



# Actinium-225 User Group Meeting

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

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# RayzeBio Company Overview

***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 ($^{225}$Ac-DOTATATE) – Currently enrolling in Phase 1→3 trial for GEP-NETs. Additional clinical indications being evaluated.
- Three novel small molecule and peptide based $^{225}$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

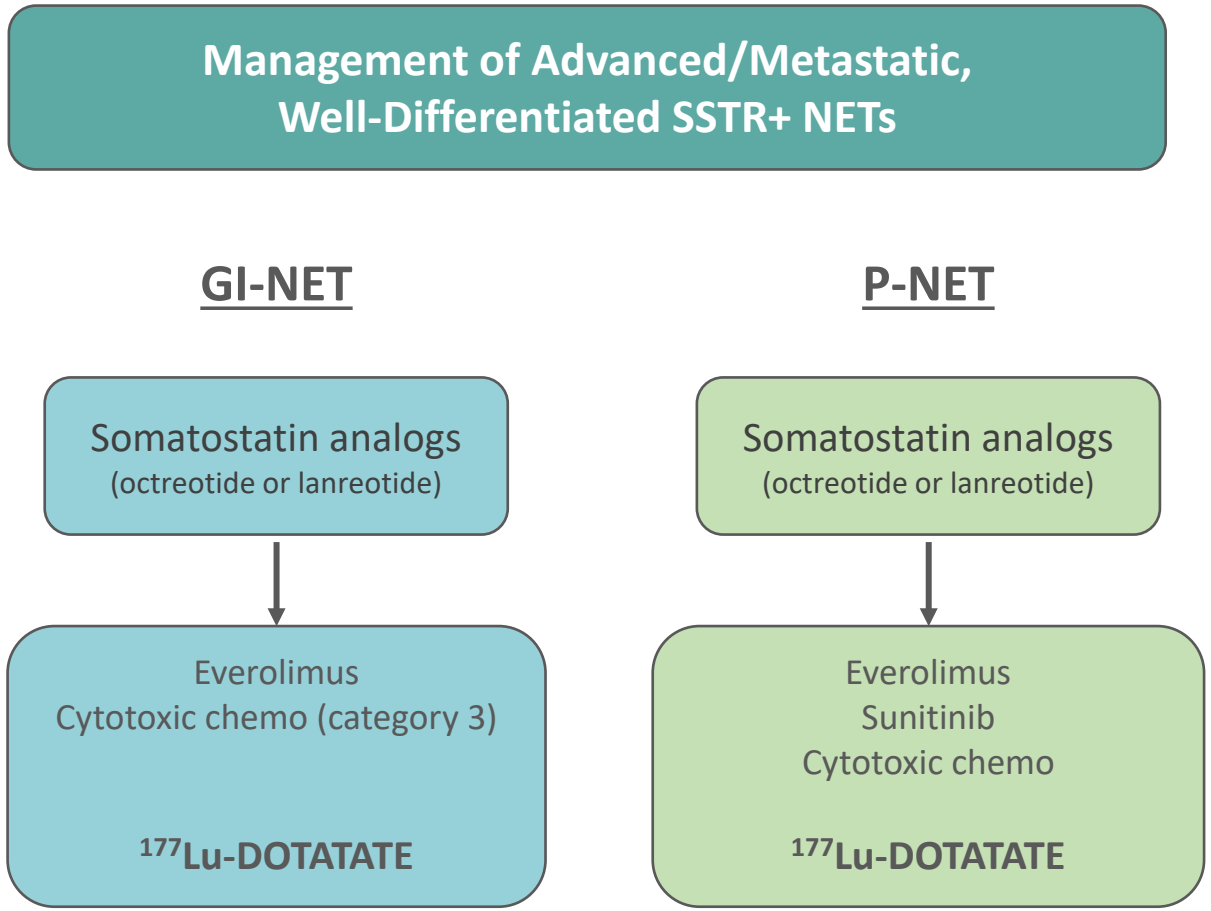
venBio, VERSANT ventures, SAMSARA BIOCAPITAL, venrock, OrbiMed, Redmile Group, Viking, CORMORANT ASSET MANAGEMENT, LOGOS CAPITAL, RYZB Holdings, LifeSci Advisors, ALEXANDRIA VENTURE INVESTMENTS, PERCEPTIVE ADVISORS, VIVO CAPITAL, DEERFIELD, ACUTA CAPITAL PARTNERS, LLC, TCGX

