Preliminary Safety and Efficacy Data of [^{212}Pb]VMT-α-NET in Somatostatin Receptor 2 (SSTR2) Expressing Neuroendocrine tumors (NETs)

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Disclosures for Dr. Richard Wahl and FDA Status

Abdera: consultant
Molecular Targeting Technologies, Inc.: consultant, stock options
Siemens Healthineers: consultant
Voximetry: consultant, stock options
Techspert: consultant
Clarity Pharmaceuticals: stockholder
Perspective Therapeutics: consultant, research
Fusion Pharmaceuticals: research contract
Rayze Pharmaceuticals: research contract
White Rabbit AI: research contract

[^{212}Pb]VMT-α-NET is not FDA approved. It is being used under an FDA IND in a clinical trial

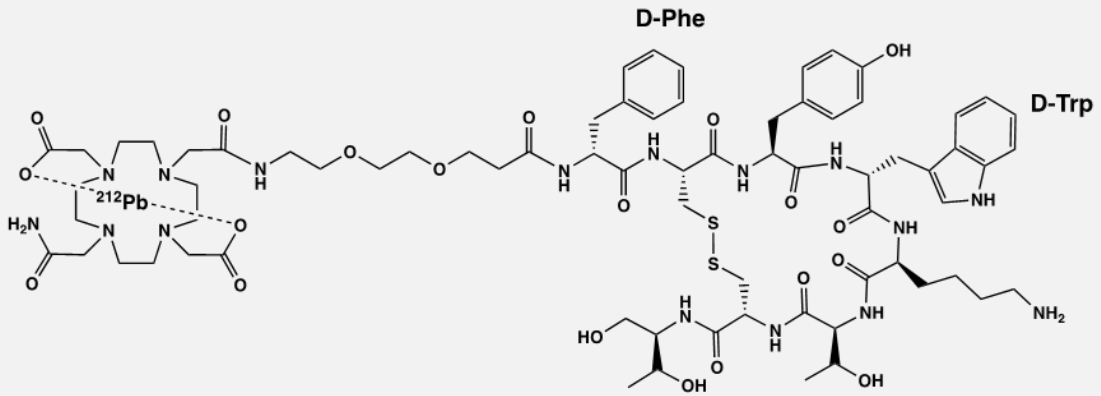
Learning Objectives

- Understand ^{212}Pb VMT-α-NET phase I/IIa clinical trial design
- Understand preliminary assessments of toxicity from the therapeutic agent at the 2.5 and 5.0 mCi administered activity levels
- Understand initial evidence of anti-tumor effect in the first cohorts of patients

Background: NENs and [^{212}Pb]VMT-α-NET

- Neuroendocrine tumors are heterogenous
- >80% overexpress somatostatin receptor 2 (SSTR2)
- Despite the availability of [^{177}Lu]Lu-DOTATATE, there remains a high unmet medical need for novel therapies
- [^{212}Pb]VMT-α-NET is a modified SSTR2 binding peptide with proprietary chelation technology for ^{203}Pb, ^{212}Pb and ^{212}Bi allowing for optimized delivery and retention of the payload in the tumor microenvironment
- [^{212}Pb]VMT-α-NET, a novel targeted alpha radionuclide therapy (TAT) to the SSTR2, is being investigated for safety and efficacy in PRRT-naïve patients with SSTR2-expressing tumors

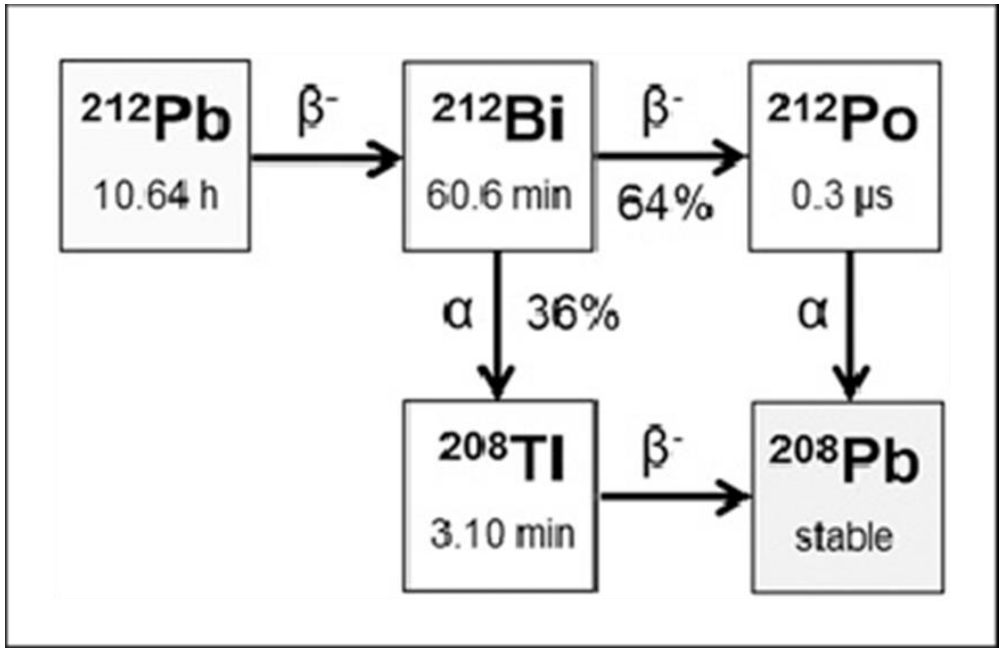
[^{212}Pb]-VMT-α-NET



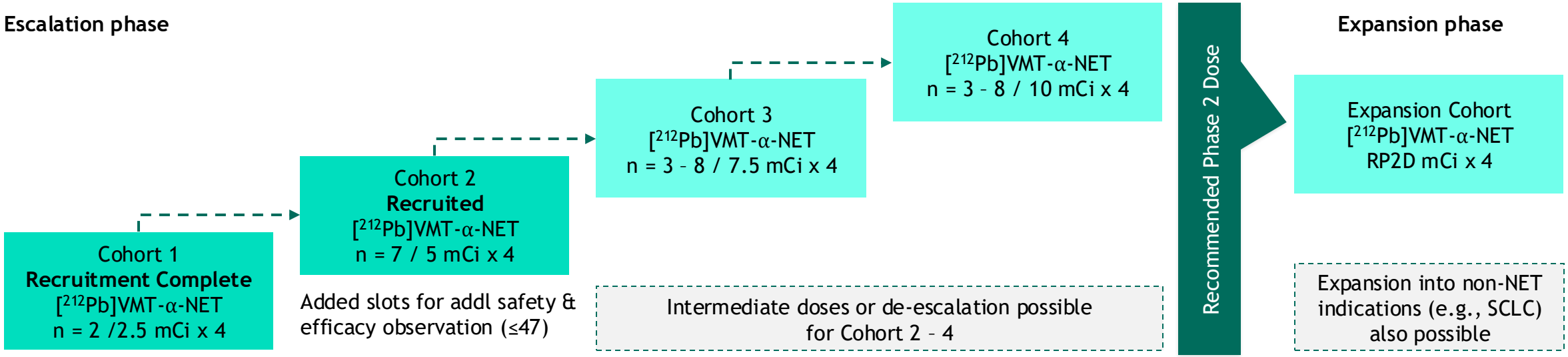
Molecular Weight: 1789.83

Background: [^{212}Pb] Decay

- Single alpha particle per decay
- 10.64 hour half-life
- Well-suited to radiopeptide therapy



