



2025

DEBATES AND DIDACTICS in Hematology and Oncology

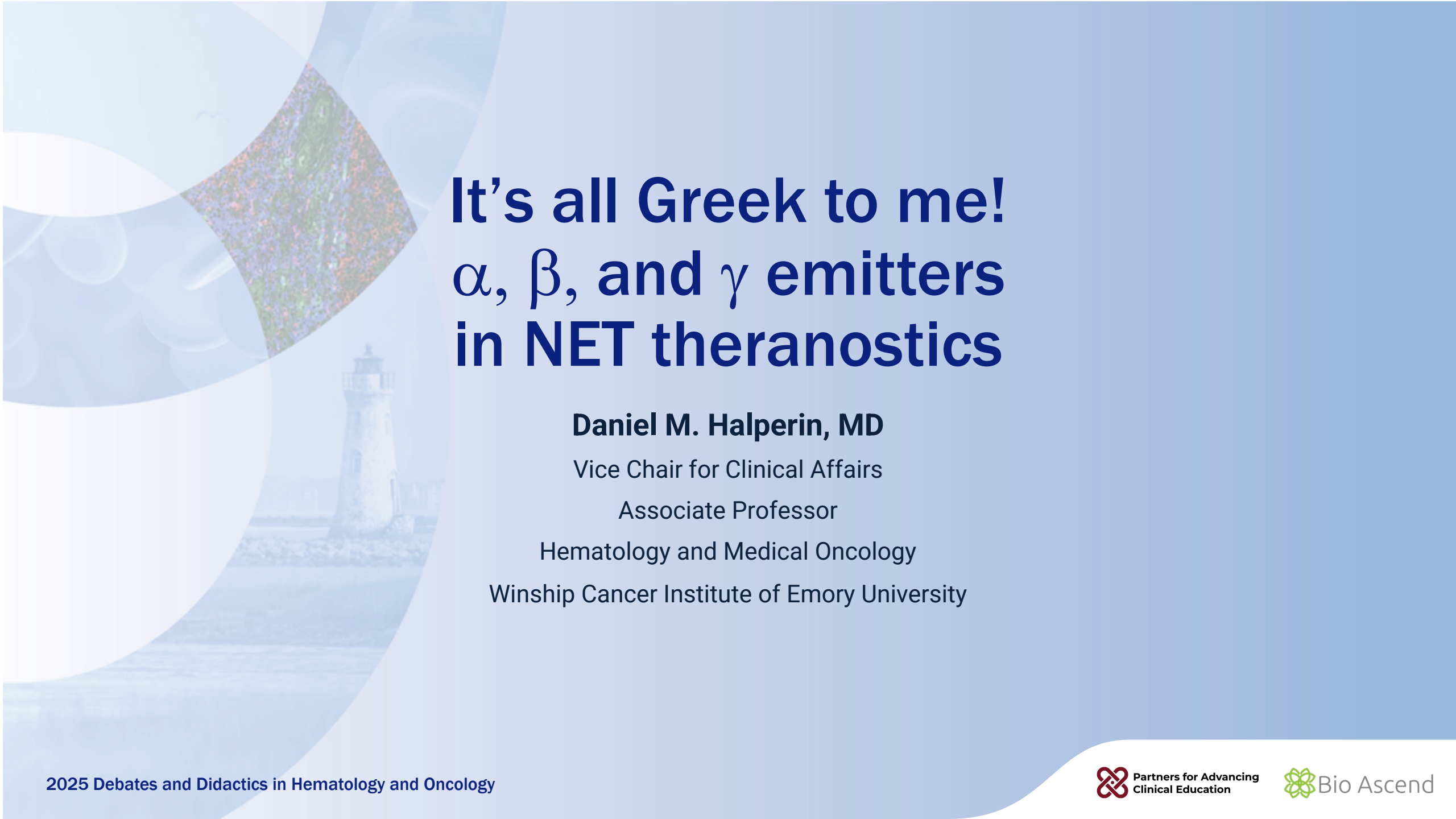


Where Science Becomes Hope

JULY 24 - 27, 2025 • SEA ISLAND, GEORGIA

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It's all Greek to me! α , β , and γ emitters in NET theranostics

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Disclosures (24 months)

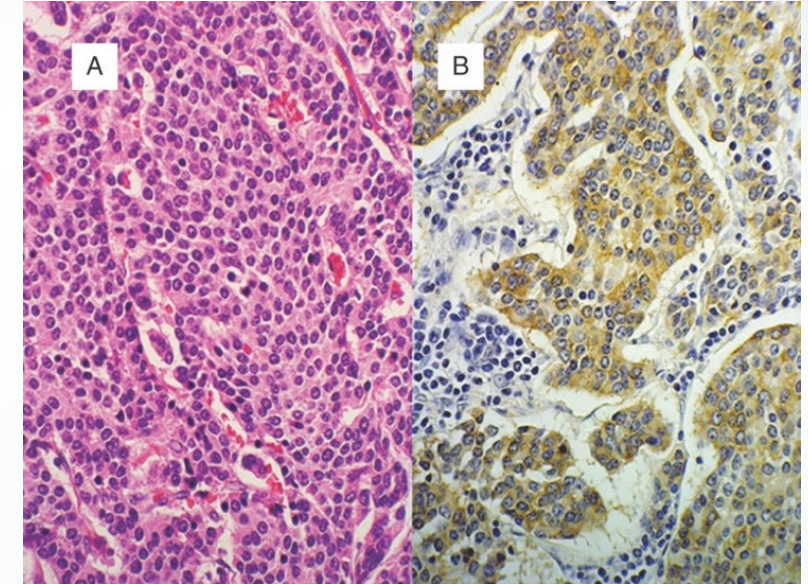
- Consultant for Exelixis, AbbVie, Harpoon Therapeutics, ITM, Novartis, Crinetics, Amryt, Camurus, Alphamedix, Chimeric Therapeutics.
- Research funded by Chimeric Therapeutics, Novartis, Genentech, ThermoFisher Scientific, ITM, Camurus, RayzeBio.
- I will discuss off-label and/or investigational use.

