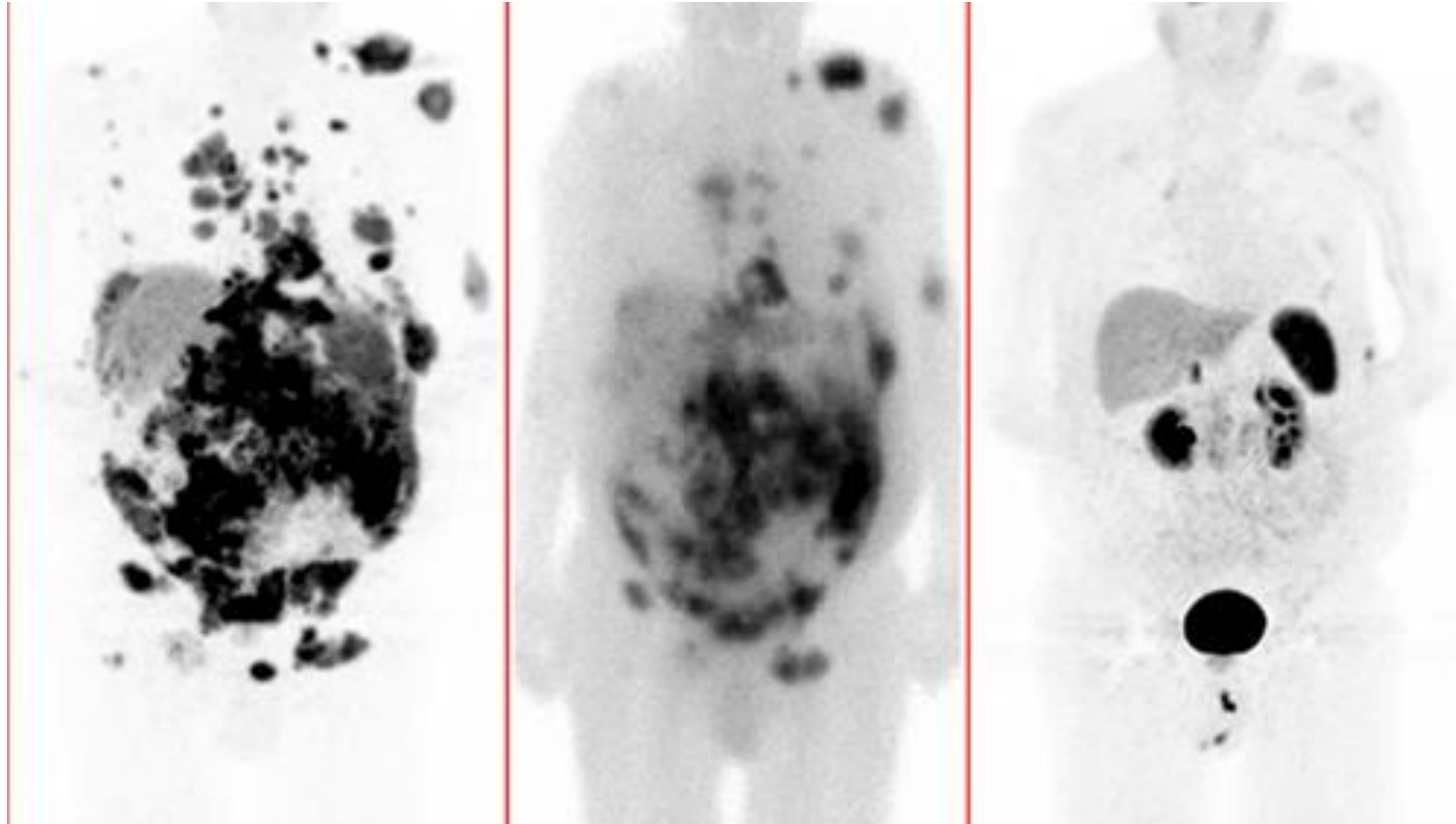# Maximizing the Therapeutic Potential of PRRT for Neuroendocrine Tumors

Udhayvir Singh Grewal, MD

University of Iowa Hospitals and Clinics,

Iowa City, IA

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.
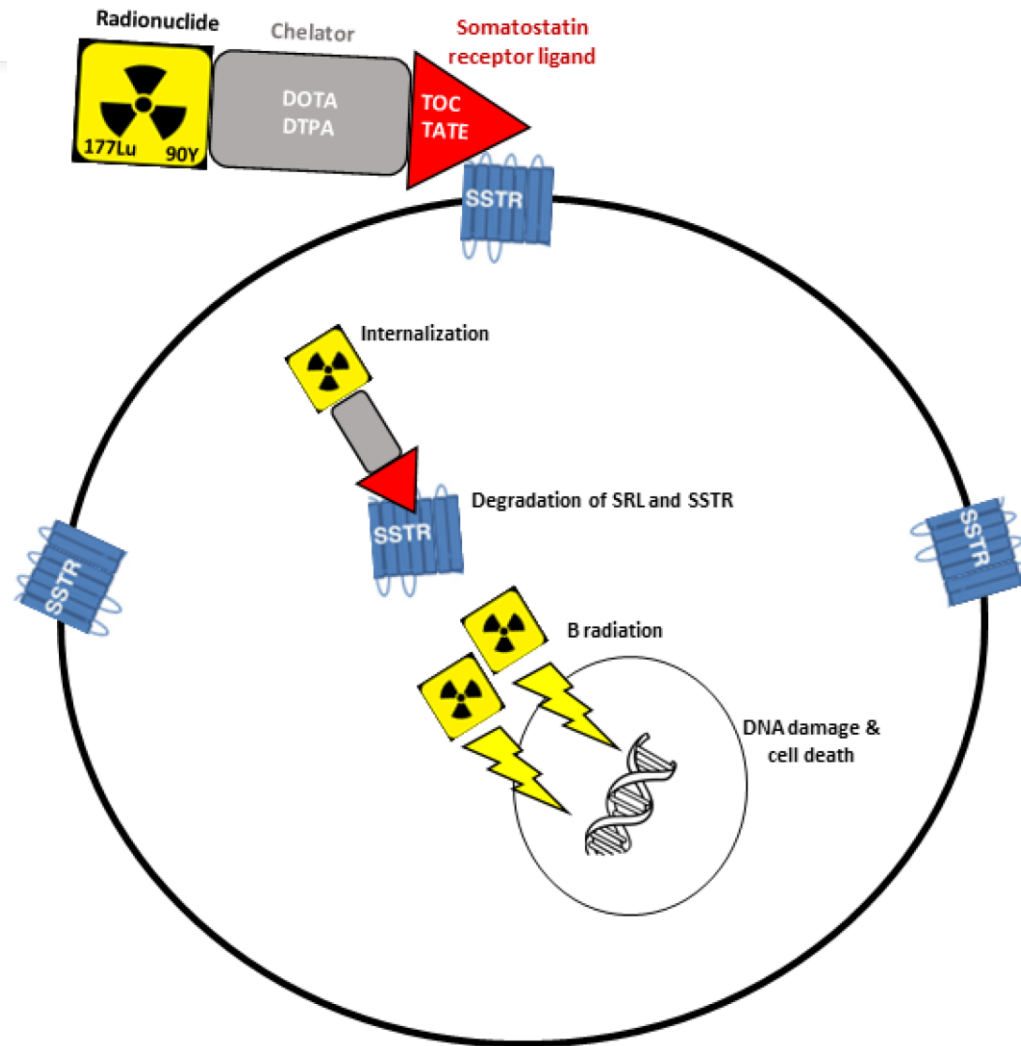
Therapeutic paradigm for NETs