Trial Design: [^{212}Pb]VMT-α-NET mTPI-2 Phase 1/2a For Neuroendocrine Tumors



Trial Parameters

Escalation Stage Population

- Advanced/unresectable or metastatic NETs
- Progressive disease on prior therapy
- PRRT naïve
- FDA approved SSTR2 PET/CT avid disease

Key Study Features

- Bayesian mTPI-2 design based on iterative toxicity probability monitoring
- Dosimetry to be assessed during screening period for cohorts 1 & 2 using 5-7 mCi [^{203}Pb]VMT-α-NET

Study Endpoints

- **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 and PFS by RECIST v1.1, OS
  - Using dosimetry, estimate selected organ and whole body absorbed radiation doses for [^{212}Pb]VMT-α-NET

[1] mTPI-2: Modified toxicity probability index | https://clinicaltrials.gov/study/NCT05636618

Patient Characteristics (all patients as treated)

	All Treated (N = 9)
Age (years)	
Median	63
Range	37,78
Sex, n (%)	
Female	4 (44)
Male	5 (56)
Race, n (%)	
White	8 (89)
Asian	1 (11)
Tumor Type, n (%)	
Pancreatic NET	3 (33)
Non-pancreatic NET	6 (66)
Grade, n (%)	
G1	3 (33)
G2	6 (66)

Data cutoff 10/31/24

	All Treated (N = 9)
Time since diagnosis (months)	
Mean	70
Median	37
Range	12, 181
Number of prior systemic therapies	
Median	1
Range	0, 2
Prior systemic therapies (patients with each)	
Somatostatin analogues	7
Capecitabine, temozolomide	1
Small molecule (sunitinib, everolimus)	2
ECOG Performance Status, n (%)	
0	8 (89)
1	1 (11)
Disease at Baseline, median (range)	
RECIST median sum of target lesions (cm)	6.7 (2.9, 8.7)
SUV max SUV mean	41.5 (18, 162) 30 (12, 102)

Patient Disposition and Exposure (all patients as treated)

Green line denotes timepoint through which all post-cycle scans are available to the study team.

Cohort	Subject	Subject Status	Weight (kg)	Adm Activity (mCi)	Adm Activity per Weight (µCi/kg)	C1D1	C2D1	C3D1	C4D1
1	103-101	Follow-Up	53	2.5	50.1	✓	✓	✓	✓
1	103-102	Follow-Up	61	2.5	40.8	✓	✓	✓	✓
2	103-103	Follow-Up	157	5	31.7	✓	✓	✓	✓
2	109-103	Progressive disease	78	5	63.9	✓			
2	102-101	Follow-Up	91	5	54.5	✓	✓	✓	✓
2	103-104	Follow-Up[1]	59	5/2.5	84.5/42.3	✓	✓	✓	✓
2	102-103	Follow-Up	80	5	62.1	✓	✓	✓	*scheduled*
2	112-101	Follow-up	101	5	49.1	✓	✓	✓	✓
2	103-105	Follow-up	73	5	68.7	✓	✓	✓	✓

1 Patient experienced syncope and dose was reduced for cycle 3 and cycle 4 to 2.5 mCi of administered activity
Additional notes: (1) 17 patients screened, (2) one patient (102-102) experienced a decline in renal function prior to administration of [^{212}Pb]VMT-α-NET and was not treated.
Data cutoff 10/31/24

Treatment Emergent Adverse Events (occurring in ≥ 2 patients and/or Grade ≥ 2) (1/2)

Incidence of TEAEs	[^{212}Pb]-VMT-a-NET 92.5 MBq (2.5 mCi) (N=2)			[^{212}Pb-VMT-a-NET 185 MBq (5.0 mCi) (N=7)			Total (n=9)		
Grade	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 1**	**Grade 2**	**Grade 3**
AEs by Preferred Term and Grade Reported by Patient *[Number patients with AE (% of pts treated per cohort)]*									
Most Common (Occurring in ≥ 2 patients and/or grade ≥ 2									
Fatigue	1 (50)	1 (50)	-	3 (43)	2 (28)	-	4 (44)	3 (33)	-
Alopecia	2 (100)	-	-	4 (57)	-	-	6 (66)	-	-
Lymphocyte count decreased	-	1 (50)	-	2 (29)	3 (42)	-	2 (22)	4 (44)	-
Nausea	-	1 (50)	-	4 (57)	1 (14)	-	4 (44)	2 (22)	-
Anaemia	-	2 (100)	-	3 (43)	-	-	3 (33)	2 (22)	-
Diarrhoea	2 (100)	-	-	2 (29)	1 (14)	1 (14)	4 (44)	1 (11)	1 (11)
Haematocrit decreased	1 (50)	1 (50)	-	2 (29)	-	-	3 (33)	1 (11)	-
Red blood cell count decreased	1 (50)	1 (50)	-	2 (29)	-	-	3 (33)	1 (11)	-
White blood cell count decreased	2 (100)	-	-	-	-	-	2 (22)	-	-
Abdominal pain	-	-	-	2 (29)	-	-	2 (22)	-	-
Haemoglobin decreased	-	-	-	2 (29)	-	-	2 (22)	-	-
Hyperglycaemia	-	-	-	2 (29)	-	-	2 (22)	-	-
Blood alkaline phosphatase	-	-	-	2 (29)	-	-	2 (22)	-	-
Constipation	-	-	-	2 (29)	-	-	2 (22)	-	-
Haematuria	-	-	-	2 (29)	-	-	2 (22)	-	-
Headache	1 (50)	-	-	1 (14)	-	-	2(22)	-	-
Lethargy	1 (50)	-	-	1 (14)	-	-	2(22)	-	-
Aspartate aminotransferase incr'd	1 (50)	-	-	1 (14)	-	-	2(22)	-	-
Dizziness	1 (50)	-	-	1 (14)	-	-	2(22)	-	-

