Update on Neuroendocrine Cancers

October 29, 2022

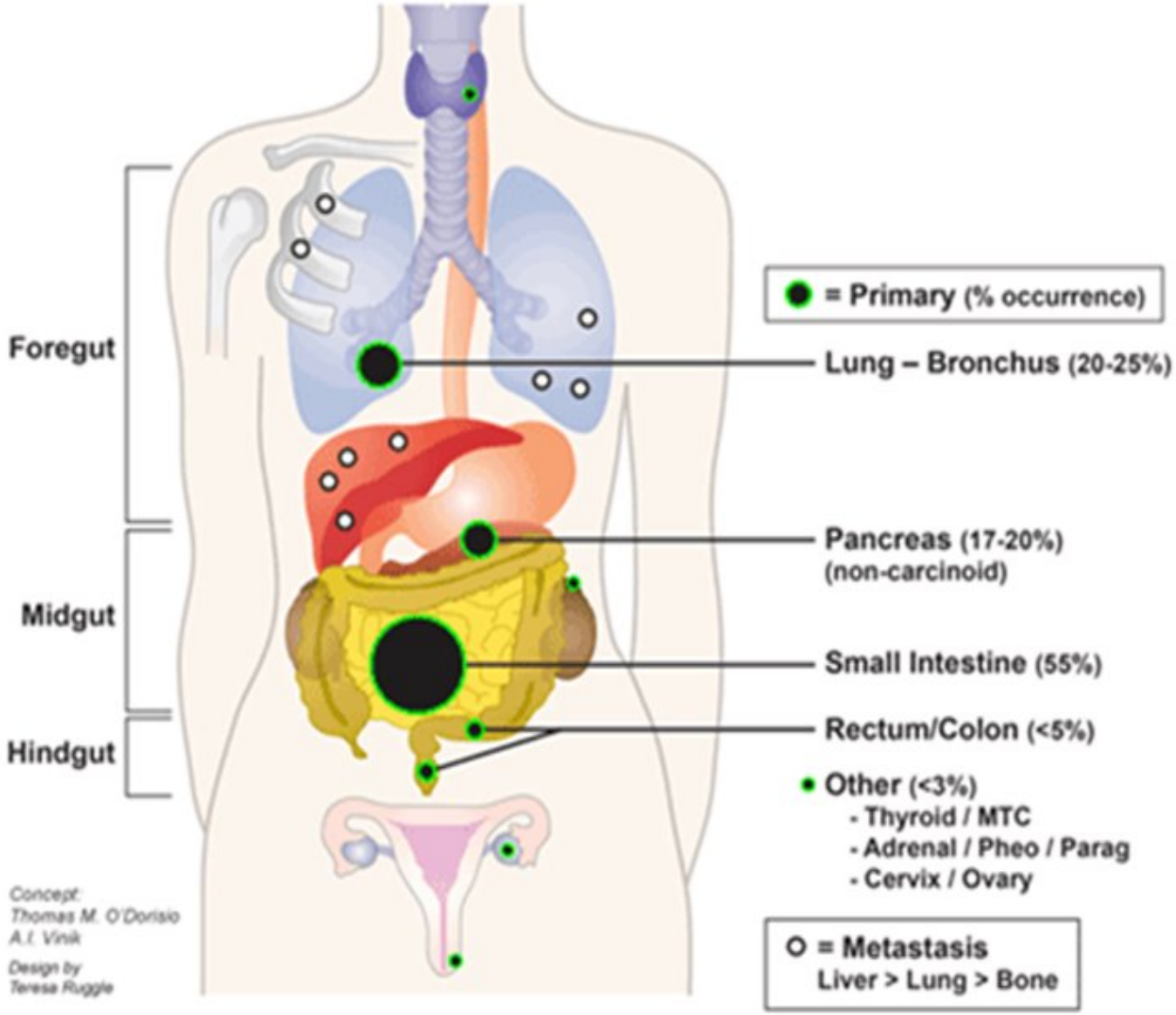
James P. Thomas MD,PhD

Outline

- **Neuroendocrine Cancers**
  - Background
  - Treatment
    - SSRAs
    - Targeted Agents
    - Chemotherapy
    - Peptide Receptor Radionuclide Therapy
    - Newer Therapies and Combinations
  - Summary

Neuroendocrine Cancers

Figure 1: Anatomical Distribution of Neuroendocrine Tumors

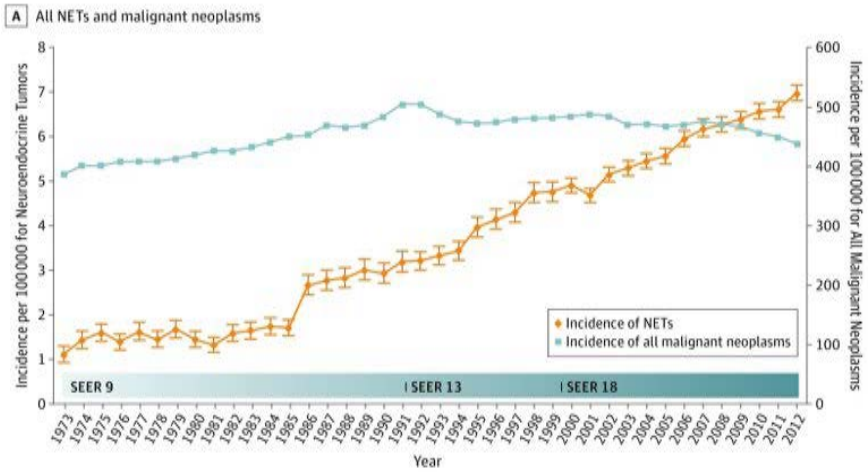


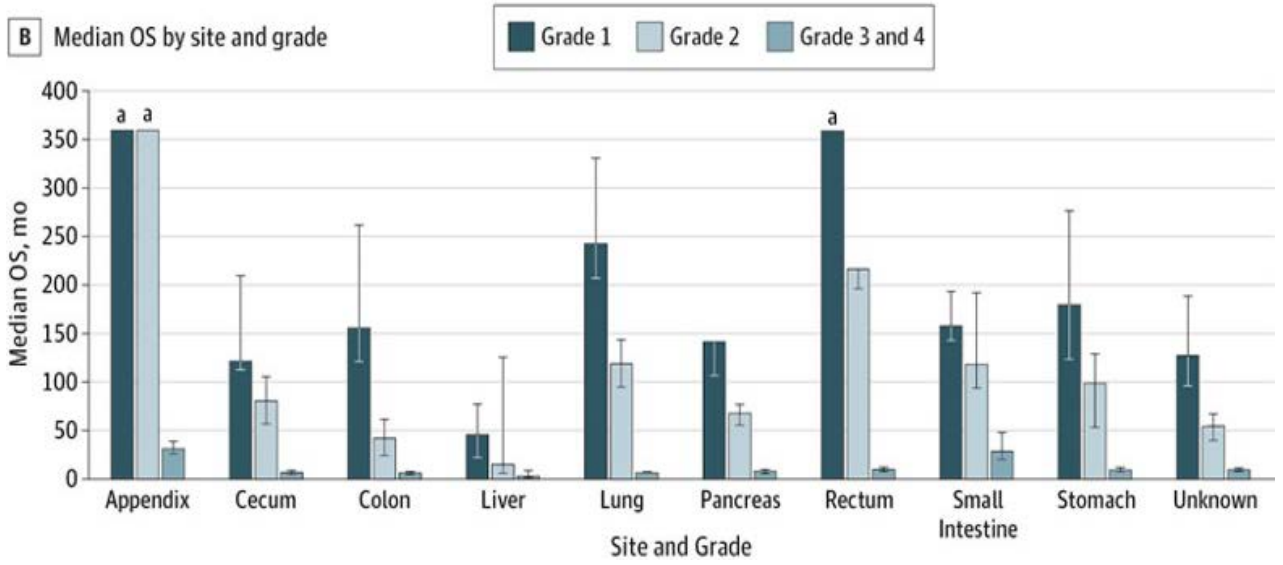
Neuroendocrine Cancers:

Incidence and Survival

6.4 fold increase over ~40 years

Etiology unclear: Environmental Factors
Improved Detection
Improved Identification





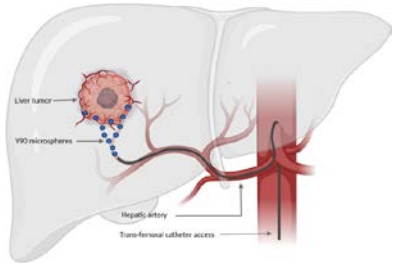
NETs

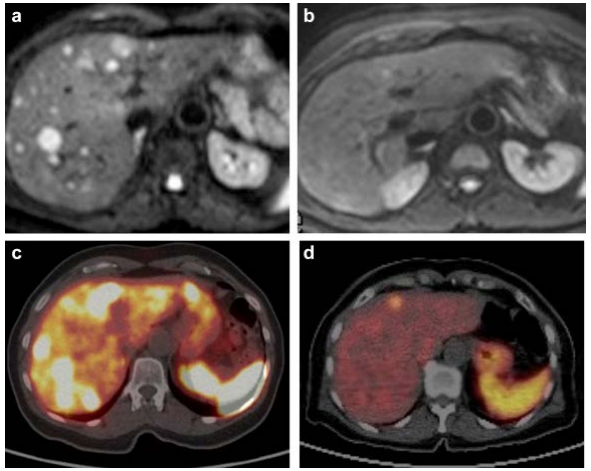
Debulking

Rationale:

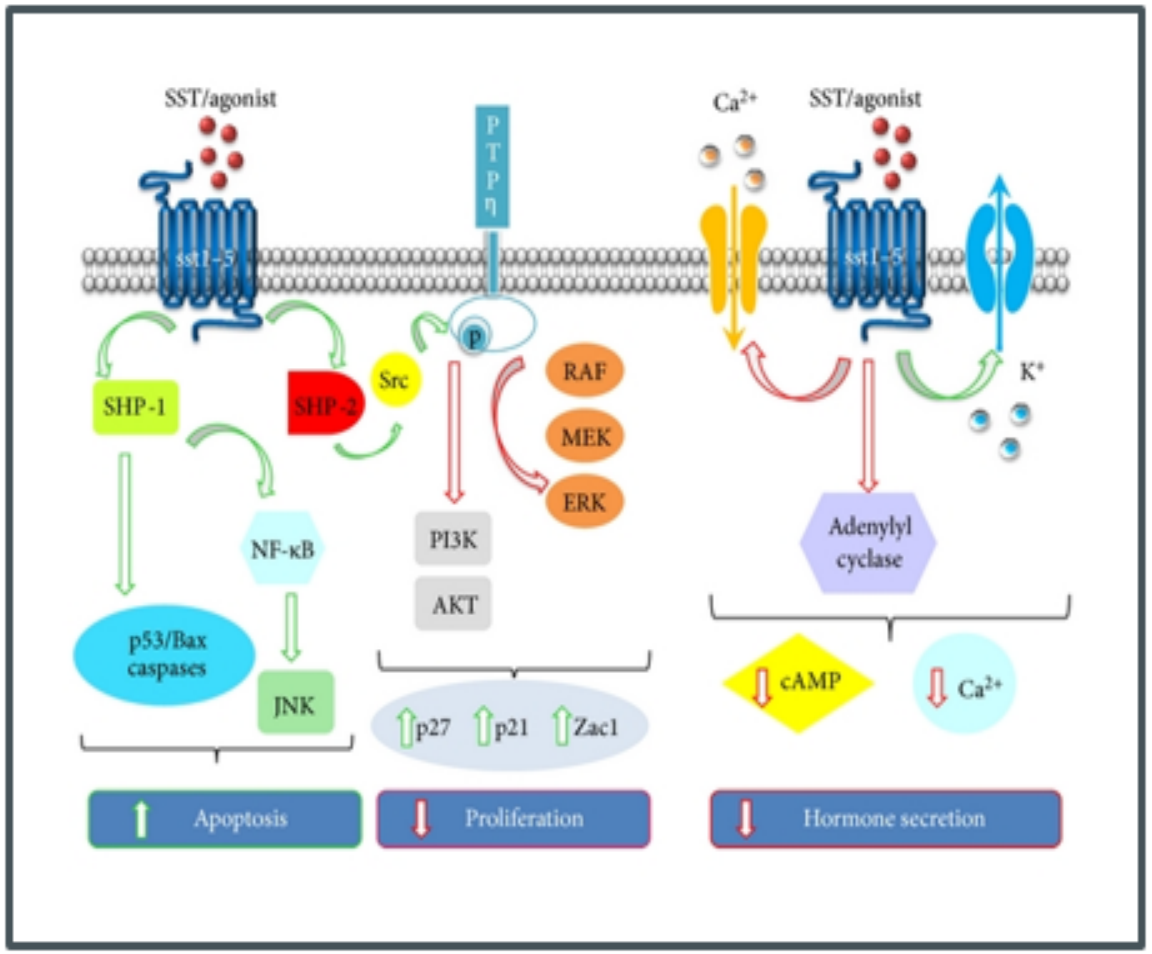
- Decrease mediators
  - Carcinoid Syndrome
  - Carcinoid valvular Disease
- Improved Survival
  - Gompertzian rules need not apply
- Avoiding abdominal catastrophes
  - SBO
  - Biliary tree obstruction

