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Solid Tumors

Gastroenteropancreatic Neuroendocrine Tumors: Addressing Diagnostic Challenges and Understanding Current and Emerging Therapies

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Disclosures

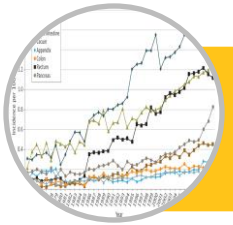
- **Namrata (Neena) Vijayvergia, MD, FACP:** Advisory Board—Exelixis, Pfizer; Grant/Research Support—Arcus, Exelixis, ITM, Puma, RayzeBio

Learning Objectives

- Define GEP-NETs and assess therapeutic challenges and unmet needs
- Describe strategies for the timely diagnosis and accurate assessment of GEP-NETs
- Evaluate the current treatment landscape and most recent clinical trial data associated with available and emerging therapies for GEP-NETs

GEP-NET = gastroenteropancreatic neuroendocrine tumor.

Objectives



Background and epidemiology

Clinical testing and biomarkers

Therapeutic options and advances

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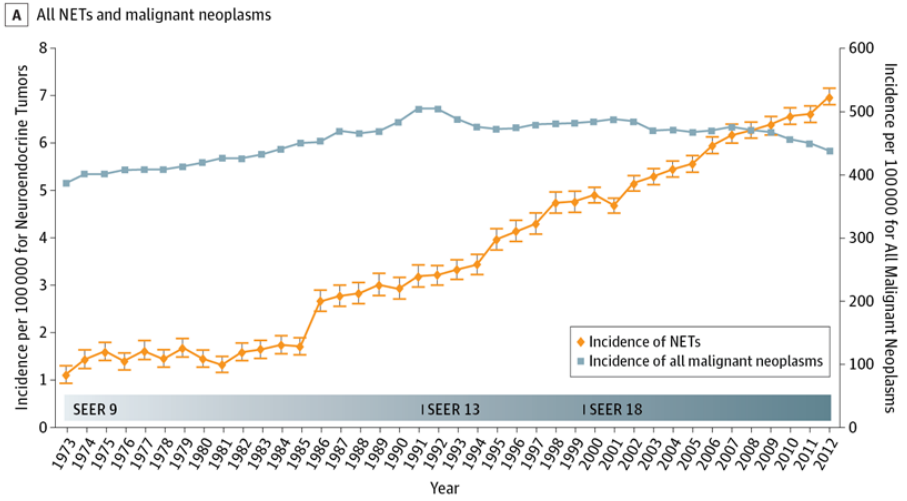
Background

- Increasing incidence (1.09 in 1973 to 6.98/100,000 in 2012, a 6.4-fold increase)
- > 90% of NENs are sporadic
- Remaining ~10% associated with familial syndromes
  - Multiple endocrine neoplasia 1 (MEN1) syndrome
  - Von Hippel-Lindau (VHL)
  - Tuberous sclerosis (TSC)
  - Neurofibromatosis (NF1)



NEN = neuroendocrine neoplasm.
Dasari A, et al. *JAMA Oncol*. 2017;3(10):1335-1342.

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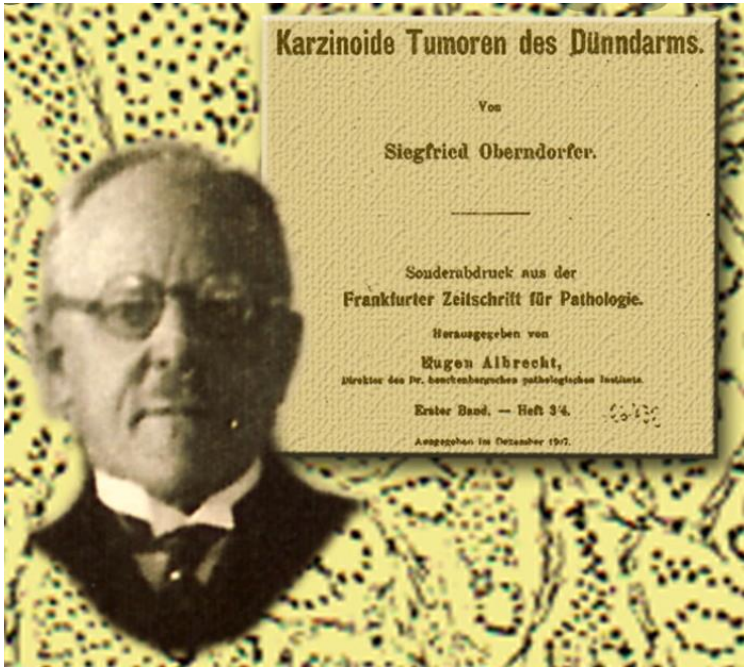
Nomenclature

How it started



How it's going

Differentiation	Ki67 index (%)	Mitotic rate (mitoses/2mm^2)
Well differentiated NENs		
NET Grade 1	<3	<2
NET Grade 2	3-20	2-20
NET Grade 3	>20	>20
Poorly differentiated NENs		
Neuroendocrine carcinoma (NEC) grade 3	>20	>20
Small cell type		
Large cell type		
Mixed neuroendocrine-non neuroendocrine neoplasm (MiNEN), well or poorly differentiated		
	Variable	Variable

Modlin IM, et al. *Hum Pathol*. 2004;35(12):1440-1451. Nagtegaal ID, et al. *Histopathology*. 2020;76(2):182-188.

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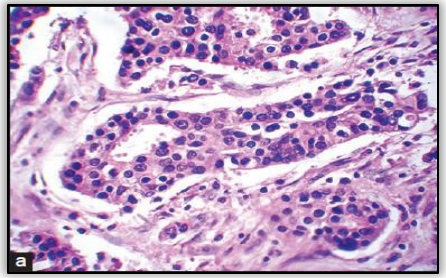
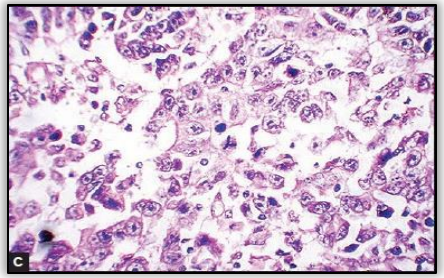
Pathology

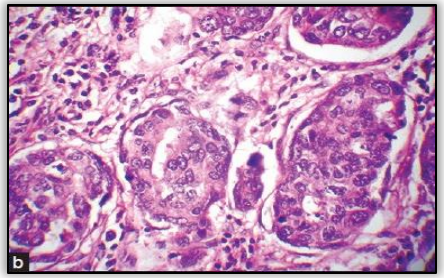
- Grade/differentiation
- Immunohistochemistry



Grade 1



Grade 2



Grade 3

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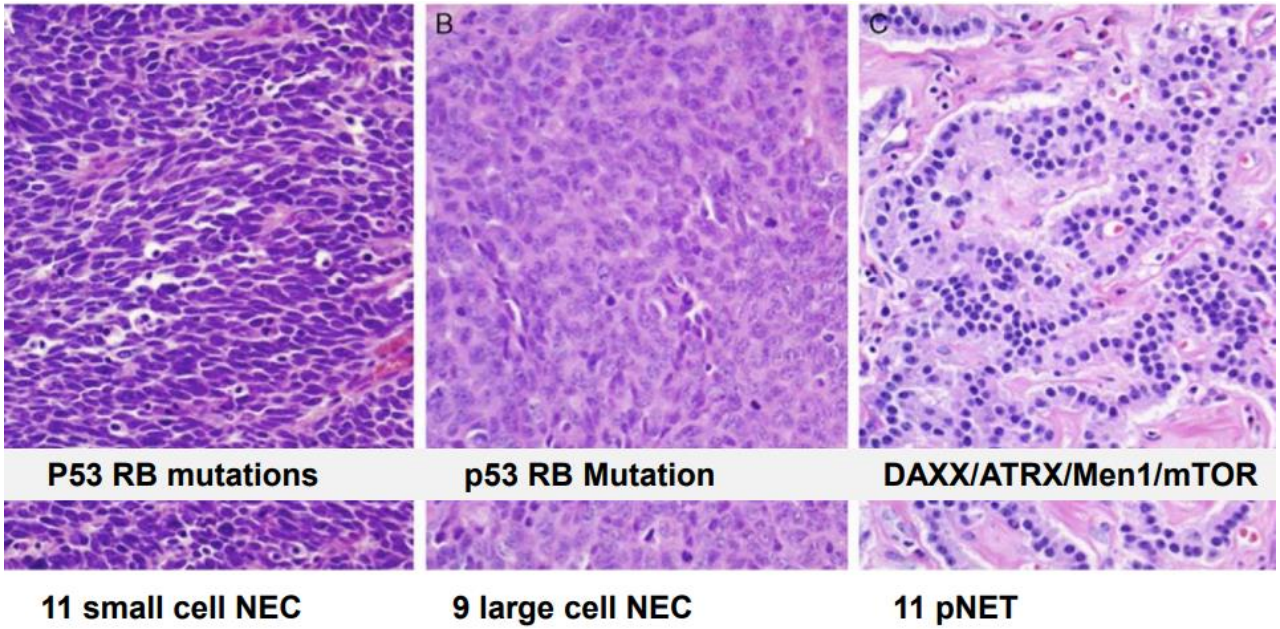
Genetic Differences in G3 Subtype



pNET = primitive neuroectodermal tumor.

Yachida S, et al. *Am J Surg Pathol*. 2012;36(2):173-184.

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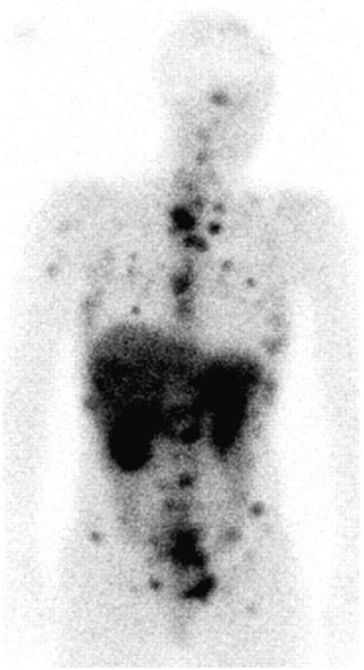
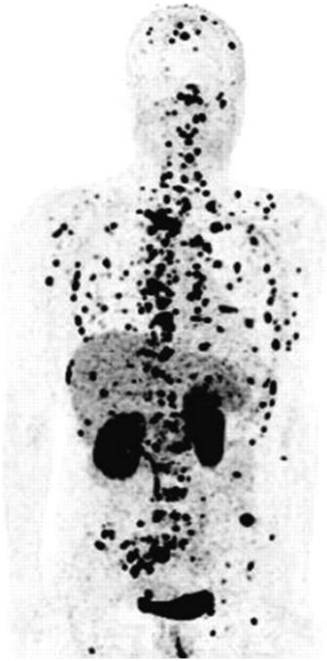
Diagnosis

How It Started…



^{111}In-DTPA-octreotide

And How It's Going



^{64}Cu-DOTATATE

Pfeifer A, et al. *J Nucl Med*. 2012;53(8):1207-1215.

Prospective Study of ^{68}Ga-DOTATATE Positron Emission Tomography/Computed Tomography for Detecting Gastro-Entero-Pancreatic Neuroendocrine Tumors and Unknown Primary Sites

Samira M. Sadowski, Vladimir Neychev, Corina Millo, Joanna Shih, Naris Nilubol, Peter Herscovitch, Karel Pacak, Stephen J. Marx, and Electron Kebebew

131 patients underwent ^{68}Ga-DOTATATE PET/CT, ^{111}In-pentetreotide SPECT along with anatomic imaging in blinded fashion.

SPECT = single-photon emission computed tomography.
Sadowski SM, et al. *J Clin Oncol*. 2016;34(6):588-596.

Improved Efficacy

- ^{68}Ga-DOTATATE PET/CT imaging detected 95%, and ^{111}In-pentetreotide SPECT/CT detected 31% of lesions

- ^{68}Ga-DOTATATE PET/CT **found a previously unknown primary** tumor in >25% patients

- In patients with **carcinoid symptoms** but negative biochemical testing, ^{68}Ga-DOTATATE PET/CT **detected lesions in 65.2% of patients**, 40% of which were detected neither by anatomic imaging nor by ^{111}In-pentetreotide SPECT/CT

Sadowski SM, et al. *J Clin Oncol*. 2016;34(6):588-596.

