Oncology Learning Network

Held in Partnership with NCAN

Neuroendocrine Cancer Awareness Network

GASTROENTEROPANCREATIC NEUROENDOCRINE TUMORS

Personalized Diagnostic and Therapeutic Strategies for Optimized Outcomes

Faculty

- **Nitya Raj, MD**
  Associate Attending Physician, Gastrointestinal Oncology
  Memorial Sloan Kettering Cancer Center
  New York, NY

- **Jonathan R. Strosberg, MD**
  Professor, Gastrointestinal Oncology
  Moffitt Cancer Center
  Tampa, FL

Faculty Disclosures

- **Nitya Raj, MD**
  Advisory Board: BI; Exelixis; Speakers Bureau: Peerview Institute (terminated); Intellisphere, LLC (terminated); Research Institution: Camurus AB; ITM
- **Jonathan R. Strosberg, MD**
  Advisory Board: BI; Curium; Exelixis; ITM

Disclosures

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration)
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  - This activity has been independently reviewed for balance

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Learning Objectives

Upon completion of this educational activity, learners will be able to:

- Identify therapeutic challenges and unmet needs associated with the clinical management of gastroenteropancreatic neuroendocrine tumors (GEP-NETs)
- Evaluate the efficacy and safety of current and emerging treatment strategies across GEP-NET subtypes
- Apply tumor-specific factors—such as grade, differentiation, and functional status—to select and implement evidence-based diagnostic and treatment algorithms tailored to individual GEP-NET clinical scenarios

GEP-NET = gastroenteropancreatic neuroendocrine tumor.

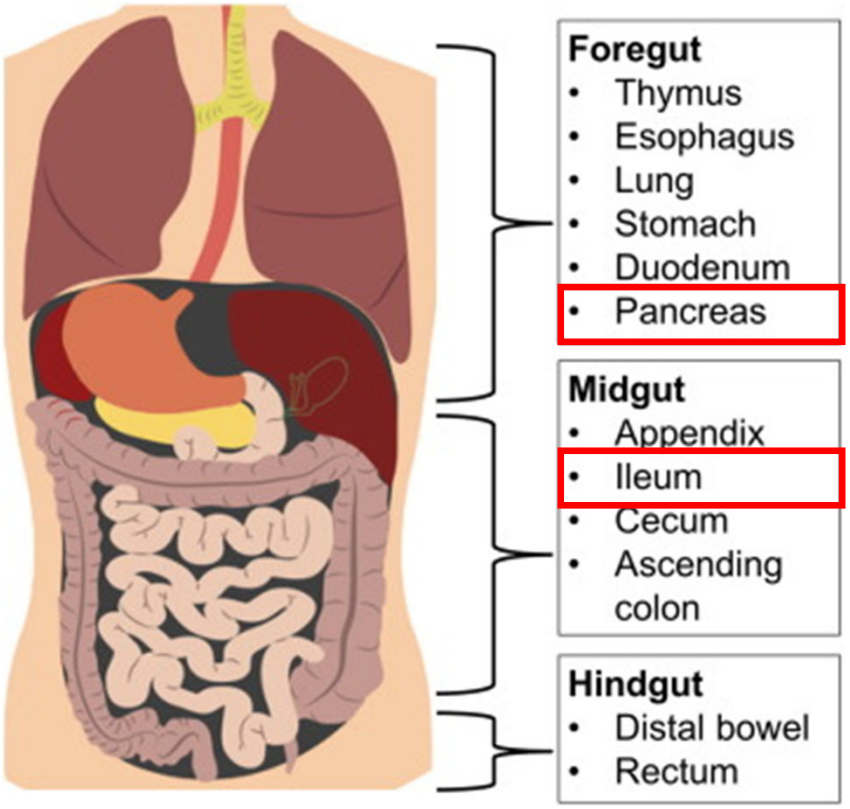
Navigating the Expanding NET Treatment Arsenal

Key Advances in Targeted Therapy and Nuclear Medicine

Nitya Raj, MD
Associate Attending Physician, Gastrointestinal Oncology
Memorial Sloan Kettering Cancer Center
New York, NY

Introduction and Overview of NETs
Epidemiology and Classification

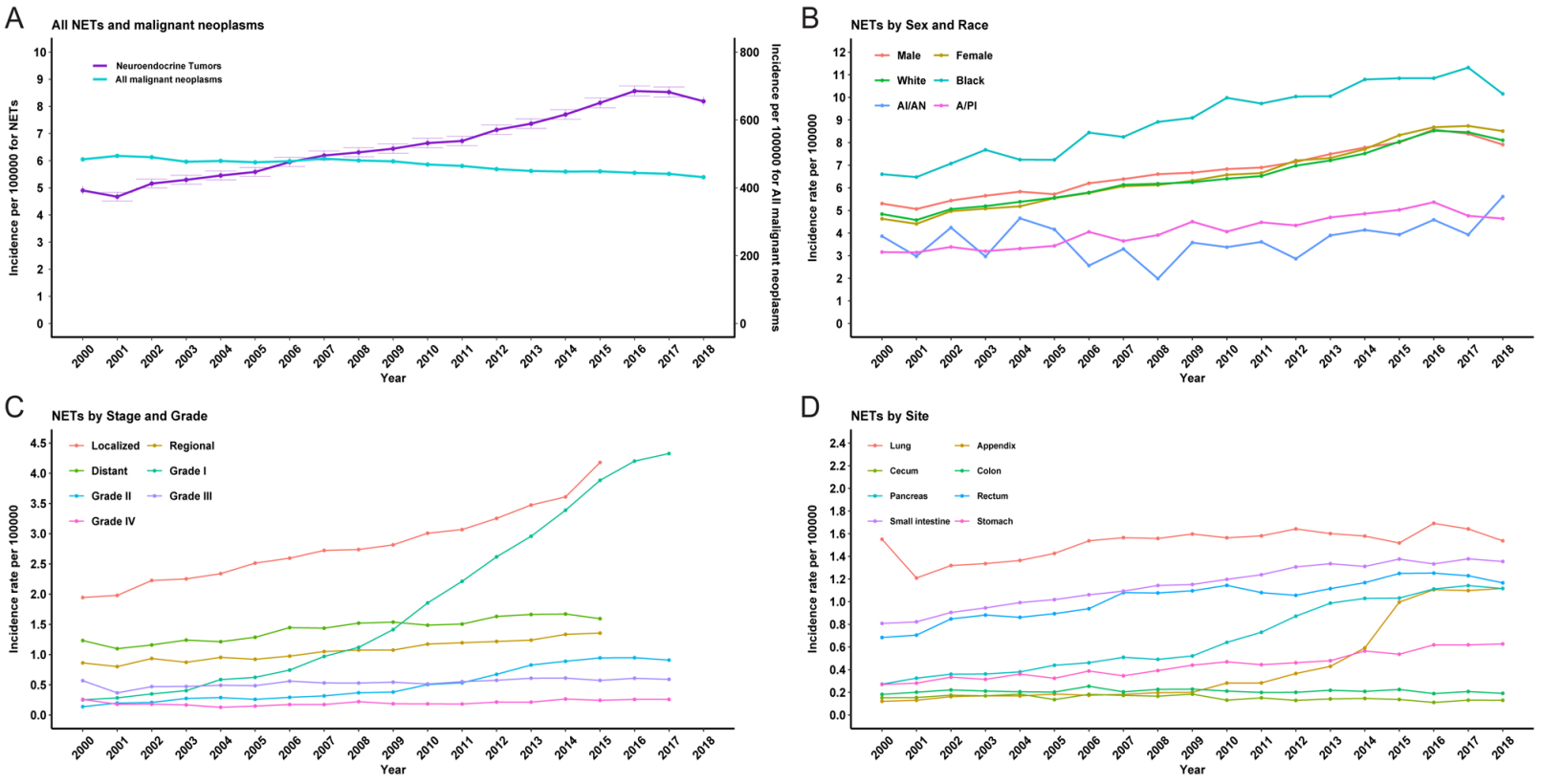
NETs Develop Anywhere in the Body



- A disease that can help us better understand tumor biology, heterogeneity, clonal evolution
- First – do no harm! Do not take credit for good biology

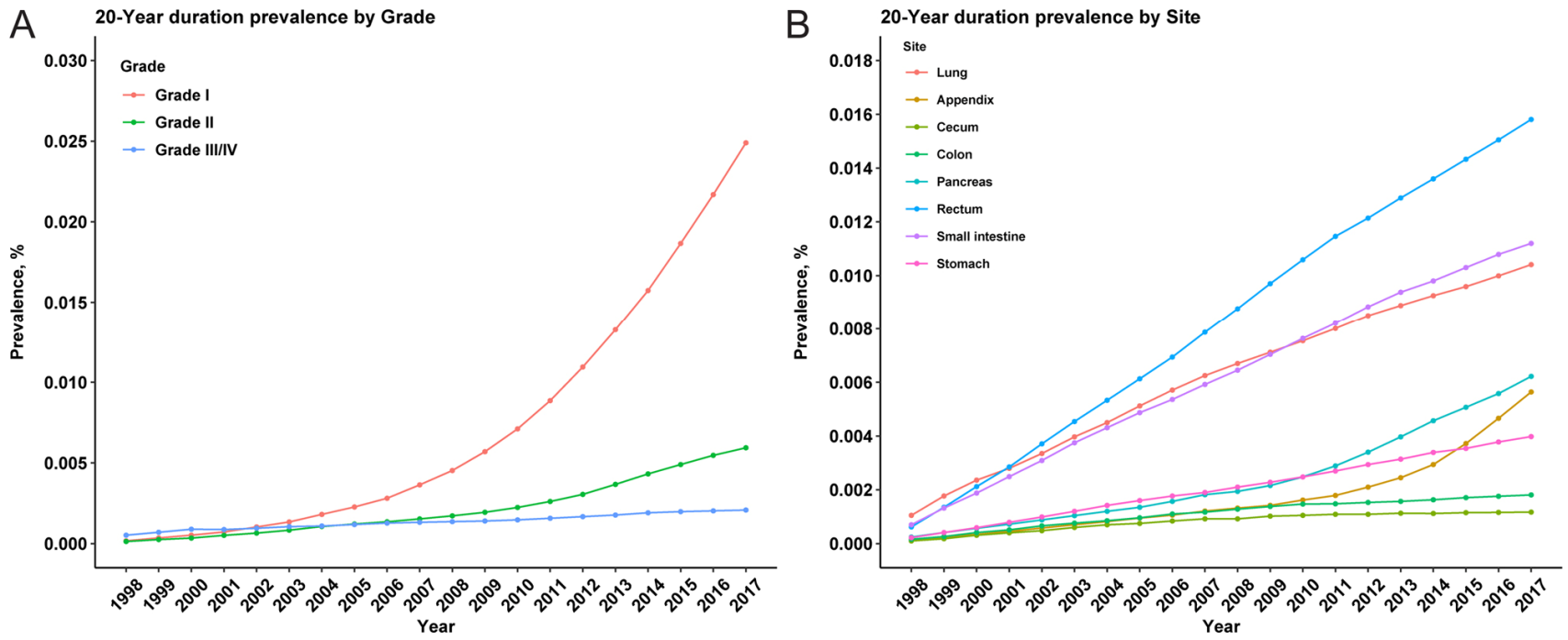
Oronsky B, et al. *Neoplasia.* 2017;19(12):991-1002.

Rising NET Incidence (SEER Data)



Wu P, et al. *Endocr Connec.* 2023;12(12):e230331.

Rising NET Prevalence (SEER Data)



Wu P, et al. *Endocr Connec.* 2023;12(12):e230331.

Patient Video 60-90 seconds

References

Classifications of NETs

WHO Pathology Grading for Neuroendocrine Neoplasms

Uses differentiation, cytologic grade
*Pathology is one of our most important prognostic tools

Increasing aggressiveness

Grade	Differentiation	Mitotic Count/Ki-67
1 (Low)	Well differentiated	<2 mitoses/10 HPF <3% Ki-67 index
2 (Intermediate)	Well differentiated	2-20 mitoses/10 HPF 3-20% Ki-67 index
3 (High)	Well differentiated	>20 mitoses/10 HPF >20% Ki-67 index
3 (High)	Poorly differentiated Small cell Large cell Non small cell Mixed (MiNEN)	>20 mitoses/10 HPF >20% Ki-67 index

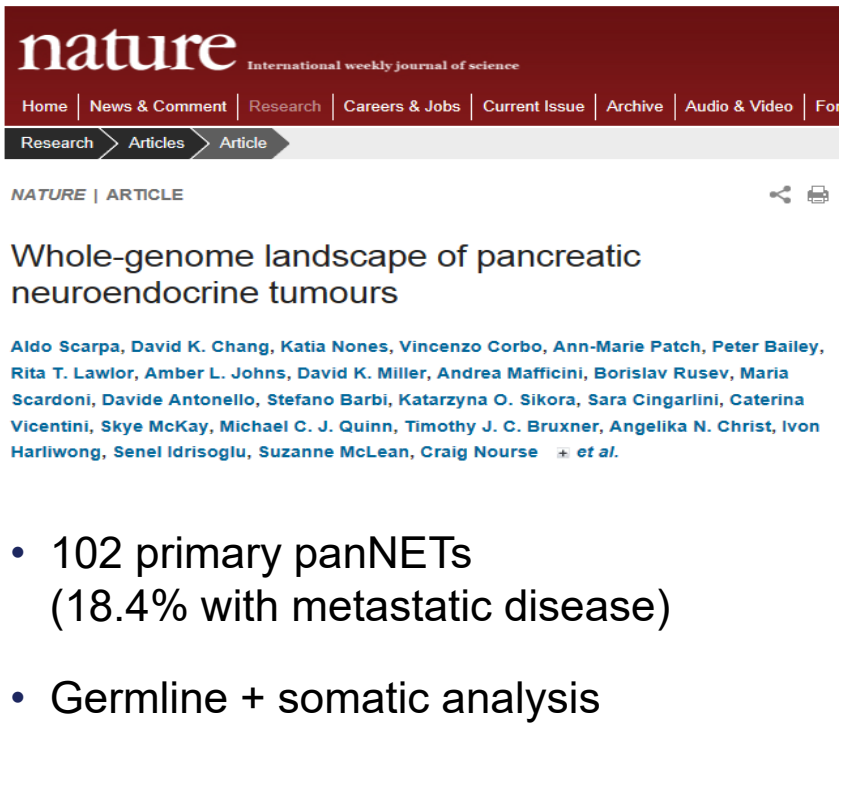
WHO 2017 + 2019

Mutations in Well Differentiated Pancreatic NETs

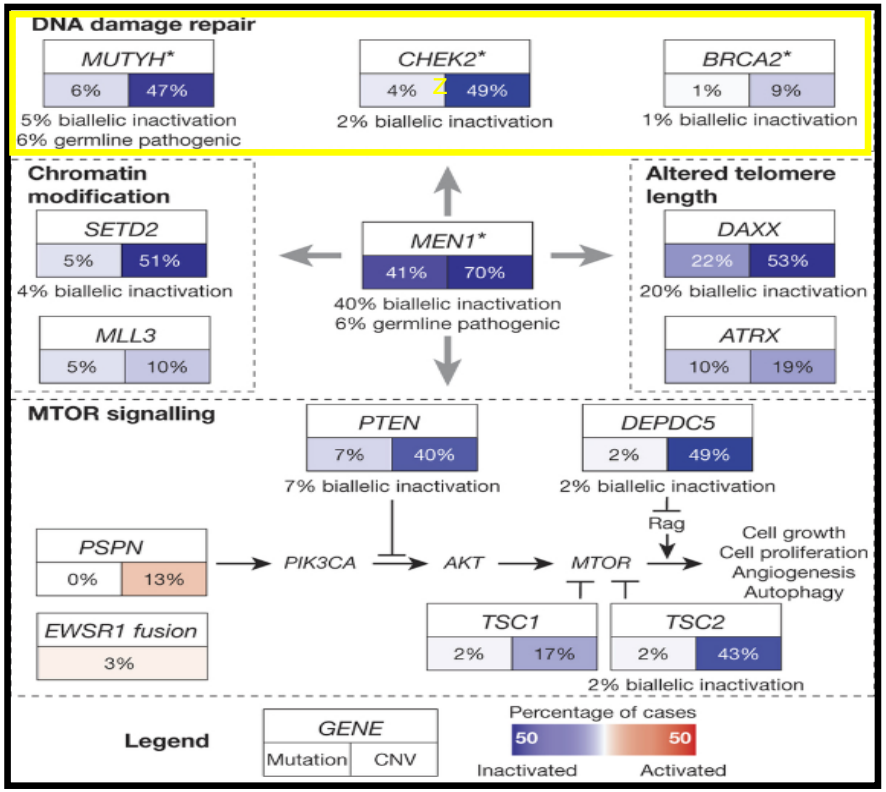
- Whole-exome sequencing → targeted sequencing
- Early stage (59%), metastatic (41%)
  - Chromatin remodeling genes (MEN1/DAXX/ATRX)
  - mTOR pathway (PTEN, TSC2)
  - No RB1
- Disease prognostication
  - **Survival benefit with MEN1 + DAXX/ATRX mutated status**

Jiao Y, et al. *Science.* 2011;331(6021):1199-1203.

