Actinium-225 User Group Meeting

Ken Song, MD  
*President and CEO*  
RayzeBio, Inc.

September 1, 2022
Mission: Improve cancer patient survival by efficiently developing targeted innovative drugs that harness the power of radioisotopes

Pipeline and capabilities
- First-in-class diverse pipeline spanning discovery, preclinical, and clinical stage programs
- RYZ101 (\(^{225}\text{Ac-DOTATATE}\)) – Currently enrolling in Phase 1→3 trial for GEP-NETs. Additional clinical indications being evaluated.
- Three novel small molecule and peptide based \(^{225}\text{Ac}\) drugs to start clinical imaging studies in near term
- Customized 28,000 sq ft radiopharmaceutical R&D facility in San Diego
- Commercial scale 63,000 sq ft cGMP manufacturing facility to be completed 2H 2023

Proven team and elite investor base
- 77 FTEs led by a repeatedly successful management team in life sciences
- $256 million raised from inception August 2020 to July 2022
# RayzeBio Radiopharmaceuticals Therapy (RPT) Pipeline

<table>
<thead>
<tr>
<th>Program</th>
<th>Binder</th>
<th>Indication</th>
<th>Discovery</th>
<th>Lead Optimization</th>
<th>Development candidate</th>
<th>Clinical imaging, IND enabling</th>
<th>Clinical trials (Phase 1→3)</th>
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<tbody>
<tr>
<td>RYZ101 (SSTR2)</td>
<td>DOTATATE</td>
<td>Neuroendocrine tumors</td>
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<td>Other solid tumors</td>
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<td>Program A</td>
<td>Novel Peptide</td>
<td>GI tract cancers</td>
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<td>Program B</td>
<td>Novel Peptide</td>
<td>Multiple solid tumors</td>
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<tr>
<td>Program C</td>
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<td>Novel Peptide</td>
<td>Multiple solid tumors</td>
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<td>Program E</td>
<td>Novel Peptide</td>
<td>Liver cancer</td>
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<td>Other programs</td>
<td>Peptide/small molecules</td>
<td>Multiple solid tumors</td>
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Lead Clinical Indication – Neuroendocrine Tumors (NETs)

- Neuroendocrine tumors of the GI tract (GI-NET) and pancreas (P-NET) have limited treatment options.
- **Somatostatin receptor 2 (SSTR2)** is overexpressed in majority of tumors
- Limited FDA approved treatments and disease progression inevitable
- $^{177}$Lu-DOTATATE (Lutathera®) approved in 2018 was a major advance for NET patients
  - $^{177}$Lu is a $\beta$-particle radioisotope
  - DOTATATE is a somatostatin analog that binds SSTR2

Management of Advanced/Metastatic, Well-Differentiated SSTR+ NETs

**GI-NET**
- Somatostatin analogs (octreotide or lanreotide)
- Everolimus
- Cytotoxic chemo (category 3)
- $^{177}$Lu-DOTATATE

**P-NET**
- Somatostatin analogs (octreotide or lanreotide)
- Everolimus
- Sunitinib
- Cytotoxic chemo
- $^{177}$Lu-DOTATATE
**177Lu** (β-isotope) DOTATATE Clinically Effective But Patients Eventually Progress

**Reference:** Strosberg et al, NEJM, 2017

Phase 3 NETTER-1 trial of Lutathera (177Lu-DOTATATE) versus Control (octreotide LAR)

- Hazard ratio of 0.21
- FDA approved in 2018 based on PFS

Lutathera developed by AAA which was acquired by Novartis

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<tr>
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<th># of patients</th>
<th>Median PFS (months)</th>
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<tbody>
<tr>
<td>Lutathera</td>
<td>117</td>
<td>28.4</td>
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<tr>
<td>Control</td>
<td>114</td>
<td>8.5</td>
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177Lu-DOTATATE

- Octreotide (somatostatin analogue)
- DOTA chelator with 177Lu
- Binds to Somatostatin Receptor 2 (SSTR2) on NETs

Reference: Strosberg et al, NEJM, 2017
NETs – Long Survival Post Progression on $^{177}$Lu DOTATATE

- NET patients continue to survive 21 to 34 months after progression on $^{177}$Lu DOTATATE treatment
- Following inevitable disease progression on $^{177}$Lu DOTATATE, there are no recommended treatment options

Reference: Brabander et al, Clin Cancer Res 2017
RYZ101 (\(^{225}\text{Ac-DOTATATE}\)) – Addresses the Unmet Need in NETs

**Development strategy**
- Evaluate RYZ101 in GI-NET and P-NET patients previously treated with Lutathera that have now progressed
  - Use similar dosing schedule frequency
  - Leverage clinical centers with RPT experience with Lutathera
- Pursue orphan drug designation
- Patent estate on novel formulation for RYZ101

