Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NEN)

David B. Zhen, MD

Associate Professor of Medicine

GI Medical Oncology

Director, Neuroendocrine Tumor Program

Fred Hutch Cancer Center | University of Washington
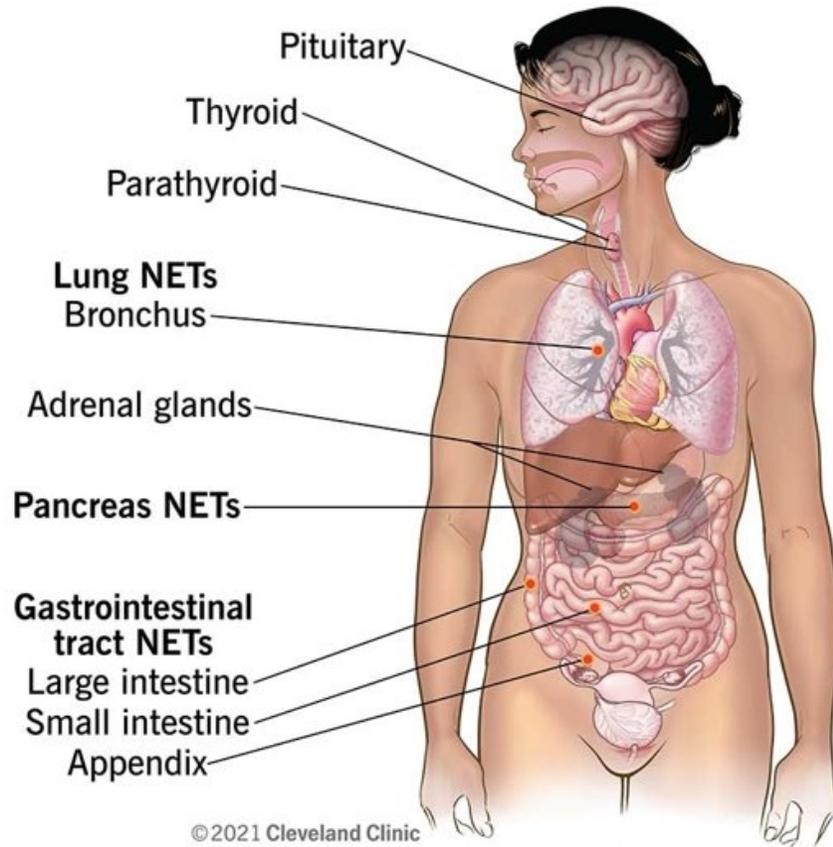
October 6, 2025

Disclosures

- **Advisory Board/Consulting:** Exelixis, Boehringer Ingelheim, Bristol Myers Squibb, Legend Biotech

- **Independent Data Monitoring Committee:** Jazz Pharmaceuticals/Zymeworks, Inc

- **Research Funding:** AstraZeneca, Bayer, Bristol Myers Squibb, Clasp Therapeutics, Cornerstone Pharmaceuticals, Daiichi-Sankyo, Eli Lilly, Roche/Genentech, Legend Biotech, Merck, Pfizer

Outline

- Overview and Clinical Symptoms of GEP-NEN

- Workup and Staging of GEP-NEN

- Treatments for GEP-NET

- Treatments for GEP-NEC

Overview and Clinical Presentations of GEP-NEN

Neuroendocrine Neoplasms (NEN)

Pituitary
Thyroid
Parathyroid
Lung NETs
Bronchus
Adrenal glands
Pancreas NETs
Gastrointestinal tract NETs
Large intestine
Small intestine
Appendix

©2021 Cleveland Clinic

https://my.clevelandclinic.org/health/diseases/22006-neuroendocrine-tumors-net

- Neuroendocrine cells found through various body sites
- Produce hormones and peptides with biological activity
- NEN arise in different organs
- GI tract and lung are common sites of origin for NEN
- Some cases of unknown primary
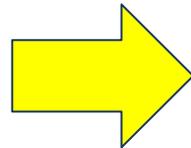- GI NEN often referred as gastroenteropancreatic (GEP-NEN)

2022 WHO Pathological Classification of GEP-NEN

Differentiation	Proliferation Indices	Designation
Well differentiated Neuroendocrine tumor (NET)	Ki-67 <3% Mitotic index <2/HPF	Low grade/ Grade 1
	Ki-67 3 – 20% Mitotic index <2-20/HPF	Intermediate grade/ Grade 2
	Ki-67 >20% Mitotic index >20/HPF	High grade/ Grade 3
Poorly Differentiated Neuroendocrine carcinoma (NEC)	Ki-67 >20% Mitotic index >20/HPF	High grade by default
		Subclassified by histology • Small Cell • Large Cell

New category compared to prior WHO classifications

Adapted from Rindi G et al. *Mod. Pathol.* 2018; 31; 1770 – 1786.
Rindi G et al. Endocr Pathol 2022; 33(1):115-154

