Case #3

Optimal time to do PRRT

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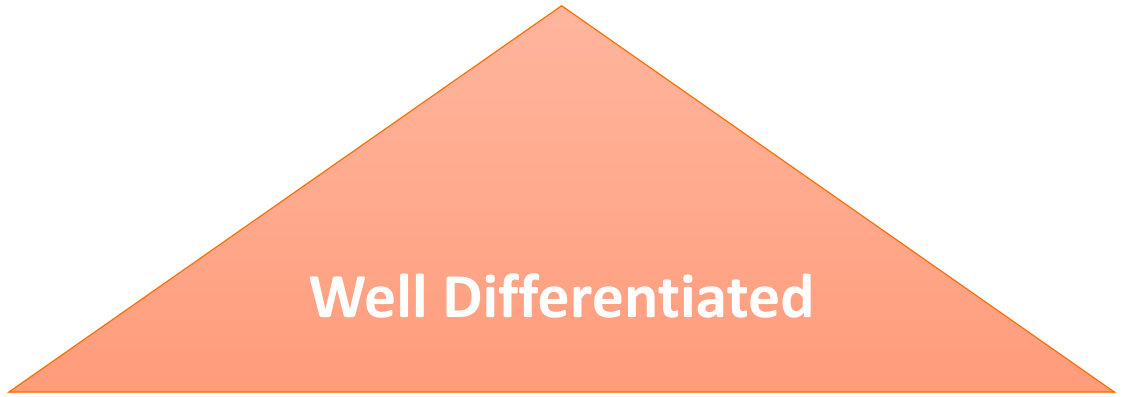
UNIVERSITY OF MIAMI HEALTH SYSTEM

NCI Designated Cancer Center

NET



Scan → DOTATATE PET

Diagnostic Blood Test → Chromogranin A

Treatment → SSA, mTORi, TKI, PRRT, Cabo

NEC

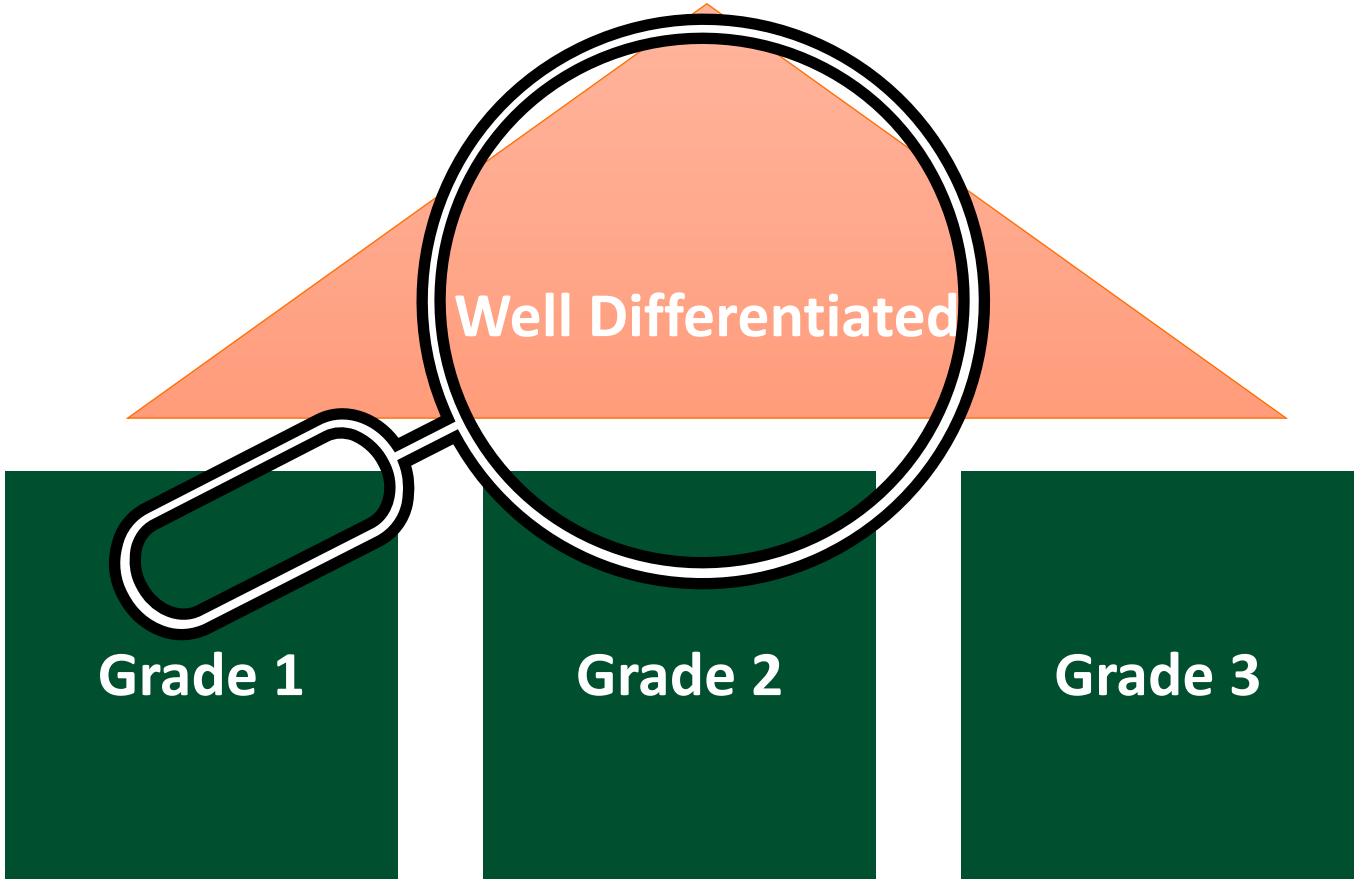
Poorly Differentiated
-Small Cell
-Large Cell