Appropriate Use Criteria

TABLE 3
Clinical Scenarios for SSTR PET

Scenario no.	Description	Appropriateness	Score
1	Initial staging after histologic diagnosis of NETs	Appropriate	9
2	Localization of primary tumor in patients with known metastatic disease but unknown primary	Appropriate	9
3	Selection of patients for SSTR-targeted PRRT	Appropriate	9
4	Staging NETs before planned surgery	Appropriate	8
5	Evaluation of mass suggestive of NET not amenable to endoscopic or percutaneous biopsy (e.g., ileal lesion, hypervascular pancreatic mass, mesenteric mass)	Appropriate	8
6	Monitoring of NETs seen predominantly on SSTR PET	Appropriate	8
7	Restaging of patients after the completion of PRRT	Appropriate	7
8	Evaluation of patients with biochemical evidence and symptoms of NET without evidence on CI and without prior histologic diagnosis of NET	Appropriate	7
9	Restaging at time of clinical or laboratory progression without progression on CI	Appropriate	7
10	New indeterminate lesion on CI, with unclear progression	Appropriate	7
11	Restaging of patients with NETs at initial follow-up after resection with curative intent	May be appropriate	6
12	Selection of patients with nonfunctional NETs for SSA treatment	May be appropriate	6
13	Monitoring in patients with NETs seen on both CI and SSTR PET with active disease and no clinical evidence of progression	May be appropriate	5

SSTR = somatostatin receptor; CI = conventional imaging.
Hope TA, et al. *J Nucl Med*. 2018;59(1):66-74.

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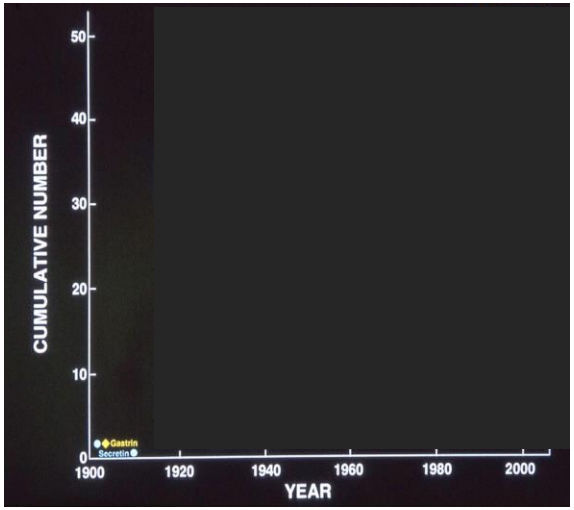
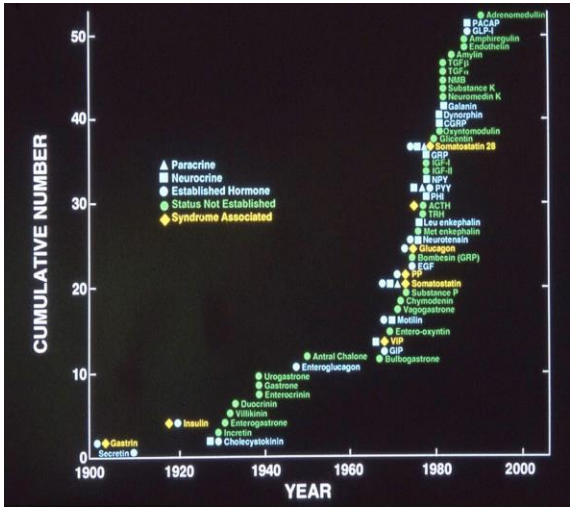
Diagnosis: Blood-Based Testing

How It Started…



And How It's Going



Substantial increase in identified peptides in the gut/pancreas due to specific antibodies and RIAs

RIA = radioimmunoassay.

Öberg K. *Endocrinol Metab Clin North Am*. 2018;47(3):711-731.

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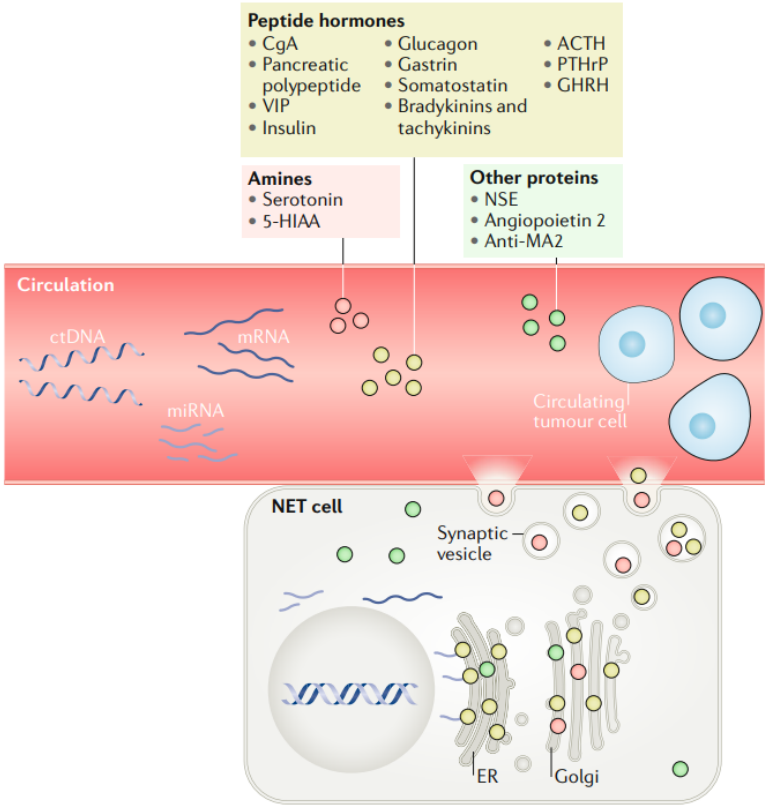
Figure Depicting Blood-Based Testing in NETs



Hofland J, et al. *Nat Rev Endocrinol*. 2018;14(11):656-669.

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Chromogranin A

- Most ordered liquid biomarker in NETs
- PROS: Correlates with disease burden if elevated
- CONS
  - Meta-analysis of 13 heterogeneous studies reported an overall sensitivity of 73%, a specificity of 95%
  - IBD, renal failure or gastric disorders, and PPI use reduce the sensitivity significantly
  - Testing not standardized between laboratories

IBD = irritable bowel disease; PPI = proton pump inhibitor.
Yang X, et al. *PLoS One*. 2015;10(4):e0124884. Molina R, et al. *Tumor Biol*. 2011;32(1):13-22.

Chromogranin A

Category 3 biomarker—Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

NCCN = National Comprehensive Cancer Network.

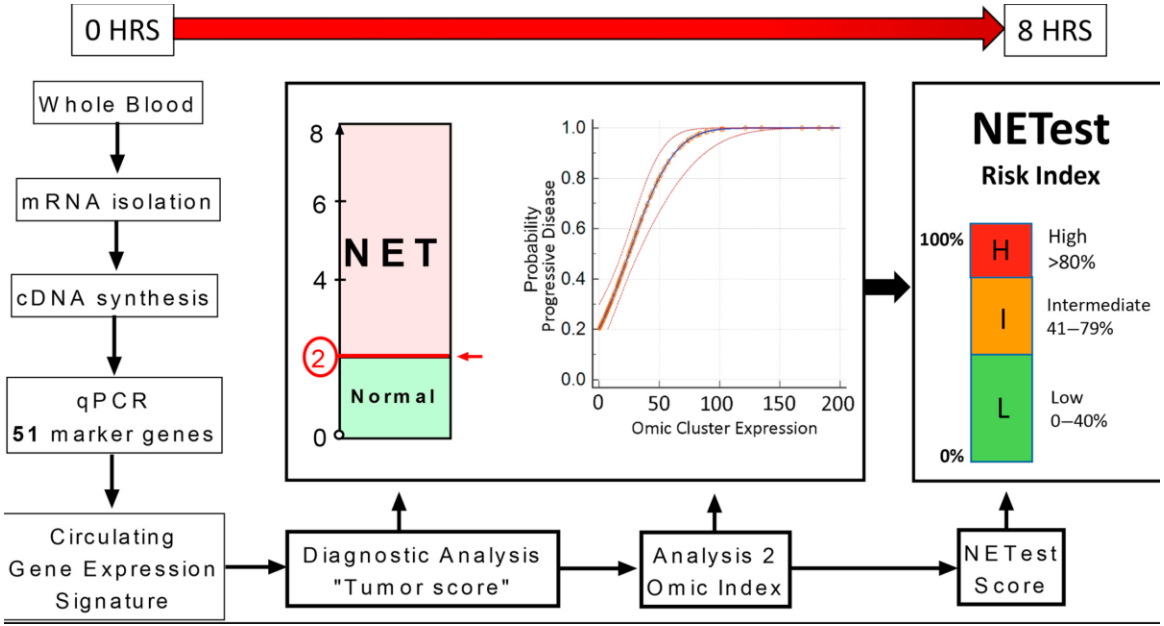
Diagnosis

- Urinary excretion of 5-hydroxyindoleacetic acid (24 hr)
  - 90% sensitivity and specificity in suspected carcinoid syndrome
  - Avoid caffeine, nicotine around the test
  - More accurate for midgut carcinoids
  - Good predictor for carcinoid heart disease

- VIP, gastrin, insulin, glucagon, ACTH—based on symptoms
- Pancreastatin
- Serotonin—not reliable

Sjöblom SM. *Scand J Gastroenterol*. 1988;23(7):779-787. Campana D, et al. *J Clin Oncol*. 2007;25(15):1967-1973.

NETest: New Kid on the Block



mRNA = messenger RNA; cDNA = complementary DNA; qPCR = quantitative polymerase chain reaction.

Modlin IM, et al. *Endocrinol Metab Clin North Am*. 2018;47(3):485-504.

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Diagnostic Accuracy: Early Data

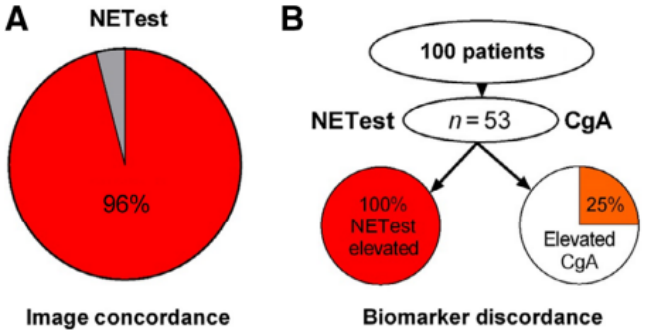
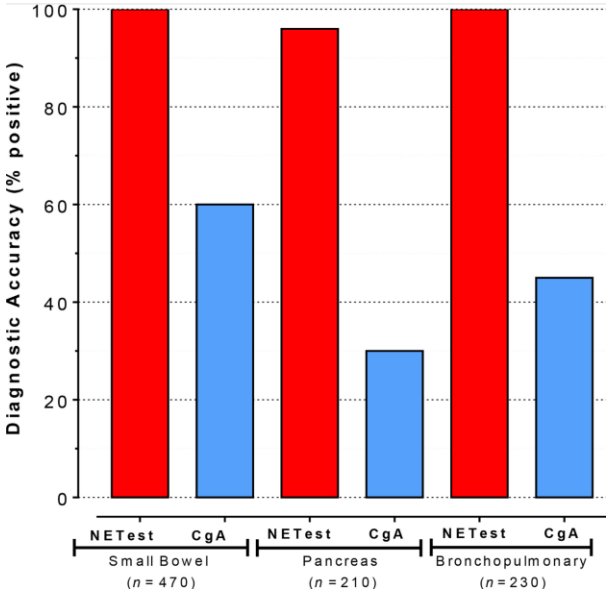


Figure 1. Diagnostic efficacy and concordance with imaging. **(A):** The NETest was concordant with image-confirmed disease in 96% of patients. **(B):** CgA was ordered for 53 of the 100 patients. The NETest was positive in all 53 (100%). CgA was positive in 25%. NETest positivity was significantly greater than CgA (p = .0004).
Abbreviation: CgA, chromogranin A.



Liu E, et al. *Oncologist*. 2019;24(6):783-790. Modlin IM, et al. *Endocrinol Metab Clin North Am*. 2018;47(3):485-504.

