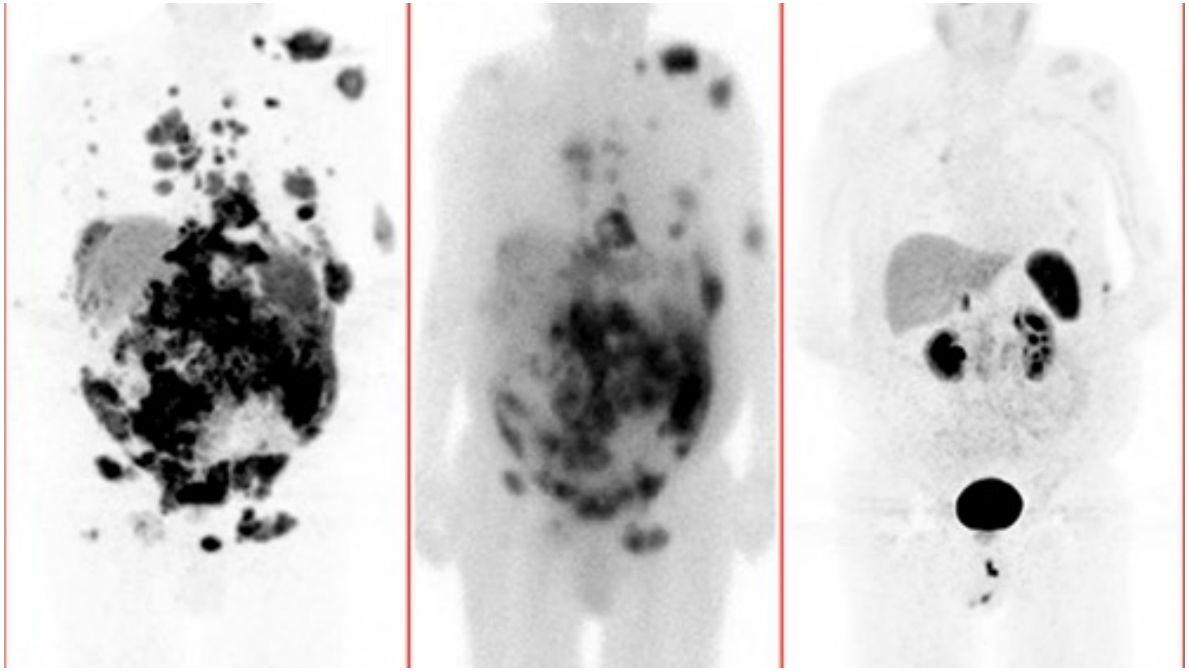
Understanding Alpha & The Evolving PRRT Landscape



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Atlanta, GA

EMORY
WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

WHO Classification of NENs

Terminology	Differentiation	Grade	Mitotic rate*, mitoses/2 mm^2	Ki-67 index*, %
NET, G1	Well differentiated	Low	<2	<3
NET, G2	Well differentiated	Intermediate	2–20	3–20
NET, G3	Well differentiated	High	>20	>20
NEC, small cell type	Poorly differentiated	High	>20	>20
NEC, large cell type	Poorly differentiated	High	>20	>20
Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)	Well or poorly differentiated	Variable	Variable	Variable

NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma. * Final grade is based on whichever of the two proliferation indexes places the neoplasm in the higher category.

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NEC, sr	orly differentiated	High		
NEC, la	orly differentiated	High		
Mixed ne	ell or poorly differentiated	Variat		
neoplasm (MiNEN)				

NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma. * Final grade is based on whichever of the two proliferation indexes places the neoplasm in the higher category.

Every patient is different

Every tumor is different

WHO Classification of NENs

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NEC, la	orly differentiated	High		
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neoplasm (MiNEN)	differentiated			

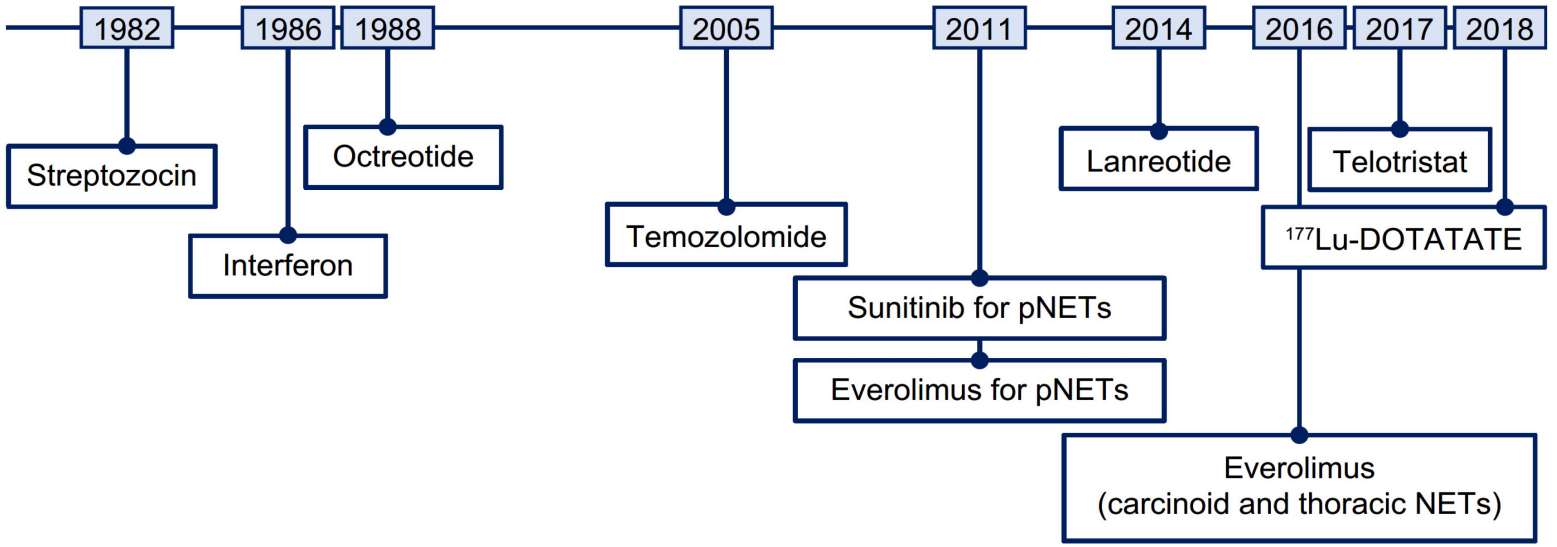
NET, neuroendocrine tumor; NEC, neu ndocrine carcinoma. * Final grade is based on w ever of the two proliferation indexes places the neoplasm in the higher category.

Every patient is different

Every tumor is different

Even patients with the same type of NEN have very different response to therapies. Biology is key!

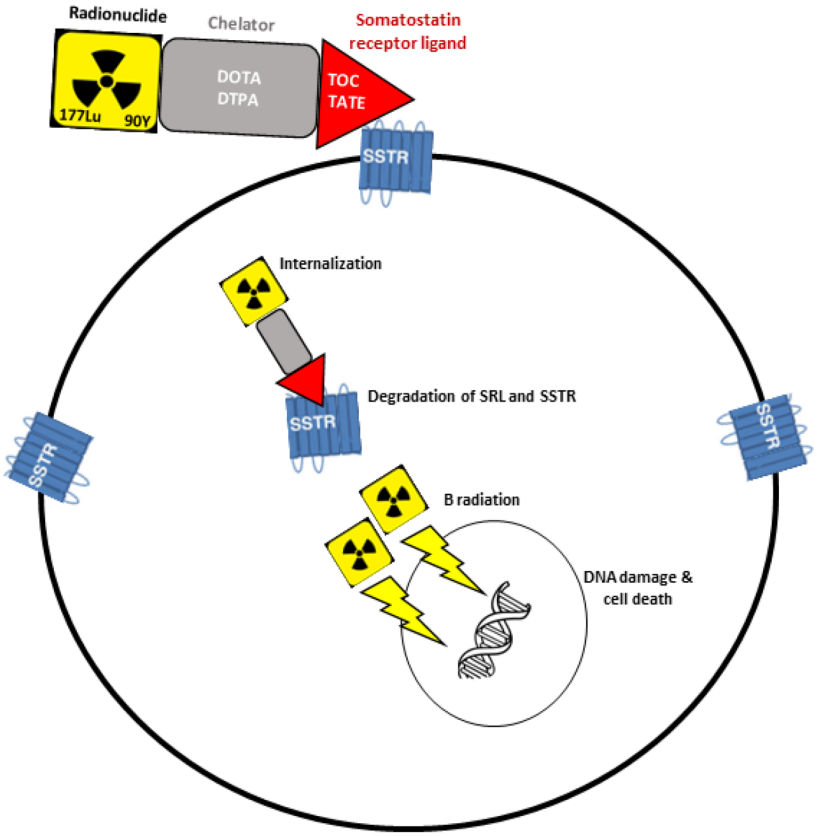
Therapeutic paradigm for NETs



CABINET
Cabozantinib
2024

Chauhan *et al.* 2022

Peptide Receptor Radionuclide Therapy



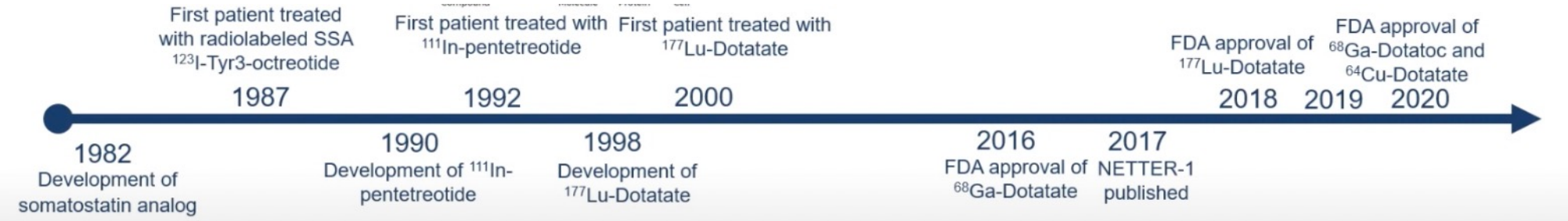
DNA, deoxyribonucleic acid;
DOTA, tetraazacyclododecane-tetraacetic acid;
DTPA, diethylenetriamine pentaacetic acid;
Lu, Lutetium;
SRL, somatostatin receptor ligand;
SSTR, somatostatin receptor;
TATE, tyr3-octreotate;
TOC, tyr3-octreotide;
Y, Yttrium.