Whole-Genome Sequencing of Pancreatic NETs



- 102 primary panNETs
  (18.4% with metastatic disease)
- Germline + somatic analysis



Scarpa A, et al. *Nature.* 2017;550(7677):548.

The Work-Up

Presentation

- While diagnosis as early as possible is essential, presentation of this disease can vary
  - Many NETs are discovered incidentally (this is occurring with greater frequency 2/2 use of high-quality imaging)
  - If symptomatic at diagnosis, this is due to
    1) tumor bulk or
    2) hormone-secreting component to the disease

NET Tumor Bulk Symptoms

- Common tumor bulk symptoms
  - Abdominal pain
  - Jaundice
  - Weight loss
  - Nausea
  - Vomiting

NET Hormonal Syndromes

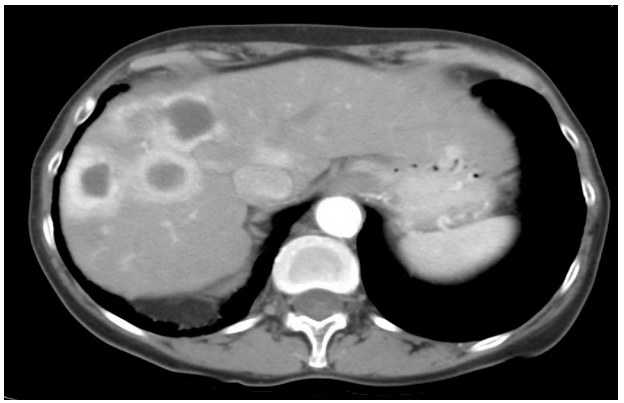
- Work-up is driven by **symptoms**
  - Serotonin secretion/carcinoid syndrome (most commonly seen in **small bowel NETs**): diagnosis confirmed with elevated 24-hr urine 5HIAA
  - Gastrinoma: recurrent peptic ulcers, diarrhea, reflux esophagitis
  - VIP: severe secretory diarrhea
  - Glucagon: hyperglycemia
  - Insulinoma, proinsulinoma: hypoglycemia

5HIAA = 5-Hydroxyindoleacetic acid.

The diagnosis is confirmed with biopsy… further work-up and necessary tests

Additional Work-Up

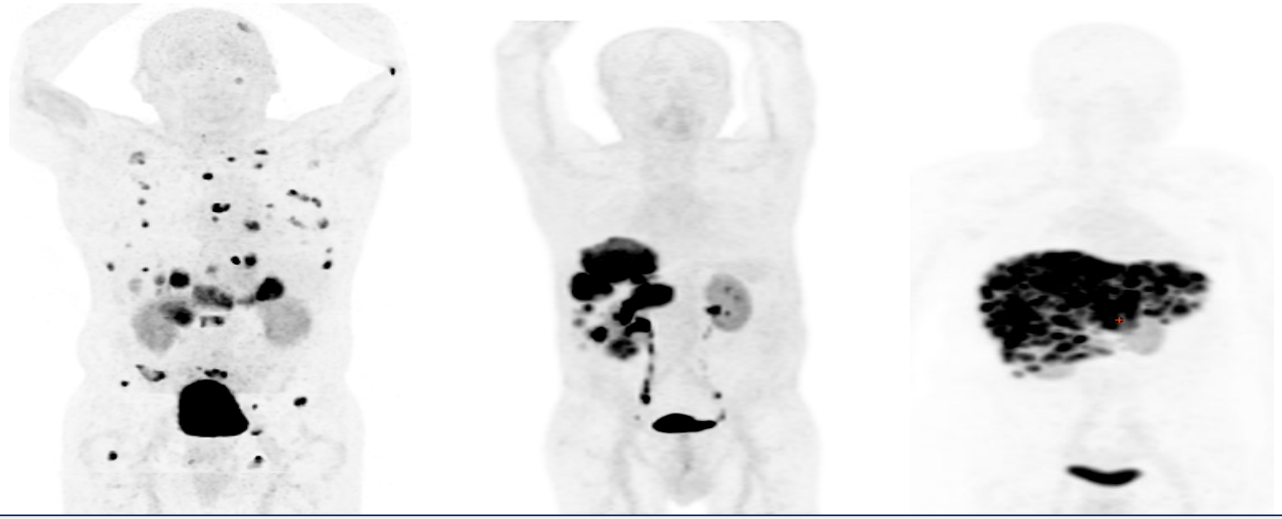
- Cross-sectional imaging (CT **Liver triphasic** or MRI)
  - Best way to evaluate disease extent and response to therapy
- Functional Imaging **x1** (Ga68-Dotatate)
- Do not search for the primary…
  Yield is low if not detected in the above
- Blood-based biomarkers? Unlikely to help, and **we do not track**
  - Chromogranin A: beware of proton pump inhibitors and other meds, renal/cardiac dysfunction that impact levels!
  - Not on NCCN!
- TTE baseline for anyone with carcinoid syndrome
  - Monitor for right-sided heart failure symptoms



NCCN = National Comprehensive Cancer Network; TTE = transthoracic echocardiogram.

Evolving Diagnostic Imaging

Ga-68 and Cu-64 Dotatate

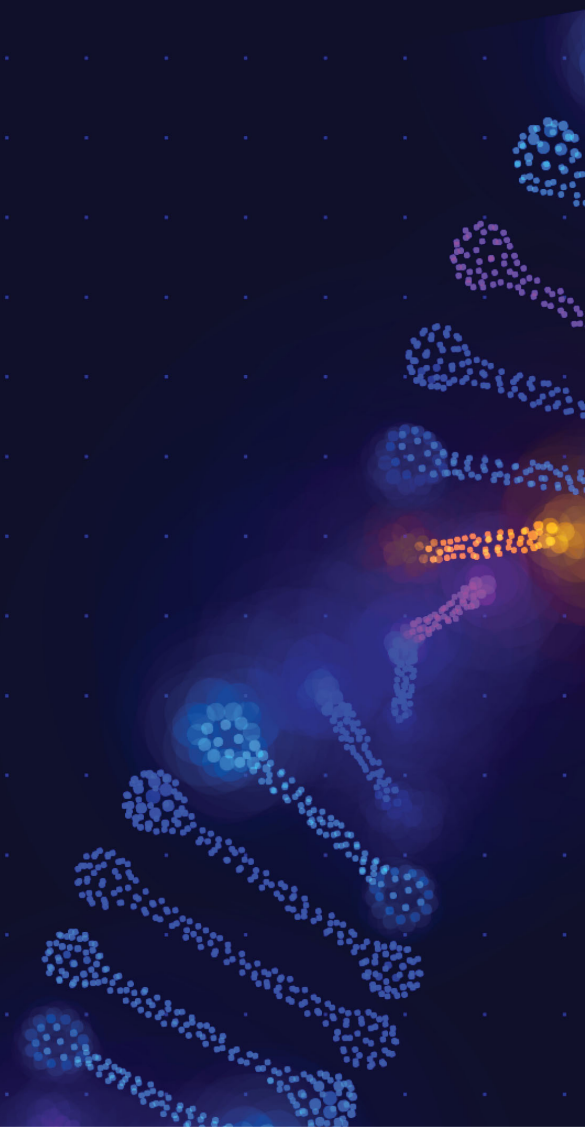


- PET-Dotatate improved sensitivity compared to octreotide imaging
- Radioactive diagnostic agent indicated for localization SSTR-positive disease
- SSRT PETs help predict responsiveness to SSAs and PRRT
- Beware of comparing apples to oranges; PET should not be compared to cross-sectional imaging to define extent of disease

SSTR = somatostatin receptors; SSA = somatostatin analogue.

Current Therapeutic Options

Jonathan R. Strosberg, MD
Professor, Gastrointestinal Oncology
Moffitt Cancer Center
Tampa, FL



NETs Are Heterogeneous

Extent of Disease	Low tumor burden			High tumor burden		
	Liver dominant			Widely metastatic		
Pace of Growth	Stable			Progressive		
Primary Site	Lung	Gastric	Duodenal	Pancreatic	Small bowel	Colorectal
Grade/ Differentiation	Low-grade (G1)		Intermediate-grade (G2)		High-grade (G3)	
	Well diff. (NET)				Poorly diff. (NEC)	
Hormone Status	Functional			Non-functional		
SSTR	High expression			Low/absent expression		

GEP-NET Grade Classification

Differentiation	Grade	WHO Grading	WHO Nomenclature
Well-differentiated NET	Low (G1)	<2 mitoses/10 HPF and <3% Ki67 index	NET grade 1
	Intermediate (G2)	2 to 20 mitoses/10 HPF or 3%-20% Ki67 index	NET grade 2
	High (G3)	>20 mitoses/10 HPF or >20% ki-67 index	NET grade 3
Poorly differentiated NEC	High (G3)	>20 mitoses/10 HPF or >20% Ki67 index	Neuroendocrine carcinoma, grade 3 (large-cell or small-cell type)

- Low-grade (G1) typically very slow-growing
- High-grade (G3) typically aggressive
- Poorly differentiated, extremely aggressive: more than well-differentiated G3
- Tumors can transform over time, increasing in grade and even (rarely) converting from well-differentiated to poorly differentiated

GEP-NET = gastroenteropancreatic neuroendocrine tumor.

Klimstra DS, et al. Digestive System Tumours. In: WHO Classification of Tumours, 5th Edition, Volume 1. International Agency for Research on Cancer (IARC). Lyon, France; 2019.

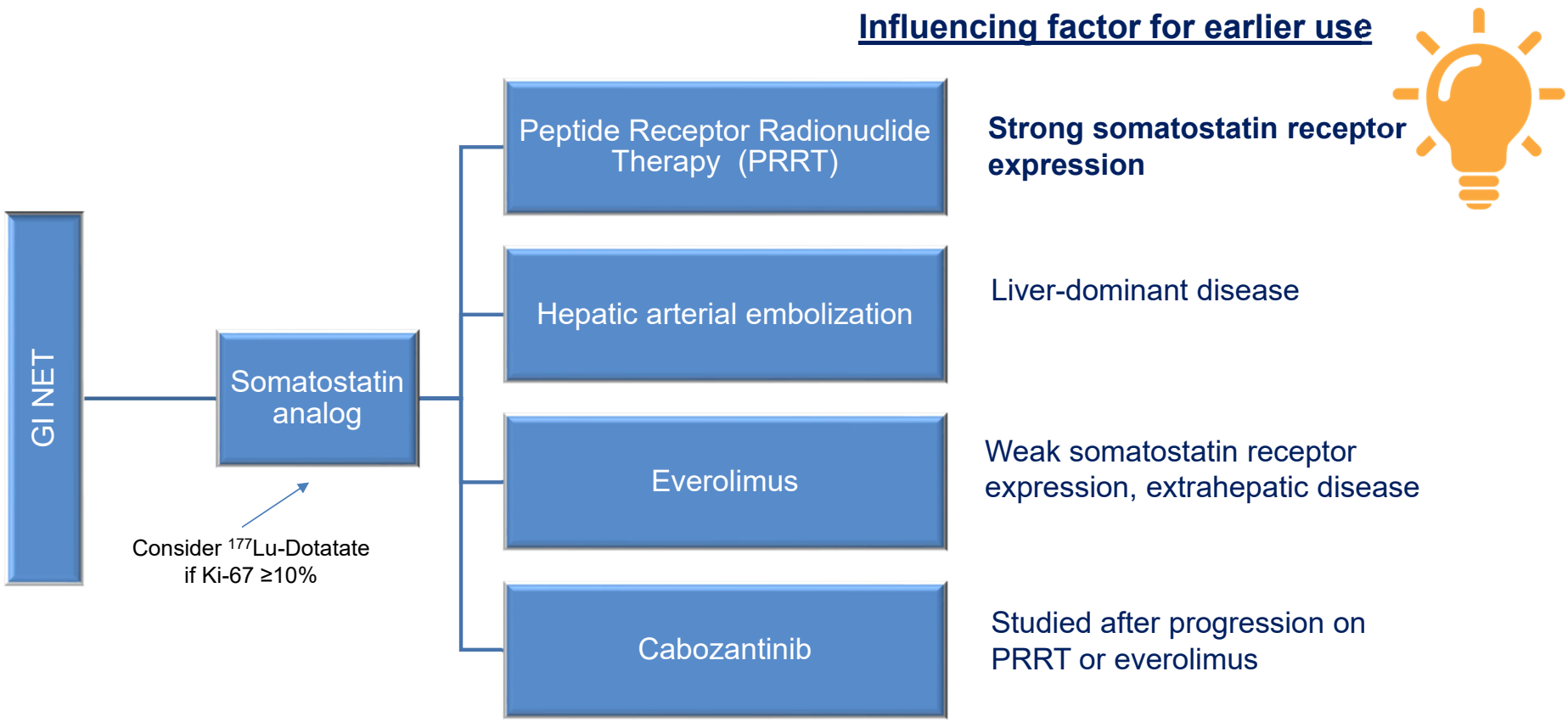
What Does Sequencing Mean?

What is the right treatment for the right patient at the right time?

- NETs are a heterogeneous disease with no simple algorithmic approach
- Different primary sites, metastatic sites, grades, patterns of somatostatin receptor expression, hormone secretion
- Tumor biology can change significantly over time
- Few studies have compared new treatments to SOC

Current Standard of Care

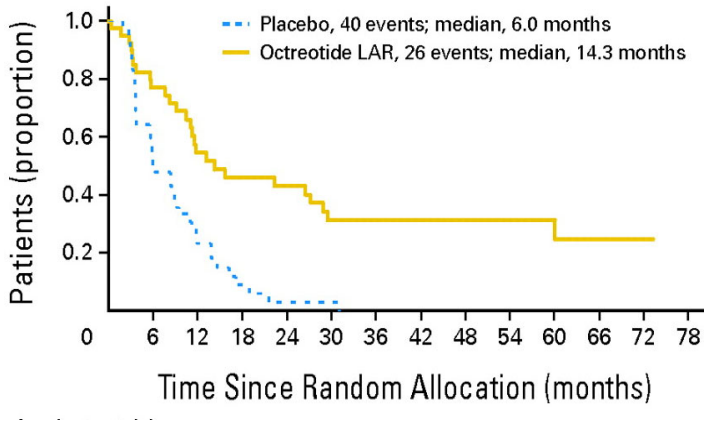
Metastatic Gastrointestinal NET

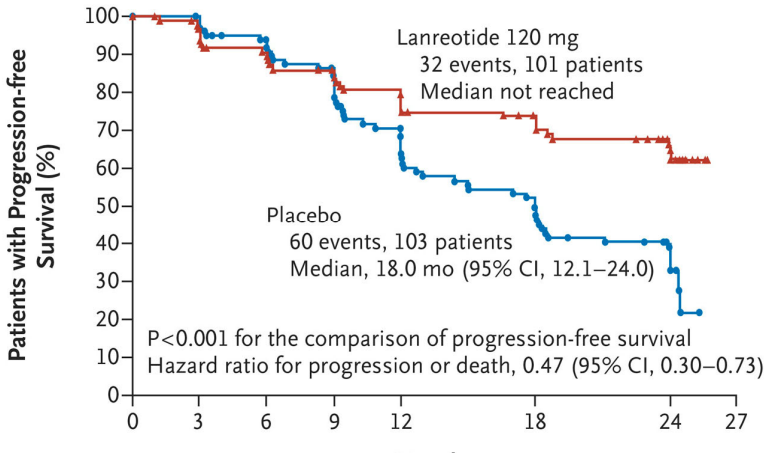


*Always consider cytoreductive surgery/resection of primary

Why Do We Usually Begin with SSA?

- Statistically significant improvement in progression-free survival (PFS) (PROMID/CLARINET: similar hazard ratio ~0.35 for small bowel NETs)
- Palliates carcinoid syndrome
- Safe
- Tolerable





PFS = progression-free survival; SSA = somatostatin analog.
Rinke A, et al. *J Clin Oncol*. 2009;27(28):4656-4663. Caplin ME, et al. *N Engl J Med*. 2014;371(3):224-233.