- ***Liver Directed Therapy***
  - Radioembolization
  - Radiation Segmentectomy
  - TACE
  - Histotripsy





Treatment Options – SSTR Agonists



https://www.hindawi.com/journals/ijpep/2013/926295/

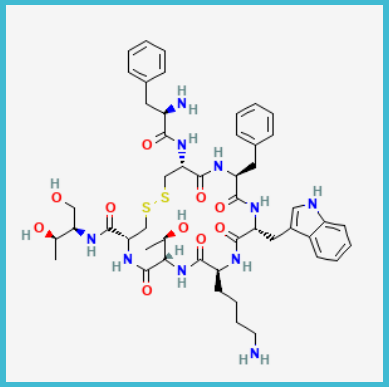
Tumor	SST1 (%)	SST2 (%)	SST3 (%)	SST4 (%)	SST5 (%)
Gastrinoma	79[a]	93	36	61	93
Insulinoma	76	81	38	58	57
Non-functioning pancreatic tumor	58	88	42	48	50
Carcinoid tumor of the gut	76	80	43	68	77

SST, somatostatin receptor.

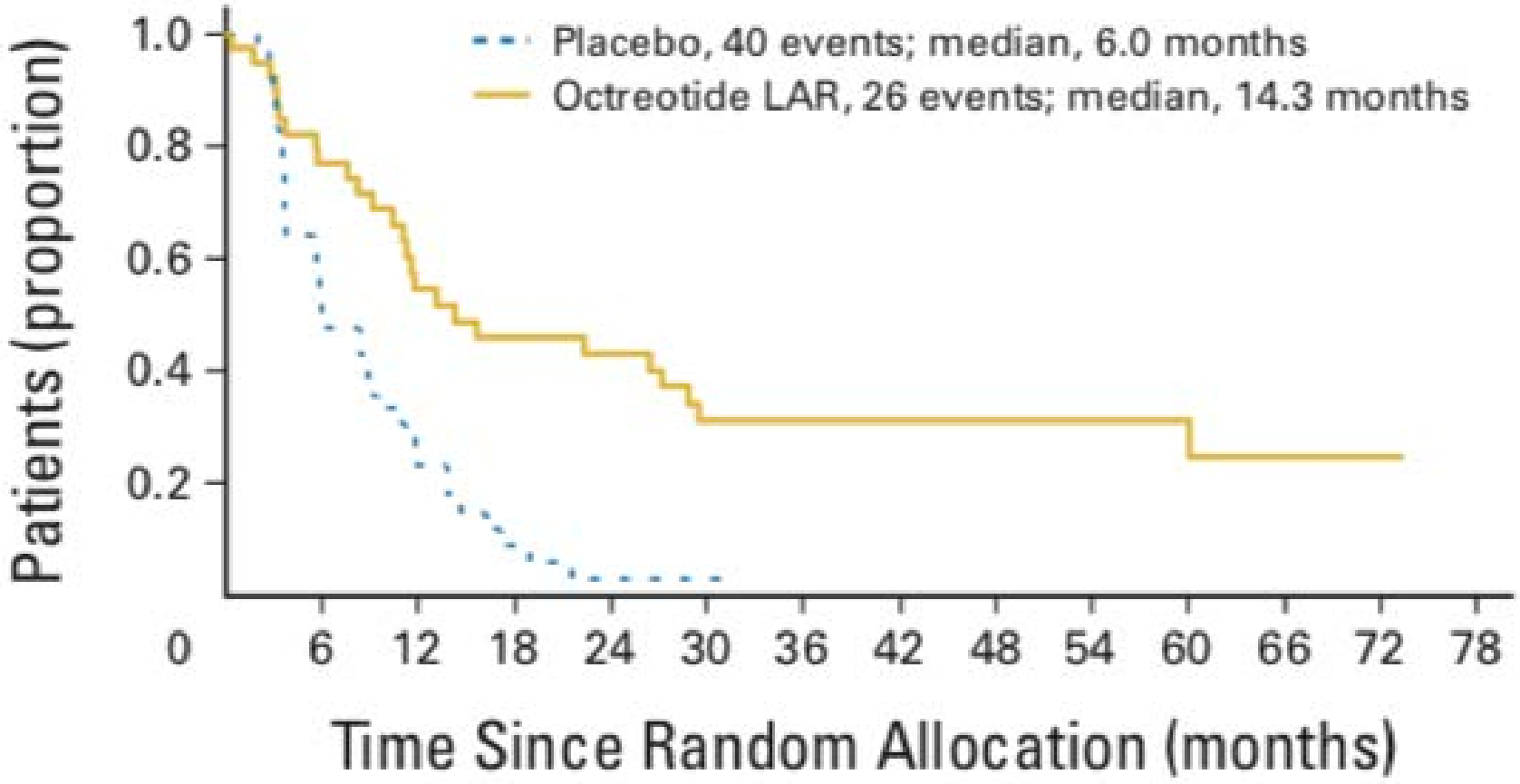
[a]Indicates the percentage of positive tumors for each SSTRs mRNA expression may overestimate the number of receptors present, depending on the technique used (PR-polymerase chain reaction, Northern blot, in situ hybridization). Modified from Plockinger (19).