# RayzeBio Radiopharmaceuticals Therapy (RPT) Pipeline

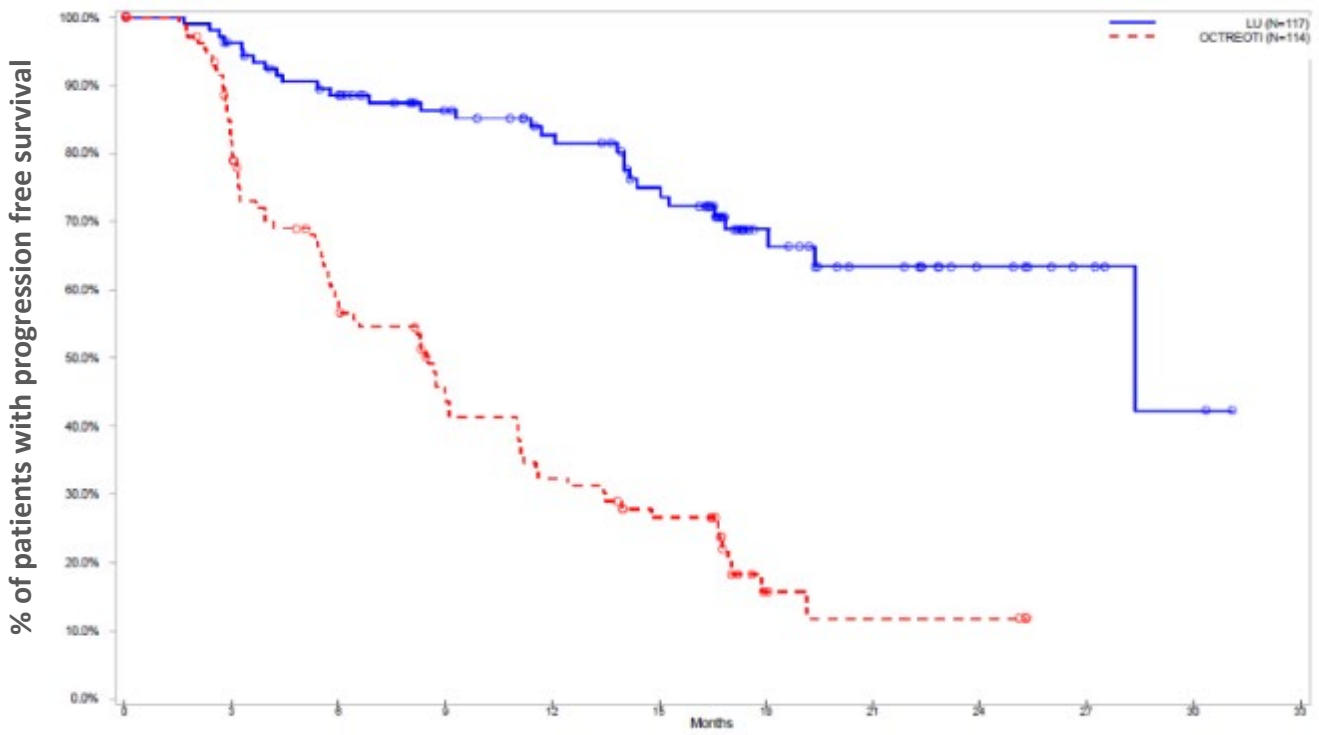
| Program | Binder | Indication | Discovery | Lead Optimization | Development candidate | Clinical imaging, IND enabling | Clinical trials (Phase 1→3) |
|---|---|---|---|---|---|---|---|
| **RYZ101 (SSTR2)** | *DOTATATE* | Neuroendocrine tumors | | | | | |
| | | Other solid tumors | | | | | |
| **Program A** | *Novel Peptide* | GI tract cancers | | | | | |
| **Program B** | *Novel Peptide* | Multiple solid tumors | | | | | |
| **Program C** | *Novel Small molecule* | GU cancers | | | | | |
| | | GI tract cancers | | | | | |
| **Program D** | *Novel Peptide* | Multiple solid tumors | | | | | |
| **Program E** | *Novel Peptide* | Liver cancer | | | | | |
| **Other programs** | *Peptide/small molecules* | Multiple solid tumors | | | | | |

# 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 β-particle radioisotope
  - DOTATATE is a somatostatin analog that binds SSTR2



# $^{177}$Lu (β-isotope) DOTATATE Clinically Effective But Patients Eventually Progress

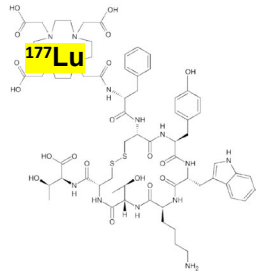



| | # of patients | Median PFS (months) |
|---|---|---|
| Lutathera | 117 | 28.4 |
| Control | 114 | 8.5 |

