Innovations in Treatment of Pancreatic Neuroendocrine Tumors

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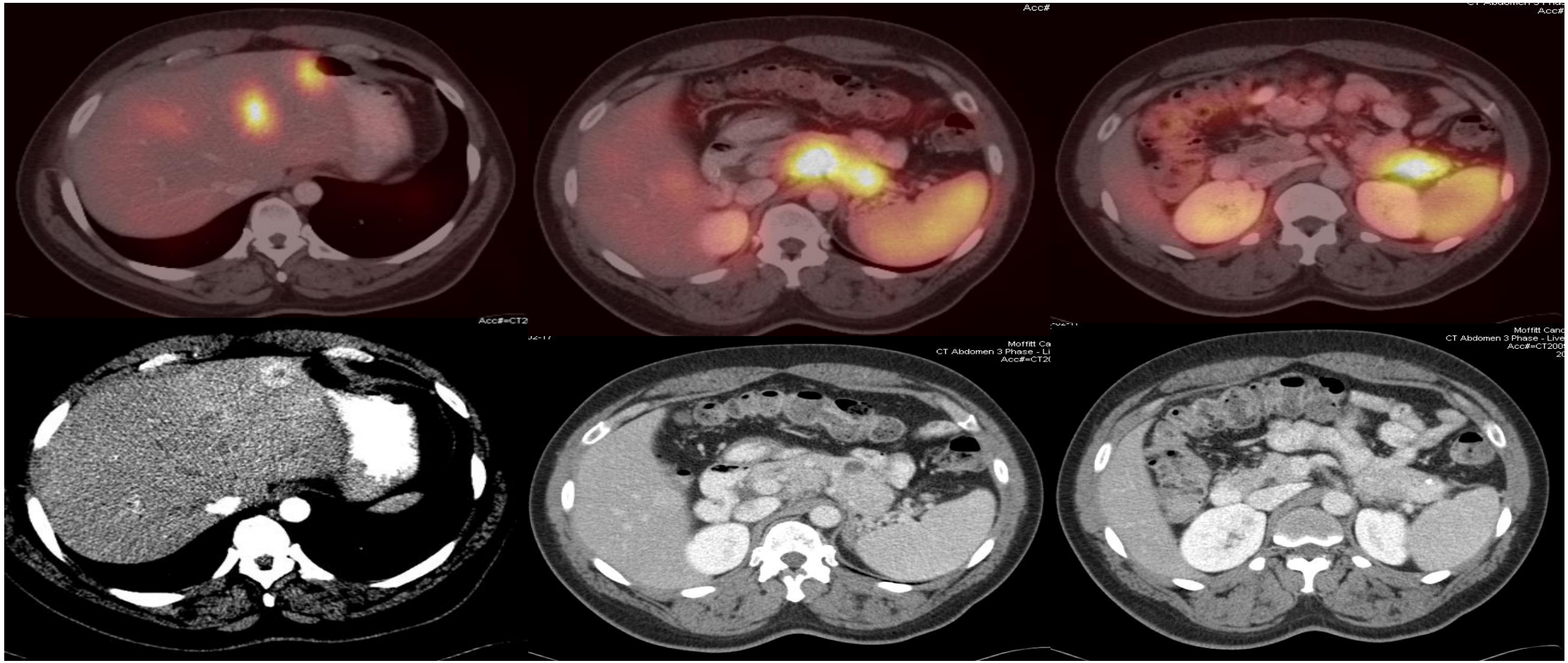
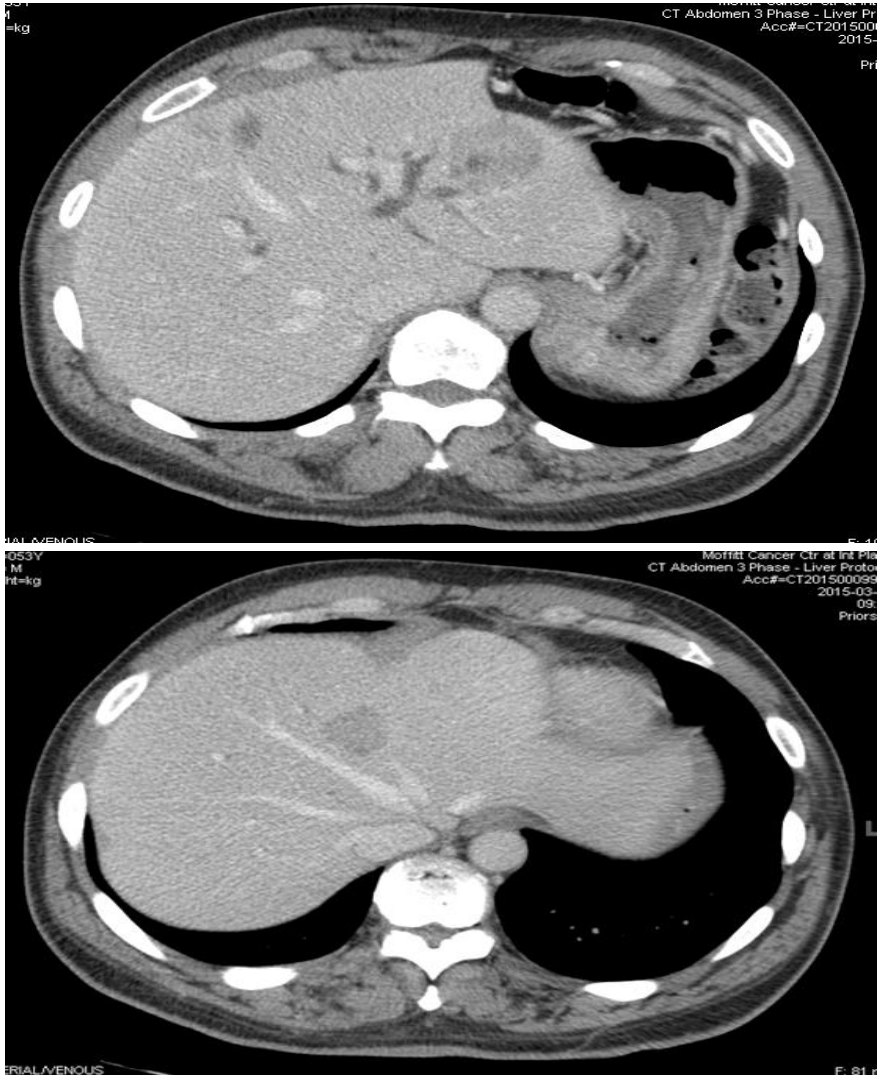
Case: Patient with metastatic well-differentiated pancreatic neuroendocrine tumor

- 47-year-old man presented in 2009 with intermittent abdominal pain for 12 months and night sweats.
- CT scan: 5x2 cm pancreatic tail tumor with large retroperitoneal lymph nodes and several scattered hypervascular lesions in left hepatic lobe.
- Liver biopsy: well-differentiated neuroendocrine tumor with 1 mitosis per 10 HPF, ki-67 4%
- OctreoScan: Avid radiotracer uptake



- Started on Octreotide LAR. Stable disease after 3 months.
- Case discussed in multidisciplinary tumor board. Surgery recommended if response to neoadjuvant treatment.
- 3 cycles of capecitabine/temozolomide administered: minor response.
- Distal pancreatectomy/splenectomy, lymph node dissection, wedge resection of liver tumor, and radiofrequency ablation x 3

- Patient maintained on octreotide LAR
- Disease remained stable x 5 years.
- Scans in 4/2015 demonstrated growth of 5 left lobe liver metastases

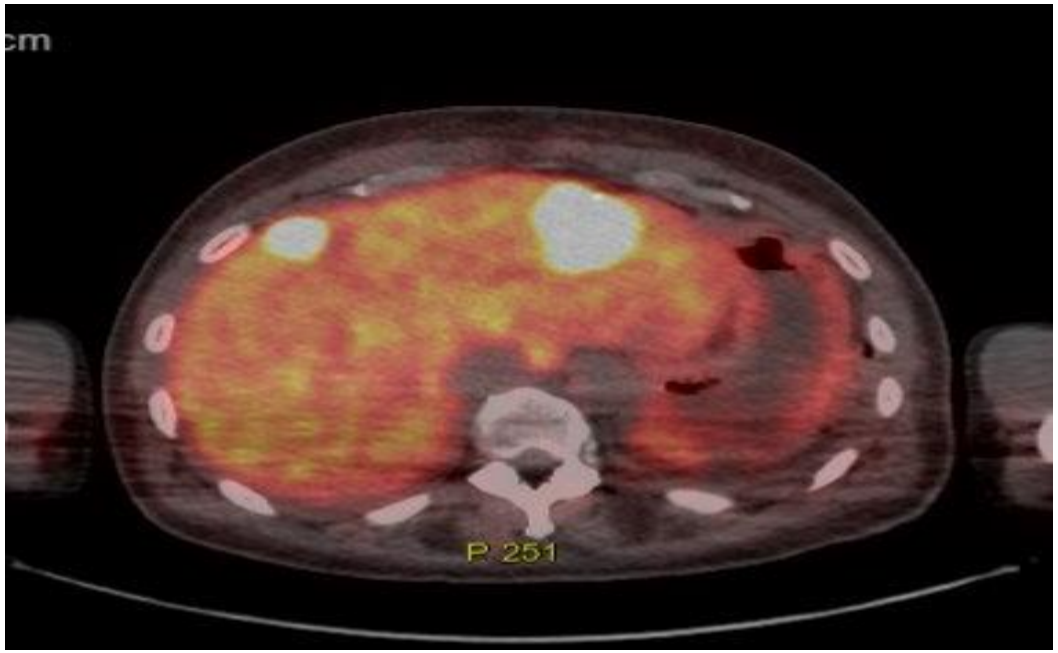


- Declined operation: underwent left liver bland embolization. Progressed in right liver lobe and lymph nodes in 10/2016.

- Resumed capecitabine/temozolomide with progression.

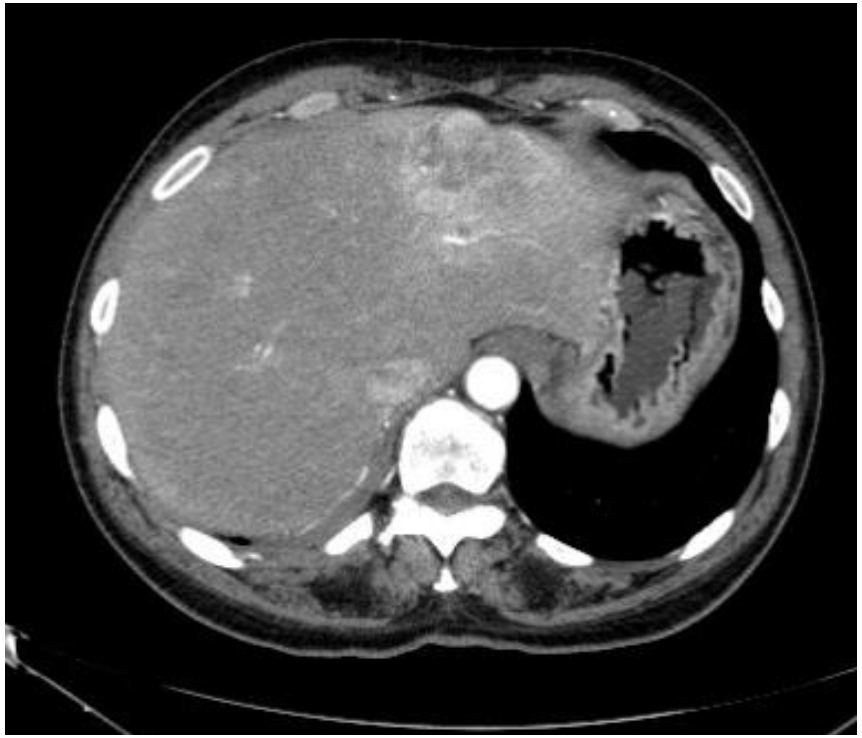
- Started everolimus in 1/2017 and progressed in 3/2018

- ^{68}Ga-Dotatate PET showed strong somatostatin receptor expression. Treated with ^{177}Lu-Dotatate x 4 treatments between 8/2018 and 1/2019

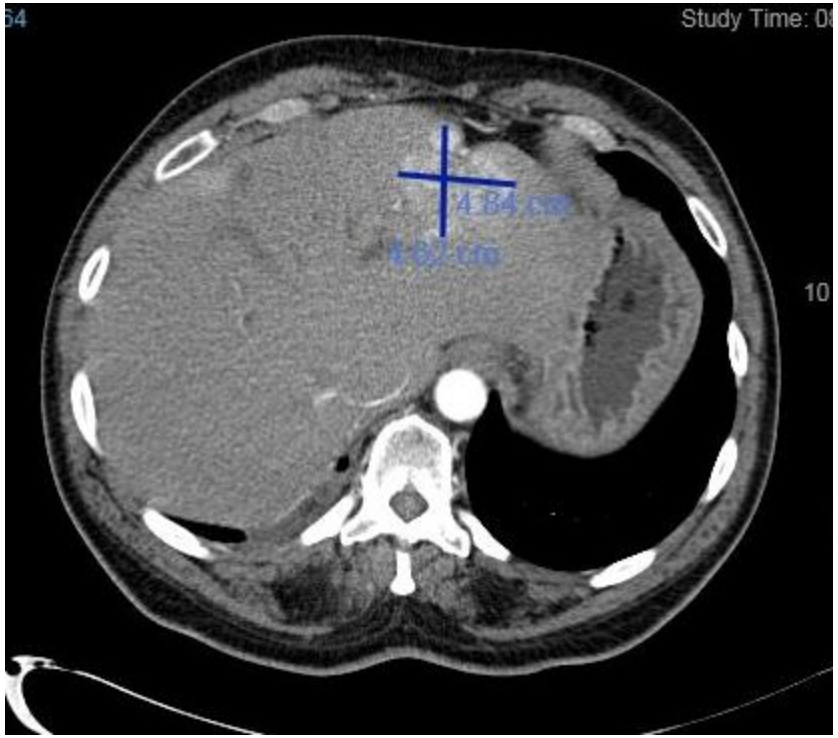


^{68}Ga-Dotatate PET scan

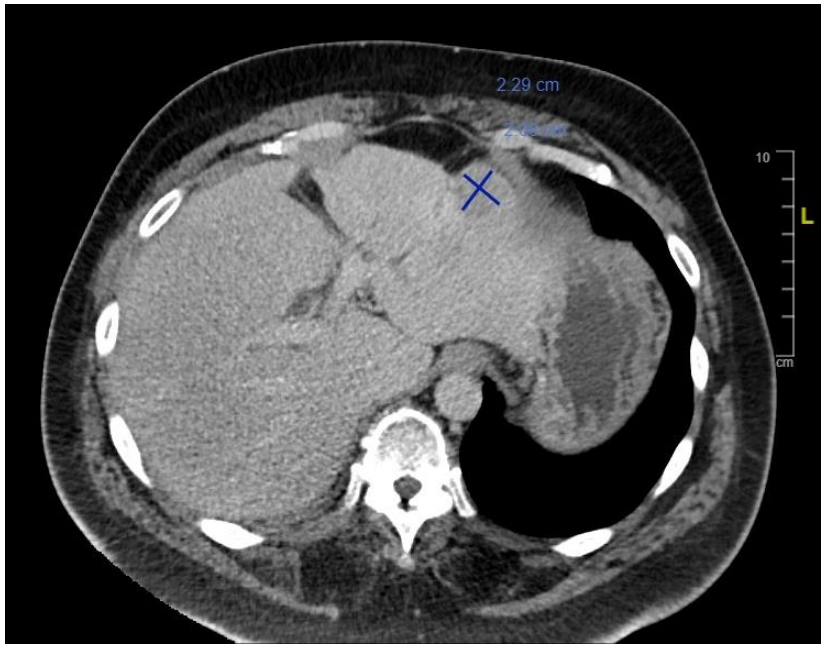
Response to ^{177}Lu-Dotatate

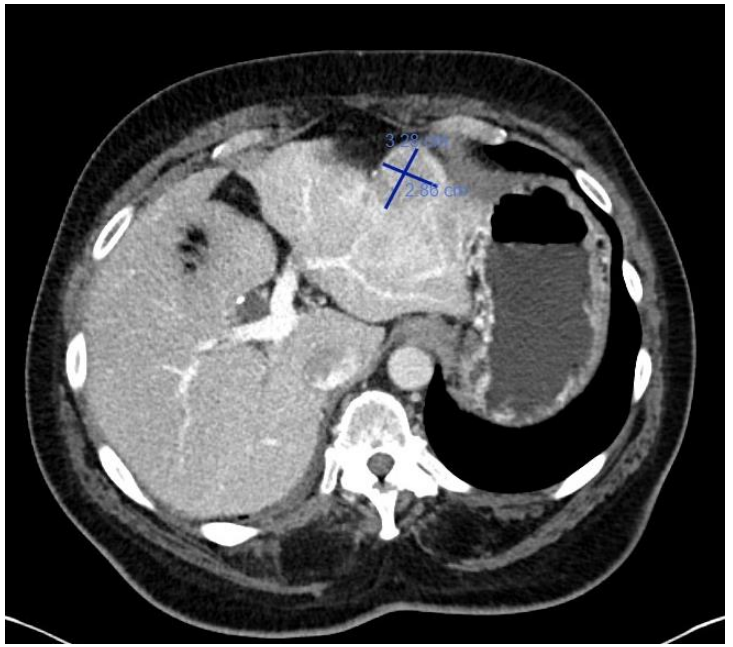


Pre-PRRT (8/2018)