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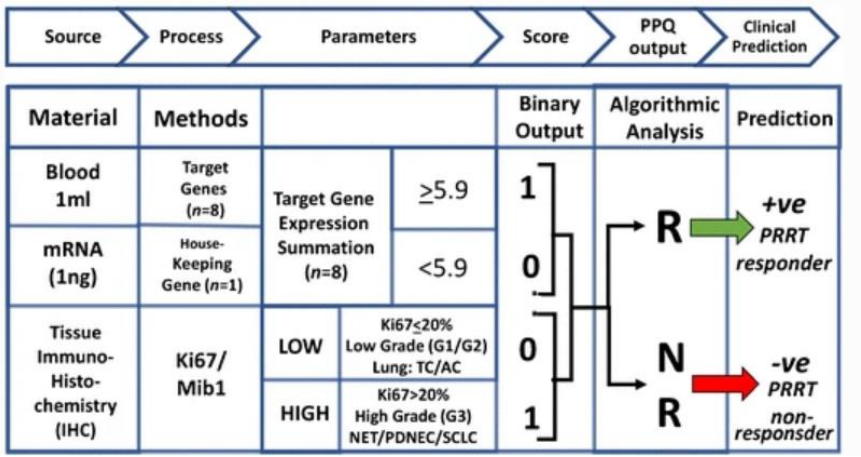
Positive Predictive Quotient (PPQ)

- Gene expression pattern different for responders vs non-responders to PRRT (growth factor signaling and metabolism regulating)
- Grade of tumor also predicting response to therapy
- Integration of gene expression and grading using logistic regression modelling

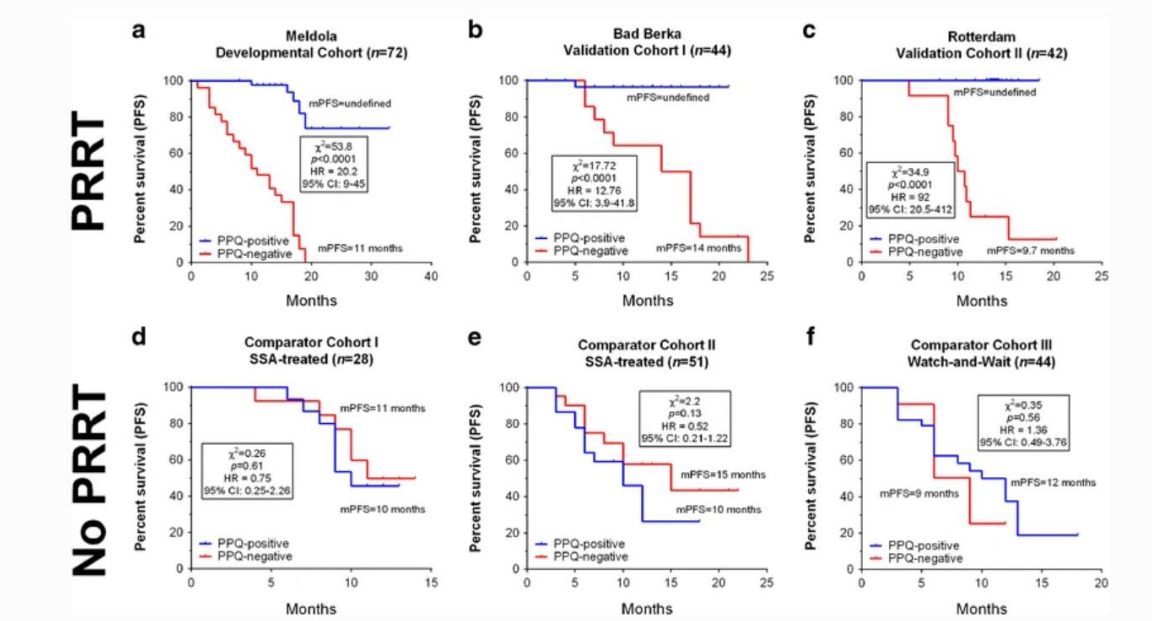


METHOD

PRRT = peptide receptor radionuclide therapy; TC = typical carcinoid; AC = atypical carcinoid; PDNEC = poorly differentiated neuroendocrine carcinoma; SCLC = small-cell lung cancer.

Bodei L, et al. *Eur J Nucl Med Mol Imaging*. 2018;45(7):1155-1169.

PFS in PPQ+ve and -ve cohorts



- Predictive accuracy of 94% for response to PRRT
- Median PFS was NR vs 11 m in PQ +ve versus PQ-ve patients

PFS = progression-free survival.

Bodei L, et al. *Eur J Nucl Med Mol Imaging*. 2018;45(7):1155-1169.

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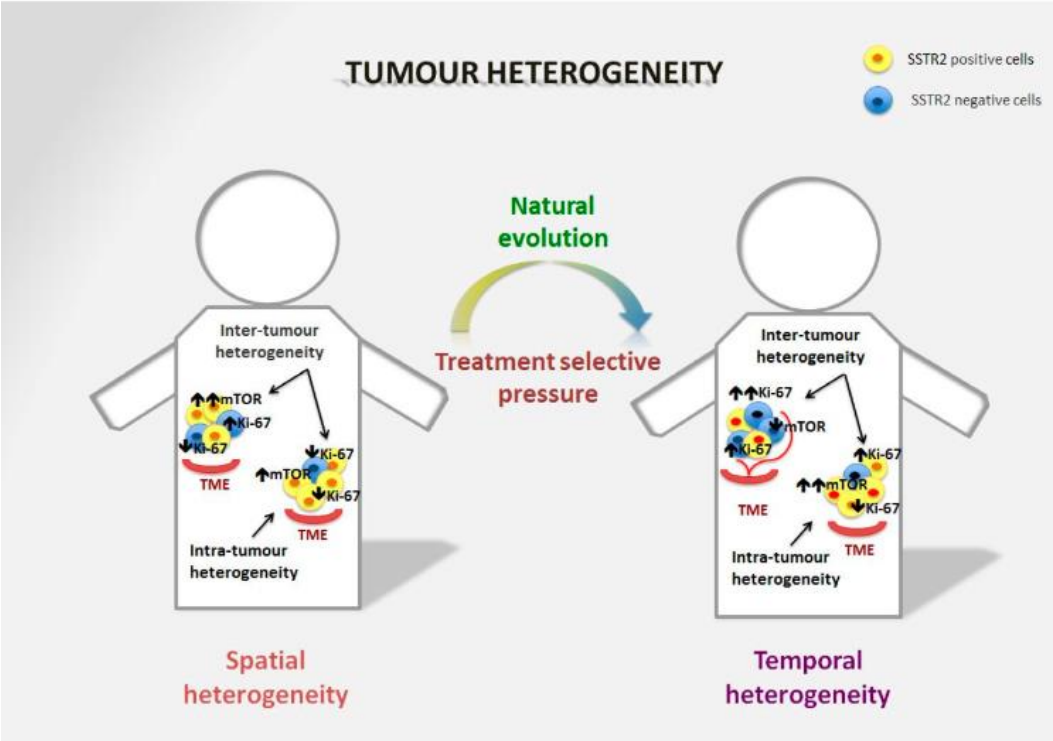
Therapeutic Challenge



Reccia I, et al. *Cancers*. 2023;15(6):1861.

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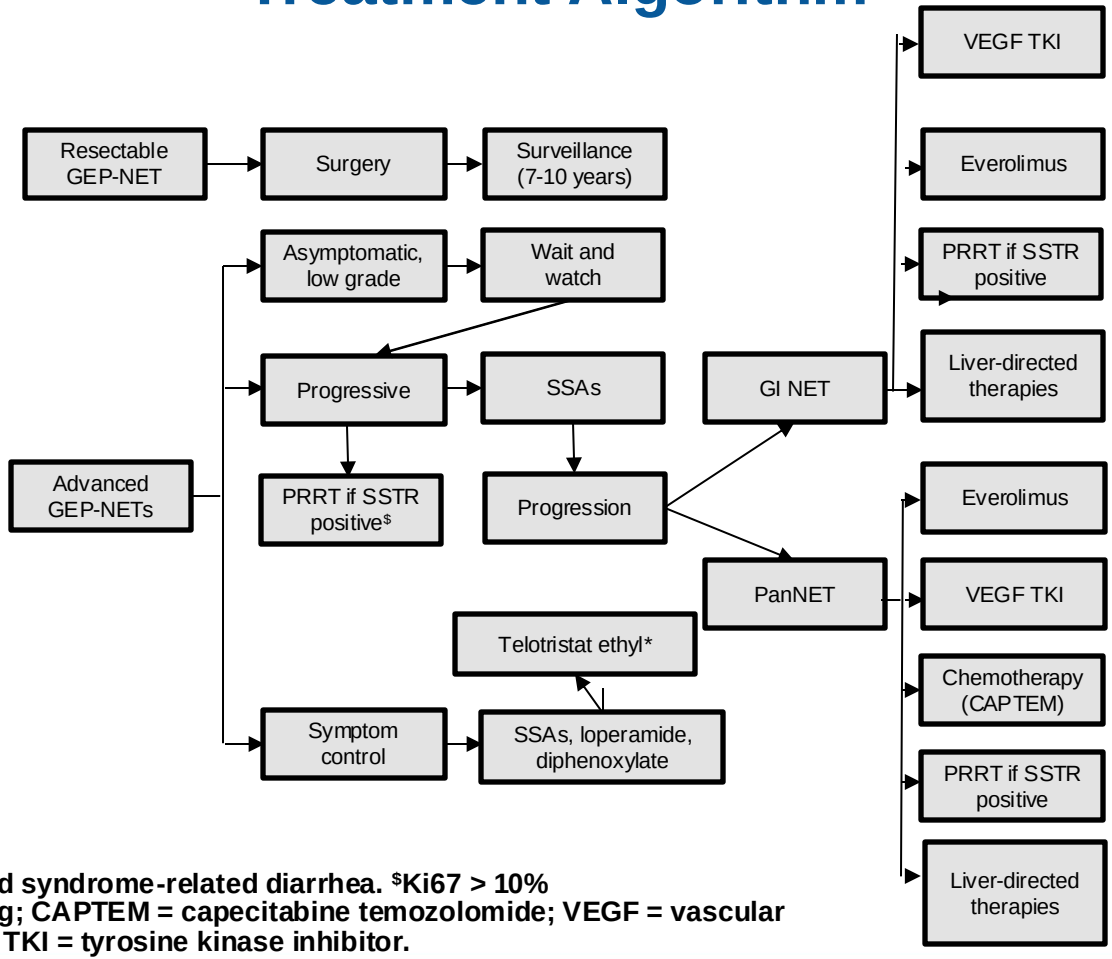
Treatment Algorithm



Only effective for carcinoid syndrome-related diarrhea. $Ki67 > 10%
SSA = somatostatin analog; CAPTEM = capecitabine temozolomide; VEGF = vascular endothelial growth factor; TKI = tyrosine kinase inhibitor.

Key Randomized Trials for Tumor Control in Gastroenteropancreatic (GEP) NENs

Drug	Target	# of pts	Tumor type	ORR (%)	Median TTP or PFS (months)	Reference
Resulted trials						
Octreotide	SSTR2,5	90	Midgut	2%	14.3	Rinke, et al.
Lanreotide	SSTR2,5	204	GEP-NET	NR	Not reached	Caplin, et al.
Sunitinib	VEGF TKI	171	PanNET	9%	11.4	Raymond, et al.
Everolimus	mTOR	410	PanNET	5%	11	Yao, et al.
Everolimus	mTOR	302	GI and lung NET	2%	11	Yao, et al.
^{177}Lu-DOTATATE (NETTER1/2)	SSTR2,5	229; 226	Midgut, GEPNETs	18%; 40%	28m; 22.8m	Strosberg, et al.; Singh, et al.
Capecitabine/ temozolomide	Chemotherapy	144	PanNET	33%	22.7	Kunz, et al.
Cabozantinib vs placebo (CABINET)	Oral TKI	395	GEP NENs and lung	4%, 18%	GI: 8.3 vs 3.2 PNET: 11 vs 3	Chan, et al., ESMO 2023

TTP = time to progression; ORR = objective response rate; GI = gastrointestinal.