FDG PET

NSE

Chemotherapy
Immune Checkpoint inhibitors
DLL-3 BiTE

NET

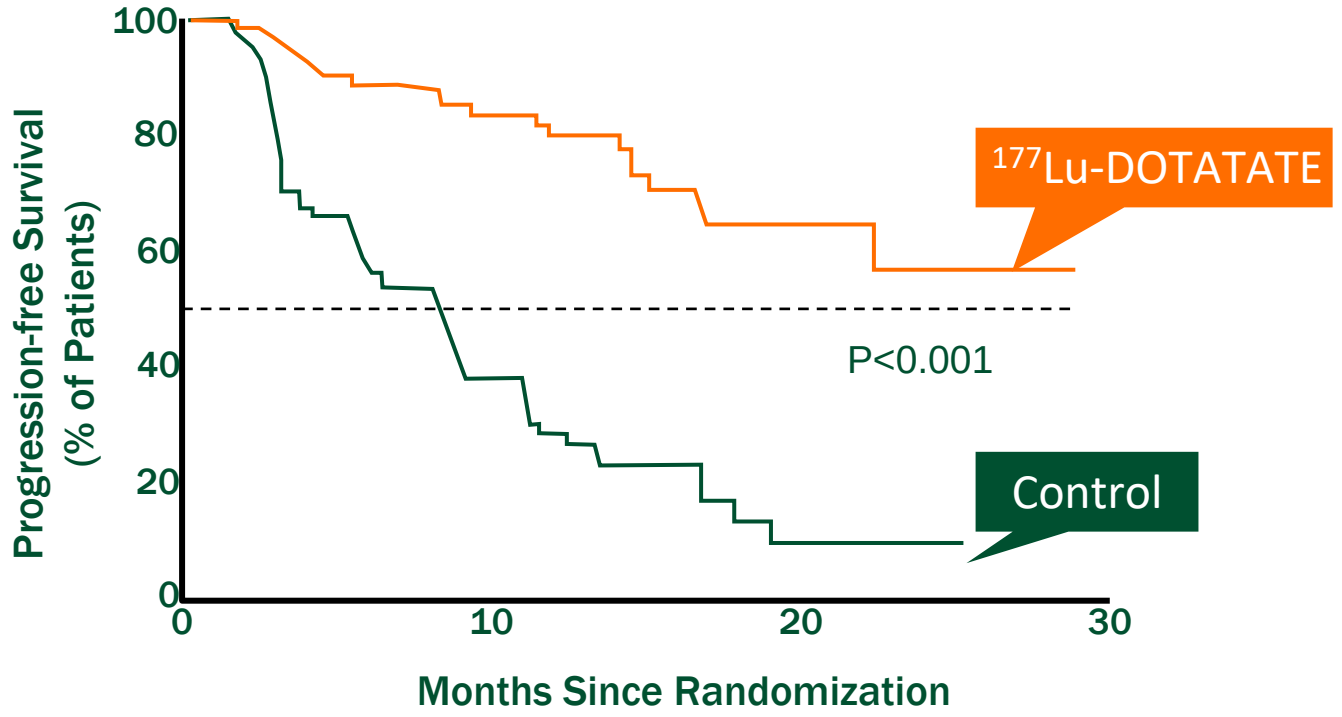


NEC

Poorly Differentiated
-Small Cell
-Large Cell

Grade 3

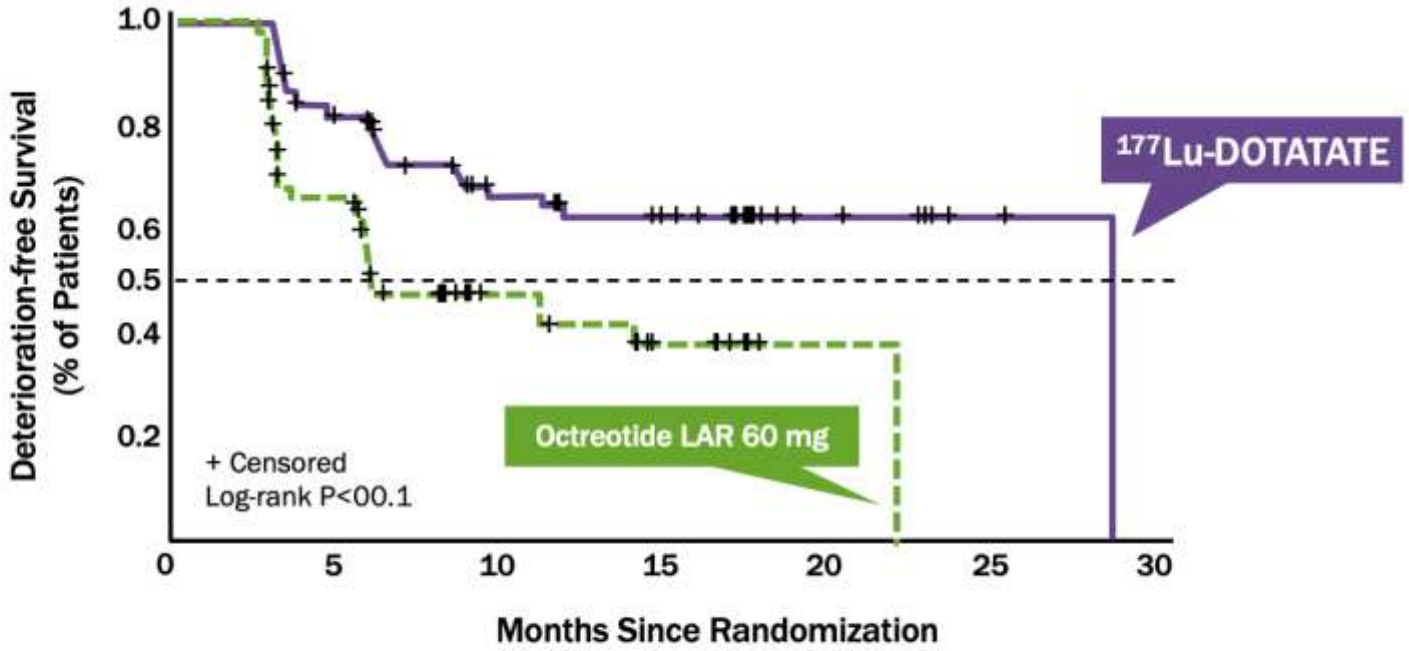
^{177}Lu-Dotatate Significantly Improves Progression-Free Survival in Patients with Midgut Neuroendocrine Tumors: Results of the Phase III NETTER-1 Trial