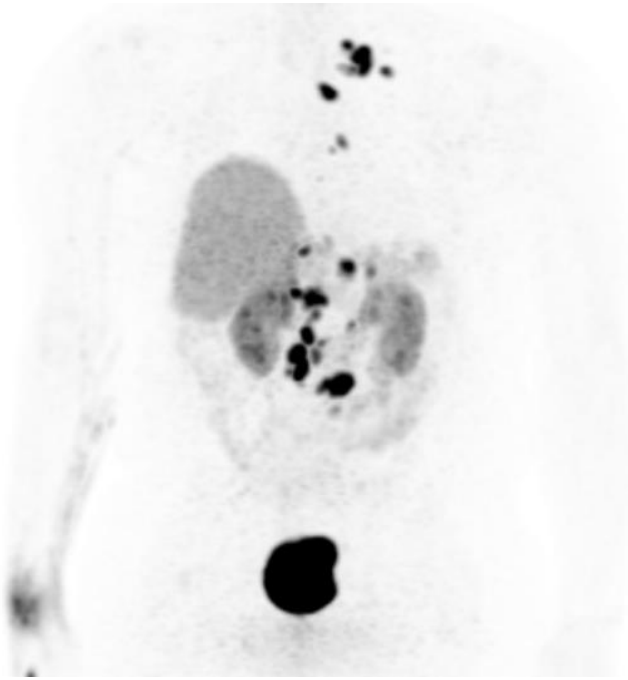
Post-PRRT (3/2019) Partial response



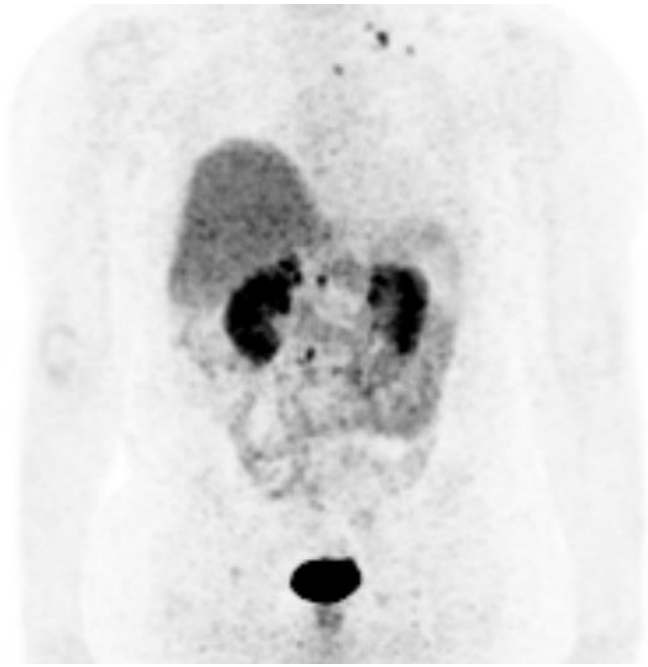


Progressed 1/2022. Left lateral hepatectomy in 2/2022: 3 metastases measuring up to 5cm with ki-67 of 40% (grade 3).

- 11/2022: Extensive new lymphadenopathy on CT and Dotatate PET with pains and sweats
- ^{177}Lu-Dotatate re-treatment x 4 cycles: 1/2023-7/2023

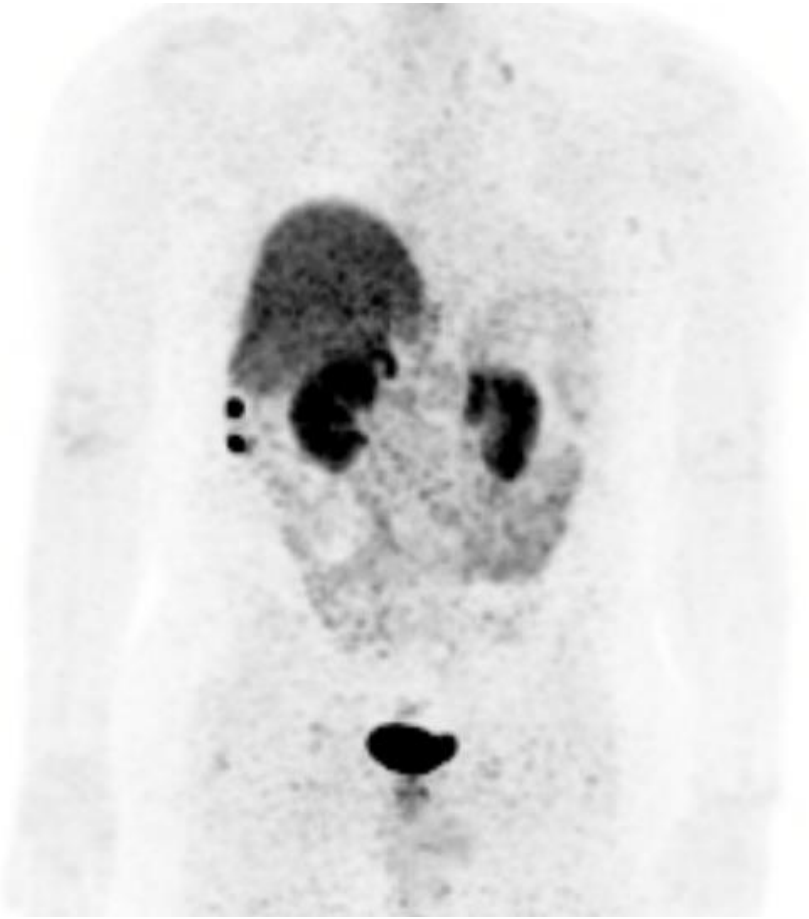


Dotatate PET MIP images 11/2022



Dotatate PET MIP images 4/2024

- 10/2024: Patient developed new right flank pain
- Dotatate PET reveals intensely avid RUQ peritoneal lesions
- Discussed palliative radiation and cabozantinib. Patient elected to proceed with radiation
- 12/2024: radiated tumors responded, but new perihepatic lesions.
- Starting Cabozantinib

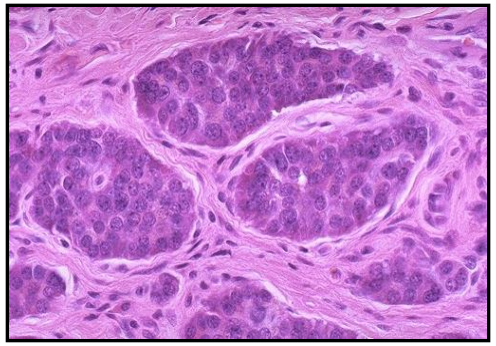


Principles of Therapy

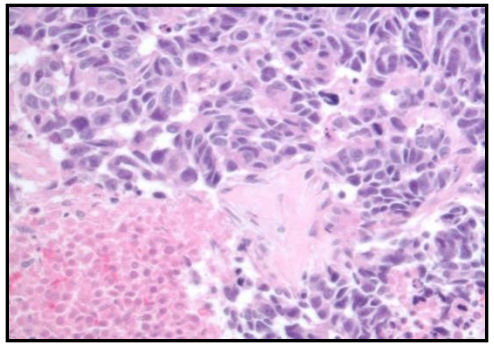
- Multi-disciplinary management
- Systemic therapy not always necessary: consider local therapy for local progression
- Optimal treatment sequencing to maximize overall survival is unclear

Differentiation/Grading

Differentiation	Grade	WHO grading	WHO nomenclature
Well differentiated	**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	**High**	>20 mitoses/10 HPF or >20% Ki67 index	Neuroendocrine carcinoma, grade 3 (large-cell or small-cell type)



Well-Differentiated NET



Poorly-Differentiated NEC

- IHC: chromogranin (80-90%) and synaptophysin (~100%)
- INSM1 is emerging as sensitive and specific marker
- For Ki-67, ≥500 cells recommended (in hotspots).
- If difficult to distinguish G3 NET from NEC, consider IHC or molecular testing for MEN1 (NET), DAXX/ATRX (NET), p53 (NEC), Rb1 (NEC)

‘Functioning’ Tumor Types: approximately 10-20% of total

Tumor	Hormone	Symptoms	Labs
Insulinoma	Insulin	Hypoglycemia	Glucose, insulin, proinsulin, C-peptide
Gastrinoma	Gastrin	ZES: Peptic Ulceration, GERD, Diarrhea	Gastrin
VIPoma	Vasoactive Intestinal Polypeptide	Watery Diarrhea, Hypokalemia	VIP
Glucagonoma	Glucagon	Necrolytic Migratory Erythemia, Diabetes, Cachecxia	Glucagon
ACTHoma	ACTH	Cushing’s Syndrome	ACTH, cortisol, dexamethasone suppression test

- Definition: Secrete hormone and cause clinical syndrome
- IHC staining NOT diagnostic for functional tumor and should not be routinely performed

Genetic Syndromes

- Multiple Endocrine Neoplasia Type 1 (MEN1)
- Von Hippel Lindau Syndrome (VHL)
- Tuberous Sclerosis Types 1 and 2 (TSC)

Prevalence of classical genetic syndrome about 2-5%

Recommend thorough personal and family history

Universal germline testing for pancreatic NETs?

Imaging

- Pancreatic protocol CT (arterial and venous phases)

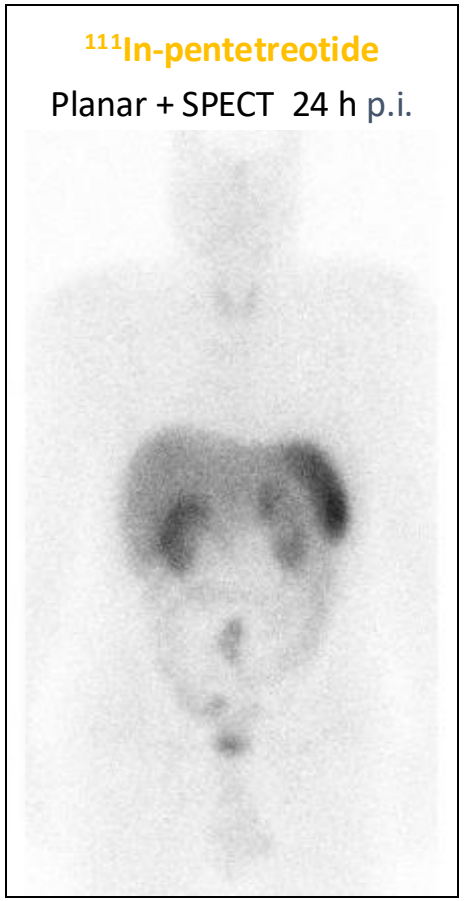
  OR

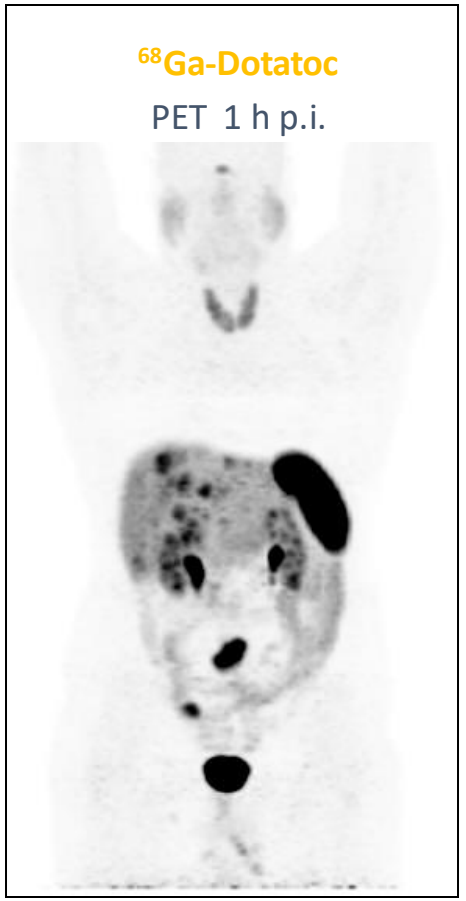
- MRI with gadoxetate (Eovist) optimal for liver metastases

- SSTR-PET (e.g. ^{68}Ga or ^{64}Cu-Dotatate PET)

- EUS in particular circumstances (need biopsy, assess for multifocal disease).

Anatomic imaging preferred for routine monitoring of disease. SSTR-PET useful in particular situations (e.g. bone, peritoneal metastases).





Incidental Non-functional Tumors <2cm

- Observation appropriate for tumors <1cm
- Can consider observation in tumors 1-2cm based on patient factors (age, comorbidities) and tumor factors (ki67, location, etc.)
- Surgery recommended for most patients with tumors >2cm or associated with main pancreatic duct dilation
- Role for enucleation of small tumors?

Kos-Kudła B, et al. J Neuroendocrinol. 2023 Dec;35(12):e13343.

Surgery in MEN 1

- Non-functional tumors <1cm should be observed and tumors >2cm should generally be resected if there is dominant lesion
- Goal is to resect dominant/progressive tumors while preserving pancreatic tissue
- Management of functional tumors depends on symptoms: gastrinomas can often be managed medically (i.e. PPI)

Cytoreductive Surgery in Patients with Liver Metastases

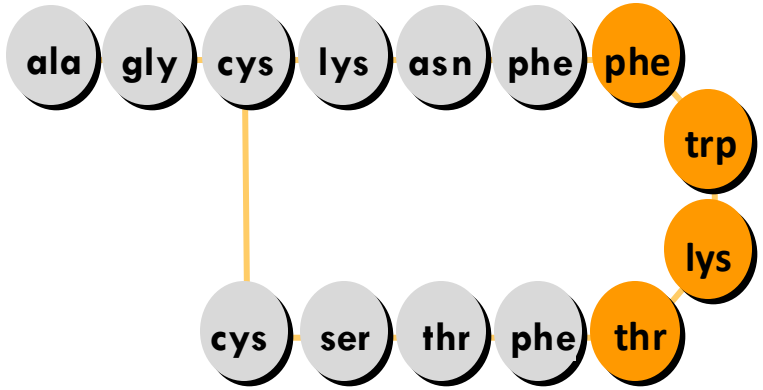
- Evidence is strongest for patients with oligometastases where >90% of disease can be resected
- No consensus on >70% cytoreduction threshold
- Can combine with resection of primary pancreatic tumor in select cases
- Recurrence more rapid in patients with pancreatic NETs versus small bowel NETs: associated with grade.
- Weak evidence to support resection of primary tumor in patient with unresectable metastases. Can consider in select cases.
- Patients with poorly differentiated NEC should NOT undergo cytoreductive liver surgery. Can consider in select cases of NET G3.