Objectives

- ✓ Review the current landscape of diagnostic radionuclides in NET.
- ✓ Describe the current standard of care therapeutic radionuclide in NET.
- ✓ Discuss the subtleties of the experimental radionuclide agents in the NET field.

NET 101

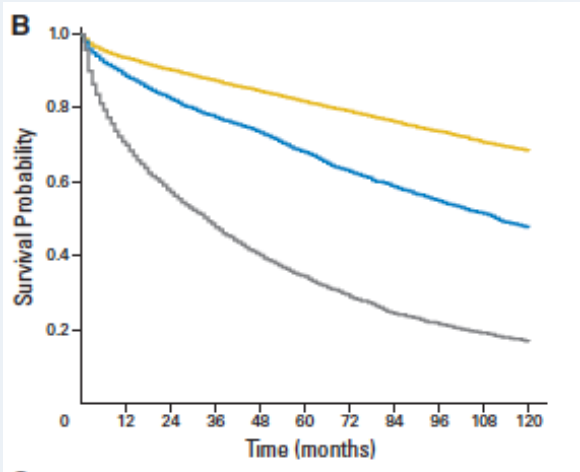
- NETs arise from epithelial endocrine cells distributed throughout the lungs, digestive tract, and pancreas.
- Previously called carcinoid tumors because they are “carcinoma-like.”
- Characterized by secretory granules and metal salt uptake.
- These granules can be secreted and lead to assorted functional syndromes.
- ~80% express somatostatin receptors



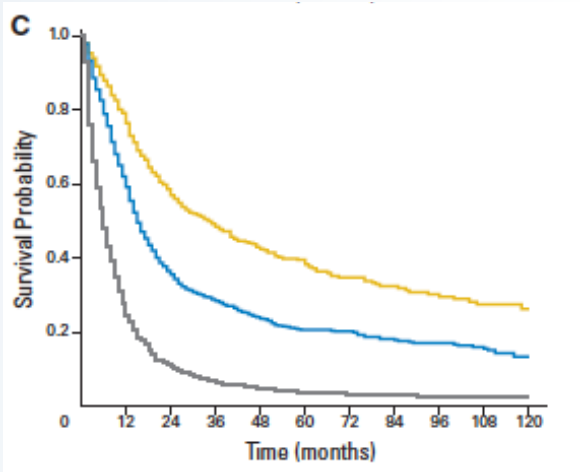
Reproduced with permission from Halperin and Yao, MD Anderson Manual of Medical Oncology, 3e.
Histology of NET. A: H&E; B: CgA

Grade, Stage, Primary Site

Grade 1-2



Grade 3



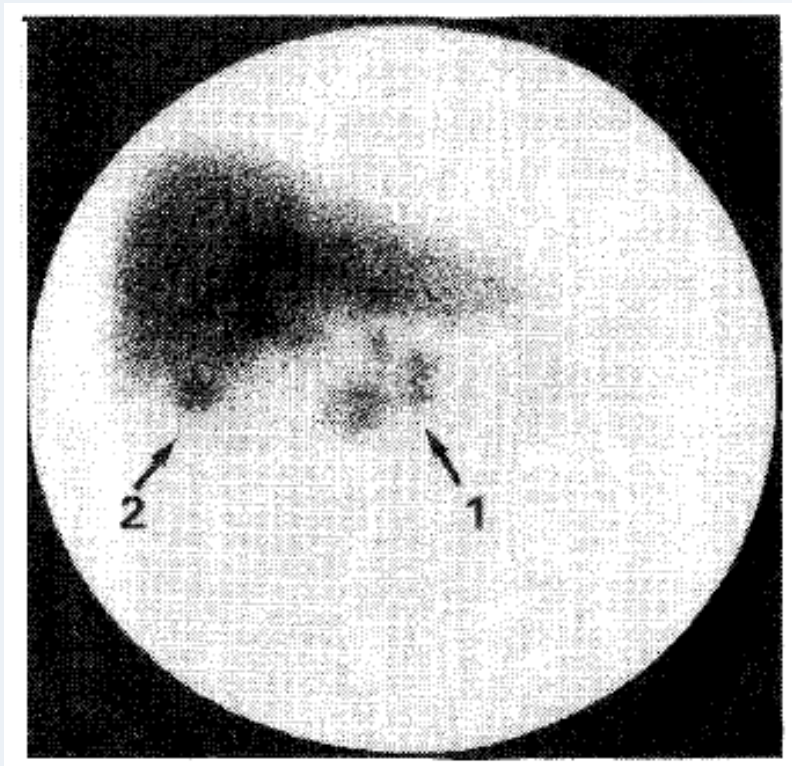
Metastatic Grade 1-2 NET

Primary Tumor Site	Median Survival (months)
Appendix	NA
Cecum	98
Colon	14
Lung	24
Pancreas	60
Rectum	33
Small Intestine	103
Stomach	29

