New Directions in PRRT

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Disclosures:

Consultant: Novartis, Exelixis

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Peptide Receptor Radiotherapy

Isotope	Emission	Tissue penetration	Maximum energy	Half life
^{111}Indium	Auger electron, gamma	0.02–10 μm	<30 KeV	64h
^{90}Yttrium	beta	12 mm	2.27 MeV	64h
^{177}Lutetium	gamma and beta	2 mm	0.5 MeV	160h

Capello A *et al. J Nucl Med* 2003;44(1);98–104; Kam BL *et al Eur J Nucl Med Mol Imaging* 2012;39(Suppl 1): SA103–S12.

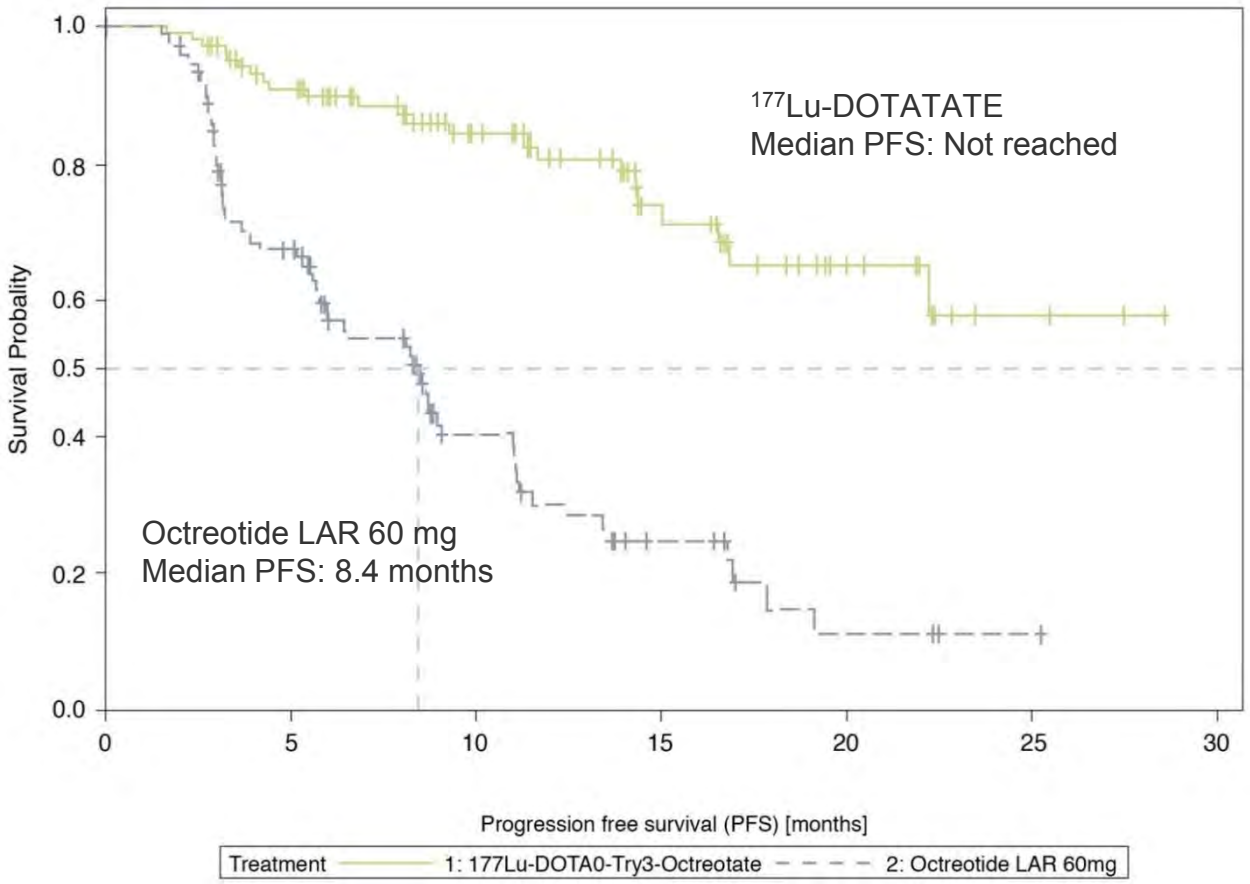
Current state of PRRT

- NETTER-1: ^{177}Lu-Dotatate Grade 1-2 (ki-67 <20%) metastatic midgut (jejunal/ileal/cecal) neuroendocrine tumor following progression on somatostatin analog
  - FDA approved for gastroenteropancreatic (GEP) NET in 2018 based on NETTER-1 trial and registry data

- NETTER-2: ^{177}Lu-Dotatate as first line therapy in higher grade 2 and grade 3 (ki-67 10-55%) GEP-NET

NETTER-1 Progression-free survival

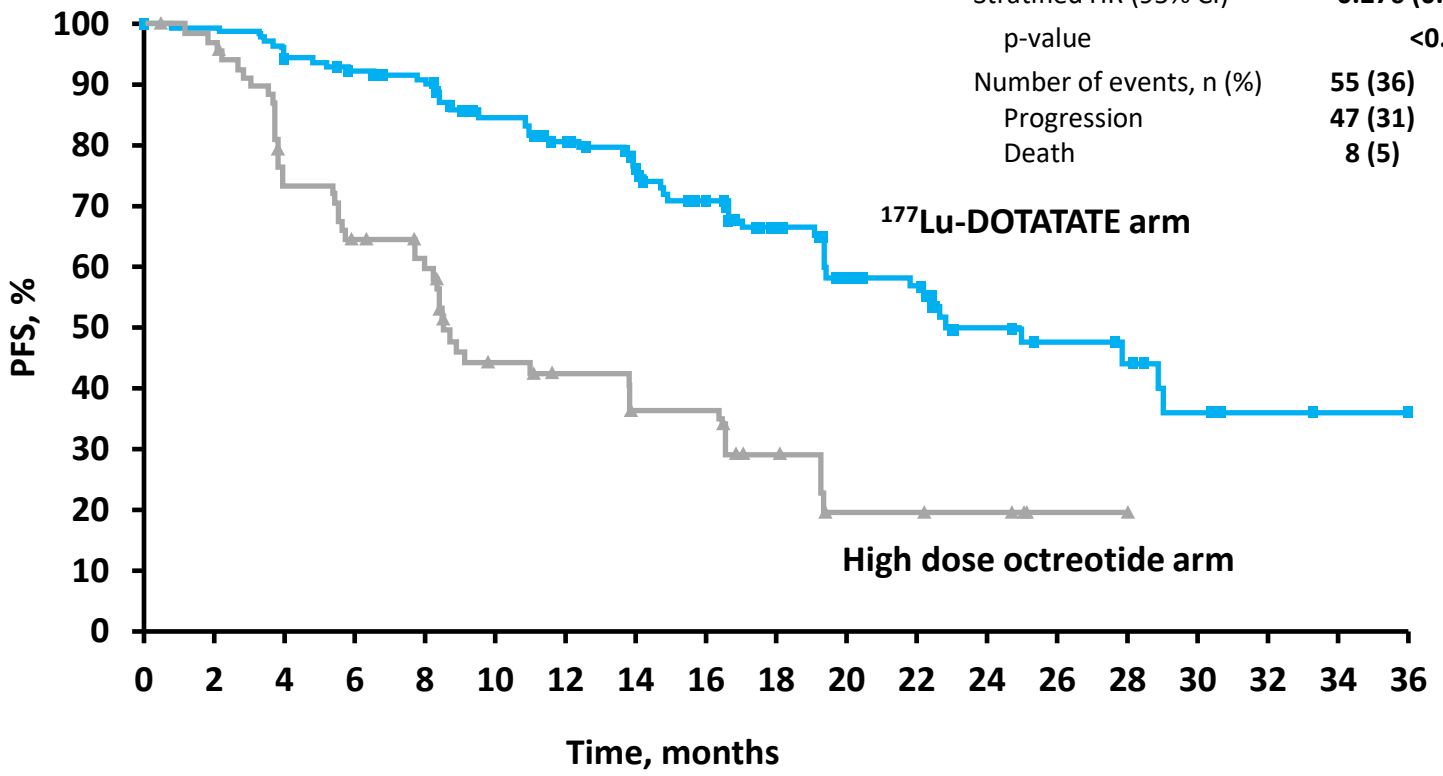
- N=229 (ITT)
- Number of events: 90
  - ^{177}Lu-DOTATATE: 23
  - Oct 60 mg LAR: 67
- **HR 0.21**, 95% CI 0.129–0.338; ***P*<0.0001**
- **79% reduction** in the risk of disease progression/death



Strosberg J *et al. N Engl J Med* 2017;376(2):125–35.