Somatostatin Analogs

Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group

Anja Rinke, Hans-Helge Müller, Carmen Schade-Brittinger, Klaus-Jochen Klose, Peter Barth, Matthias Wied, Christina Mayer, Behnaz Aminossadati, Ulrich-Frank Pape, Michael Bläker, Jan Harder, Christian Arnold, Thomas Gress, and Rudolf Arnold

ORIGINAL ARTICLE

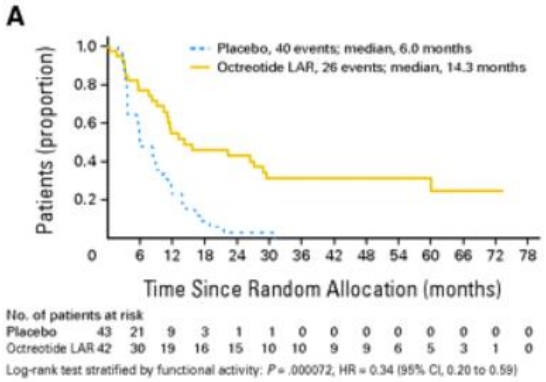
Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors

Martyn E. Caplin, D.M., Marianne Pavel, M.D., Jarosław B. Ćwikła, M.D., Ph.D., Alexandria T. Phan, M.D., Markus Raderer, M.D., Eva Sedláčková, M.D., Guillaume Cadiot, M.D., Ph.D., Edward M. Wolin, M.D., Jaume Capdevila, M.D., Lucy Wall, M.D., Guido Rindi, M.D., Ph.D., Alison Langley, M.Sc., Séverine Martinez, B.Sc., Joëlle Blumberg, M.D., and Philippe Ruszniewski, M.D., Ph.D., for the CLARINET Investigators*

Rinke A, et al. *Neuroendocrinology*. 2017;104(1):26-32. Caplin ME, et al. *N Engl J Med*. 2014;371(3):224-233.

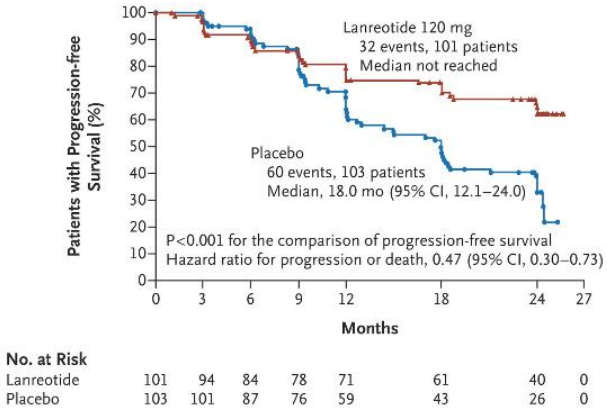
Primary Endpoint: PFS

PROMID trial



PFS 14.3 vs 6.0 m
HR 0.32 (0.19-0.55, p<0.001)

CLARINET trial



Lanreotide Autogel 120 mg
32 events / 101 patients
median, not reached

Placebo
60 events / 103 patients
median, 18.0 months [95% CI: 12.1, 24.0]

Rinke A, et al. *Neuroendocrinology*. 2017;104(1):26-32. Caplin ME, et al. *N Engl J Med*. 2014;371(3):224-233.

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Comparing PROMID and CLARINET

	PROMID	CLARINET
Somatostatin analog	Octreotide LAR	Lanreotide autogel
Sample size	85	205
Population	Midgut	All GEP-NETs
Ki 67/Grade	Ki67 < 3%	Ki 67 up to 10% (30% intermediate grade)
Functional/non-functional	Both	Non-functional tumors
Liver tumor burden	<10%	1/3rd with burden >25%

LAR = long-acting repeatable.

Rinke A, et al. *Neuroendocrinology*. 2017;104(1):26-32. Caplin ME, et al. *N Engl J Med*. 2014;371(3):224-233.

Radioligand Therapy

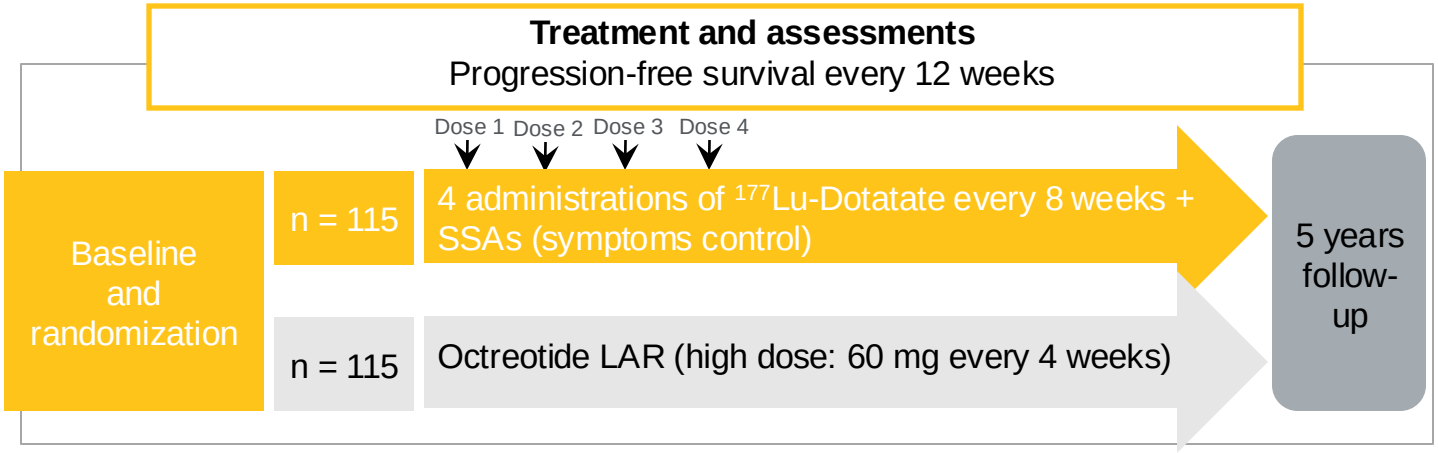
Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*

Strosberg J, et al. *N Engl J Med*. 2017;376(2):125-135.

NETTER-1 Study Objectives and Design

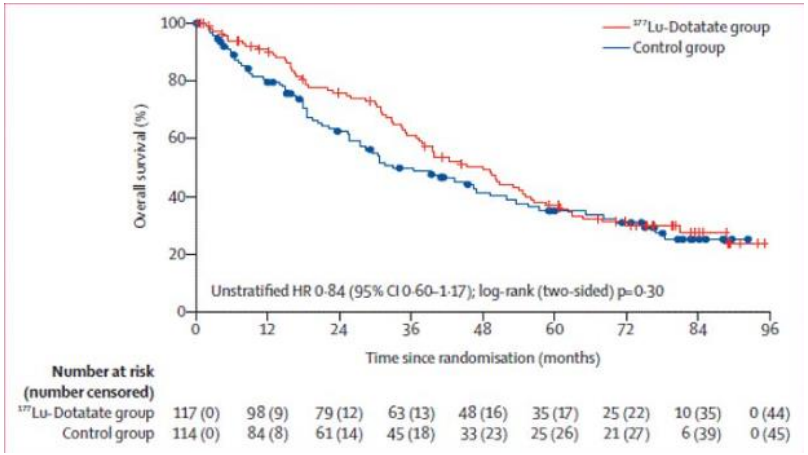
Aim	Evaluate the efficacy and safety of ^{177}Lu-Dotatate + SSAs (symptoms control) compared to octreotide LAR 60 mg in patients with inoperable, somatostatin receptor-positive, midgut NET, progressive under octreotide LAR 30 mg
Design	International, multicenter, randomized, comparator-controlled, parallel-group

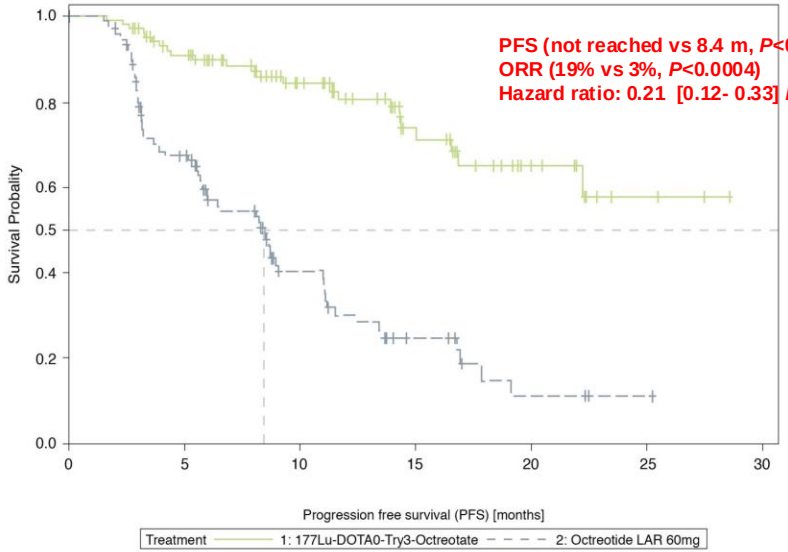


Strosberg JR, et al. *N Engl J Med*. 2017;376(2):125-135.

Primary Endpoint: PFS

Overall Survival





Strosberg JR, et al. *N Engl J Med*. 2017;376(2):125-135. Strosberg JR, et al. *Lancet Oncol*. 2021;22(12):1752-1763.

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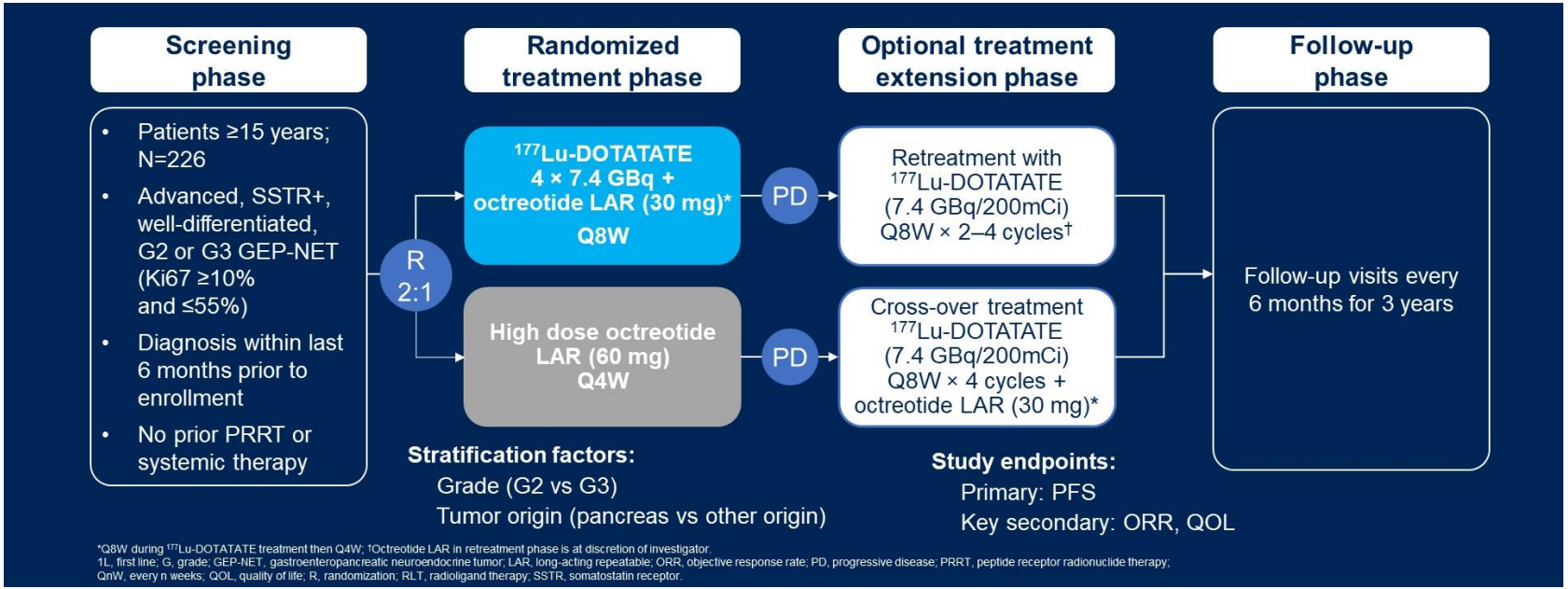
NETTER-2 (NCT03972488) Is the First Randomized Trial to Evaluate RLT as 1L Treatment in Any Solid Tumor



Singh S, et al. *J Clin Oncol*. 2024;42(Suppl 3):LBA588.