Chauhan *et al.* 2022
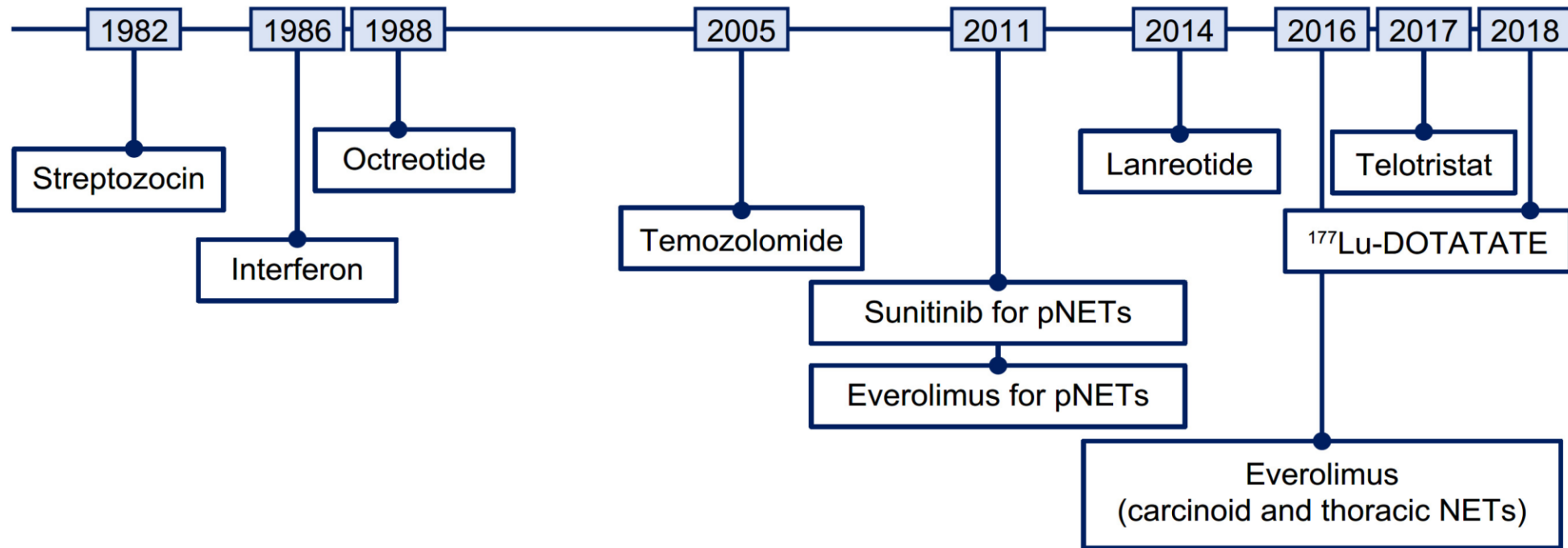
Peptide Receptor Radionuclide Therapy

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.

Peptide Receptor Radionuclide Therapy

Decades of work from development to approval.

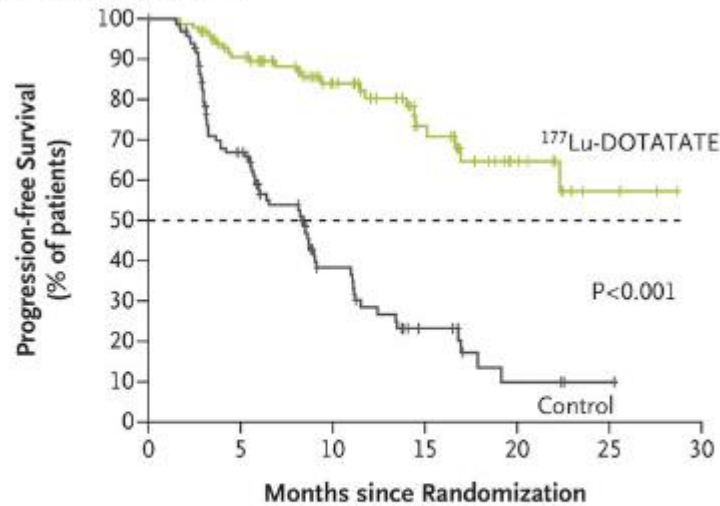Arguably the most significant therapeutic advancement for the management of NETs.

Iravani. LACNETS. 2022

NETTER-1

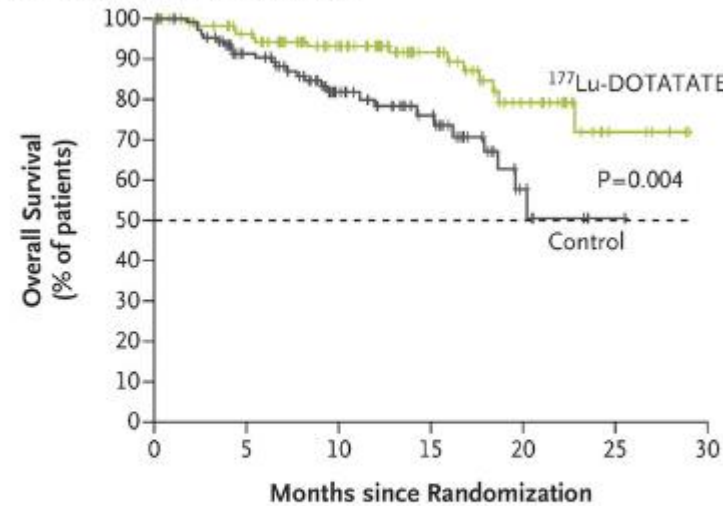Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

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 long-term follow up
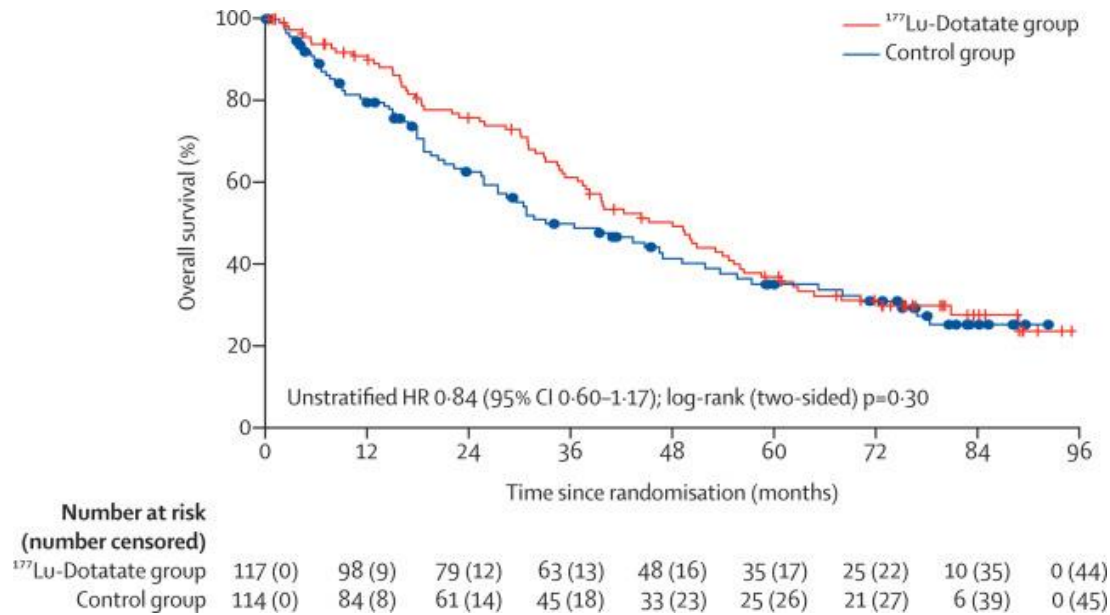
The secondary endpoint of overall survival was **not met**: **median overall survival was 48·0 months** (95% CI 37·4–55·2) in the ^{177}Lu-Dotatate group and **36·3 months** (25·9–51·7) in the control group (HR 0·84 [95% CI 0·60–1·17]; two-sided p=0·30).