The NEW ENGLAND JOURNAL of MEDICINE

N. Engl J Med376;2 NEJM.ORG January 12, 2017

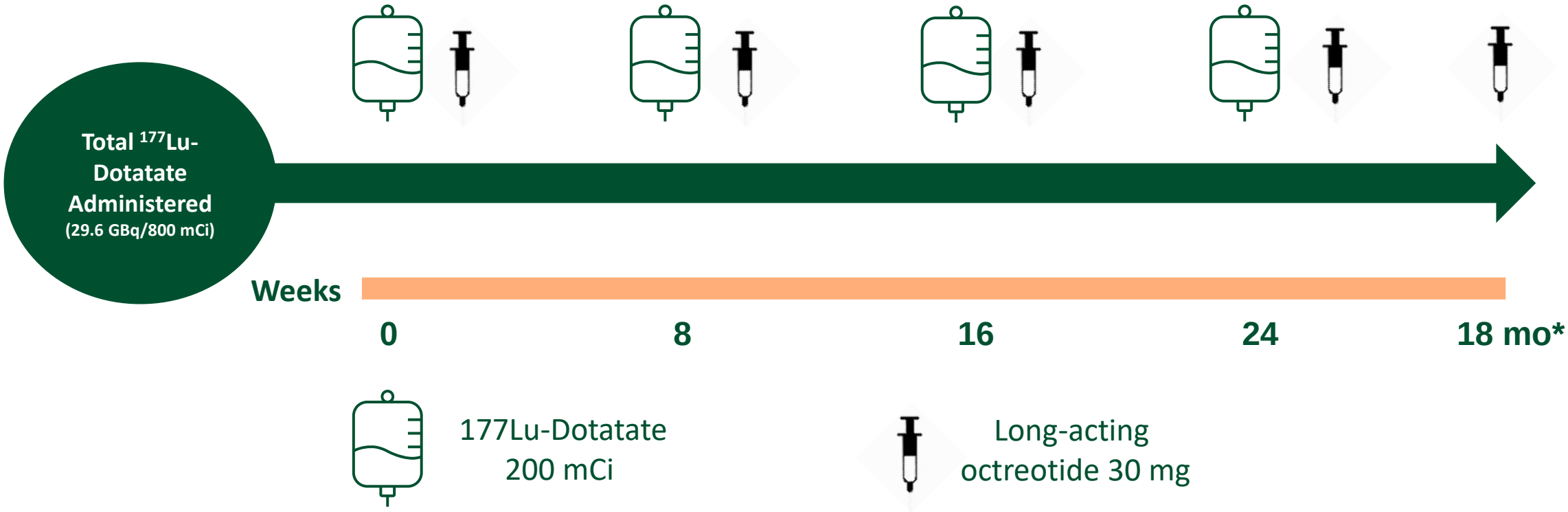
QOL: Global Health Status



No. at Risk											
^{177} Lu-DOTATATE	117	72	52	39	30	28	13	9	2	1	0
Octreotide LAR	114	54	28	19	13	7	1	1	0		

J Clin Oncol 36:2578-2584

Treatment Regimen



*Continue Q4W to PD or up to 18 months.

BOARD ANSWER

Progressive metastatic somatostatin receptor positive gastroenteropancreatic neuroendocrine tumor

If only life was as easy as board questions!