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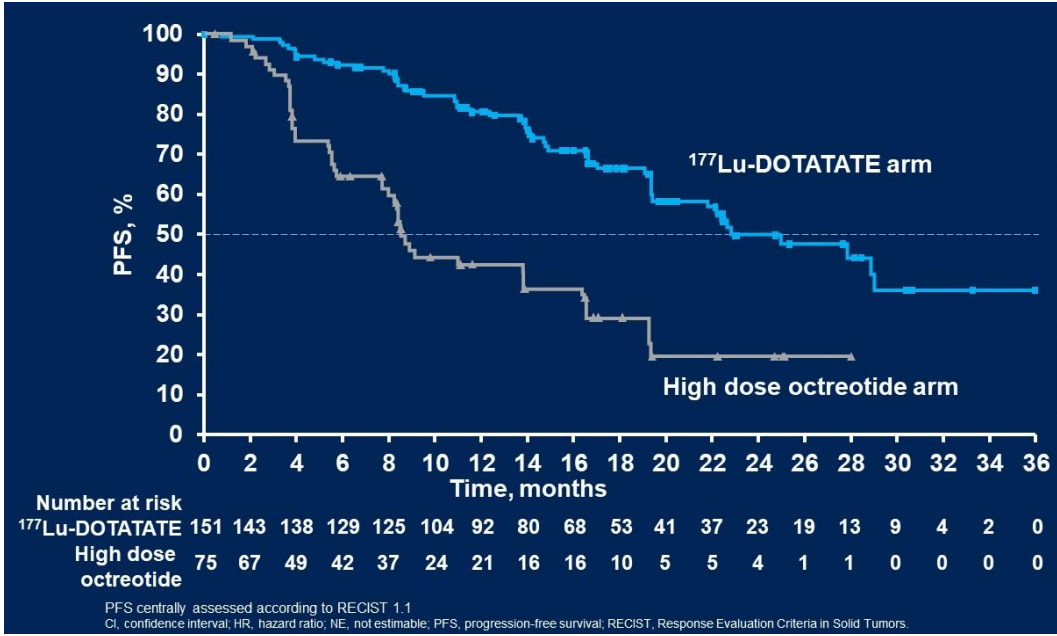
^{177}Lu-DOTATATE Showed Significant Improvement in Primary PFS Endpoint



PFS centrally assessed according to RECIST 1.1

CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

	^{177}Lu-DOTATATE arm n=151	High dose octreotide arm 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)

72% reduction in the risk of disease progression or death in the ^{177}Lu-DOTATATE arm versus the high dose octreotide arm

RESPONSE RATE over 40% in this subgroup of patients.
Singh S, et al. *J Clin Oncol*. 2024;42(Suppl 3):LBA588.

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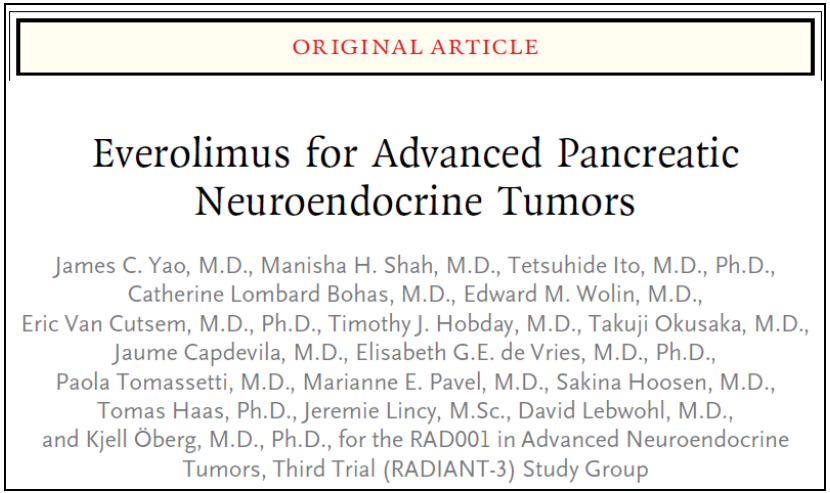
NETTER-1 Toxicities

Adverse Events	^{177}Lu-Dotatate (N=111)		Octreotide LAR (N=110)	
	All grades	Grade 3-4	All grades	Grade 3-4
	%	%	%	%
Nausea	**59%**	**4%**	**12%**	**2%**
Vomiting	**47%**	**7%**	**10%**	**0%**
Diarrhea	29%	3%	19%	2%
Abdominal pain	26%	3%	26%	5%
Abdominal distension	13%	0%	14%	0%
Fatigue/asthenia	40%	2%	25%	2%
Edema peripheral	14%	0%	7%	0%
Thrombocytopenia	**25%**	**2%**	**1%**	**0%**
Lymphopenia	**18%**	**9%**	**2%**	**0%**
Anemia	**14%**	**0%**	**5%**	**0%**
Leukopenia	**10%**	**1%**	**1%**	**0%**
Neutropenia	**5%**	**1%**	**1%**	**0%**

Strosberg J, et al. *N Engl J Med*. 2017;376(2):125-135.

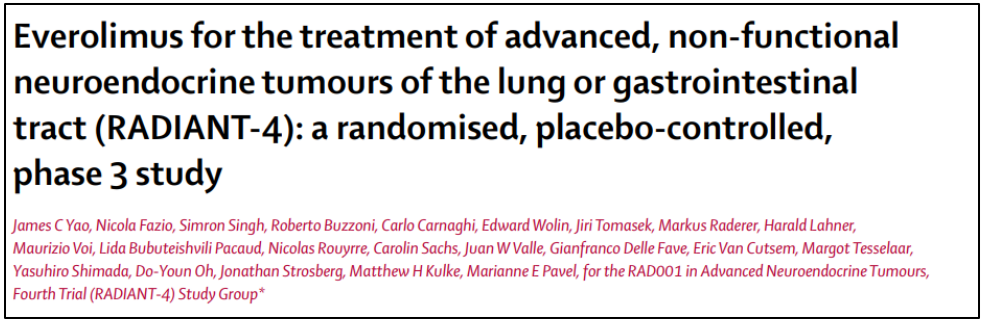
mTOR Inhibitors



ORIGINAL ARTICLE

Everolimus for Advanced Pancreatic Neuroendocrine Tumors

James C. Yao, M.D., Manisha H. Shah, M.D., Tetsuhide Ito, M.D., Ph.D., Catherine Lombard Bohas, M.D., Edward M. Wolin, M.D., Eric Van Cutsem, M.D., Ph.D., Timothy J. Hobday, M.D., Takuji Okusaka, M.D., Jaume Capdevila, M.D., Elisabeth G.E. de Vries, M.D., Ph.D., Paola Tomassetti, M.D., Marianne E. Pavel, M.D., Sakina Hoosen, M.D., Tomas Haas, Ph.D., Jeremie Lincy, M.Sc., David Lebwohl, M.D., and Kjell Öberg, M.D., Ph.D., for the RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group

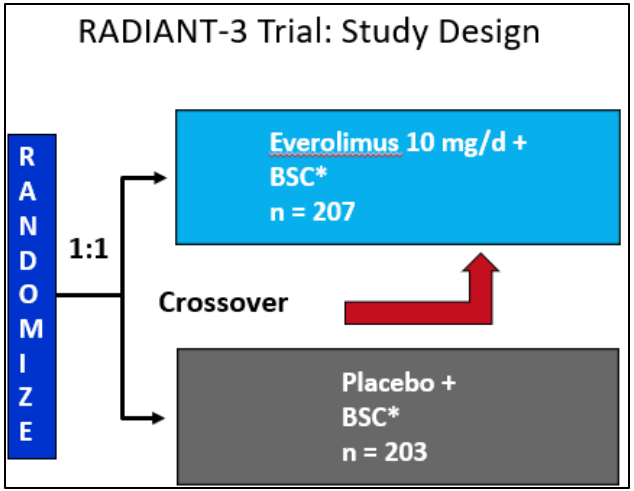


Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study

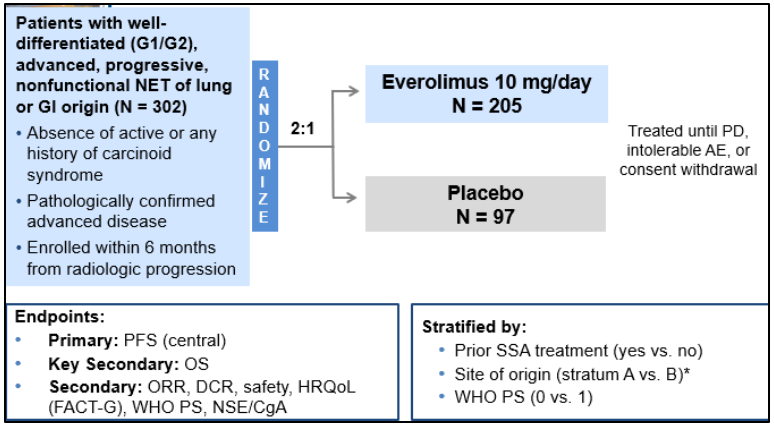
*James C Yao, Nicola Fazio, Simron Singh, Roberto Buzzoni, Carlo Carnaghi, Edward Wolin, Jiri Tomasek, Markus Raderer, Harald Lahner, Maurizio Voi, Lida Bubuteishvili Pacaud, Nicolas Rouyrre, Carolin Sachs, Juan W Valle, Gianfranco Delle Fave, Eric Van Cutsem, Margot Tesselaar, Yasuhiro Shimada, Do-Youn Oh, Jonathan Strosberg, Matthew H Kulke, Marianne E Pavel, for the RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4) Study Group**

Yao JC, et al. *N Engl J Med*. 2011;364(6):514-523. Yao JC, et al. *Lancet*. 2016;387(10022):968-977.

RADIANT-3



RADIANT-4

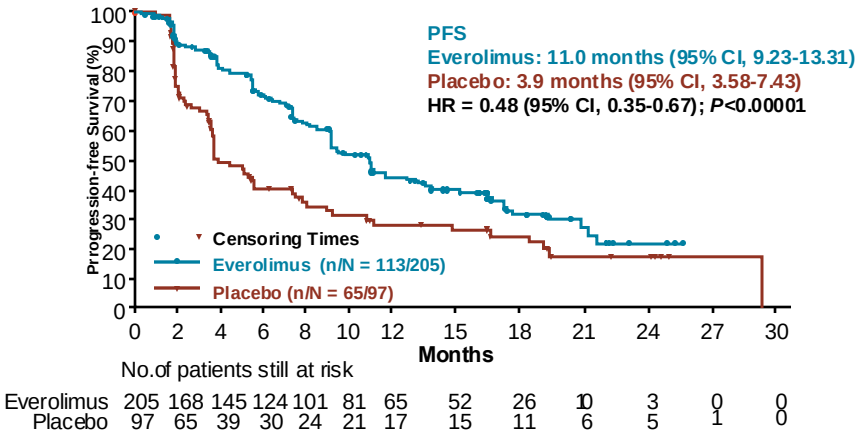


BSC = best supportive care; PD = progressive disease; AE = adverse event; DCR = disease control rate; HRQoL = health-related quality of life; FACT-G = Functional Assessment of Cancer Therapy—General; WHO PS = World Health Organization performance status.

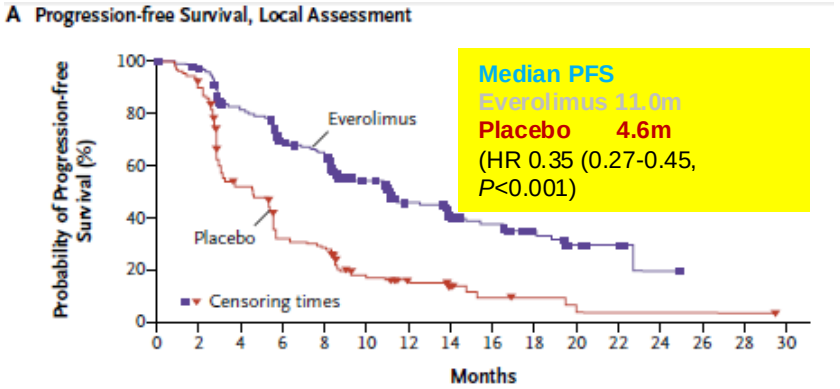
Yao JC, et al. Presented at: 12th World Congress on Gastrointestinal Cancer; June 30-July 3, 2010; Barcelona, Spain. Yao JC, et al. Presented at: 2015 European Cancer Congress; September 25-29, 2015; Vienna, Austria. Abstract 5LBA.

Primary Endpoint: PFS by Central Review

GI NETs



PanNETs



Yao JC, et al. *N Engl J Med*. 2011;364(6):514-523. Yao JC, et al. *Lancet*. 2016;387(10022):968-977.