Treatment-related serious adverse events of grade 3 or worse were recorded in three (3%) of 111 patients in the ^{177}Lu-Dotatate group.

Two (2%) of 111 patients given ^{177}Lu-Dotatate developed myelodysplastic syndrome.

Strosberg *et al*. Lancet Oncol. 2021

Post-Marketing Surveillance
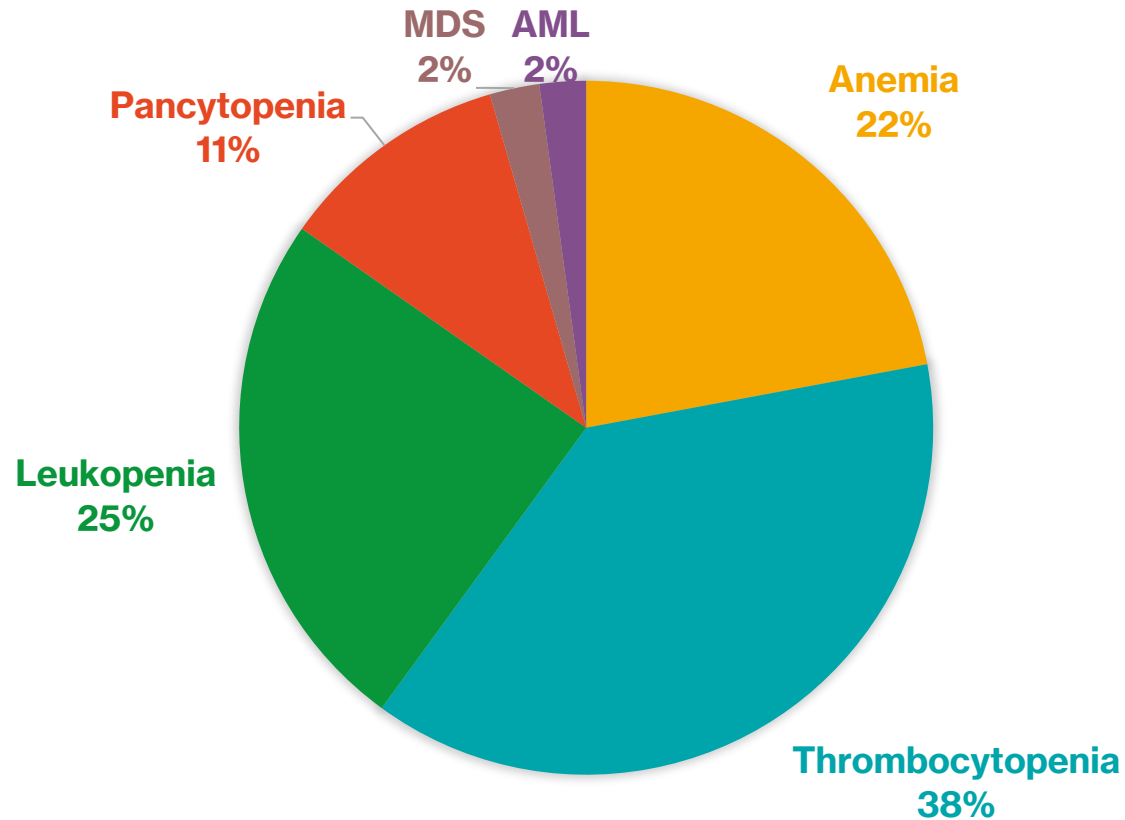
	Lutathera	Doxorubicin	Topotecan	Etoposide
	ROR (CI)			
Thrombocytop.	11.4(10.1-13.1)	8.3(8.9-8.6)	17.6(15.5-20.1)	12.6(12.1-13.1)
Anemia	4.9(4.2-5.8)	6.1(5.8-6.3)	11.3(9.8-13.1)	7.2(6.8-7.5)
Leukopenia	4.4(3.8-5.2)	10.3(9.9-10.6)	15.4(13.7--17.3)	8.3(8.1-8.7)
Pancytopenia	5.2(4.1-6.6)	15.6(15.1-16.3)	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* (unpublished)

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

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?

Sequencing?

NCCN Guidelines Version 1.2023
Neuroendocrine Tumors of the Pancreas
(Well-Differentiated Grade 1/2)

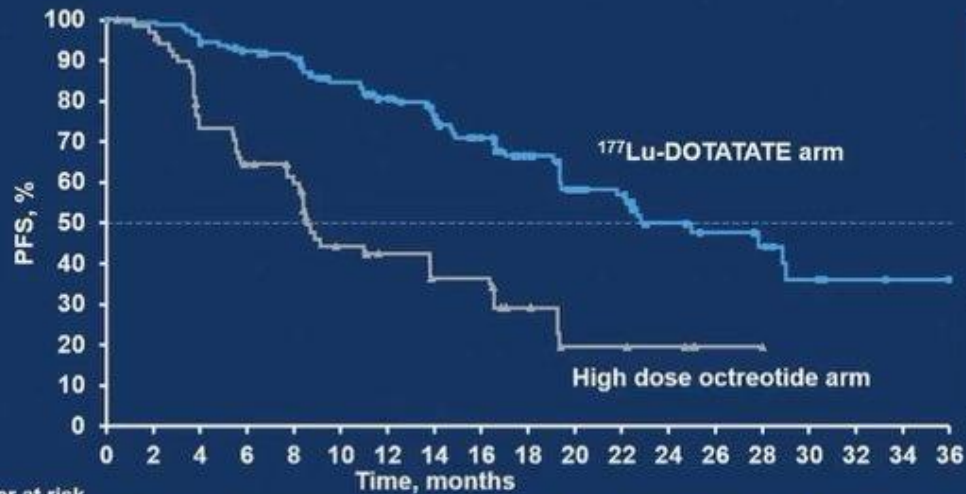**MANAGEMENT OF LOCOREGIONAL ADVANCED DISEASE AND/OR DISTANT METASTASES**

SUBSEQUENT THERAPY

Several options, no clear guidance on sequencing.
Upfront PRRT or after chemo/targeted therapy?