Ziogas IA et al. Ann Surg Oncol. 2023 Jan;30(1):148-160

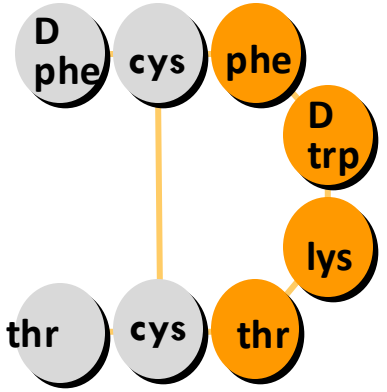
Systemic Treatments for Metastatic Disease

Somatostatin Analogs

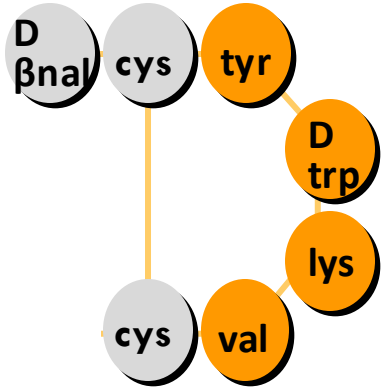
Human somatostatin



Octreotide



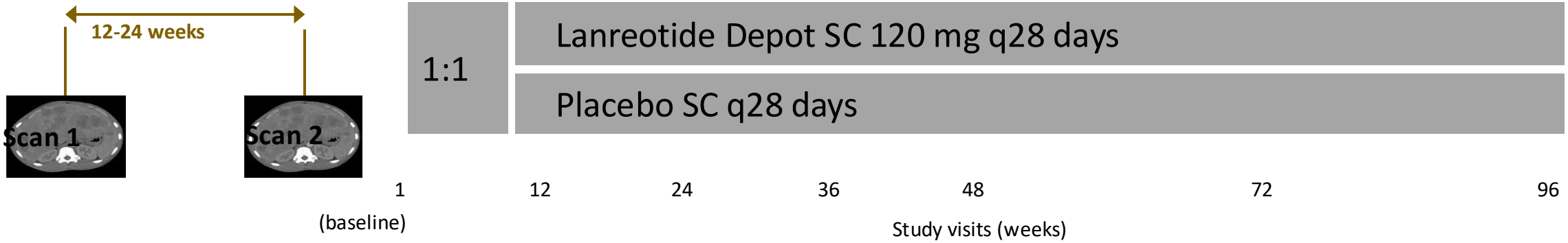
Lanreotide



CLARINET Study

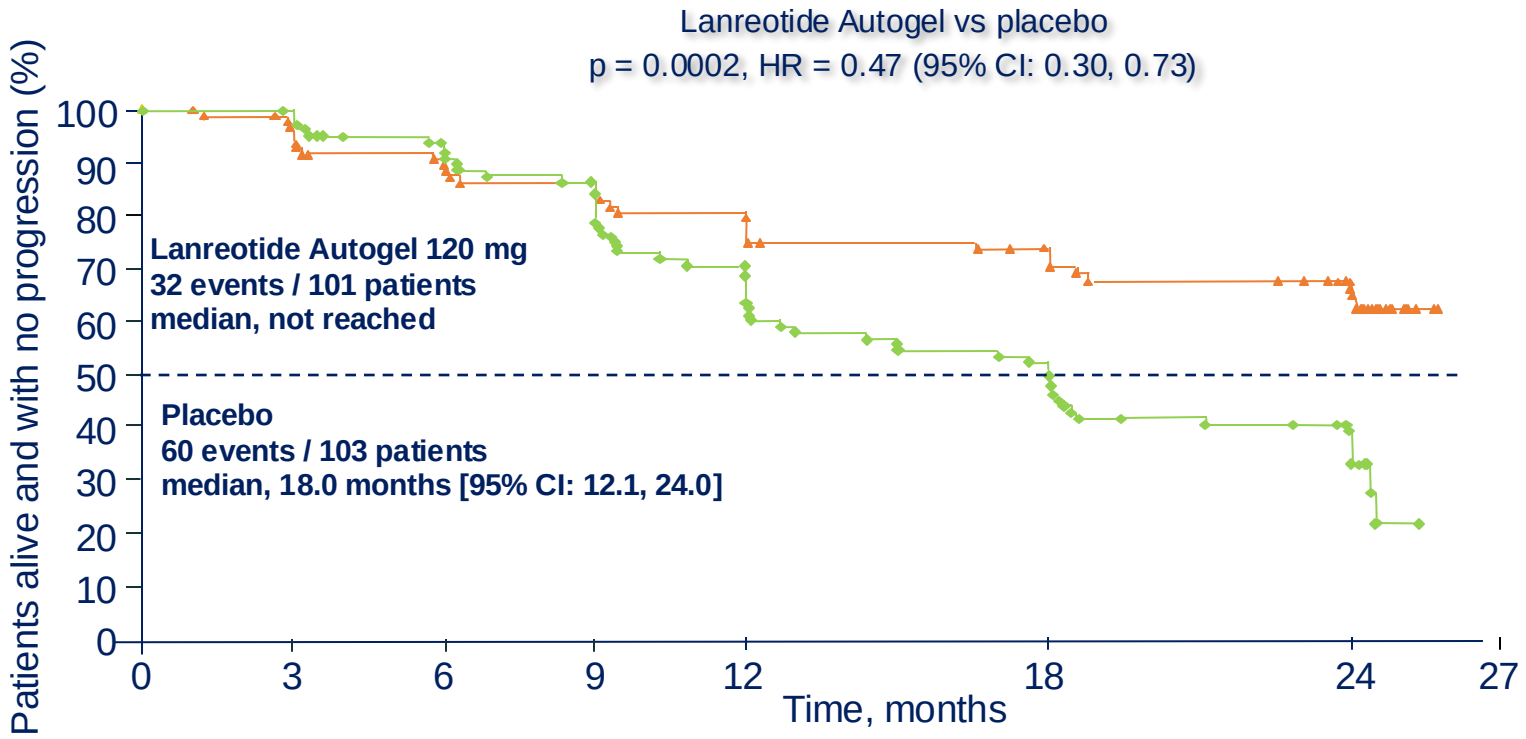
Study design: Phase 3, 96-week, randomized, double-blind, placebo-controlled

Population: N=204 adults with metastatic nonfunctional GEP-NETs, Ki-67 <10%, OctreoScan positive



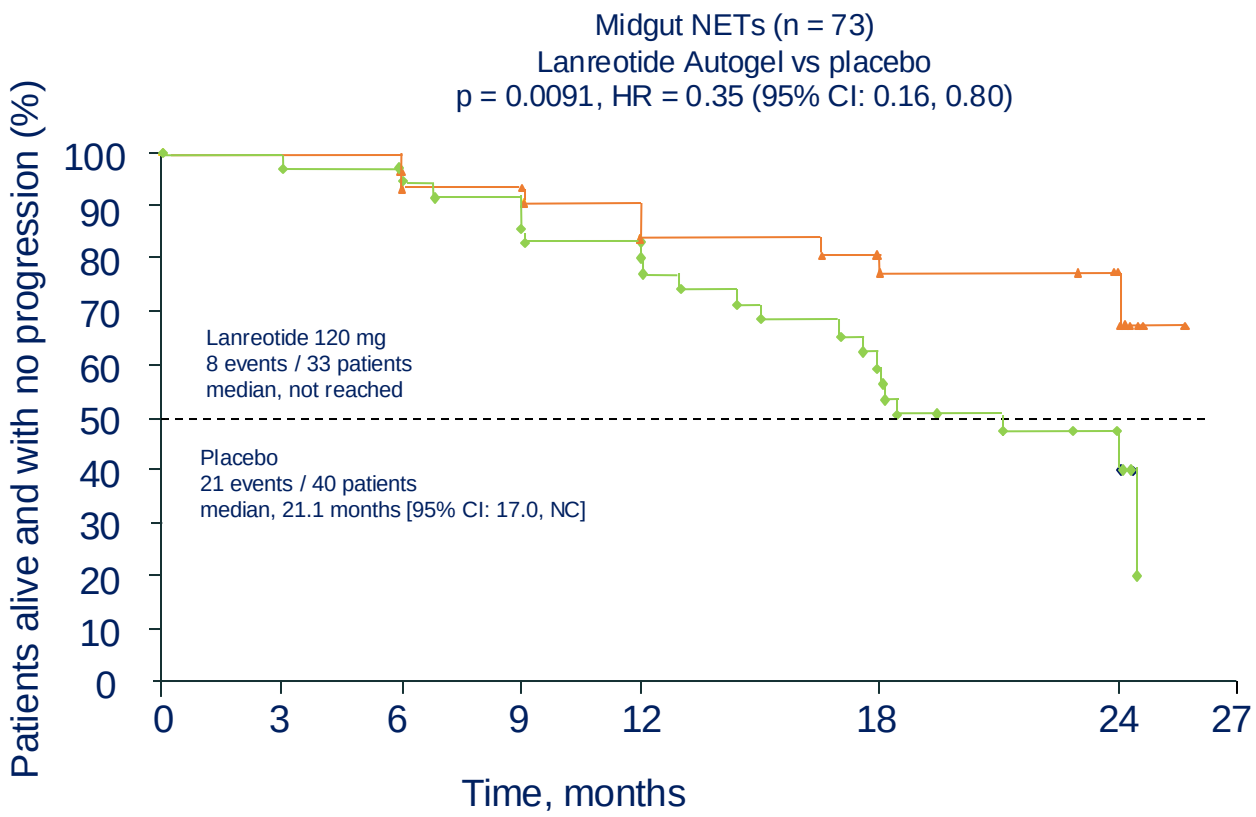
Caplin ME, et al. *N Engl J Med*. 2014;371(3):224-233.

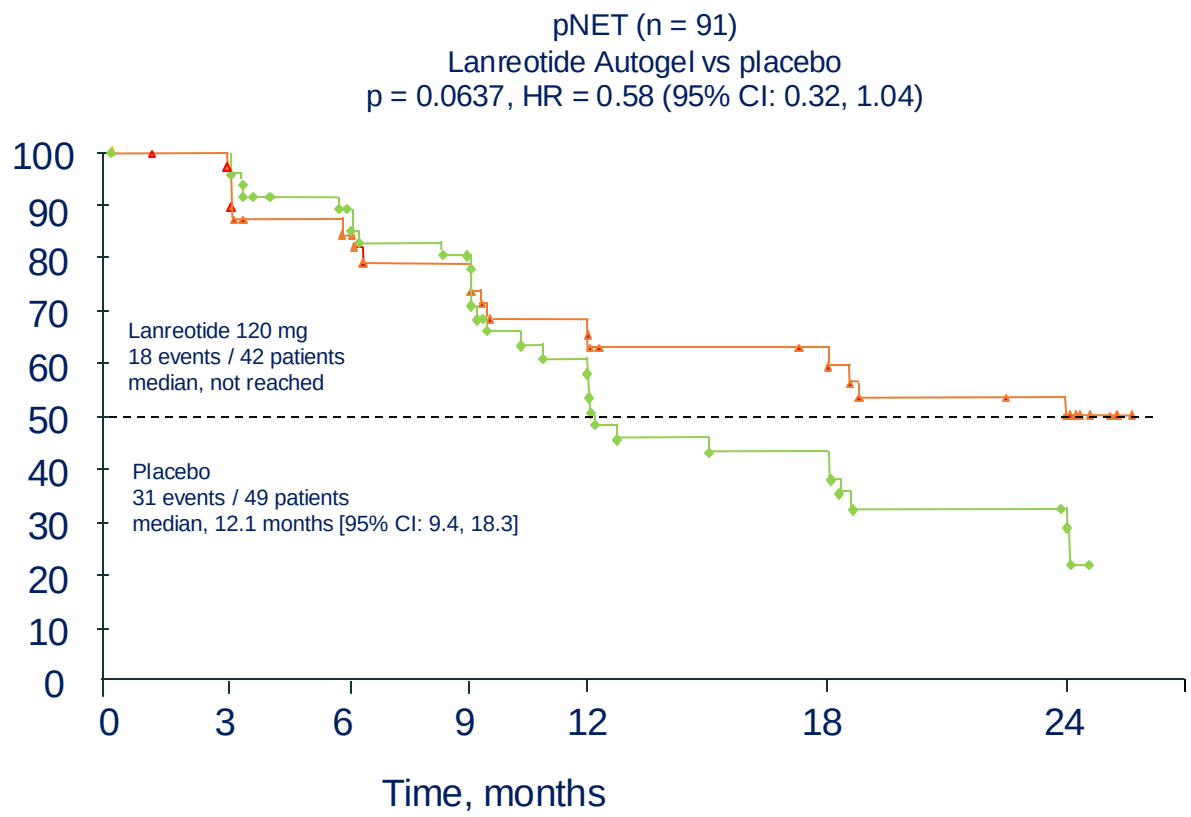
Primary Endpoint: PFS (N=204)



Caplin ME, et al. *N Engl J Med*. 2014;371(3):224-233.

Subgroup Analysis (ITT): Midgut vs. pNET





Caplin ME, et al. *N Engl J Med*. 2014;371(3):224-233.

Peptide Receptor Radiotherapy (PRRT)

Isotope	Emission	Tissue penetration	Maximum energy	Half life
^{111}Indium	Auger electron, gamma	0.02-10 µm	<30 KeV	64h
^{90}Yttrium	beta	12mm	2.27 MeV	64h
^{177}Lutetium	gamma and beta	2mm	0.5 MeV	160h

Capello A, et al. *J Nucl Med.* 2003;44(1):98-104

Kam B, et al. *Eur J Nucl Med Mol Imaging.* 2012;39 (Suppl 1): SA103-S112

NETTER 2: First-line ^{177}Lu-DOTATATE vs. high dose octreotide for well-differentiated GEP-NET with ki-67 10-55%

Screening phase

- Patients ≥15 years; N=226
- Advanced, SSTR+, well-differentiated, G2 or G3 GEP-NET (Ki67 ≥10% and ≤55%)
- Diagnosis within last 6 months prior to enrollment
- No prior PRRT or systemic therapy

R 2:1

Randomized treatment phase

^{177}Lu-DOTATATE 4 × 7.4 GBq + octreotide LAR (30 mg)* Q8W

High dose octreotide LAR (60 mg) Q4W

Stratification factors:

- Grade (G2 vs G3)
- Tumor origin (pancreas vs other origin)

Study endpoints:

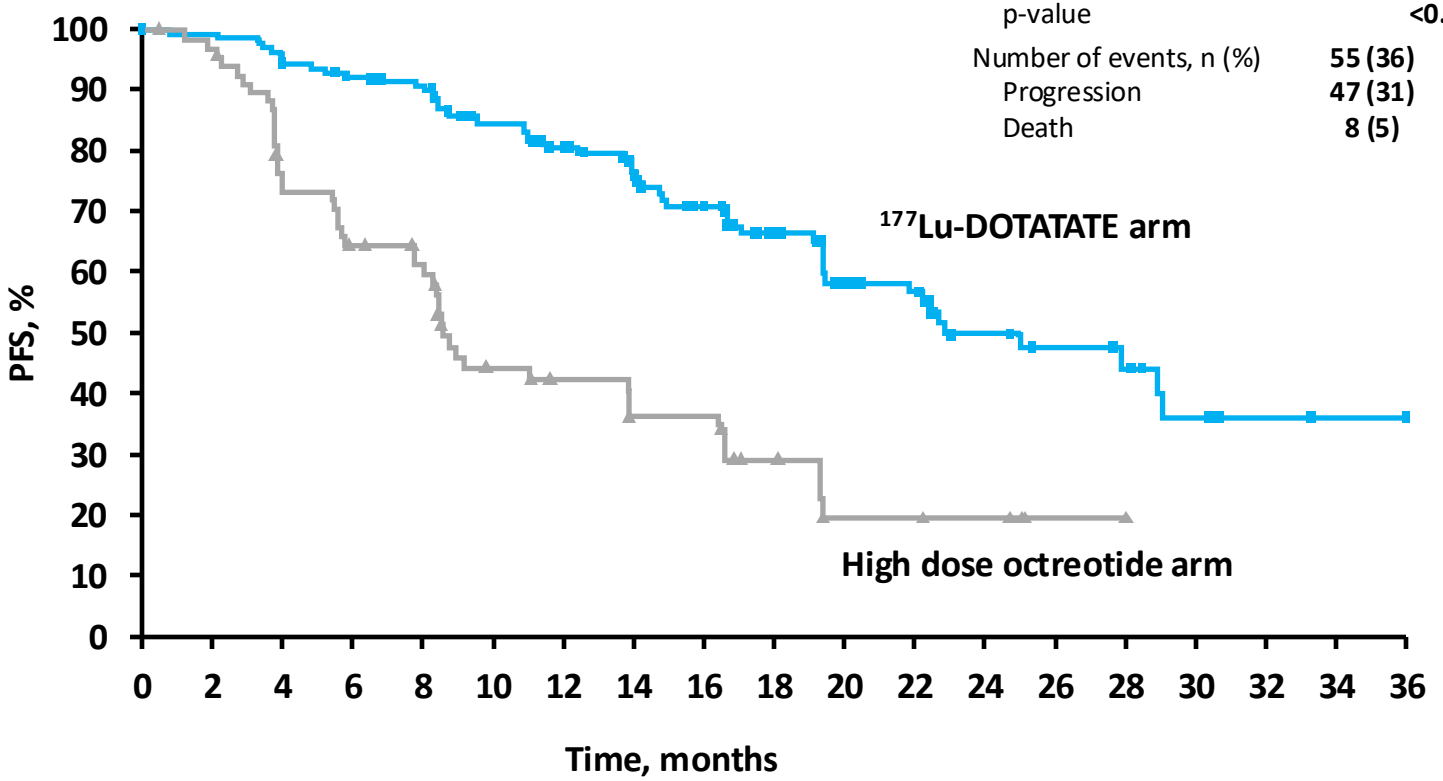
- Primary: PFS
- Key secondary: ORR, QOL

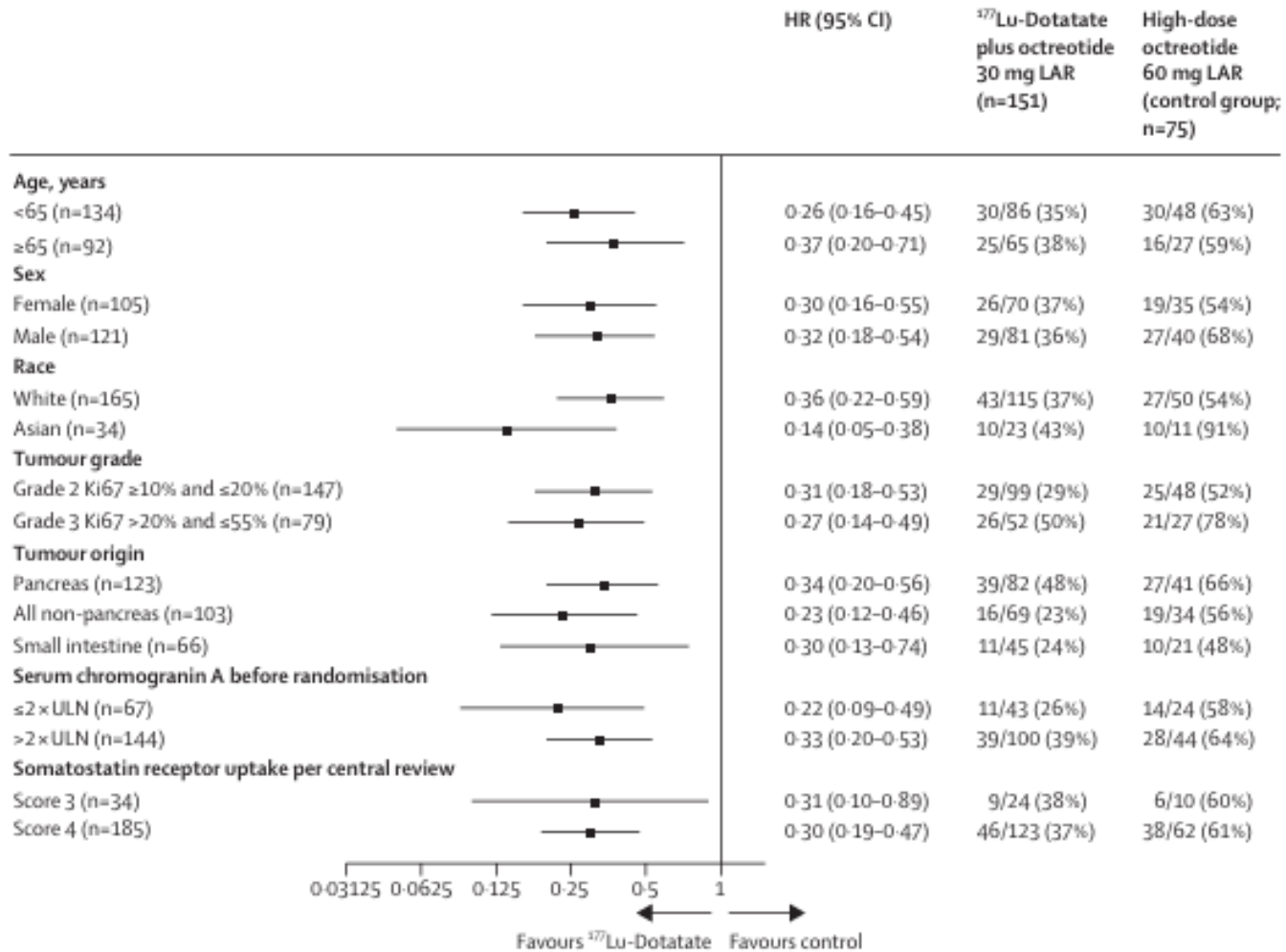
Primary tumour site	
Pancreas	123 (54%)
Small intestine	66 (29%)
Rectum	11 (5%)
Stomach	10 (4%)
Other	16 (7%)

Singh S et al. Lancet. 2024 Jun 29;403(10446):2807-2817

Progression-Free Survival

	^{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)**




HR (95% CI)
177Lu-Dotatate plus octreotide 30 mg LAR (n=151)
High-dose octreotide 60 mg LAR (control group; n=75)
Age, years
<65 (n=134) 0·26 (0·16–0·45) 30/86 (35%) 30/48 (63%)
≥65 (n=92) 0·37 (0·20–0·71) 25/65 (38%) 16/27 (59%)
Sex
Female (n=105) 0·30 (0·16–0·55) 26/70 (37%) 19/35 (54%)
Male (n=121) 0·32 (0·18–0·54) 29/81 (36%) 27/40 (68%)
Race
White (n=165) 0·36 (0·22–0·59) 43/115 (37%) 27/50 (54%)
Asian (n=34) 0·14 (0·05–0·38) 10/23 (43%) 10/11 (91%)
Tumour grade
Grade 2 Ki67 ≥10% and ≤20% (n=147) 0·31 (0·18–0·53) 29/99 (29%) 25/48 (52%)
Grade 3 Ki67 >20% and ≤55% (n=79) 0·27 (0·14–0·49) 26/52 (50%) 21/27 (78%)
Tumour origin
Pancreas (n=123) 0·34 (0·20–0·56) 39/82 (48%) 27/41 (66%)
All non-pancreas (n=103) 0·23 (0·12–0·46) 16/69 (23%) 19/34 (56%)
Small intestine (n=66) 0·30 (0·13–0·74) 11/45 (24%) 10/21 (48%)
Serum chromogranin A before randomisation
≤2×ULN (n=67) 0·22 (0·09–0·49) 11/43 (26%) 14/24 (58%)
>2×ULN (n=144) 0·33 (0·20–0·53) 39/100 (39%) 28/44 (64%)
Somatostatin receptor uptake per central review
Score 3 (n=34) 0·31 (0·10–0·89) 9/24 (38%) 6/10 (60%)
Score 4 (n=185) 0·30 (0·19–0·47) 46/123 (37%) 38/62 (61%)
0·03125 0·0625 0·125 0·25 0·5 1
Favours 177Lu-Dotatate
Favours control

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)

Does NETTER 2 change the treatment paradigm for high G2 and G3 NET?

- Data provide 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 (e.g. capectabine/temozolomide)

First line ^{177}Lu-DOTATATE should be *considered* for WD-GEPNET with ki-67 >10% but other options exist, including SSA monotherapy for patients with relatively low-volume disease

Randomized Trials for Progressive Pancreatic NET

Trial	N	Arms	PFS	OS	RR
RADIANT 3	410	Everolimus vs. Placebo	11.0 vs. 4.6	44.0 vs. 37.7	5% vs. 2%
Su011248	171	Sunitinib vs. Placebo	12.6 vs. 5.8	38.6 vs. 29.1	9% vs. 0%
ECOG 2211	133	Cap/Tem vs. Tem	22.7 vs. 14.4	58.7 vs. 53.8	40% vs. 34%
Oclurandom*	84	^{177}Lu-Dotatate vs. Sunitinib	20.7 vs. 11.0	N/A	N/A
CABINET (pNET)	95	Cabozantinib vs. Placebo	13.8 vs. 4.4	40.0 vs. 31.1	19% vs. 0%

*Oclurandom not powered for comparison between arms

Yao JC et al. N Engl J Med. 2011 Feb 10;364(6):514-23
Raymond E et al. . N Engl J Med. 2011 Feb 10;364(6):501-13
Kunz PL et al. J Clin Oncol. 2023 Mar 1;41(7):1359-1369
Baudin et al. Abstract 8870 ESMO 2022
Salazar et al. Abstract LBA45 ESMO 2022

RADIANT 3 Study

Patients with advanced pNET

n=410

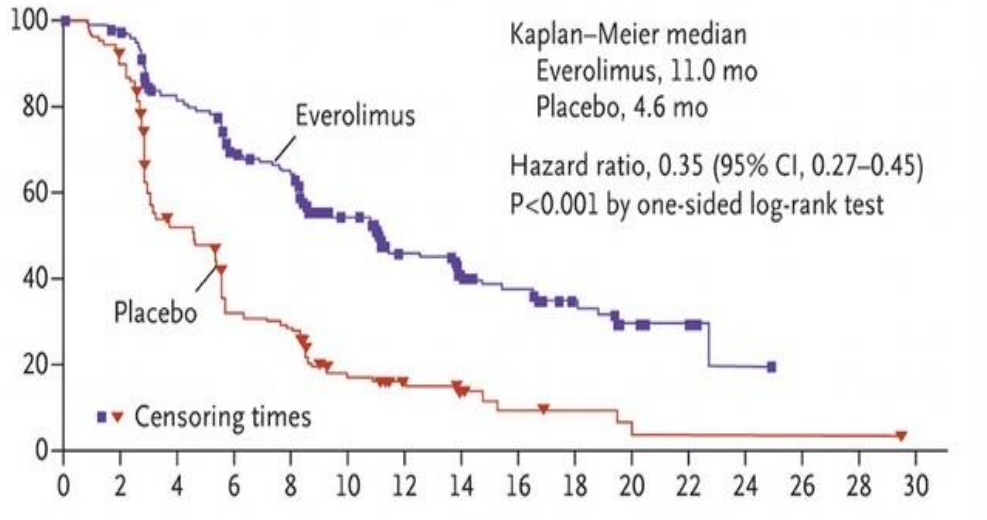
RANDOMISE

1:1

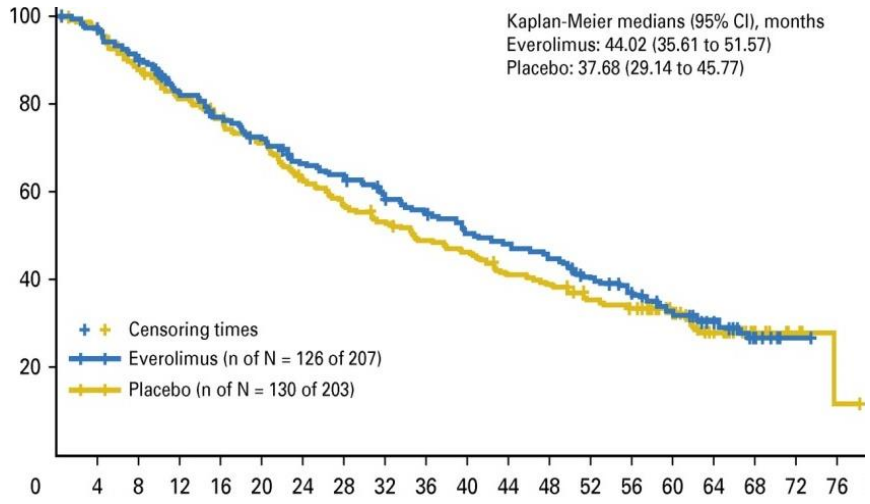
Everolimus 10 mg/d + best supportive care*

Cross over at progression

Placebo + best supportive care*



Progression-free survival



Overall-survival

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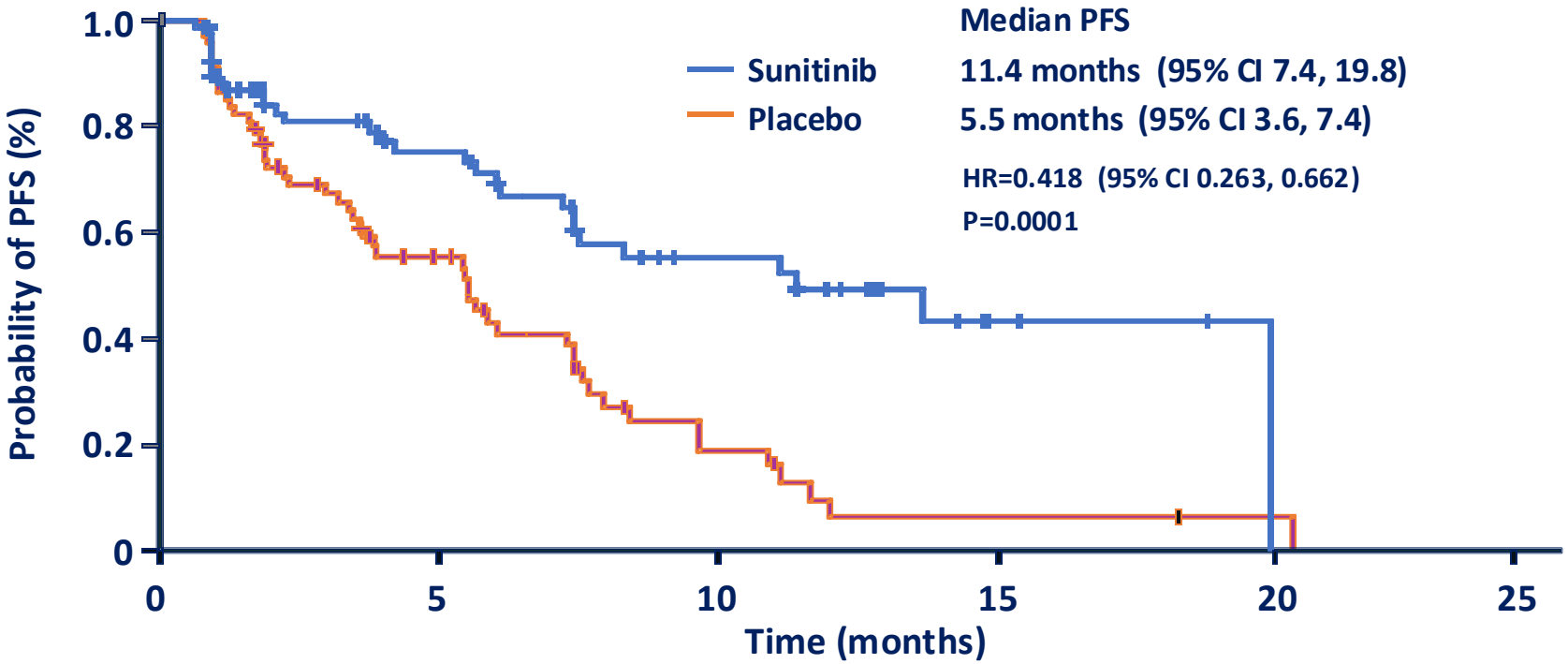
Yao JC, et al. *N Engl J Med.* 2011; 364: 514-523.