Randomized Trials Progressive GI/Thoracic NET

Trial	Population	N	Arms	PFS (mo)	HR	OS (mo)	RR
NETTER-1	Midgut (small bowel)	229	^{177}Lu-Dotatate + octreotide vs high-dose octreotide	NR vs 8.4	0.21	48 vs 36	18% vs 3%
RADIANT-2	h/o carcinoid syndrome (primarily midgut)	429	Everolimus + octreotide vs placebo + octreotide	16.4 vs 11.3	0.77 (NS)	29 vs 35	9% vs 0%
RADIANT-4	GI+ Lung (no h/o carcinoid syndrome)	302	Everolimus vs placebo	11 vs 3.9	0.48	NR (no final analysis published)	2% vs 1%
CABINET epNET Cohort*	GI + Thoracic (after everolimus or PRRT)	203	Cabozantinib vs placebo	8.4 vs 3.9	0.38	21.9 vs 19.8	5% vs 0%

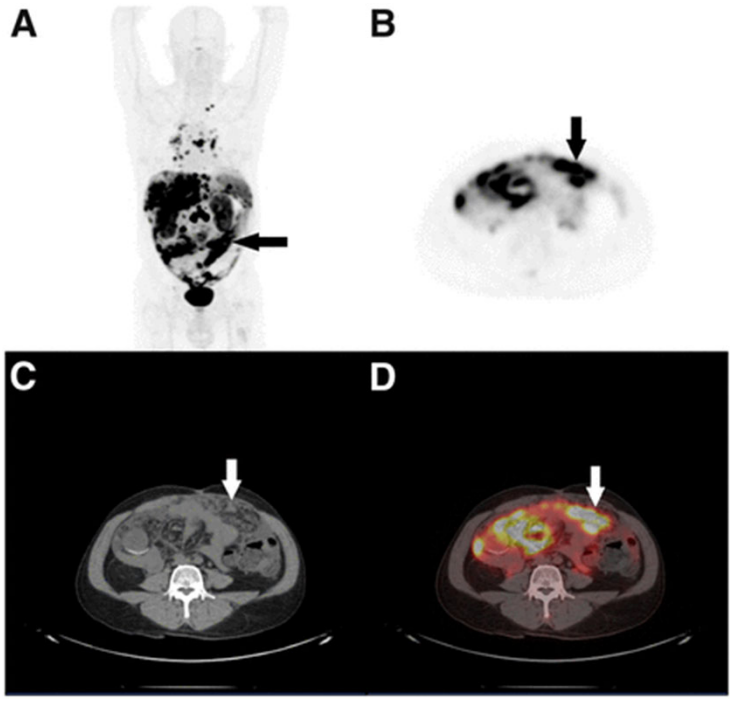
*CABINET included G3 NETs

Strosberg JR, et al. *Lancet Oncol*. 2021;22(12):1752-1763. Strosberg JR, et al. *N Engl J Med.* 2017;376(2):125-135. Pavel ME, et al. *Ann Oncol*. 2017;28(7):1569-1575. Pavel ME, et al. *Lancet*. 2011;378(9808):2005-2012. Chan J, et al. *N Engl J Med*. 2025; 392(7):653-665.

Comparing Side Effects:

^{177}Lu-Dotatate vs Everolimus vs Cabozantinib

- ^{177}Lu-Dotatate associated with 2%-3% risk of MDS/AL; fatigue and nausea generally mild
- ^{177}Lu-Dotatate can be risky for patients with high-burden peritoneal disease
- Everolimus: oral ulcers, pneumonitis, immunosuppression, fatigue, diarrhea, hyperglycemia, rash
- Cabozantinib: HTN, fatigue, PPE, DVT/PE, cardiovascular events, diarrhea
- Impact of daily pill on quality of life



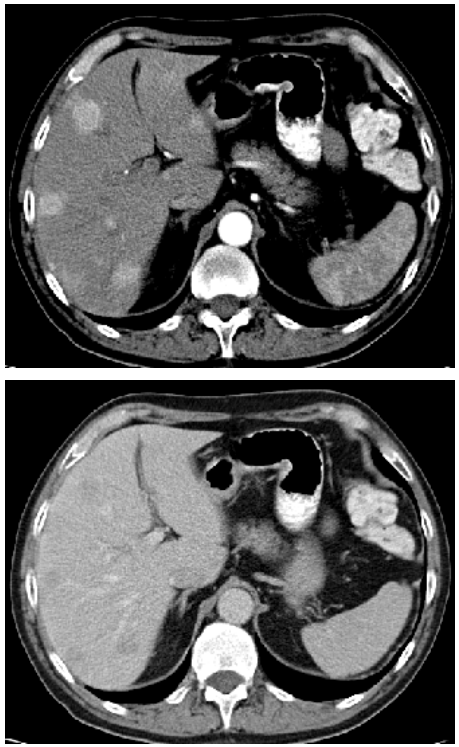
High burden peritoneal disease and risk of bowel obstruction

Strosberg J, et al. *J Nucl Med*. 2021;62(1):69-72.

Brabander T, et al. *Clin Cancer Res*. 2017;23(16):4617-4624. Strosberg J, et al. *J Nucl Med*. 2021;62(1):69-72. Pavel ME, et al. *Lancet Oncol*. 2017;18(10):1411-1422. Chan J, et al. *N Engl J Med.* 2025;392(7):653-665.

Comparing Systemic Therapy to Hepatic Arterial Embolization

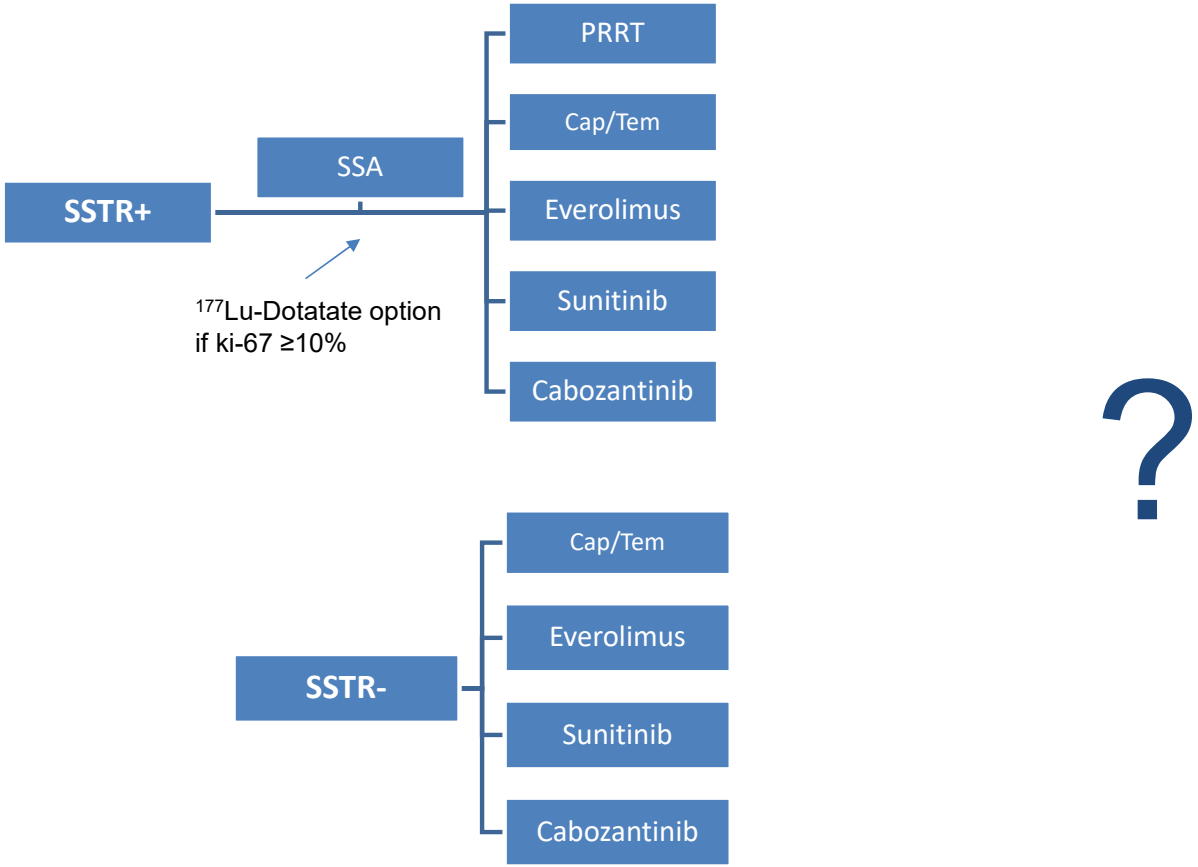
- Data for embolization primarily from retrospective series/small prospective studies
- High hepatic response rate (~50%), high rate of symptomatic response
- Bland/chemoembolization can have short-term toxicities but few long-term toxicities
- Bilobar radioembolization (^{90}Y) can lead to long-term hepatic dysfunction: consider primarily for segmental or lobar treatment and/or aggressive disease



Progressive, unresectable liver-dominant NET on SSA: PRRT or embolization?

Strosberg JR, et al. *J Nucl Med*. 2021;62(12):1669-1671.

Pancreatic NET Systemic Treatments



?

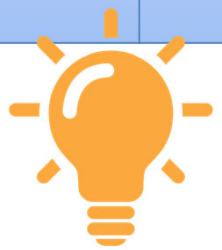
How Do We Decide?

- If SSTR-negative, aggressive, high-tumor burden: chemotherapy (eg, capecitabine/temozolomide)
- Otherwise… it’s complicated!

Randomized Pancreatic NET Studies

Trial	N	Arms	PFS	HR	OS	RR
RADIANT-3	410	Everolimus vs placebo	11.0 vs 4.6	0.35	44.0 vs 37.7	5% vs 2%
SU011248	171	Sunitinib vs placebo	12.6 vs 5.8	0.42	38.6 vs 29.1	9% vs 0%
ECOG 2211	133	Capecitabine/temozolomide vs temozolomide	22.7 vs 14.4	0.58	58.7 vs 53.8	40% vs 34%
OCLURANDOM*	84	^{177}Lu-Dotatate vs sunitinib	20.7 vs 11.0	N/A	N/A	N/A
CABINET** (pNET cohort)	95	Cabozantinib vs placebo	13.8 vs 4.4	0.23	40 vs 31.1	19% vs 0%

*Oclurandom not powered for comparison between arms
** CABINET included G3 NETs



Yao JC, et al. *N Engl J Med*. 2011;364(6):514-523. Raymond E, et al. *N Engl J Med*. 2011;364(6):501-513. Kunz PL, et al. *J Clin Oncol*. 2023;41(7):1359-1369. Baudin E, et al. Abstract 8870. Presented at: European Society of Medical Oncology (ESMO) Congress; Sept. 9-13, 2022; Paris, France. Abstract 8870. Chan J, et al. *N Engl J Med*. 2025;392(7):653-665.

SSTR+: Sequencing Treatments after SSA

- Everolimus, sunitinib, and cabozantinib appear to have fairly similar outcomes (median PFS about 1 yr, hazard ratio (HR) and overall response rate (ORR) slightly superior with cabozantinib)
- Capecitabine/temozolomide and PRRT have higher response rates and (likely) higher PFS
- Capecitabine/temozolomide and ^{177}Lu-Dotatate tend to have fewer daily side effects/less adverse effect on QoL
- But... There are concerns regarding early PRRT and chemotherapy: risk of MDS/AML, induction of higher mutation burden, disease transformation?

HR = hazard ratio; ORR = overall response rate; MDS = myelodysplastic syndrome/acute myeloid leukemia.

Cordero-Hernandez IS, et al. *Endocr Relat Cancer*. 2024;31(4):e230203. Backman S, et al. *J Pathol.* 2024;264(4):357-370.

Efficacy and safety of [^{177}Lu]Lu-edotreotide vs everolimus in patients with grade 1 or grade 2 gastroenteropancreatic neuroendocrine tumours: COMPETE Phase 3 trial

Jaume Capdevila[1], Holger Amthauer[2], Catherine Ansquer[3], Emmanuel Deshayes[4], Rocio Garcia-Carbonero[5], Alexandre Teulé Vega[6], Johanna Wilmink[7], Jaroslaw B. Cwikla[8], Raj Srirajaskanthan[9], Andreas Buck[10], Chiara Maria Grana[11], Richard P. Baum[12], Lawrence O. Dierickx[13], Michael Michael[14], Jonathan Strosberg[15], Louis De Mestier[16], Andreas Kluge[17], Konstantin Zhernosekov[18], Thomas P. Walter[19]

[1]Vall d'Hebron University Hospital, Barcelona, Spain; [2]Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [3]Centre Hospitalier Universitaire de Nantes, Nantes, France; [4]Institut du Cancer de Montpellier Val d'Aurelle, Montpellier University, Montpellier, France; [5]Hospital Universitario 12 de Octubre, Imas12, UCM, Madrid, Spain; [6]Institut Català d'Oncologia, Barcelona, Spain; [7]Amsterdam UMC, Amsterdam, Netherlands; [8]Diagnostic and Therapeutic Center – Gammed, Warsaw, Poland; [9]King's College Hospital, London, United Kingdom; [10]Universitätsklinikum Würzburg, Würzburg, Germany; [11]IRCCS European Institute of Oncology Milano, Italy; [12]Curanosticum Wiesbaden-Frankfurt, Wiesbaden, Germany; [13]Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France; [14]Peter MacCallum Cancer Centre, University of Melbourne, Melbourne, Australia; [15]Moffitt Cancer Center, Tampa, FL; [16]Beaujon Hospital, Clichy, France; [17]ABX-CRO advanced pharmaceutical services Forschungsgesellschaft mbH, Dresden, Germany; [18]ITM Medical Isotopes GmbH, Garching, Germany; [19]Edouard Herriot Hospital, Lyon, France

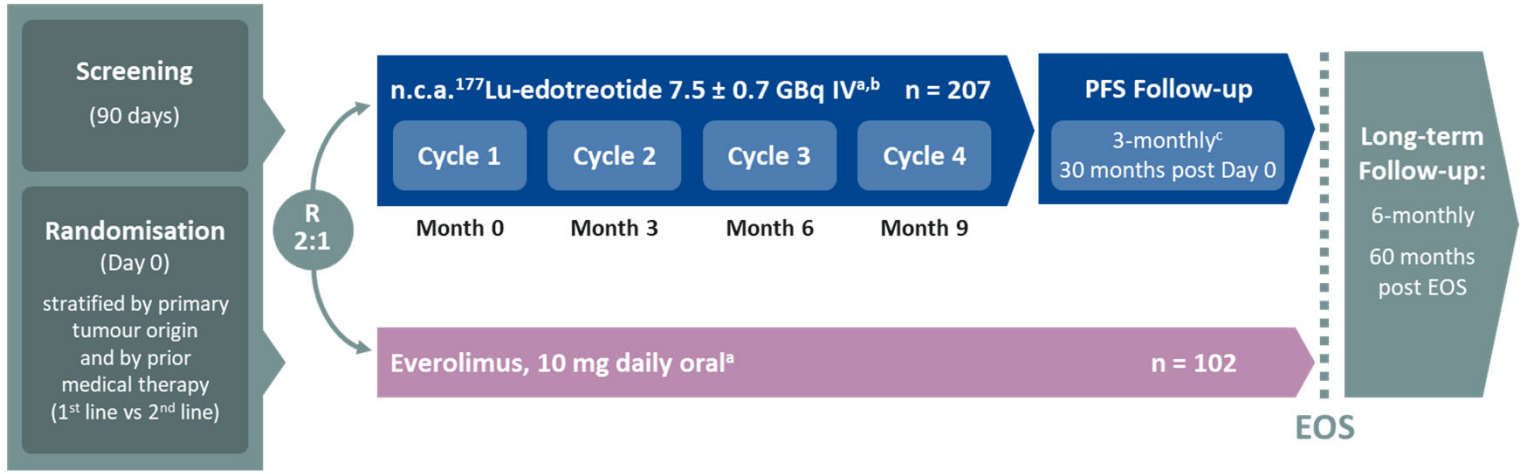
European Neuroendocrine Tumor Society (ENETS) Conference, March 5-7, 2025. Krakow, Poland.
***J Neuroendocrinol*. 2025;37 Suppl 1:e70018. Erratum in: *J Neuroendocrinol*. 2025;37(8):e70025.**

COMPETE Trial Design

Prospective, randomized, phase 3 trial with active comparator

Key inclusion criteria

- ☑ ≥18 years of age
- ☑ Well-differentiated, non-functional GE-NET, or functional/non-functional P-NET
- ☑ Grade 1 or 2 (Ki-67 ≤20%), unresectable or metastatic, progressive, SSTR+ disease (evidenced by SSTR imaging)
- ☑ Treatment naïve (1st line) or progressed under prior therapy (2nd line)
- ☑ GFR ≥60 mL/min/1.73 m²



Primary endpoint: PFS[d] (per RECIST 1.1 by BICR)
Secondary endpoints: ORR, OS, DCR, DDC, HRQoL, safety, and tolerability

[a]Until diagnosis of progression or EOS; [b]With concomitant infusion of a nephroprotective amino acid solution (starting 30–60 min before administration of n.c.a. ^{177}Lu-edotreotide, and lasting 4-6 hrs); [c]Or until diagnosis of progression, whichever is earlier; [d]PFS was determined from randomisation until disease progression or death and analysed using a stratified log-rank test to confirm the hypothesis of a PFS benefit with n.c.a. ^{177}Lu-edotreotide vs everolimus with a power of 0.8 and a significance level α=0.05 (two-sided)

BICR= Blinded Independent Central Review; DCR = disease control rate; DDC = duration of disease control; EOS = end of study; GE-NET = gastroentero neuroendocrine tumour; GFR = glomerular filtration rate; HRQoL = health-related quality of life; n.c.a. = non-carrier-added; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; P-NET = pancreatic neuroendocrine tumour; R = randomisation; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours, version 1.1; SSTR = somatostatin receptor.