Marques *et al*. Cancers. 2023

Peptide Receptor Radionuclide Therapy

Decades of work from development to approval.

Arguably the most significant therapeutic advancement for the management of NETs.



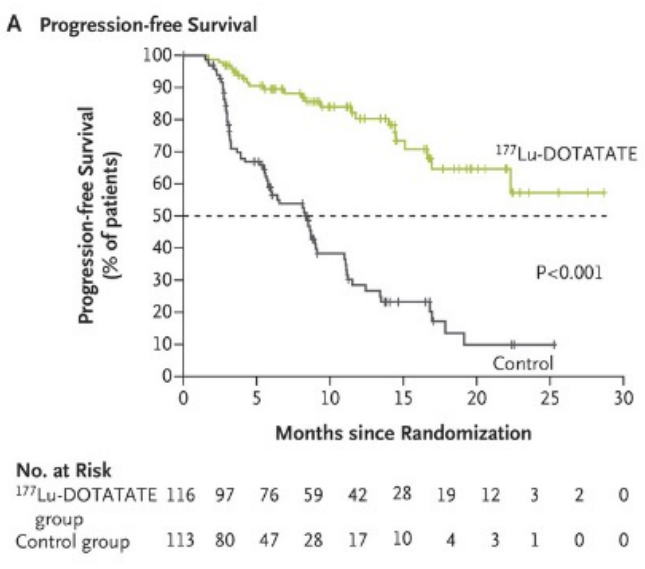
Iravani. LACNETS. 2022

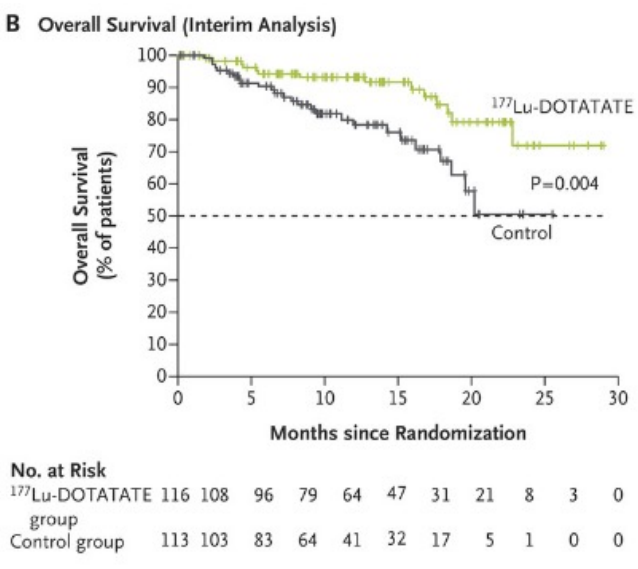
NETTER-1

ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

Jonathan Strosberg, M.D., Ghassan El-Haddad, M.D., Edward Wolin, M.D., Andrew Hendifar, M.D., James Yao, M.D., Beth Chasen, M.D., Erik Mittra, M.D., Ph.D., Pamela L. Kunz, M.D., Matthew H. Kulke, M.D., Heather Jacene, M.D., David Bushnell, M.D., Thomas M. O'Dorisio, M.D., et al., for the NETTER-1 Trial Investigators*





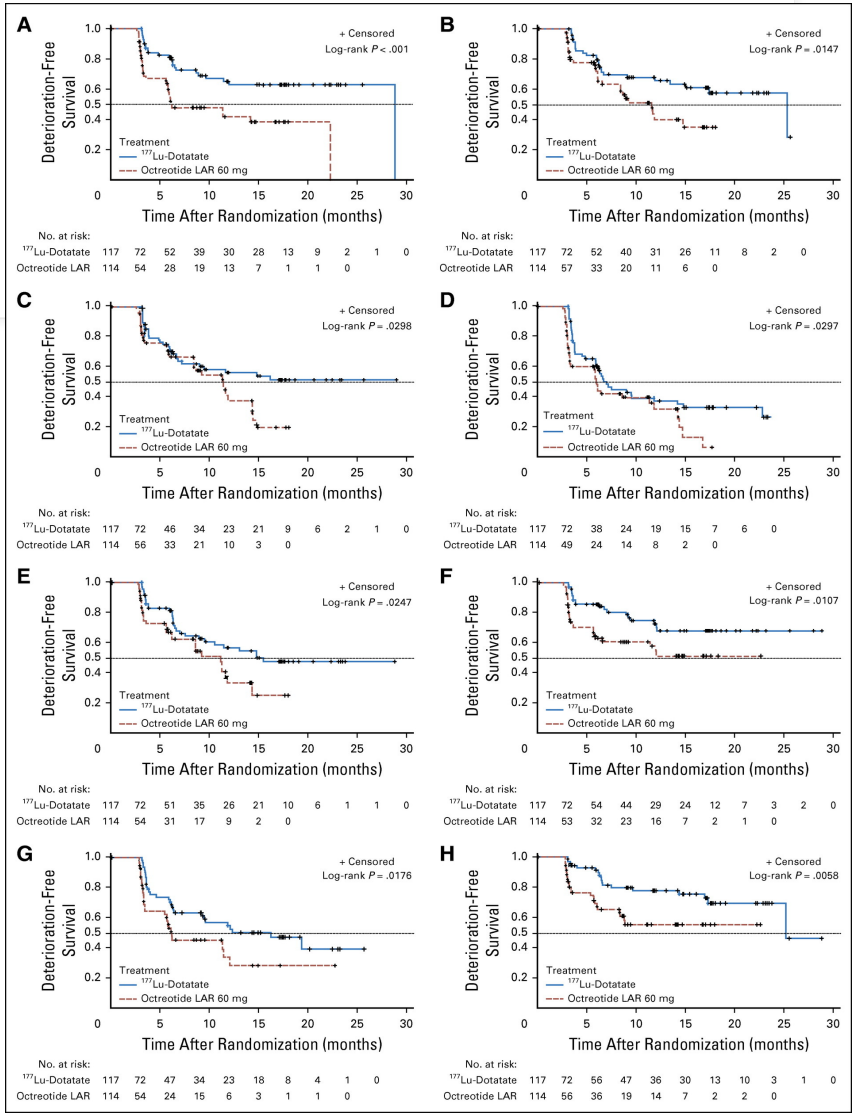
- PFS at month 20 was 65.2% (95% confidence interval [CI], 50.0 to 76.8) in the ^{177}Lu-Dotatate group and 10.8% (95% CI, 3.5 to 23.0) in the control group.
- The response rate was 18% in the ^{177}Lu-Dotatate group versus 3% in the control group (P<0.001).
- Minimal G3 toxicities.

Strosberg *et al*. NEJM. 2017

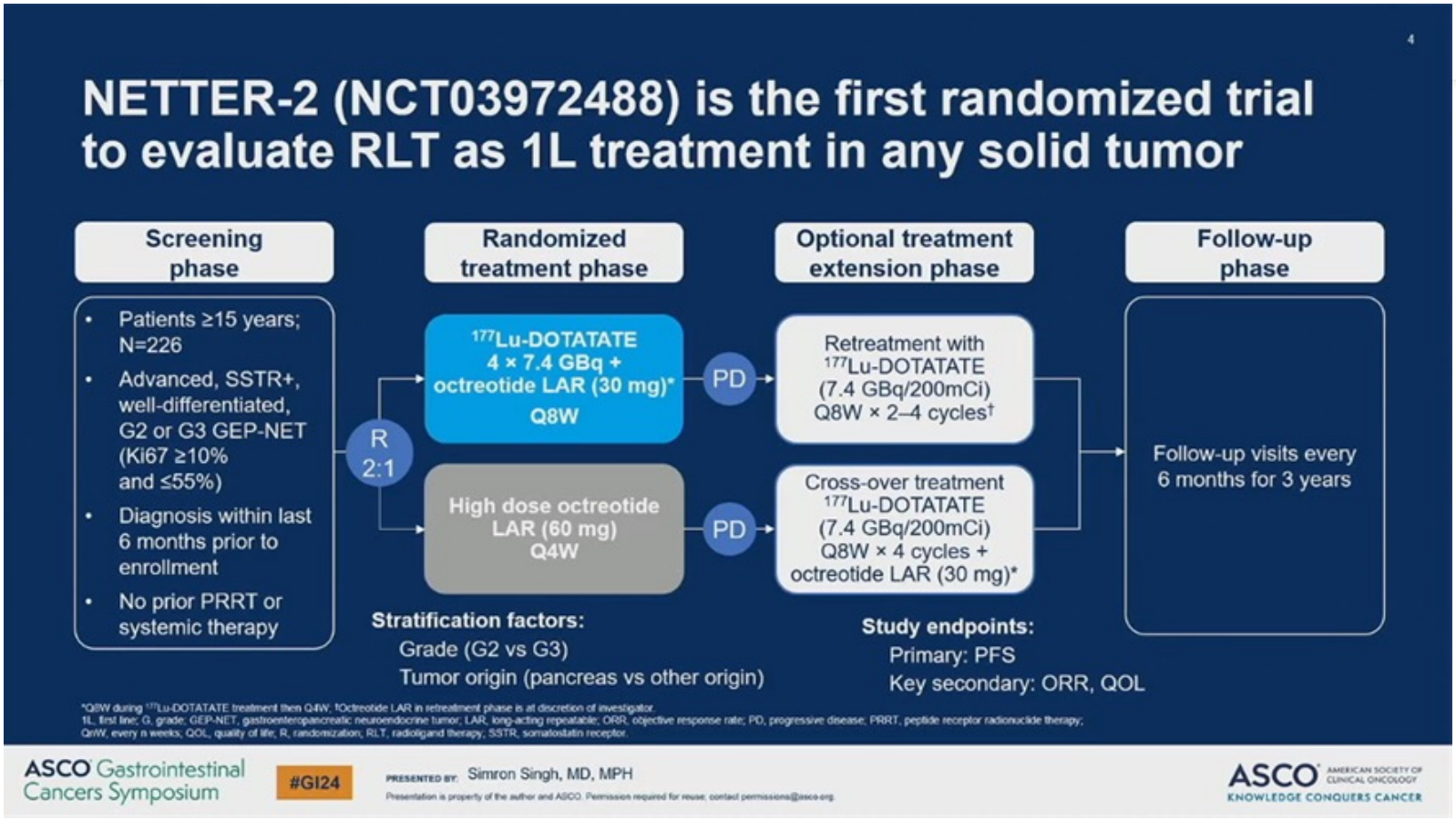
NETTER-1 QoL/PROs

Kaplan-Meier plots showing European Organisation for Research and Treatment of Cancer quality of life questionnaire domains with significantly improved time to deterioration in the ^{177}Lu-Dotatate arm compared with the octreotide arm.