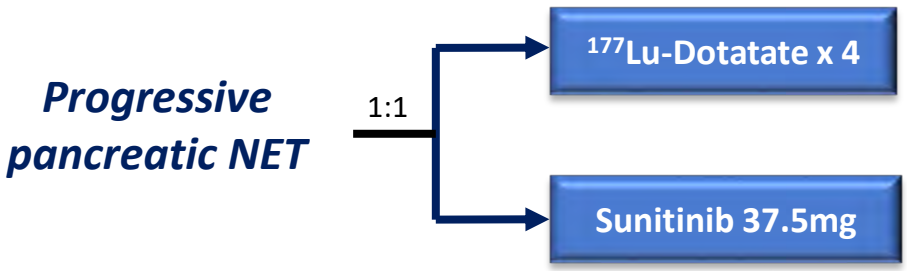
NETTER-2 Progression-Free Survival

	^{177}Lu-DOTATATE arm	High dose octreotide arm
	n=151	n=75
PFS median, months (95% CI)	22.8 (19.4, NE)	8.5 (7.7, 13.8)
Stratified HR (95% CI)	0.276 (0.182, 0.418)	
p-value	<0.0001	
Number of events, n (%)	55 (36)	46 (61)
Progression	47 (31)	41 (55)
Death	8 (5)	5 (7)



Singh S, Lancet. 2024 Jun 29;403(10446):2807-2817

Oclurandom Trial



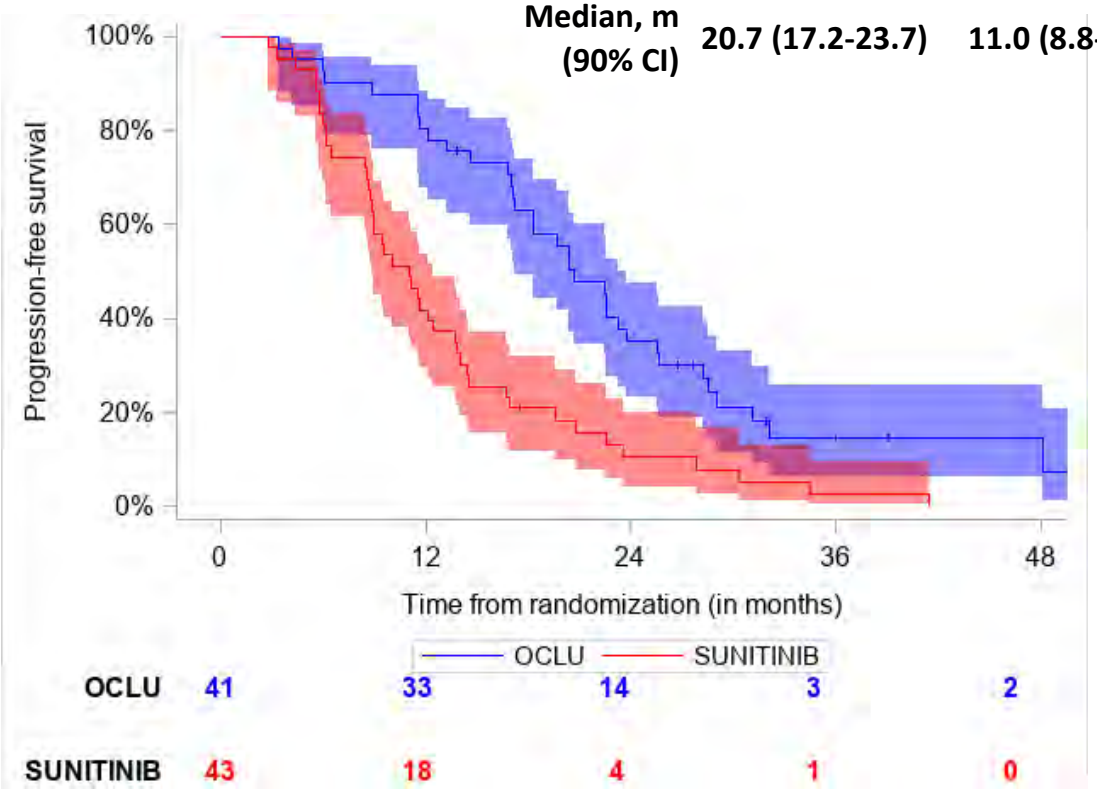
Primary endpoint: PFS rate at 12 months

- **Non comparative** randomized phase II with single-stage Fleming design (α:5% - power:95%)
- **Hypothesis:** Increase in 12-months PFS rate from 35% to 60%)
- **N=40 patients in the ^{177}Lu-Dotatate arm**
- Number of patients without progression at 12m required to consider **^{177}Lu-Dotatate** as effective **(Fleming design conclusion): at least 19 out of 40 pts**
- SUN arm : internal control to validate the hypothesis
- If 35% is included in the 90% Confidence Interval (CI) of the **12-months PFS rate of the SUN arm, the final conclusion will be the Fleming design conclusion**

Baudin et al. ESMO 2022

Progression-Free Survival

	177Lu-Dotatate (n =41)	SUNITINIB (n =43)
N events	34	42
Median, m (90% CI)	**20.7 (17.2-23.7)**	**11.0 (8.8-12.4)**

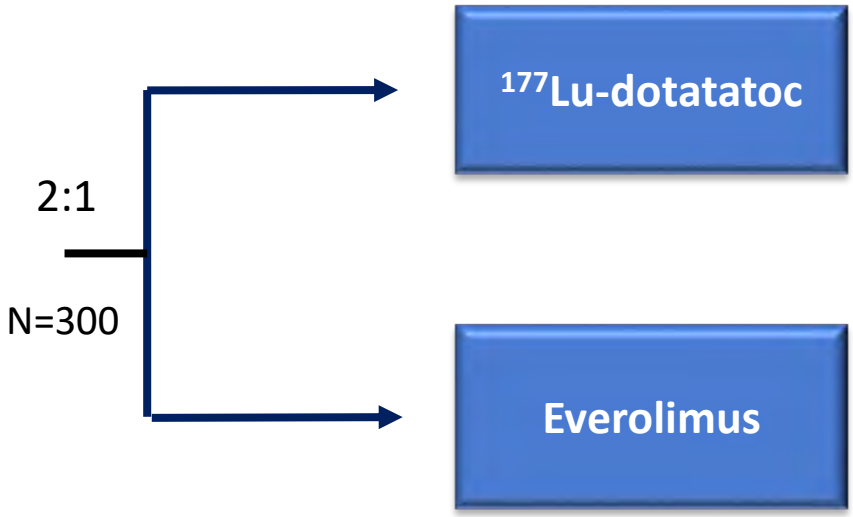


Baudin et al. ESMO 2022

Efficacy and Safety of ^{177}Lu-edotreotide (Dotatoc) in GEP-NET Patients (COMPETE)