All patients as treated
Data cutoff 10/31/24

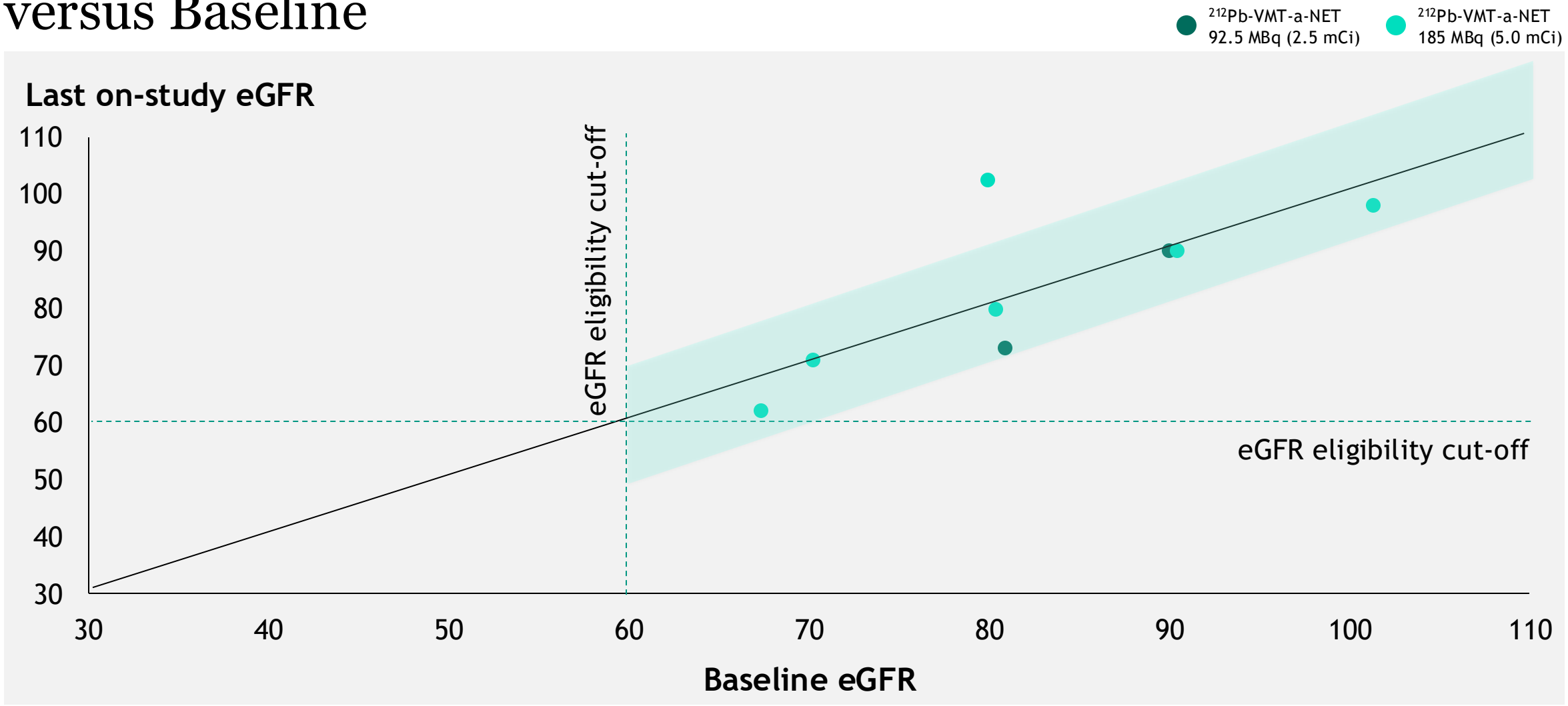
Treatment Emergent Adverse Events (Occurring in ≥ 2 patients and/or Grade ≥ 2) (2/2)

Incidence of TEAEs	[^{212}Pb]-VMT-a-NET 92.5 MBq (2.5 mCi) (N=2)			[^{212}Pb-VMT-a-NET 185 MBq (5.0 mCi) (N=7)			Total (n=9)		
Grade	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 1**	**Grade 2**	**Grade 3**
AEs by Preferred Term and Grade Reported by Patient *[No patients with AE (% of pts treated per cohort)]*									
Grade ≥ 2									
Presyncope	-	-	-	-	1 (14)		-	1 (11)	
Syncope	-	-	-	-	-	1 (14)	-	-	1 (11)
Amylase increased	-	1 (50)	-	-	-	-	-	1 (11)	-
Hypercalcemia	-	1 (50)	-	-	-	-	-	1 (11)	-
Weight decreased	-	-	-	-	1 (14)	-	-	1 (11)	-

Note: No renal insufficiency or dysphagia were observed.