Reference: Strosberg et al, NEJM, 2017

## $^{177}$Lu-DOTATATE

- *Octreotide (somatostatin analogue)*
- *DOTA chelator with* **$^{177}$Lu**
- *Binds to Somatostatin Receptor 2 (SSTR2) on NETs*




**Phase 3 NETTER-1 trial** of **Lutathera ($^{177}$Lu-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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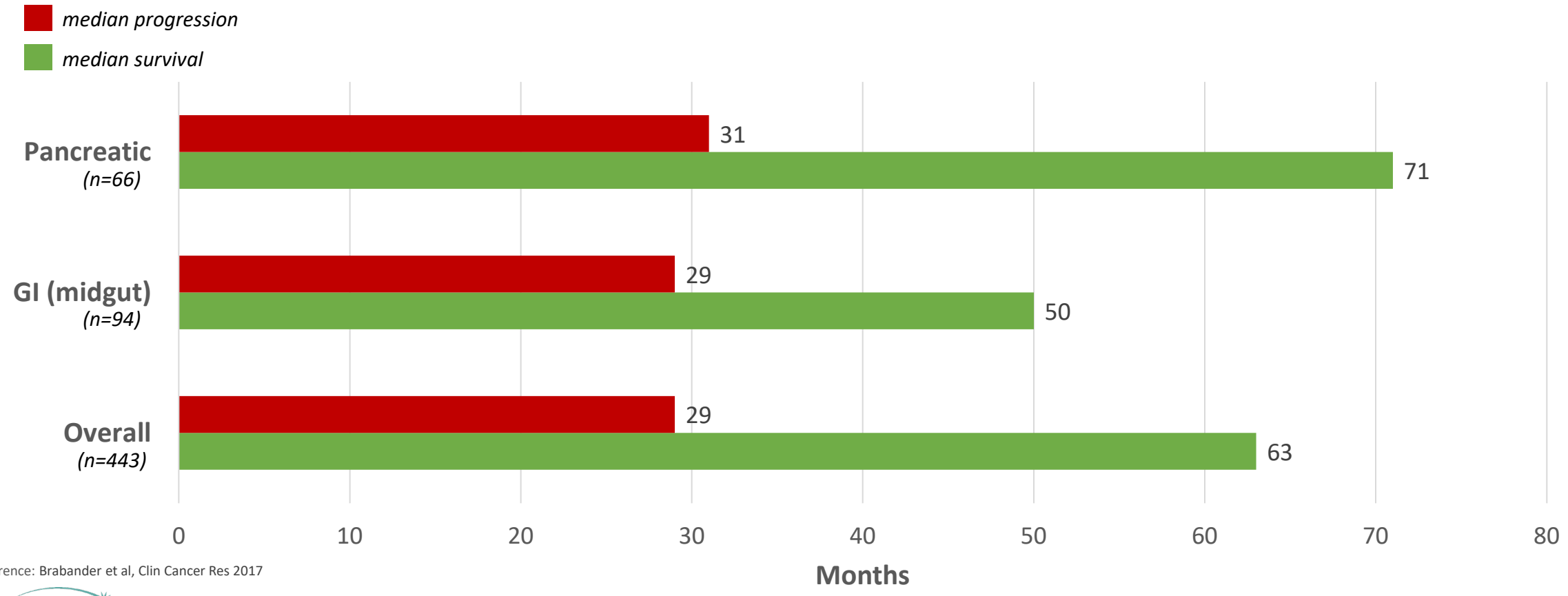
# NETs – Long Survival Post Progression on $^{177}$Lu DOTATATE

- 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

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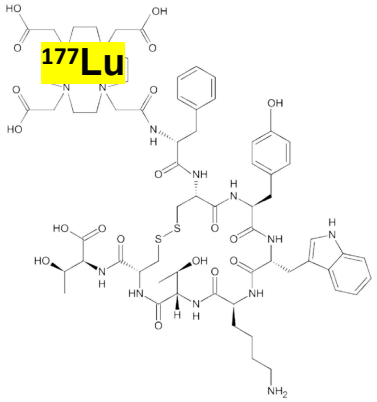
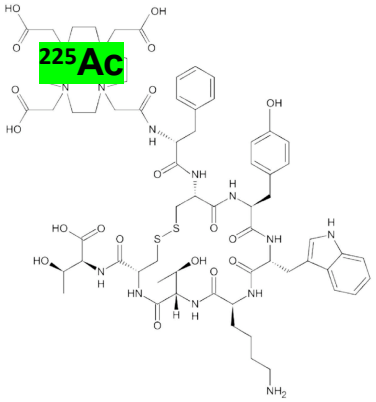
# RYZ101 ($^{225}$Ac-DOTATATE) – Addresses the Unmet Need in NETs