Great Debates Solid Tumors

VEGF TKIs

Phase 3 Trial of Cabozantinib to Treat Advanced Neuroendocrine Tumors

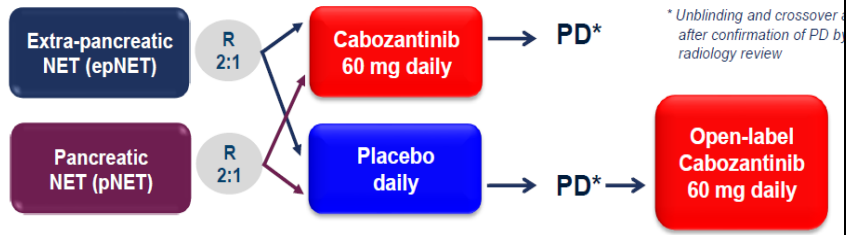
Jennifer A. Chan, M.D., M.P.H., Susan Geyer, Ph.D., Tyler Zemla, M.S., Michael V. Knopp, M.D., Ph.D., Spencer Behr, M.D., Sydney Pulsipher, M.P.H., Fang-Shu Ou, Ph.D., Amylou C. Dueck, Ph.D., Jared Acoba, M.D., Ardaman Shergill, M.D., Edward M. Wolin, M.D., Thorvardur R. Halfdanarson, M.D., Bhavana Konda, M.D., M.P.H., Nikolaos A. Trikalinos, M.D., Bernard Tawfik, M.D., Nitya Raj, M.D., Shagufta Shaheen, M.D., Namrata Vijayvergia, M.D., Arvind Dasari, M.D., Jonathan R. Strosberg, M.D., Elise C. Kohn, M.D., Matthew H. Kulke, M.D., Eileen M. O'Reilly, M.D., and Jeffrey A. Meyerhardt, M.D., M.P.H.

Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors

Eric Raymond, M.D., Ph.D., Laetitia Dahan, M.D., Ph.D., Jean-Luc Raoul, M.D., Ph.D., Yung-Jue Bang, M.D., Ivan Borbath, M.D., Ph.D., Catherine Lombard-Bohas, M.D., Juan Valle, M.D., Peter Metrakos, M.D., C.M., Denis Smith, M.D., Aaron Vinik, M.D., Ph.D., Jen-Shi Chen, M.D., Dieter Hörsch, M.D., Pascal Hammel, M.D., Ph.D., Bertram Wiedenmann, M.D., Ph.D., Eric Van Cutsem, M.D., Ph.D., Shem Patyna, Ph.D., Dongrui Ray Lu, M.Sc., Carolyn Blanckmeister, Ph.D., Richard Chao, M.D., and Philippe Ruszniewski, M.D.

Chan JA, et al. *N Engl J Med*. 2025;392(7):653-665. Raymond E, et al. *N Engl J Med*. 2011;364(6):501-513.

CABINET Trial Study Design



Stratification factors:

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

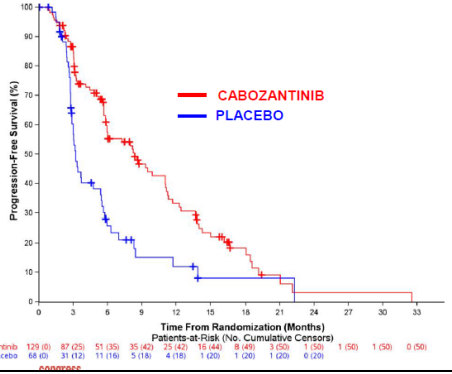
Study Endpoints:

- **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

In the recent Phase 3 CABINET clinical trial, treatment with cabozantinib reduced the risk of disease progression or death by 50% when compared with placebo in patients with gastrointestinal NETs.

epNET Cohort: Progression-Free Survival (Local Review)

ORR 4%



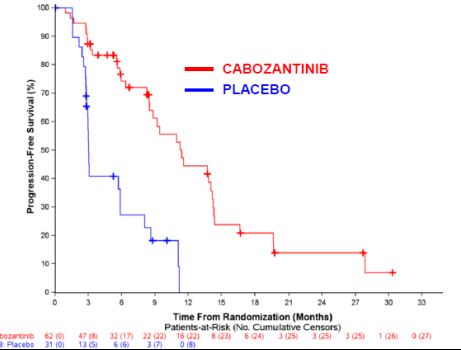
Stratified HR = 0.45
(95% CI: 0.30 – 0.66)
log-rank p<0.0001

Median PFS:
Cabozantinib = 8.3 months
Placebo = 3.2 months

Median follow-up: 13.9 months

pNET Cohort: Progression-Free Survival (Local Review)

ORR 18%



Stratified HR = 0.27
(95% CI: 0.14 – 0.49)
log-rank p<0.0001

Median PFS:
Cabozantinib = 11.4 months
Placebo = 3.0 months

Median follow-up: 16.7 months

epNET = extra-pancreatic NET.

Chan J, et al. *Ann Oncol*. 2023;34(Suppl 2):S1254-S1335.

Sunitinib in Pancreatic NETs

Inclusion criteria

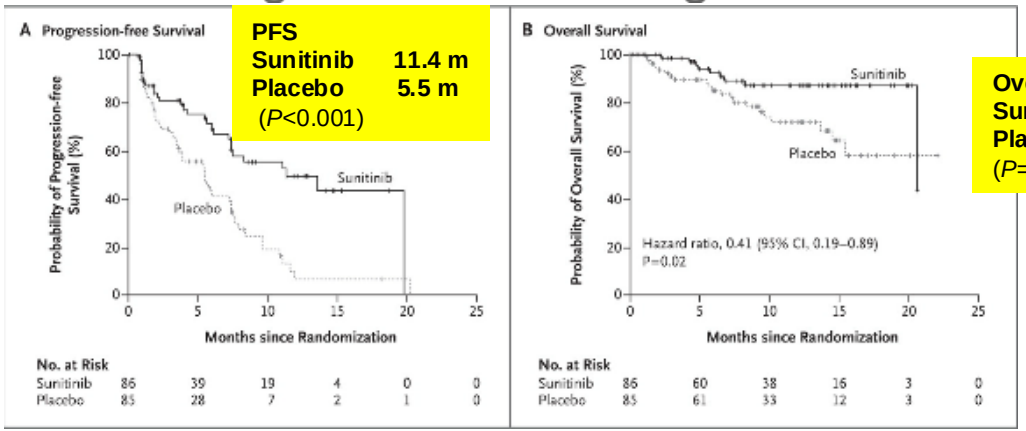
- pNET
- Well differentiated (OMS)
- Progressive within 12 months (RECIST)
- Not amenable to curative treatment
- **Stratification :**
  Europe. Asia. America. Australia

R

Sunitinib 37.5 mg/d
***p.o.* continuous**
(n=86)

Placebo
(n=85)

Primary objective → Progression free survival



PFS
Sunitinib 11.4 m
Placebo 5.5 m
(*P*<0.001)

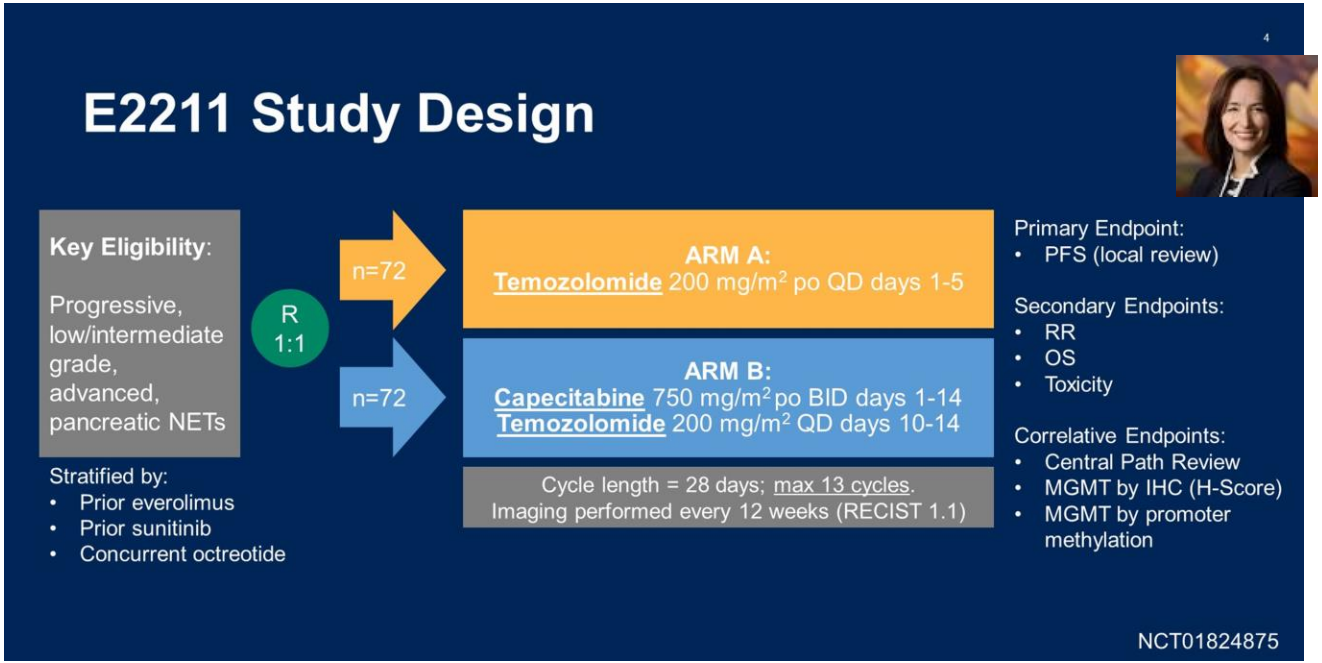
Overall Survival
Sunitinib 30.5 m
Placebo 24.4 m
(*P*=0.19)

OMS = World Health Organization.

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

Great Debates Solid Tumors

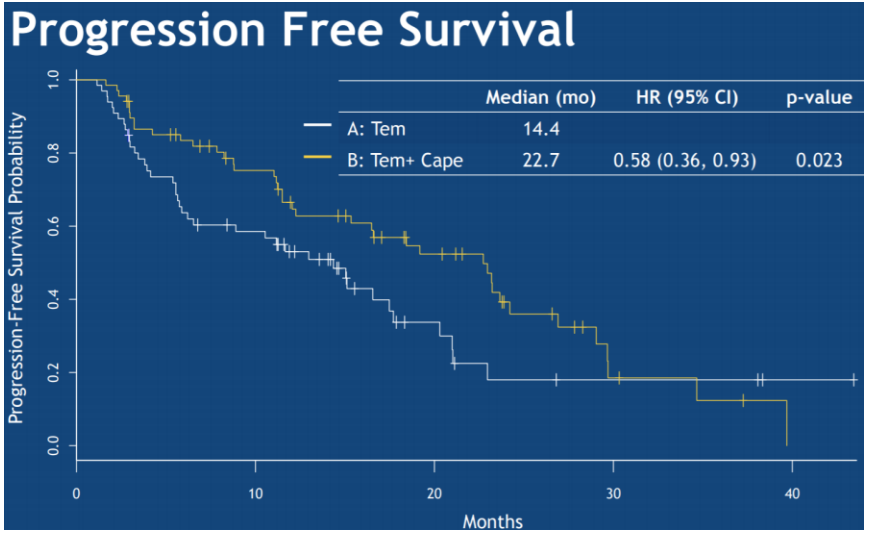
First Prospective, Multicenter, Randomized Trial of Capecitabine and Temozolomide in Advanced Pancreatic NETs

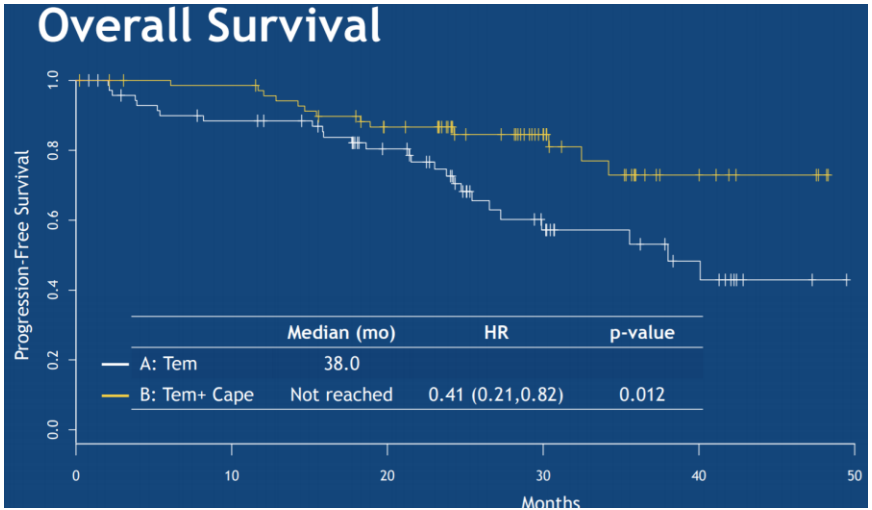


RR = response rate; IHC = immunohistochemistry.

