Spain, The Netherlands, The UK, and the following US states: Arizona, Colorado, Florida, Georgia, Massachusetts, Michigan, Minnesota, Missouri, New York, Ohio, Pennsylvania, Texas, Utah, Virginia, and Washington.



ACKNOWLEDGMENTS

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

REFERENCES

1. Bray F, et al. CA Cancer J Clin 2024;74(3):229–63.
2. Iqbal J, et al. JAMA 2015;313(2):165–73.
3. Nguyen A, et al. J Med Imaging Radiat Oncol 2022;66:731–737.
4. Ulaner G, et al. Radiology 2024;312(1):e233408.

Presented at the San Antonio Breast Cancer Symposium, Dec 10–13, 2024