**Lutathera**
*($^{177}$Lu-DOTATATE)*




**RYZ101**
*($^{225}$Ac-DOTATATE)*

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

## 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

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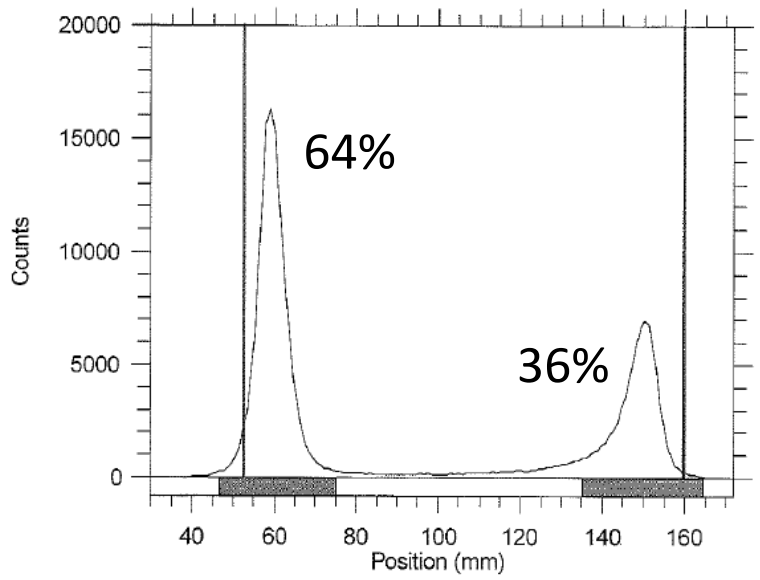
# RYZ101 ($^{225}$Ac-DOTATATE) – Formulation Development

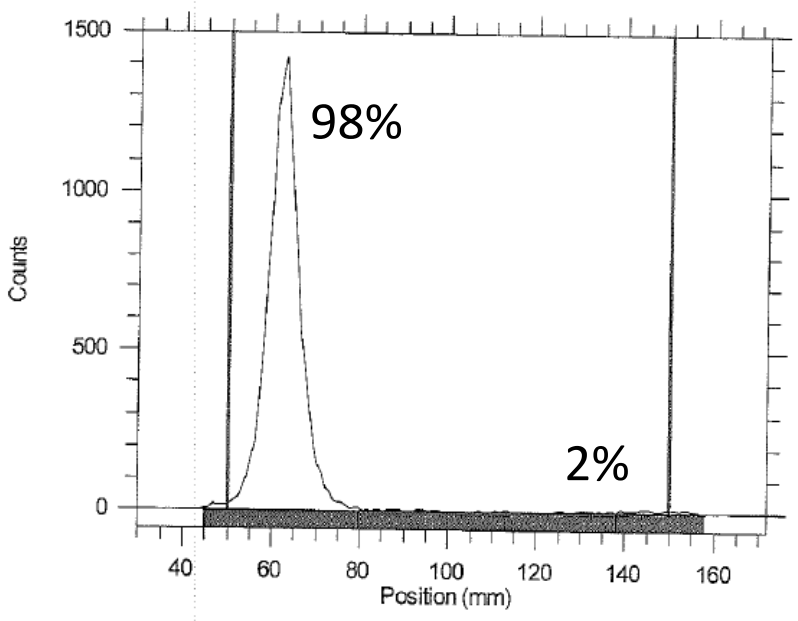
- $^{225}$Ac and $^{177}$Lu have distinct properties
- Radiolabeling and stability conditions cannot be readily transferred between radioisotopes
- Numerous formulations were evaluated to optimize RYZ101 labeling efficiency and stability
- RYZ101 has stability out to 120 hours (5 days) and has been scaled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