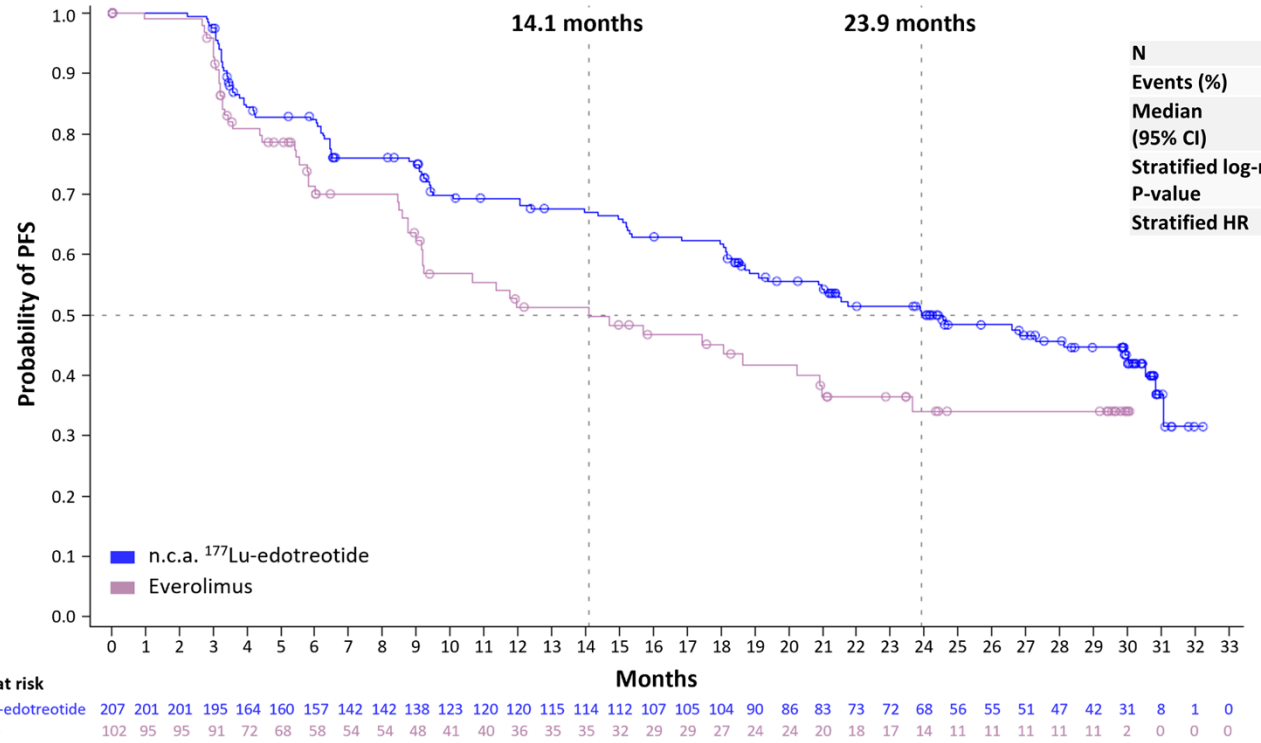
Baseline Patient Demographics and Disease Characteristics

Characteristic	n.c.a. ^{177}Lu-edotreotide (N = 207)	Everolimus (N = 102)
Age, years, mean (SD)	62.8 (11.6)	59.7 (12.2)
Sex, n (%)		
Female	97 (46.9)	44 (43.1)
Male	110 (53.1)	58 (56.9)
WHO GEP-NET classification,[a] n (%)		
Grade 1	43 (20.8)	29 (28.4)
Grade 2	164 (79.2)	73 (71.6)
Primary tumour origin, n (%)		
GE-NET (non-functional)	88 (42.5)	43 (42.2)
P-NET	119 (57.5)	59 (57.8)
Functional	20 (16.8)	8 (13.6)
Non-functional	99 (83.2)	51 (86.4)
Treatment history, n (%)		
Treatment naïve (1st line)	30 (14.5)	17 (16.7)
One prior therapy (2nd line)	177 (85.5)	85 (83.3)

[a]Local assessment

GE-NET = gastroenteric neuroendocrine tumour; GEP-NET = gastroenteropancreatic neuroendocrine tumour; n.c.a. = non-carrier-added; NET = neuroendocrine tumour; P-NET = pancreatic neuroendocrine tumour; SD = standard deviation; WHO = World Health Organization.

PFS (Primary Endpoint by BICR)



	n.c.a. ^{177}Lu-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)	

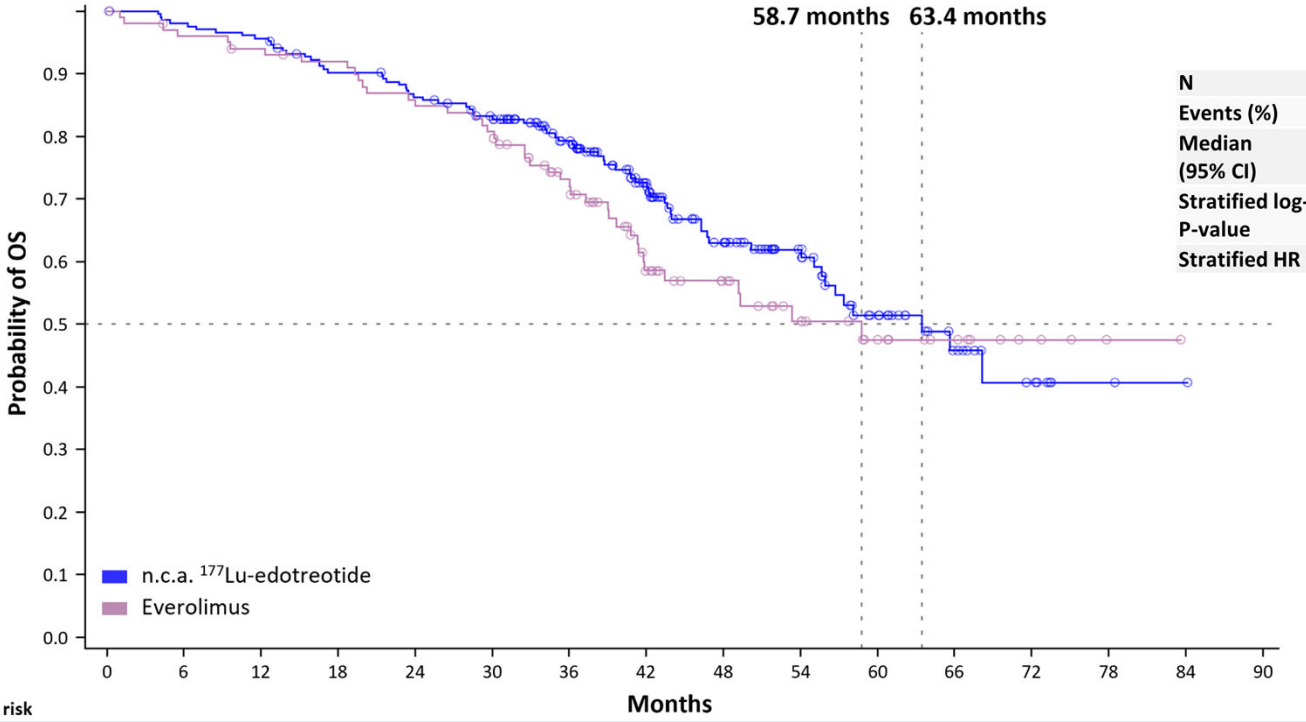
Subjects at risk

n.c.a. ^{177}Lu-edotreotide	207	201	201	195	164	160	157	142	142	138	123	120	120	115	114	112	107	105	104	90	86	83	73	72	68	56	55	51	47	42	31	8	1	0
Everolimus	102	95	95	91	72	68	58	54	54	48	41	40	36	35	35	32	29	29	27	24	24	20	18	17	14	11	11	11	11	11	2	0	0	0

Median PFS was significantly longer with n.c.a. ^{177}Lu-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.

Interim OS (Key Secondary Endpoint)



	n.c.a. ^{177}Lu-edotreotide	Everolimus
N	207	102
Events (%)	73 (35.3)	42 (41.2)
Median (95% CI)	63.4 (55.7, NE)	58.7 (41.8, NE)
Stratified log-rank P-value	0.206	
Stratified HR	0.78 (0.53, 1.15)	

Interim median OS was numerically higher, but not conclusive for n.c.a. ^{177}Lu-edotreotide vs everolimus
(**63.4 vs 58.7 months**; p=0.206; HR 0.78, 95% CI [0.53, 1.15])

CI = confidence interval; HR = hazard ratio; n.c.a. = non-carrier-added; NE = not evaluable; OS = overall survival.

Safety

TEAE	n.c.a. ^{177}Lu-edotreotide (N = 217)[a]	Everolimus (N = 99)[b]
Any TEAE, n (%)	211 (97.2)	99 (100)
Any TEAE related to the study drug, n (%)	179 (82.5)	96 (97.0)
Any TE SAE, n (%)	66 (30.4)	44 (44.4)
Any TE SAE related to the study drug, n (%)	7 (3.2)	15 (15.2)
Any Grade ≥ 3 TEAE, n (%) Grade 3 Grade 4 Grade 5	 79 (36.4) 11 (5.1) 14 (6.5)	 48 (48.5) 8 (8.1) 7 (7.1)
At least one TEAE leading to action[c] on study treatment, n (%)	23 (10.6)	67 (67.7)

Median duration of follow-up:

- 40.9 months in the n.c.a.^{177}Lu-edotreotide group
- 40.8 months in the everolimus group

A lower proportion of patients experienced TEAEs related to study medication n.c.a. ^{177}Lu-edotreotide vs everolimus (**82.5% vs 97.0%**); one serious (Grade 2) TEAE of MDS related to n.c.a. ^{177}Lu-edotreotide; there were no unforeseen TEAEs

[a]The number of patients treated (N = 217) in the n.c.a. ^{177}Lu-edotreotide arm is higher than the number of patients randomised (N = 207) because patients treated in the non-randomised cohort of sub-study C are also included; [b]The number of patients treated (N = 99) in the everolimus arm is smaller than the number of patients randomised (N = 102) because 3 patients were randomised but not treated; [c]Dose reduction, delay to next treatment cycle or treatment discontinuation

MDS = myelodysplastic syndrome; n.c.a. = non-carrier-added; SAE = serious adverse event; TE = treatment-emergent; TEAE = treatment-emergent adverse event.

Conclusions from COMPETE

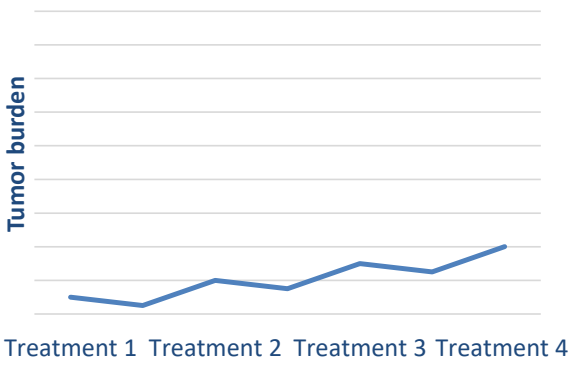
- Evidence that PRRT should be preferred over everolimus and prioritized in treatment sequencing due to clinically and statistically significant PFS benefit, minor trend towards OS benefit, and fewer adverse effects
  - Limited head-to-head comparative data among PRRT, targeted therapies, and chemotherapy continue to make sequencing decisions challenging

- Concurrent SSA likely not necessary in non-functional NETs treated with PRRT

Does Treatment Influence Pattern of Progression?

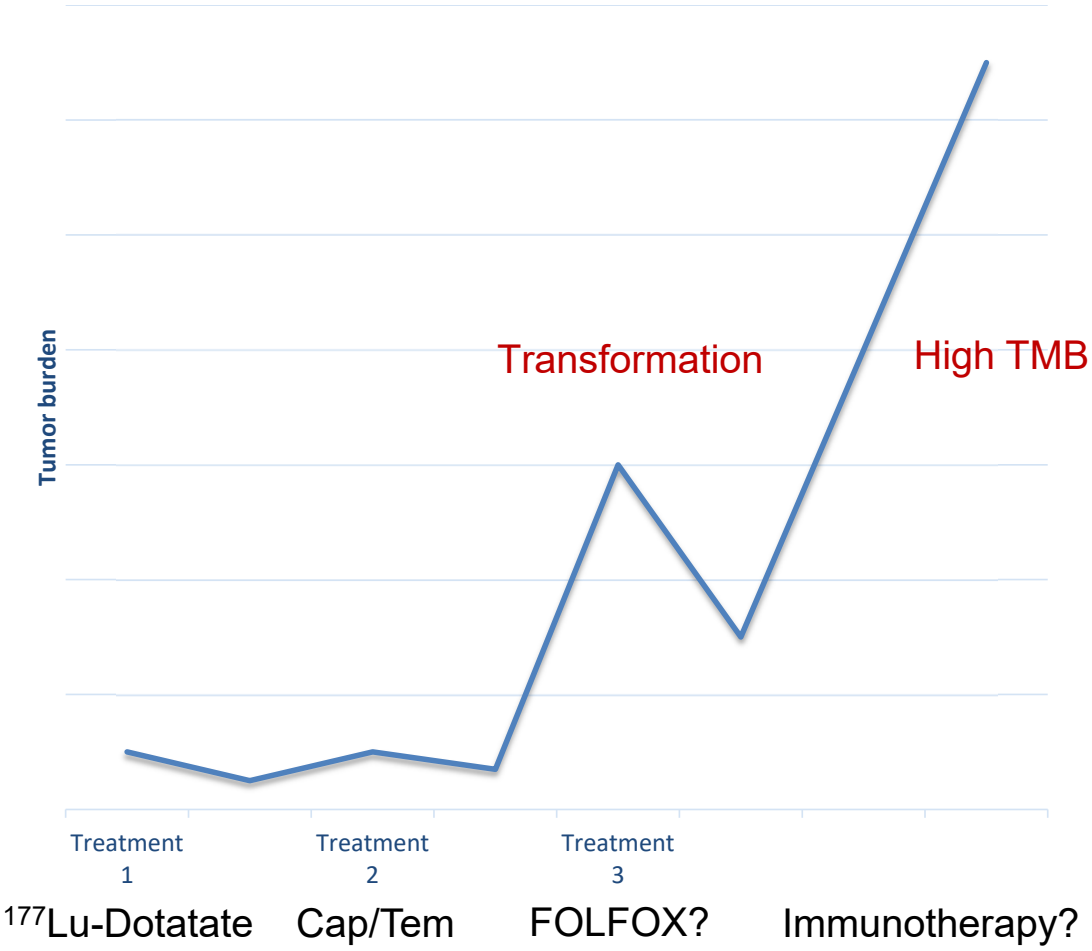
- Alkylating agents (eg, temozolomide) can lead to hypermutator phenotype
- PRRT may induce clonal mutations

Typical Progression Pattern



Atypical Progression Pattern

Cordero-Hernandez IS, et al. Presented at: North American Neuroendocrine Tumor Society (NANETS); Oct. 27-29, 2022; Washington, D.C.; Abstract 21416.

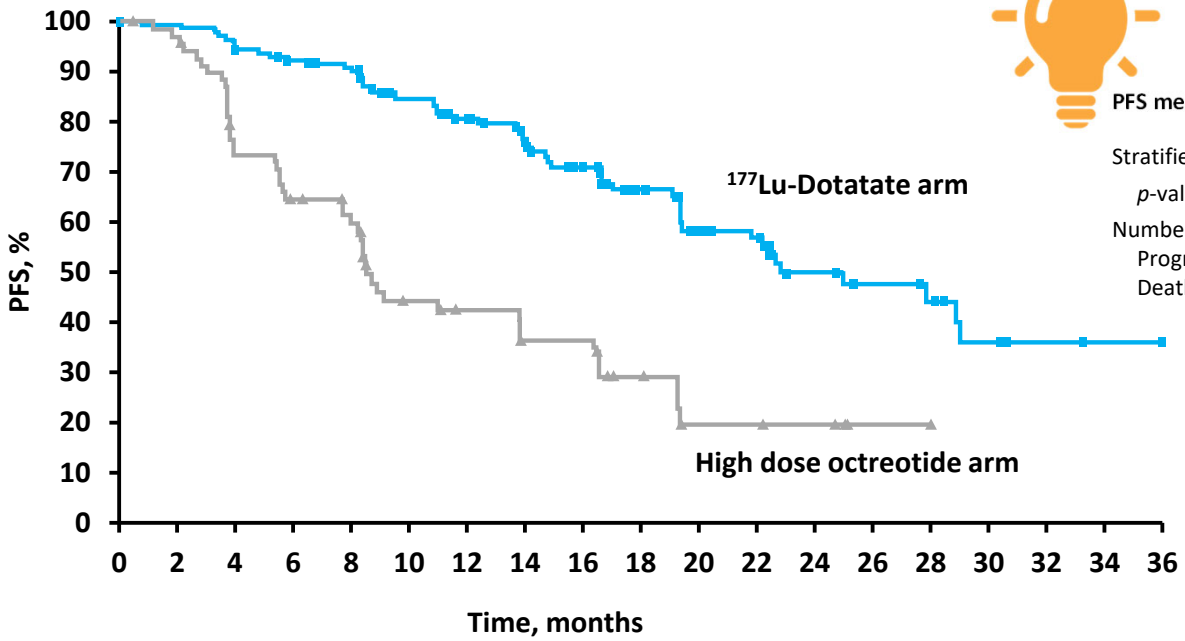


Al-Toubah T, et al. *Oncologist*. 2021;26(2):115-119. Cao Y, et al. *Cancer Commun* (Lond). 2020;40(12):746-751.