1/2025 press release: Study is positive

Nonfunctional GEP-NET*



*functional pNET allowed

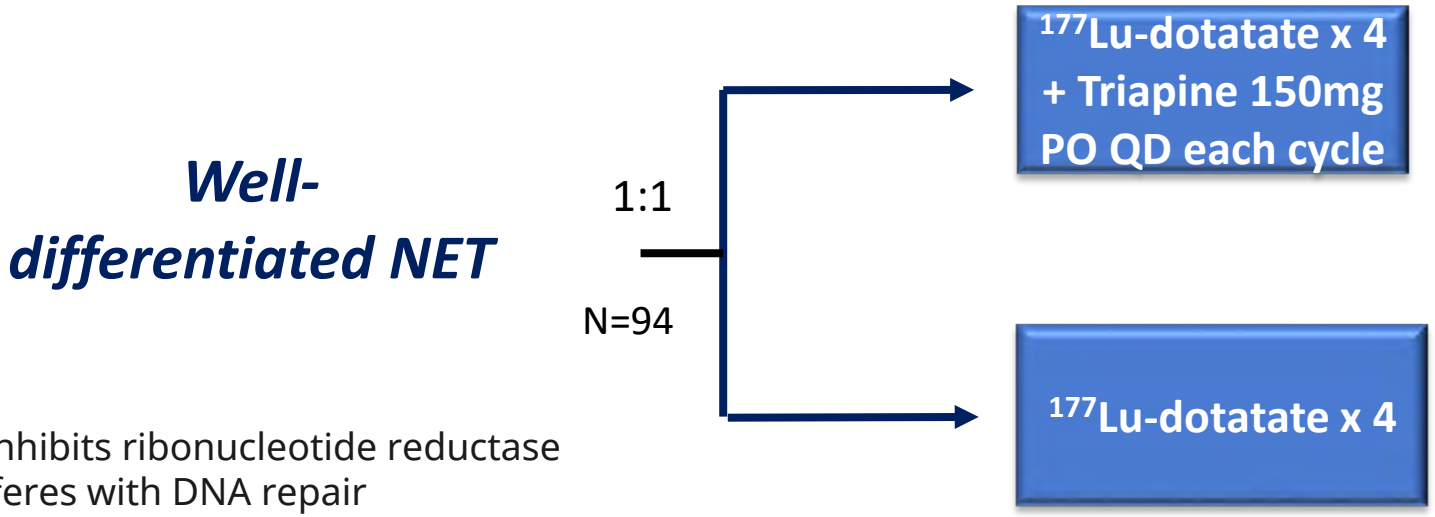
New Directions

1. ^{177}Lu-based therapy

2. Alpha emitters

Adding radiosensitizers to ^{177}Lu-Dotatate

Randomized phase II study of ^{177}Lu-Dotatate + Triapine



Triapine inhibits ribonucleotide reductase and interferes with DNA repair

PI Dr. Chauhan

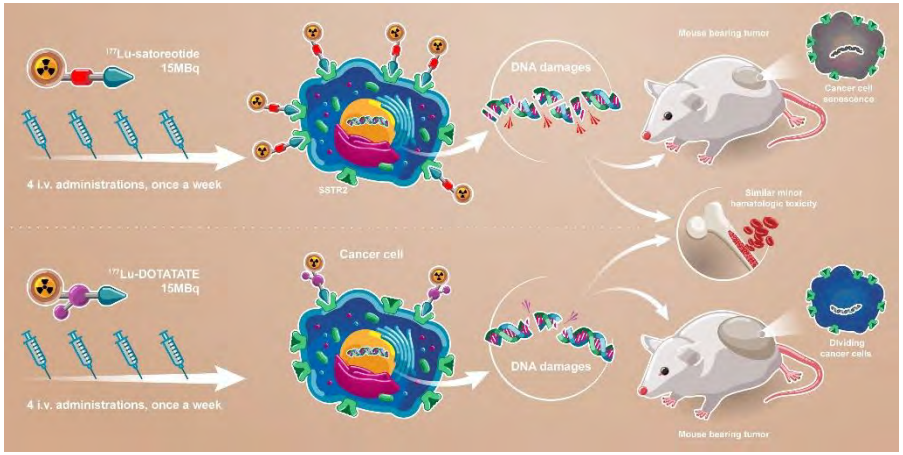
Phase I/II Study of ^{177}Lu-DOTATATE in Combination With Olaparib in GEP-NETs

PI Dr. Lin

Olaparib is Poly (ADP-Ribose) polymerase Inhibitor

Somatostatin receptor antagonist: ^{177}Lu-Satoreotide tetraxetan (aka JR11 aka OPS201)

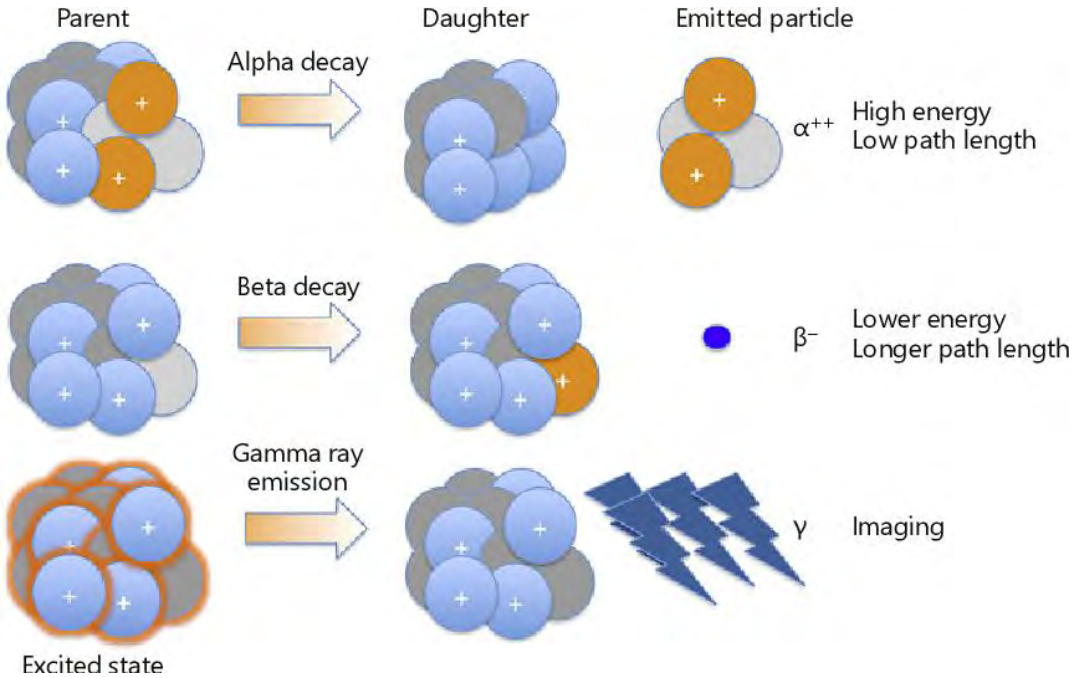
- SSTR antagonists can bind to receptor in active and inactive states
- Higher tumor binding affinity
- Phase I study: 20 patients 7.4GBq x 1 → 7.4GBq x 2→ 7.4GBq x1 + 3.7GBq x 1
- ORR 40%. Median PFS 21 months.
- High rate of hematologic toxicity (primarily grade 4 thrombocytopenia) at 7.4GBq x 2 dose.



Reidy-Lagunes et al. Clin Cancer Res. 2019 Dec 1;25(23):6939-6947.