https://www.frontiersin.org/articles/10.3389/fendo.2014.00007/full

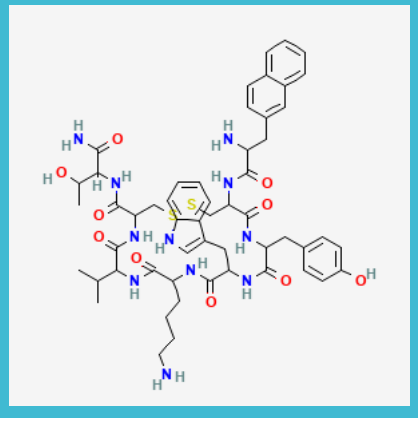
Midgut NETs



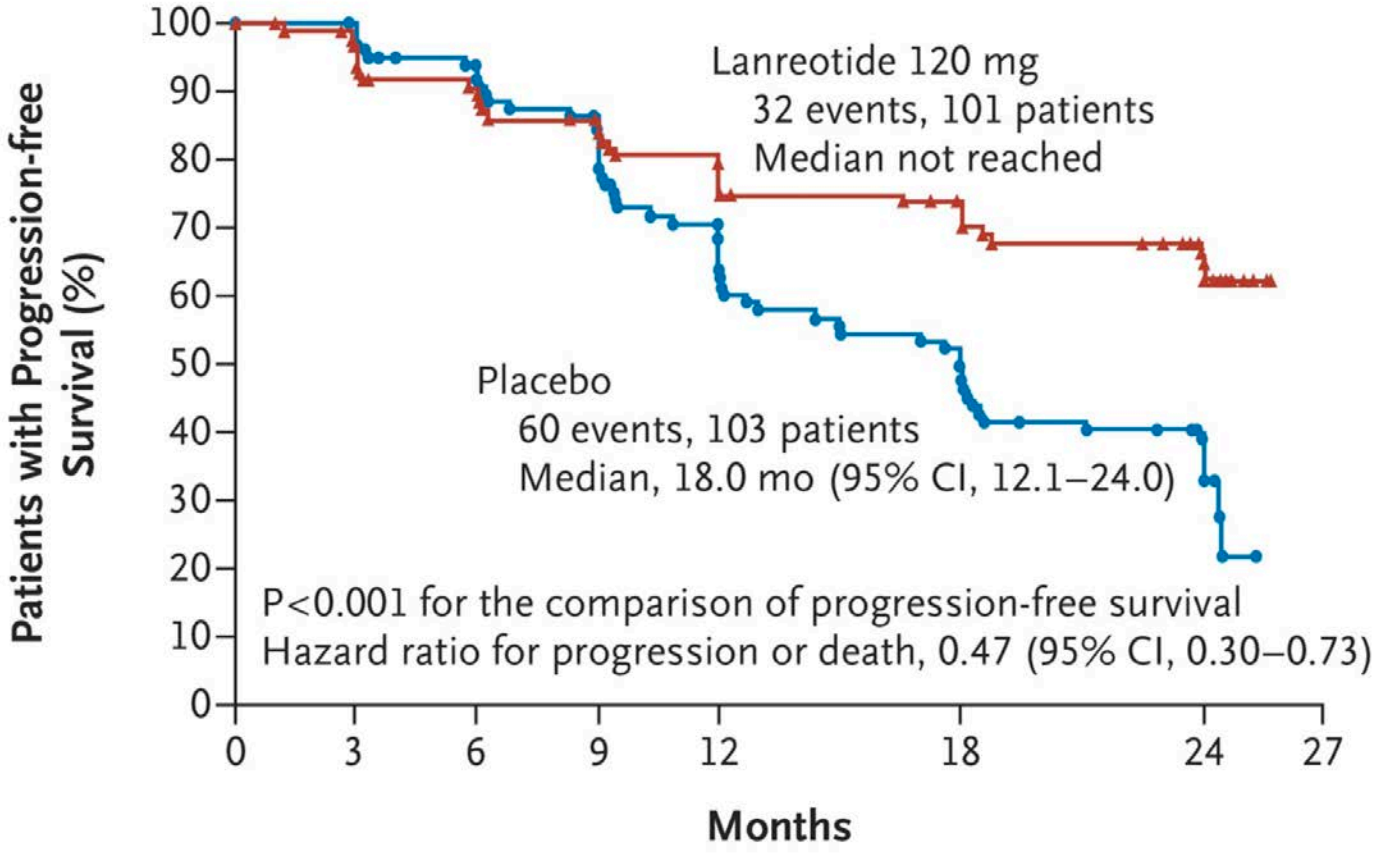
PROMID STUDY: Octreotide LAR vs Placebo



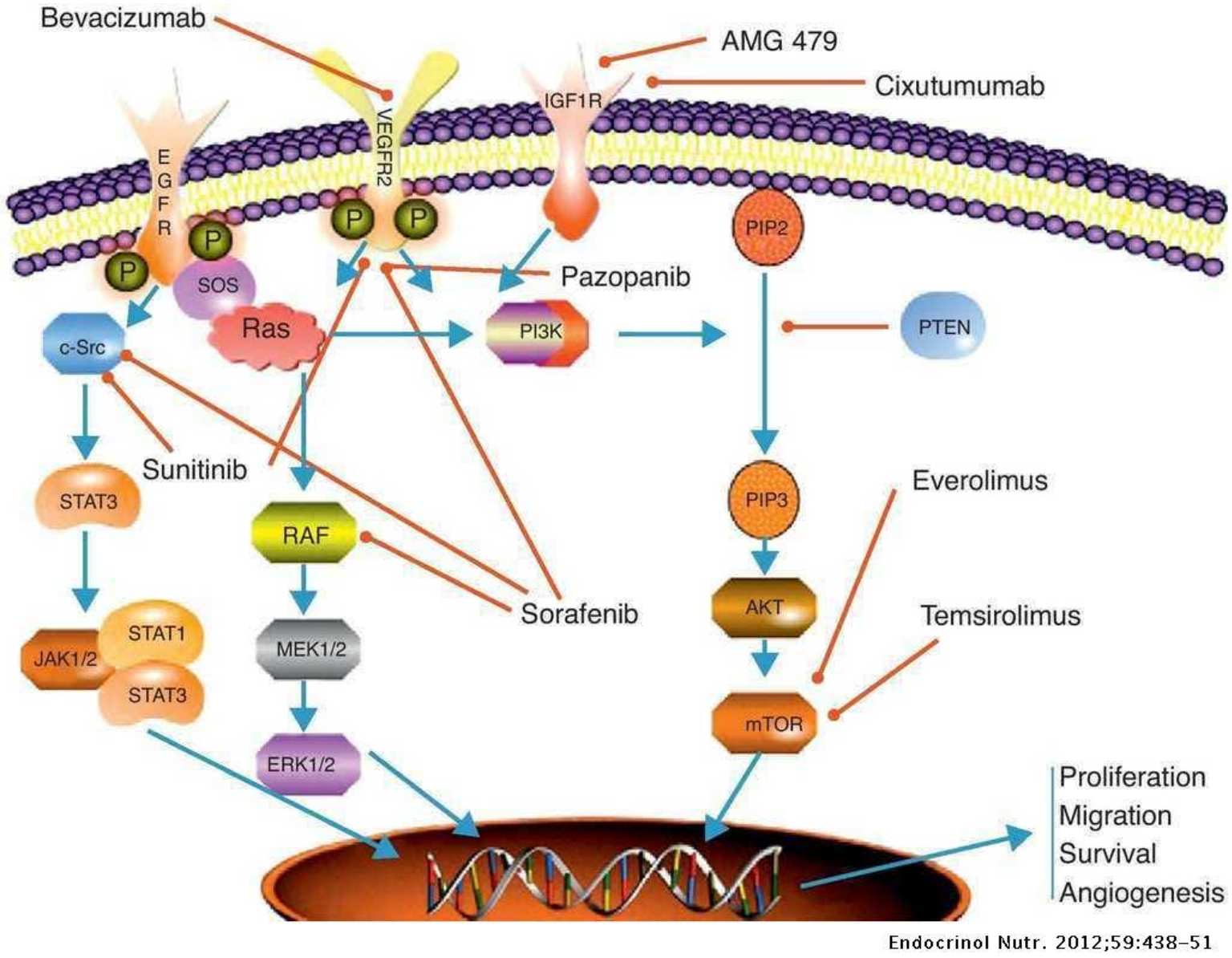
Enteropancreatic NETs



Clarinet Study: Lanreotide vs. Placebo



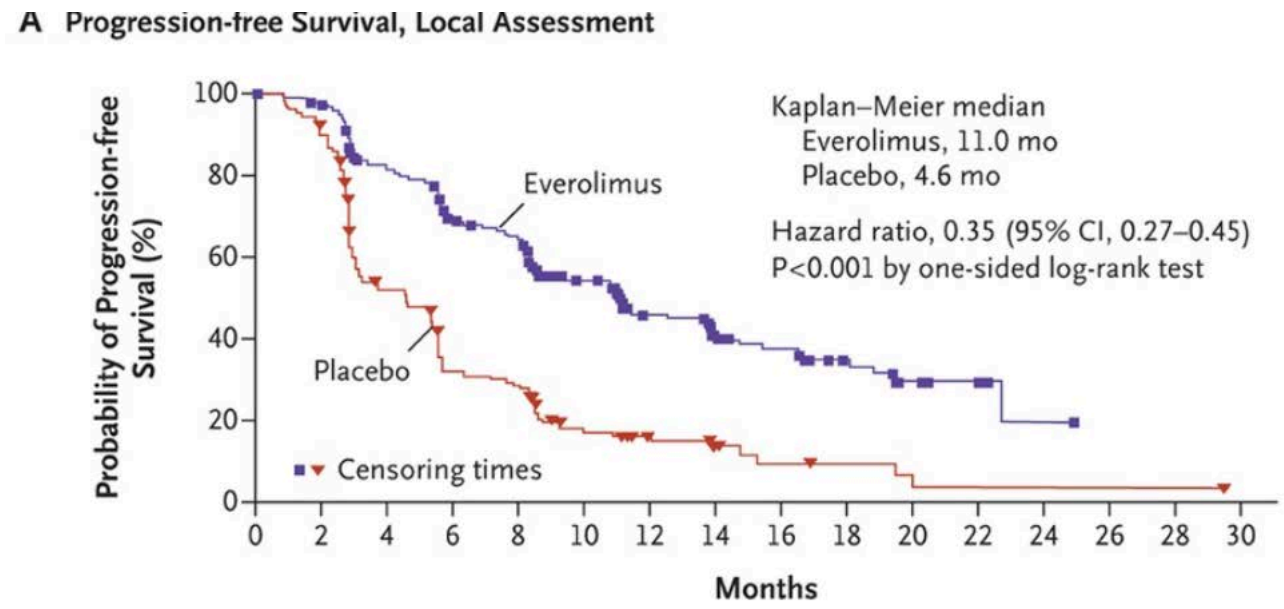
Targeted Agents

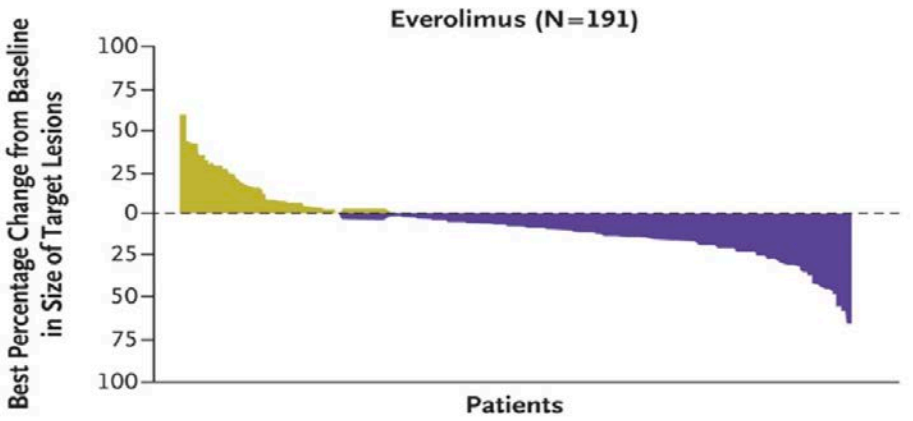


PNETs

Everolimus

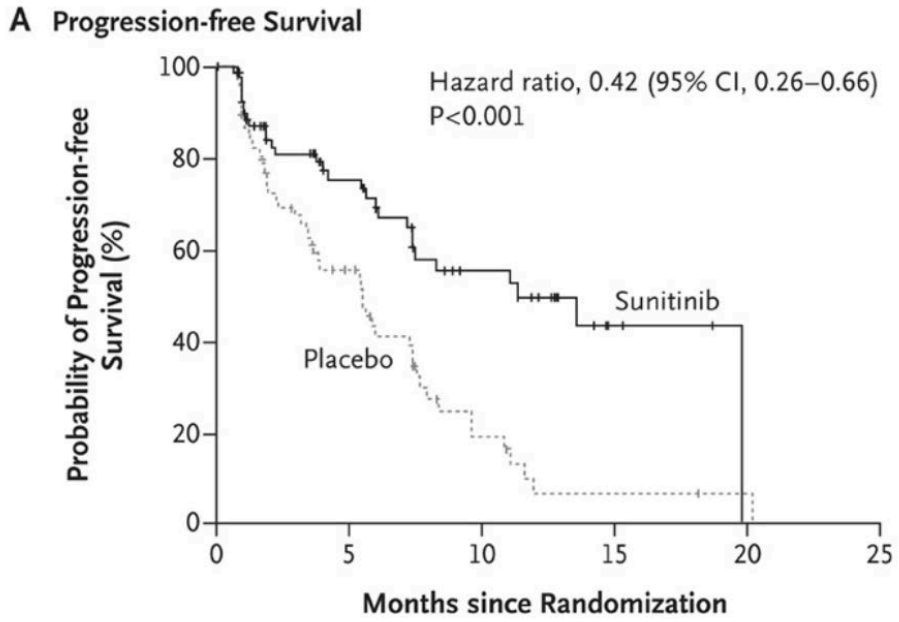
Everolimus

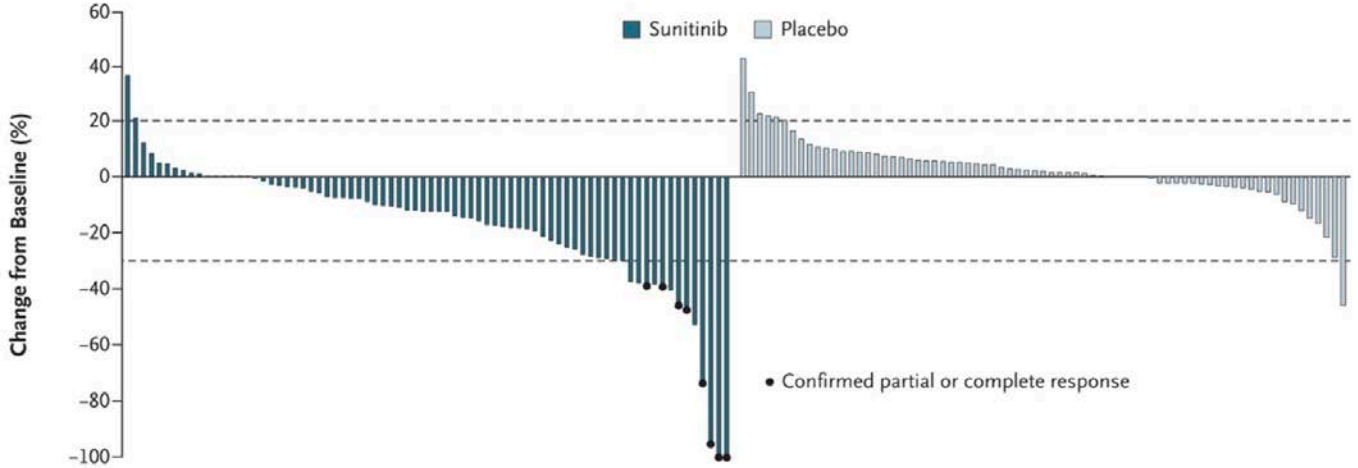




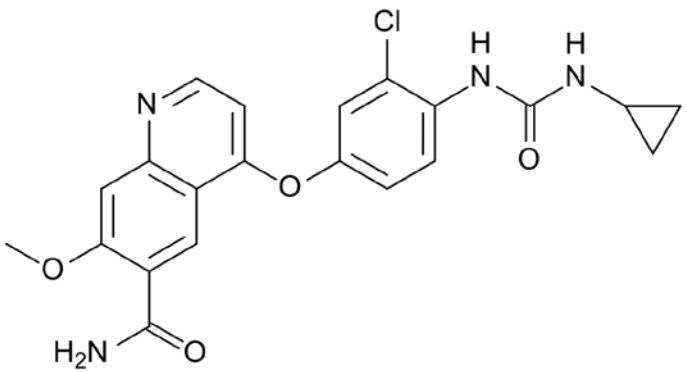
PNETS

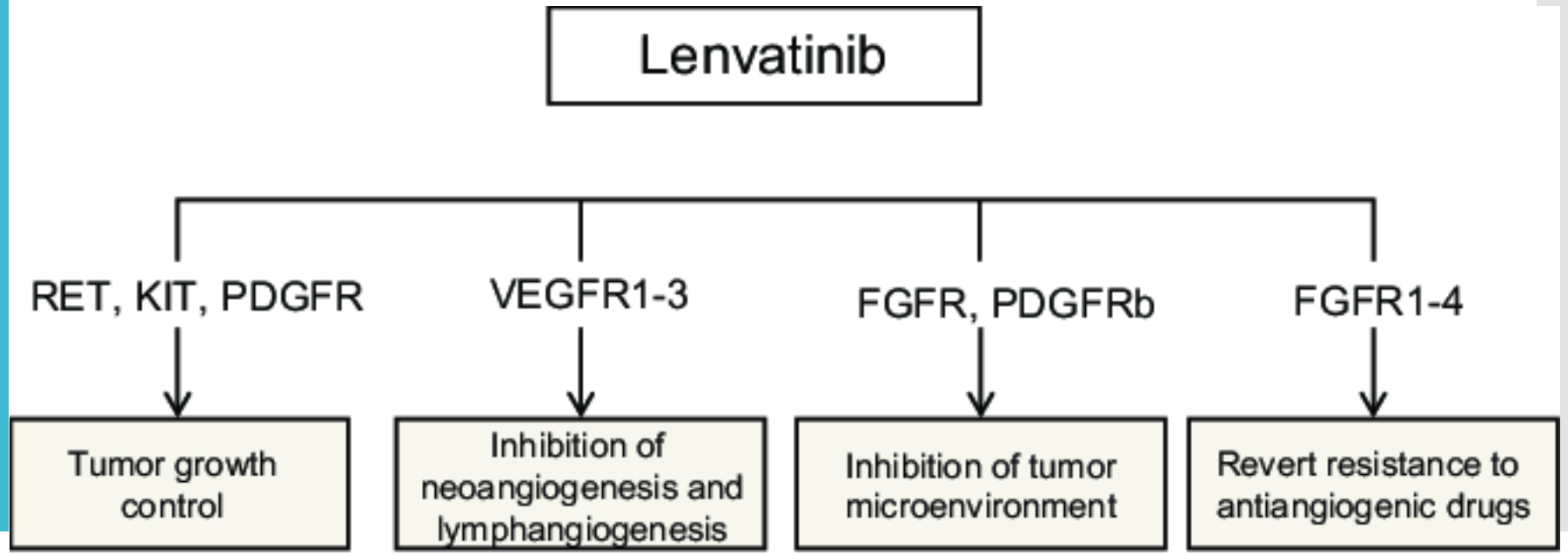