Kunz PL, et al. *J Clin Oncol*. 2022;41(7):1359-1369.

ORR: 27.8% vs 33.3% *P*=0.47

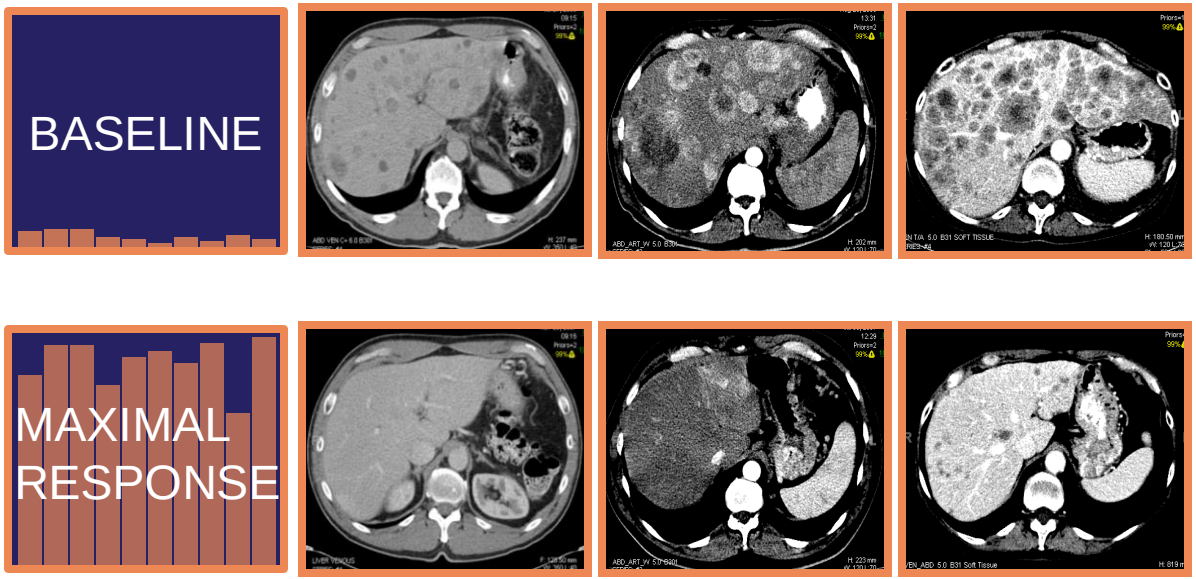




Kunz PL, et al. *J Clin Oncol*. 2022;41(7):1359-1369.

Great Debates
Solid Tumors

Examples of Response with CAPTEM



Strosberg JR, et al. *Cancer*. 2011;117(2):268-275.

Great Debates Solid Tumors

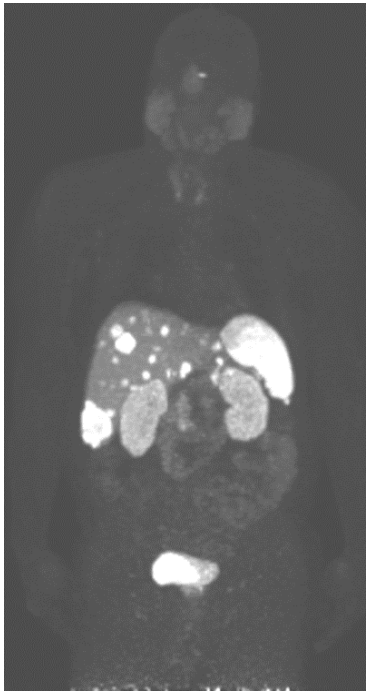
Clinical Scenario

59 y.o. male who presented with 4 months of severe diarrhea, heartburn, and vomiting. His heartburn was so bad that he describes taking baking soda up to three times daily to help with acid reflux.

- CT scans showed multiple liver mets and 2 lesions in the tail of the pancreas
- Liver biopsy showed WD, grade 3 NET (WHO grade 3 based on Ki-67 of 27%), >20 lesions
- He was started on an SSA by his local oncologist and referred to a tertiary center due to rapid disease progression and persistence of symptoms

What would you consider next for treatment?

1. PRRT
2. CAPTEM
3. VEGF TKI
4. Everolimus



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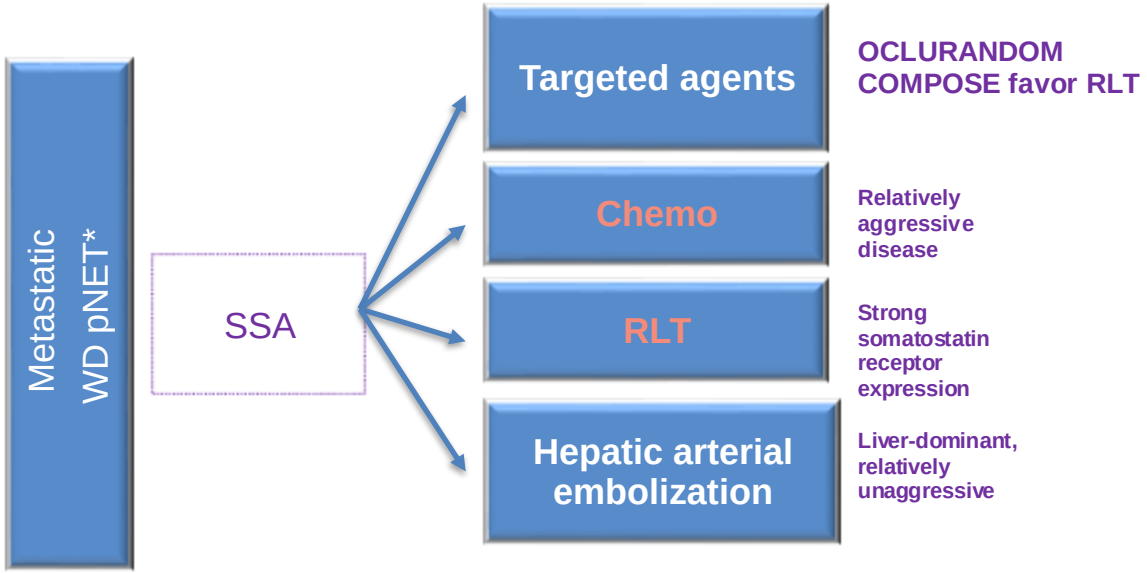
WD = well-differentiated; WHO = World Health Organization.

Sequencing Challenging



And next?

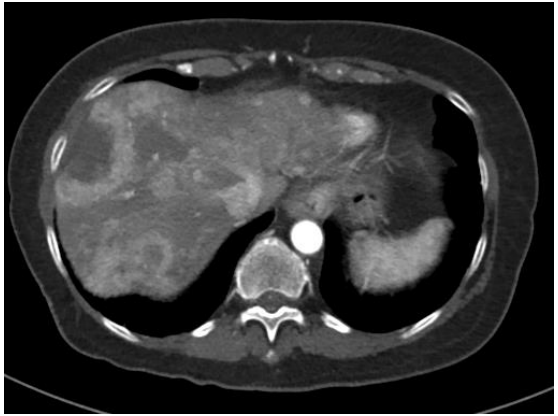
RLT = radioligand therapy.

Chauhan A, et al. *Cancers (Basel)*. 2022 Oct 26;14(21):5248. Baudin E, et al. *Ann Oncol*. 2022;33(Suppl 7):S410-S416. Capdevila J, et al. Presented at: 22nd Annual European Neuroendocrine Tumor Society (ENETS) Conference; March 5-7, 2025; Krakow, Poland. Abstract L01.

What Should Be Taken into Consideration?

Considerations

- Grade
- Volume of disease
- Symptoms
- Need for response



- Biomarkers of response for RLT and CAPTEM
- Prospective comparison

G3 NENs

- Well-differentiated
- Poorly differentiated

How to Treat G3 NENs

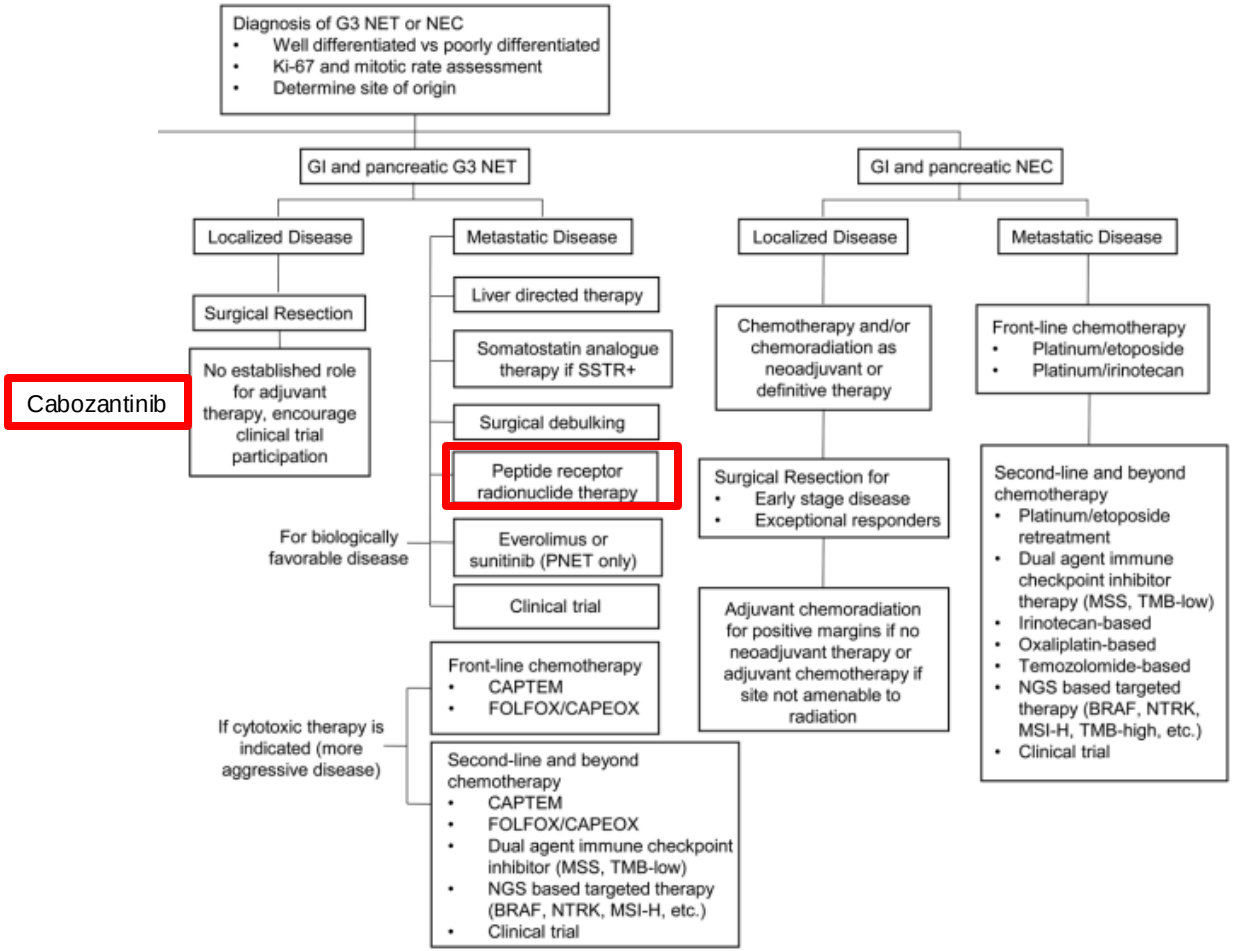
GUIDELINES AND GUIDANCE

Expert Consensus Practice Recommendations of the North American Neuroendocrine Tumor Society for the management of high grade gastroenteropancreatic and gynecologic neuroendocrine neoplasms

Jennifer R Eads[1], Thorvardur R Halfdanarson[2], Tim Asmis[3], Andrew M Bellizzi[4], Emily K Bergsland[5], Arvind Dasari[6], Ghassan El-Haddad[7], Michael Frumovitz[8], Joshua Meyer[9], Erik Mittra[10], Sten Myrehaug[11], Eric Nakakura[12], Nitya Raj[13], Heloisa P Soares[14], Brian Untch[15], Namrata Vijayvergia[16] and Jennifer A Chan[17]

Eads JR, et al. *Endocr Relat Cancer*. 2023;30(8):e220206.