**Radiolabeling Stability at 120 hr by TLC**

**Early Formulation**




**Optimized Formulation**

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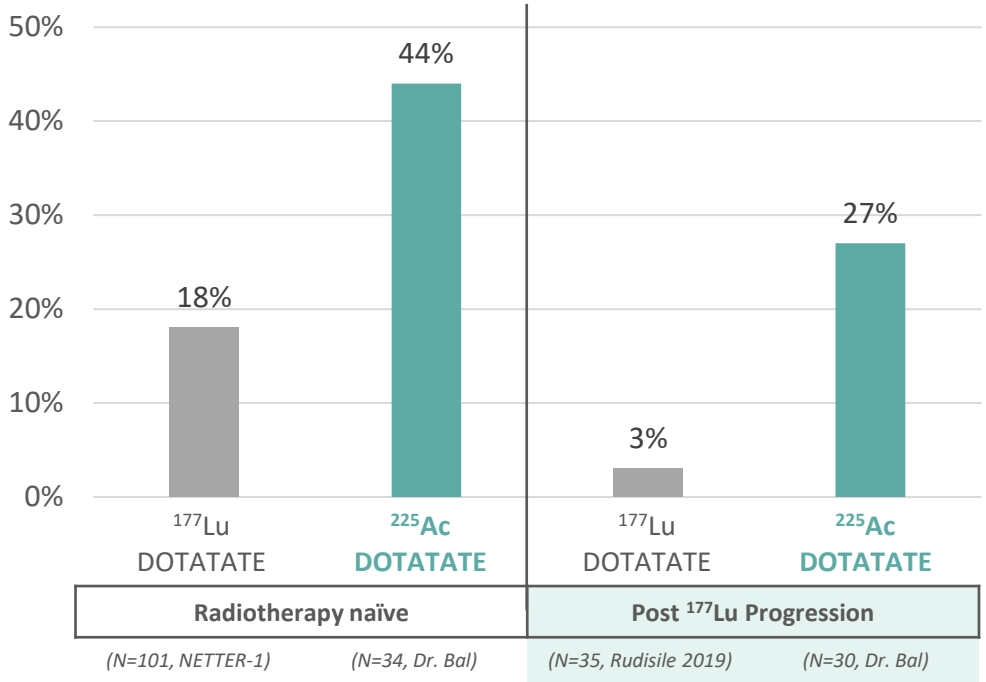
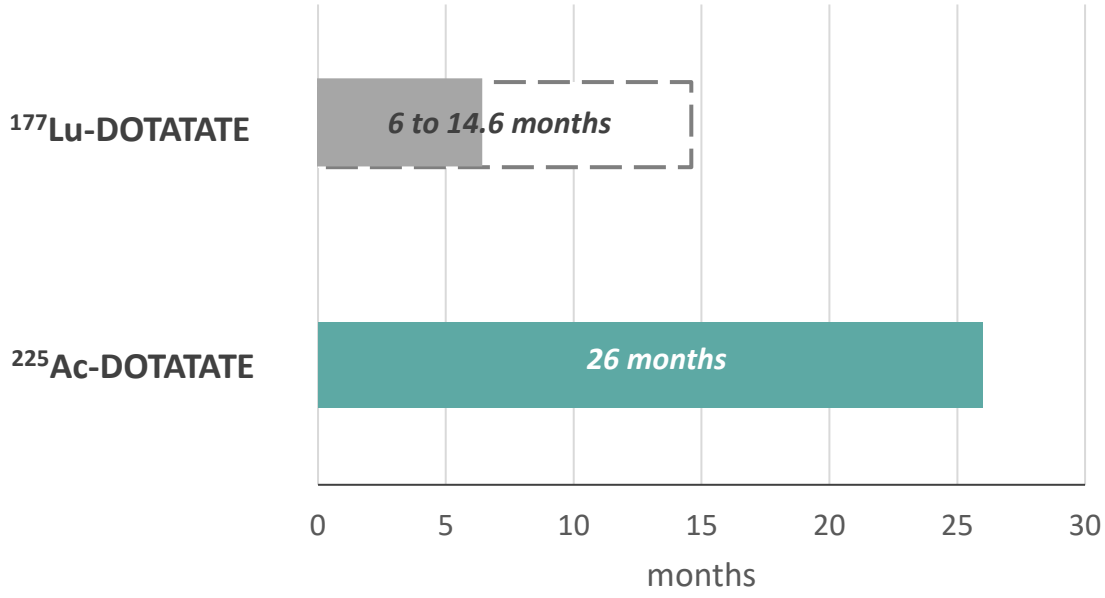
# $^{225}$Ac-DOTATATE (α-isotope) Demonstrates Efficacy in Patients Previously Treated with $^{177}$Lu-DOTATATE (β-isotope)

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

## Objective Response Rate (%)




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




References: Strosberg et al (2017); Strosberg et al (2021); Bal et al (2022), internal analysis