(A) Global health status;
(B) physical functioning;
(C) role functioning;
(D) fatigue;
(E) pain;
(F) diarrhea;
(G) disease-related worries;
(H) body image.



NETTER-2


4
NETTER-2 (NCT03972488) is the first randomized trial to evaluate RLT as 1L treatment in any solid tumor
Screening phase
Randomized treatment phase
Optional treatment extension phase
Follow-up phase
• Patients ≥15 years; N=226
• Advanced, SSTR+, well-differentiated, G2 or G3 GEP-NET (Ki67 ≥10% and ≤55%)
• Diagnosis within last 6 months prior to enrollment
• No prior PRRT or systemic therapy
R 2:1
177Lu-DOTATATE 4 × 7.4 GBq + octreotide LAR (30 mg)* Q8W
High dose octreotide LAR (60 mg) Q4W
PD
PD
Retreatment with 177Lu-DOTATATE (7.4 GBq/200mCi) Q8W × 2–4 cycles†
Cross-over treatment 177Lu-DOTATATE (7.4 GBq/200mCi) Q8W × 4 cycles + octreotide LAR (30 mg)*
Follow-up visits every 6 months for 3 years
Stratification factors:
Grade (G2 vs G3)
Tumor origin (pancreas vs other origin)
Study endpoints:
Primary: PFS
Key secondary: ORR, QOL
*Q8W during 177Lu-DOTATATE treatment then Q4W; †Octreotide LAR in retreatment phase is at discretion of investigator.
1L, first line; G, grade; GEP-NET, gastroenteropancreatic neuroendocrine tumor; LAR, long-acting repeatable; ORR, objective response rate; PD, progressive disease; PRRT, peptide receptor radionuclide therapy; QnW, every n weeks; QOL, quality of life; R, randomization; RLT, radioligand therapy; SSTR, somatostatin receptor.
ASCO Gastrointestinal Cancers Symposium
#GI24
PRESENTED BY: Simron Singh, MD, MPH
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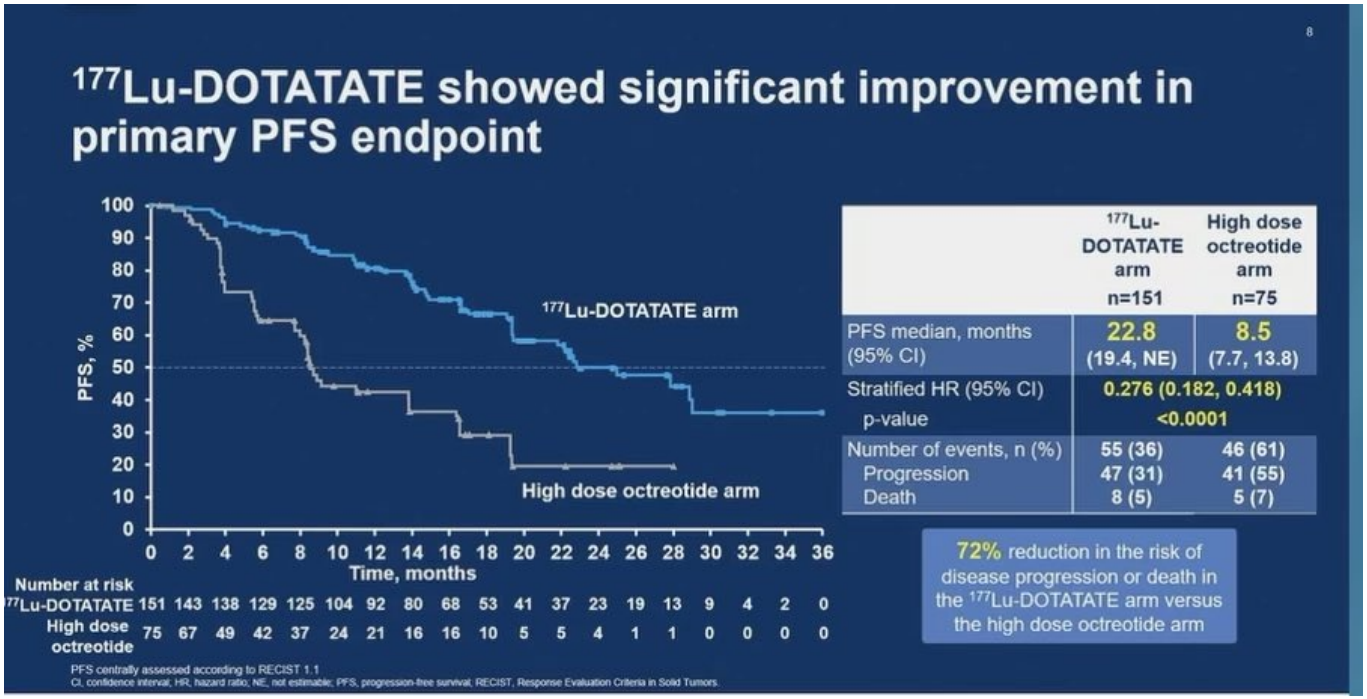
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

Primary endpoint met!!



Prospective data for high G2 and G3 NETs.

Should PRRT be considered for everyone upfront?

Is HD SSA the optimal control arm here?

Toxicity with sequencing of PRRT and chemo?

Alpha RLT: The New Kid On the Block

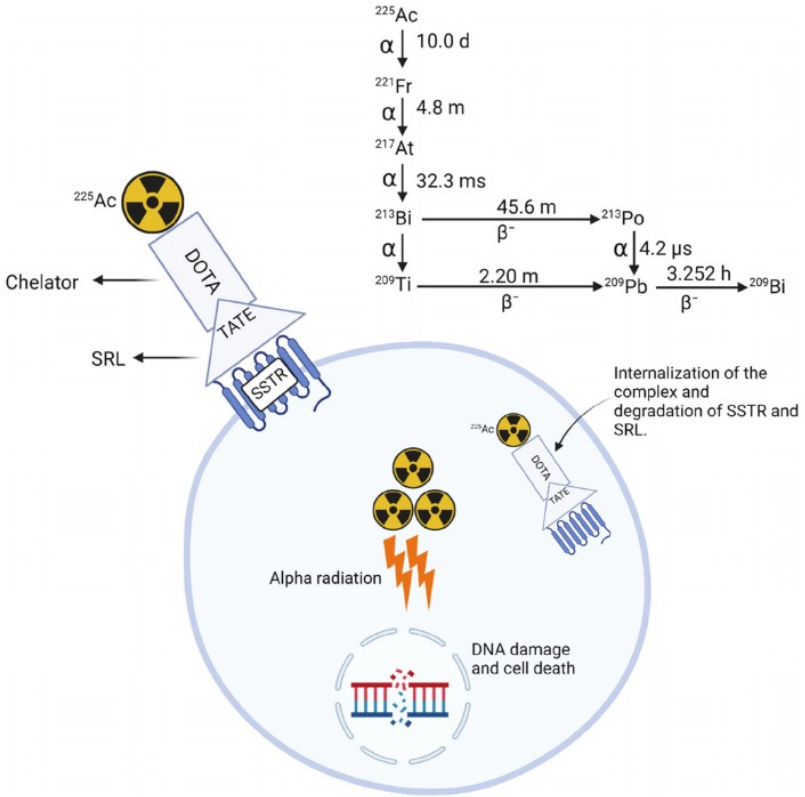


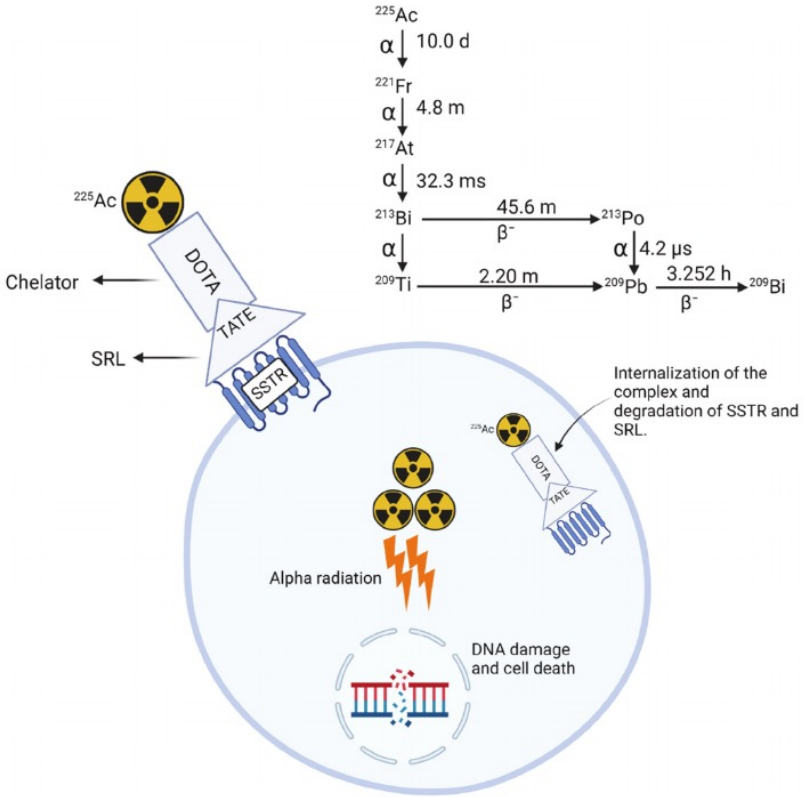
Table 1. Key differences between alpha and beta particle radiation [reference = 30352433].