All patients as treated
Data cutoff 10/31/24

Estimated Glomerular Filtration Rate (eGFR), Most Recent versus Baseline



Data cutoff 10/31/24

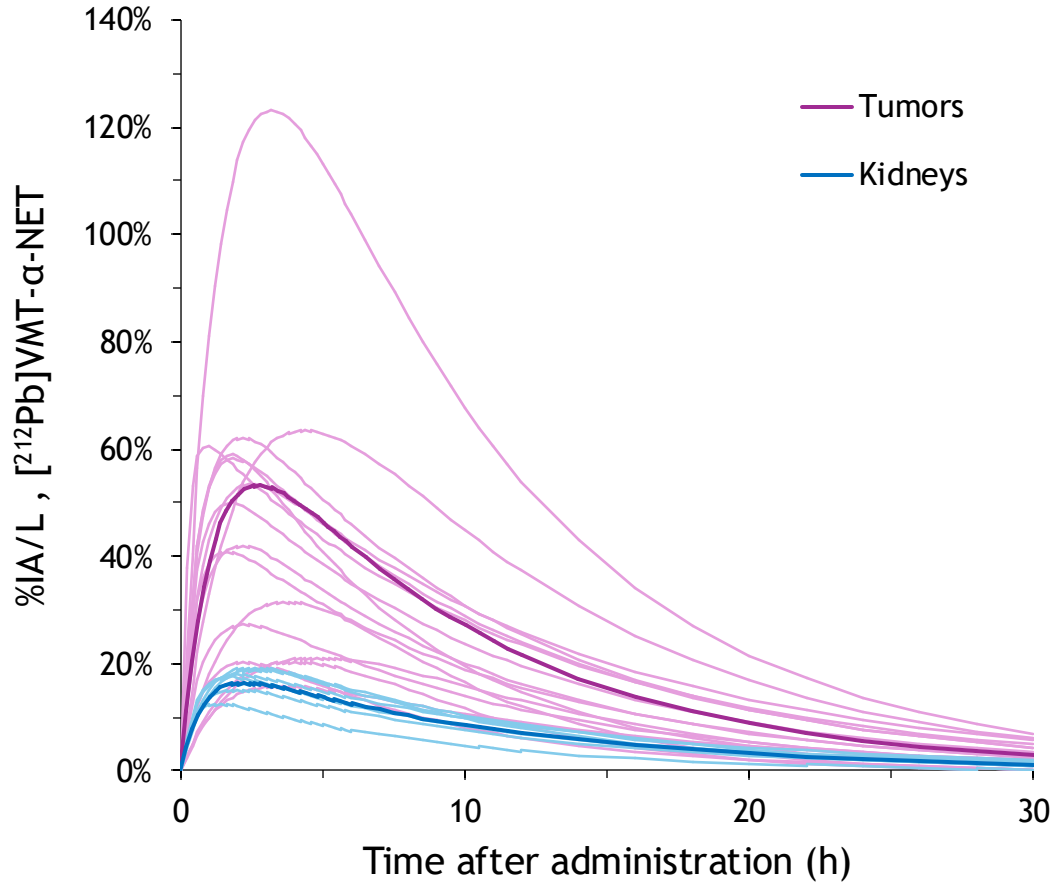
Safety Summary

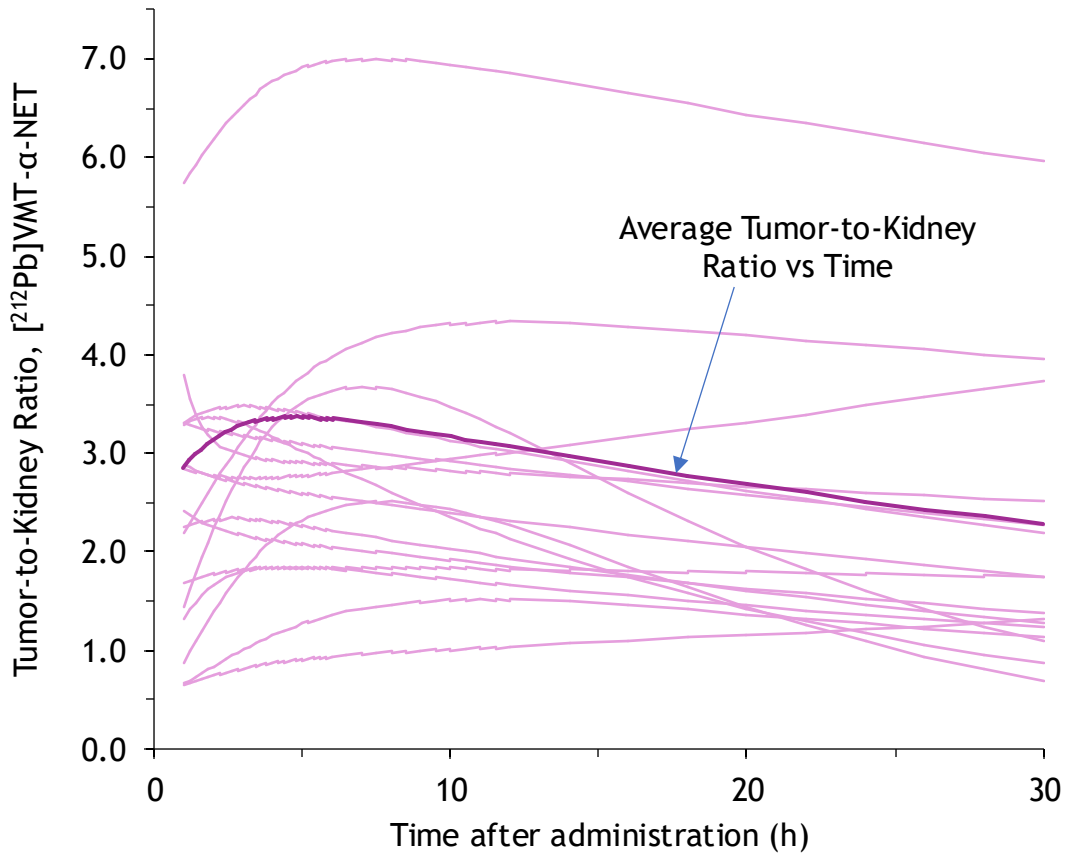
- No DLTs were observed in either cohort
- No grade 4, grade 5 or serious AEs were observed
- No decline in renal function was observed
- Hematologic AEs were few in number and low grade
- No dysphagia was observed
- No treatment discontinuations due to AE have occurred

Data cutoff 10/31/24

Predicted Tumor to Kidney Activity of [^{212}Pb]VMT-α-NET Over Time

(Based on Pre-Treatment [^{203}Pb]VMT-α-NET SPECT Imaging and Dosimetry Analysis)

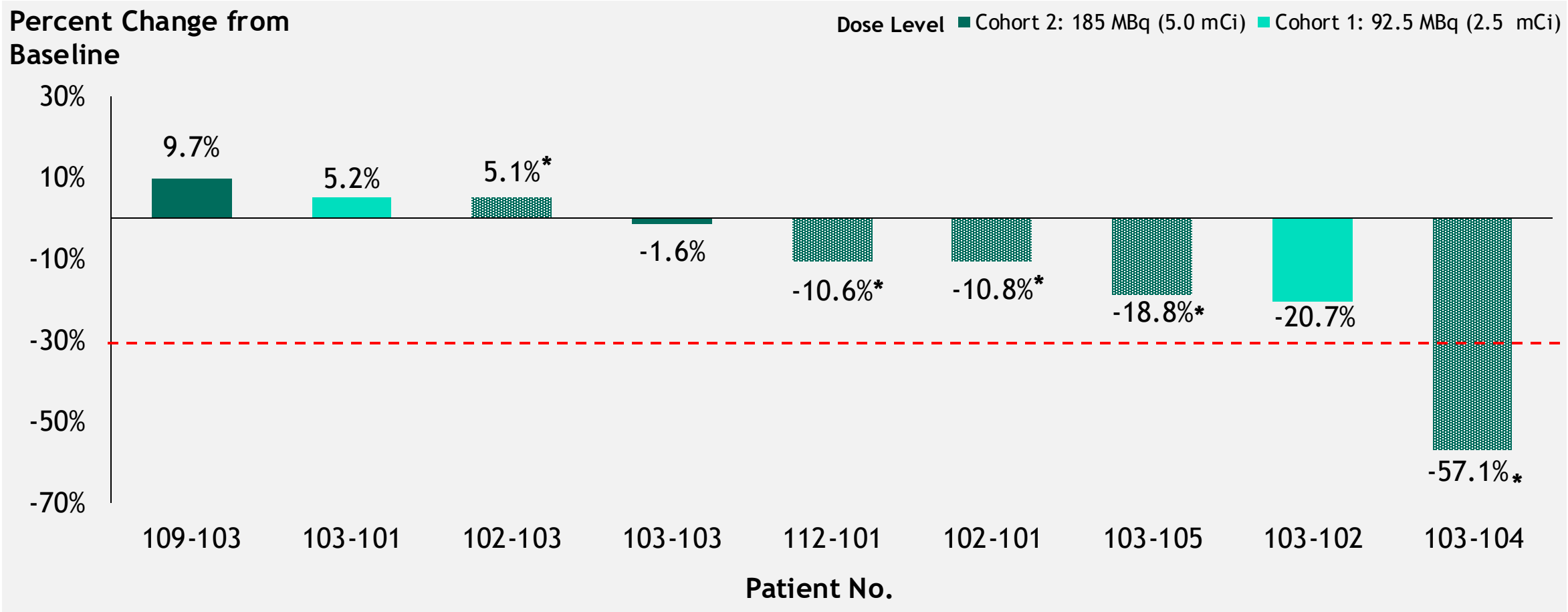




Time activity curves for [^{212}Pb]VMT-α-NET are derived from pre-treatment SPECT imaging using 5-7 mCi [^{203}Pb]VMT-α-NET at 1, 4, and 24 hours (n=6). The bold line represents the average across all samples in the dataset for tumors (magenta) and kidney (blue). Measurements of %IA/L in tumors and kidneys has been corrected for partial volume effects. However, SPECT imaging may still underestimate the true tumor to kidney ratio of absorption.