Disease Progression[dd] →

Clinical trial
or
Systemic therapy options[hh]
- **Preferred:**
  - ▸ **Everolimus (category 1 for progressive disease)**
  - ▸ **Sunitinib (category 1 for progressive disease)**
  - ▸ **PRRT with lutetium Lu 177 dotatate (if SSTR-positive and progression on octreotide LAR or lanreotide)[jj]**
  - ▸ **Temozolomide + capecitabine (preferred when tumor response is needed for symptoms or debulking)**
- **Other Recommended Regimens:**
  - ▸ **Consider cytotoxic chemotherapy (in patients with bulky, symptomatic, and/or progressive disease)**
    - ◊ **FOLFOX (leucovorin + 5-FU + oxaliplatin)**
    - ◊ **CAPEOX (capecitabine + oxaliplatin)**
- **Useful in Certain Circumstances:**
  - ▸ **If progression on standard SSA doses, above-label dose octreotide LAR[kk] or lanreotide[kk] (if SSTR-positive)**
  - ▸ **Consider belzutifan in the setting of germline *VHL* alteration in patients with progressive PanNETs[ll,mm]**
or
Locoregional therapy options
- **Consider RT[nn] ± concurrent fluoropyrimidine-based chemotherapy for locally advanced unresectable disease (excluding small bowel mesenteric)**
- **Consider liver-directed therapy for liver-predominant disease[oo,pp]**
- **Palliative RT for oligometastatic disease and/or symptomatic metastases (excluding mesenteric masses)[nn]**

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

N = 309

Key Inclusion Criteria
- Male or female ≥18 years of age
- Well-differentiated nonfunctional GE-NET or both functional or non-functional P-NET, tumor grade G1 or G2 (Ki-67 ≤20%) in a patient who is either treatment-naïve (1st line) or who has progressed under prior therapy (2nd line)
- SSTR (+) disease, as evidenced by SSTR imaging
- Glomerular filtration rate (GFR, MDRD) ≥60 mL/min/1.73 m^2

R 2:1

n.c.a. ^{177}Lu-Edotreotide Arm

n.c.a. ^{177}Lu-Edotreotide 7.5 ± 0.7 GBq IV*

| Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 |
| Month 0 | Month 3 | Month 6 | Month 9 |

Comparator Arm

Everolimus 10 mg PO QD**

Follow-up months: 12-90***
12-30/3-monthly
30-90/6-monthly

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

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)

n.c.a. ^{177}Lu-Edotreotide Arm

n.c.a. ^{177}Lu-Edotreotide 7.5 ± 0.7 GBq IV*

R 1:1	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
	Week 0	Week 6	Week 14	Week 22	Week 30	Week 38

Comparator Arm

Either CAPTEM or everolimus or FOLFOX therapy as prescribed by the study doctor
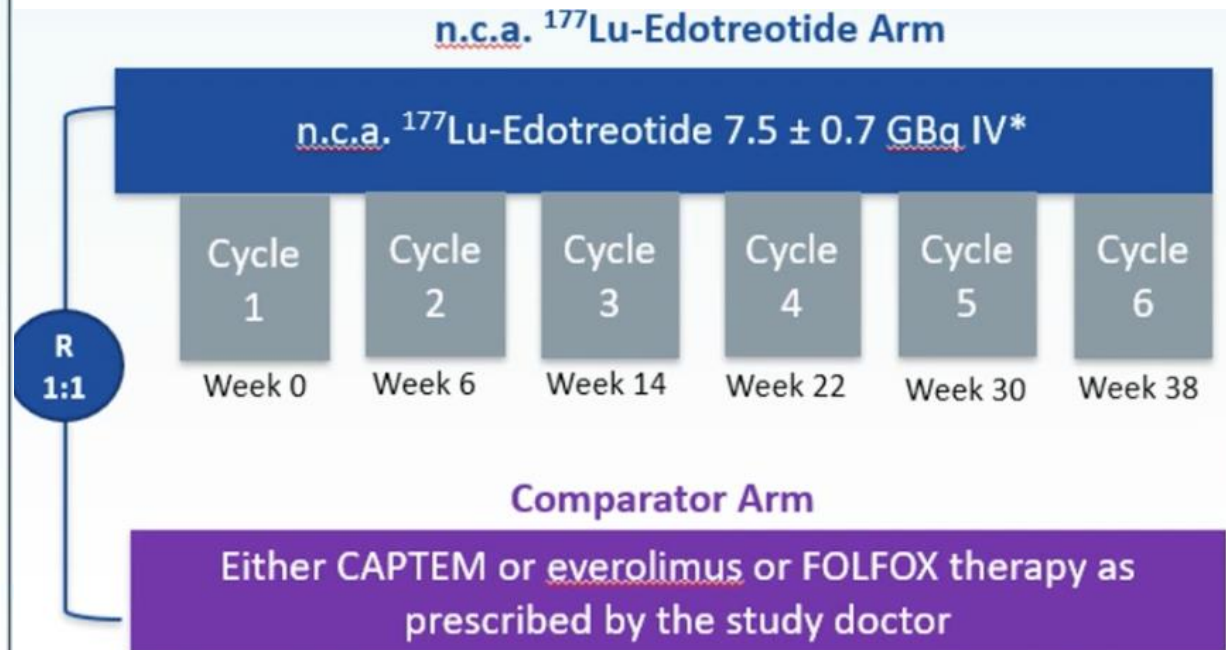
Phase III enrolment ongoing.
Primary outcome: PFS
1ST and 2nd line
Dosimetry
Physician choice
Full genomic analysis

Cycle 2 at week 6.

Repeat PRRT in NETs
University of Iowa NET COE Experience

- Limited data (retrospective) from studies from Europe and Asia: repeat PRRT is safe and effective.

- NANETS consensus statement: Reasonable to consider if patient responds well to one complete course of ^{177}Lu-DOTATATE.
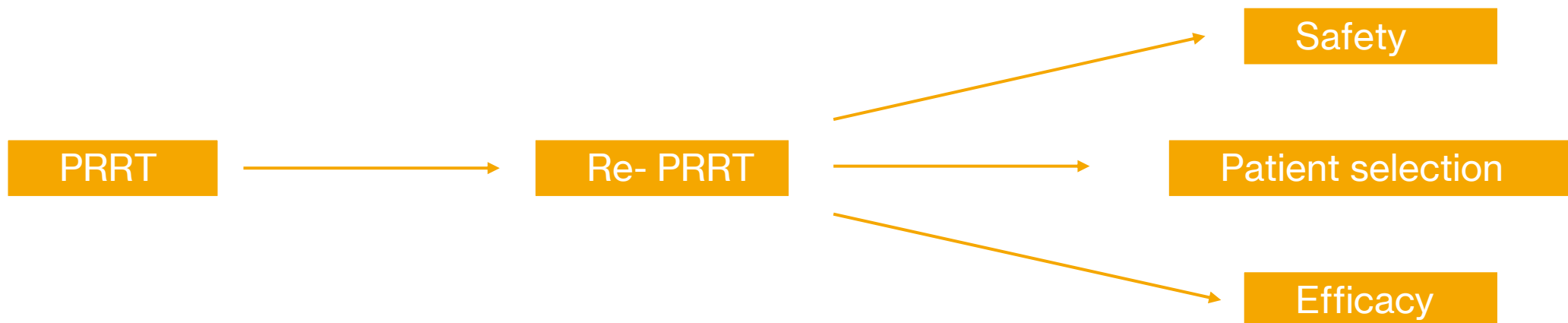
PRRT 1

^{177}Lu DOTOTATE or ^{90}Y DOTATOC

Radiographic
disease progression

PRRT 2

^{177}Lu DOTOTATE

Results

- From June 2018 to July 2023, a total of 153 patients received at least 1 dose of ^{177}Lu DOTATATE PRRT at our institution post FDA approval, out of which, 13/153 (8.5%) patients received repeat PRRT.