Yao et al., J Clin Oncol 2008; 26:3063
Dasari et al., JAMA Oncol. 2017 Oct 1;3(10):1335-1342

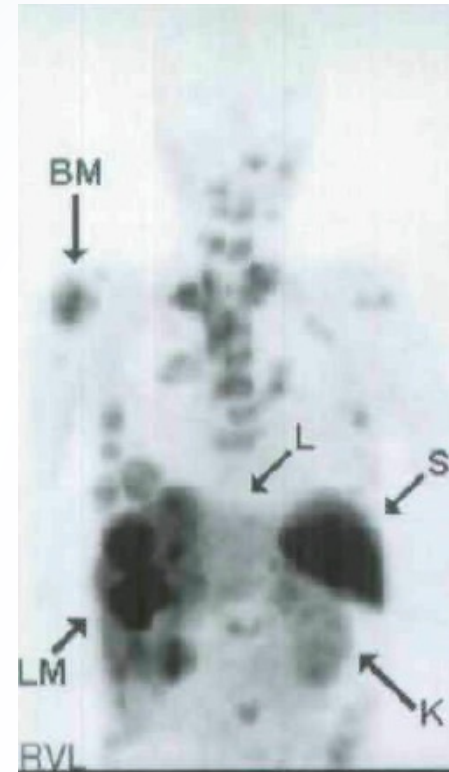
SSTR Imaging (1 vs 2 γ emissions)

^{123}I -tyr-3-octreotide SPECT
(SINGLE photon emission)

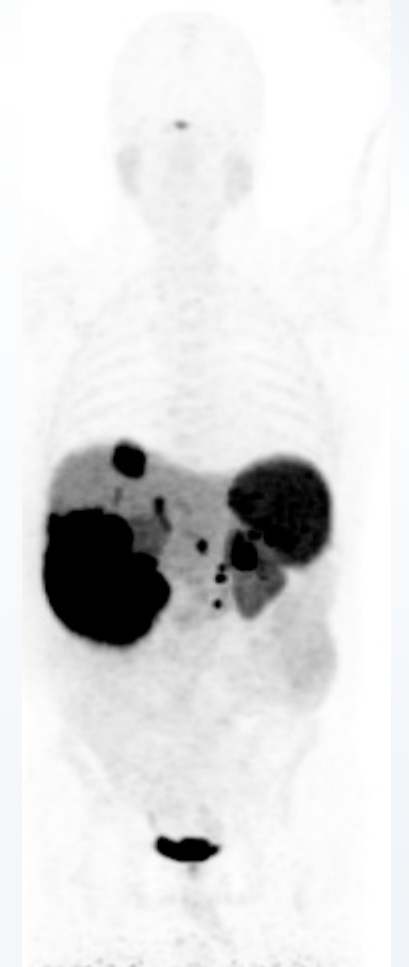


Krenning et al., Lancet 1989

^{68}Ga -DOTATOC PET
(POSITRON emission)



Hofmann et al., Eur J Nucl Med 2001



Imaging

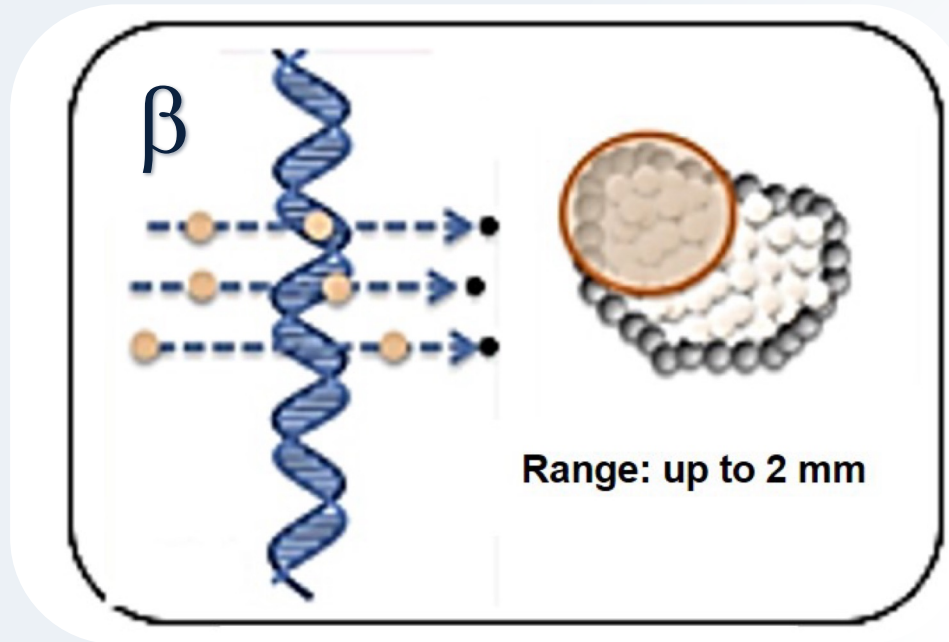
- Current common PET agents: ^{68}Ga -DOTATATE and ^{64}Cu -DOTATATE
- ^{68}Ga has a ~68-minute $t_{1/2}$ and sites need a local radiopharmacy
- ^{64}Cu has a ~12.7-hour $t_{1/2}$ and can be drop-shipped
- Some technical adjustments are required based on emissions
- Images generally interchangeable
- Physiologic uptake in pituitary, spleen, kidney/bladder, (occasionally uncinata)
- Uptake > liver (or spleen) is the foundation of therapy