Alpha Emitters

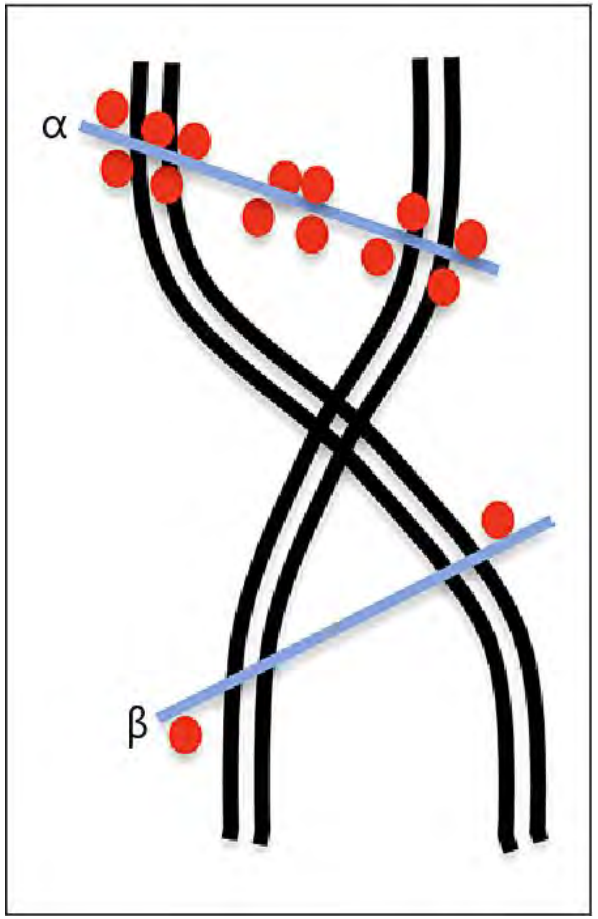
Radioactive Emissions



Alpha particles = 2 protons + 2 neutrons (He^{2+})

Navalkissoor et al. Neuroendocrinology2019;108(3):256-264

Alpha Emitters Can Induce Double-Strand DNA Breaks



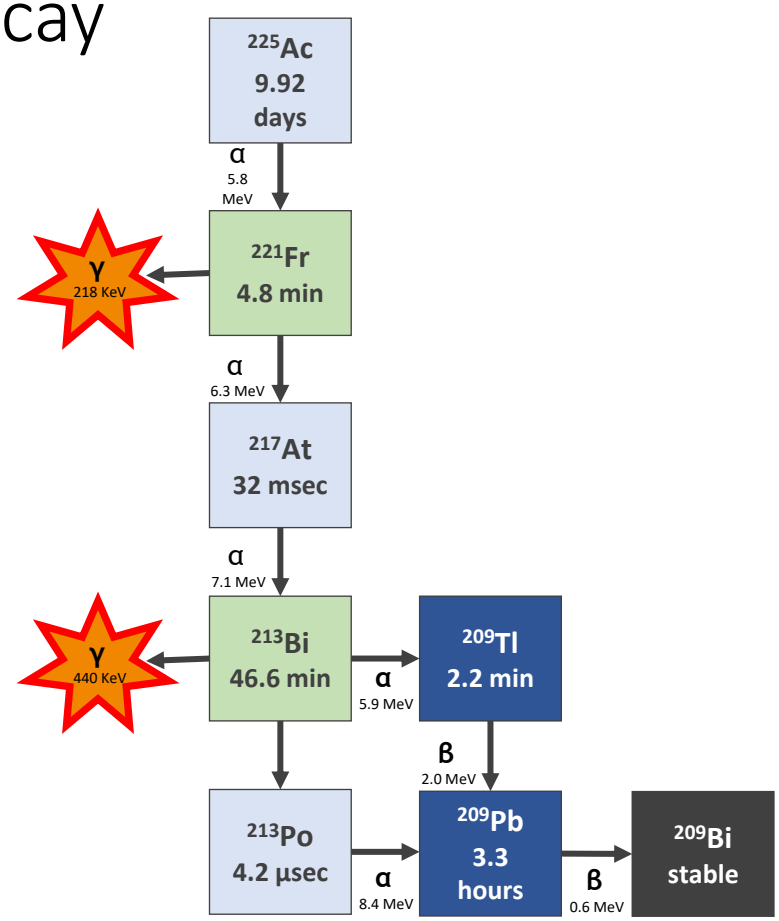
α particles: high particle energy (5-9 MeV)
high LET(~80 KeV/μm)
short range (40-100 μm=1-3 cells)

β particles: low particle energy (50-2300 KeV)
low LET (~0.2 keV/μm)
long range (0.05mm-12mm)

Navalkissoor et al. Neuroendocrinology2019;108(3):256-264

^{225}Acitinium (Ac) radioactive decay

- ^{225}Ac: $T_{1/2}$ ~ 10 days
- First decay ~ 6 MeV
- 4 daughter alpha emitters (^{221}Fr, ^{217}At, ^{213}Bi and ^{213}Po)
- Total alpha emission (all particles) 27.5MeV
- Both ^{221}Fr and ^{213}Bi emit imageable gamma rays at 218 KeV and 440 KeV, respectively



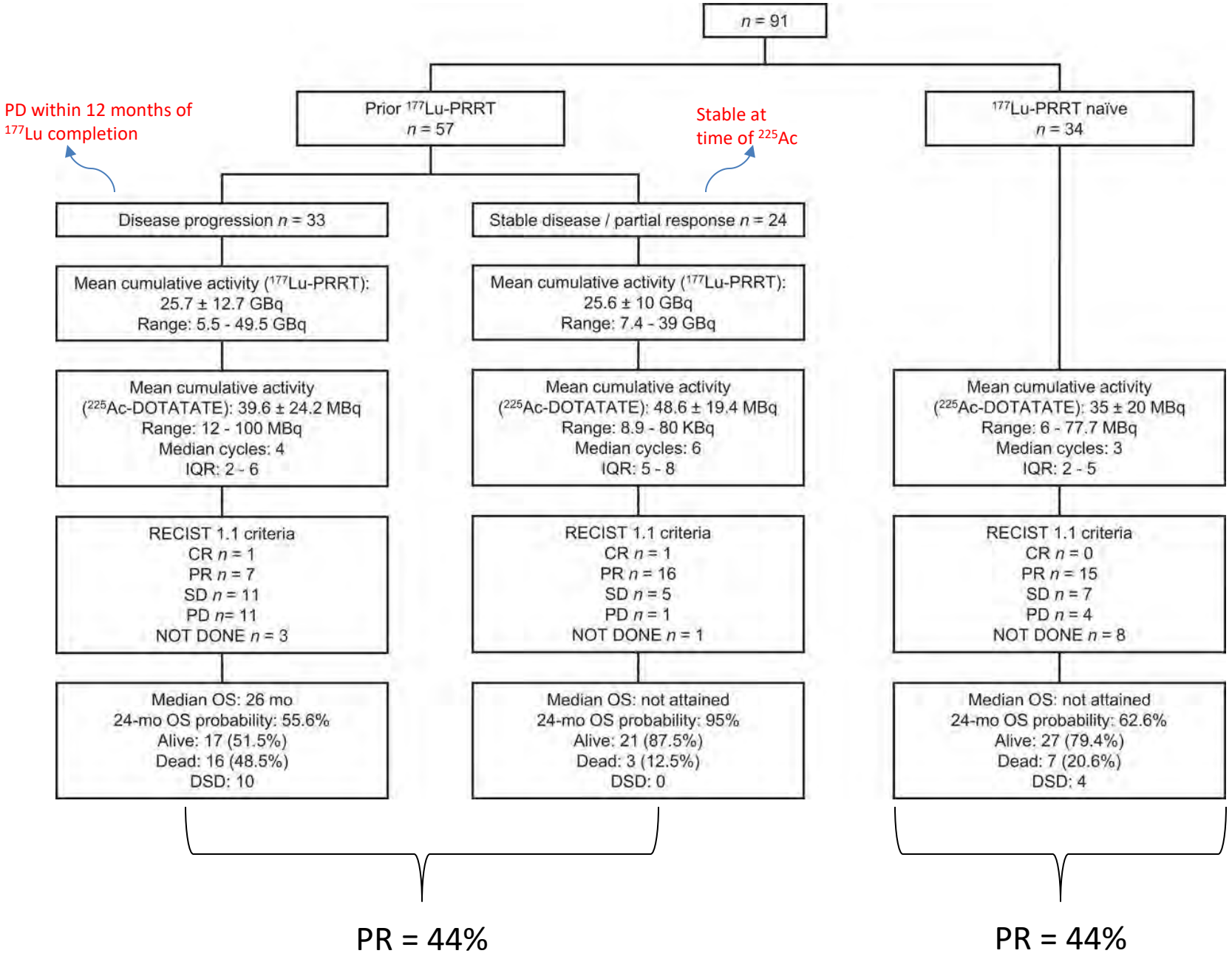
^{225}Ac-Dotatate: The New Delhi Real World Experience in GEP-NET patients