First-Line PRRT:
When Is it Appropriate?

NETTER-2:

First-line ^{177}Lu-Dotatate + octreotide vs high-dose octreotide for *higher* G2 and G3 GEP-NETs (Ki-67 10%-55%)



	^{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, et al. *Lancet.* 2024;403(10446):2807-2817.

Objective Response

	^{177}Lu-Dotatate arm n=151	High-dose octreotide arm n=75
Best overall response, n (%)		
CR	8 (5.3)	0 (0)
PR	57 (37.7)	7 (9.3)
SD	72 (47.7)	42 (56.0)
Non-CR / Non-PD	0 (0)	1 (1.3)
PD	8 (5.3)	14 (18.7)
Unknown	6 (4.0)	11 (14.7)
ORR, n (%)	**65 (43.0)**	**7 (9.3)**
[95% CI]	[35.0, 51.3]	[3.8, 18.3]
Stratified odds ratio (95% CI)	7.81 (3.32, 18.40)	
p-value	<0.0001	
Responders, n	65	7
Duration of response median (95% CI), months	23.3 (18.4, NE)	NE (2.3, NE)

Singh S, et al. *Lancet*. 2024;403(10446):2807-2817.

Does NETTER-2 Change the Treatment Paradigm for High G2 and G3 GEP-NET?

- Data provides strong rationale for early PRRT in this population

However…

PRRT carries more risk than SSA. Survival benefit of early PRRT is unclear. There may be patients (especially G2) who could be started on SSA and wait until progression before switching to PRRT.

Was octreotide legitimate comparator? There are other potential treatments that are more active than SSA in this population (eg, capecitabine/temozolomide).

First-line PRRT should be *considered* for WD-GEPNET with Ki-67 >10%, but other options exist, including SSA monotherapy for patients with relatively low-volume disease.

Thoracic NET (Lung and Thymus)

- Grade 1, “typical carcinoid,” 0-1 mitoses/10 HPF
- Grade 2, “atypical carcinoid,” 2-10 mitoses/10 HPF
- Grade 3, well-differentiated, not well-defined category
- Weak/heterogeneous SSTR expression is observed in majority of metastatic tumors
- Brain metastases much more common than in GI NETs
- Thymic NETs tend to metastasize to regional LNs, pleura, bone

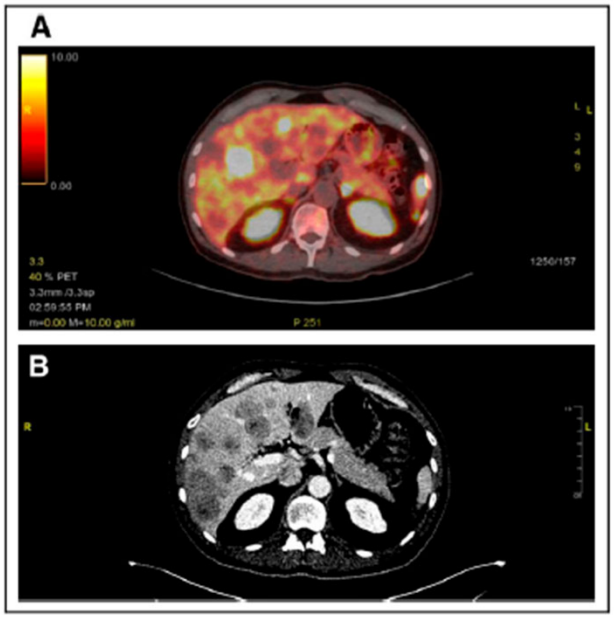


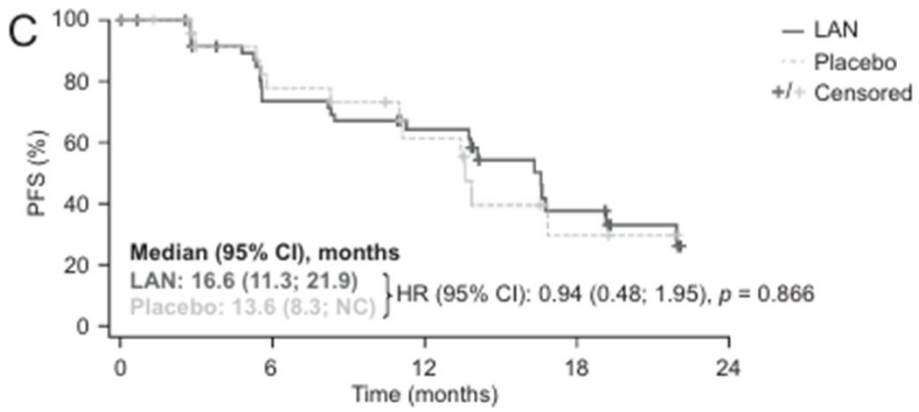
FIGURE 2. Heterogeneous SSTR expression on PET/CT (A) compared with metastatic lesions on contrast-enhanced CT (B).

HPF = high-power field.

Al-Toubah T, et al. *J Nucl Med.* 2023;64(12):1895-1898.

Systemic Treatments: SSA

- Role of SSAs uncertain: consider if tumors express SSTR uniformly and/or carcinoid syndrome
- SPINET study (lanreotide vs placebo in lung NETs) closed prematurely for slow accrual



Baudin E, et al. *Endocr Relat Cancer*. 2024;31(9):e230337.

^{177}Lu-Dotatate Outcomes in Lung NETs Compared to Other Primary Sites

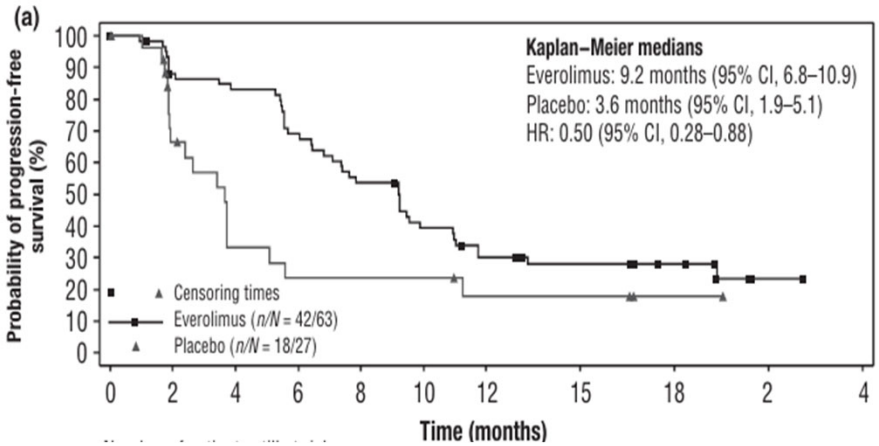
Primary Site	Total	PR + CR		SD		PD		Median PFS and OS (months)	
	N	N	%	N	%	N	%		
Midgut NET	181	57	31	99	55	16	9	30	60
Non-PD	32	10	31	18	56	3	9	24	82
PD	94	29	31	50	53	9	10	29	50
Pancreatic NET	138	72	55	40	30	17	13	30	71
Non-PD	21	10	48	10	48	1	5	31	ND
PD	66	38	58	15	23	10	15	31	71
Hindgut	12	4	33	6	50	1	8	29	ND
Lung	**23**	**7**	**30**	**7**	**30**	**6**	**26**	**20**	**52**
Other foregut	12	5	42	5	42	2	17	25	ND
Unknown primary	82	29	35	35	43	11	13	29	53
Total	443	174	39	192	43	53	12	29	63

ND = not defined.

Brabander T, et al. *Clin Cancer Res.* 2017;23(16):4617-4624.

Everolimus, Cabozantinib, and Chemotherapy

- **Everolimus:** Subset of 90 lung NET patients on RADIANT-4 trial shows comparable outcomes with everolimus in GI NETs (HR 0.5 for PFS)
- **Cabozantinib:** Subset of 49 lung and thymic NETs on CABINET showed HR of 0.17 for PFS
- **Chemo:** Small retrospective series of temozolomide or capecitabine/ temozolomide demonstrated ORR of ~20%-30%

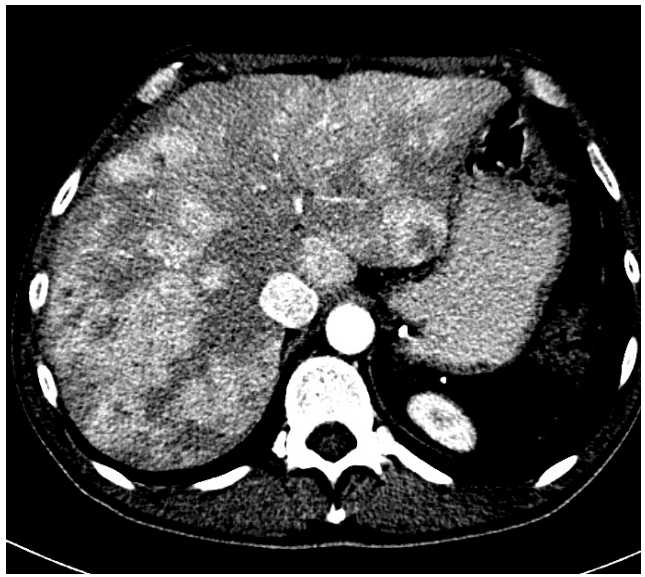


Tumor Site	Cabo Events/ Total	Placebo Events/ Total	HR (95% CI)
GI	37/70	26/26	0.47 (0.28-0.8)
Lung/thymus	15/33	9/16	0.17 (0.07-0.42)
Other	6/9	3/5	0.13 (0.03-0.54)

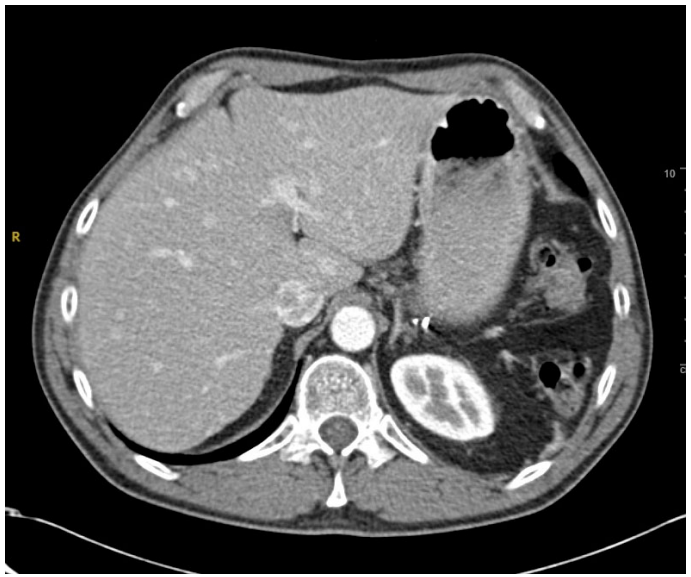
Fazio N, et al. *Cancer Sci*. 2018;109(1):174-181. Chan JA, et al. *N Engl J Med*. 2025;392(7):653-665. Al-Toubah T, et al. *Oncologist.* 2020;25(1):e48-e52

Local Treatments for Local Progression

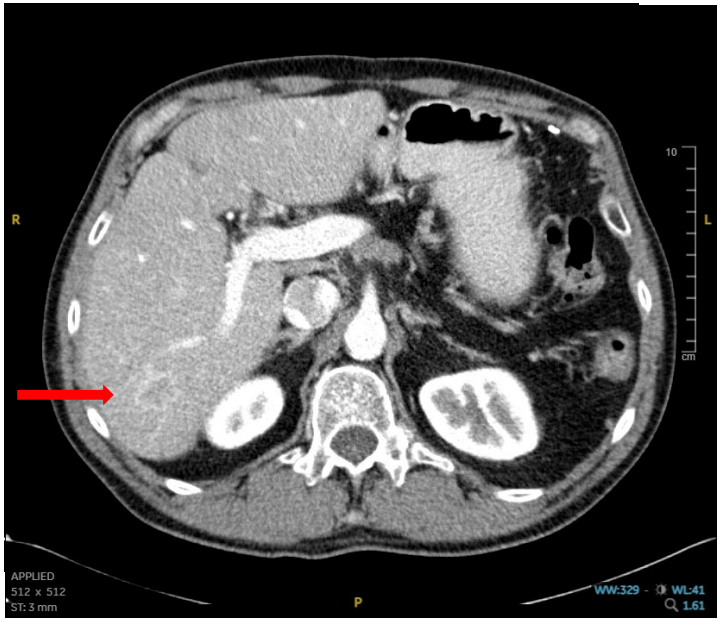
Metastatic grade 2 pNET to the liver; primary resected



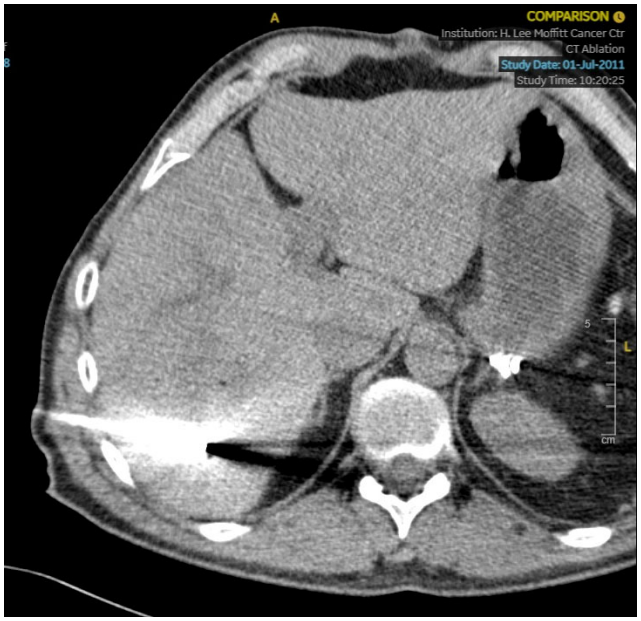
11/2009: Started capecitabine/temozolomide



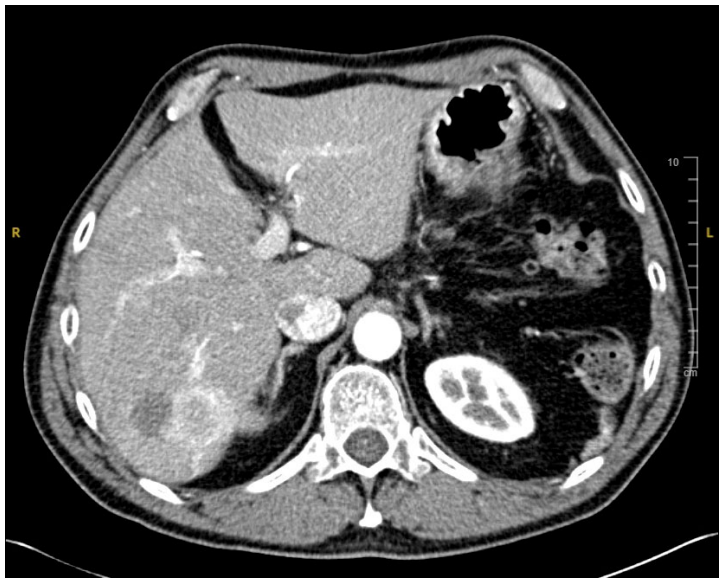
3/2011: Near CR



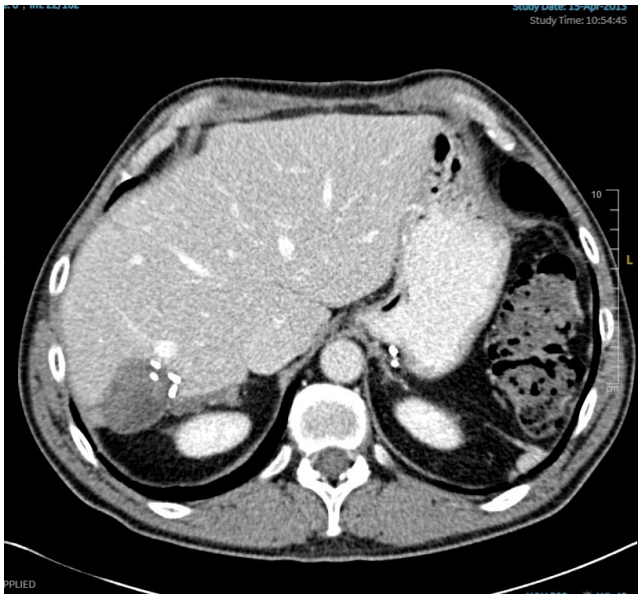
6/2011: Solitary progression segment 6



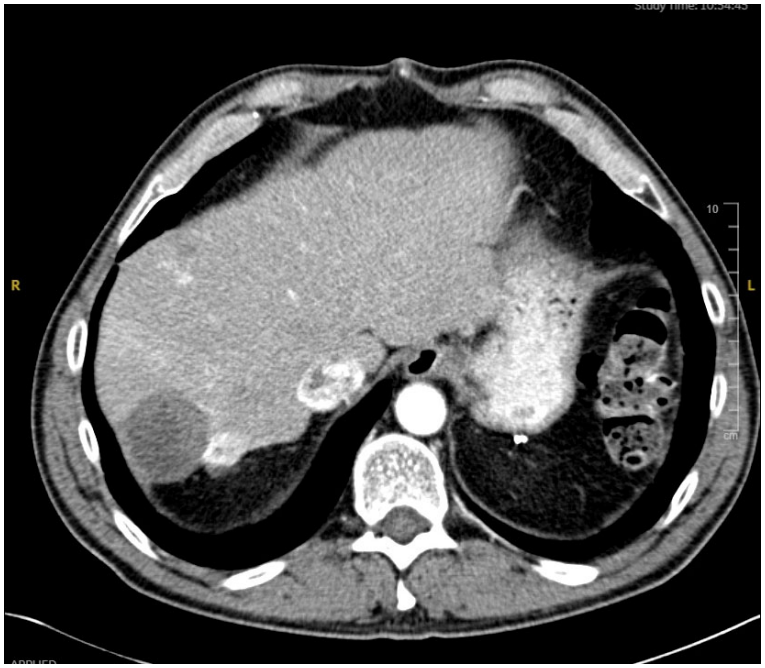
Radiofrequency ablation



3/2012: Recurrence adjacent to ablation site



Resection



4/2013: Another recurrence next to resection site and 2 other subcm hypervascular lesions