Some straightforward PRRT indications for Stage IV SSTR +ve disease

1. **Widespread bone metastasis/bone pain**

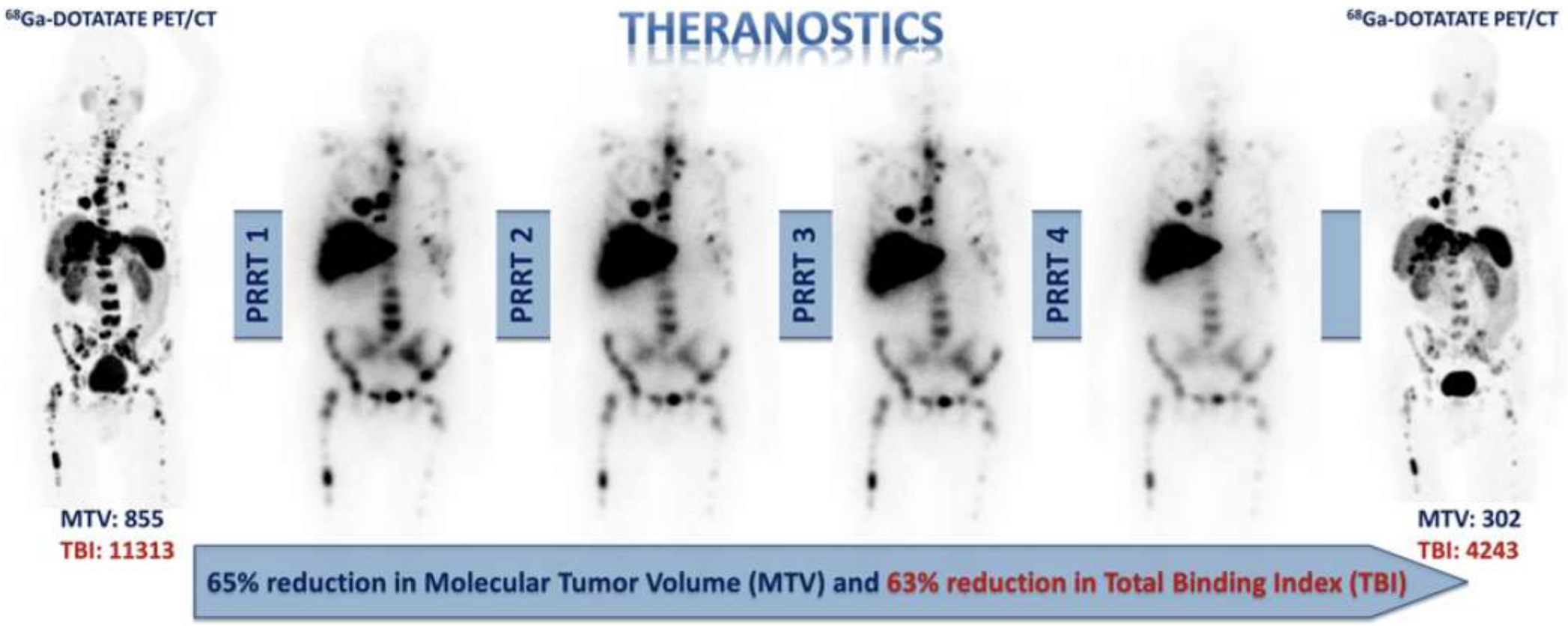


Fig. 5. Eighty-year-old male diagnosed in June 2014 with atypical lung carcinoid with diffuse metastasis to liver, lymph nodes, and bone which has progressed on octreotide, capecitabine / temozolomide, everolimus, and liver embolization procedure. Started on PRRT in May 2018 and completed in November 2018, status post 4 doses now with continued complete resolution of severe bony pain which was previously requiring narcotic pain medications. **Molecular Tumor Volume (MTV)**: volume in cm^3 of tumor showing increased Ga-68 dotatate uptake; **Total Binding Index (TBI):** the product of mean SUV and MTV.

Some straightforward PRRT indications for Stage IV SSTR +ve disease

1. Widespread bone metastasis/bone pain
2. G1/2 (Ki67<10%) Progressive disease 2nd-3rd line, especially extra hepatic disease burden
3. Frontline management of metastatic G2 (Ki67>10%) or G3 NET
4. Functional NET, symptomatic disease, need disease shrinkage

Some not so straightforward PRRT indications

1. Liver dominant progressive disease: PRRT vs Locoregional Therapy (TACE/Bland Embolization
2. Mesenteric disease: some concern for SBO, ORR poor in mesenteric disease
3. Poor Marrow Reserve: Baseline thrombocytopenia.
   Be careful in patient with prior use of extensive alkylator therapy (Temozolomide)
4. Progressive low volume disease
5. SUVs 2.5 - 10 on dotatate scan

When not to do PRRT

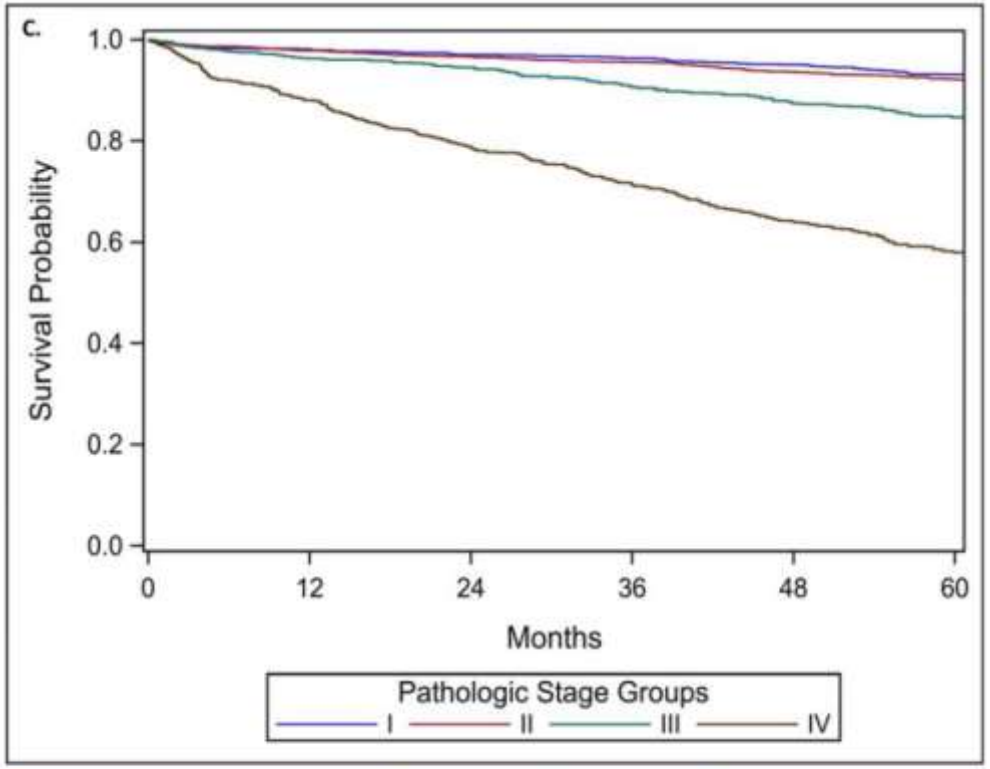
1. Pregnant patient
2. Thrombocytopenia (<75K)
3. SSTR negative NET or low receptor density (These are usually higher grade NETs)
4. Hepatic insufficiency (T Bili > 2.5-3 x ULN)
5. Renal insufficiency w/o dialysis support
6. ECOG PS >3

Surgery is Curative for Early Stage

Pt underwent distal pancreatectomy and splenectomy on 7/3/2014

Surgical pathology confirmed grade 2 pancreatic neuroendocrine tumor (ki 67-4%). LN were negative for malignancy.

Surgery is Curative for Early Stage



	Stage I	Stage II	Stage III	Stage IV
Case number	1210	1453	705	680
5-year overall survival rate	92.98%	91.86%	85.18%	53.59%