- Multiple cycles (up to 10)
- 100-120 kBq/kg per cycle
- ^{177}Lu naïve and refractory (stable or progressive)
- Concurrent capecitabine (days 1-14)
- Plurality (33%) pancreatic primary.

Patient Characteristics at Baseline (n = 91)

Characteristic	Value
Age (y)	
Mean ± SD	54.3 ± 11.6
Range	25–75
Sex	
Male	54 (59.4%)
Female	37 (40.6%)
Tumor location	
Pancreas	30 (33%)
Stomach	7 (7.7%)
Appendix	1 (1%)
Ileum	12 (13%)
Duodenum	13 (14.3%)
Jejunum	2 (2.2.%)
Colon	2 (2.2%)
Rectum	8 (8.8%)
Abdominal neuroendocrine tumor with unknown primary	16 (17.6%)
WHO tumor grade (Ki-67 tumor proliferation index)	
Grade I (<2%)	33 (36.2%)
Grade II (3%–20%)	48 (52.7%)
Grade III (>20%)	7 (7%)
Not accessible	3 (3.3%)
Previous surgery	20 (22%)
Prior chemotherapy	20 (22%)
Prior ^{177}Lu-DOTATATE therapy	57 (62.6%)
ECOG status	
1–2	63 (69%)
3–4	28 (31%)

Ballal et al. J Nucl Med. 2022 Jul 21:jnumed.122.264043


n = 91
Prior 177Lu-PRRT
n = 57
177Lu-PRRT naïve
n = 34
PD within 12 months of 177Lu completion
Stable at time of 225Ac
Disease progression n = 33
Stable disease / partial response n = 24
Mean cumulative activity (177Lu-PRRT): 25.7 ± 12.7 GBq
Range: 5.5 - 49.5 GBq
Mean cumulative activity (177Lu-PRRT): 25.6 ± 10 GBq
Range: 7.4 - 39 GBq
Mean cumulative activity (225Ac-DOTATATE): 39.6 ± 24.2 MBq
Range: 12 - 100 MBq
Median cycles: 4
IQR: 2 - 6
Mean cumulative activity (225Ac-DOTATATE): 48.6 ± 19.4 MBq
Range: 8.9 - 80 KBq
Median cycles: 6
IQR: 5 - 8
Mean cumulative activity (225Ac-DOTATATE): 35 ± 20 MBq
Range: 6 - 77.7 MBq
Median cycles: 3
IQR: 2 - 5
RECIST 1.1 criteria
CR n = 1
PR n = 7
SD n = 11
PD n= 11
NOT DONE n = 3
RECIST 1.1 criteria
CR n = 1
PR n = 16
SD n = 5
PD n = 1
NOT DONE n = 1
RECIST 1.1 criteria
CR n = 0
PR n = 15
SD n = 7
PD n = 4
NOT DONE n = 8
Median OS: 26 mo
24-mo OS probability: 55.6%
Alive: 17 (51.5%)
Dead: 16 (48.5%)
DSD: 10
Median OS: not attained
24-mo OS probability: 95%
Alive: 21 (87.5%)
Dead: 3 (12.5%)
DSD: 0
Median OS: not attained
24-mo OS probability: 62.6%
Alive: 27 (79.4%)
Dead: 7 (20.6%)
DSD: 4
PR = 44%
PR = 44%

Issues

- Real-world experience: not prospective phase II with well-defined eligibility/treatment protocol
- Response not strictly based on RECIST criteria (PET imaging used in many cases)
- Mix of patients with stable/progressive disease

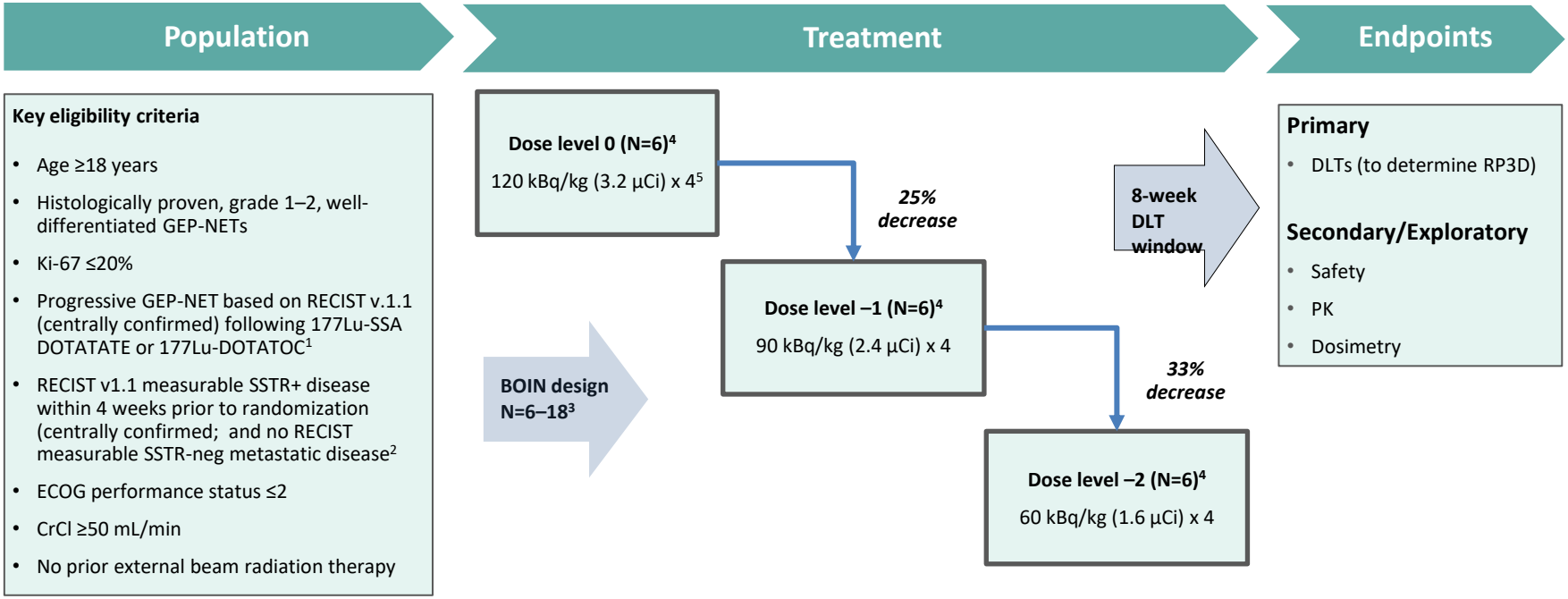
Strosberg et al. J Nucl Med. 2023 Feb;64(2):219-220