- Operative ablation x3
- Continued capecitabine/temozolomide until 2019 (10 yrs total)
- Stopped treatment, remains in remission

Conclusion: Think about locoregional treatments for local progression

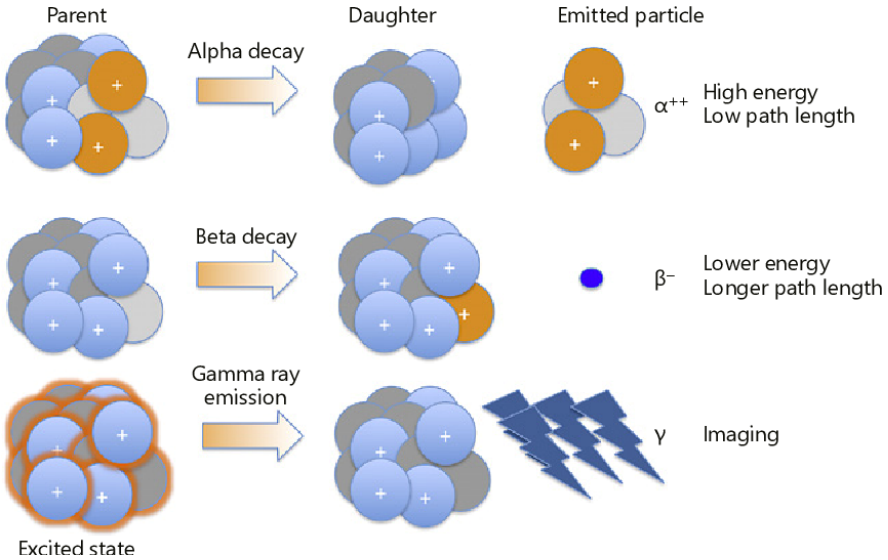
Conclusions

- Treatment of metastatic NETs involves complex and individualized selection of systemic and liver-directed therapies
- Few trials have compared active therapies
- COMPETE provides reassurance that relatively early use of PRRT in appropriate patients with GEP-NET is a favorable strategy

Alpha-Emitting PRRT:

Current Research

Radioactive Emissions

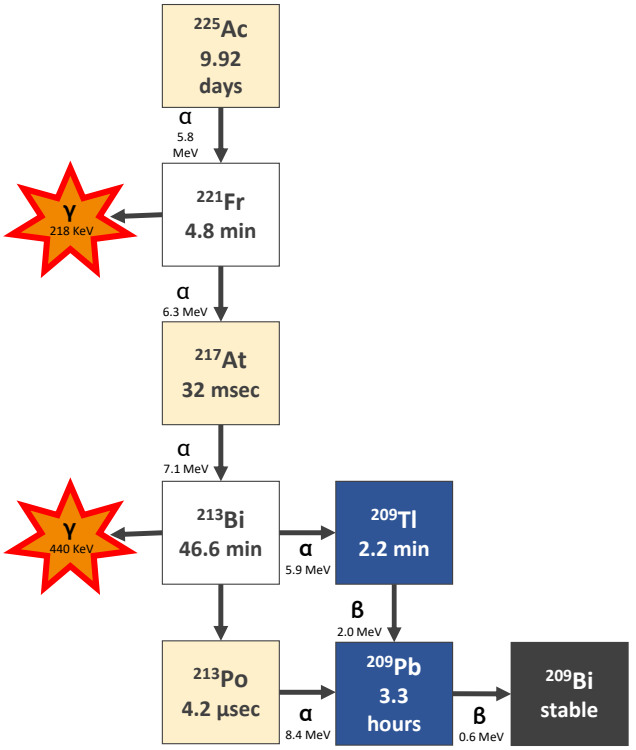


Alpha particles = 2 protons + 2 neutrons (He^{2+})

Navalkissoor S, et al. *Neuroendocrinology.* 2019;108(3):256-264.

^{225}Actinium (^{225}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) 27.5 MeV
- Both ^{221}Fr and ^{213}Bi emit imageable gamma rays at 218 KeV and 440 KeV, respectively



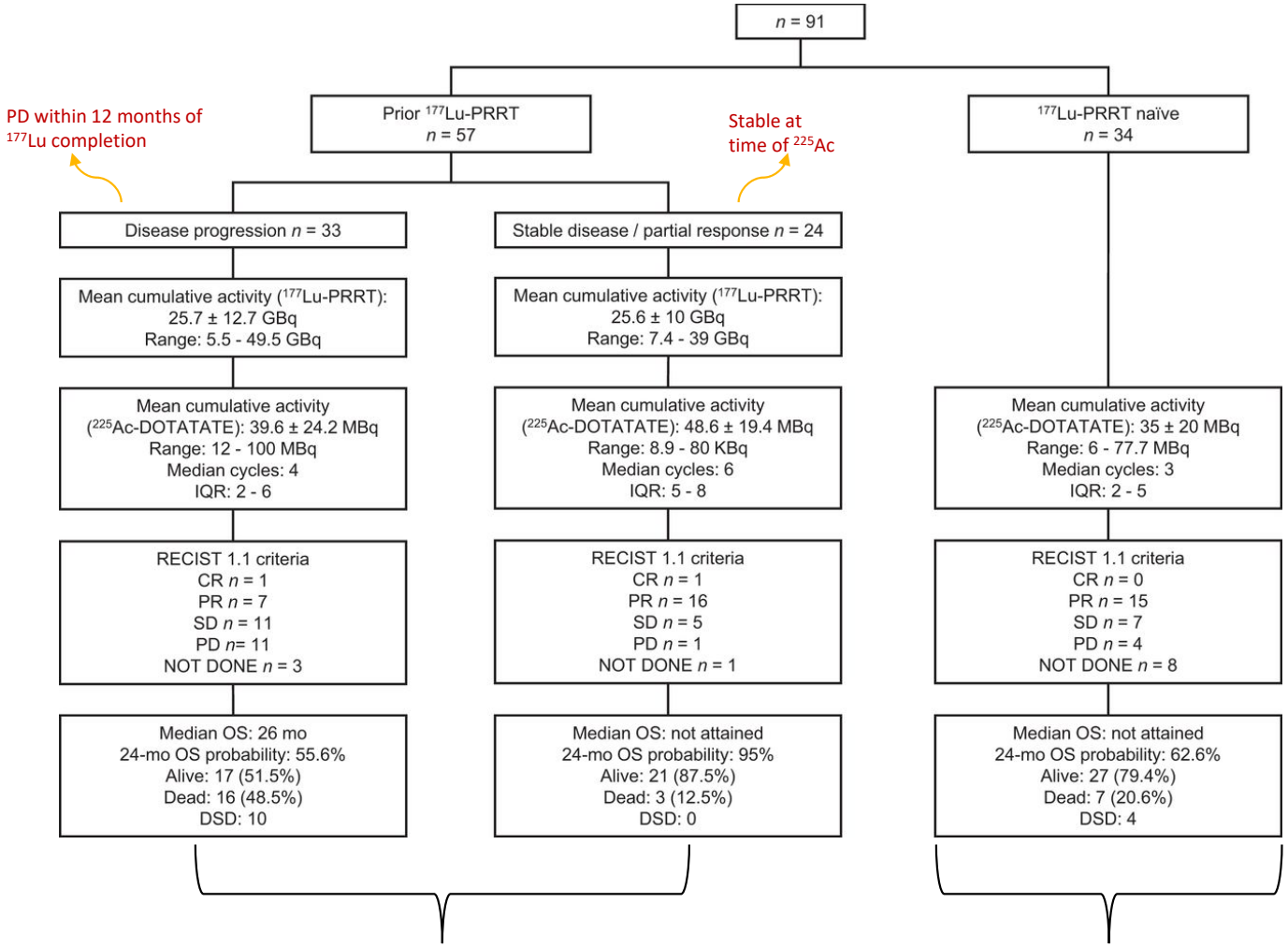
^{225}Ac-Dotatate: The New Delhi Real World Experience in GEP-NET Patients

- 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

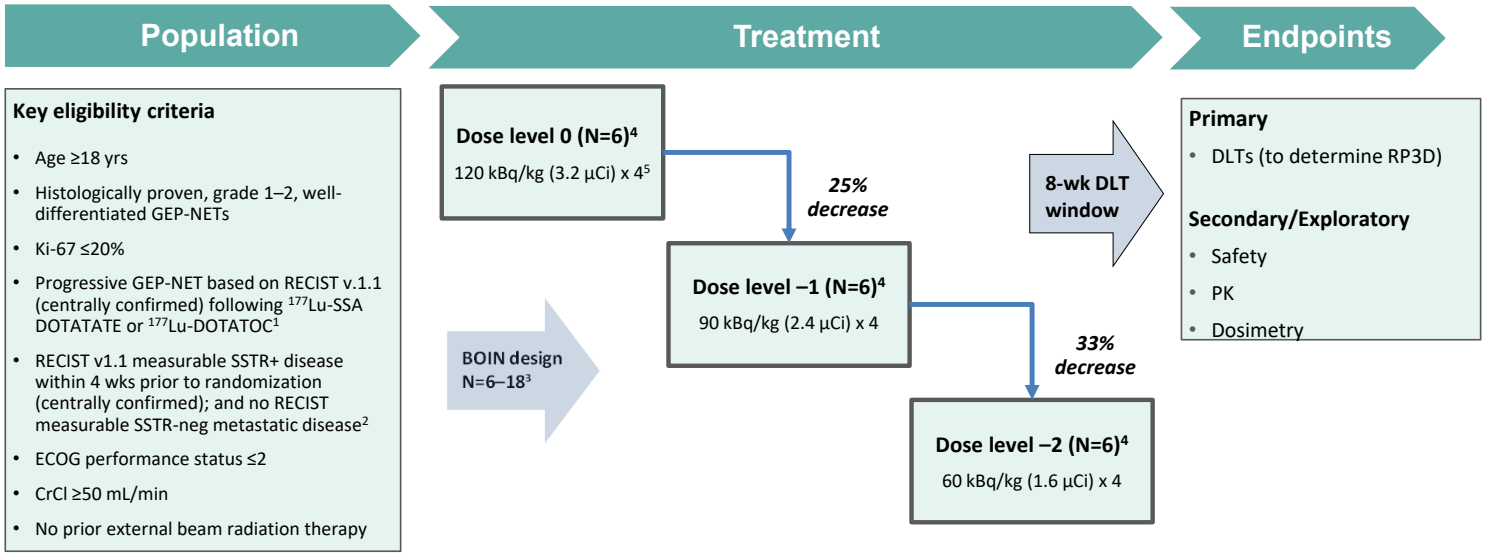
Patient Characteristics at Baseline (n = 91)

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 S, et al. *J Nucl Med*. 2022: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%

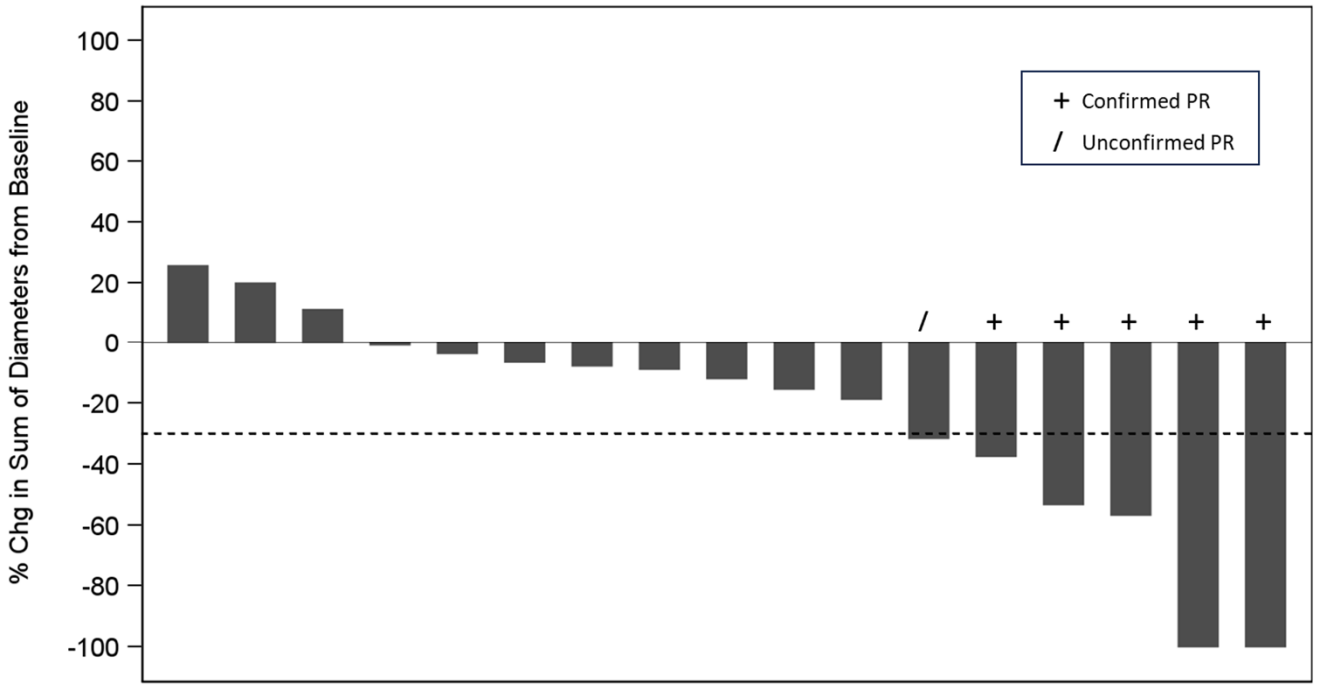
ACTION-1: ^{225}Ac-Dotatate – Part 1 (Phase 1b)



[1] The oldest scan must not be older than 3 yrs from the date of screening, and the most recent scan must not be older than 4 wks prior to enrollment [2] SSTR PET imaging must be completed within 12 wks (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 wks, 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 J, et al. European Society for Medical Oncology (ESMO). October 20-24, 2023. Madrid, Spain.

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



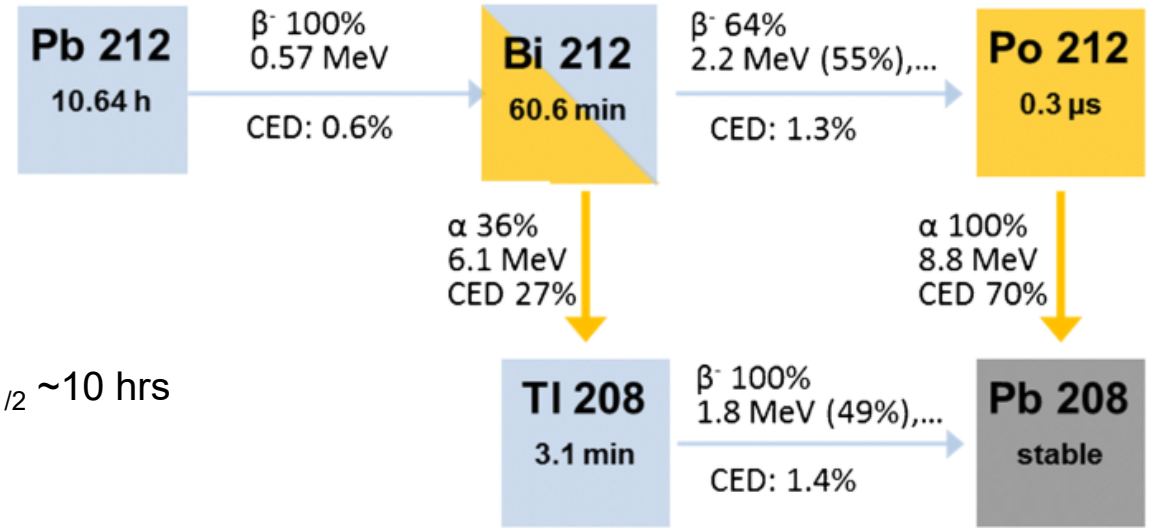
Efficacy evaluable population are subjects who received at least 1 RYZ101 dose and had at least 1 efficacy evaluable assessment

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)

[a]Includes the terms hemoglobin decreased and anemia; [b]Includes the terms chronic kidney disease and creatinine renal clearance decreased.
SAE = serious adverse event; TEAE = treatment-emergent adverse event.