Standard of Care

¹⁷⁷Lu-DOTATATE

β emitting radionuclide

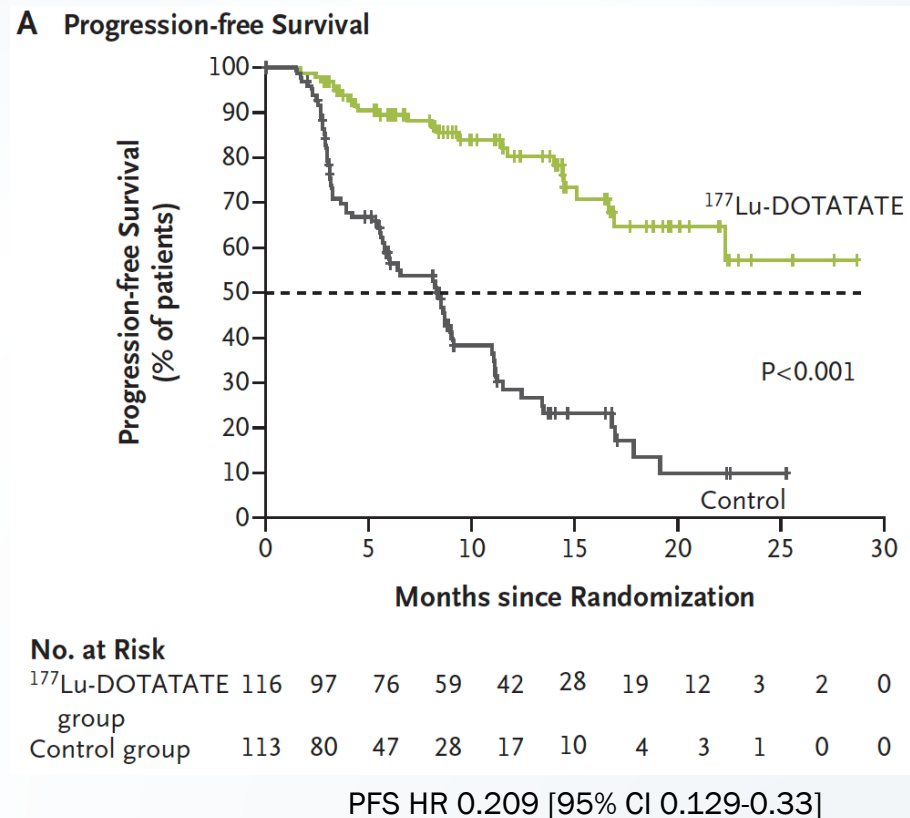
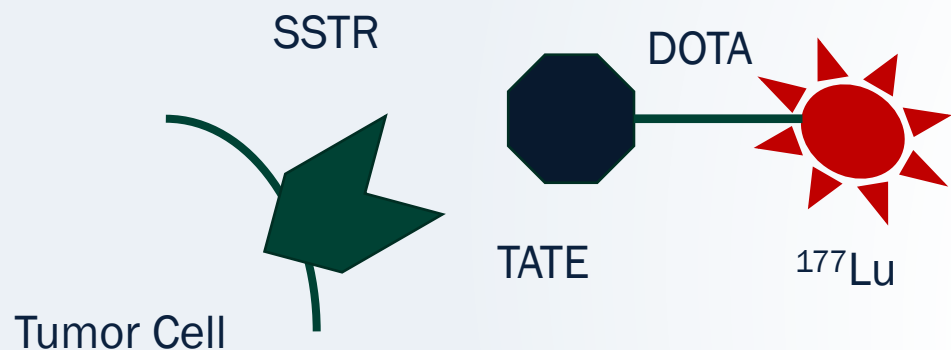


$\sim 0.2 \text{ keV}/\mu\text{m}$

$\sim 2\text{-}12 \text{ mm}$ penetration
(10 cells/mm)