Phase Ib portion of the ACTION-1 phase Ib/3 trial of RYZ101 in gastroenteropancreatic neuroendocrine tumors (GEP-NET) progressing after 177Lu somatostatin analogue (SSA) therapy: preliminary safety and efficacy

[1]Jonathan Strosberg; [2]Gary Ulaner; [3]Daniel Halperin; [4]Samuel Mehr; [5]Daneng Li; [6]Heloisa Soares; [7]Lowell Anthony; [8]Sandy Kotiah; [9]Heather Jacene; [10]Pamela L. Kunz; [11]Denis Ferreira; [11]Joanne Li; [11]Kimberly Ma; [11]Jessica Rearden; [11]Susan Moran; [12]Thomas Hope; [13]Simron Singh; [14]Michael Morris

[1]Moffitt Cancer Center, Tampa, FL; [2]Hoag Family Cancer Institute, Newport Beach, CA; [3]MD Anderson Cancer Center, Houston, TX; [4]Nebraska Cancer Specialists, Omaha, NE; [5]City of Hope Comprehensive Cancer Center, Duarte, CA; [6]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; [7]University of Kentucky Markey Cancer Center, Lexington, KY; [8]Mercy Medical Center, Baltimore, MD; [9]Dana Farber Cancer Institute, Boston, MA; [10]Yale Cancer Center, New Haven, CT; [11]RayzeBio, San Diego, CA; [12]University of California San Francisco, CA; [13]University of Toronto, Odette Cancer Center at Sunnybrook Health Sciences Center, Toronto, ON, Canada; [14]Advanced Molecular Imaging and Therapy, Glen Burnie, MD, USA

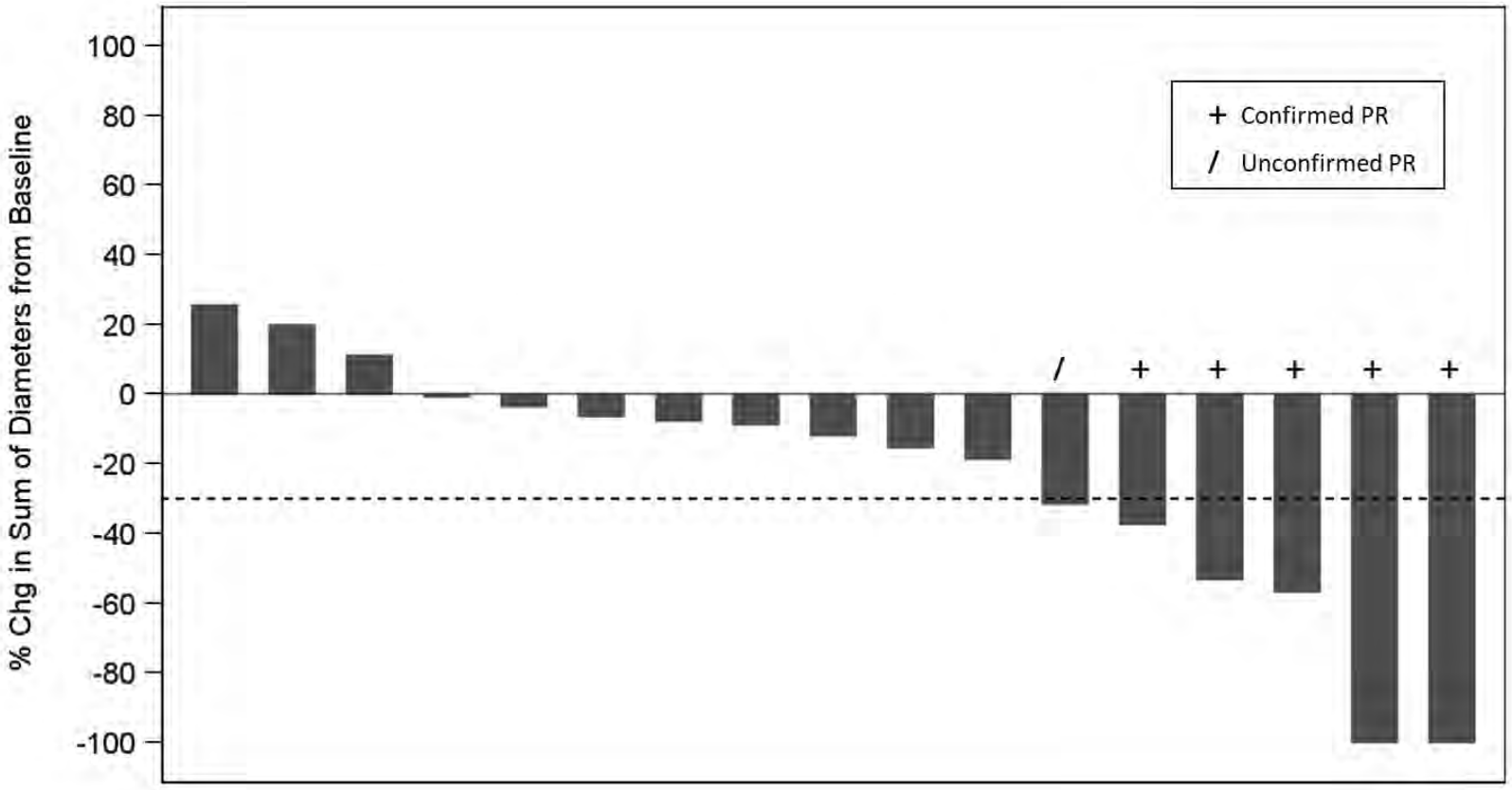
ACTION-1: ^{225}Ac-Dotatate– Part 1 (phase 1b)



[1] The oldest scan must not be older than 3 years from the date of screening and the most recent scan must not be older than 4 weeks prior to enrollment
[2] SSTR PET imaging must be completed within 12 weeks (84 days inclusive) of enrollment.
[3] Additional de-escalation cohort may be added depending on observed safety
[4] Concomitant amino acids will be given with each RYZ101 administration for renal protection.
[5] Patients will be eligible to receive additional cycles every 8 weeks, up to 4 cycles if they do not experience a DLT or if they recover from a DLT and subsequent treatment is approved by the investigator and Sponsor.
SSTR: Somatostatin receptor; µCi= microcurie; kBq= kilobequerel

Strosberg et al. ESMO 2023

Figure 4. Best percentage change in tumor size (investigator-assessed)