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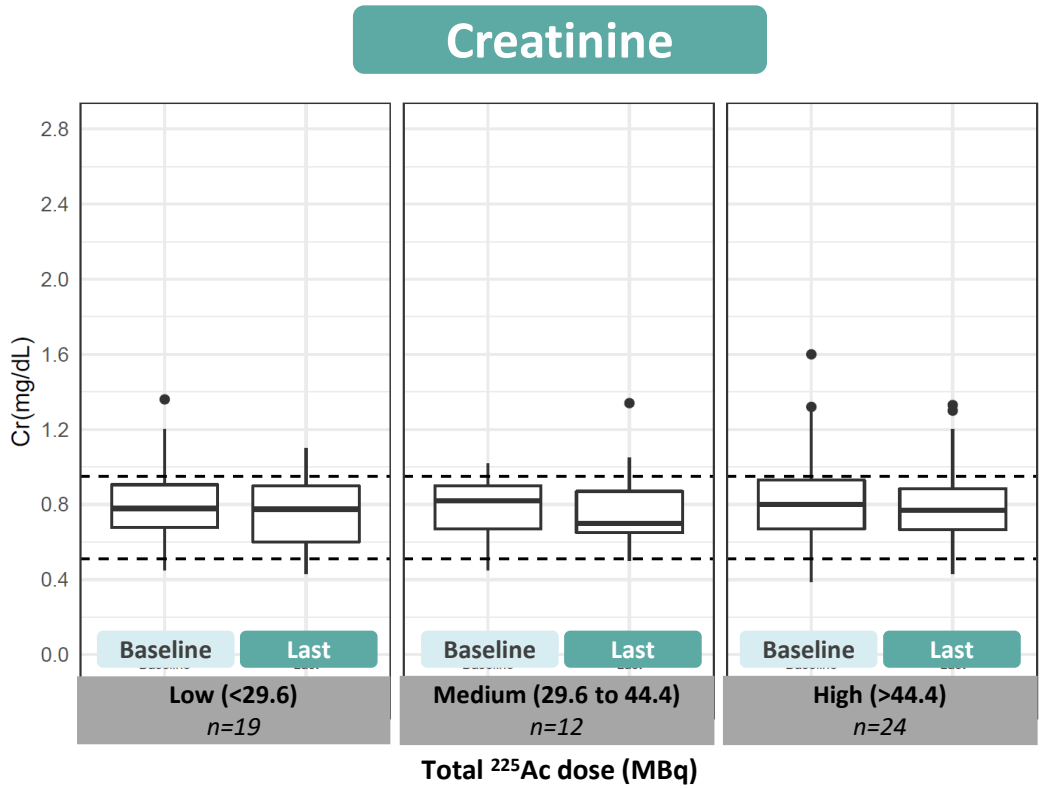
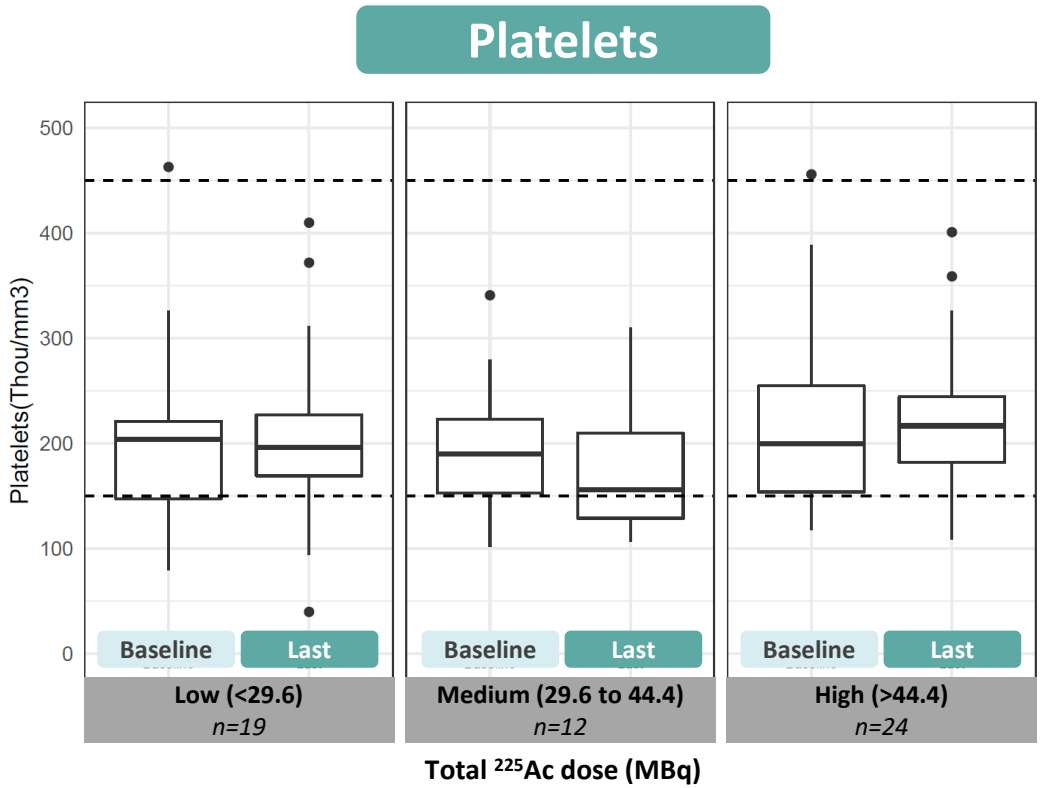
# $^{225}$Ac-DOTATATE is Well Tolerated