Sunitinib





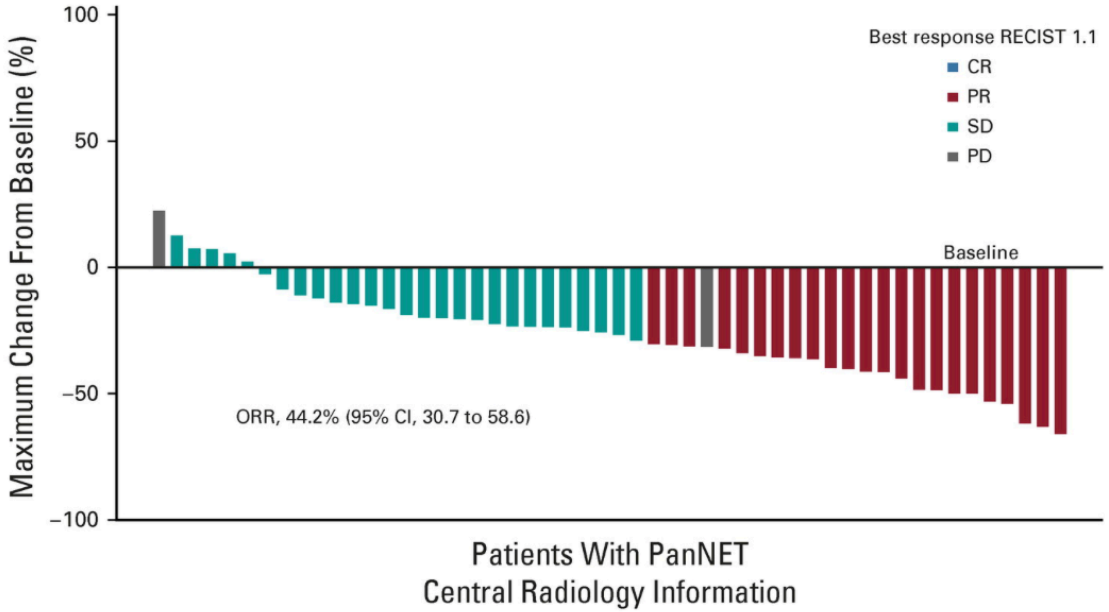
TKIs: Lenvatinib

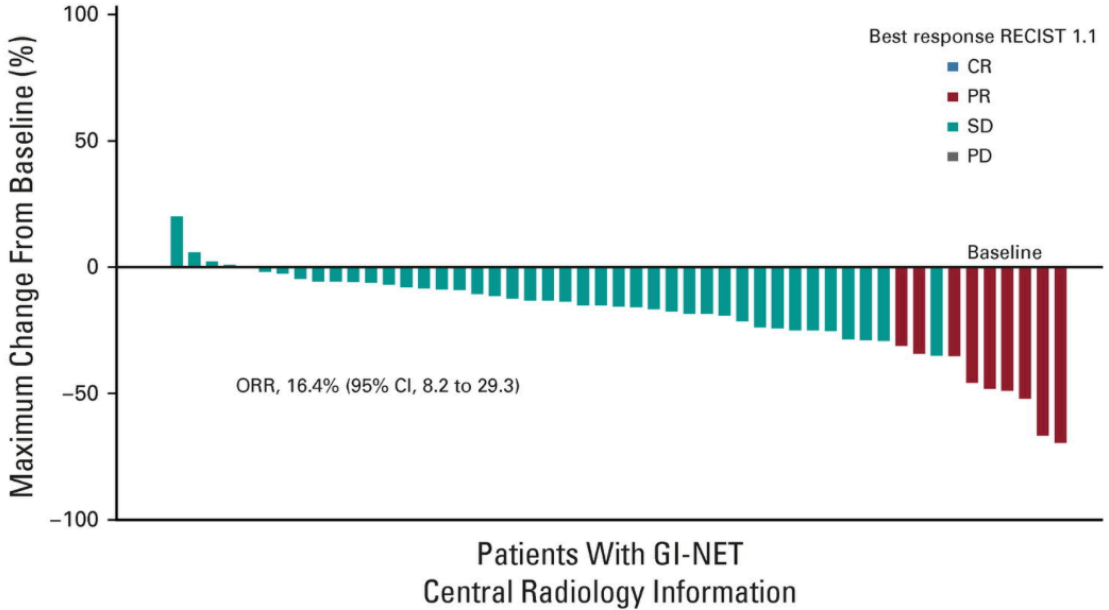




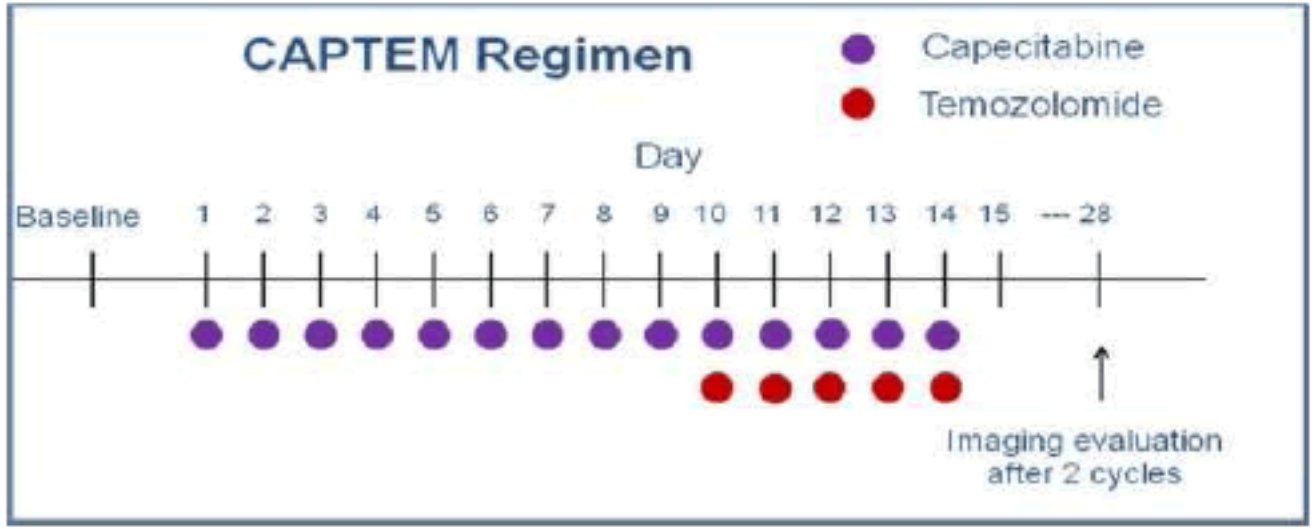
Enteropancreatic NETs

Lenvatinib

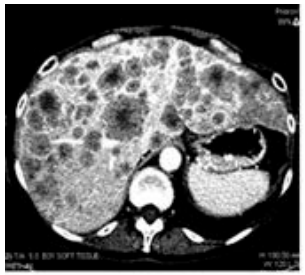


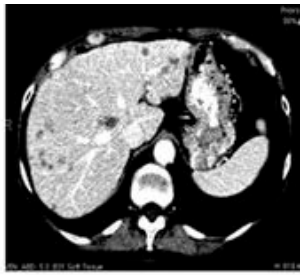


Chemotherapy Capecitabine/ Temozolomide



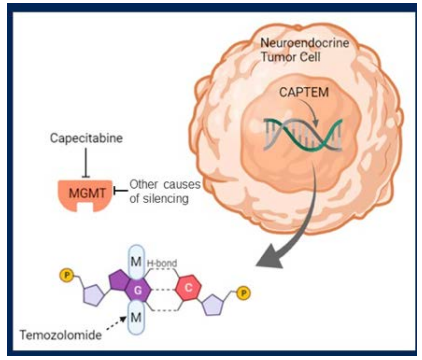
Grade 3 PNET

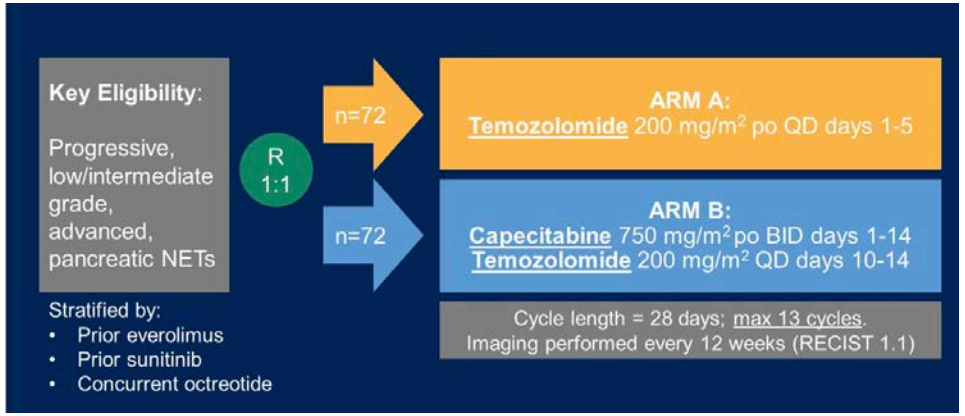




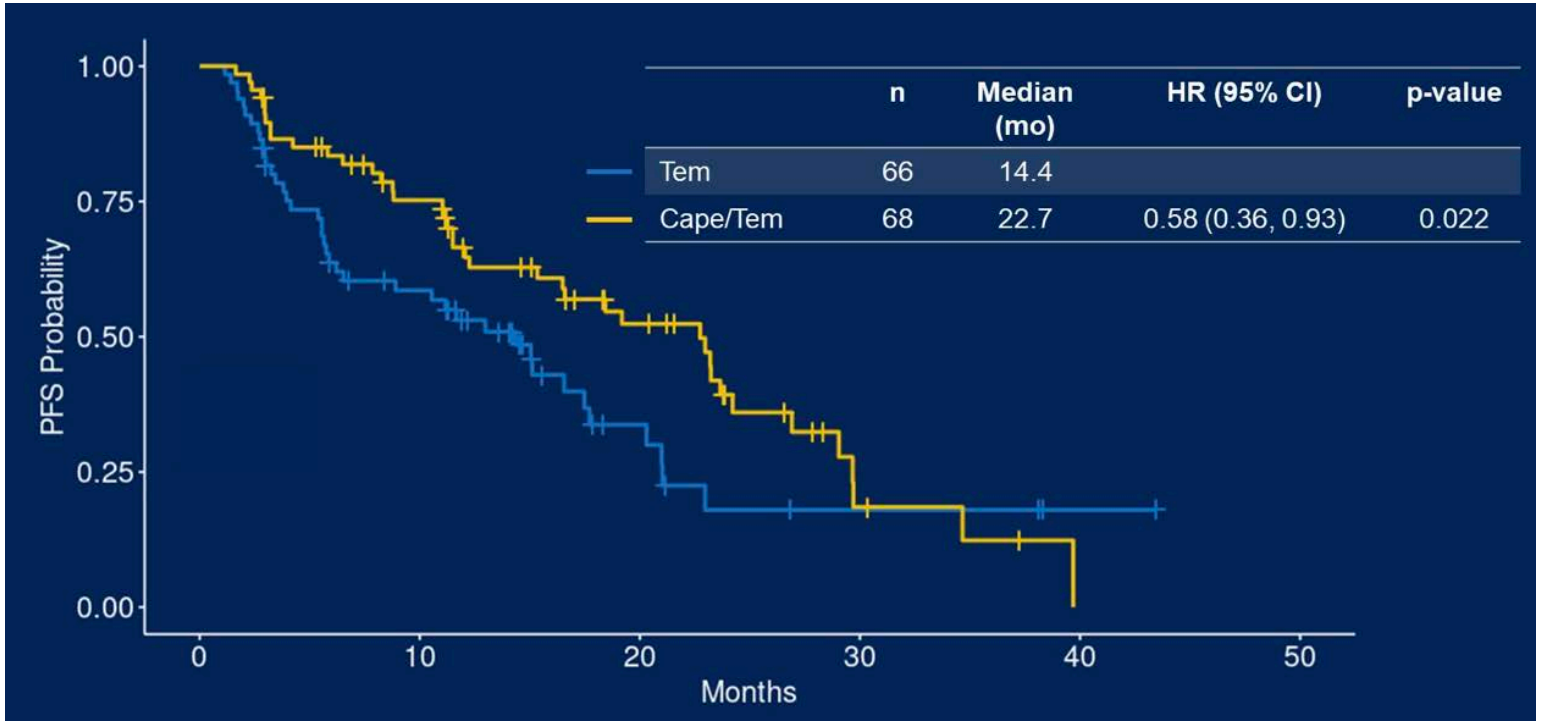
Cape/Tem vs. Tem: PNET

ECOG 2211





RR: 34% vs 40%



PNET Cape/Tem:

MGMT

MGMT deficiency is associated with response