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].

Grewal et al. Future Oncol. 2025

Alpha RLT: The New Kid On the Block



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[Abbreviations: DNA: deoxyribonucleic acid].

Alpha RLT

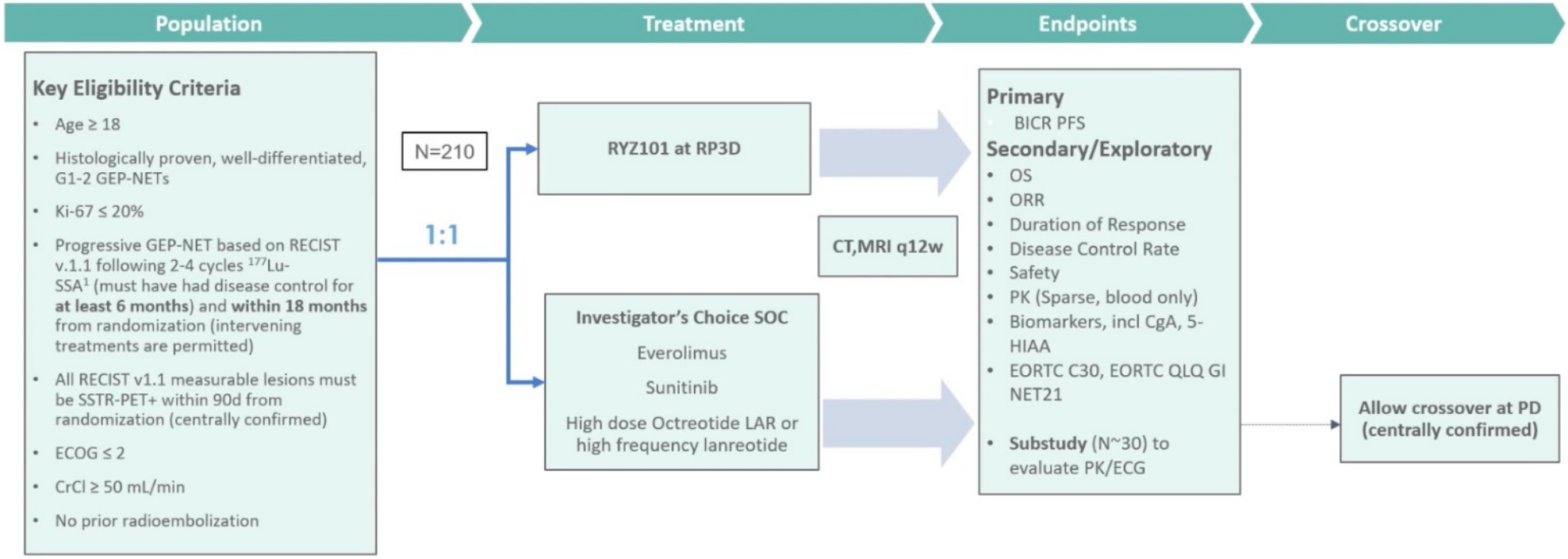
Stronger?

Safer?

More effective

Grewal et al. Future Oncol. 2025

ACTION-1: A New SOC in the making?



Other alpha agents in the pipeline

Pb212-DOTAMTATE

Pb212-VMT-α-NET

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.].

Grewal *et al*. *Future Oncol*. 2025

Outstanding questions

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Where does alpha RLT fit in the paradigm?

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What is the safety of RLT in naïve and pre-treated disease?

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Is one alpha product better than the others?

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Do we have effective strategies to personalize choice between beta and alpha RLT?

Outstanding questions

Where does alpha RLT fit in the paradigm?

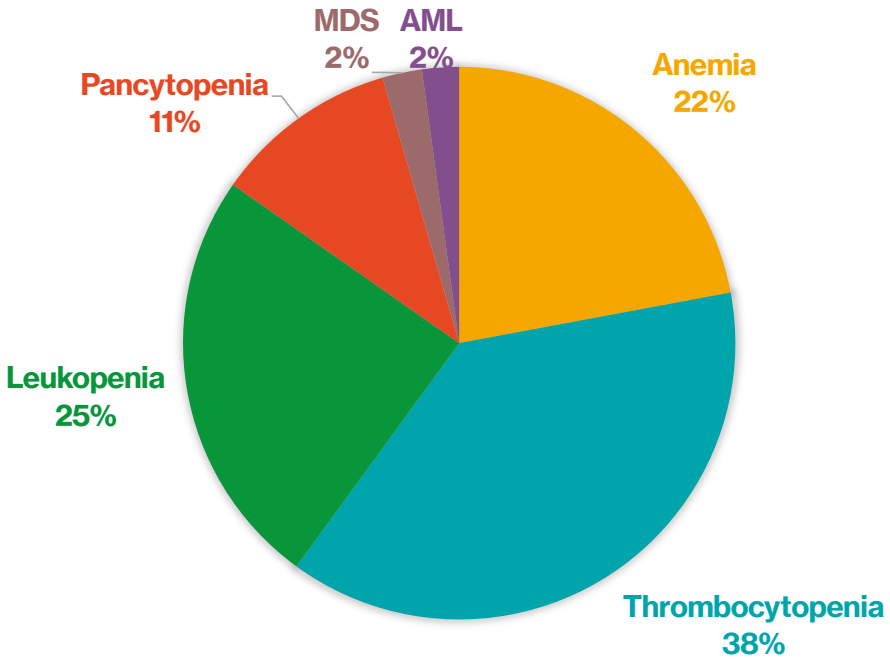
What is the safety of RLT in naïve and pre-treated disease?

Is one alpha product better than the others?

Do we have effective strategies to personalize choice between beta and alpha RLT?

Is alpha RLT really more effective and safer than beta RLT?

Long-term Bone Marrow Toxicity



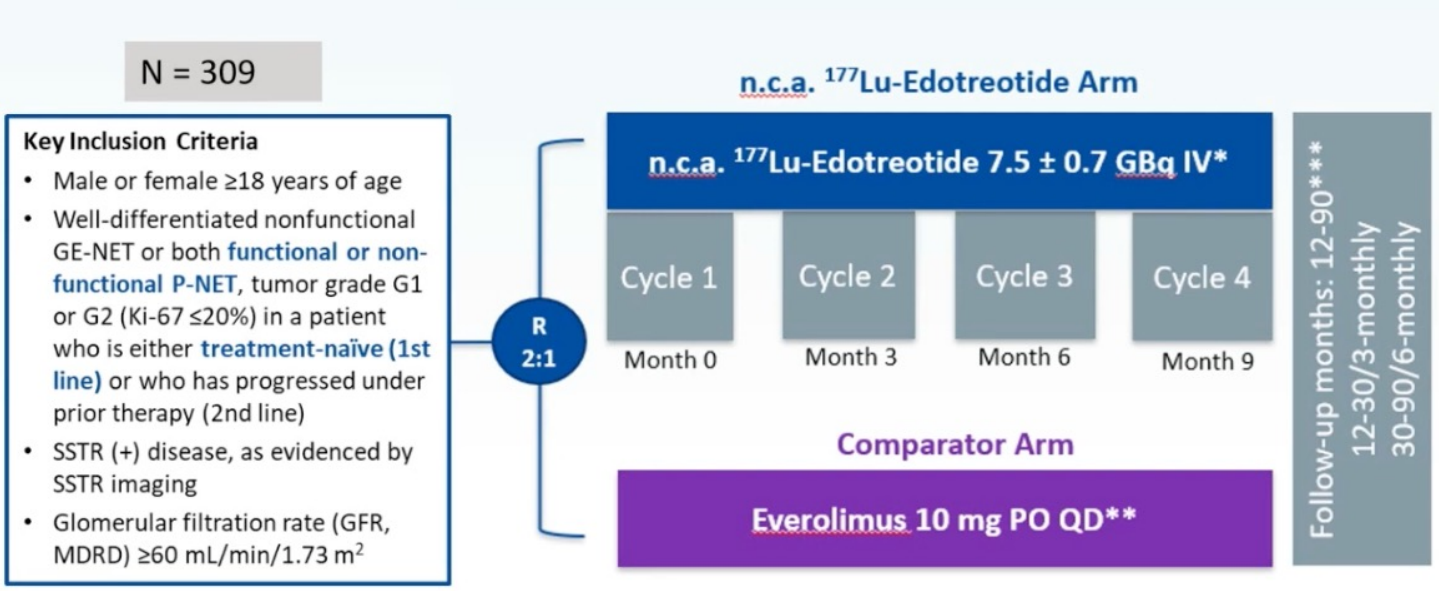
	ROR (CI)			
	Lutathera	Doxorubicin	Topotecan	Etoposide
Thrombocytop.	11.4(10.1-13.1)	8.3(8.9-8.6)	17.6(15.5-20.1)	12.6(12.1-13.1)
Anemia	4.9(4.2-5.8)	6.1(5.8-6.3)	11.3(9.8-13.1)	7.2(6.8-7.5)
Leukopenia	4.4(3.8-5.2)	10.3(9.9-10.6)	15.4(13.7--17.3)	8.3(8.1-8.7)
Pancytopenia	5.2(4.1-6.6)	15.6(15.1-16.3)	23.6(20.3-27.3)	11.4(10.8-12.1)
MDS	11.8(7.1-19.6)	49.2(45.6-53.2)	38.3(26.9-54.4)	54.5(49.9-59.5)
AML	4.8(2.8-8.1)	25.6(24.01-27.4)	24.7(18.5-33.1)	26.8(24.8-29.1)
MDS/AML	6.5(4.4-9.5)	33.1(31.4-34.7)	29.3(23.4-36.7)	35.6(33.6-37.8)