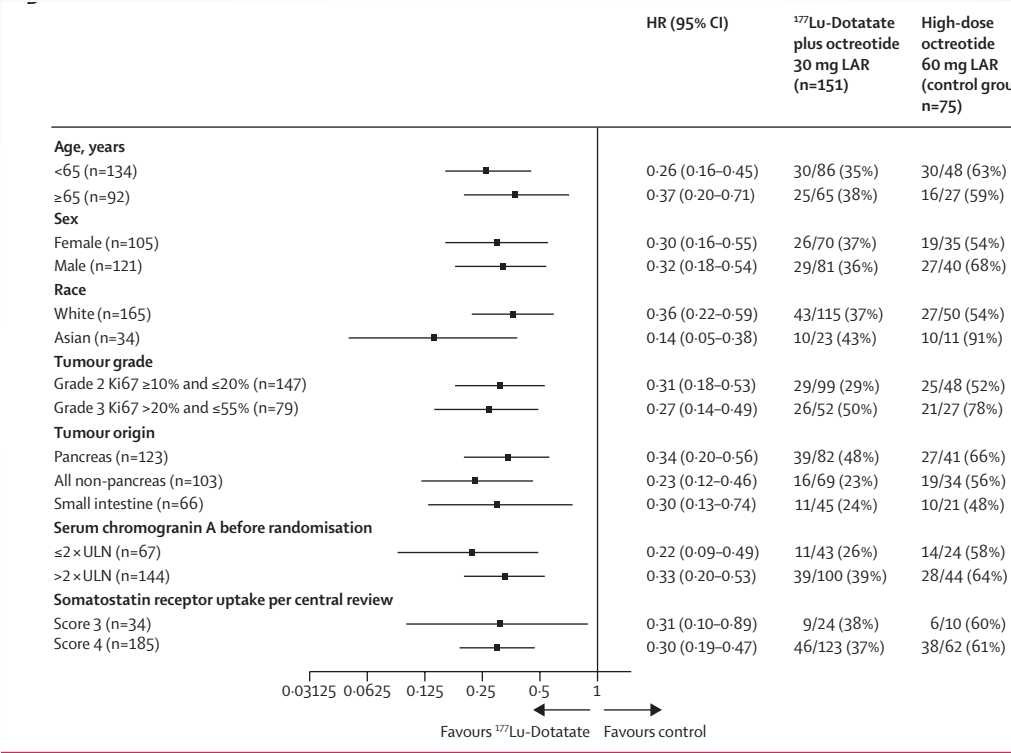
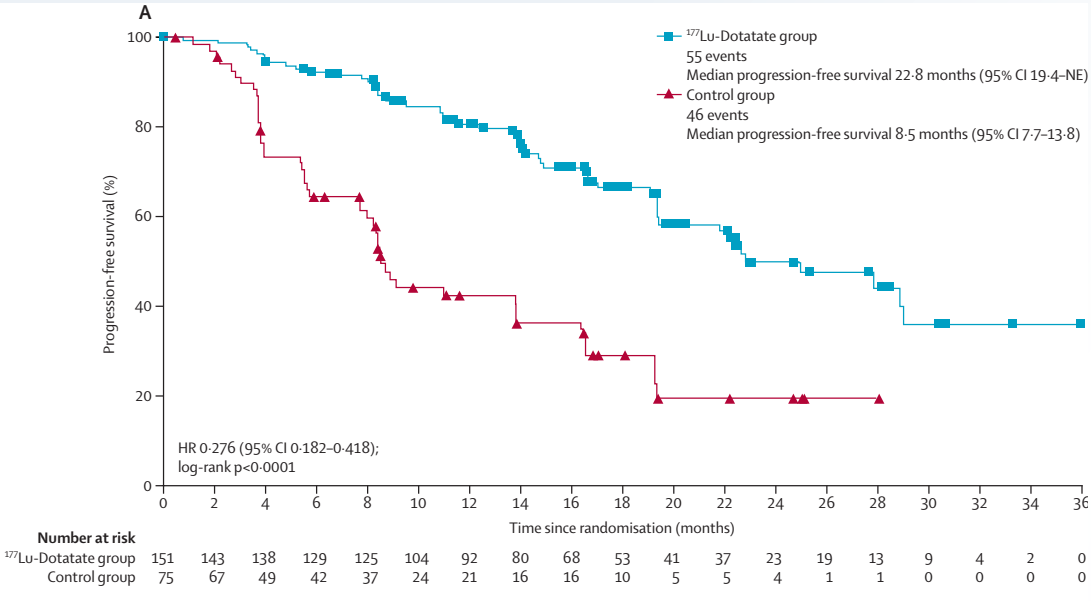
Peptide Receptor Radionuclide Therapy (PRRT) in midgut NET

- NETTER-1
- ^{177}Lu -DOTA-Octreotate (DOTATATE): a radioactive isotope conjugated to somatostatin analogue.
- Patients with G1-2 midgut NET, PD on octreotide LAR 30, somatostatin-avid.
- ^{177}Lu -DOTATATE vs. octreotide LAR 60mg.



Strosberg et al., NEJM 2017; 376:125-135

1L ¹⁷⁷Lu-DOTATATE Improves PFS in G2/3 GEP-NET



Singh, Halperin, Meyerhaug et al., Lancet 2024

ORR With ¹⁷⁷Lu-DOTATATE Across Grade and Primary Site

Subgroup	Complete response, n (%)	Partial response, n (%)	Total responders/N	ORR (95% CI)	Odds ratio (95% CI)
NET grade: Grade 2					
¹⁷⁷ Lu-DOTATATE	6 (6.1)	34 (34.3)	40/99	40.4 (30.7, 50.7)	5.83
High-dose octreotide	0	5 (10.4)	5/48	10.4 (3.5, 22.7)	(2.12, 16.00)
NET grade: Grade 3					
¹⁷⁷ Lu-DOTATATE	2 (3.8)	23 (44.2)	25/52	48.1 (34.0, 62.4)	11.57
High-dose octreotide	0	2 (7.4)	2/27	7.4 (0.9, 24.3)	(2.48, 53.97)
NET origin: Pancreas					
¹⁷⁷ Lu-DOTATATE	5 (6.1)	37 (45.1)	42/82	51.2 (39.9, 62.4)	7.56
High-dose octreotide	0	5 (12.2)	5/41	12.2 (4.1, 26.2)	(2.70, 21.19)
NET origin: Small intestine					
¹⁷⁷ Lu-DOTATATE	1 (2.2)	11 (24.4)	12/45	26.7 (14.6, 41.9)	7.27
High-dose octreotide	0	1 (4.8)	1/21	4.8 (0.1, 23.8)	(0.88, 60.24)