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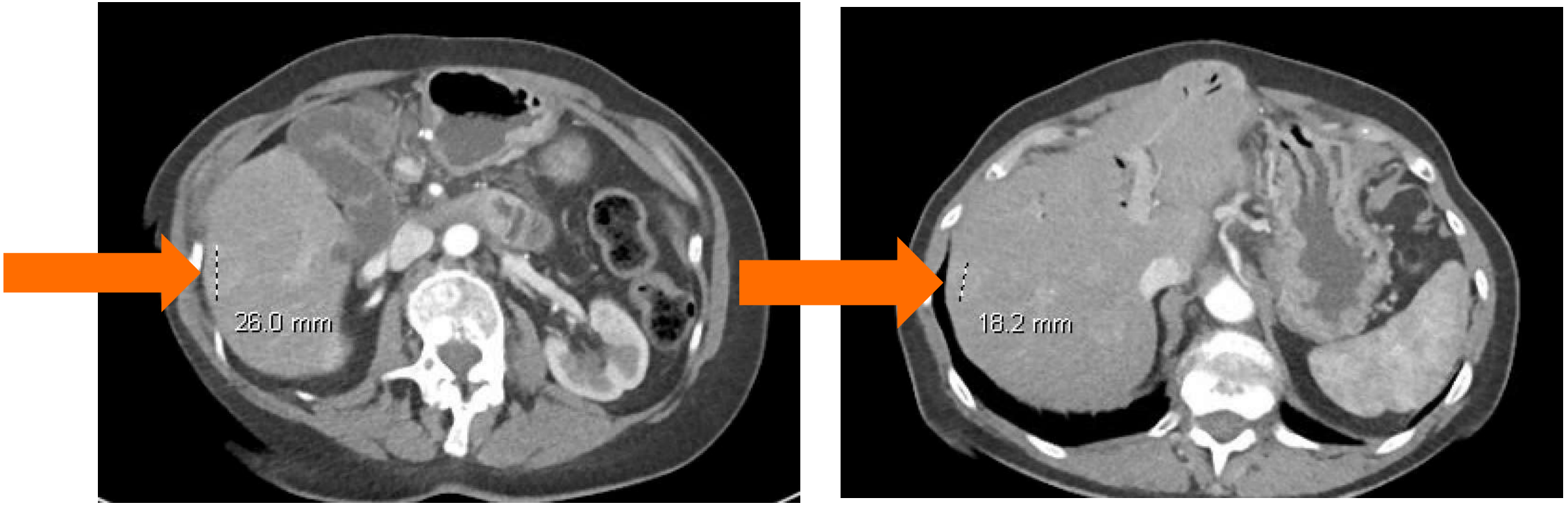
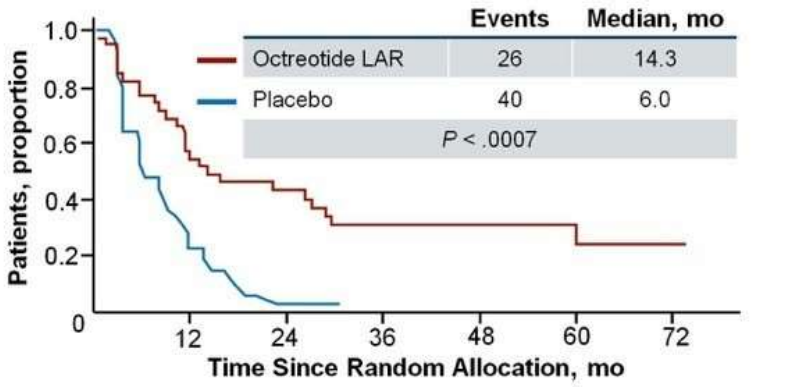
Metastatic Progression

- CT abdomen with contrast noted new hypodense lesion in the periphery of the segment 6 of the liver. More conspicuous arterially enhancing lesions in the segment 5 and 8 of the liver.
- Biopsy confirmed metastatic relapse all new compared to a prior February 2018



Patient was initiated on monthly octreotide

PROMID Study Results



No. of patients at risk

Octreotide LAR	42	19	15	10	9	5	1
Placebo	43	9	1	0	0	0	0

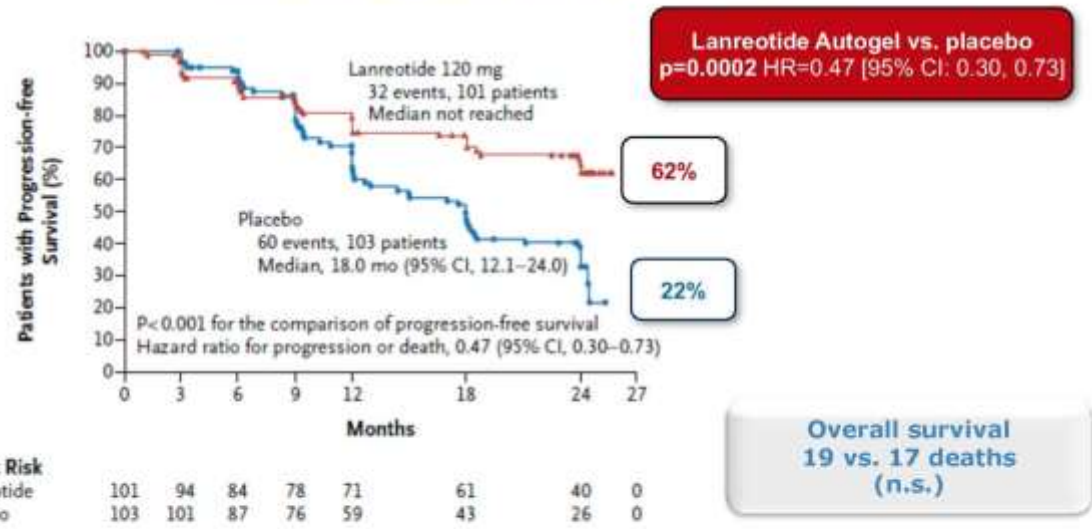
Log-rank test stratified by functional activity: $P = .000072$, HR = 0.34 (95% CI, 0.2-0.59)

From Rinke A, et al. *J Clin Oncol*. 2009;27:4656-4663.[18] Reproduced with permission. © 2009 American Society of Clinical Oncology. All rights reserved.