Grewal *et al. Endocrine.* 2024

Sequencing

COMPETE trial

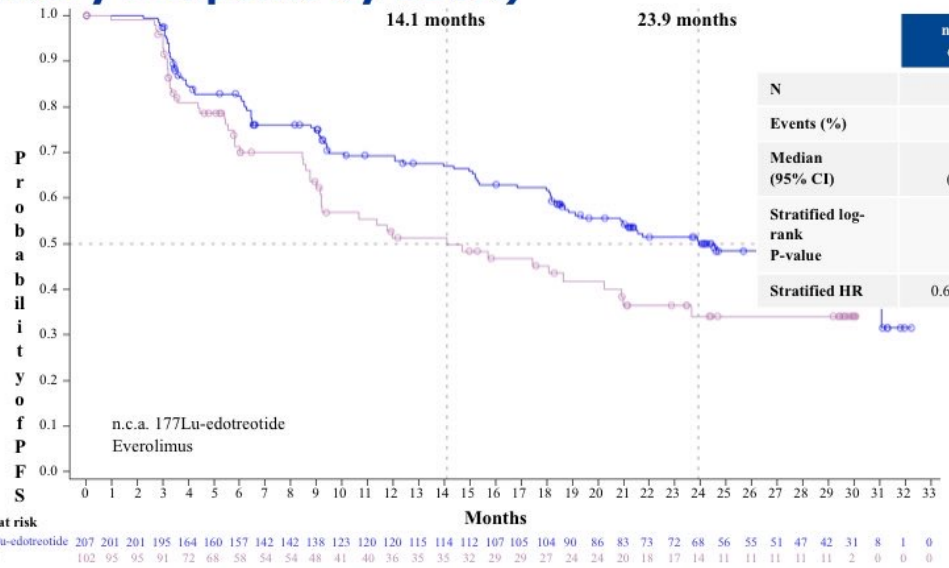
A Prospective, Randomised, Controlled, Open-label, Multicentre Phase III Study to Evaluate Efficacy and Safety of Peptide Receptor Radionuclide Therapy (PRRT) With 177Lu-Edotreotide Compared to Targeted Molecular Therapy



Primary outcome: PFS.
Dosimetry modulated trial.
PRRT frequency q3 months.
Completed recruitment.
Results awaited.

Results- ENETS 2025

PFS (primary endpoint by BICR)



	n.c.a. 177Lu-edotreotide	Everolimus
N	207	102
Events (%)	101 (48.8)	51 (50.0)
Median (95% CI)	23.9 (18.7, 30.0)	14.1 (9.2, 20.9)
Stratified log-rank P-value	0.022	
Stratified HR	0.67 (0.48, 0.95)	

Median PFS was significantly longer with n.c.a. 177Lu-edotreotide vs everolimus (**23.9 vs 14.1 months**; p=0.022; HR 0.67, 95% CI [0.48, 0.95])

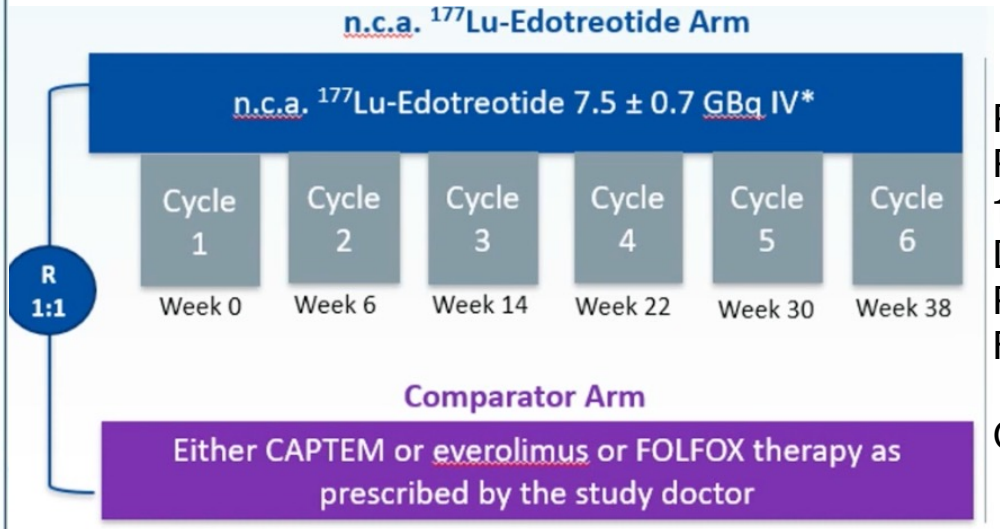
BICR, Blinded Independent Central Review; CI, confidence interval; HR, hazard ratio; n.c.a., non-carrier-added; PFS, progression-free survival

COMPOSE trial

A Prospective, Randomised, Controlled, Open-label, Multicentre Study to Evaluate Efficacy, Safety and Patient-Reported Outcomes of Peptide Receptor Radionuclide Therapy (PRRT) With 177Lu-Edotreotide Compared to Best Standard of Care

Key Inclusion Criteria

- ≥18 years of age
- Well-differentiated **GE-NETs or Pan-NETs with a Ki-67 15-55%**
- SSTR+ disease, as evidenced by ^{68}Ga-based or ^{64}Cu-based SSTR PET within 2 months prior to randomization and as close as possible to the FDG PET
- All patients need to undergo **a FDG PET scan** within 2 months prior to randomization
- Patients may be **treatment naïve** (first-line) or have a maximum of one prior line of therapy, including SSAs (for tumor control vs symptomatic*), (second-line)

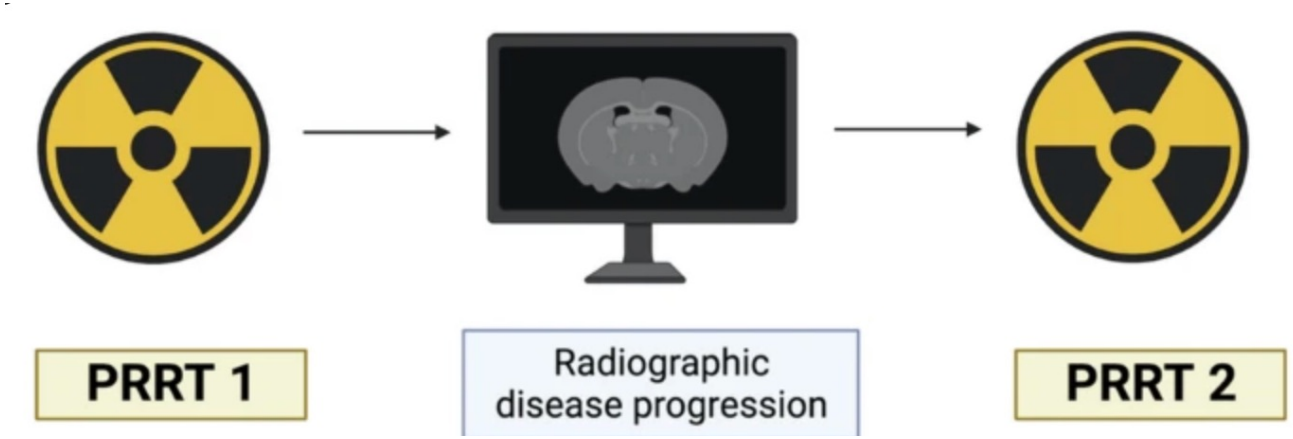


Phase III enrolment ongoing.
Primary outcome: PFS
1ST and 2nd line
Dosimetry
Physician choice
Full genomic analysis

Cycle 2 at week 6.

Repeat PRRT in NETs

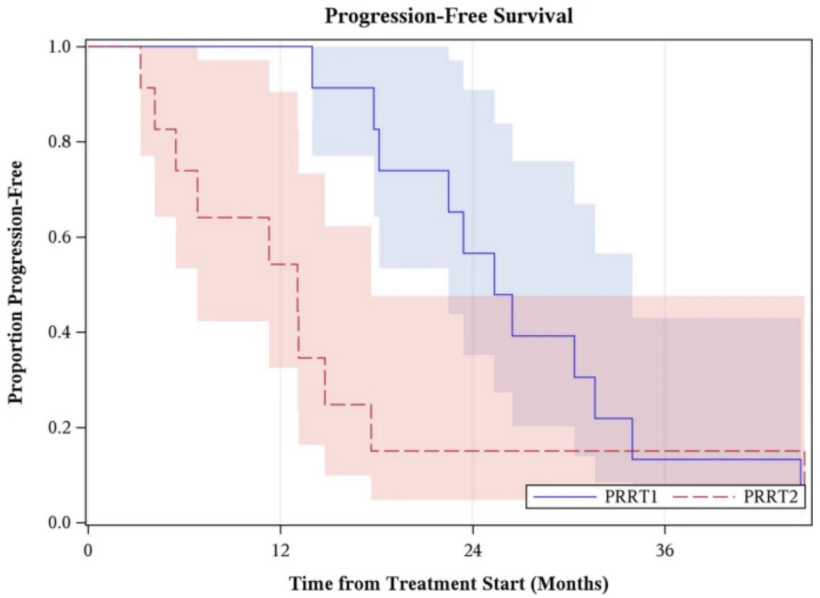
- Limited data (retrospective) from studies from Europe and Asia: repeat PRRT is safe and effective.
- NANETS consensus statement: Reasonable to consider if disease responds well to one complete course of ^{177}Lu-DOTATATE.