Lutathera
\((^{177}\text{Lu-DOTATATE})\)

RYZ101
\((^{225}\text{Ac-DOTATATE})\)

- Lutathera and RYZ101 share the same binder and chelator – DOTATATE
- RYZ101 has more potent alpha radioisotope \(^{225}\text{Ac}\)
- Novel proprietary formulation developed on RYZ101 given different radioisotope
RYZ101 (\(^{225}\)Ac-DOTATATE) – Formulation Development

- \(^{225}\)Ac and \(^{177}\)Lu have distinct properties
- Radiolabeling and stability conditions cannot be readily transferred between radioisotopes
- Numerous formulations were evaluated to optimize RYZ101 labeling efficiency and stability
- RYZ101 has stability out to 120 hours (5 days) and has been scaled up successfully

Radiolabeling Stability at 120 hr by TLC

Early Formulation

- 64%
- 36%

Optimized Formulation

- 98%
- 2%
$^{225}$Ac-DOTATATE ($\alpha$-isotope) Demonstrates Efficacy in Patients Previously Treated with $^{177}$Lu-DOTATATE ($\beta$-isotope)

Clinical experience with $^{225}$Ac-DOTATATE in NET patients highlight efficacy advantages using $\alpha$ isotope

### Objective Response Rate (%)

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<tr>
<th></th>
<th>$^{177}$Lu-DOTATATE</th>
<th>$^{225}$Ac-DOTATATE</th>
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<tbody>
<tr>
<td>Radiotherapy naïve</td>
<td>18%</td>
<td>44%</td>
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<tr>
<td>Post $^{177}$Lu Progression</td>
<td>3%</td>
<td>27%</td>
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</tbody>
</table>

**Reference:**

- Strosberg et al (2017)
- Strosberg et al (2021)
- Bal et al (2022), internal analysis

### Progression Free Survival (post progression on $^{177}$Lu-DOTATATE)

- $^{177}$Lu-DOTATATE: 6 to 14.6 months
- $^{225}$Ac-DOTATATE: 26 months

**References:**

- Strosberg et al (2017)
- Strosberg et al (2021)
- Bal et al (2022), internal analysis
225Ac-DOTATATE is Well Tolerated

Based on clinical laboratory data, 225Ac-DOTATATE appears to be well tolerated with no notable significant toxicities and no evidence of dose dependent changes.

References: Bal et al (2022), internal analysis
RYZ101 ACTION-1 Study: Streamlined Phase 1b to Phase 3 Trial

Key Eligibility Criteria
- Age ≥ 18
- Well-differentiated GI and pancreatic NETs with positive SSTR-PET imaging
- Progressive disease following treatment with $^{177}$Lu SSTR RPT

Phase 1b: Dose de-escalation underway
- Initial cohort is at top dose of 120 kBq/kg
- Dose limiting toxicity period of evaluation is 8 weeks after RYZ101 administration
- Primary endpoint is safety. Clinical response will also be measured.

Phase 3: Pivotal trial
- Randomized clinical trial of RYZ101 against standard of care (high dose SSA, everolimus, sunitinib)
- Primary endpoint of progression free survival
- Global study

ClinicalTrials.gov identifier: NCT05477576
Our Discovery Workflow for Novel RPT Oncology Drugs

**28,000 sq ft R&D center in San Diego**
- Alpha and beta isotope radiolabeling lab
- Vivarium with molecular imaging and biodistribution capabilities
- Full in vitro biological capabilities (e.g. SPR, cell assays, flow cytometry)
- Internal small molecule and peptide chemistry
- DMPK suite

**Target Selection**

**Binder discovery and optimization**
- Peptides
- Small Molecules
- Other Binder Moiety

**In vitro screening** *(SPR, cell based, DMPK, kidney assays)*

**X-ray crystallography**

**Linker exploration and optimization**

**Radiolabeling optimization**

**In vivo screening** *(200+ studies completed)*
**225Ac Demonstrates Robust Preclinical Efficacy**

- Cell surface target selectively overexpressed in several solid tumors
- Novel small binder with high affinity and selectivity against the target
- Single dose efficacy studies in xenograft studies using $^{225}\text{Ac}$ and $^{177}\text{Lu}$

**Tumor Model A - $^{225}\text{Ac}$ shows clear superiority over $^{177}\text{Lu}$**

**Tumor Model B – Similar efficacy with $^{225}\text{Ac}$ and $^{177}\text{Lu}$**

References: internal data and analysis
Summary

• $^{225}\text{Ac}$ has already demonstrated robust clinical efficacy and safety

• New radiopharmaceutical drugs leveraging the potency of $^{225}\text{Ac}$ have the potential to significantly improve the lives of cancer patients

• Continued collaboration and investment is needed across the industry to bring forth $^{225}\text{Ac}$ based therapies to the market