- We excluded 2/13 patients due to lack of adequate follow up and included a total of 11 patients for the final analysis.

Variable	Level	N=11
Sex	F	5 (45.5)
	M	6 (54.5)
Race	W	11 (100.0)
Primary Site	Pancreas	6 (54.5)
	Small Bowel	4 (36.4)
	Unclear Origin	1 (9.1)
Functional	Functional	7 (63.6)
	NF	4 (36.4)
Grade	1	2 (18.2)
	2	9 (81.8)
Number of Prior Therapies	1	1 (9.1)
	2	5 (45.5)
	3	1 (9.1)
	4	1 (9.1)
	5	2 (18.2)
	6	1 (9.1)

PRRT1
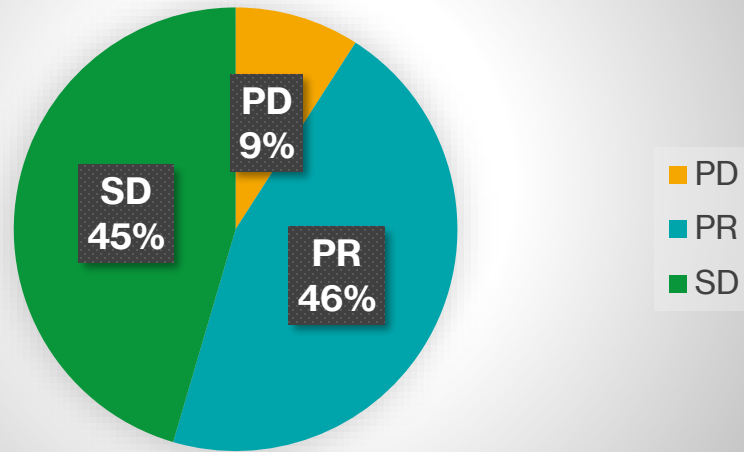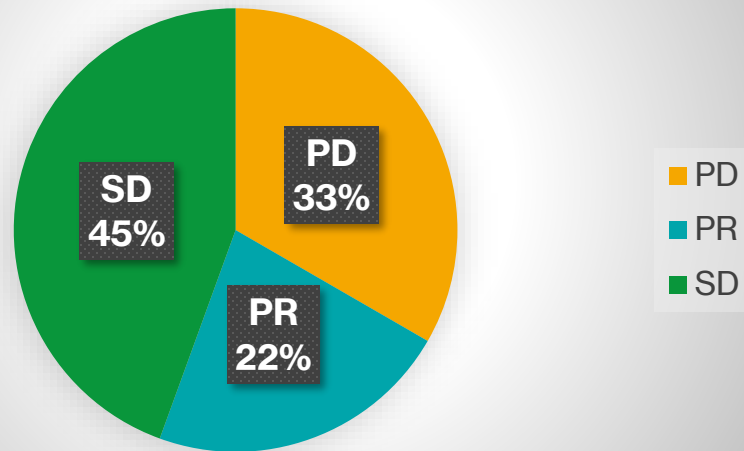
Variable	Level	N = 11
Type (PRRT1)	^{177}Lu	5 (45.5)
	^{90}Y	6 (54.5)
Number of Cycles (PRRT1)	1	1 (9.1)
	2	1 (9.1)
	3	6 (54.5)
	4	3 (27.3)
Number of Therapies between PRRT1 and PRRT2	1	6 (54.5)
	2	5 (45.5)
Number of Cycles (PRRT2)	1	3 (27.3)
	2	2 (18.2)
	3	3 (27.3)
	4	3 (27.3)

Progression free survival
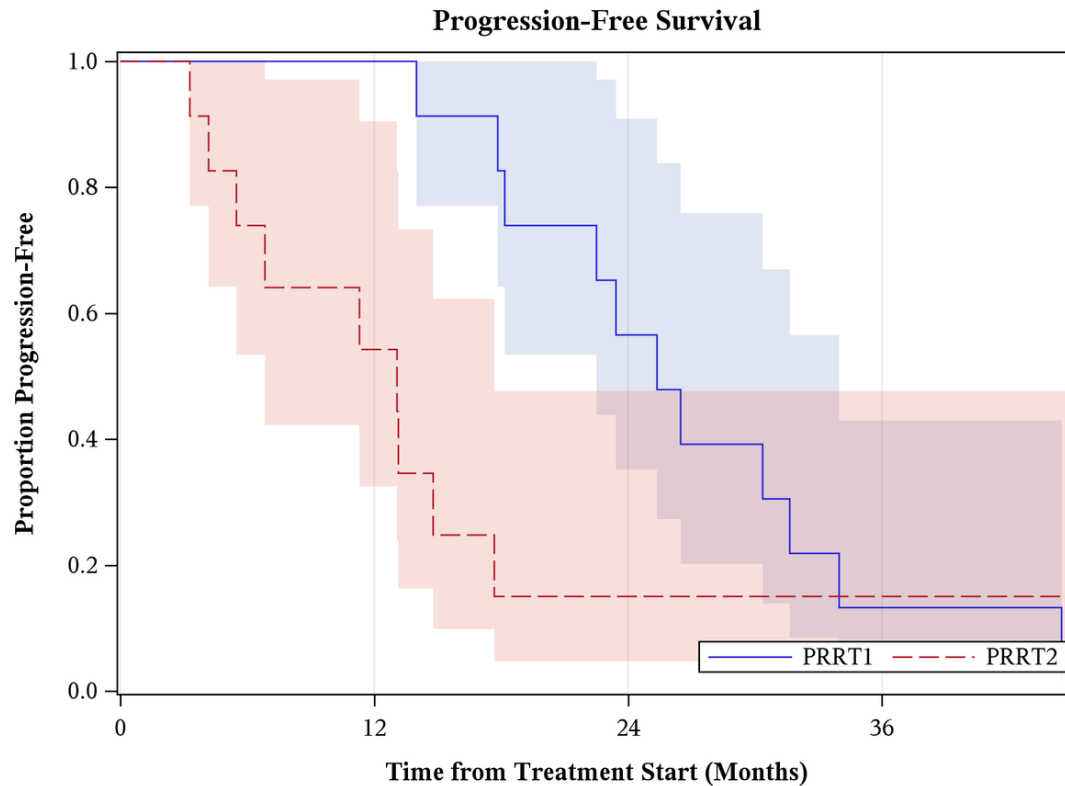
Median PFS for PRRT1 (n=11) was 25.4 months and median PFS (n=10) for PRRT2 was 13.1 months.