Adverse Events

Adverse Event	Everolimus (N = 204)		Placebo (N = 203)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	no. of patients (%)			
Stomatitis*	131 (64)	14 (7)	34 (17)	0
Rash	99 (49)	1 (<1)	21 (10)	0
Diarrhea	69 (34)	7 (3)	20 (10)	0
Fatigue	64 (31)	5 (2)	29 (14)	1 (<1)
Infections†	46 (23)	5 (2)	12 (6)	1 (<1)
Nausea	41 (20)	5 (2)	37 (18)	0
Peripheral edema	41 (20)	1 (<1)	7 (3)	0
Decreased appetite	40 (20)	0	14 (7)	2 (1)
Headache	39 (19)	0	13 (6)	0
Dysgeusia	35 (17)	0	8 (4)	0
Anemia	35 (17)	12 (6)	6 (3)	0
Epistaxis	35 (17)	0	0	0
Pneumonitis‡	35 (17)	5 (2)	0	0
Weight loss	32 (16)	0	9 (4)	0
Vomiting	31 (15)	0	13 (6)	0
Pruritus	30 (15)	0	18 (9)	0
Hyperglycemia	27 (13)	11 (5)	9 (4)	4 (2)
Thrombocytopenia	27 (13)	8 (4)	1 (<1)	0
Asthenia	26 (13)	2 (1)	17 (8)	2 (1)
Nail disorder	24 (12)	1 (<1)	2 (1)	0
Cough	22 (11)	0	4 (2)	0
Pyrexia	22 (11)	0	0	0
Dry skin	21 (10)	0	9 (4)	0

Yao JC, et al. *N Engl J Med.* 2011; 364: 514-523

Phase III Study of Sunitinib vs. Placebo in Pancreatic NETs



Raymond, et al. *N Engl J Med*. 2011;364(6):501-513.

Adverse Events

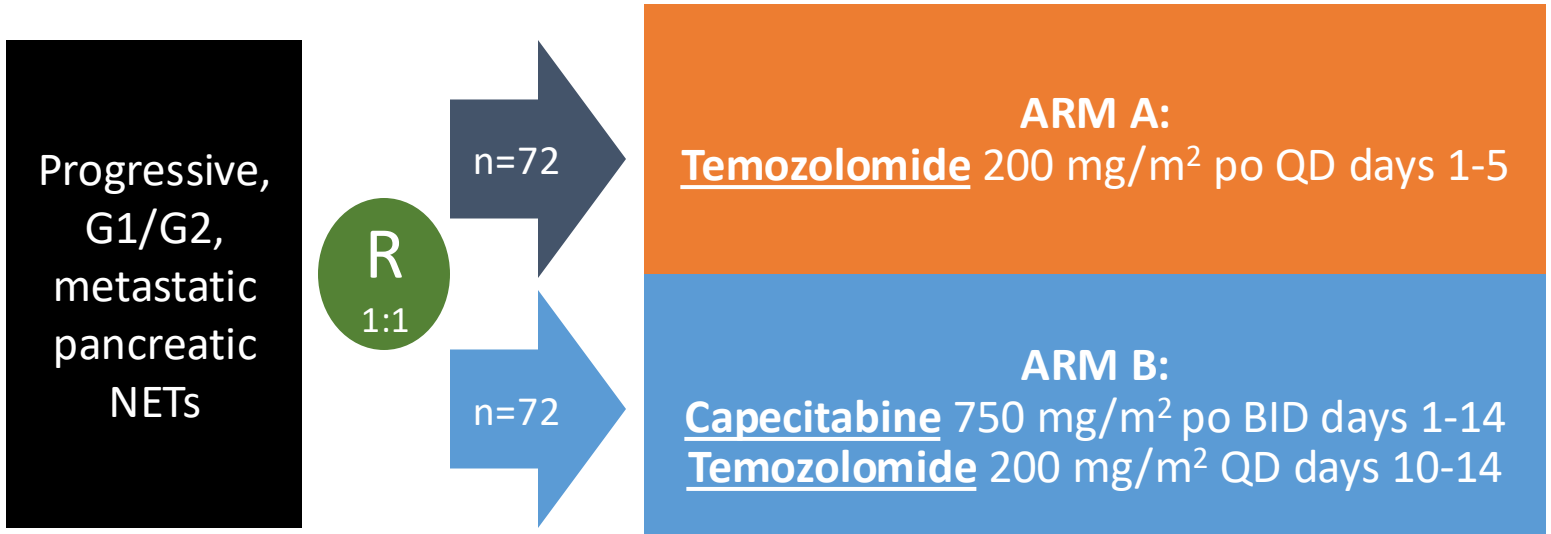
Event	Sunitinib (N=83)			Placebo (N=82)		
	All Grades	Grade 1 or 2	Grade 3 or 4	All Grades	Grade 1 or 2	Grade 3 or 4
	number of patients (percent)					
Diarrhea	49 (59)	45 (54)	4 (5)	32 (39)	30 (37)	2 (2)
Nausea	37 (45)	36 (43)	1 (1)	24 (29)	23 (28)	1 (1)
Asthenia	28 (34)	24 (29)	4 (5)	22 (27)	19 (23)	3 (4)
Vomiting	28 (34)	28 (34)	0	25 (30)	23 (28)	2 (2)
Fatigue	27 (32)	23 (28)	4 (5)	22 (27)	15 (18)	7 (8)
Hair-color changes	24 (29)	23 (28)	1 (1)	1 (1)	1 (1)	0
Neutropenia	24 (29)	14 (17)	10 (12)	3 (4)	3 (4)	0
Abdominal pain	23 (28)	19 (23)	4 (5)	26 (32)	18 (22)	8 (10)
Hypertension	22 (26)	14 (17)	8 (10)	4 (5)	3 (4)	1 (1)
Palmar–plantar erythro-dysesthesia	19 (23)	14 (17)	5 (6)	2 (2)	2 (2)	0
Anorexia	18 (22)	16 (19)	2 (2)	17 (21)	16 (20)	1 (1)
Stomatitis	18 (22)	15 (18)	3 (4)	2 (2)	2 (2)	0

Raymond, et al. *N Engl J Med*. 2011;364(6):501-513.

Sunitinib vs. Everolimus in Pancreatic NETs

Comorbidity	Favors sunitinib	Favors everolimus
Hypertension		✓
Cardiovascular disease		✓
Bleeding diathesis		✓
Risk of perforation/fistula		✓
Diabetes	✓	
Underlying lung disease	✓	

E2211 Capecitabine/Temozolomide vs. Temozolomide



Stratified by:
- Prior everolimus
- Prior sunitinib
- Concurrent octreotide

Primary Endpoint:
- PFS (local review)

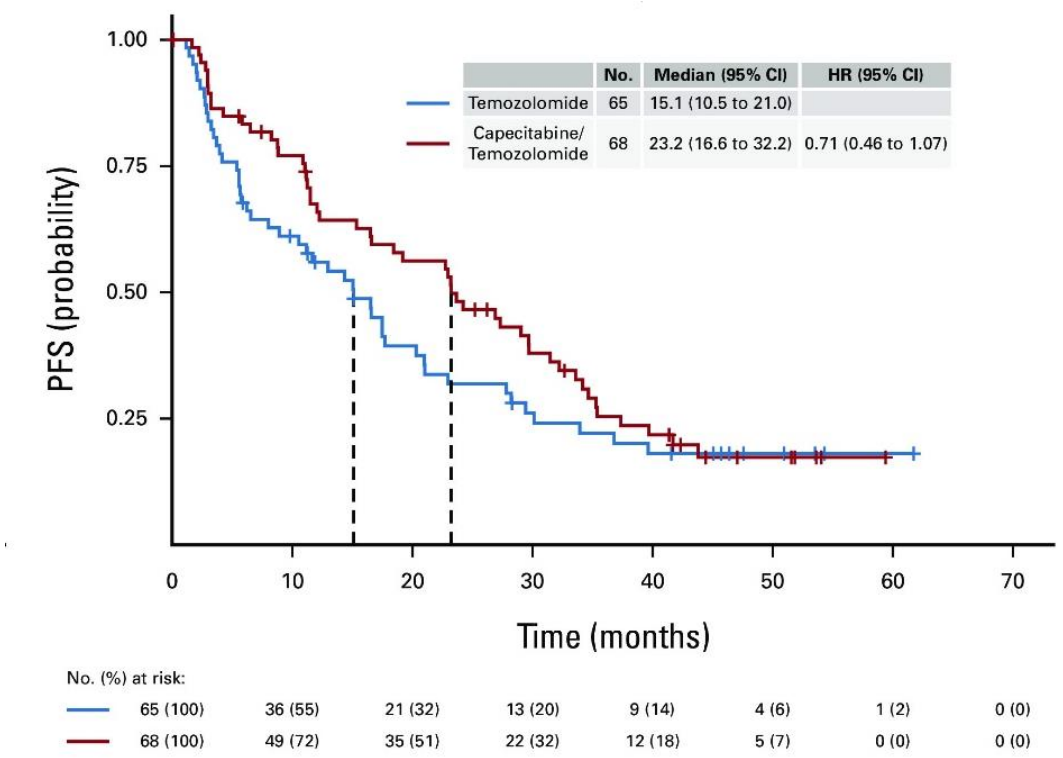
Secondary Endpoints:
- RR
- OS
- Toxicity

Correlative Endpoints:
- MGMT by IHC
- MGMT by promoter methylation

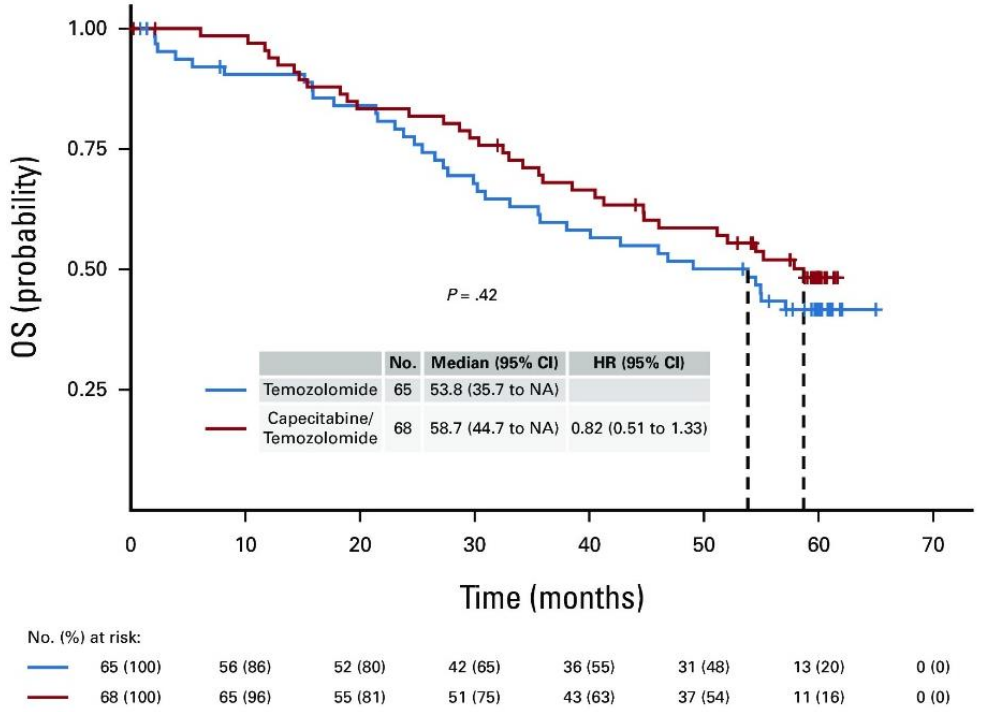
NCT01824875

Kunz PL, et al. *J Clin Oncol.* 2018;36 [ASCO 2018: Abstract 4004]

Final PFS and OS data



PFS



OS

Kunz PL et al. J Clin Oncol. 2023 Mar 1;41(7):1359-1369

Safety Profile

AE Category	AE Term	Temozolomide (N= 68)	Temozolomide + Capecitabine (N= 71)	p-value
Worst degree for all treatment-related, Grade 3-4 AEs				
		22%	44%	p=0.007
Treatment related, Grade 3-4 AEs ≥ 5%				
Hematologic	Neutropenia	4%	13%	
	Lymphopenia	4%	5%	
	Thrombocytopenia	13%	8%	
Gastrointestinal	Nausea	0	8%	
	Vomiting	0	8%	
	Diarrhea	0	8%	
Constitutional	Fatigue	1%	8%	

Kunz PL, et al. *J Clin Oncol.* 2018;36 [ASCO 2018: Abstract 4004]

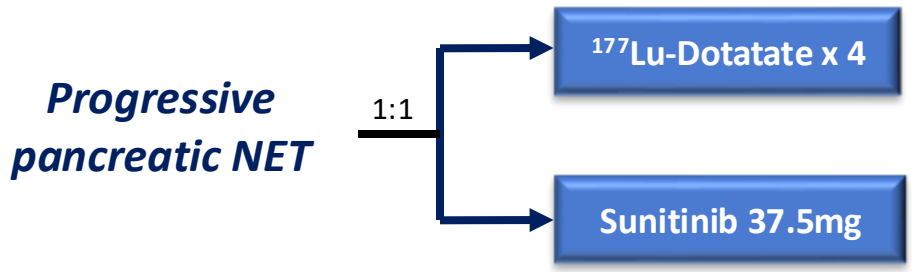
Peptide Receptor Radiotherapy (PRRT)

Isotope	Emission	Tissue penetration	Maximum energy	Half life
^{111}Indium	Auger electron, gamma	0.02-10 µm	<30 KeV	64h
^{90}Yttrium	beta	12mm	2.27 MeV	64h
^{177}Lutetium	gamma and beta	2mm	0.5 MeV	160h

Capello A, et al. *J Nucl Med.* 2003;44(1):98-104

Kam B, et al. *Eur J Nucl Med Mol Imaging.* 2012;39 (Suppl 1): SA103-S112

Oclurandom Trial: 177Lu-Dotatate vs. Sunitinib



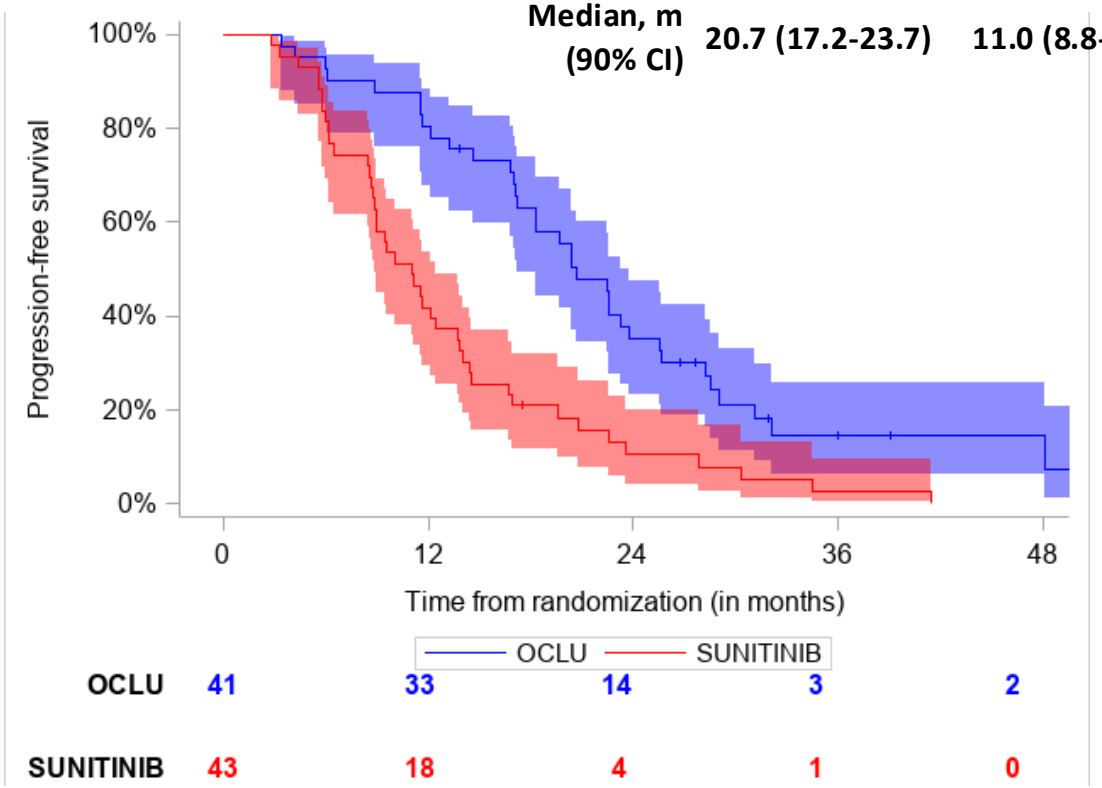
Primary endpoint: PFS rate at 12 months

- **Non comparative** randomized phase II with single-stage Fleming design (α:5% - power:95%)
- **Hypothesis:** Increase in 12-months PFS rate from 35% to 60%)
- **N=40 patients in the ^{177}Lu-Dotatate arm**
- Number of patients without progression at 12m required to consider **^{177}Lu-Dotatate** as effective **(Fleming design conclusion): at least 19 out of 40 pts**
- SUN arm : internal control to validate the hypothesis
- If 35% is included in the 90% Confidence Interval (CI) of the **12-months PFS rate of the SUN arm, the final conclusion will be the Fleming design conclusion**