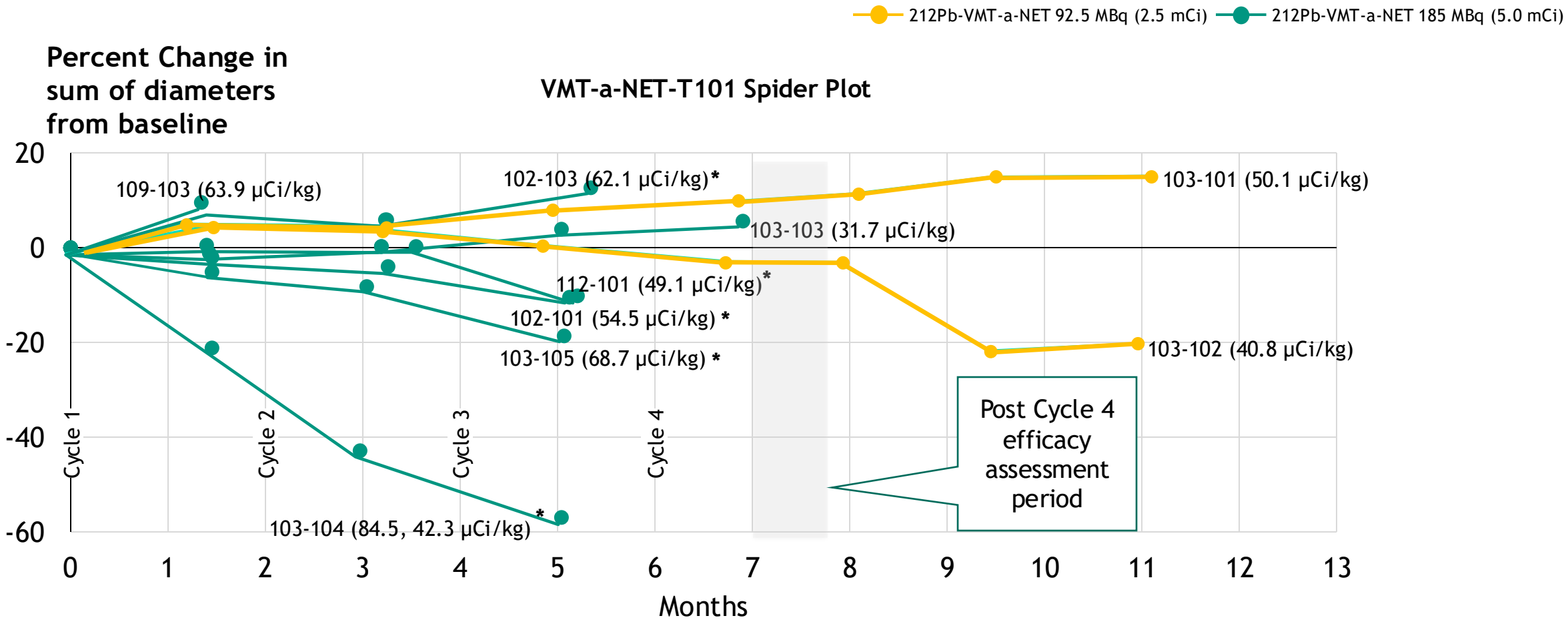
Data cutoff 10/31/24

Preliminary Response Assessment by RECIST v1.1 by Patient



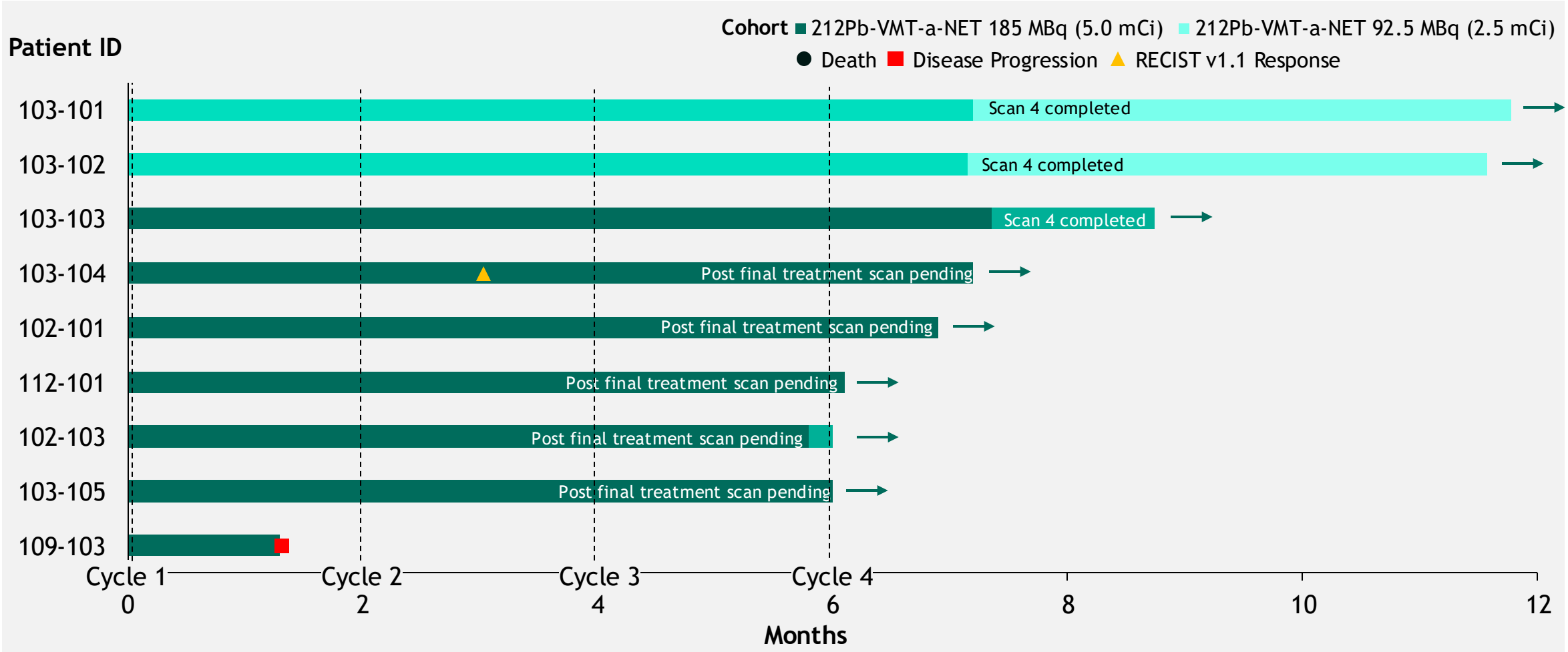
* The full sets of scans following cycle 4 are not yet available to the study team for five patients.
Note: Patient 109-103 experienced progressive disease by unambiguous progression of non-target lesions
Data cutoff 10/31/24

Kinetics of Treatment Response



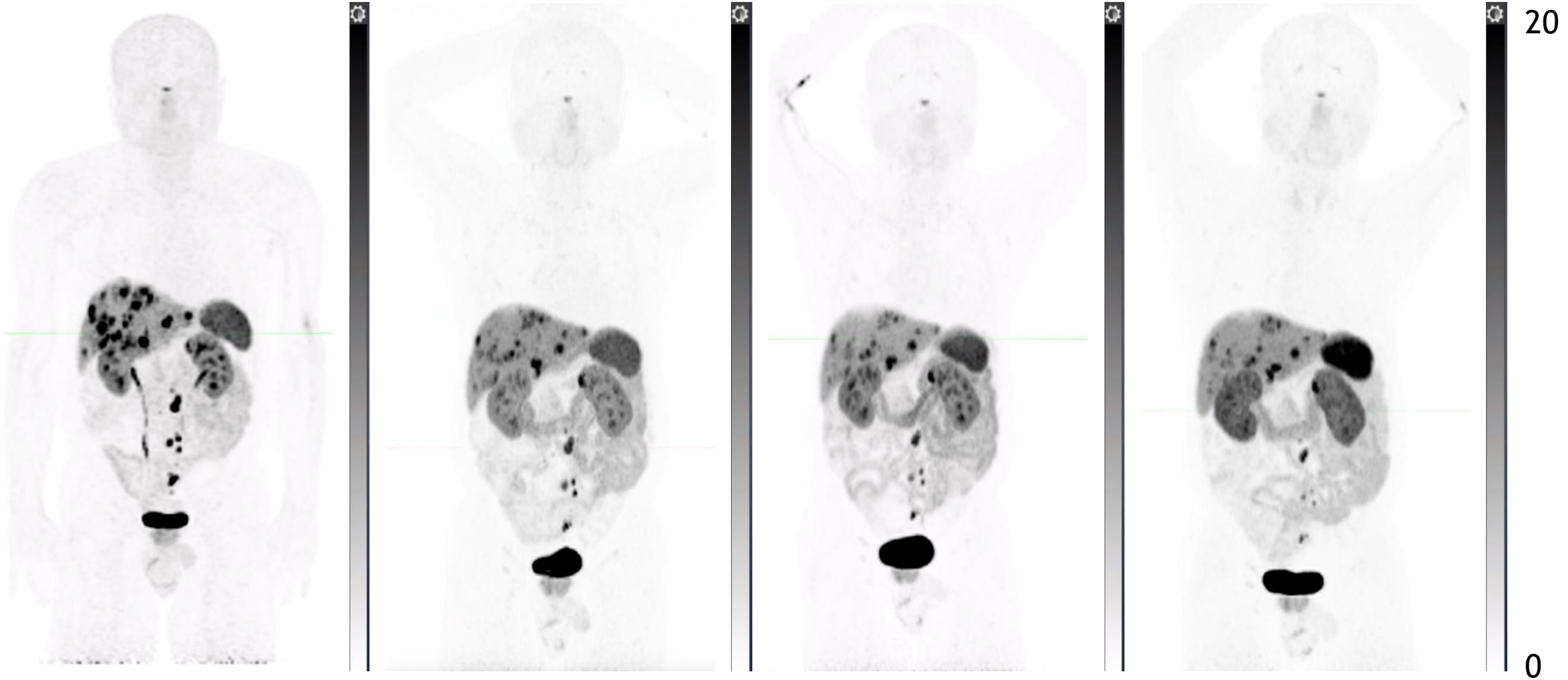
* The full sets of scans following cycle 4 are not yet available to the study team for five patients.
Notes: Patients had progressive disease prior to enrollment on study, and patient 109-103 experienced progressive disease by unambiguous progression of non-target lesions
Data cutoff 10/31/24