PFS for PRRT2 was significantly lower than PRRT1 (p=0.001)

Functional status/ Site of origin
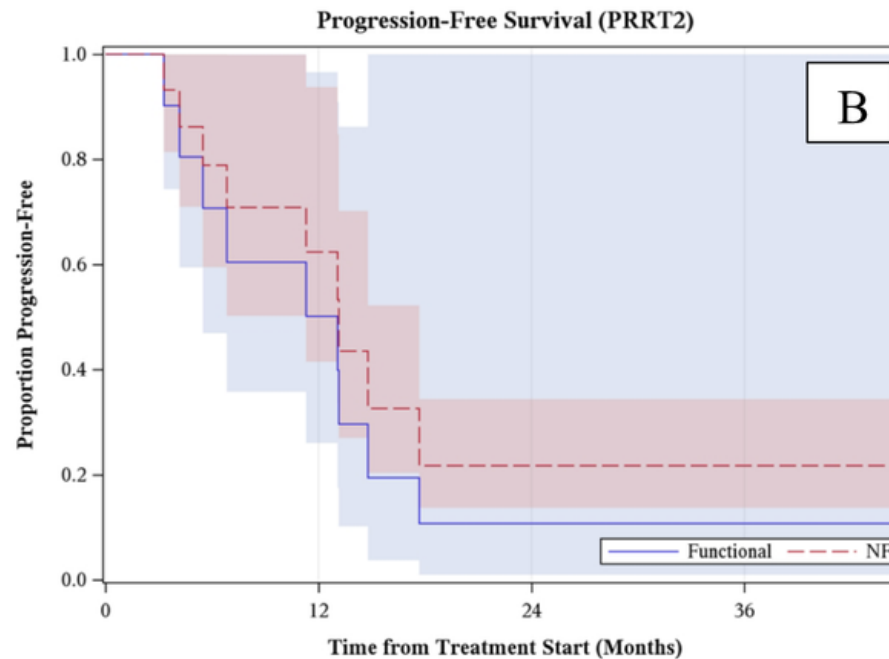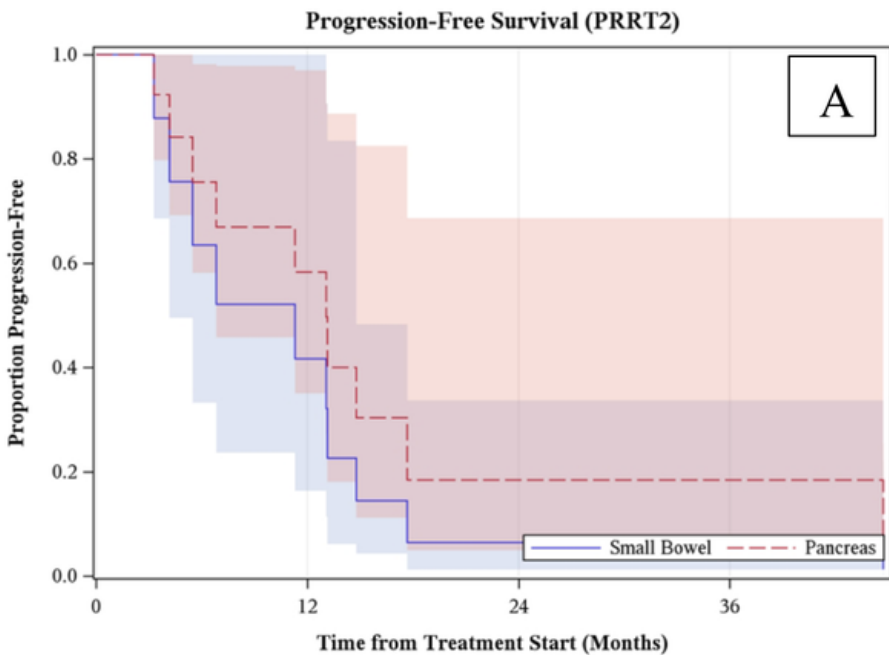
Median PFS after PRRT2 for pancreatic NETs was not statistically different from PFS for small bowel NETs (13.1 months vs 11.3 months, p=0.34).

No statistically significant difference in median PFS after PRRT2 between functional and non-functional NETs (13.1 months vs 13.1 months, p=0.43)

Toxicity data

| Covariate | Level | Statistics | Treatment Cycle | | P-value |
			PRRT1 N=11	PRRT2 N=10	
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%)	

No long-term hematological toxicities - acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS).

One patient each developed grade 3 renal toxicity after PRRT1 (9.1%) and PRRT2 (10%) and 1 patient developed grade 4 renal toxicity after PRRT1 (^{90}Y-DOTATOC).

The patient most likely developed pre-renal acute kidney injury due to carcinoid crisis in the setting of underlying VIPoma and made full recovery eventually.

Conclusions

- First US experience describing the safety and efficacy of repeat PRRT

- Safety events were comparable after PRRT1 and PRRT2

- PFS after PRRT2 is shorter than PFS after PRRT1

- Study limited by small sample size and retrospective design.

- Large randomized studies needed to establish safety and efficacy and identify patients more likely to benefit. ?functional tumors

- ?Role of repeat beta PRRT with ongoing studies of alpha PRRT trials.

NET RETREAT Trial

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

PI: Dr. Simron Singh, Dr Aman Chauhan

NET RETREAT Study Design: Phase II RCT (2:1)

PFS$_a$ = 12 months

Lu-177 dotatate (x3-4) → R →
- Lu-177 dotatate (200 mCi x2)
- Everolimus 10 mg PO daily
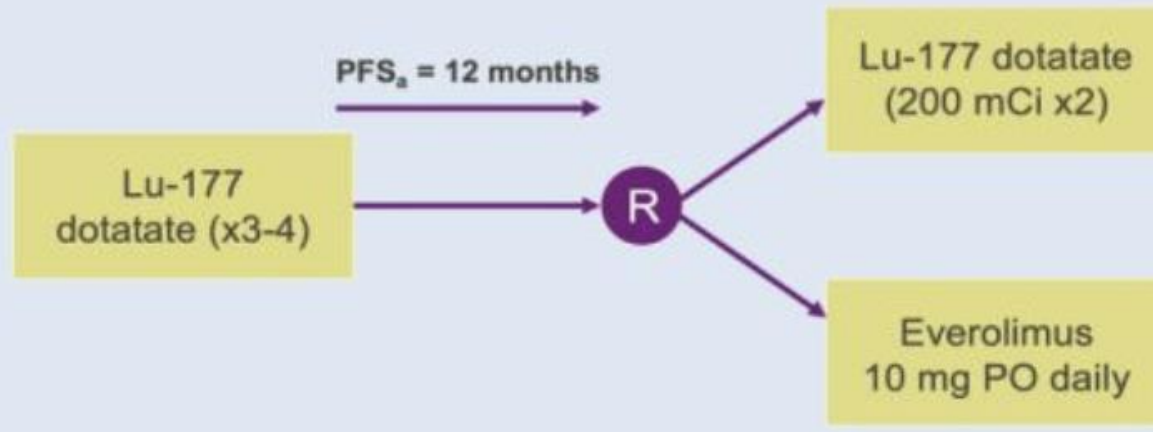
Key Inclusion/Exclusion Criteria:
- Metastatic Progressive midgut NET (Grade 1-2)
- No RECIST progression within 12 month from last dose of prior PRRT (3-4 prior PRRT doses)