Repeat PRRT in NETs

50% effective.
No new safety signals

Covariate	Level	Statistics	Treatment Cycle PRRT1 N=11	Treatment Cycle PRRT2 N=10	P-value
Anemia	No	N (Col %)	6 (54.6%)	3 (30%)	0.39
	Yes	N (Col %)	5 (45.5%)	7 (70%)	
Thrombocytopenia	No	N (Col %)	9 (81.8%)	7 (70%)	0.64
	Yes	N (Col %)	2 (18.2%)	3 (30%)	
Renal Toxicity	No	N (Col %)	6 (54.6%)	7 (70%)	0.66
	Yes	N (Col %)	5 (45.5%)	3 (30%)	



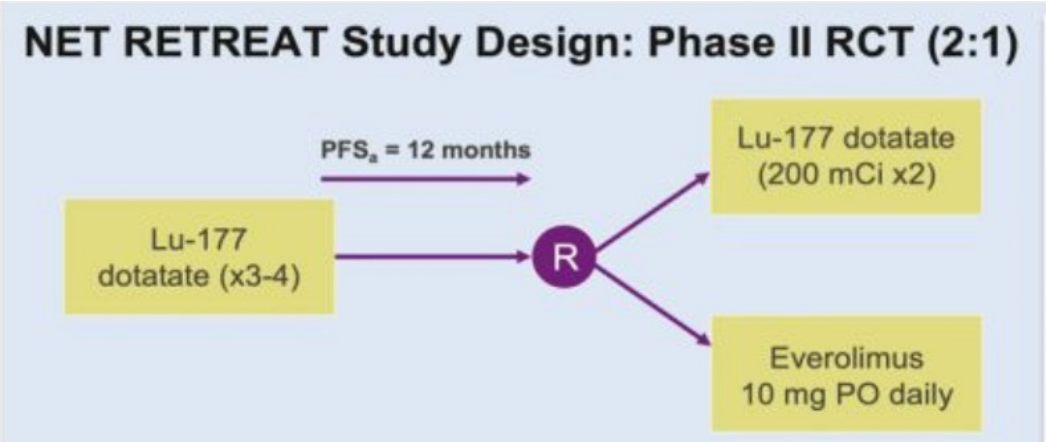
Estimated survival curves for progression-free survival (PFS). Median PFS after PRRT1 was 25.4 months and median PFS after PRRT2 was 13.1 months

Grewal *et al*. *J Gastrointestinal Cancer*. 2024

NET RETREAT Trial

A Phase II trial of Lu-177 DOTATATE retreatment vs everolimus in midgut NET

PI: Dr. Simron Singh, Dr Aman Chauhan



Key Inclusion/Exclusion Criteria:

- Metastatic Progressive midgut NET (Grade 1-2)
- No RECIST progression within 12 month from last dose of prior PRRT (3-4 prior PRRT doses)

Stratification:

- Durable response > vs < 24 mo

Statistics Design:

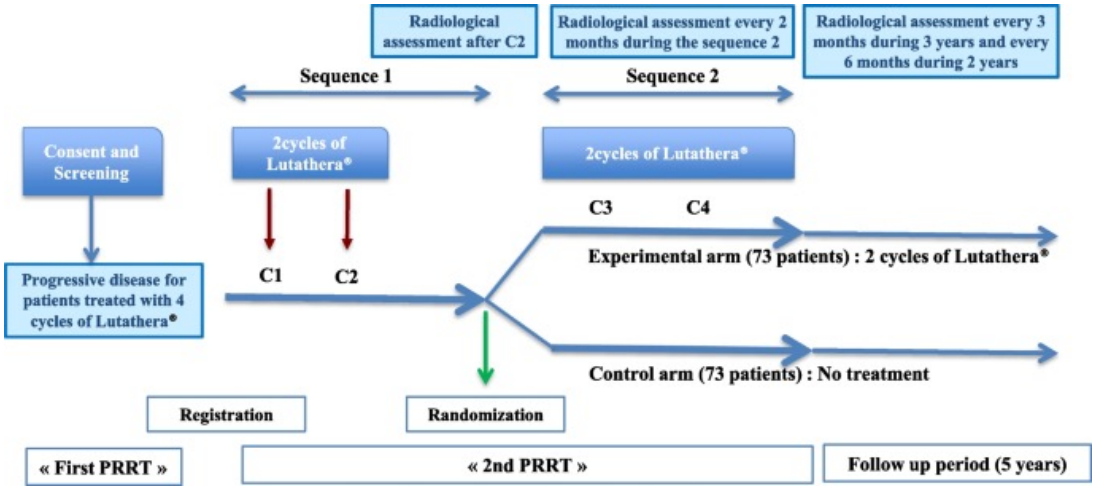
- 100 patients will be randomized in 2 (PRRT):1(Everolimus) to detect an 8 month increase in median PFS, at a one-sided 0.05% alpha and with 90% power

Objectives:

Primary: PFS
Secondary: Safety/Toxicity
Exploratory: NETTEST and hPG80

ReLUTH trial (French study)

PI: Dr Deshayes



Multicenter, randomized, open label phase II study.

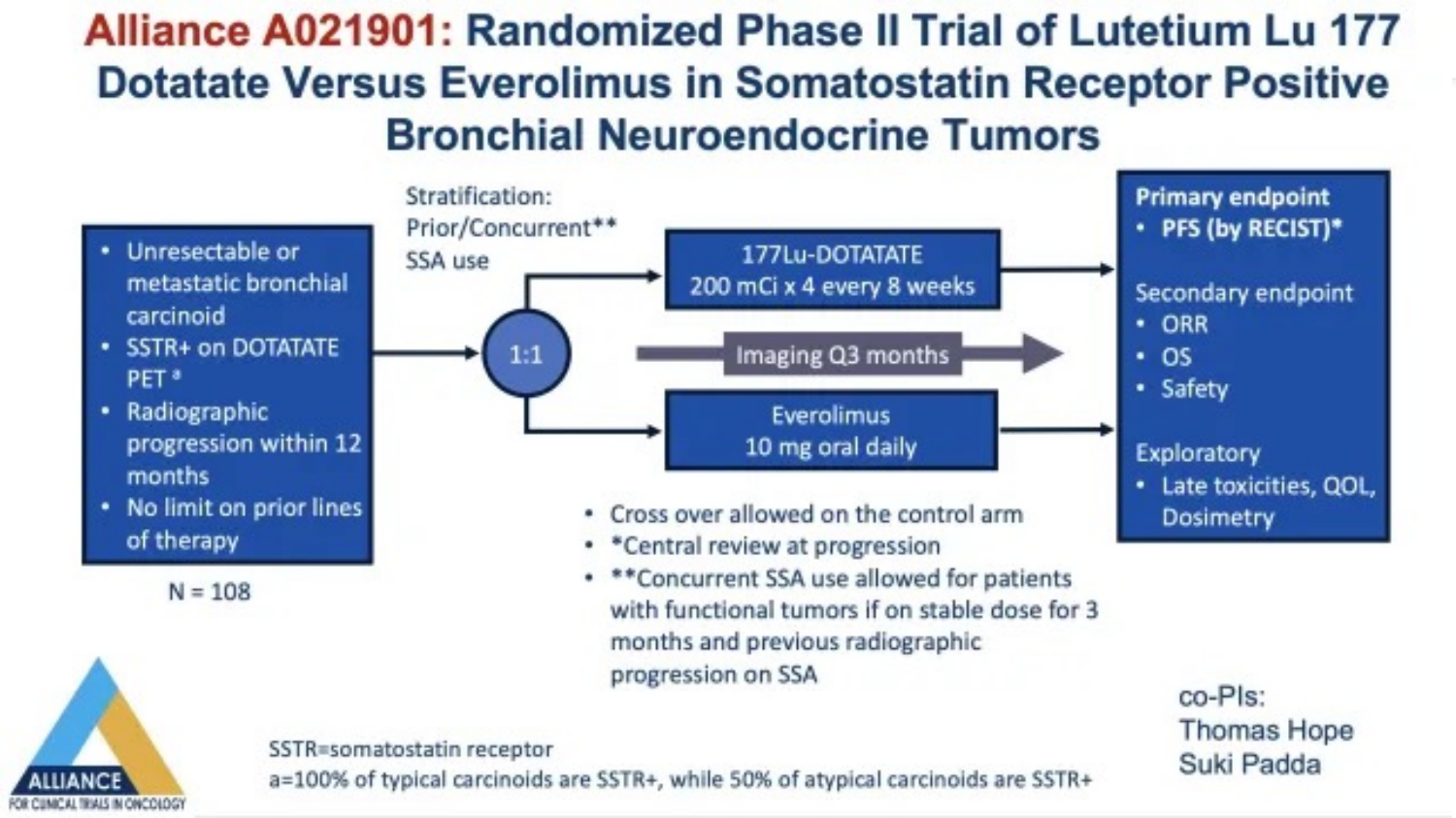
Well differentiated midgut neuroendocrine tumors.

Progressive disease after 4 cycles of Lutathera.

Primary endpoint: DCR at 6 months.