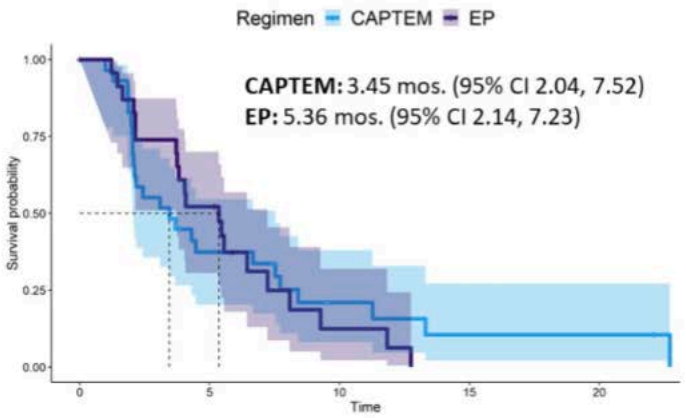
RECIST Response	MGMT (IHC, H-Score)			MGMT (Promoter Methylation)		
	1-2, low	3, high	Total	Negative	Positive	Total
No	30/63 (48%)	29/34 (85%)	59	31/50 (62%)	1/7 (15%)	32
Yes	**33/63 (52%)**	**5/34 (15%)**	**38**	**19/50 (38%)**	**6/7 (85%)**	**25**
Total	63	34	97	50	7	57
	OR [95% CI] = 6.38 [2.19, 18.60]; p = 0.0004			OR [95% CI] = 9.79 [1.09, 87.71; p = 0.04		

G3 NETs Cape/Tem vs Cis/Etop

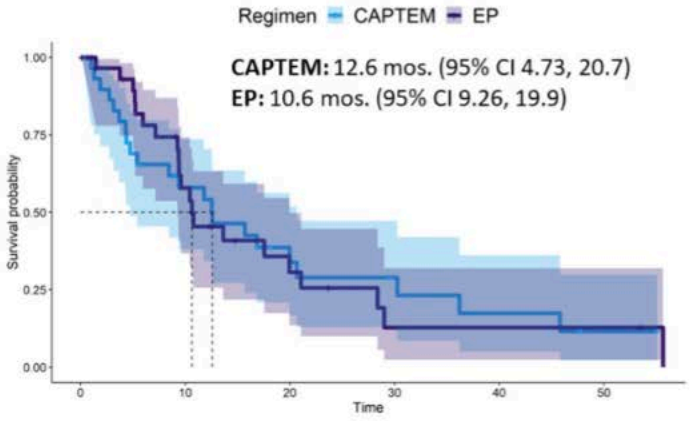
ECOG 2142

Survival Outcomes

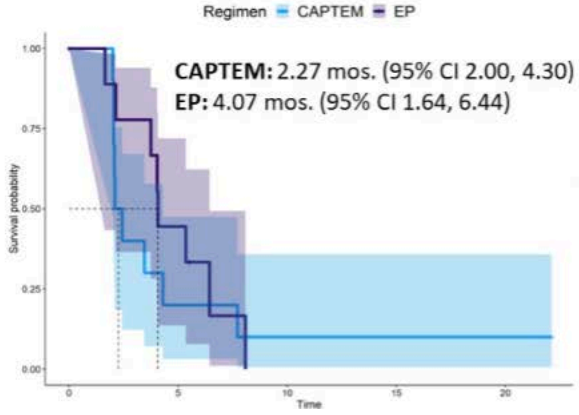
Progression Free Survival Between Treatment Arms