^{212}Pb (Lead) Radioactive Decay



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

Dos Santos JC, et al. *Eur J Nucl Med Mol Imaging.* 2019;46(5):1081-1091.

^{212}Pb-Dotamtate Phase 1 and 2 Data Evaluating GEP-NET Population

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%)

Strosberg J, et al. American Society of Clinical Oncology Annual Meeting (ASCO 2024). May 29, 2024; Chicago, IL; Abstract 4020.
Strosberg JR, et al. *J Clin Oncol.* 2024;42(16_suppl):4020-4020.

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 DoR months (95 CI#) % with observed DOR of ≥6 months* % with observed DOR of ≥12 months*	NE 15.2 months, NE 100% (5 of 5) 100% (4 of 4)	17 months 17 months, NE 100% (17 of 17) 91% (10 of 11)	NE 15.2 months, NE 100% (22 of 22) 93% (14 of 15)

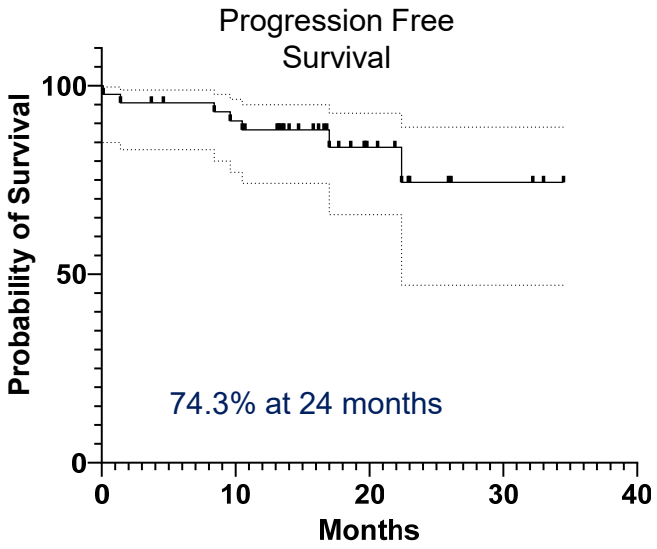
Database extraction May 28, 2024
#asymmetrical
*Landmark analysis
†GEP-NET subjects at RP2D
ORR = overall response rate; DOR = duration of response.

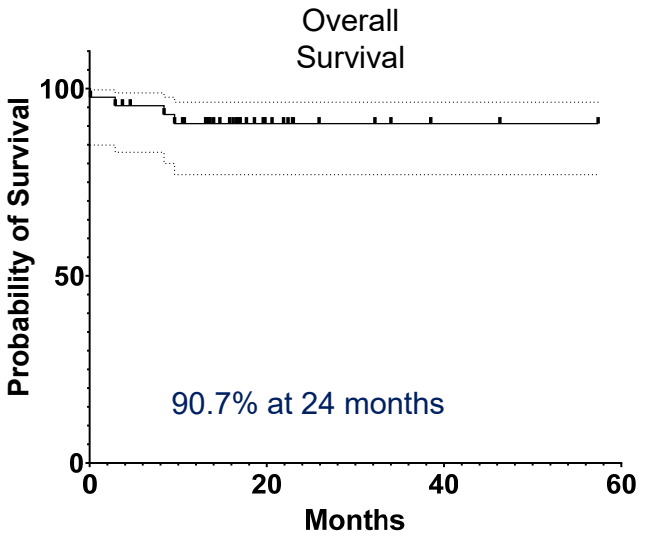
The combined ORR from both Phase 1 and Phase 2 is 56.8% (95%CI:42.2%-70.3%)

Strosberg J, et al. *J Clin Oncol.* 2024;42(16_suppl):4020-4020.

Preliminary PFS and OS in PRRT-Naïve Subjects with Metastatic SSTR+ GEP-NETs

(Phase 1 and Phase 2)





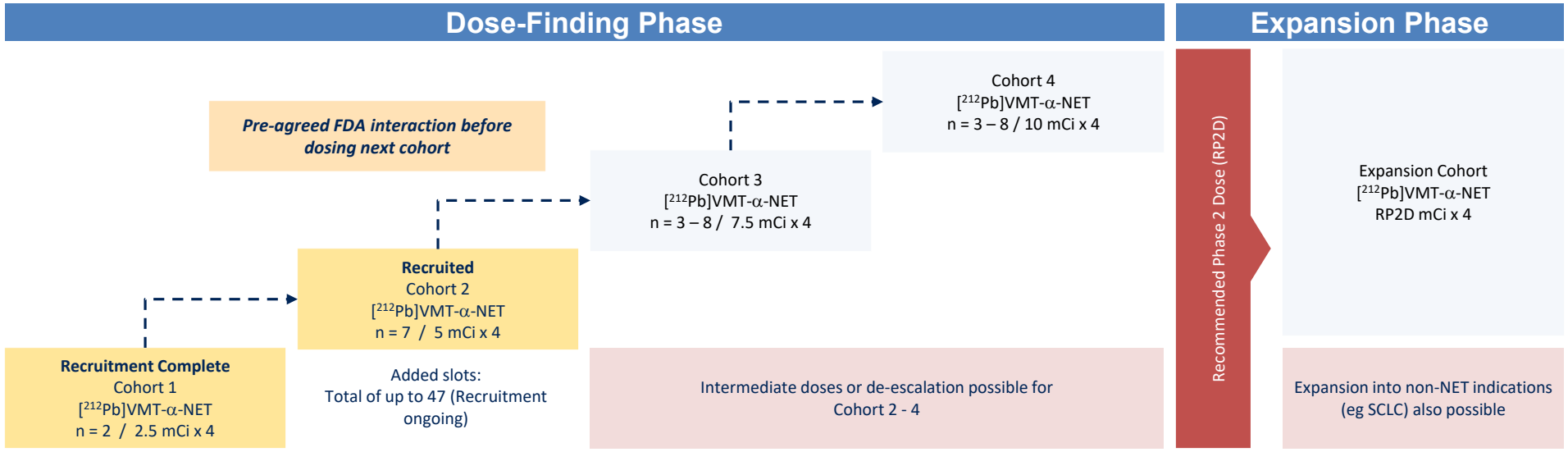
Strosberg J, et al. *J Clin Oncol.* 2024;42(16_suppl):4020-4020.

Safety

- 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

Strosberg J, et al. *J Clin Oncol.* 2024;42(16_suppl):4020-4020.

^{212}Pb-VMT-α-NET



Cohorts 1 & 2 reported here at ASCO

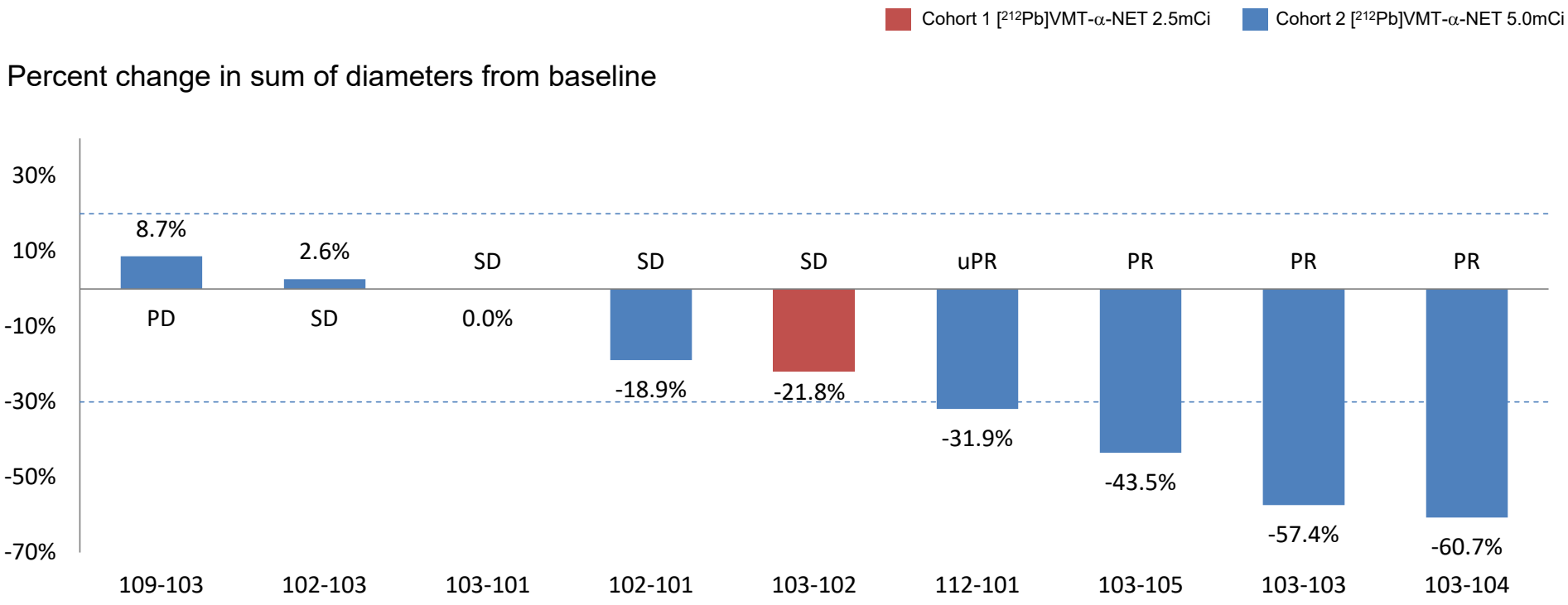
Trial Parameters

Dose-finding Population	Key Study Features	Study Endpoints
• Advanced/unresectable or metastatic NETs • Progressive disease on prior therapy • PRRT naïve • FDA-approved SSTR2 PET/CT avid disease	• Bayesian mTPI-2 design based on iterative toxicity probability monitoring • Dosimetry to be assessed during screening period for cohorts 1 & 2 using [^{203}Pb]VMT-α-NET	• **Primary:** to measure incidence of DLTs following a single administration of [^{212}Pb]VMT-α-NET in order to determine the MTD and/or MFD, and RP2D • **Secondary / exploratory** – ORR, DOR, PFS by RECIST v1.1 and OS – Using dosimetry, estimate selected organ and whole body absorbed radiation doses for [^{212}Pb]VMT-α-NET

Halfdanarson TR, et al. American Society of Clinical Oncology Annual Meeting (ASCO 2025). May 30, 2025; Chicago, IL; Abstract 3005.
Halfdanarson TR, et al. *J Clin Oncol*. 2025;43(16_suppl):3005-3005.

Waterfall Plot of Best Response by Patient

(All Patients Enrolled for DLT-Observation, n = 9)



Halfdanarson TR, et al. *J Clin Oncol*. 2025;43(16_suppl):3005-3005.

Conclusions

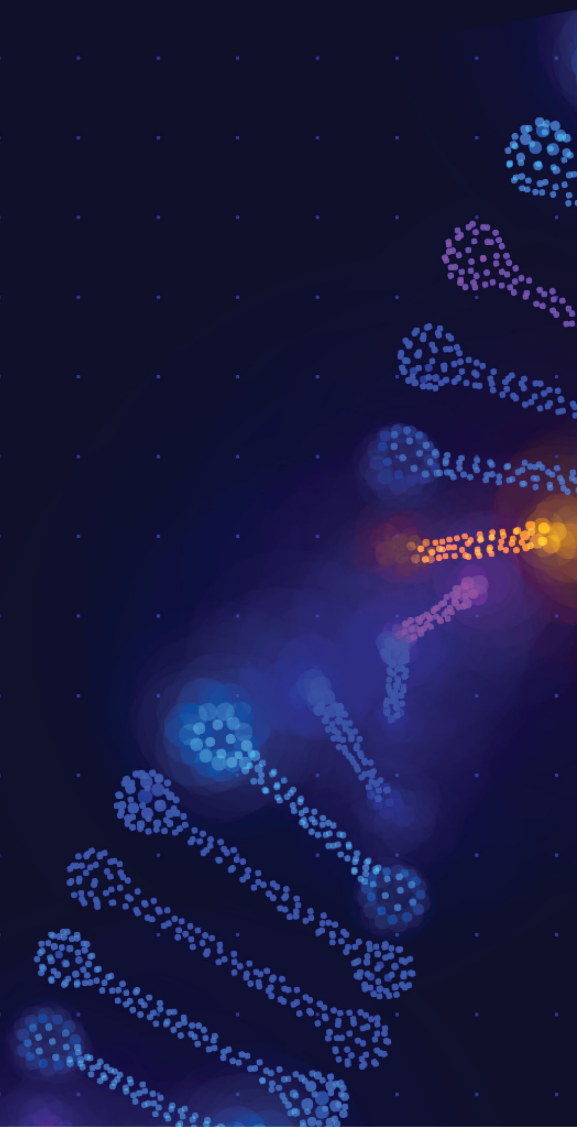
- Alpha emitters (eg, ^{225}Ac, ^{212}Pb) may be more effective than beta-emitting isotopes; however, randomized comparative studies are still pending
- Knowledge about adverse effects ─ particularly long-term risks ─ is still very limited
- Randomized trials of alpha emitters vs beta emitters are necessary for a better understanding of benefits/risks

Patient Video 60 seconds

References

Multidisciplinary and Patient-Centered Care Considerations

Nitya Raj, MD
Associate Attending Physician, Gastrointestinal Oncology
Memorial Sloan Kettering Cancer Center
New York, NY



Multidisciplinary

Surgery

- If resection is possible, even in stage IV disease, it should be considered

Nonsurgical Liver-Directed Therapy

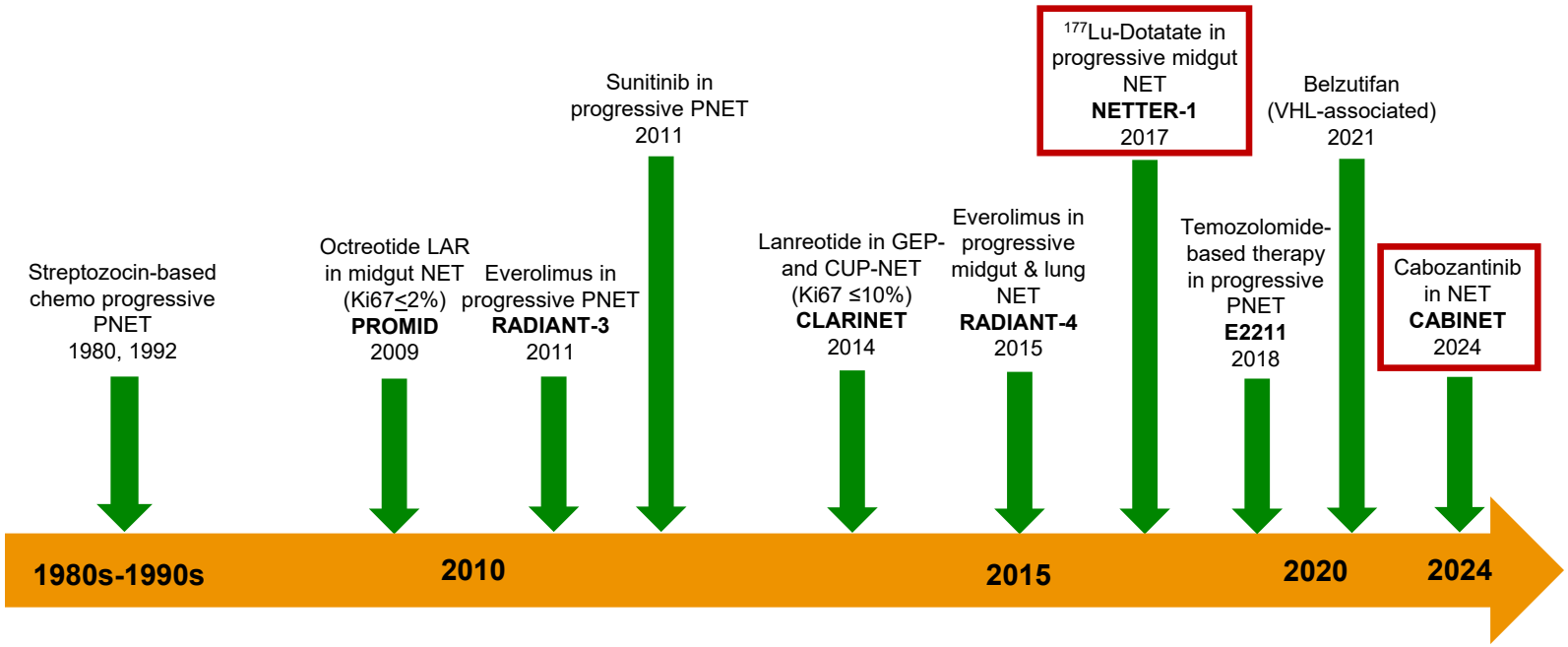
- Embolization (bland, chemo, Y90)