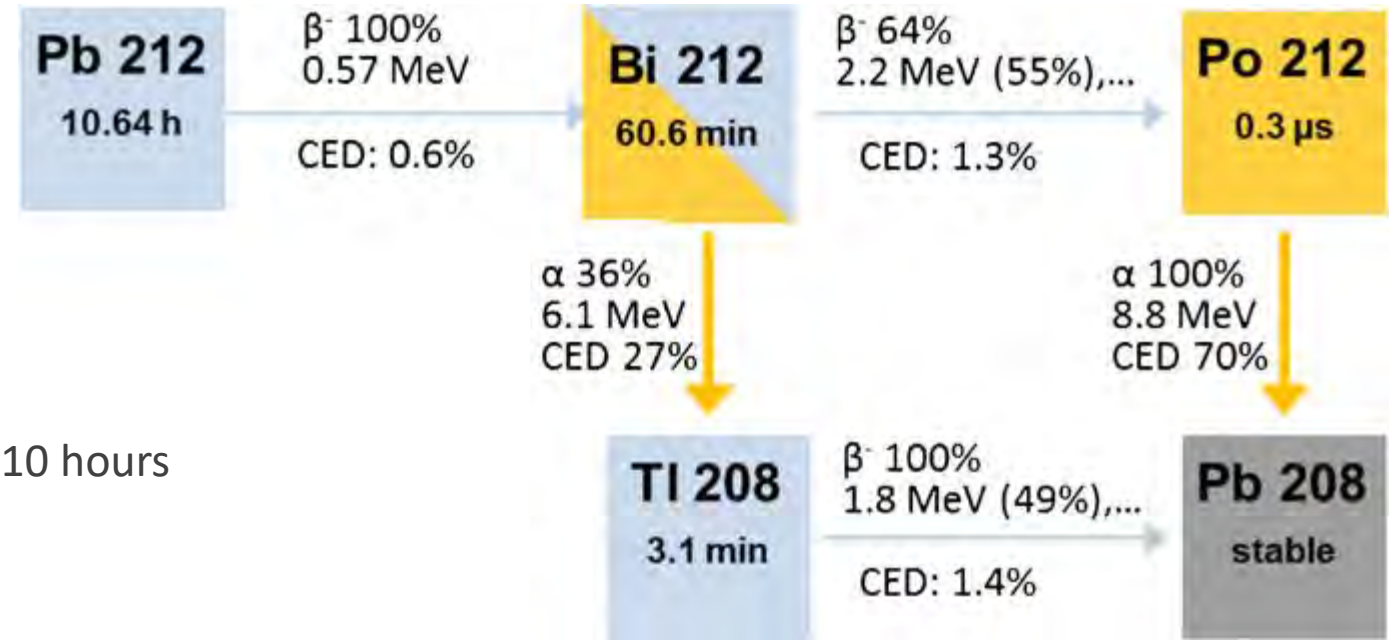
Efficacy evaluable population are those subjects who received at least one RYZ101 dose and had at least one efficacy evaluable assessment

Safety summary

Patients, n (%)	RYZ101 120 kBq/kg (n=17)
Any TEAEs	17 (100.0)
SAEs	6 (35.3)
Treatment-related TEAEs	15 (88.2)
Treatment-related SAEs	0 (0.0)
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) TEAEs	0 (0.0)
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.

^{212}Pb-Dotamtate

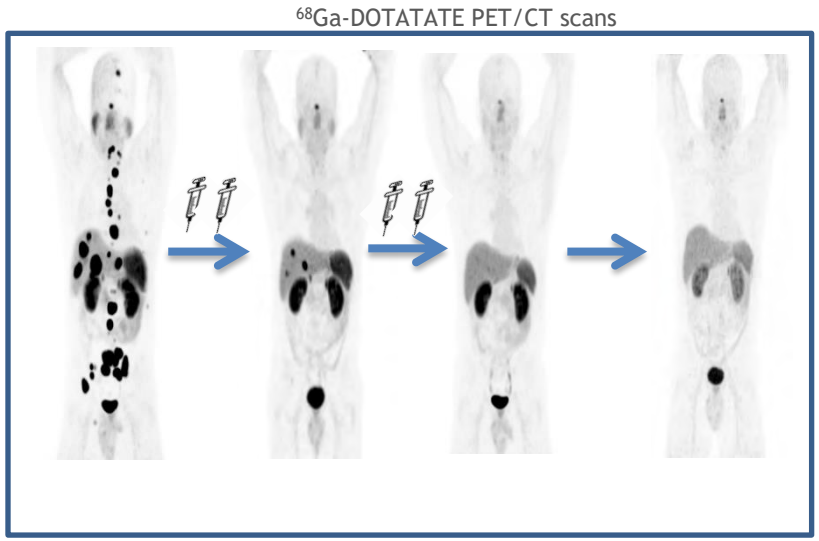


^{212}Pb: $T_{1/2}$ ~ 10 hours

dos Santos, J.C. et al. *Eur J Nucl Med Mol Imaging* **46**, 1081–1091 (2019)

Phase I Trial

- 20 SSTR-positive metastatic NET
- PRRT naïve
- Initial dose: 1.13MBq/kg x 1 cycle
- After 10 patients with dose escalation, 10 patients received 2.5MBq/kg x 4 cycles.



Delpassand et al. J Nucl Med2022 Sep;63(9):1326-1333

Patient Characteristics, Including Relevant Clinical Trial Data

Patient*	Age (y)	Sex	Type of NET	Grade	Ki-67	Stage	Time gap (y)	No. of cycles	Total dose (MBq)	RECIST 1.1 response†	^{68}Ga PET response‡	Duration of response (mo)§
SAD1-01	75	M	Small bowel	2	4	IV	8.4	1	81 (2.2)	Stable disease	NA	NP
SAD1-02	76	F	Pancreatic	2	NA	IV	8.8	1	85 (2.3)	Stable disease	NA	NP
SAD1-03	77	M	Pancreatic	3	27	IV	4.5	1	85 (2.3)	Stable disease	NA	NP
SAD2-01	56	M	Rectal	2	NA	IV	5.2	1	122 (3.3)	Stable disease	NA	NP
SAD2-02	27	F	Small bowel	1	NA	IV	4.7	1	100 (2.7)	Stable disease	NA	NP
SAD2-03	72	F	Small bowel	1	2	IV	8.1	1	115 (3.2)	Stable disease	NA	NP
MAD3-01	61	F	Small bowel	2	6	IV	10.7	3	574 (15.5)	Stable disease	NSC	0
MAD3-02	62	F	Pancreatic	2	3	IV	7.2	2‖	329 (8.9)	Stable disease	NSC	0
MAD3-03	68	F	Small bowel	NA	NA	IV	10.7	3	286 (7.2)	Stable disease	NSC	0
MAD3-04	51	M	Pancreatic	NA	NA	IV	5.6	3	455 (12.3)	Stable disease	−40%	0
MAD4-01	62	M	Small bowel	3	22	IV	2.2	4	814 (22.0)	PR	−95%	22
MAD4-02	46	M	Bronchial carcinoid	1	>20	IV	8.2	4	796 (21.5)	PR	−100%	22
MAD4-03	71	F	Bronchial carcinoid	2	15	III	4.8	4	707 (19.8)	CR	−100%	20
MAD4-04	39	F	Rectal	3	30	IV	5.1	4	807 (21.8)	Stable disease	−40%	0
MAD4-05	62	M	Pancreatic	1	2	IV	7.3	4	873 (23.6)	PR	−80%	8
MAD4-06	49	F	Pancreatic	2	19	IV	2.9	4	681 (18.4)	PR	−100%	14
MAD4-07	45	M	Rectal	2	12	IV	5.7	4	858 (23.2)	PR	−95%	5
MAD4-08	60	M	Small bowel	2	5	IV	0.3	4	692 (18.7)	Stable disease	−15%	0
MAD4-09	80	M	Bronchial carcinoid	2	10	IV	1.1	4	836 (22.6)	PR	−60%	1
MAD4-10	59	F	Bronchial carcinoid	2	5	IV	1.8	4	847 (22.9)	PR	−30%	5

- At highest dose (recommended phase II), 80% PR/CR
- No SAEs considered treatment related
- Median time to response 5.2 months
- Alopecia and nausea main side effects. Only 5% grade 3 and 0% grade 4

Delpassand et al. J Nucl Med2022 Sep;63(9):1326-1333

2024 ASCO® ANNUAL MEETING

Safety, tolerability and efficacy of ^{212}Pb-DOTAMTATE as a targeted alpha therapy for subjects with unresectable or metastatic somatostatin receptor-expressing gastroenteropancreatic neuroendocrine tumors (SSTR+ GEP-NETs): A Phase 2 Study.