Baudin et al. ESMO 2022

Progression-Free Survival

	177Lu-Dotatate (n =41)	SUNITINIB (n =43)
N events	34	42
Median, m (90% CI)	**20.7 (17.2-23.7)**	**11.0 (8.8-12.4)**



Baudin et al. ESMO 2022

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]

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[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

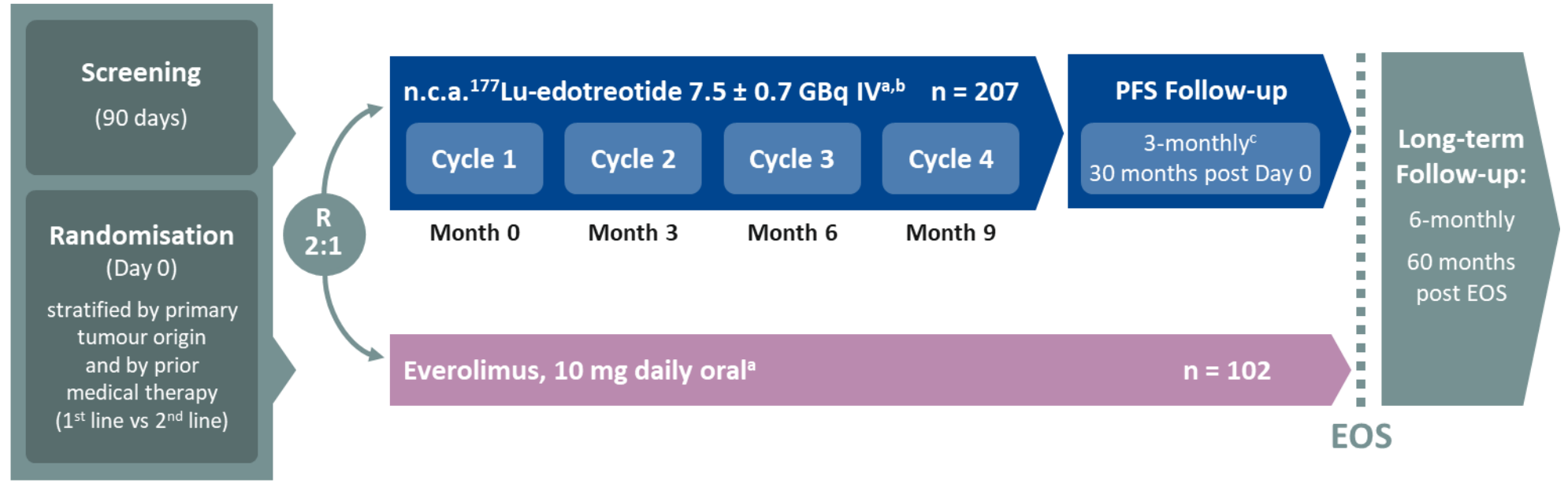
ENETS 2025

COMPETE trial design

Prospective, randomised, controlled, open-label, multi-centre phase 3 trial

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 minutes before administration of n.c.a. ^{177}Lu-edotreotide, and lasting 4–6 hours); [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; IV, intravenous; 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

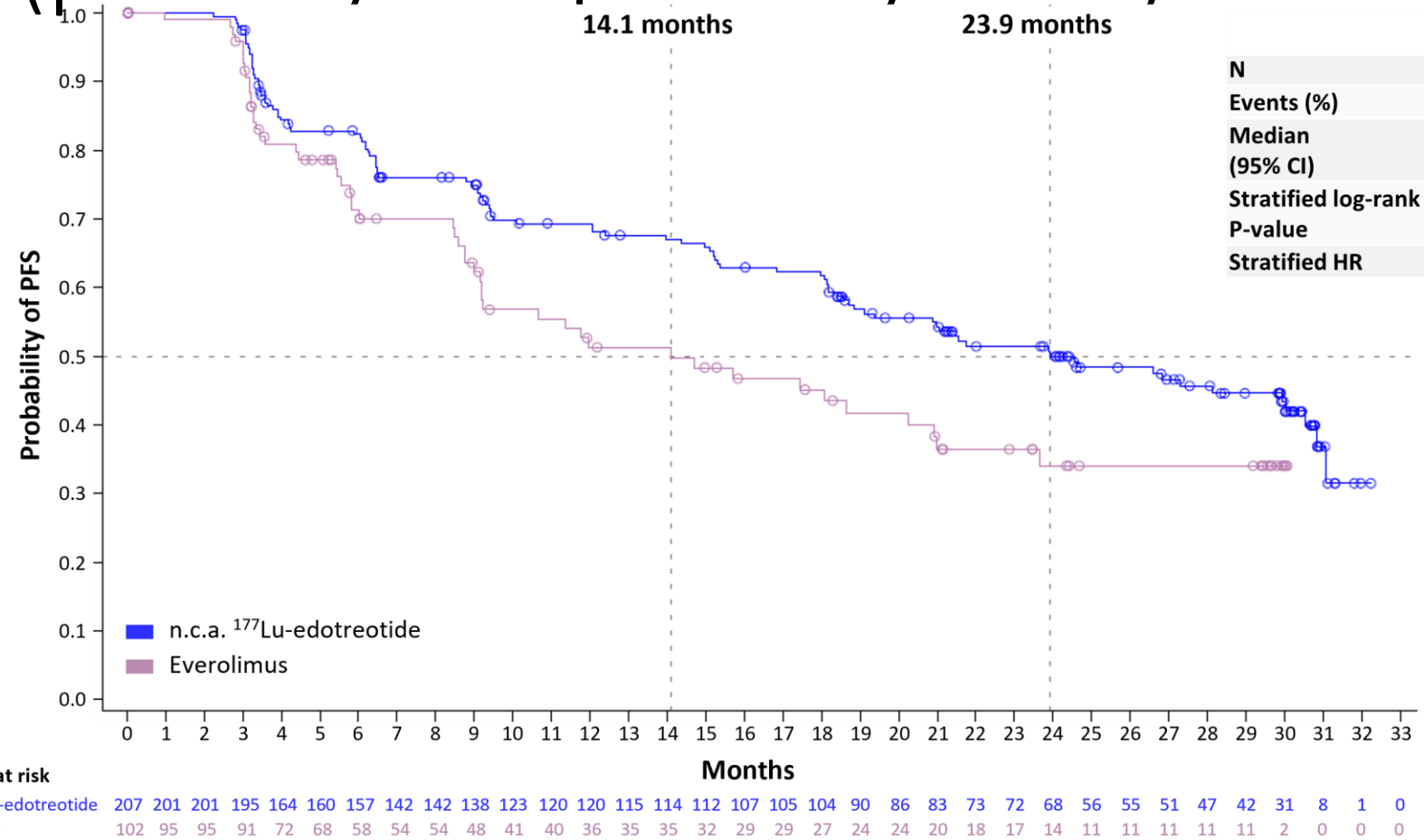
Baseline patient demographics and disease characteristics

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)

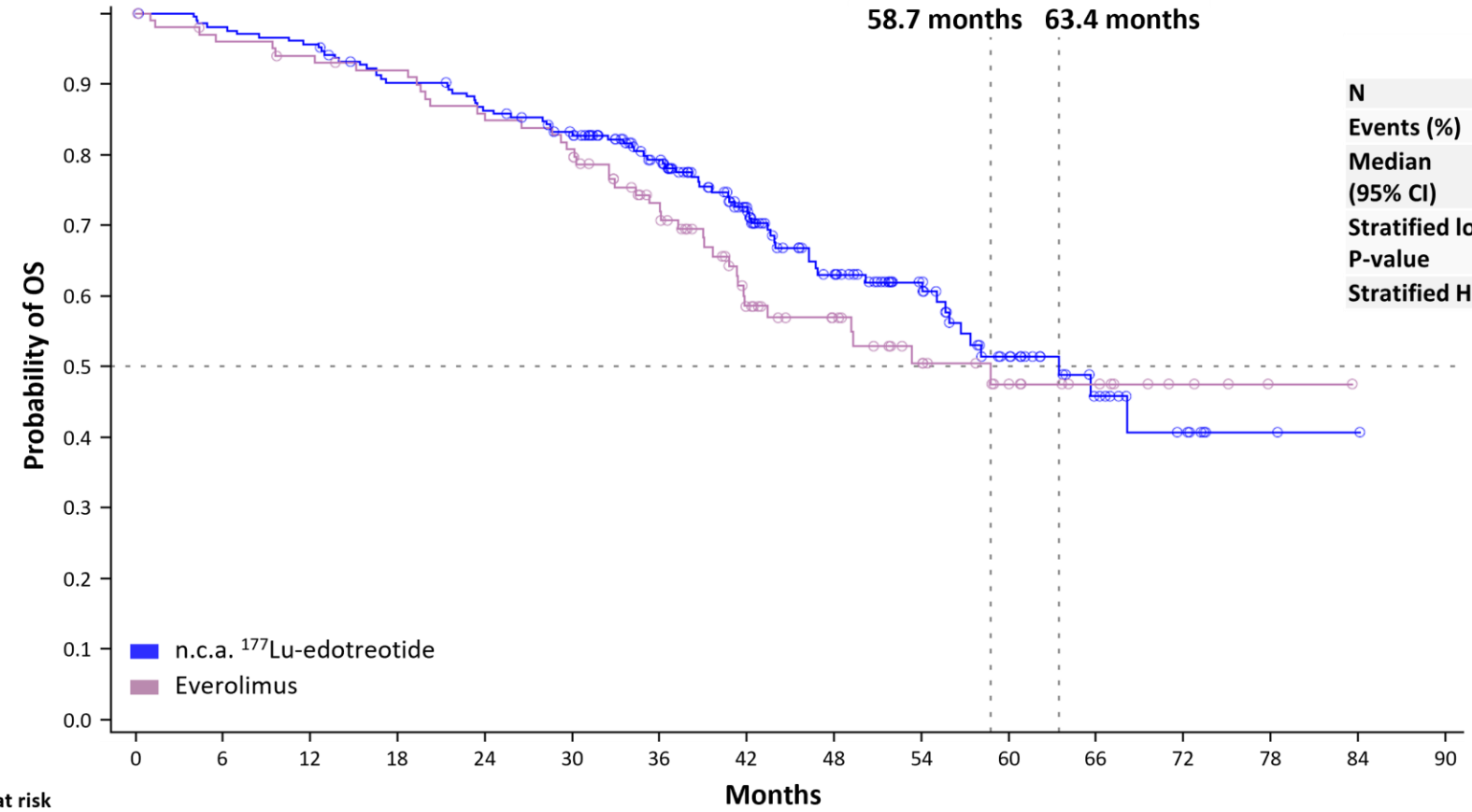


	n.c.a. ^{177}Lu-edotreotide	Everolimus
N	207	102
Events (%)	101 (48.8)	51 (50.0)
Median (95% CI)	23.9 (18.7, 30.0)	14.1 (9.2, 20.9)
Stratified log-rank P-value	0.022	
Stratified HR	0.67 (0.48, 0.95)	

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)	

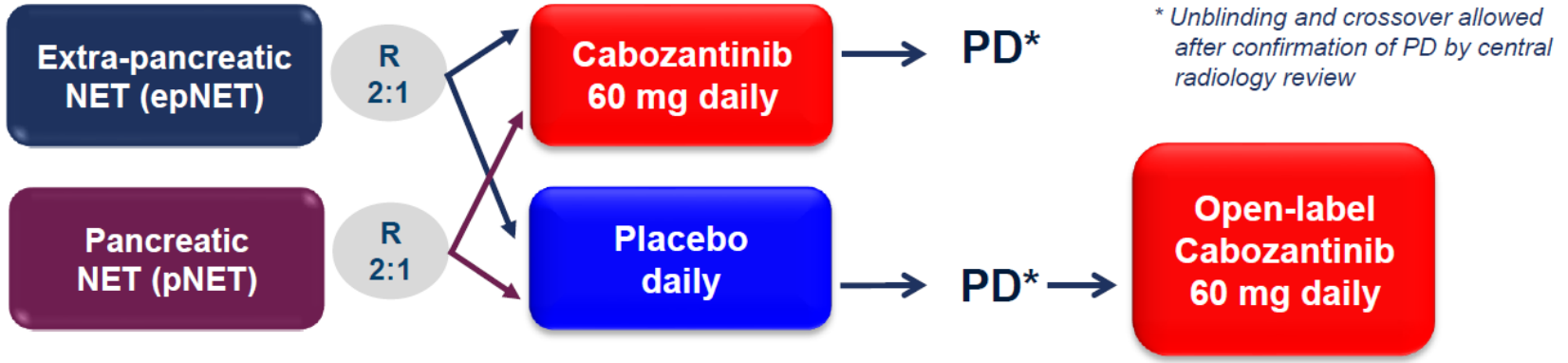
Interim median OS was numerically higher, but not conclusive for n.c.a. ^{177}Lu-edotreotide vs everolimus (**63.4 vs 58.7 months**; p=0.206; HR 0.78, 95% CI [0.53, 1.15])

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

Cabozantinib: how does the phase III CABINET trial impact treatment?