Singh et al., ESMO GI 2024

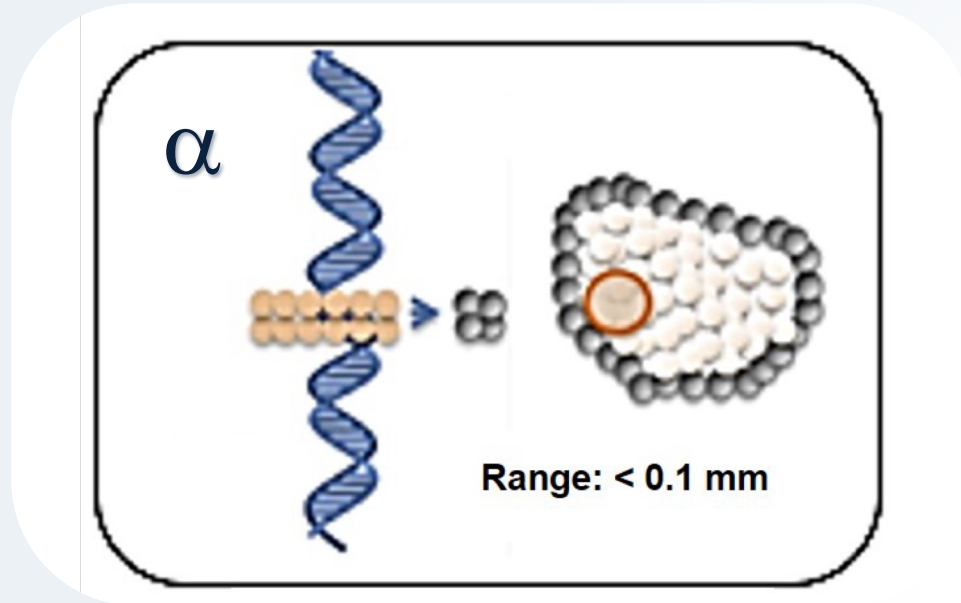
The background features a light blue gradient. On the left, there is a large, semi-transparent circular graphic. Inside this circle, a lighthouse is visible on a rocky shore. Overlapping the lighthouse and the circle is a colorful, abstract, pixelated shape in shades of green, blue, and red.

Investigational Radionuclides

¹⁷⁷Lu-edotreotide

- COMPETE (NCT03049189)
- 309 G1-2 GEP-NET patients with PD over 12 months
- ¹⁷⁷Lu-edotreotide (q12w x 4) vs everolimus (2:1)
- (no concurrent SSA)
- Primary EP PFS
- Stratified by primary site and line of tx
- PFS HR 0.67; 95% CI [0.48, 0.95], stratified p= 0.022
- 23.9 vs 14.1 months

α emitting radionuclide



- $\sim 80 \text{ keV}/\mu\text{m}$
- $\sim 50\text{-}100 \mu\text{m}$ penetration
 - (1-2 cells)

^{212}Pb -DOTAMTATE in PRRT-naïve patients

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

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

Abbreviations : ORR, Overall Response Rate; DOR, Duration of Response

Database extraction May 28, 2024

* asymmetrical

*Landmark analysis

[†]GEP-NET subjects at RP2D

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

2024 ASCO
ANNUAL MEETING

#ASCO24

PRESENTED BY: Jonathan Strosberg, MD

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KNOWLEDGE CONQUERS CANCER

^{212}Pb -DOTAMTATE in PRRT-naïve patients

Safety overview

	ALPHAMEDIX-01 (N=8)			ALPHAMEDIX-02 (N=36)			Pooled P1 & P2 (N=44)		
Grade 3-4 AEs, n (%)	2 (25%)			21 (58%)			23 (52%)		
SAEs, n (%)	2 (25%)			11 (31%)			13 (30%)		
Fatal AEs, n (%)	- (0%)			3 (8%)			3 (7%)		
AE Preferred Term (≥6 subjects, n (%))	All grades	Grade 3-4		All grades	Grade 3-4		All grades	Grade 3-4	
Alopecia	8 (100%)	-	(0%)	33 (92%)	-	(0%)	41 (93%)	-	(0%)
Nausea	7 (88%)	-	(0%)	34 (94%)	1 (3%)	(3%)	41 (93%)	1 (2%)	(2%)
Fatigue	5 (63%)	-	(0%)	34 (94%)	2 (6%)	(6%)	39 (89%)	2 (5%)	(5%)
Decreased appetite	1 (13%)	-	(0%)	19 (53%)	1 (3%)	(3%)	20 (45%)	1 (2%)	(2%)
Diarrhoea	2 (25%)	-	(0%)	18 (50%)	-	(0%)	20 (45%)	-	(0%)
Dysphagia	- (0%)	-	(0%)	15 (42%)	1 (3%)	(3%)	15 (34%)	1 (2%)	(2%)
Lymphocyte count decreased	3 (38%)	2 (25%)	(25%)	12 (33%)	9 (25%)	(25%)	15 (34%)	11 (25%)	(25%)
Abdominal pain	1 (13%)	-	(0%)	13 (36%)	-	(0%)	14 (32%)	-	(0%)
Vomiting	2 (25%)	-	(0%)	11 (31%)	-	(0%)	13 (30%)	-	(0%)
Weight decreased	3 (38%)	-	(0%)	9 (25%)	-	(0%)	12 (27%)	-	(0%)
Blood glucose increased	3 (38%)	-	(0%)	6 (17%)	-	(0%)	9 (20%)	-	(0%)
Headache	- (0%)	-	(0%)	7 (19%)	-	(0%)	7 (16%)	-	(0%)
Alanine aminotransferase increased	2 (25%)	-	(0%)	4 (11%)	1 (3%)	(3%)	6 (14%)	1 (2%)	(2%)
Haemoglobin decreased	1 (13%)	-	(0%)	5 (14%)	-	(0%)	6 (14%)	-	(0%)
Bone pain	2 (25%)	-	(0%)	4 (11%)	-	(0%)	6 (14%)	-	(0%)
Constipation	- (0%)	-	(0%)	6 (17%)	1 (3%)	(3%)	6 (14%)	1 (2%)	(2%)
COVID-19	- (0%)	-	(0%)	6 (17%)	-	(0%)	6 (14%)	-	(0%)
Eosinophilia	2 (25%)	-	(0%)	4 (11%)	-	(0%)	6 (14%)	-	(0%)
Oesophageal pain	- (0%)	-	(0%)	6 (17%)	-	(0%)	6 (14%)	-	(0%)