Preliminary Assessment of Disease Control Durability



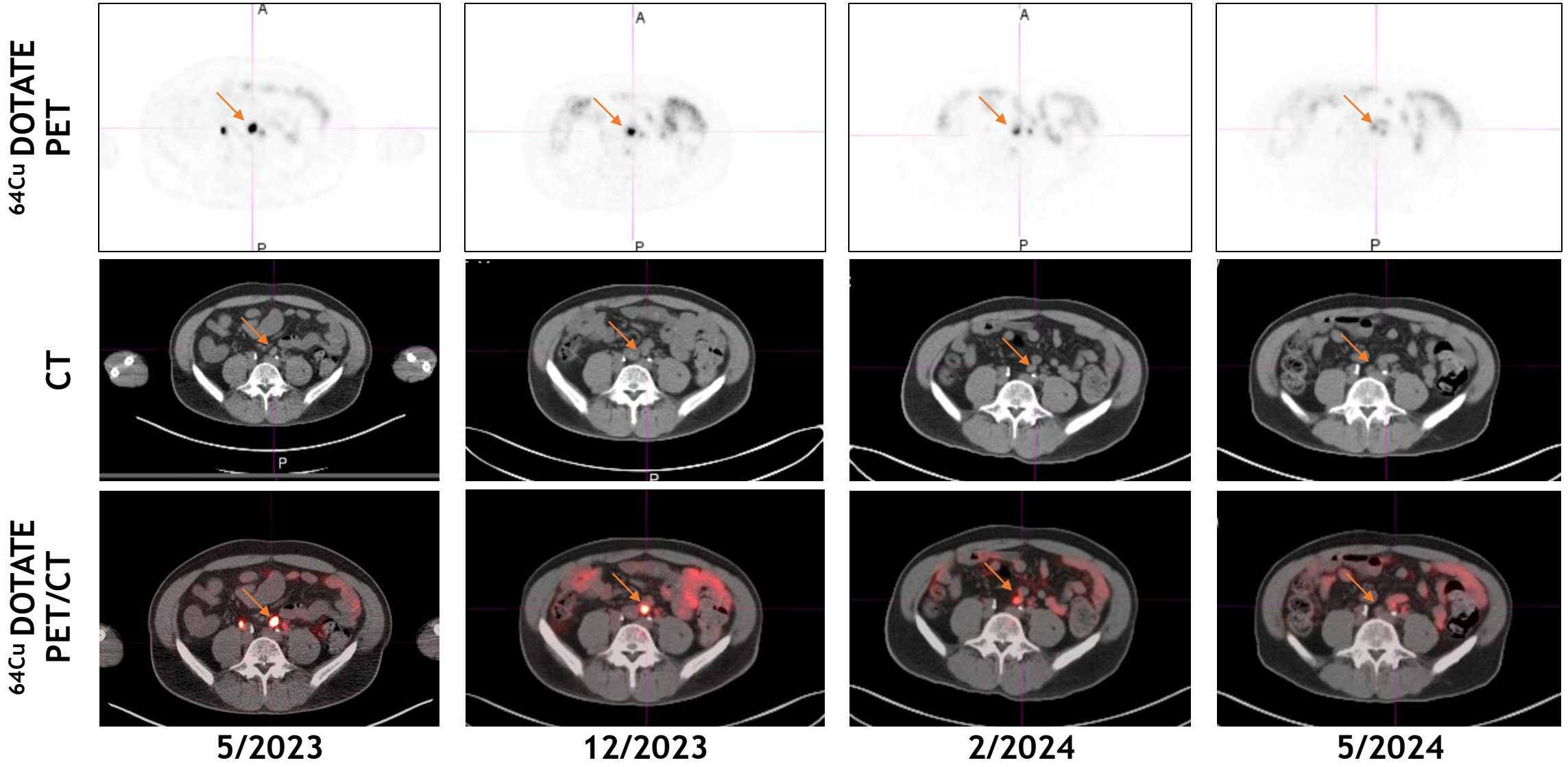
Data cutoff 10/31/24

Patient 103-101 – ^{212}Pb alpha NET 2.5 mCi x 4

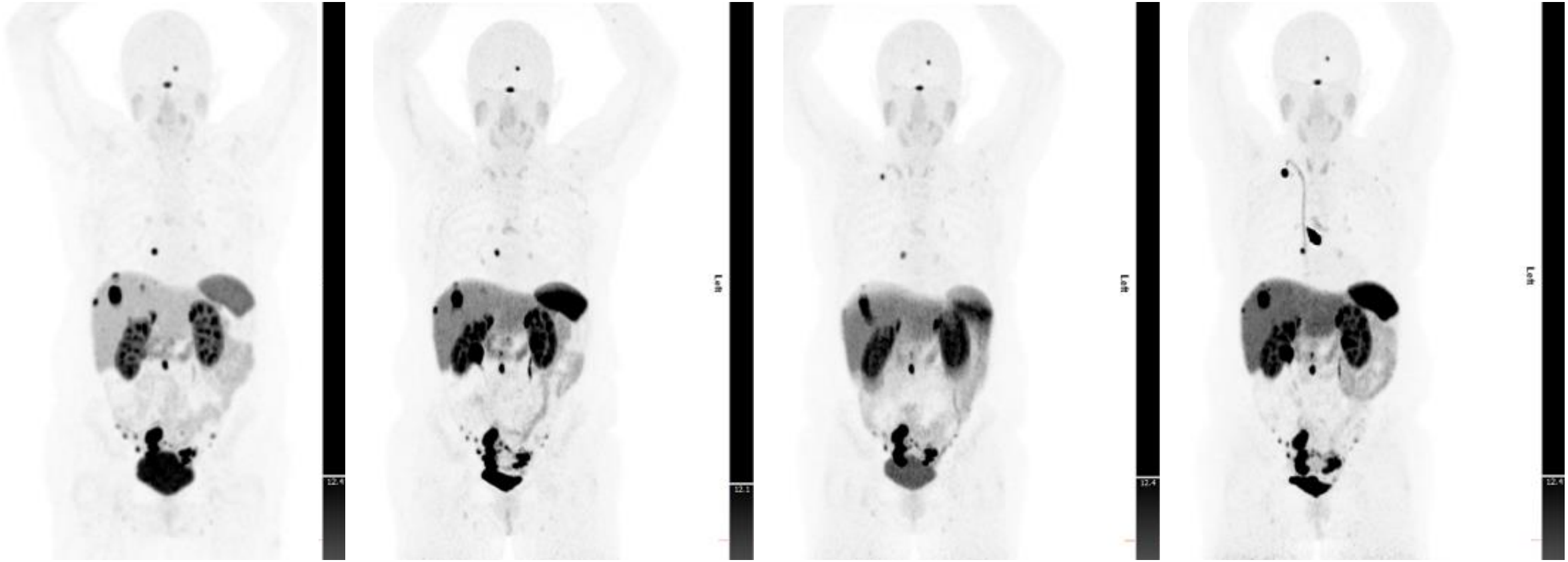


5/2023 12/2023 2/2024 5/2024