- TKI targeting VEGFR as well as MET and RET.
- Shown encouraging activity in phase 2 NET trials leading to the phase III CABINET trial

CABINET Trial Study Design



* *Unblinding and crossover allowed after confirmation of PD by central radiology review*

Stratification factors:

- epNET: Concurrent SSA & Primary site (midgut GI/unknown vs. non-midgut GI/lung/other)
- pNET: Concurrent SSA & Prior sunitinib

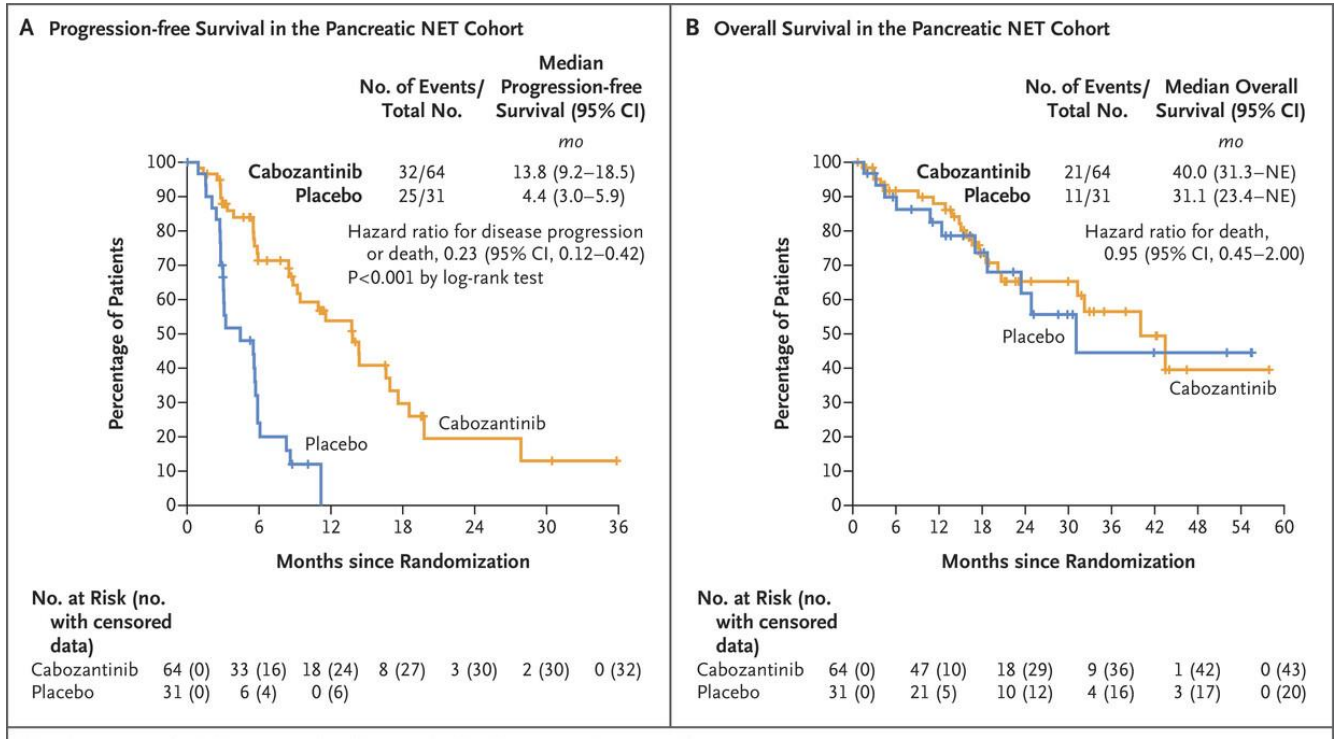
Study Endpoints:

- **Primary Endpoint per cohort:**
  - **Progression-free survival (PFS) by blinded independent central review**
- **Secondary Endpoint per cohort:**
  - **Overall survival**
  - **Objective response rate**
  - **Safety and tolerability**

Extrapancreatic = GI, lung, thymus, unknown

Chan JA, et al. N Engl J Med. 2024 Sep 16. doi: 10.1056/NEJMoa2403991.

Progression-free and Overall survival pancreatic NET



Objective Response

Table 2. Objective Tumor Response.*

Response	Extrapancreatic NET Cohort		Pancreatic NET Cohort	
	Cabozantinib (N=134)	Placebo (N=69)	Cabozantinib (N=64)	Placebo (N=31)
Objective response — % (95% CI)	5 (2 to 10)	0 (0 to 5)	19 (10 to 30)	0 (0 to 11)
Best overall response — no. (%)				
Partial response	7 (5)	0	12 (19)	0
Stable disease	87 (65)	37 (54)	39 (61)	17 (55)
Progressive disease	15 (11)	24 (35)	5 (8)	12 (39)
Not evaluable	25 (19)	8 (12)	8 (12)	2 (6)

* Objective response was defined as the percentage of patients who had a confirmed complete or partial response as assessed by blinded independent central review according to Response Evaluation Criteria in Solid Tumors, version 1.1. All responses were partial responses. Percentages may not total 100 because of rounding.

Chan JA et al. Phase 3 Trial of Cabozantinib to Treat Advanced Neuroendocrine Tumors. *N Engl J Med*. Published online September 16, 2024. doi:10.1056/NEJMoa2403991

Adverse Events

Table 3. Treatment-Related Adverse Events.*

Adverse Event	Extrapancreatic NET Cohort				Pancreatic NET Cohort			
	Cabozantinib (N=132)		Placebo (N=67)		Cabozantinib (N=63)		Placebo (N=31)	
	Any Grade	Grades 3–5†	Any Grade	Grades 3–5	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any event at least possibly related to treatment	130 (98)	82 (62)	55 (82)	18 (27)	62 (98)	41 (65)	26 (84)	7 (23)
Common treatment-related event‡								
Fatigue	82 (62)	17 (13)	28 (42)	5 (7)	47 (75)	7 (11)	10 (32)	1 (3)
Diarrhea	74 (56)	14 (11)	20 (30)	3 (4)	37 (59)	4 (6)	4 (13)	0
AST increase	86 (65)	4 (3)	12 (18)	0	40 (63)	1 (2)	9 (29)	0
ALT increase	77 (58)	1 (1)	9 (13)	0	39 (62)	1 (2)	9 (29)	0
Hypertension	70 (53)	28 (21)	13 (19)	2 (3)	36 (57)	14 (22)	7 (23)	3 (10)
Thrombocytopenia	62 (47)	1 (1)	5 (7)	1 (1)	21 (33)	0	3 (10)	0
Nausea	46 (35)	2 (2)	10 (15)	0	24 (38)	5 (8)	7 (23)	1 (3)
Oral mucositis	48 (36)	5 (4)	6 (9)	0	30 (48)	5 (8)	1 (3)	0
Palmar–plantar erythrodysesthesia	48 (36)	4 (3)	5 (7)	0	28 (44)	6 (10)	4 (13)	0
Anorexia	40 (30)	2 (2)	6 (9)	0	13 (21)	1 (2)	3 (10)	0
Dysgeusia	45 (34)	0	1 (1)	0	19 (30)	0	3 (10)	0
Neutropenia	40 (30)	4 (3)	2 (3)	0	17 (27)	1 (2)	2 (6)	0
Alkaline phosphatase increase	—	—	—	—	13 (21)	0	3 (10)	0
Vomiting	—	—	—	—	13 (21)	4 (6)	3 (10)	0
Hypophosphatemia	—	—	—	—	13 (21)	0	2 (6)	0
Thromboembolic event	—	—	—	—	11 (17)	7 (11)	0	0
Leukopenia	46 (35)	4 (3)	2 (3)	0	—	—	—	—
Anemia	28 (21)	2 (2)	8 (12)	0	—	—	—	—
Lymphopenia	31 (23)	5 (4)	6 (9)	0	—	—	—	—
Hypothyroidism	36 (27)	0	1 (1)	0	—	—	—	—
Maculopapular rash	30 (23)	0	2 (3)	0	—	—	—	—
Weight loss	28 (21)	3 (2)	2 (3)	0	—	—	—	—

* The safety population included all patients who underwent randomization and received at least one dose of cabozantinib or placebo. The presence or absence of the following adverse events was solicited for each treatment cycle: neutropenia, thrombocytopenia, alanine or aspartate aminotransferase increase, palmar–plantar erythrodysesthesia syndrome, maculopapular rash, hyperglycemia, hypothyroidism, hypertension, fatigue, diarrhea, and oral mucositis. ALT denotes alanine aminotransferase and AST aspartate aminotransferase.

† Grade 5 events in the cabozantinib group were possibly related to treatment (gastrointestinal hemorrhage in one patient, cardiac arrest in one patient, and death not otherwise specified in two patients).

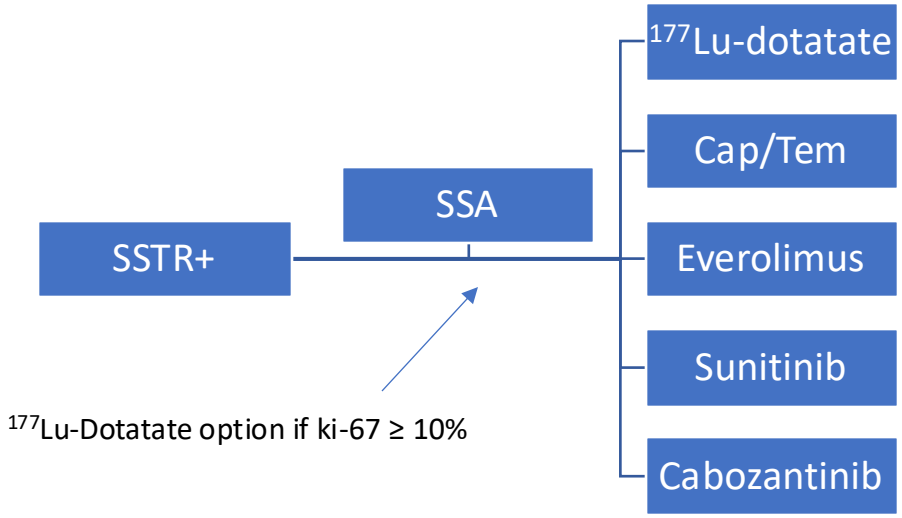
‡ Shown are all adverse events that were considered by the investigators to be at least possibly related to cabozantinib or placebo that were reported in 20% or more of the patients in the cabozantinib group across all grades, or common grade 3 or higher treatment-related adverse events that were reported in 10% or more of the patients in the cabozantinib group.

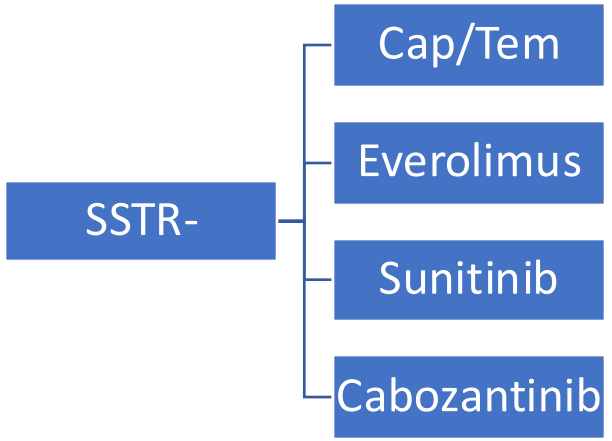
Exposure

- Dose reductions in 66% randomized to cabozantinib vs. 10% placebo
- Median exposure 38.4mg/day
- 31% discontinuation for adverse events

- Cabozantinib significantly improves PFS both in extrapancreatic and pancreatic NETs
- OS impact hard to gauge: not powered for OS, crossover allowed
- Effective in pretreated patients
- PFS hazard ratios slightly superior to sunitinib or everolimus: is this clinically meaningful?
- Need to carefully monitor patients: esp. frail, elderly.
- Most patients unable to tolerate 60mg dose. Consider starting at lower doses

Pancreatic NET Systemic Treatments: sequencing



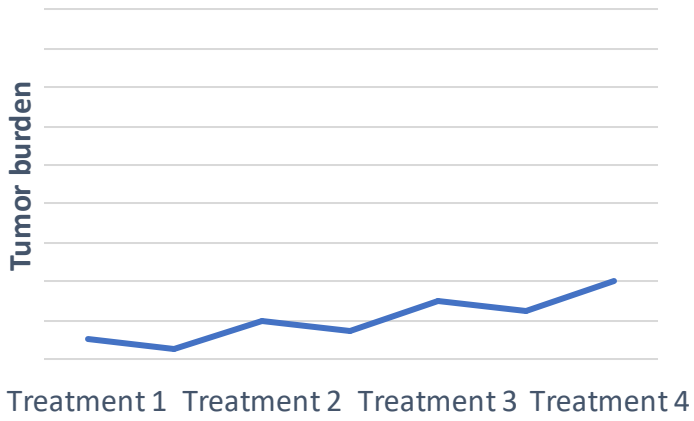


Trial	N	Arms	PFS	OS	RR
RADIANT 3	410	Everolimus vs. Placebo	11.0 vs. 4.6	44.0 vs. 37.7	5% vs. 2%
Su011248	171	Sunitinib vs. Placebo	12.6 vs. 5.8	38.6 vs. 29.1	9% vs. 0%
ECOG 2211	133	Cap/Tem vs. Tem	22.7 vs. 14.4	58.7 vs. 53.8	40% vs. 34%
Oclurandom*	84	^{177}Lu-Dotatate vs. Sunitinib	20.7 vs. 11.0	N/A	N/A
CABINET (pNET)	95	Cabozantinib vs. Placebo	13.8 vs. 4.4	40.0 vs. 31.1	19% vs. 0%
COMPETE		^{177}Lu-Dotatoc vs. Everolimus	23.9 vs. 14.1	63.4 vs. 58.7	

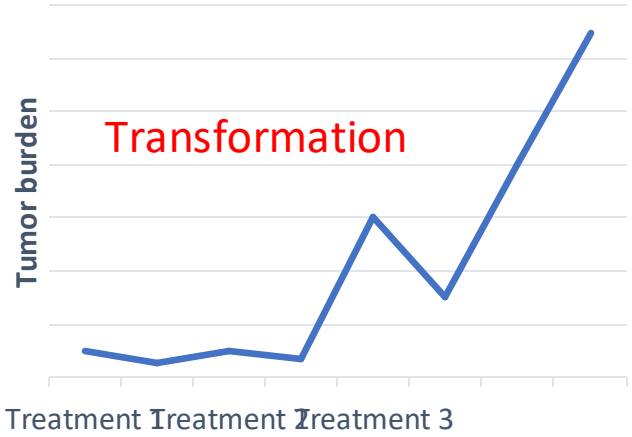
Does Treatment Influence Pattern of Progression?

Alkylating agents (e.g. temozolomide) can lead to hypermutator phenotype
PRRT may induce clonal mutations