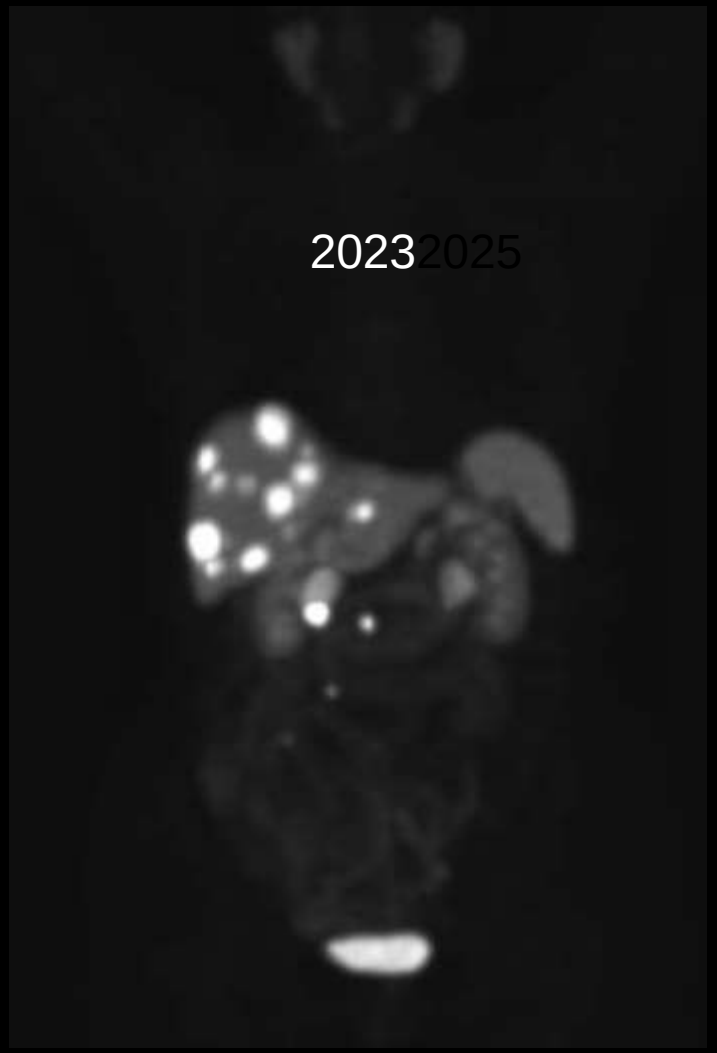
CLARINET Study

Lanreotide AG vs Placebo in NF entero-pancreatic NET (95% with stable disease; Ki67< 10%)

Primärer Endpunkt: PFS (ITT, n=204)



Chauhan A. *CA: A Cancer Jr of Clinicians 2024*: Critical Updates AJCC

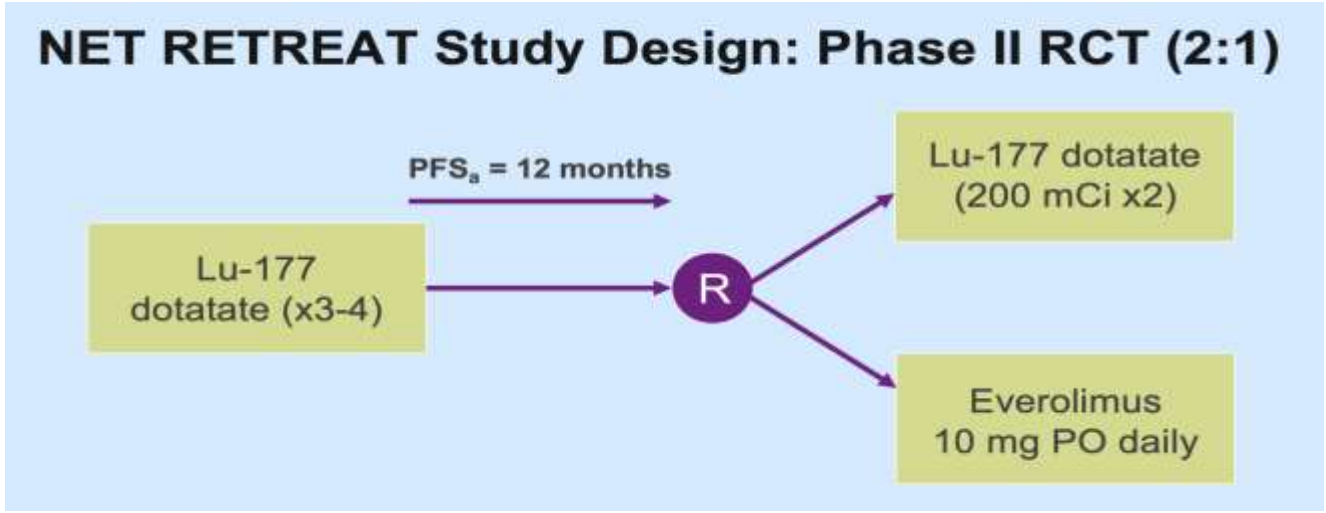


Before

4 doses of PRRT

After

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



US/ Canada Joint Effort

Key Inclusion/Exclusion Criteria

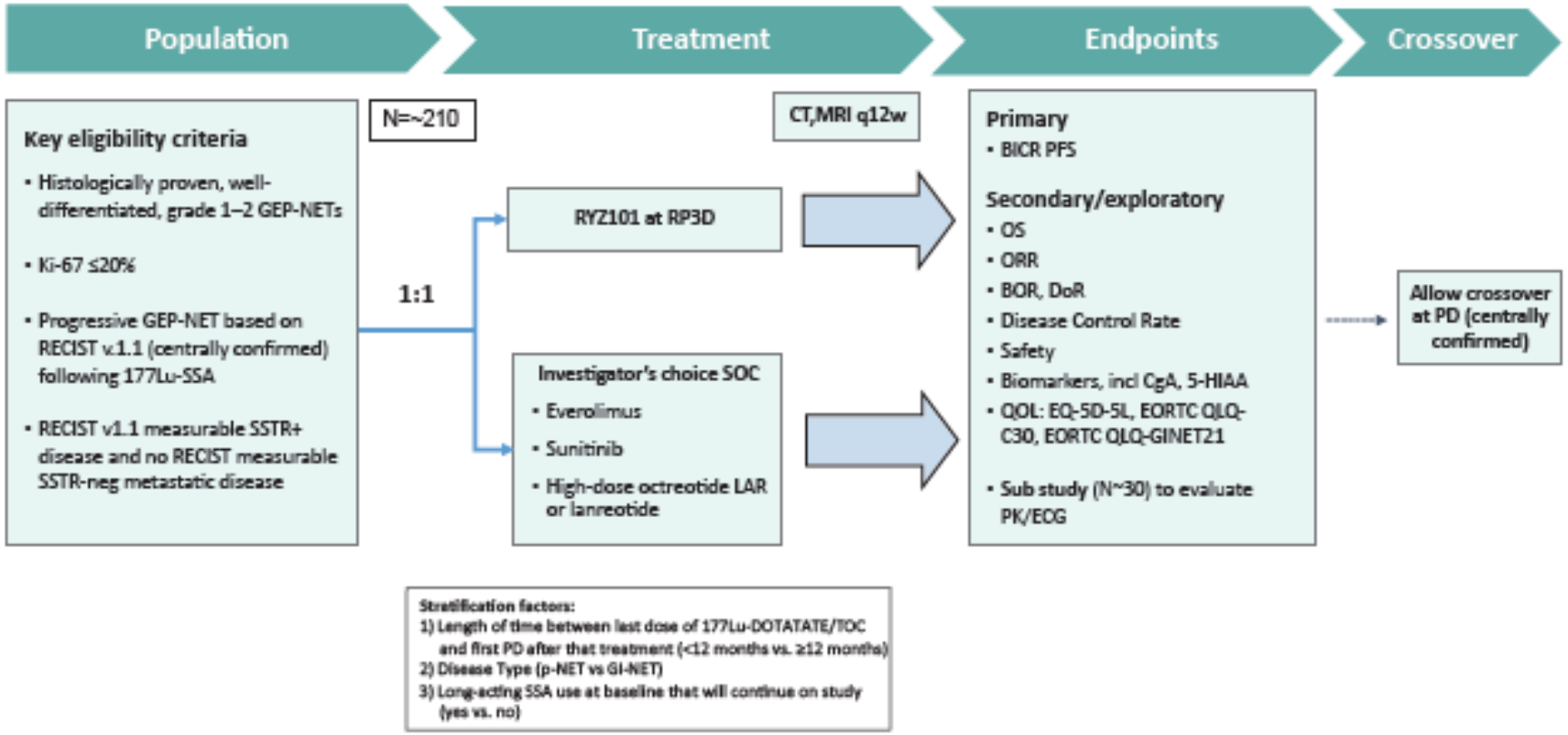
- Metastatic Progressive midgut NET (Grade 1-2)
- No RECIST progression within 12 month from last dose of prior PRRT (3-4 prior PRRT doses)