Patient 103-101 – ^{212}Pb alpha NET 2.5 mCi x 4

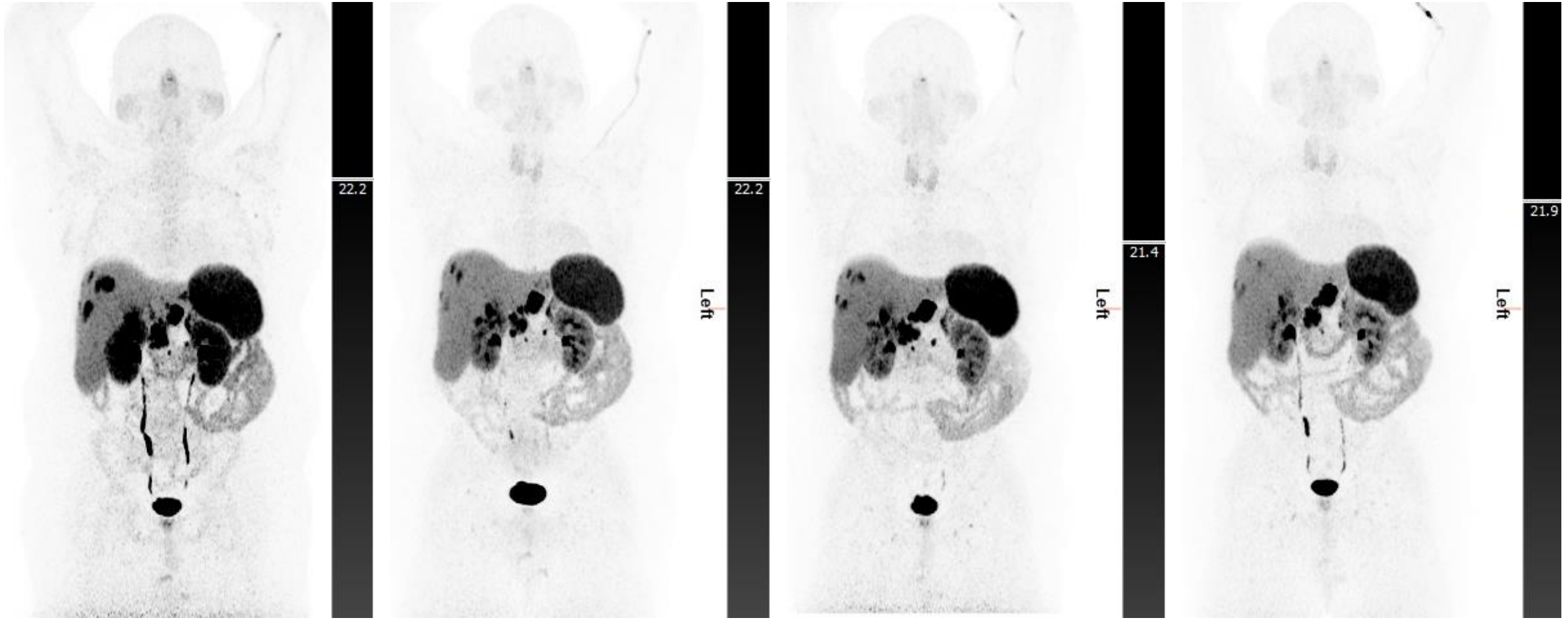


Patient 103-102 – ^{212}Pb alpha NET 2.5 mCi x 4



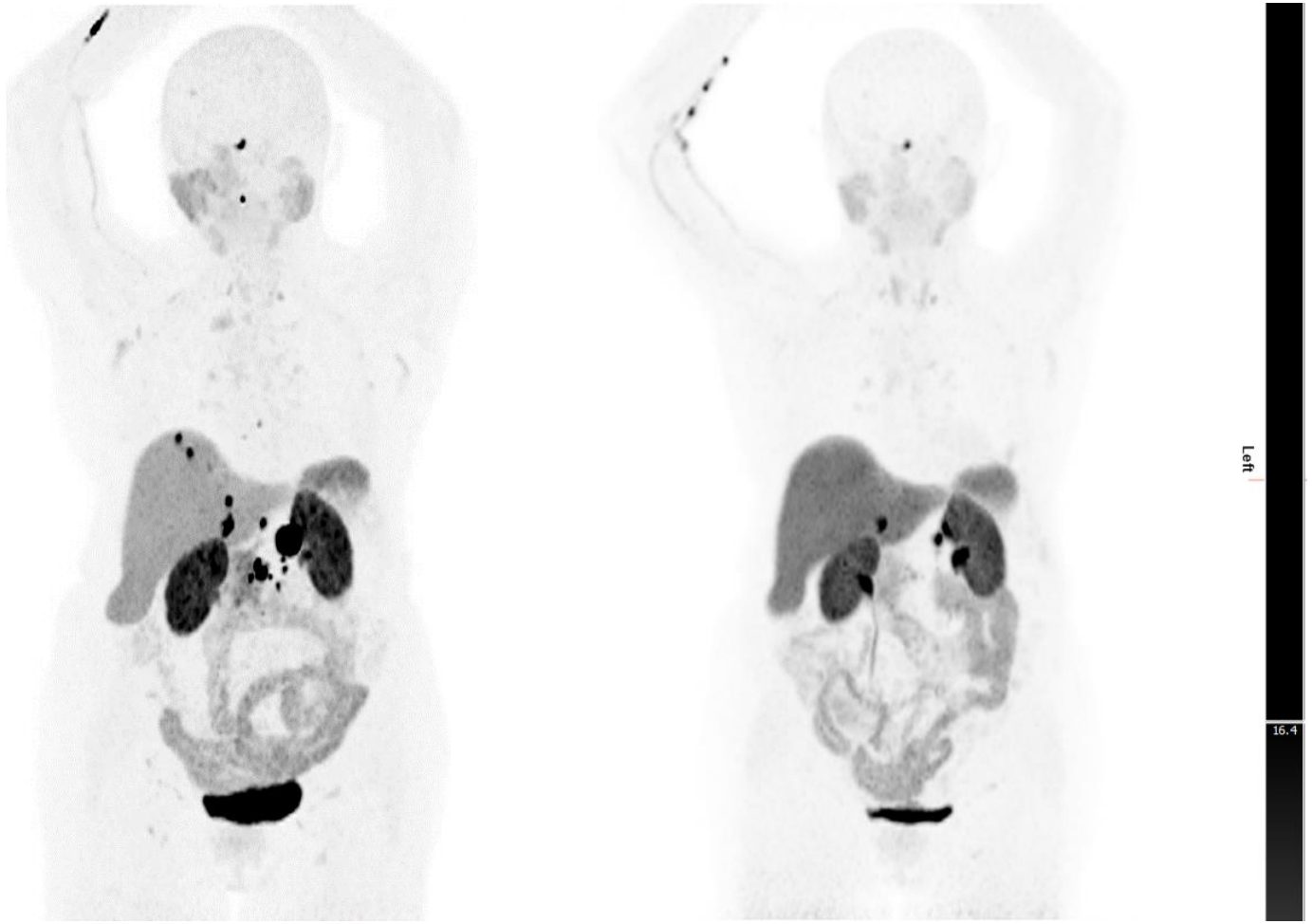
9/2023 **12/2023** **2/2024** **6/2024**