- Based on clinical laboratory data, $^{225}$Ac-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

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# RYZ101 ACTION-1 Study: Streamlined Phase 1b to Phase 3 Trial


**ACTI**nium f**O**r **N**euroendocrine tumors

*ClinicalTrials.gov identifier: NCT05477576*

**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

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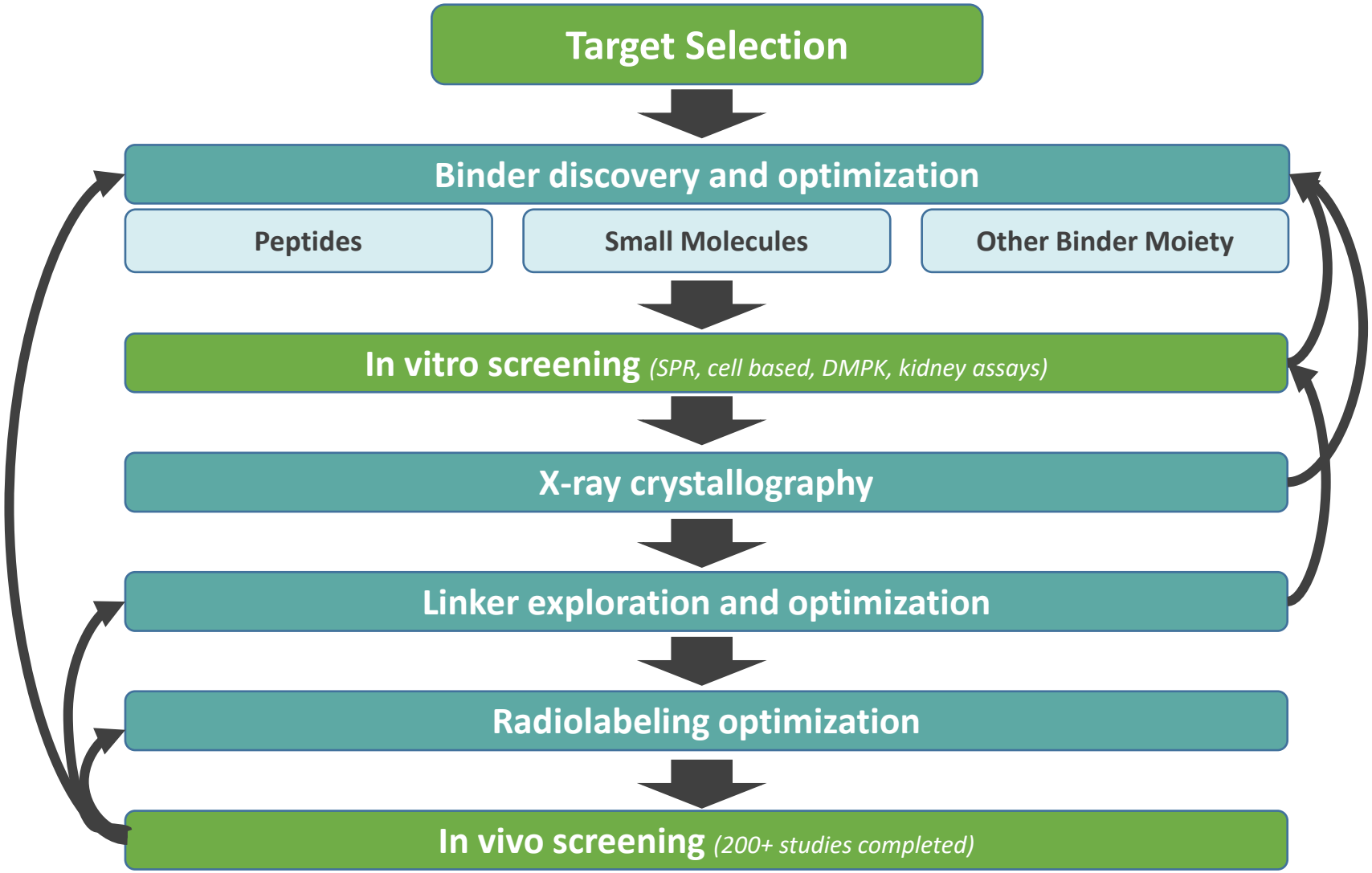
# Our Discovery Workflow for Novel RPT Oncology Drugs