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
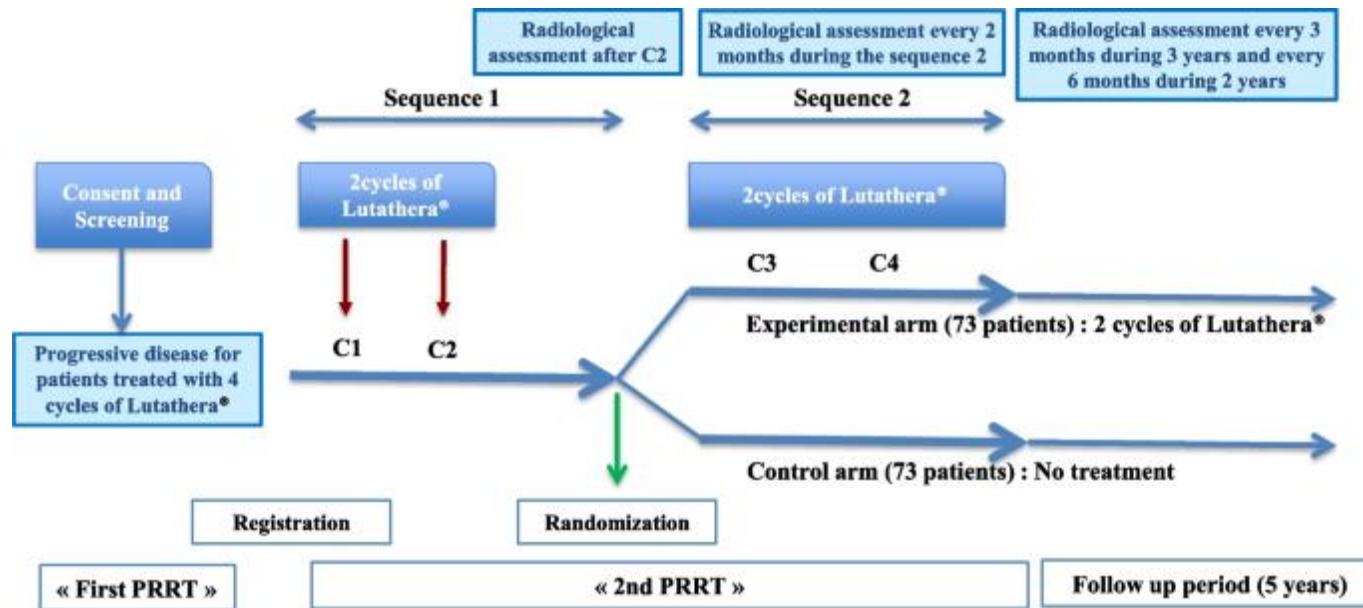
Multicenter, randomized, open label phase II study.

Well differentiated midgut neuroendocrine tumors.

Progressive disease after 4 cycles of Lutathera.

Primary endpoint: DCR at 6 months.

Deshayes *et al. BMC Cancer.* 2022

Neoadjuvant PRRT ???

The NeoLuPaNET trial (NCT04385992)

High risk PanNET → 177Lu-DOTATATE → Surgery

29 patients underwent surgery
Radiological response- 17 patients (59%)
Resection achieved in 28 patients (96.5%)
Severe postoperative complications -24% of patients.

High risk resectable panNET:
Presence of at least one of the following:
1. Tumor size > 4 cm,
2. Nearby organ/s invasion,
3. Ki67 >10%,
4. Vascular invasion,
5. Single liver metastasis,
6. Nodal involvement.

NeoNET trial ongoing.

Partelli et al. ESMO 2023

Expanding indications of PRRT

Alliance A021901: Randomized Phase II Trial of Lutetium Lu 177 Dotatate Versus Everolimus in Somatostatin Receptor Positive Bronchial Neuroendocrine Tumors

- Unresectable or metastatic bronchial carcinoid
- SSTR+ on DOTATATE PET [a]
- Radiographic progression within 12 months
- No limit on prior lines of therapy

N = 108

Stratification:
Prior/Concurrent**
SSA use

1:1

177Lu-DOTATATE
200 mCi x 4 every 8 weeks

Imaging Q3 months

Everolimus
10 mg oral daily

- Cross over allowed on the control arm
- *Central review at progression
- **Concurrent SSA use allowed for patients with functional tumors if on stable dose for 3 months and previous radiographic progression on SSA

Primary endpoint
- PFS (by RECIST)*

Secondary endpoint
- ORR
- OS
- Safety

Exploratory
- Late toxicities, QOL, Dosimetry

NCI trial for pheo/para ongoing

co-PIs:
Thomas Hope
Suki Padda

SSTR=somatostatin receptor
a=100% of typical carcinoids are SSTR+, while 50% of atypical carcinoids are SSTR+

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

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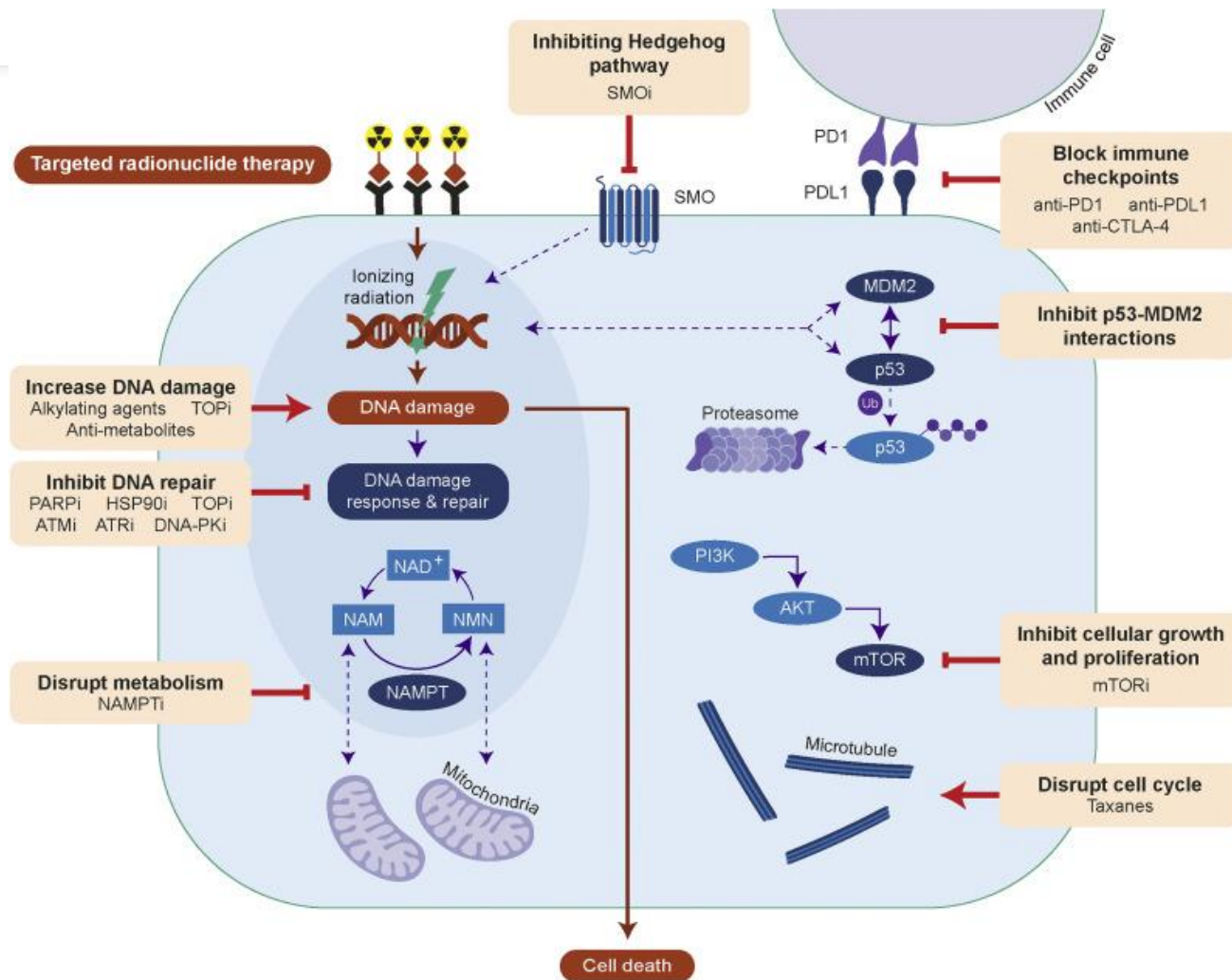
Attempts to amplify the therapeutic efficacy of PRRT by combining it with other agents.