Statistics Design

- 126 patients will be randomized in 2 (PRRT):1(Everolimus) over 3 yrs
- 91 observed PFS events would yield 90% power for target HR of 1.75 (6 month increase in median PFS over control)

Rationale: Lu-177 dotatate only FDA approved PRRT agent for metastatic progressive GEPNETS in US/Canada. Currently about 200 sites administering Lu-177 dotatate. A surge in post PRRT progressing patients increasingly being noticed and this problem is going to grow exponentially in near future. Retrospective data from Europe suggest safety and efficacy with PRRT retreatment, however, no prospective data for PRRT retreatment exists. Findings can potentially alter practice patterns and open access to PRRT retreatment for patients in need.

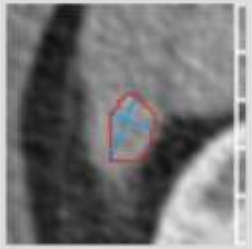
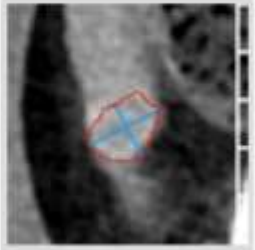
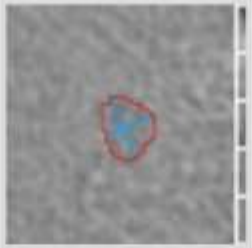
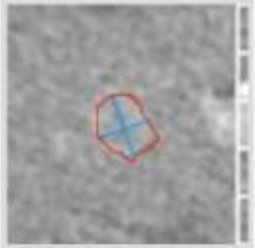
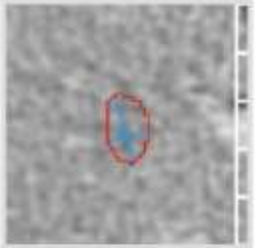
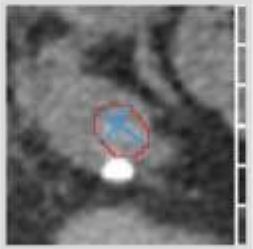
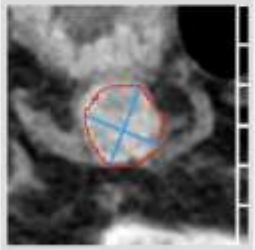
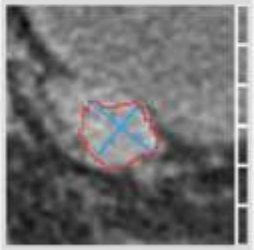
ACTION-1: Phase 1b/3 Global, Randomized, Controlled, Open-label Trial Comparing Treatment With RYZ101 to Standard of Care Therapy in Subjects With Inoperable, Advanced, SSTR+, Well-differentiated GEP-NETs That Have Progressed Following Prior 177Lu-SSA Therapy

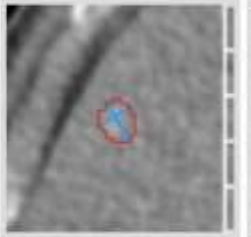
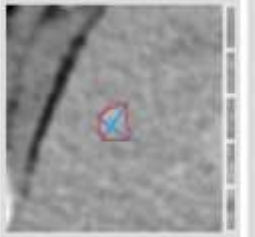
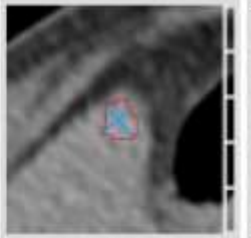
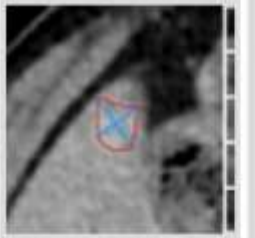
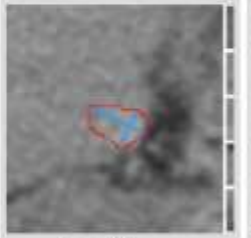
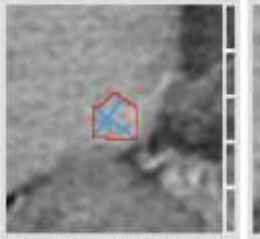
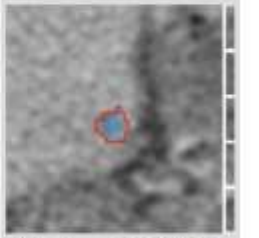