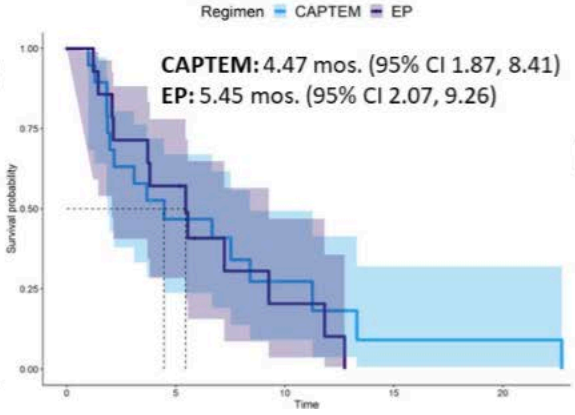
Overall Survival Between Treatment Arms



PFS among GI NETs



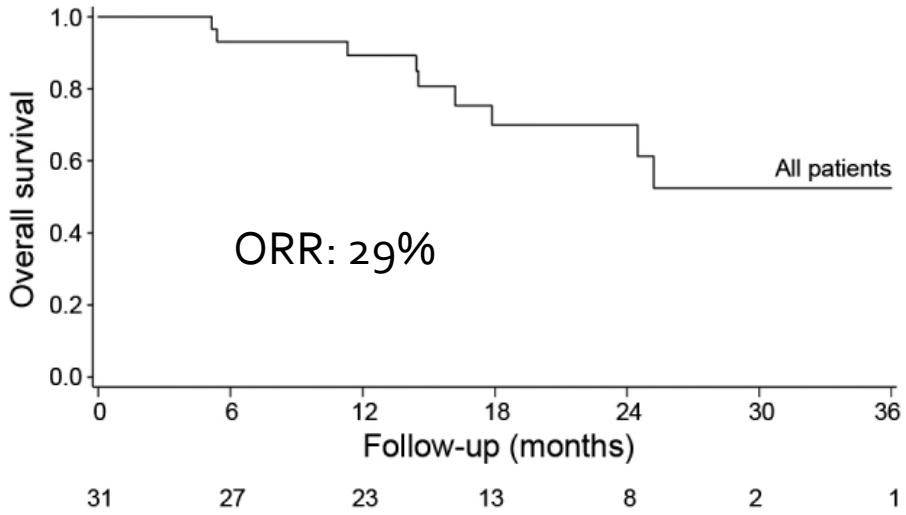
PFS among Pancreatic NETs

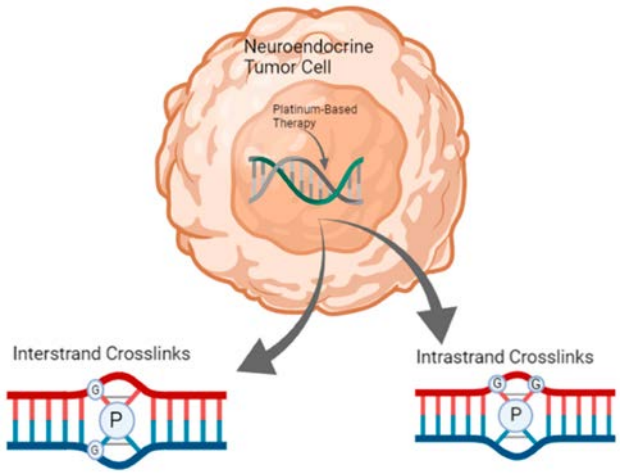


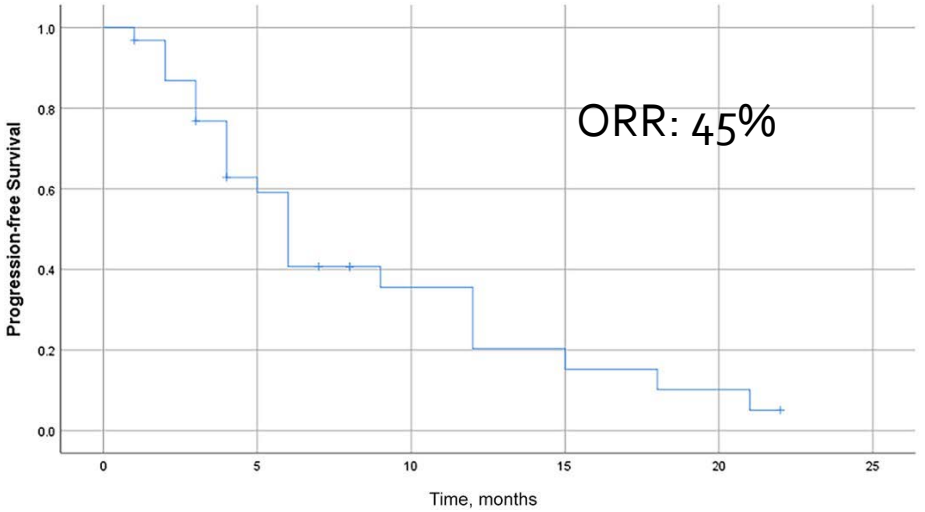
Response Rate
CAPTEM: 19%
EP: 22%

Cape/Tem does not appear superior to EP for G3 NETs

FOLFOX in NETs



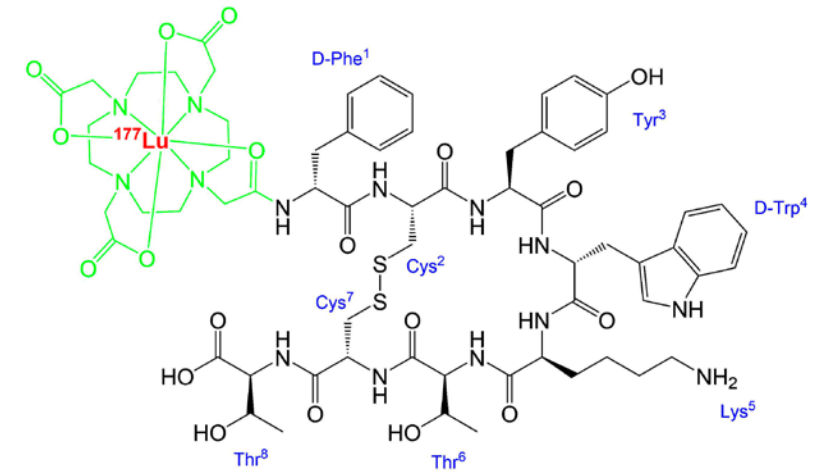




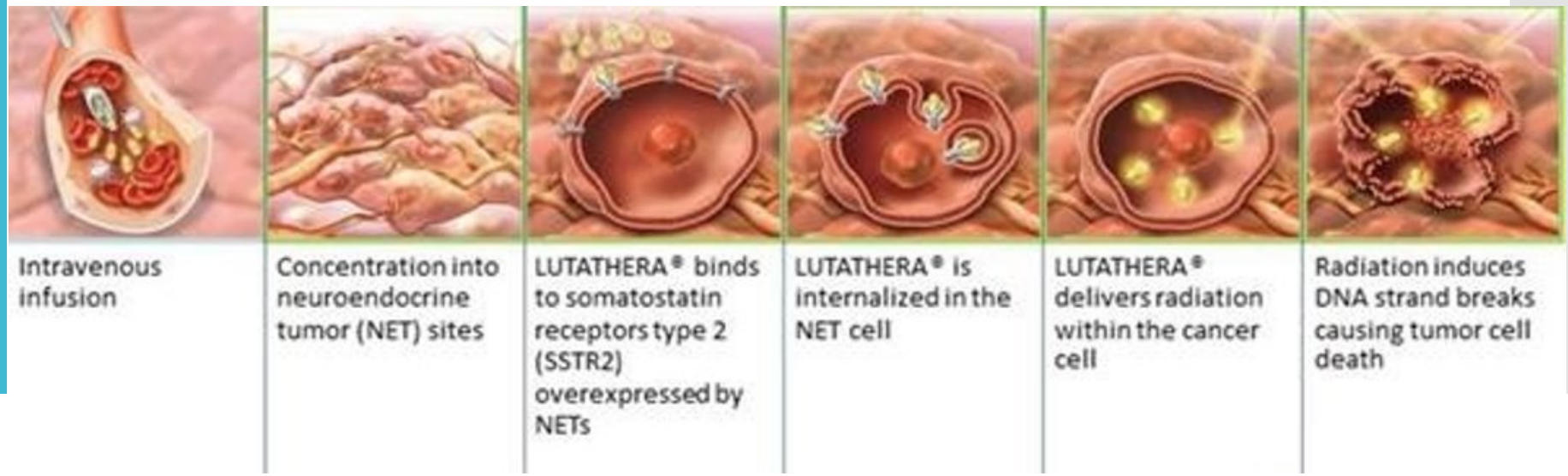
PRRT

PRRT

- 1..Binds to SSTR2 surface receptors
- 2. Internalization by phagocytosis
- 3. Radiation Induced DNA strand breaks

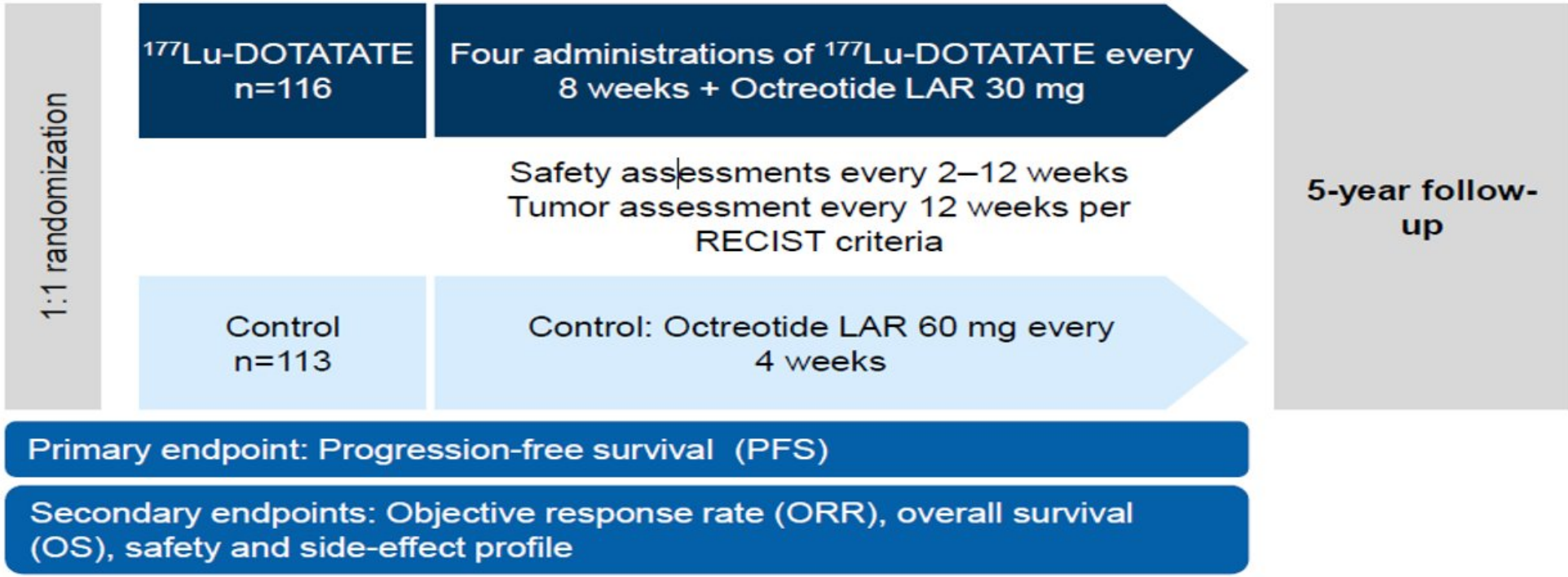


radionuclide (^{177}Lu) + chelator (DOTA) + targeting peptide (octreotate)



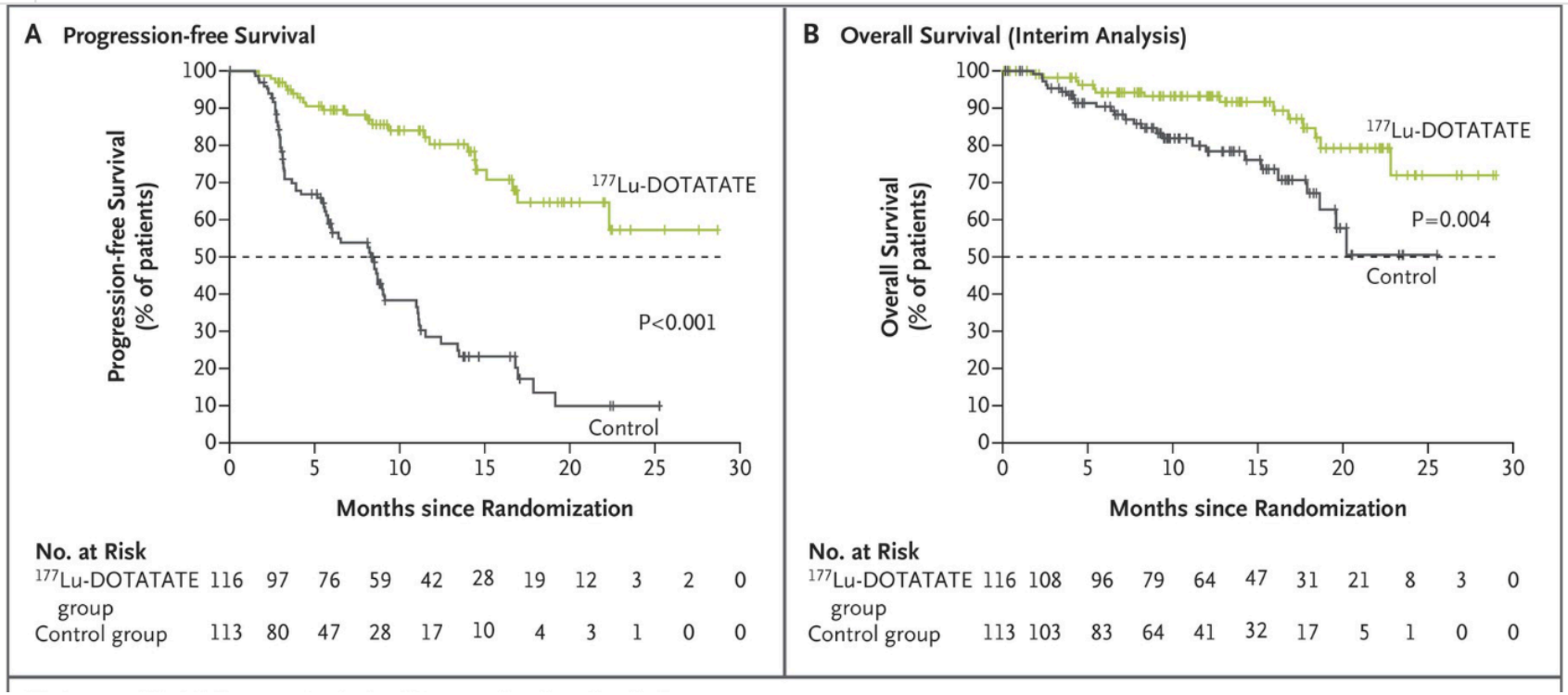
PRRT Basics

NETTER-1: international, multicenter, randomized, open-label, comparator-controlled, parallel-group Phase III study



LAR, long-acting release; RECIST, Response Evaluation Criteria In Solid Tumors.
Strosberg J, et al. *N Engl J Med*. 2017;376:125–135.