Great Debates Solid Tumors



FOLFOX = folinic acid (leucovorin), fluorouracil, oxaliplatin; CAPEOX = capecitabine, oxaliplatin; MSS = microsatellite stable; TMB = tumor mutation burden; MSI-H = high microsatellite instability.

Eads JR, et al. *Endocr Relat Cancer*. 2023;30(8):e220206.

Poorly Differentiated NECs

- Early stage: surgical resection but high risk of recurring
  - Use chemotherapy and sometimes radiation to decrease this risk
- Advanced disease
  - Survival is limited
- Sparse data to guide treatment
  - Platinum/etoposide
  - Cisplatin/irinotecan
  - FOLFIRI
  - Temozolomide + capecitabine
  - IMMUNOTHERAPY???
- Area of unmet need

FOLFIRI = folinic acid (leucovorin), fluorouracil, irinotecan.

Fjällskog ML, et al. *Cancer*. 2001;92(5):1101-1107. Mitry E, et al. *Br J Cancer*. 1999;81(8):1351-1355. Kulke MH, et al. *Dig Dis Sci*. 2006;51(6):1033-1038. Yamaguchi T, et al. *Cancer Sci.* 2014;105(9):1176-1181. Welin S, et al. *Cancer*. 2011;117(20):4617-4622. Hentic O, et al. *Endocr Relat Cancer*. 2012;19(6):751-757. Patel SP, et al. *Clin Cancer Res*. 2020;26(10):2290-2296.

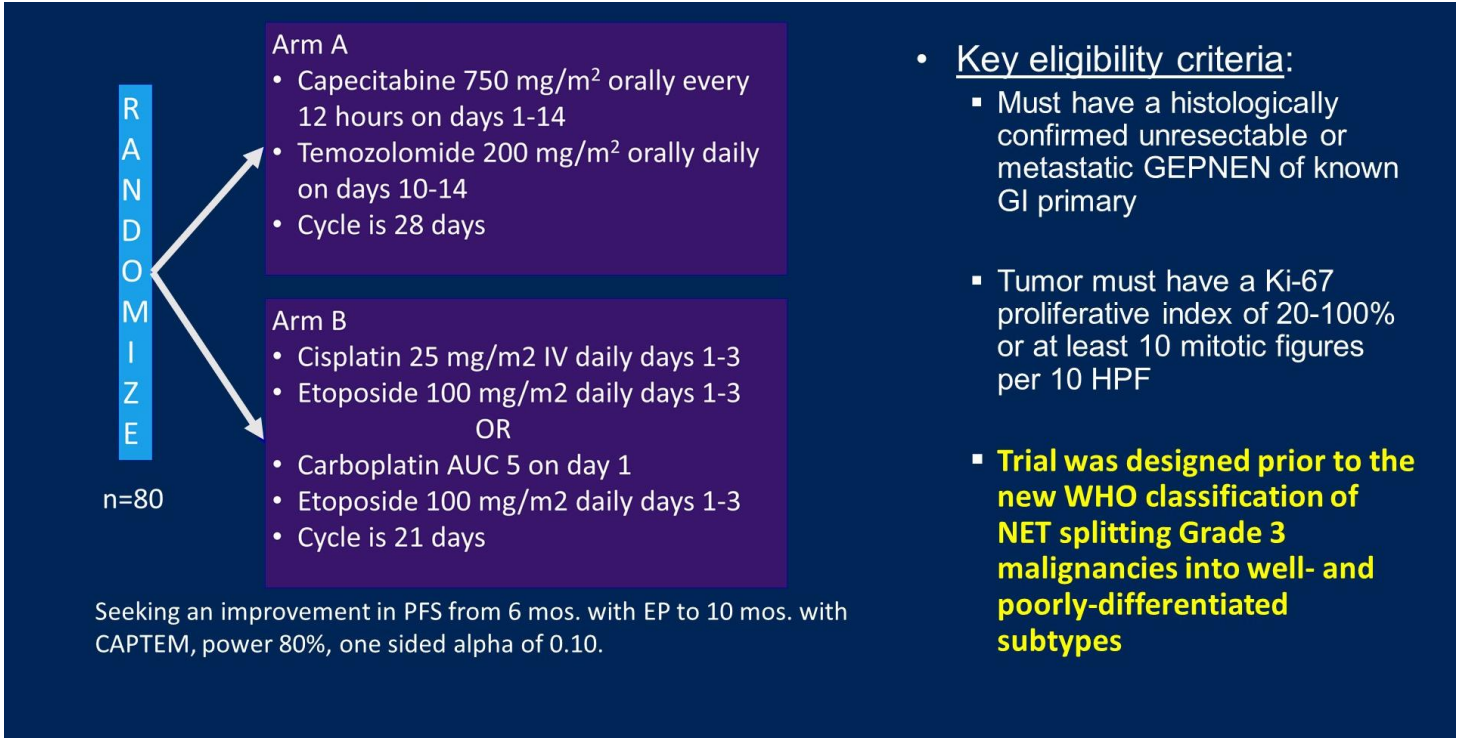
Randomized phase II study of platinum and etoposide (EP) versus temozolomide and capecitabine (CAPTEM) in patients with advanced G3 non-small cell gastroenteropancreatic neuroendocrine neoplasms (GEPNENs): ECOG-ACRIN EA2142

Jennifer R. Eads[1], Paul J. Catalano[2], George A. Fisher[3], Daniel Rubin[3], Andrei Iagaru[3], David Klimstra[4], Bhavana Konda[5], Myron S. Kwong[6], Jennifer A. Chan[7], Ana De Jesus-Acosta[8], Thorvardur R. Halfdanarson[9], Walid L. Shaib[10], Heloisa P. Soares[11], Sung Chul Hong[2], Terence Z. Wong[12], Peter J. O'Dwyer[1]

[1]University of Pennsylvania, Abramson Cancer Center, Philadelphia, PA; [2]Dana Farber Cancer Institute-ECOG-ACRIN Biostatistics Center, Boston, MA; [3]Stanford University Medical Center, Palo Alto, CA; [4]Memorial Sloan Kettering Cancer Center, New York, NY; [5]Ohio State University Comprehensive Cancer Center, Columbus, OH; [6]Kaiser Permanente-Santa Teresa-San Jose, San Jose, CA; [7]Dana Farber Cancer Institute, Boston, MA; [8]Johns Hopkins University, Sidney Kimmel Cancer Center, Baltimore, MD; [9]Mayo Clinic, Rochester, MN; [10]Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA; [11]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; [12]Duke University Medical Center, Durham, NC

Eads JR, et al. *J Clin Oncol*. 2022;40(Suppl 16):4020.

EA2142 Study Schema



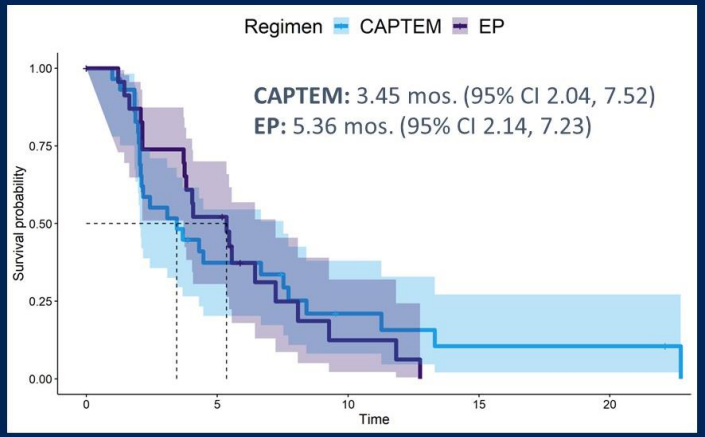
EP = etoposide, platinum-based chemotherapy; GEPNEN = gastroenteropancreatic neuroendocrine neoplasm; HPF = high-power field; AUC = area under the curve.

Eads JR, et al. *J Clin Oncol*. 2022;40(Suppl 16):4020.

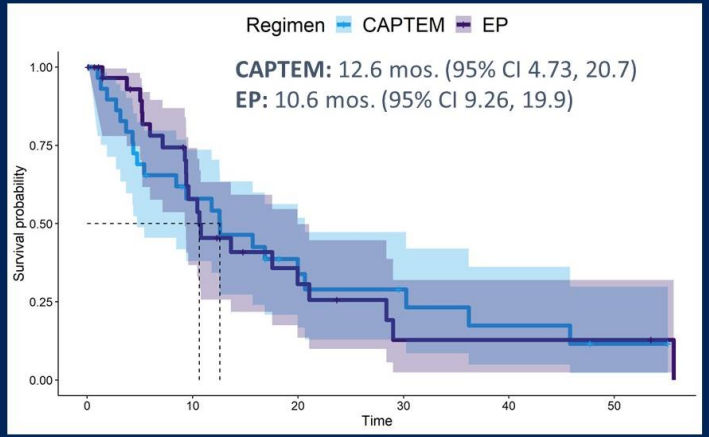
Survival Outcomes

Response Rate
CAPTEM: 19%
EP: 22%

Interim analysis at 57.5% information availability, study closed for futility



Progression-Free Survival

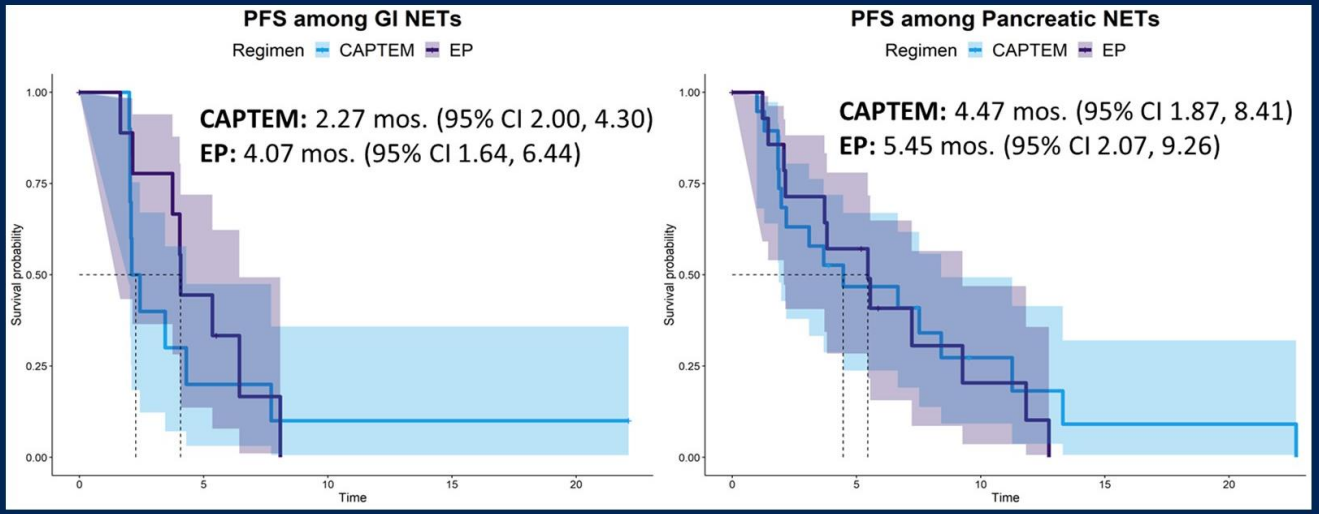


Overall Survival

Eads JR, et al. *J Clin Oncol*. 2022;40(Suppl 16):4020.

Great Debates Solid Tumors

PFS Outcomes GI NET and Pancreatic NET



PFS in GI NET

PFS in Pancreas NET

Eads JR, et al. *J Clin Oncol*. 2022;40(Suppl 16):4020.

Key Learning Points

- Heterogeneity of tumor biology and varied response to treatment represent a major therapeutic challenge in the management of GEP-NETs
- NETest can effectively quantify gene expression, provide real-time insights into a tumor's biological activity, and support early detection and personalized treatment strategies
- Treatment with cabozantinib has been shown to reduce the risk of disease progression or death when compared with placebo in patients with gastrointestinal NETs

Thank You!

Great Debates
Solid Tumors