2024 ASCO
ANNUAL MEETING

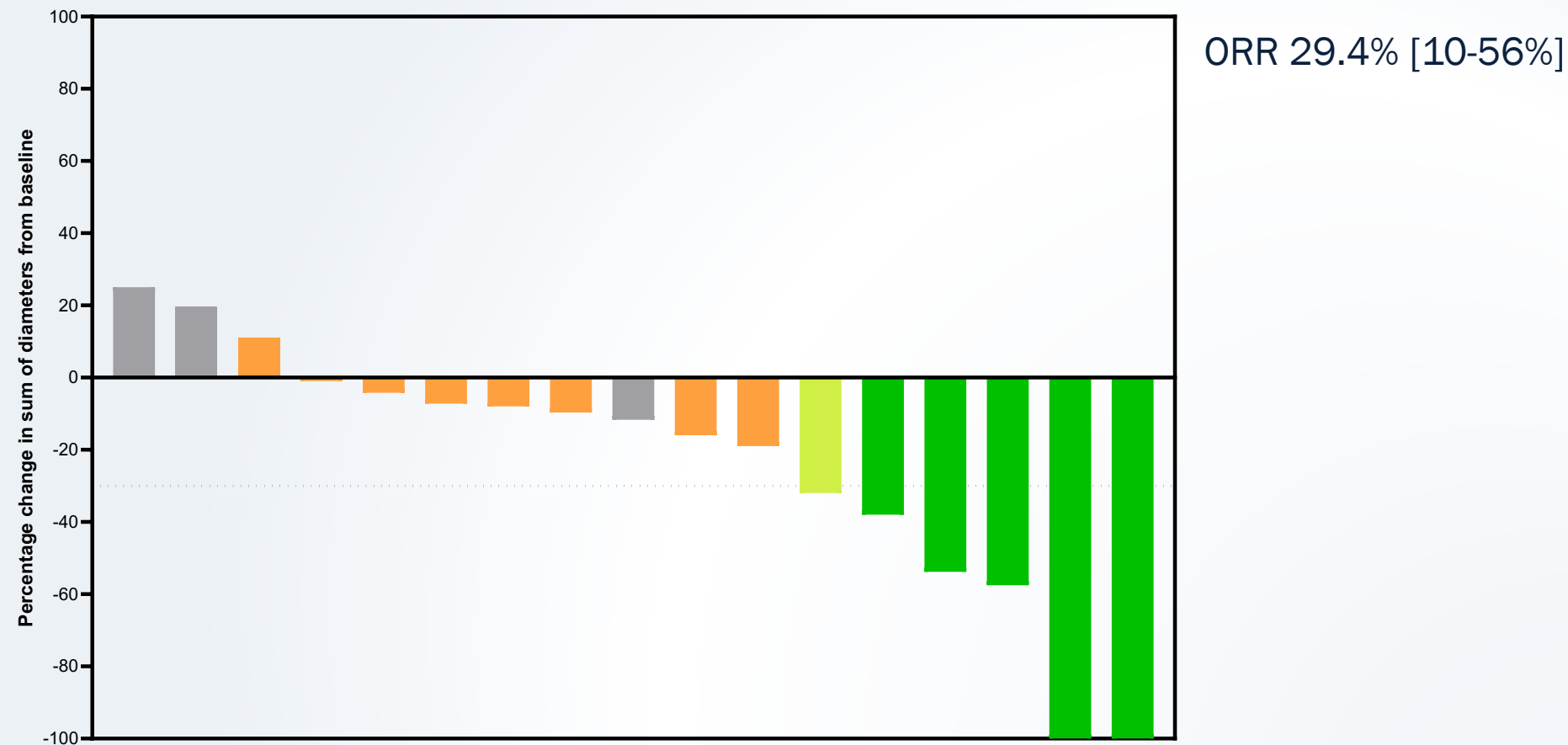
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225Ac-DOTATATE in PRRT-pretreated patients