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

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

IOWA

Alpha PRRT

Why could alpha PRRT be superior to beta PRRT?

1. High linear energy transfer (LET)→ more DNA DS breaks→ less DNA hits needed to kill the cell (1-10 vs 100-1000 for beta). High LET also means it is less affected by hypoxia and cell cycle phase.
2. Short path length of alpha PRRT→ makes it more targeted than beta PRRT. ??Less toxic

Radioactive particle effects on tumor cells

Beta particle radiation

^{90}Y

Energy: 50-2300 keV
Range: 0.05-12 mm
LET: 0.2 keV/mm

Alpha particle radiation

^{225}Ac

Energy: 5-9 MeV
Range: 40-100 μm
LET: 80 keV/mm

Auger electron radiation

^{111}In

Energy: eV-keV
Range: 2-500 nm
LET: 4-26 keV/mm

Tumor
Healthy cell
Reactive oxygenated species
Particle range
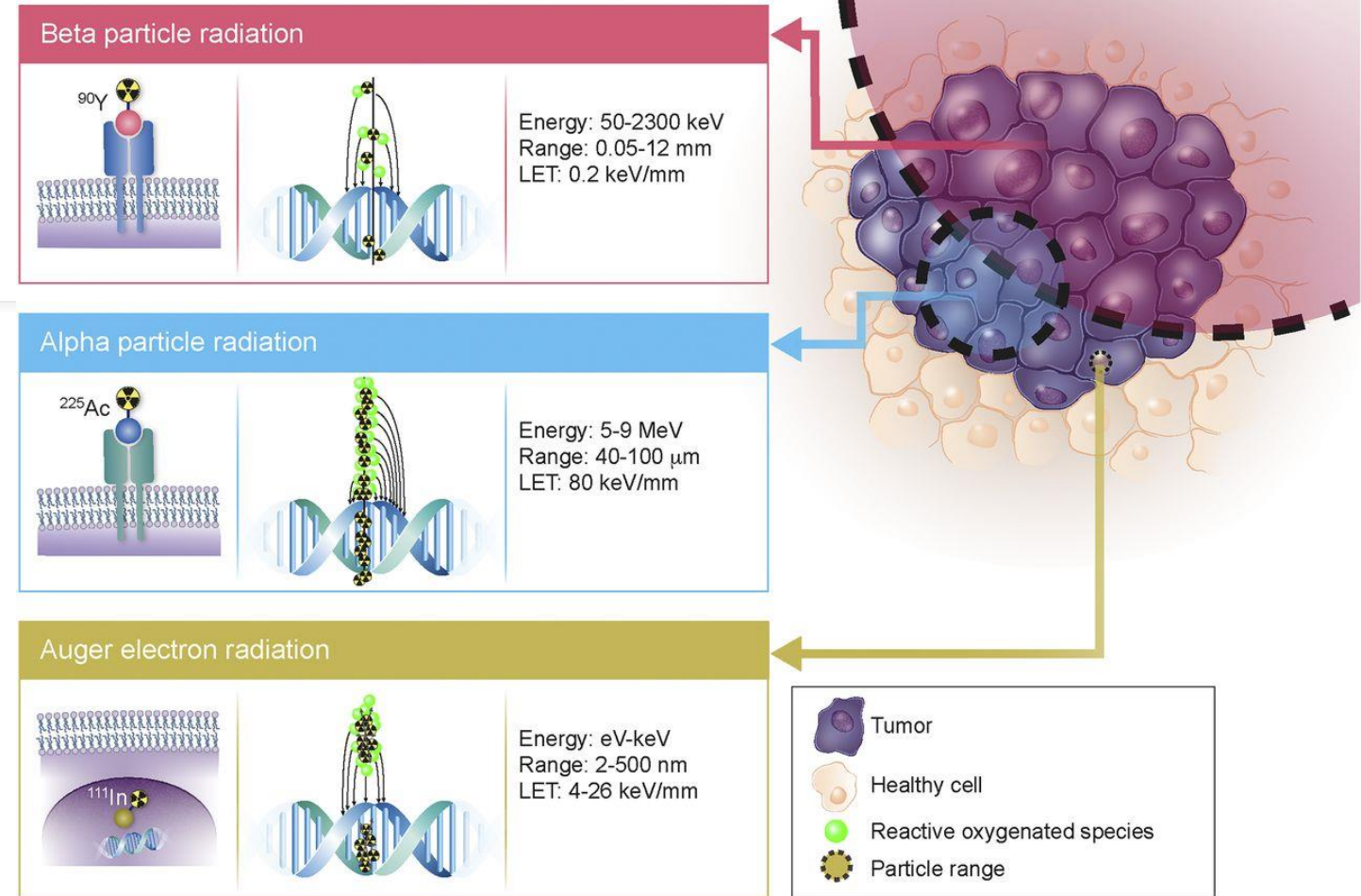
Agents under investigation:
Ac225 – DOTATATE (phase I/III)
Pb212-DOTAMTATE (phase II)
Pb212-VMT-αNET (phase I/IIa)

Poty *et al. J Nucl Med.* 2018

ACTION-1 trial

phase Ib/3 trial of RYZ101 in somatostatin receptor subtype 2–expressing (SSTR2+) gastroenteropancreatic neuroendocrine tumors (GEP-NET) progressing after ^{177}Lu somatostatin analogue (SSA) therapy

Population	Treatment	Endpoints	Crossover

Key Eligibility Criteria

- Age ≥ 18
- Histologically proven, well-differentiated, G1-2 GEP-NETs
- Ki-67 ≤ 20%
- Progressive GEP-NET based on RECIST v.1.1 following 2-4 cycles ^{177}Lu-SSA[1] (must have had disease control for **at least 6 months**) and **within 18 months** from randomization (intervening treatments are permitted)
- All RECIST v1.1 measurable lesions must be SSTR-PET+ within 90d from randomization (centrally confirmed)
- ECOG ≤ 2
- CrCl ≥ 50 mL/min
- No prior radioembolization

N=210

1:1

RYZ101 at RP3D

CT,MRI q12w

Investigator's Choice SOC

Everolimus

Sunitinib

High dose Octreotide LAR or high frequency lanreotide

Primary
- BICR PFS

Secondary/Exploratory
- OS
- ORR
- Duration of Response
- Disease Control Rate
- Safety
- PK (Sparse, blood only)
- Biomarkers, incl CgA, 5-HIAA
- EORTC C30, EORTC QLQ GI NET21

- **Substudy** (N~30) to evaluate PK/ECG

Allow crossover at PD (centrally confirmed)

Acknowledgements