**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

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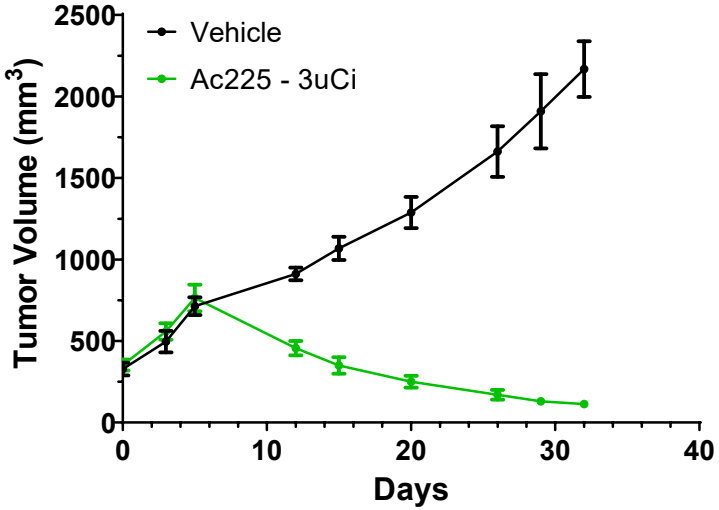
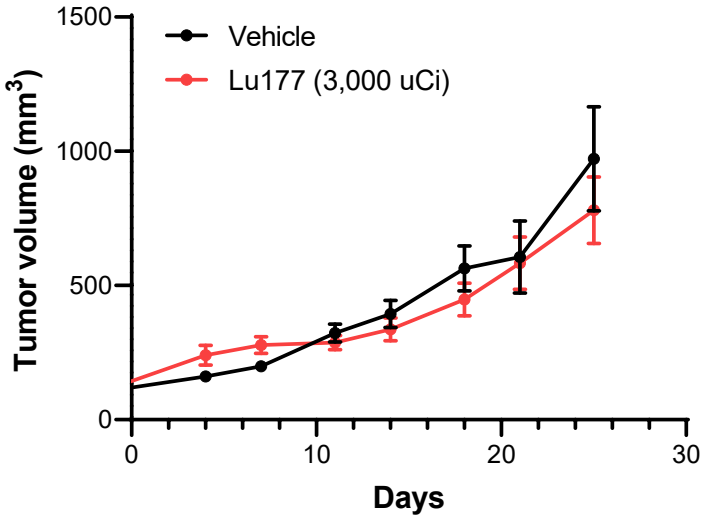
# $^{225}$Ac Demonstrates Robust Preclinical Efficacy

- 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 $^{225}$Ac and $^{177}$Lu

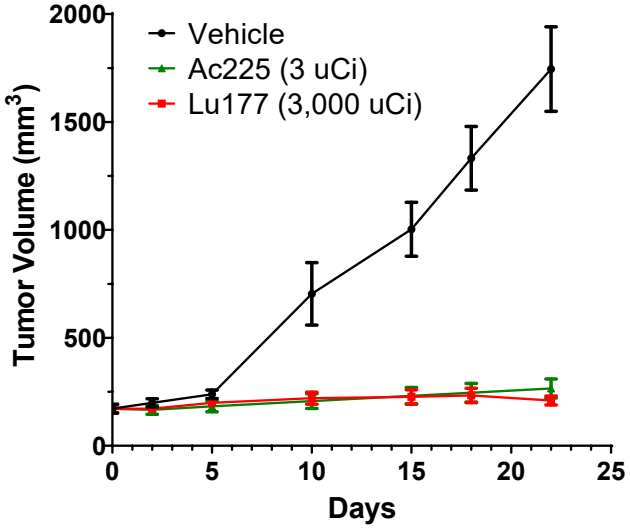
**Tumor Model A - $^{225}$Ac shows clear superiority over $^{177}$Lu**




References: internal data and analysis

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

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# Summary

- $^{225}$Ac has already demonstrated robust clinical efficacy and safety
- New radiopharmaceutical drugs leveraging the potency of $^{225}$Ac have the potential to significantly improve the lives of cancer patients
- Continued collaboration and investment is needed across the industry to bring forth $^{225}$Ac based therapies to the market