Strosberg et al., ASCO GI 2025

225Ac-DOTATATE in PRRT-pretreated patients

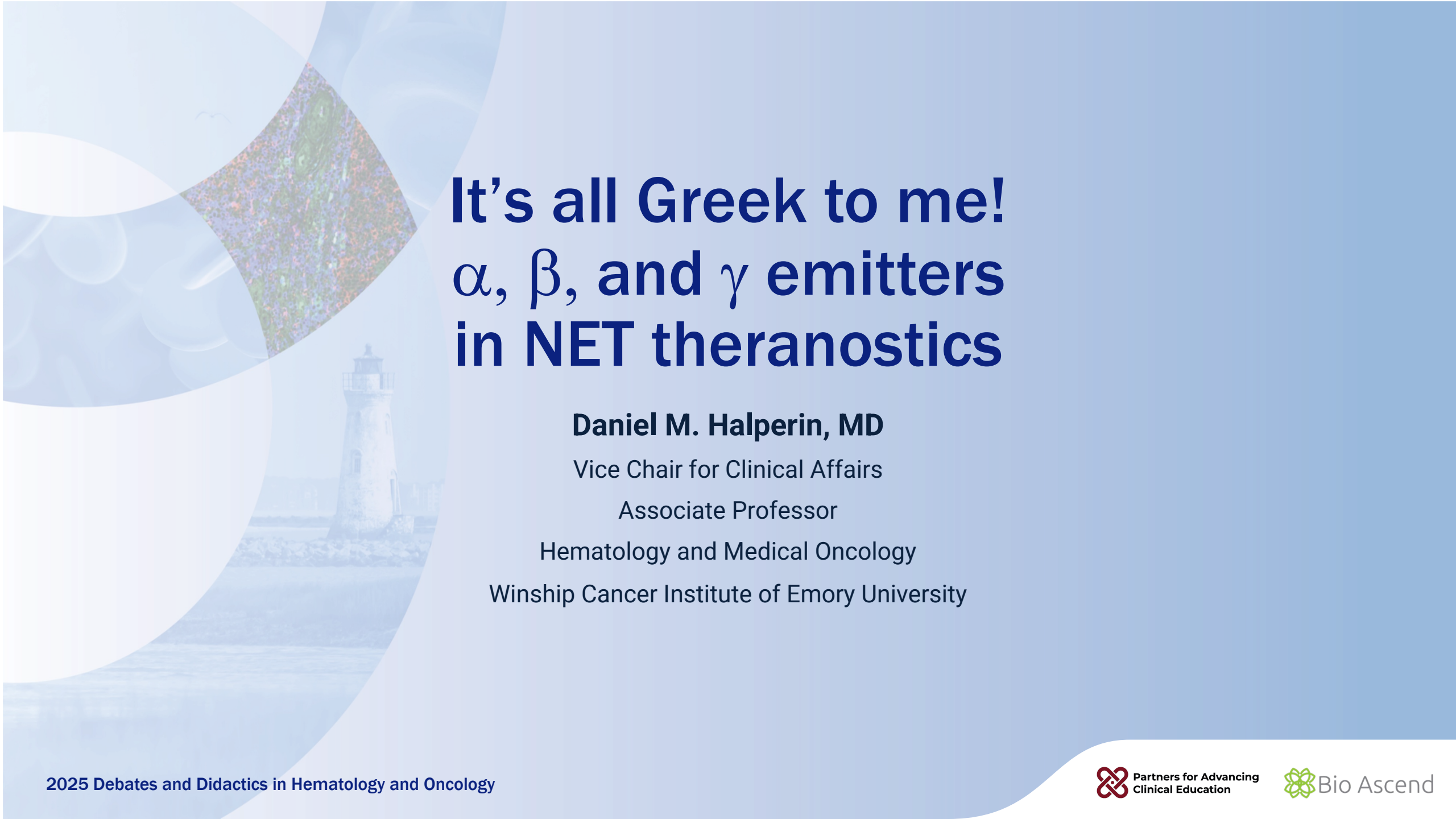
TABLE 4. Most frequent AEs (occurring in >2 patients)

Patients, n (%)	RYZ101 120 kBq/kg (N=17)	Patients, n (%)	RYZ101 120 kBq/kg (N=17)
Anemia	10 (58.8)	Constipation	4 (23.5)
Nausea	10 (58.8)	Vomiting	4 (23.5)
Fatigue	9 (52.9)	White blood cell count decreased	4 (23.5)
Weight decreased	8 (47.1)	Alopecia	3 (17.6)
Creatinine renal clearance decreased	6 (35.3)	Blood creatinine increased	3 (17.6)
Hyperglycemia	6 (35.3)	Diabetes mellitus	3 (17.6)
Lymphocyte count decreased	6 (35.3)	Diarrhea	3 (17.6)
Abdominal pain	5 (29.4)	Dyspnea	3 (17.6)
Blood alkaline phosphatase increased	5 (29.4)	Hypertension	3 (17.6)
Hyponatremia	5 (29.4)	Hypokalemia	3 (17.6)
Platelet count decreased	5 (29.4)		

Halperin et al., ASCO 2024

Summary

- PET imaging (opposing γ rays) is common with ^{68}Ga or ^{64}Cu DOTATATE
- Tumor uptake > liver (or spleen) is foundational for therapy
- ^{177}Lu -DOTATATE is the current standard beta emitter
- Additional α and β radioligands are under study
- Emerging evidence suggests that they are not necessarily interchangeable.



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