Patient 103-103 – ^{212}Pb VMT alpha NET 5.0 mCi x 4



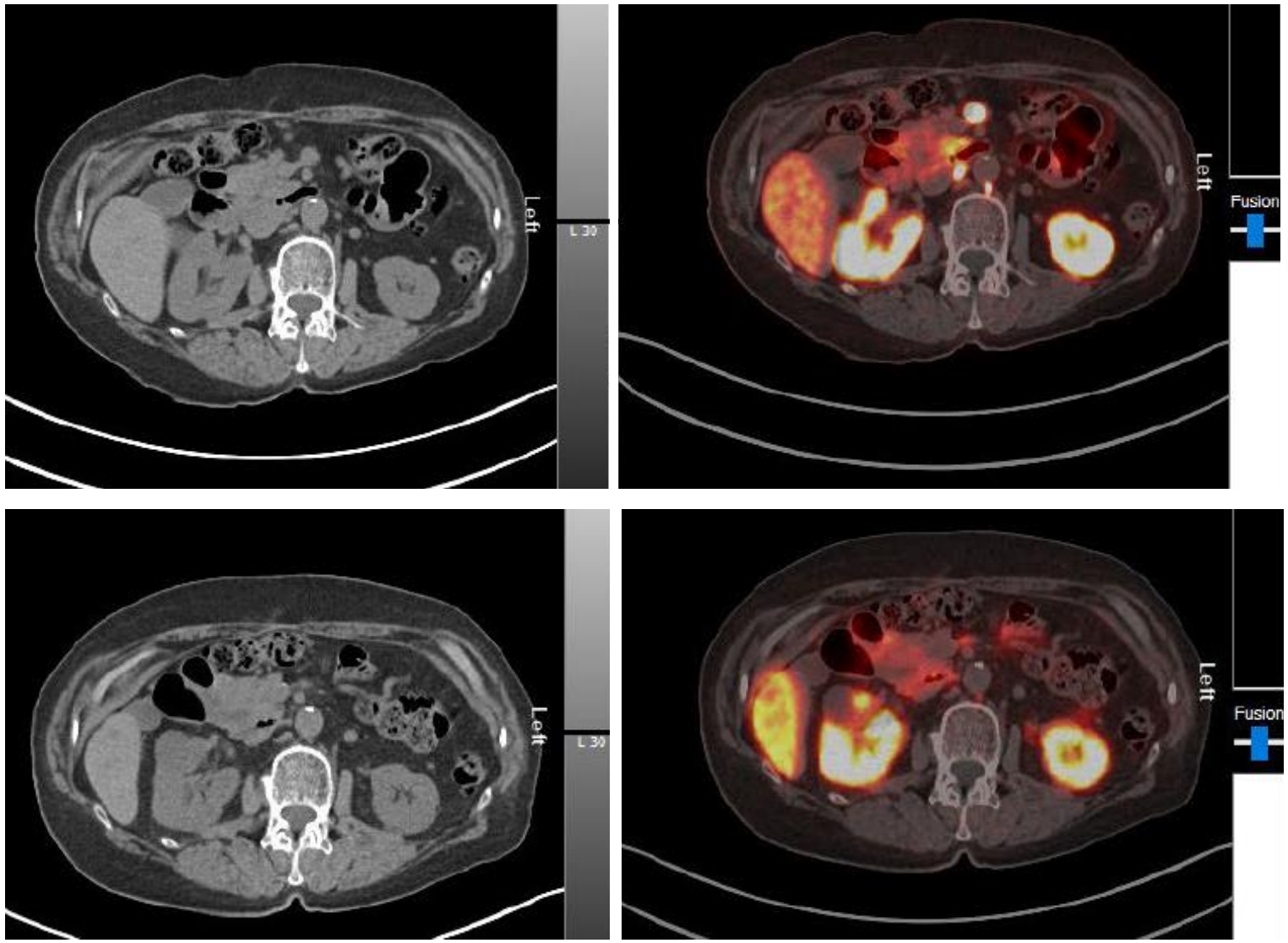
Baseline 1/2024 **3/2024** **5/2024** **9/2024**

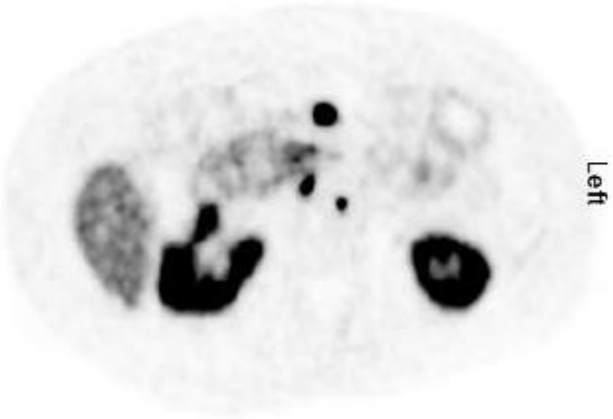
Patient 103-104 – ^{212}Pb VMT alpha NET Rx 5 mCi x 2, 2.5 mCi x 2



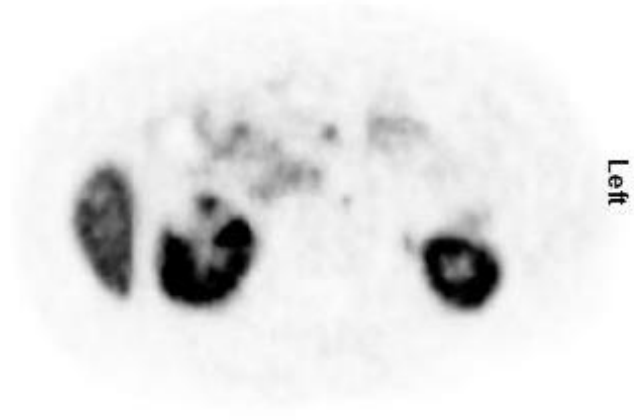
Pre-Rx 3/2024 **Post Rx 10/2024**

Patient 103-104 – ^{212}Pb VMT alpha NET Rx 5 mCi x 2, 2.5 mCi x 2





Pre-Rx
3/2024



Post Rx
10/2024

Conclusions

[^{203}Pb]VMT-α-NET and [^{212}Pb]VMT-α-NET were well-tolerated

- No DLTs were observed
- No grade 4, grade 5 AEs or SAEs were observed
- No decline in renal function was observed
- Hematologic AEs were low in number and low grade
- No treatment discontinuations due to AE have occurred

Appreciable activity was been observed with treatment at this early timepoint in the study

- 8 of 9 (89%) patients had durable control of disease
- Analysis of cohort 1 and 2 at this early stage already shows clear signs of clinical activity
- The study will continue to define the RP2D with further dose escalation cohorts

The Safety Monitoring Committee has recommended dose escalation which will be considered with FDA

Acknowledgements

Multi Center trial thanking all investigators and the patients who participated.

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Learning Objective Questions

What is the decay $t_{1/2}$ life of ^{212}Pb?	A. 1.64 hour B. 10.64 hours C. 10.64 days D. 10.64 weeks
Over how many treatment cycles may [^{212}Pb]VMT-α-NET be given?	A. 1 cycle B. 4 cycles C. 6 cycles D. 12 cycles