Deshayes *et al*. *BMC Cancer*. 2022

Expanding indications of PRRT



New data for Pheo Para- JCO 2025

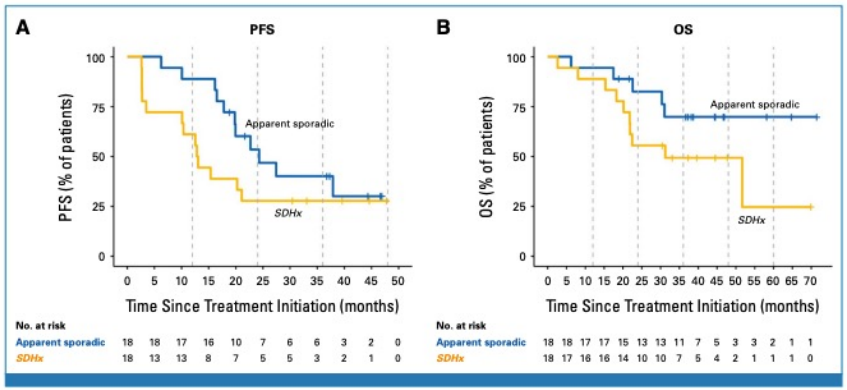
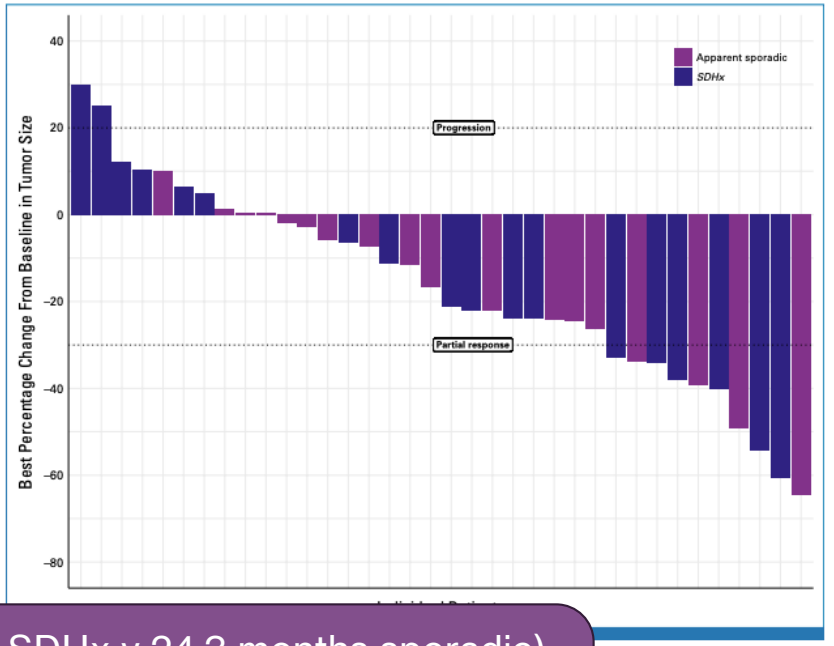


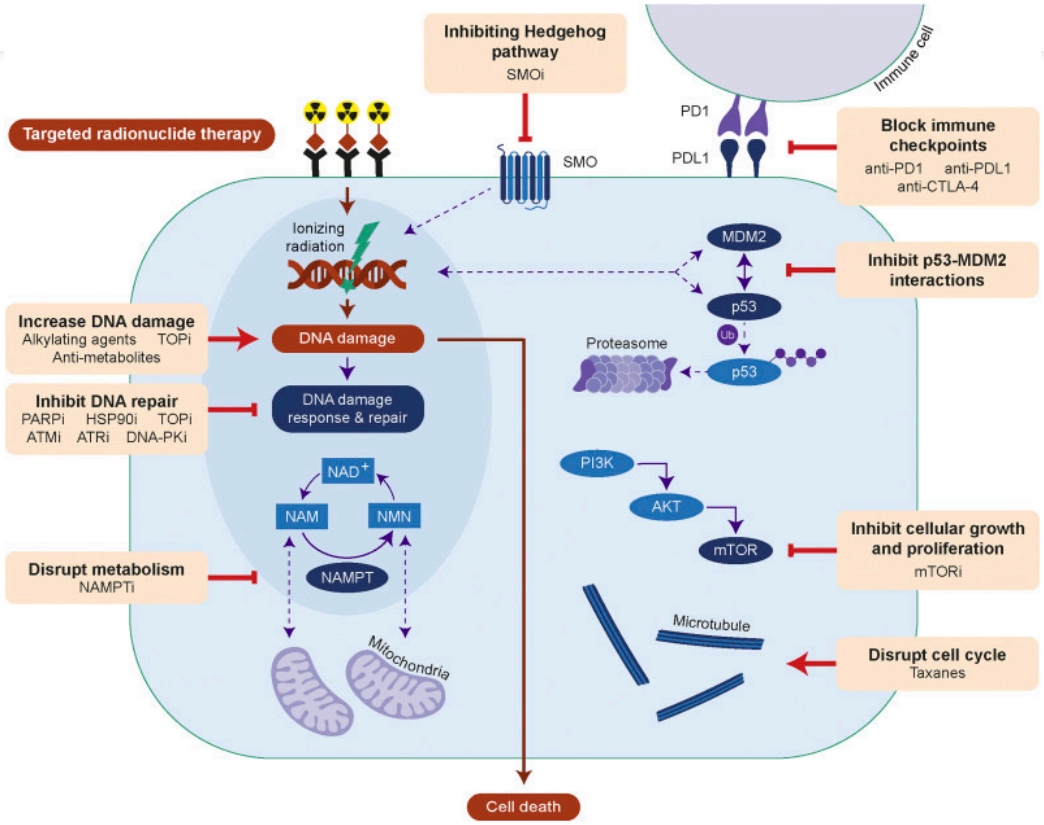
FIG 1. Kaplan-Meier plots of (A) PFS and (B) OS among patients in the apparent sporadic and *SDHx* cohorts. The vertical dashed lines indicate the 12-, 24-, 36-, and 48-month marks. OS, overall survival; PFS, progression-free survival; *SDHx*, succinate dehydrogenase.



to genetic cohort. Two patients had
thers had progression on the basis of

Median PFS was 19.9 months (12.9 months SDHx v 24.3 months sporadic) and median OS was 51.7 months (31.2 months SDHx v not reached in sporadic). Best response was achieved on average 11.0 months after completing 177Lu-DOTATATE.

Combination Therapy with PRRT



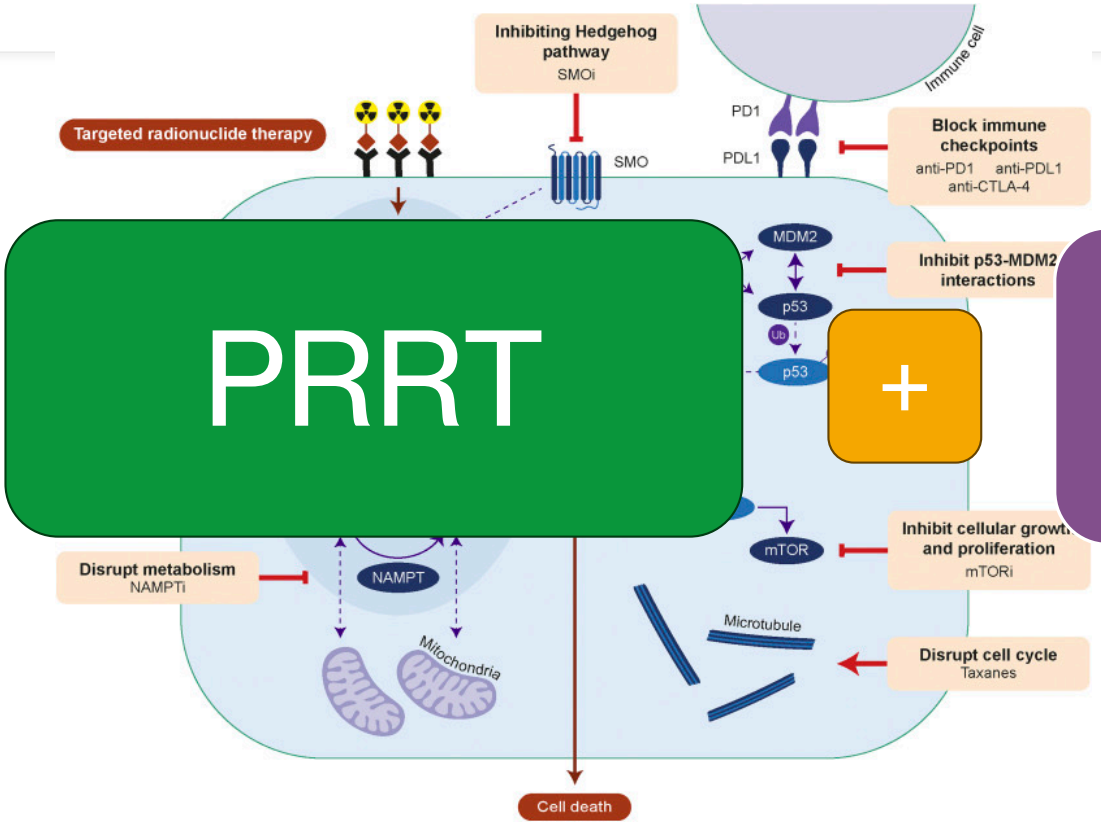
Attempts to amplify the therapeutic efficacy of PRRT by combining it with other agents.

Such strategies include administering concurrent TRT and chemotherapy, and the use of TRT with known or putative radiosensitizers.

Ultimate goal: Amplification of DNA damage and cell death.

Chan *et al. J Nucl Med.* 2020

Combination Therapy with PRRT



Attempts to amplify the therapeutic efficacy of PRRT by combining it with other putative radiosensitizers.

Ultimate goal: Amplification of DNA damage and cell death.