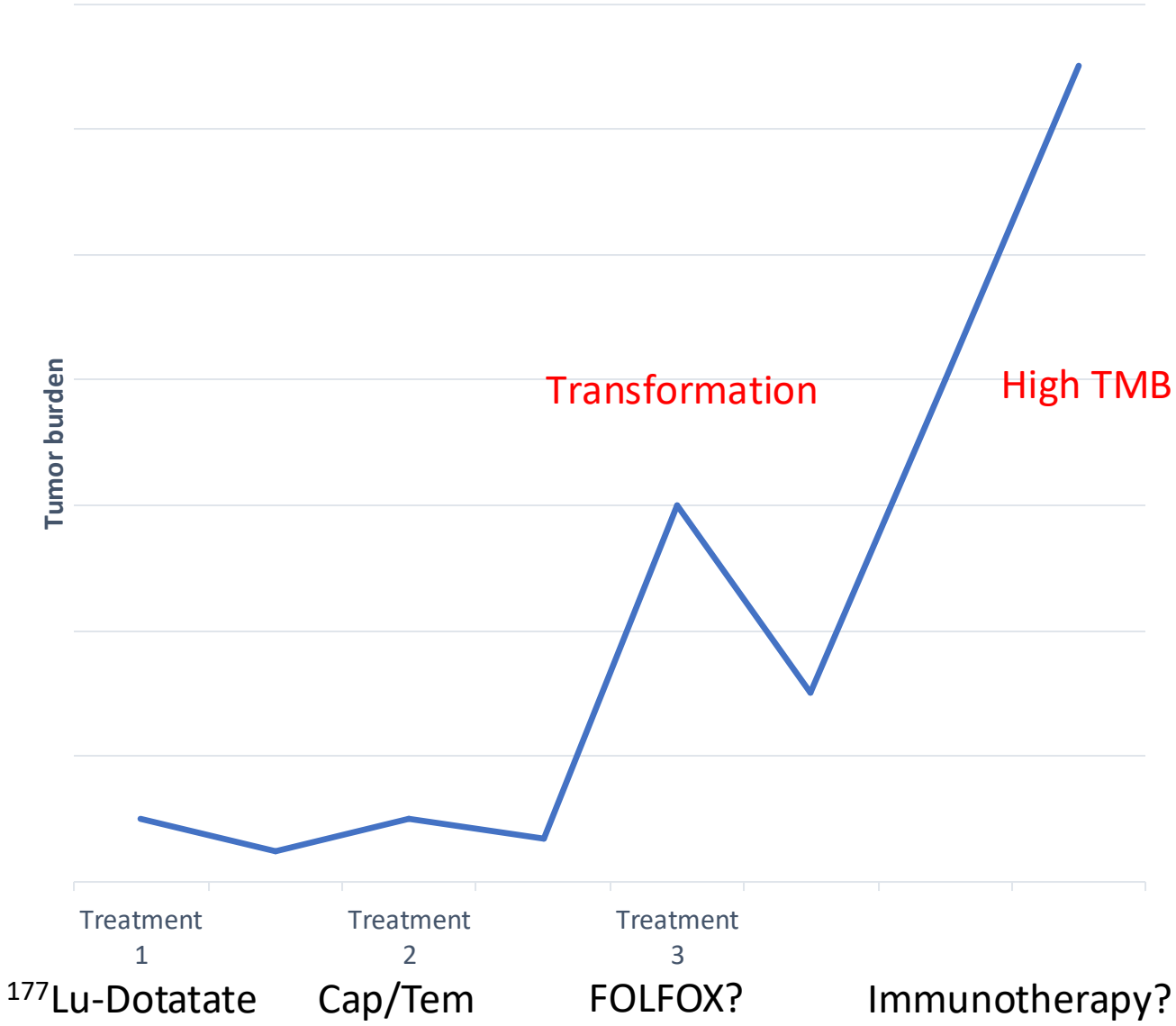
Typical Progression Pattern



Atypical progression pattern



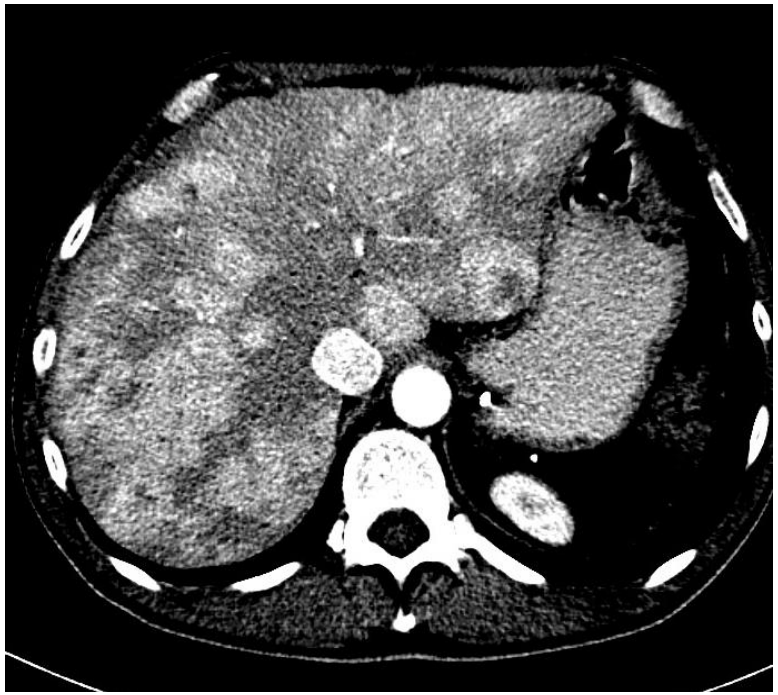
Cordero-Hernandez I, et al. . Transformation of G1-G2 Neuroendocrine Tumors (NETs) to Neuroendocrine Carcinomas (NECs) Following Peptide Receptor Radionuclide Therapy (PRRT): a Case Series *NANETS 2022*. Washington D.C



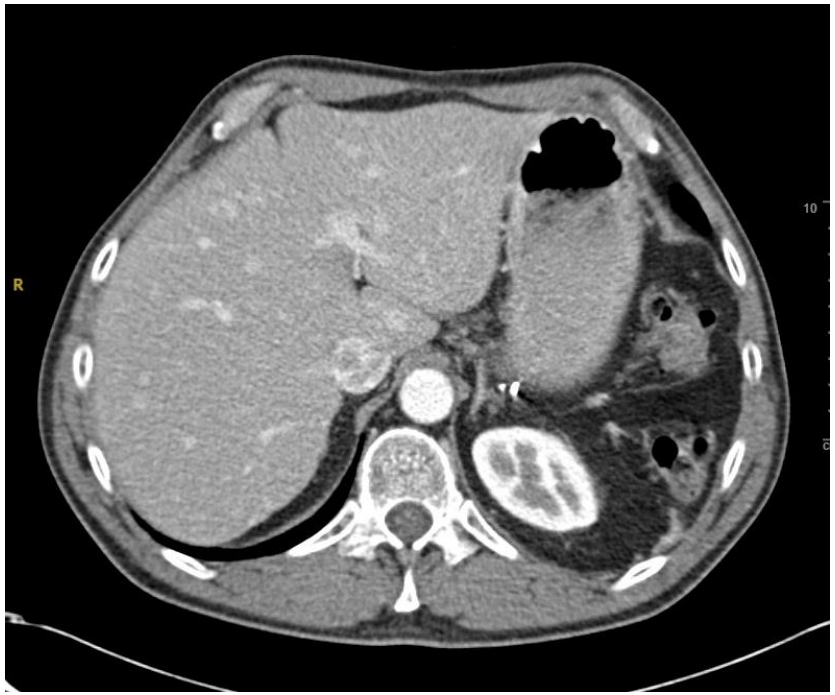
Al-Toubah T et al. Oncologist. 2021 Feb;26(2):115-119.
Cao Y et al. Cancer Commun (Lond). 2020 Dec;40(12):746-751

Local treatments for local progression

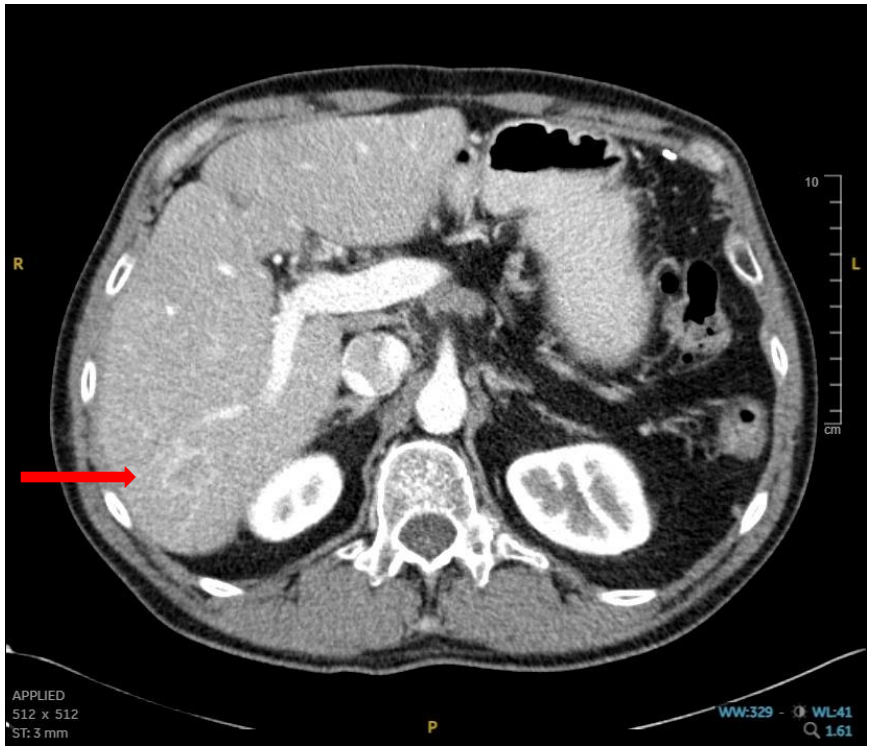
Metastatic grade 2 pancreatic NET to the liver. Primary resected



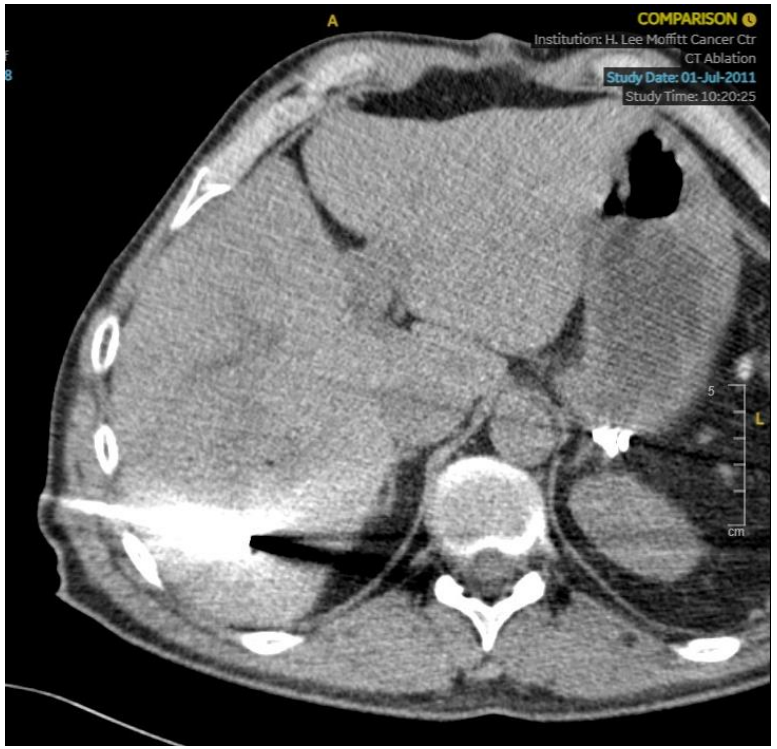
11/2009: Started capecitabine/temozolomide



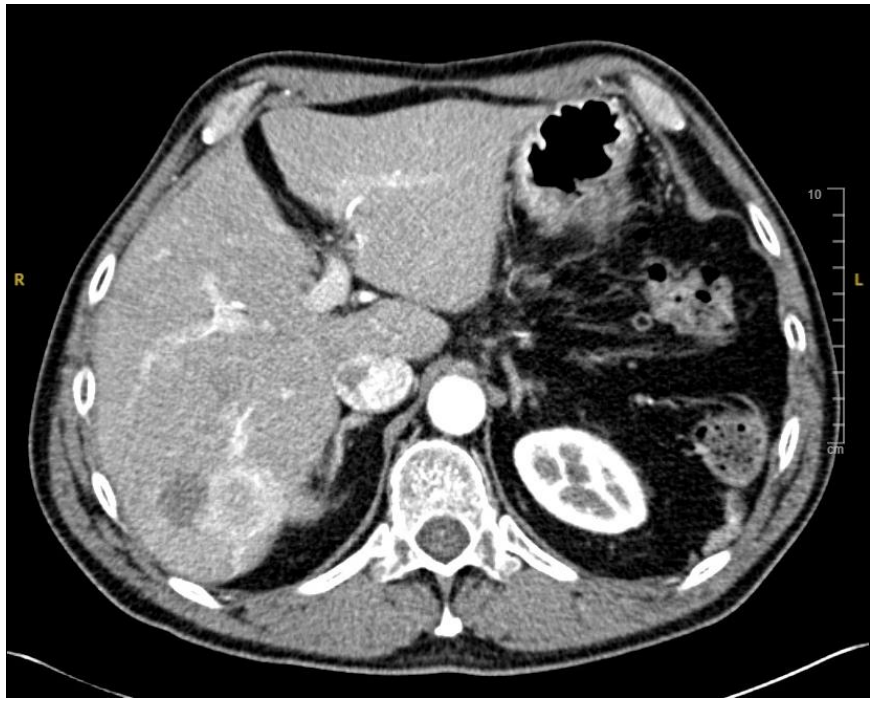
3/2011: near CR



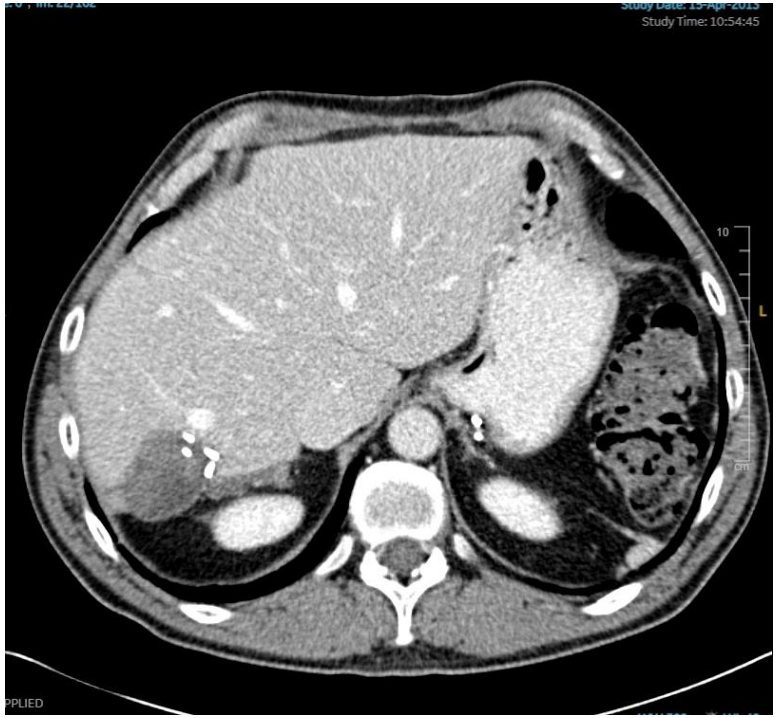
6/2011: solitary progression segment 6



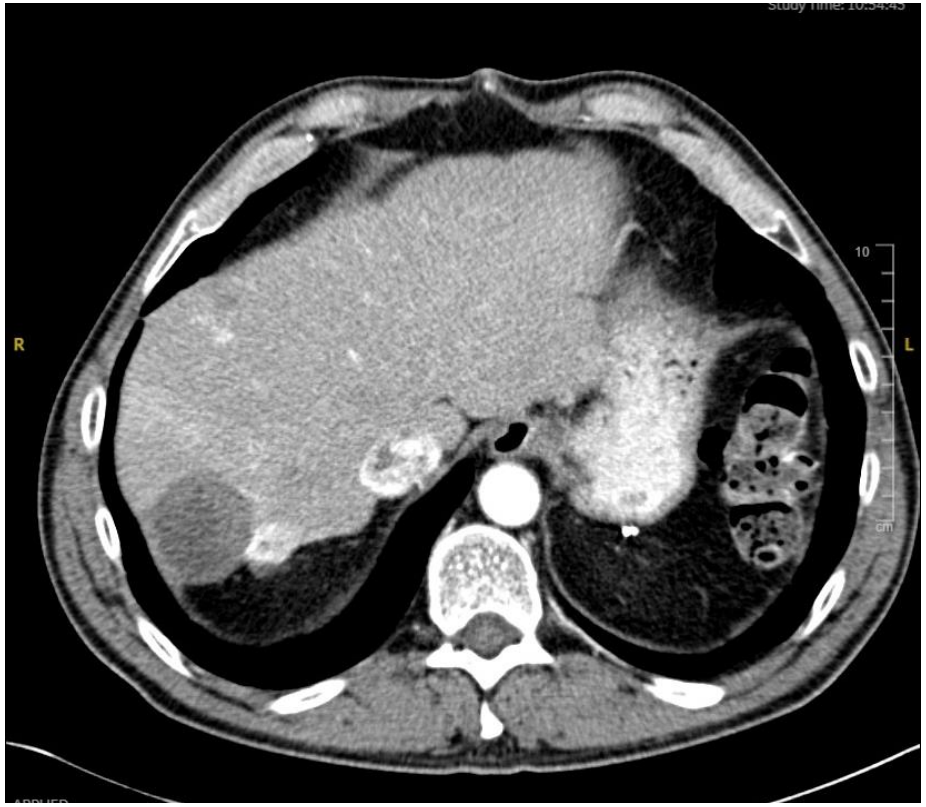
Radiofrequency ablation



3/2012: recurrence
adjacent to ablation site



Resection



4/2013: another recurrence next to resection site and two other subcm hypervascular lesions

- Operative ablation x 3
- Continued cap/tem until 2019 (10 years total)
- Stopped treatment and remains in remission

Conclusion: Think about locoregional treatments for local progression.