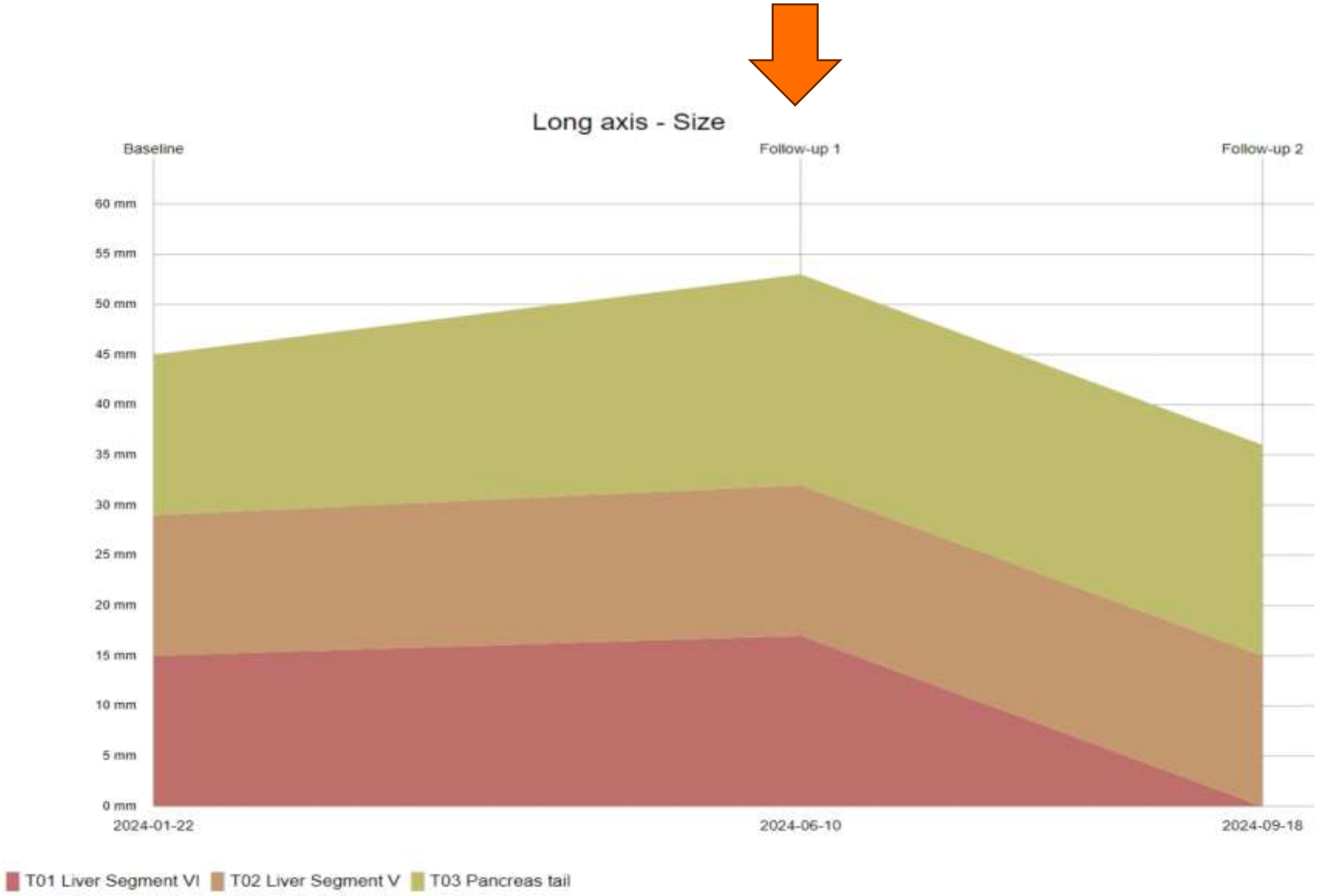
PRRT

Pseudoprogression

[redacted]

	Baseline	Follow-up 1	Follow-up 2
Target lesions			
T01 Liver Segment VI Size	 LA: 15 mm SA: 10 mm	 LA: 17 mm (+13.3% ΔP) SA: 13 mm (+30.0% ΔP)	LA: 0 mm (-100.0% ΔP) Disappeared
T02 Liver Segment V Size	 LA: 14 mm SA: 11 mm	 LA: 15 mm (+7.1% ΔP) SA: 11 mm (0.0% ΔP)	 LA: 15 mm (0.0% ΔP) SA: 9 mm (-18.2% ΔP)
T03 Pancreas tail Size	 LA: 16 mm SA: 12 mm	 LA: 21 mm (+31.3% ΔP) SA: 20 mm (+66.7% ΔP)	 LA: 21 mm (0.0% ΔP) SA: 17 mm (-15.0% ΔP)

	Baseline	Follow-up 1	Follow-up 2
Non-target lesions			
NT01 Liver Segment V Size	 LA: 10 mm SA: 8 mm Present	 LA: 9 mm (-10.0% ΔP) SA: 8 mm (0.0% ΔP) Present	Disappeared
NT02 Liver Segment VI Size	 LA: 10 mm SA: 8 mm Present	 LA: 13 mm (+30.0% ΔP) SA: 11 mm (+37.5% ΔP) Present	Disappeared
NT03 Liver Segment II Size	 LA: 14 mm SA: 10 mm Present	 LA: 12 mm (-14.3% ΔP) SA: 10 mm (0.0% ΔP) Present	 LA: 8 mm (-33.3% ΔP) SA: 8 mm (-20.0% ΔP) Present


Long axis - Size
Baseline
Follow-up 1
Follow-up 2
60 mm
55 mm
50 mm
45 mm
40 mm
35 mm
30 mm
25 mm
20 mm
15 mm
10 mm
5 mm
0 mm
2024-01-22
2024-06-10
2024-09-18
T01 Liver Segment VI
T02 Liver Segment V
T03 Pancreas tail

Final Thoughts

1. Retrospective data suggests earlier use of PRRT in treatment sequence can yield better ORR
2. Long term bone marrow toxicity and nephrotoxicity seems to not be a major concern
3. MDS and AML rates are <2%. Could be as high as 10% with prior alkylator exposure
4. Lifetime max limit of radiation exposure; should PRRT be delayed in a young patient and pts with low tumor burden?


THANK YOU