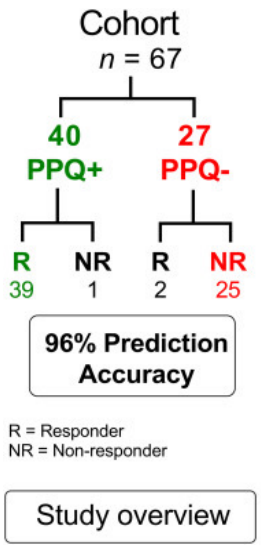
Chan *et al. J Nucl Med.* 2020

Ongoing studies

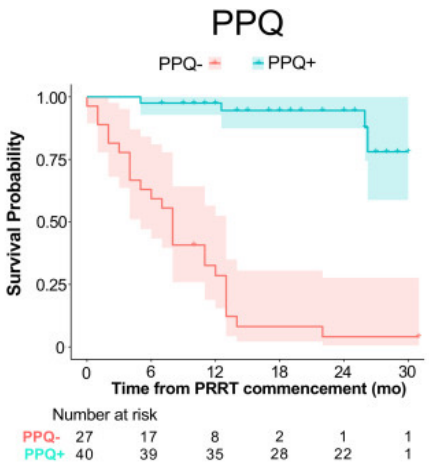
Testing the Effectiveness of an Anti-cancer Drug, **Triapine (RNRi),** When Used with Targeted Radiation-based Treatment (Lu-177 Dotatate), Compared to Lu-177 Dotatate Alone for Metastatic Neuroendocrine Tumors	**Phase I/II**	NCT05724108
Lu-177 Dotatate in Combination With **Olaparib (PARPi)** in Inoperable Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET)	Phase I/II	NCT04086485 NCI
Testing the Addition of An Anti-cancer Drug, **M3814 (Peposertib, DNA PKi),** to the Usual Radiation-Based Treatment (Lu-177 Dotatate) for Pancreatic Neuroendocrine Tumors	Phase I	NCT04750954 Ohio State University
I-131-MIBG and Lu-177 Dotatate for the Treatment of Neuroendocrine Tumors	Phase I/II	NCT04614766 University of Iowa
Pembrolizumab (PD-1 mAb) and Liver-Directed Therapy or Lu-177 Dotatate in Treating Patients with Well-Differentiated Neuroendocrine Tumors and Symptomatic and/or Progressive Liver Metastases	Phase II	NCT03457948 UCSF
Testing the Addition of **Sunitinib Malate (VEGFR TKI)** to Lutetium Lu 177 Dotatate in Pancreatic Neuroendocrine Tumors	Phase I	NCT05687123

Iravani. LACNETS. 2023

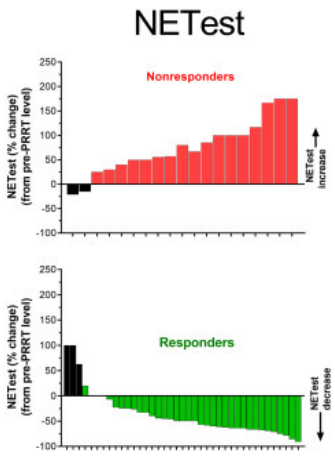
PPQ and NETest



Study overview



Predicts response



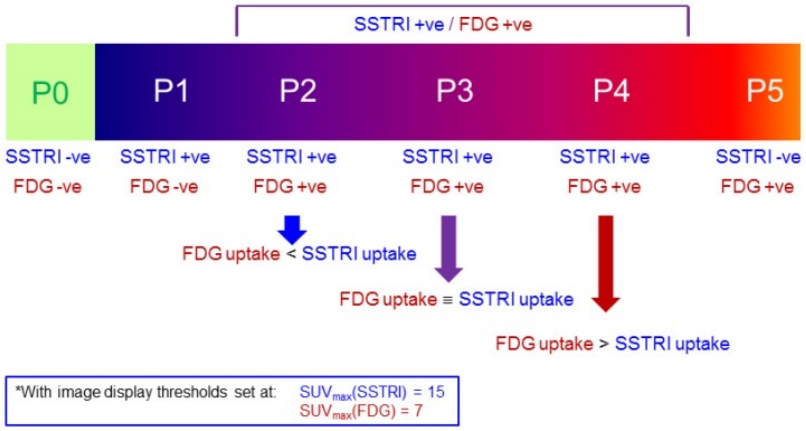
Monitors response

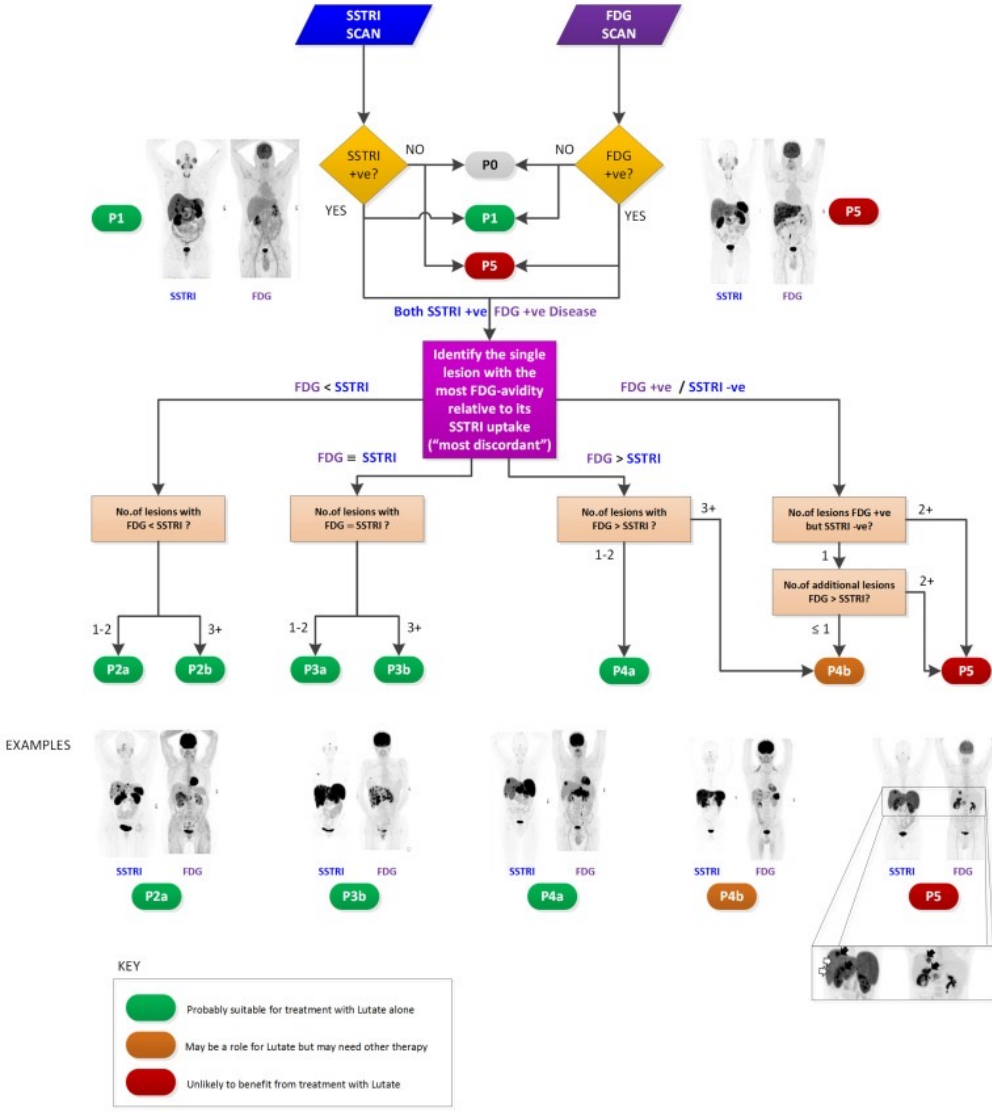
PPQ: blood-based assay comprises expression of 8 genes and captures both growth factor and metabolomic expression specifically related to oxidative stress, metabolism, and hypoxic signaling.

NETest: evaluates 51 NET-specific genes. This test functions as a surrogate biomarker, and changes in score, compared with before treatment (e.g., SSAs or surgery), strongly correlated with tumor progression measured with CT or MRI.

Bodei et al. J Nucl Med. 2023.

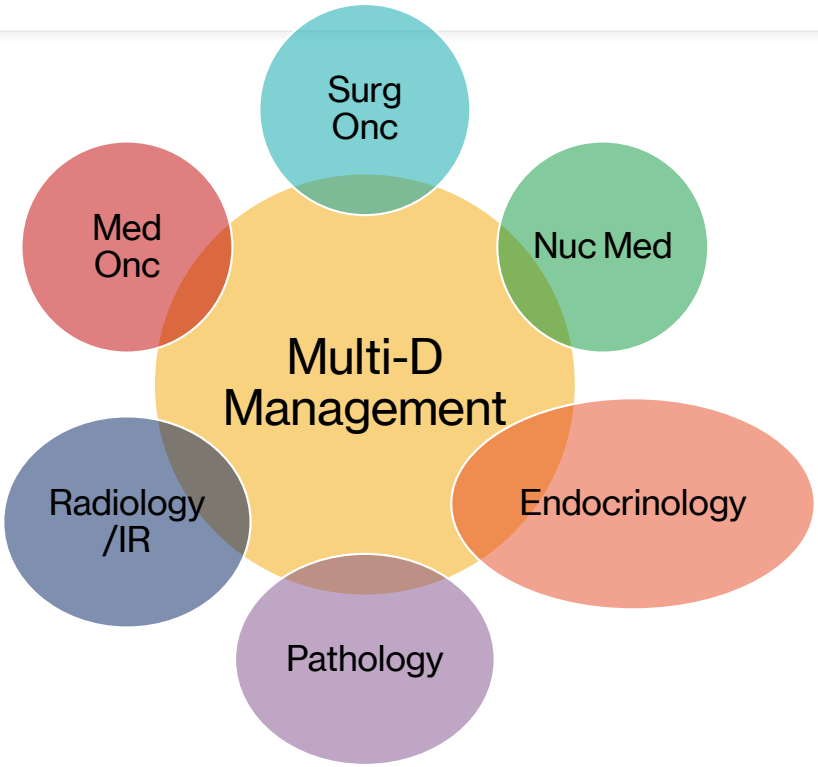
Dual Tracer Imaging





Chan et al. Theranostics. 2017

Multi-disciplinary management




Alpha RLT
Novel RLT
Biomarkers
Combination strategies
Equity
More indications

Acknowledgements