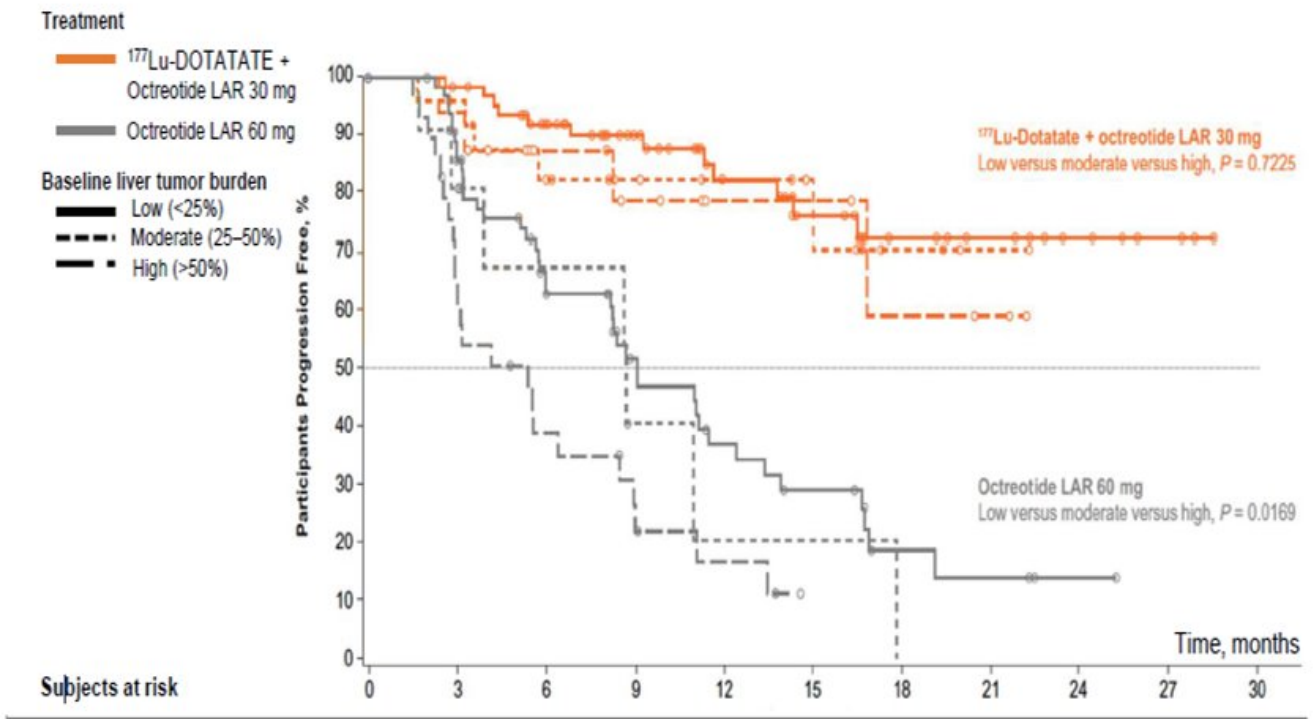
PRRT: 177Lu-DOTOTATE



Midgut tumors with Ki67<20%
RR: 18%
79% decreased chance of progression or death

Category 1 NCCN

PRRT: Liver Burden



PRRT: Tox

NETTER-1: Laboratory abnormalities

Laboratory Abnormality[a]	^{177}Lu-DOTATATE and Octreotide LAR 30 mg (N = 111)		Octreotide LAR 60 mg (N = 112)	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Hematology				
Lymphopenia	90	44	39	5
Anemia	81	0	55	1
Leukopenia	55	2	20	0
Thrombocytopenia	53	1	17	0
Neutropenia	26	3	11	0
Renal/Metabolic				
Creatinine increased	85	1	73	0
Hyperglycemia	82	4	67	2
Hyperuricemia	34	6	30	6
Hypocalcemia	32	0	14	0
Hypokalemia	26	4	21	2
Hyperkalemia	19	0	11	0
Hypernatremia	17	0	7	0
Hypoglycemia	15	0	8	0
Hepatic				
GGT increased	66	20	67	16
Alkaline phosphatase increased	65	5	55	9
AST increased	50	5	35	0
ALT increased	43	4	34	0
Blood bilirubin increased	30	2	28	0

[a] Occurring at higher incidence in patients receiving ^{177}Lu-DOTATATE and octreotide LAR 30 mg compared to octreotide LAR 60 mg (between arm difference of ≥5% all grades or ≥2% Grades 3-4).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT gamma-glutamyl transferase; LAR, long-acting release.

Lutathera [prescribing information]; Advanced Accelerator Applications USA, Inc., 2020.

PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY
Locoregionally Advanced and/or Metastatic Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus

- Systemic therapy may not be appropriate for every patient with locoregionally advanced or metastatic disease. Consider multidisciplinary discussion to determine the best choice of treatment, including: observation for patients with stable disease with mild tumor burden, hepatic regional therapy for patients with liver-predominant metastases, cytoreductive surgery, or systemic therapy, which may be appropriate considerations.
- Currently, there are no data to support a specific sequence of regional versus systemic therapy, and no data to guide sequencing of the following systemic therapy options.
- There is no known role for systemic treatment in the adjuvant setting for NETs.
- Doses and schedules are subject to appropriate modifications depending on the circumstances.
- For management of hormone-related symptoms for GI tumors, see NET-11. For management of carcinoid syndrome, see NET-12.

Neuroendocrine Tumors of the Gastrointestinal Tract[a,b,c]

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Locoregional Advanced Disease and/or Distant Metastases (if progression on octreotide or lanreotide)[c]	• Everolimus[d,1,2] • PRRT with 177Lu-dotatate (if SSR-positive imaging and progression on octreotide/lanreotide) (category 1 for progressive mid-gut tumors)[e]	• None	• Consider (listed in alphabetical order): ▸ Cytotoxic chemotherapy, if no other options feasible (all category 3): Anticancer agents such as 5-fluorouracil (5-FU), capecitabine, dacarbazine, oxaliplatin, streptozocin, and temozolomide can be used in patients with progressive metastases for whom there are no other treatment options. (See Discussion for details.)

[a]For symptom control, octreotide 150–250 mcg SC TID or octreotide LAR 20–30 mg IM or lanreotide 120 mg SC every 4 weeks. Dose and frequency may be further increased for symptom control as needed. Therapeutic levels of octreotide would not be expected to be reached for 10–14 days after LAR injection. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.

[b]The PROMID trial showed an antitumor effect of octreotide in advanced neuroendocrine tumors of the midgut.[3] The CLARINET trial showed an antitumor effect of lanreotide in advanced, well-differentiated metastatic grade 1 and grade 2 gastroenteropancreatic NETs.[4]

See Evidence Blocks on NET-10A

[c]If disease progression, treatment with octreotide or lanreotide should be continued in patients with functional tumors and may be used in combination with any of the systemic therapy options. For details on the administration of octreotide or lanreotide with 177Lu-dotatate, see NE-F.

[d]Safety and effectiveness of everolimus in the treatment of patients with carcinoid syndrome have not been established.

[e]See Principles of PRRT with 177Lu-dotatate (NE-F).

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY
Locoregionall Advanced and/or Metastatic Pancreatic Neuroendocrine Tumors

- Systemic therapy may not be appropriate for every patient with locoregionally advanced or metastatic disease. Consider multidisciplinary discussion to determine the best choice of treatment, including: observation for patients with stable disease with mild tumor burden, hepatic regional therapy for patients with liver-predominant metastases, cytoreductive surgery, or systemic therapy.
- Currently, there are no data to support a specific sequence of regional versus systemic therapy and no data to guide sequencing of the following systemic therapy options.
- There is no known role for systemic treatment in the adjuvant setting for PanNETs.
- Doses and schedules are subject to appropriate modifications depending on the circumstances.
- For management of hormone-related symptoms and complications with octreotide or lanreotide, see PanNET-1 through PanNET-5.

Pancreatic Neuroendocrine Tumors

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Locoregional Advanced Disease and/or Distant Metastases	• Everolimus[12] (category 1 for progressive disease) 10 mg by mouth, daily • Octreotide[a,b] LAR or lanreotide[a,4] (if SSR-positive imaging) • Sunitinib[13] (category 1 for progressive disease) 37.5 mg by mouth, daily • Temozolomide + capecitabine[14] (preferred when tumor response is needed for symptoms or debulking) • PRRT with 177Lu-dotatate (if SSR-positive imaging and progression on octreotide or lanreotide)[e]	• Cytotoxic chemotherapy options considered in patients with bulky, symptomatic, and/or progressive disease include: ◊ 5-FU + doxorubicin + streptozocin (FAS)[15] ◊ Streptozocin + doxorubicin[16] ◊ Streptozocin + 5-FU[17] ◊ FOLFOX (leucovorin + 5-FU + oxaliplatin)[18] ◊ CAPEOX (capecitabine + oxaliplatin)[19]	• None

See Evidence Blocks on NE-E (EB-1)

[a]For symptom control, octreotide 150–250 mcg SC TID or octreotide LAR 20–30 mg IM or lanreotide 120 mg SC every 4 weeks. Dose and frequency may be further increased for symptom control as needed. Therapeutic levels of octreotide would not be expected to be reached for 10–14 days after LAR injection. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.

[b]The PROMID trial showed an antitumor effect of octreotide in advanced neuroendocrine tumors of the midgut.[1] The CLARINET trial showed an antitumor effect of lanreotide in advanced, well-differentiated metastatic grade 1 and grade 2 gastroenteropancreatic NETs.[2]

[e]See Principles of PRRT with 177Lu-dotatate (NE-F).

References

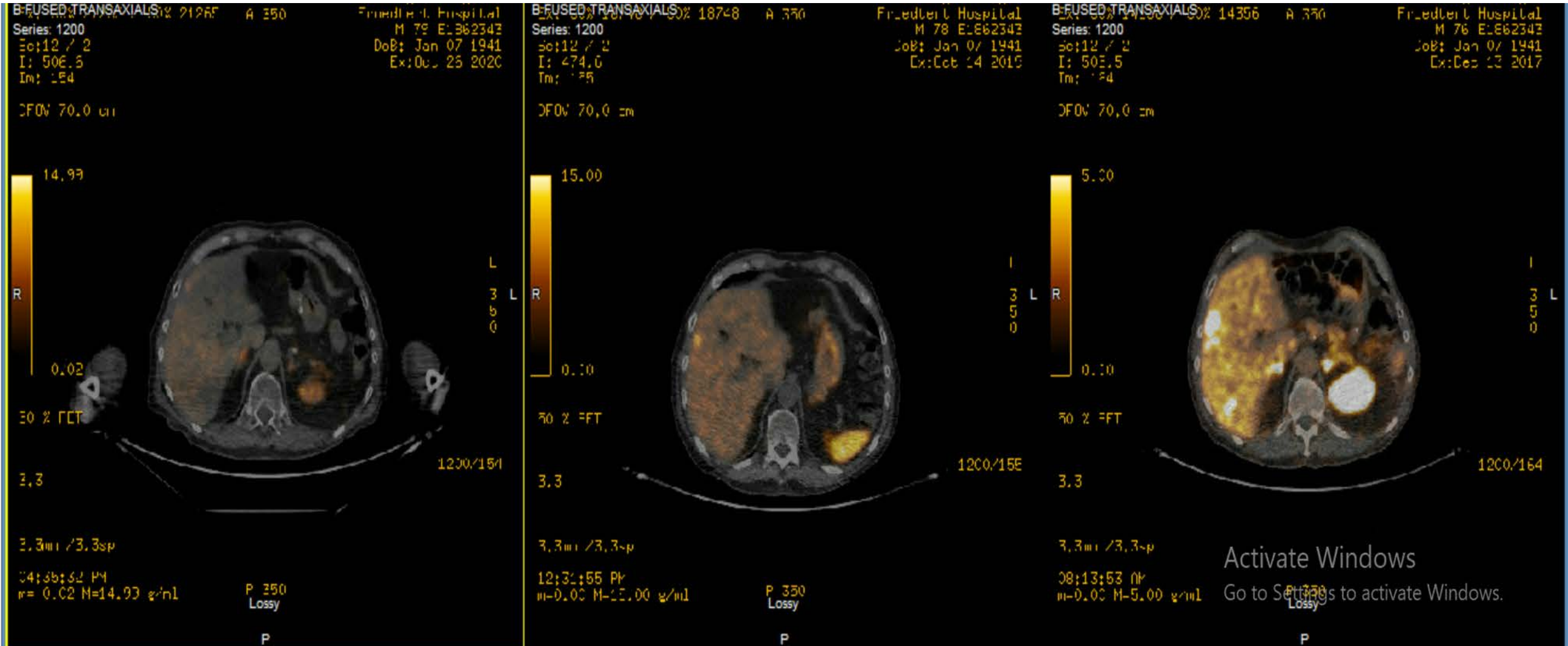
Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Real Life Example:

70 yo male dx in 2010

Ki67:15%

Prior TACE, everolimus, sunitinib, cape/tem



Froedtert&MCW

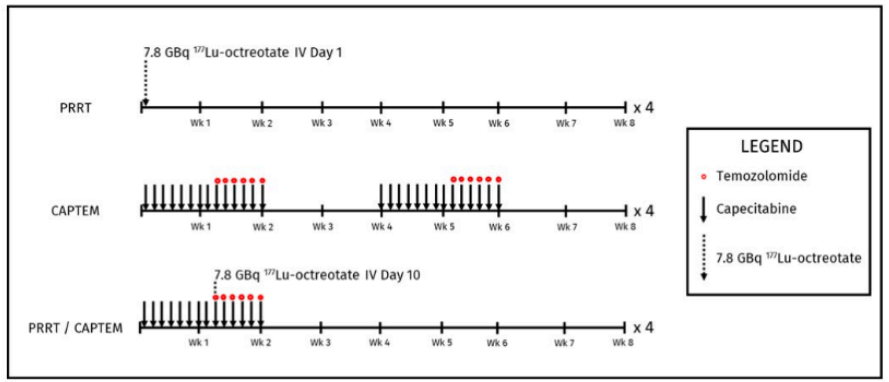
PRRT Experience

- Between May 2018 to March 2021
- Treated 58 patients
- Primary sites = pancreas (26), small bowel (20), paraganglioma/pheochromocytoma (6), others/unknown (6)
- Ki-67 = <2% to 40% (paraganglioma)
- Cycles of PRRT completed = all 4 cycles (42)
- Metastatic sites = liver, bones, adenopathy, lungs, peritoneum
- PFS (as of Mar 2021) = 30 patients did not progress at time of analysis (51.7%)
- Overall status (as of Mar 2021) = alive (40, 69%), deceased (14, 24%), hospice/unknown (4)
- Y-90 patients with subsequent PRRT have tolerated therapy well with only 1/11 having grade 2 hepatotoxicity

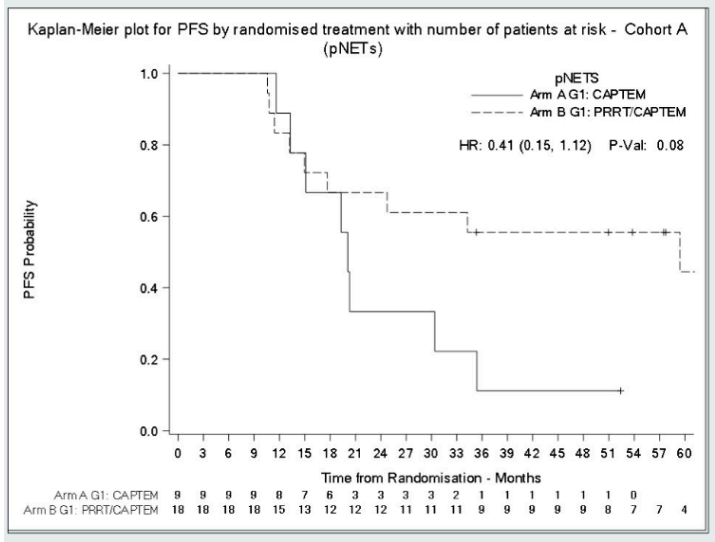
PRRT: Next steps

Combinations:

PRRT and Cape/Tem

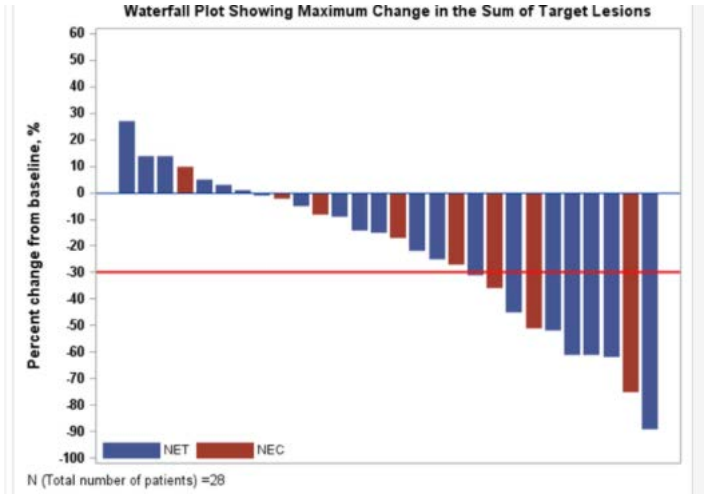


Objective Tumour Response Rate - pNETs			
Best response to treatment	**PRRT/CAPTEM (n=18)**	**CAPTEM (n=9)**	**Difference (95% CI)**
CR - Complete Response	0 (0%)	1 (11%)	
PR - Partial Response	13 (72%)	2 (22%)	
SD - Stable Disease	5 (28%)	6 (67%)	
PD - Progressive Disease	0 (0%)	0 (0%)	

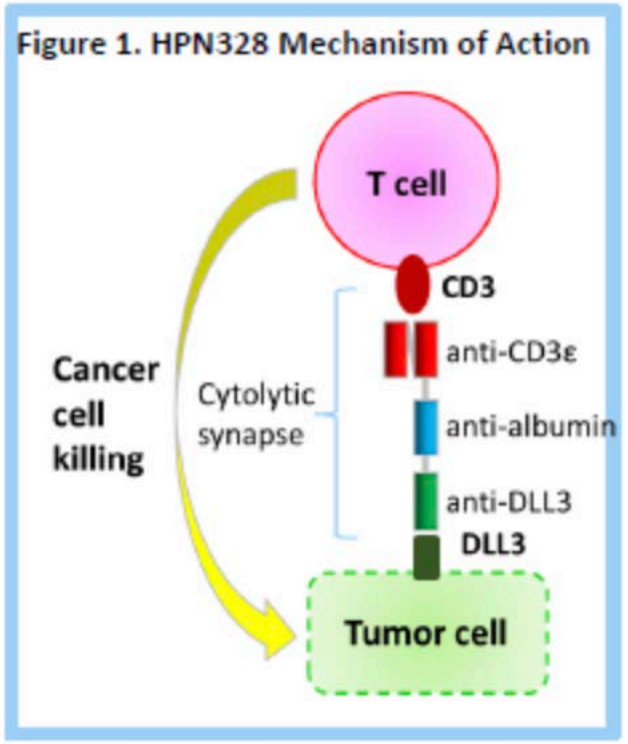


Immune-based Approaches

Temozolomide + Nivo

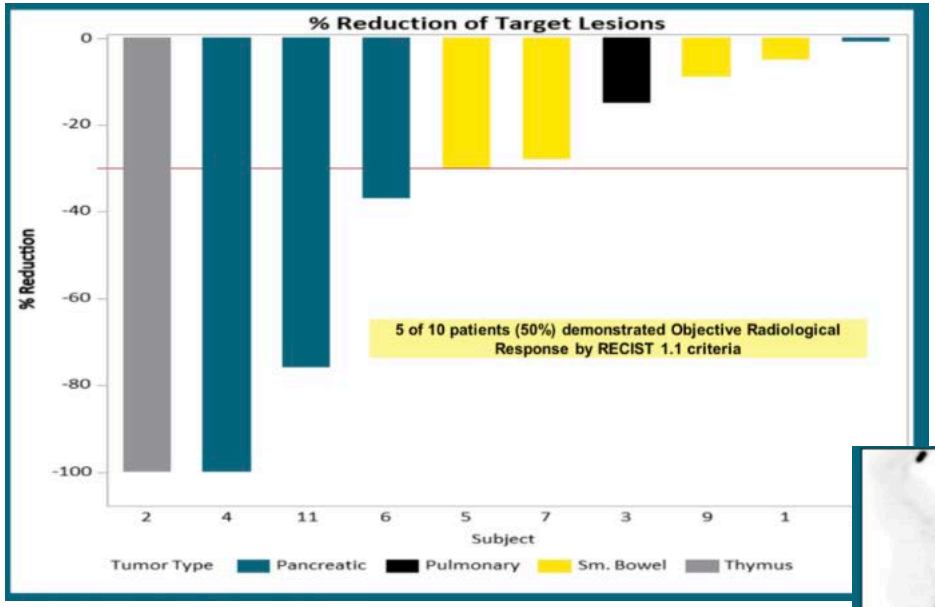


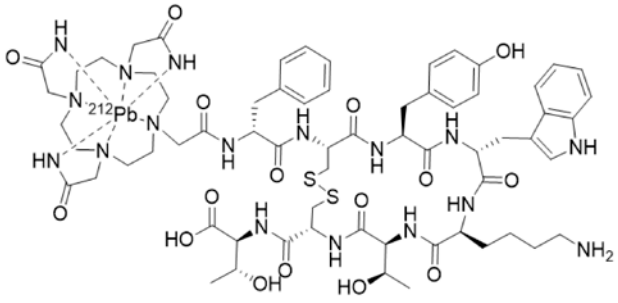
HPN328" T-Cell Engager

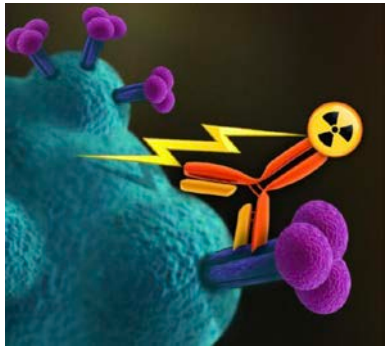


212Pb: Alpha Emitter in patients previously treated with Lu-DOTOTATE

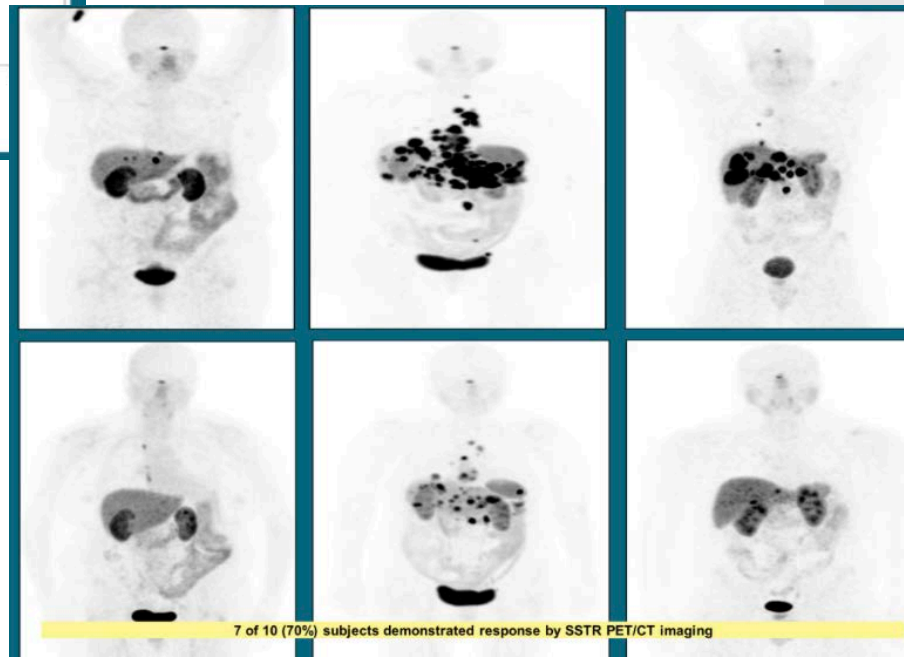
PRRT: Next Steps







Delpassand et al, ASCO 2022



Summary:

Neuroendocrine Cancers

- Heterogenous group of malignancies
- Requires multi-disciplinary care
- Choice and sequence of treatment options is complex and the data evolving
- PRRT represents an important advance, offering marked efficacy and limited toxicity
- Promising newer therapies are being developed including targeted therapies, radionuclides and immune-based treatments.

Alexandria Phan MD