Jonathan Strosberg, Shagufta Naqvi, Allen Cohn, Ebrahim Delpassand, Volker Wagner, Julien Torgue, Rachel Woloski, Allison Manuel, Mary Maluccio

Jonathan Strosberg, MD
Professor, Medical Director Clinical Research, GI Oncology
Moffitt Cancer Center, Tampa / FL

Demographics and baseline characteristics

Characteristics	ALPHAMEDIX01 (N=8)		ALPHAMEDIX02 (N=36)		Total (N=44)	
Sex - no (%)						
Male	5	(63%)	18	(50%)	23	(52%)
Female	3	(38%)	18	(50%)	21	(48%)
Age - yr	54	±9	60	±10	59	±10
Median time since diagnosis - yr	2	±2	5	±4	4	±4
Primary tumor site - no (%)						
Pancreas	4	(50%)	14	(39%)	18	(41%)
Small intestine, not otherwise specified	-	(0%)	14	(39%)	14	(32%)
Right colon	-	(0%)	1	(3%)	1	(2%)
Rectum	-	(0%)	1	(3%)	1	(2%)
Other, GEP-NET	4	(50%)	4	(11%)	8	(18%)
Unknown	-	(0%)	2	(6%)	2	(5%)
Grading - no (%)						
Grade 1	-	(0%)	8	(22%)	8	(18%)
Grade 2	6	(75%)	24	(67%)	30	(68%)
Grade 3	1	(13%)	2	(6%)	3	(7%)
Functional status						
Yes	3	(38%)	14	(39%)	17	(39%)
History						
Prior cancer surgery	5	(63%)	29	(81%)	34	(77%)
Somatostatin and analogues	8	(100%)	35	(97%)	43	(98%)
Targeted Therapy (non PRRT)	2	(25%)	6	(17%)	8	(18%)
Embolization	3	(38%)	13	(36%)	16	(36%)
Chemotherapy	2	(25%)	9	(25%)	11	(25%)
External Beam	1	(13%)	3	(8%)	4	(9%)

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Efficacy in PRRT-naïve subjects with metastatic SSTR+ GEP-NETs

	ALPHAMEDIX-01	ALPHAMEDIX-02	Pooled Results 01/02
N (patients)	8†	36	44
ORR (95% CI)	5/8 responders/total 62.5% ORR (30.6-86.3%)	20/36 responders/total 55.6% ORR (39.6-70.5%)	25/44 responders/total 56.8% ORR (42.2-70.3%)
DoR Median	NE	17 months	NE
DoR months (95 CI#)	15.2 months, NE	17 months, NE	15.2 months, NE
% with observed DOR of ≥ 6 months*	100% (5 of 5)	100% (17 of 17)	100% (22 of 22)
% with observed DOR of ≥ 12 months*	100% (4 of 4)	91% (10 of 11)	93% (14 of 15)

Abbreviations : ORR, Overall Response Rate; DOR, Duration of Response
Database extraction May 28, 2024
asymmetrical
*Landmark analysis
†GEP-NET subjects at RP2D

The combined ORR from both Phase 1 and 2 is 56.8% (95%CI:42.2-70.3%).

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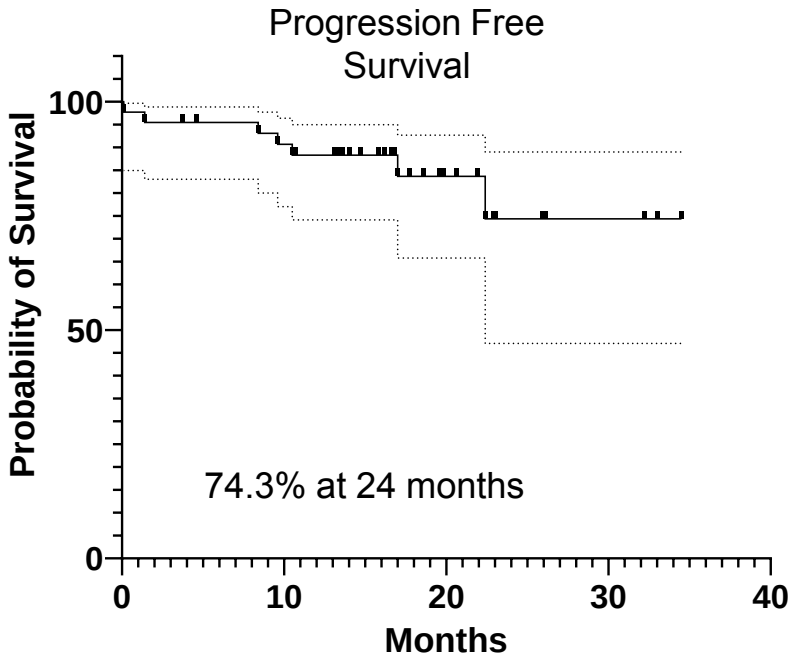
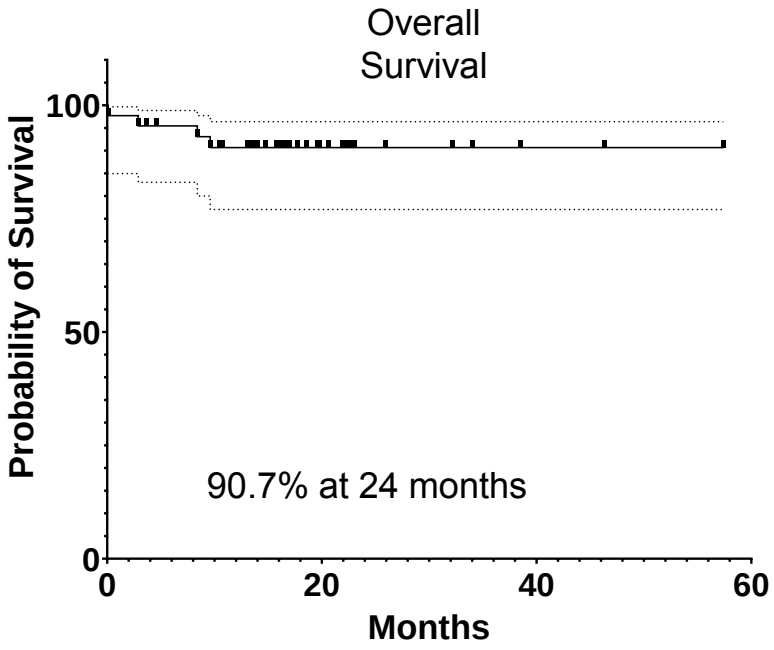
Preliminary PFS and OS in PRRT-naïve subjects with metastatic SSTR+ GEP-NETs (phase 1 and phase 2)





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Safety considerations

- 3 fatal adverse events have been reported so far
  - Death from underlying disease / progressive disease (N=2), multi-organ failure / sepsis (N=1)
- No substantial high grade hematologic toxicity: largely limited to grade 3/4 lymphocytopenia that is reversible
- Alopecia is mild to moderate and appears to be transient: SSTR is expressed in hair follicles
- Dysphagia: manometry demonstrates “achalasia”. Botox injection to the lower esophageal sphincter provides relief in many cases. Pathophysiology unclear.

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Other trials

NCT05636618 Phase I/IIa study of ^{212}Pb-VMT-α-NET (PSC-PEG2-TOC) Targeted Alpha-Particle Therapy for Advanced SSTR2 Positive Neuroendocrine Tumors

NCT05557708 A Safety Study of ^{212}Pb-Pentixather Radioligand Therapy (targets CXCR4)

Conclusions

- PRRT in NETs is highly active field of study, potentially generating new paradigms for other cancers

- Alpha emitters are potentially more effective than beta emitters, but risks and long-term toxicities are still under invesetigation