Systemic Treatment

- Somatostatin analogs
- Chemotherapy (alkylating, platinum) → foregut NET
- Targeted agents (everolimus, sunitinib, **cabozantinib**)
- Radioligand therapy (**^{177}Lu-Dotatate**)

Advances through Level 1 Evidence

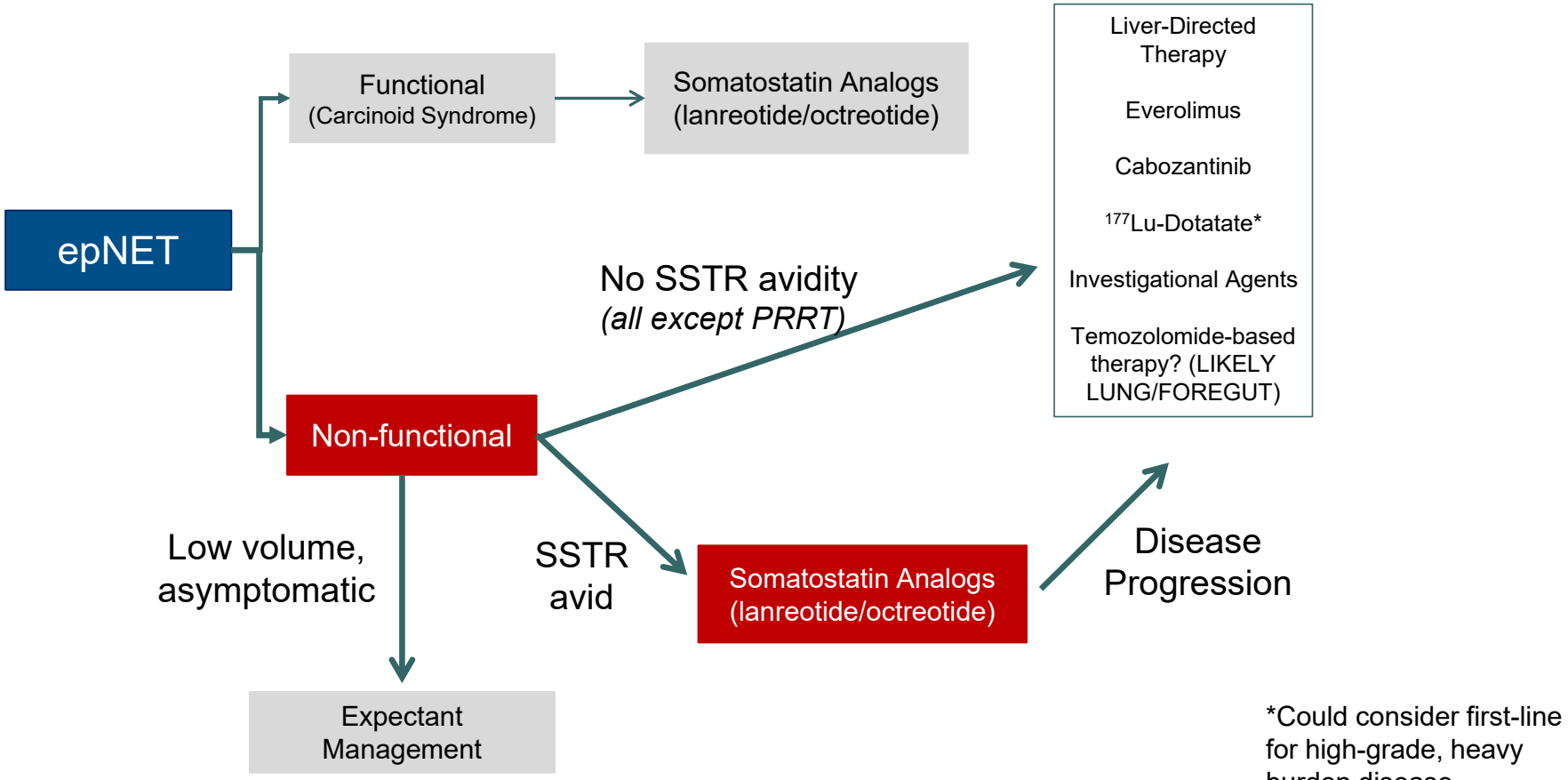
Neuroendocrine tumor treatment paradigm has evolved



Pearls for Decision-Making

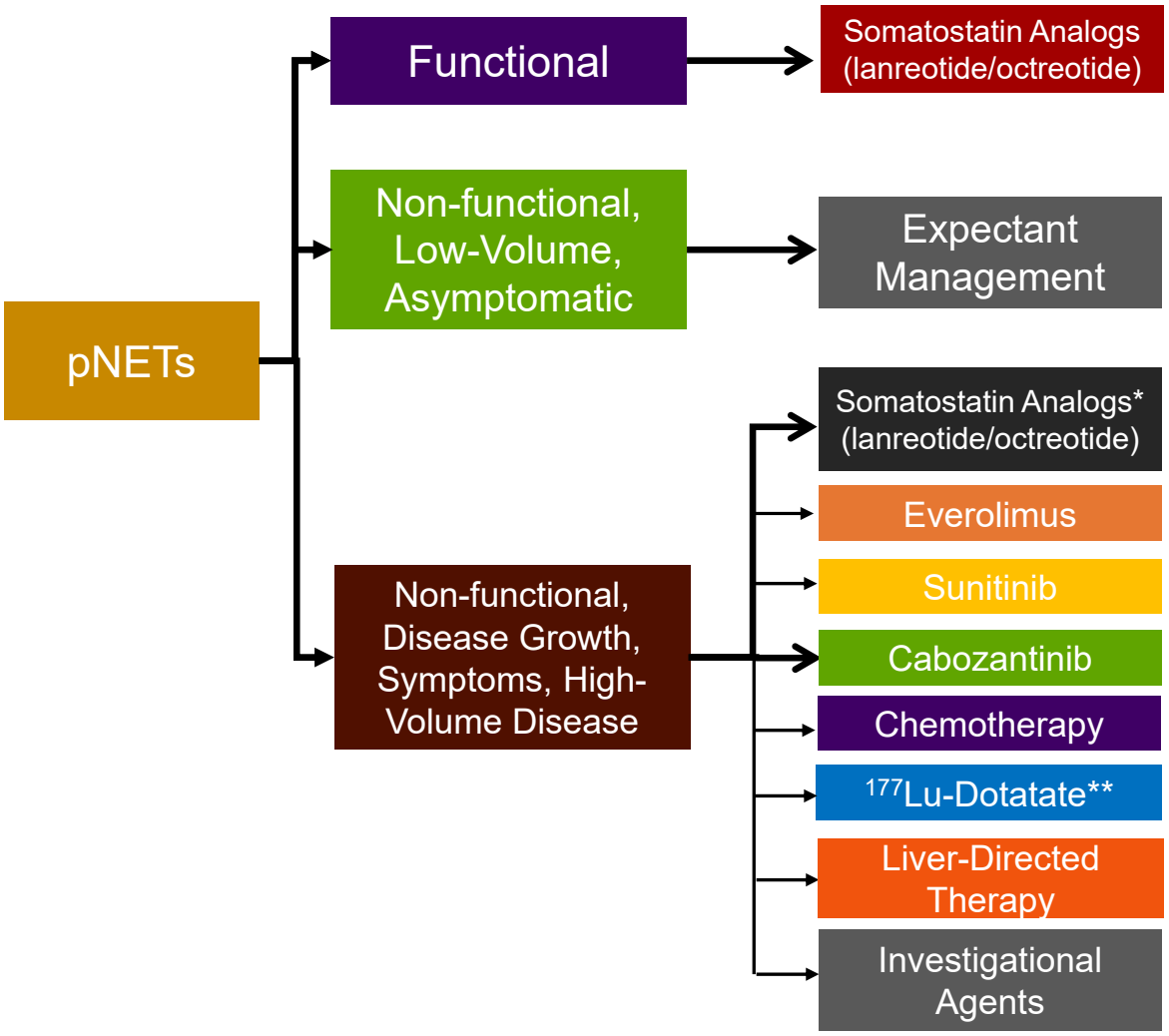
- When making treatment choices, one must consider
  - Pathology (ie, grade)
  - Goals of therapy (stabilization vs shrinkage)
  - Intrahepatic disease only? Consider *liver-directed approaches* before jumping to systemic…
- Involvement of the multidisciplinary team (NET tumor boards are essential!)
  - Medical oncology
  - Surgery
  - Interventional radiology
  - Nuclear medicine/radiation oncology (team administering radioligand therapy)
- Patient preference for treatment, patient education for shared decision-making
  - There is usually more than one right choice!

2025 Treatment Outlook for Advanced epNET



*Could consider first-line for high-grade, heavy burden disease

2025 Treatment Outlook for Advanced pNET



*For SSTR avid tumors
**Could consider first-line for high-grade, heavy burden disease

With limited prospective data
to guide decision-making,

Choose Biology

Clinical cases follow to illustrate sequencing…

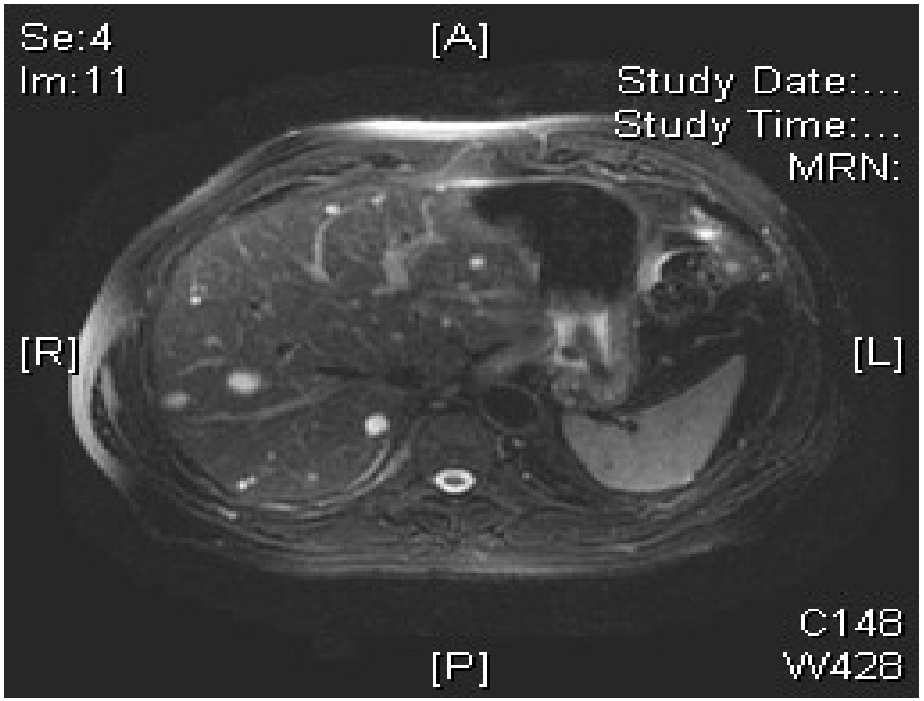
Case #1

NET small bowel, non-functional

- 40-year-old with non-specific abdominal pain
- Otherwise, asymptomatic; no weight loss, no diarrhea, no flushing
- Cross-sectional imaging: Mass in the terminal ileum (SB) and bilobar liver lesions
- Biopsy proven well-differentiated NET low-grade (1mitosis/50HPF)
- Ga-68 Dotatate: SSTR avid disease

Case #1

Initial Scan: How would you treat?



A. Observation

B. Liver-directed therapy

C. Somatostatin analog

D. Everolimus

E. ^{177}Lu-Dotatate

F. Cabozantinib

Case #1

- Patient followed expectantly for 14 months
- 14 months later, all lesions grew <1 cm from 1 yr prior in most lesions; biggest lesion increased from 0.8 cm → 1.5 cm
- Is there enough growth now to call this “progressive disease?”
  - If not now, then when?

Case #1

- Patient continued to be followed expectantly. Now 30 months with stable disease on imaging (every 6 months)
- What would you recommend at progression?

A. Liver-directed therapy
B. Somatostatin analog
C. Everolimus
D. ^{177}Lu-Dotatate
E. Cabozantinib

- What would you recommend after second progression? Third?

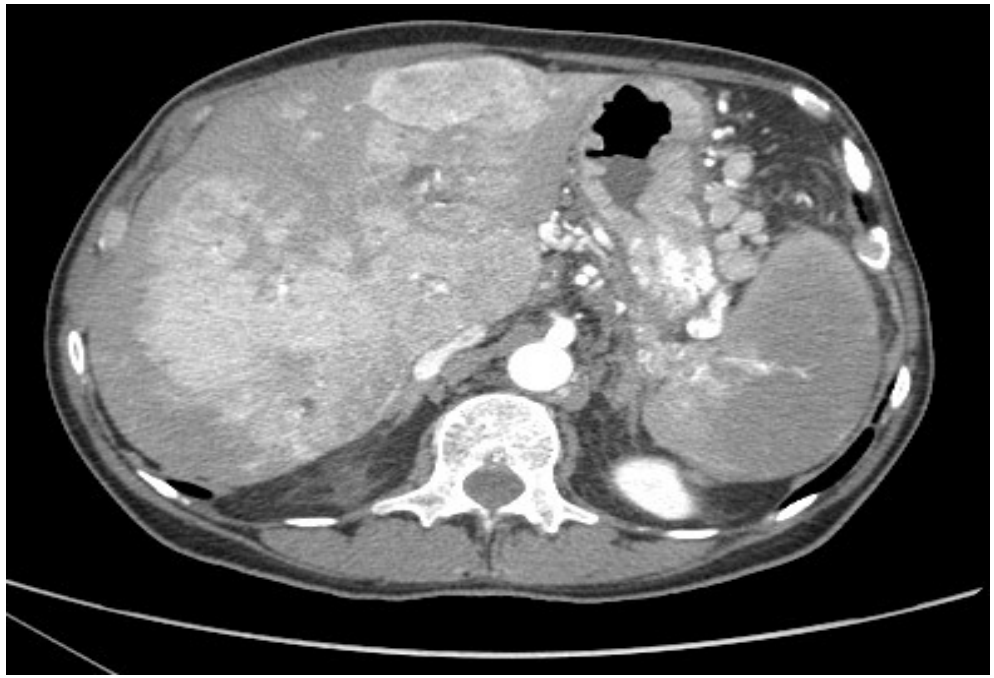
Case #1

- A yr later, the patient is felt to have radiographic disease progression and commences octreotide LAR
- 4 yrs into treatment with octreotide LAR, the liver lesions demonstrate further growth, and new lesions are identified in the bone
- What would you recommend at this time?
  A. Liver-directed therapy
  B. Everolimus
  C. ^{177}Lu-Dotatate
  D. Cabozantinib
- Patient proceeds to treatment with ^{177}Lu-Dotatate with ongoing control of the disease now 1.5 yrs after completion!

Case #2

pNET non-functional with heavy tumor burden

- 60-year-old with diabetes, HTN, and CAD develops abdominal discomfort, weight loss
- Cross-sectional imaging reveals unresectable bilobar liver disease and a pancreatic mass
- Ga-68 dotatate: highly somatostatin receptor avid
- Biopsy well-differentiated pNET, Ki-67 25%



HTN = hypertension; CAD = coronary artery disease.

Case #2

Management

How would you initially treat this patient?

A. Observation

B. ^{177}Lu-Dotatate

C. Surgery

D. Chemotherapy

E. Somatostatin analog

- Started on capecitabine/temozolomide to decrease tumor burden
- Treatment holiday after 9 months with no progression for 3.5 yrs!

Case #2

- Unfortunately, the patient ultimately experiences progression of the disease
- Receives ^{177}Lu-Dotatate, however, with lack of response to radioligand therapy with progression in the liver and primary pancreatic mass on first imaging after PRRT completion
- What are your next treatment options?

A. Liver-directed therapy

→ B. Somatostatin analog

→ C. Everolimus

→ D. Cabozantinib

→ E. Other chemotherapy

Case #2

- The patient commences cabozantinib
- Which of the following is not a common adverse effect of cabozantinib?
  - A. Hypertension
  - B. Palmar-plantar erythrodysesthesia
  - C. Elevation of liver function tests
  - D. Elevation of creatinine
  - E. Mucositis
  - F. Nausea and diarrhea

Shared Decision-Making

Patient Video 60 seconds

Q&A

Thank You