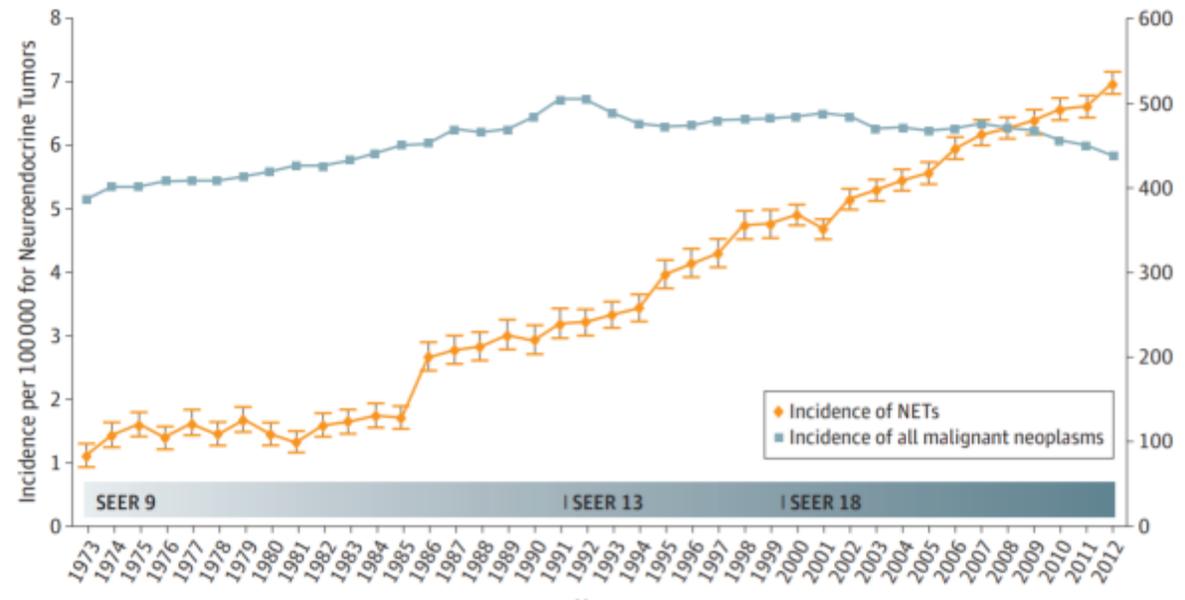# Relevance of 2022 WHO GEP-NEN Pathological Criteria
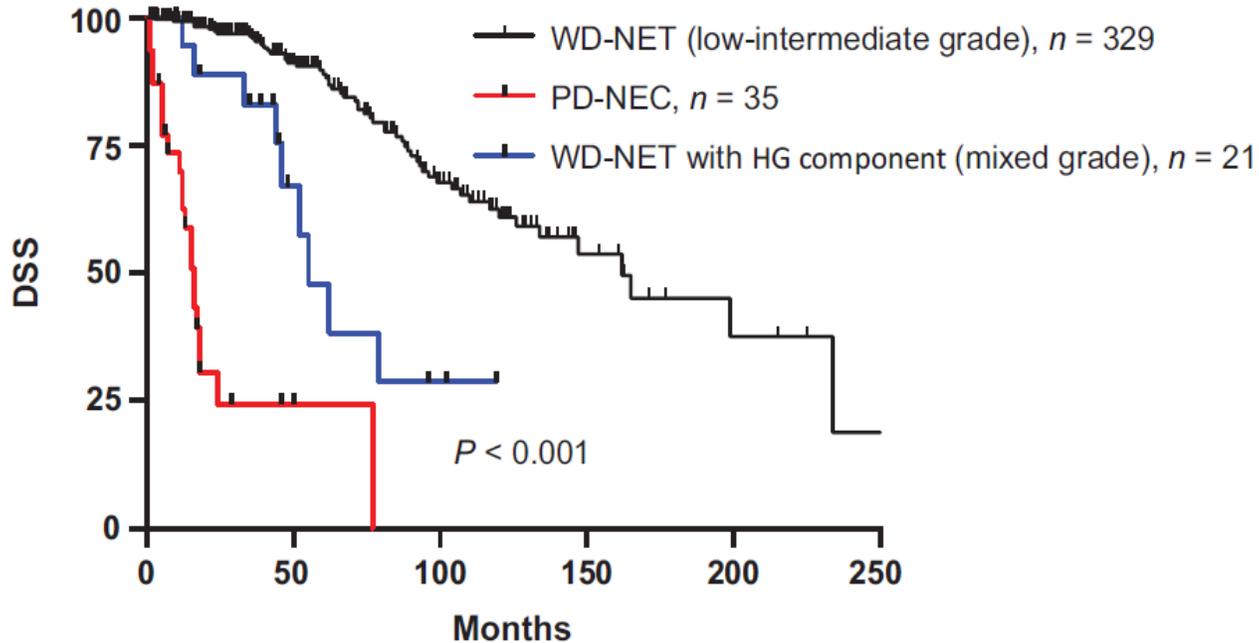
Tang et al. Clin Cancer Res 2015; 22:1011.

WD: Well differentiated, PD: Poorly differentiated
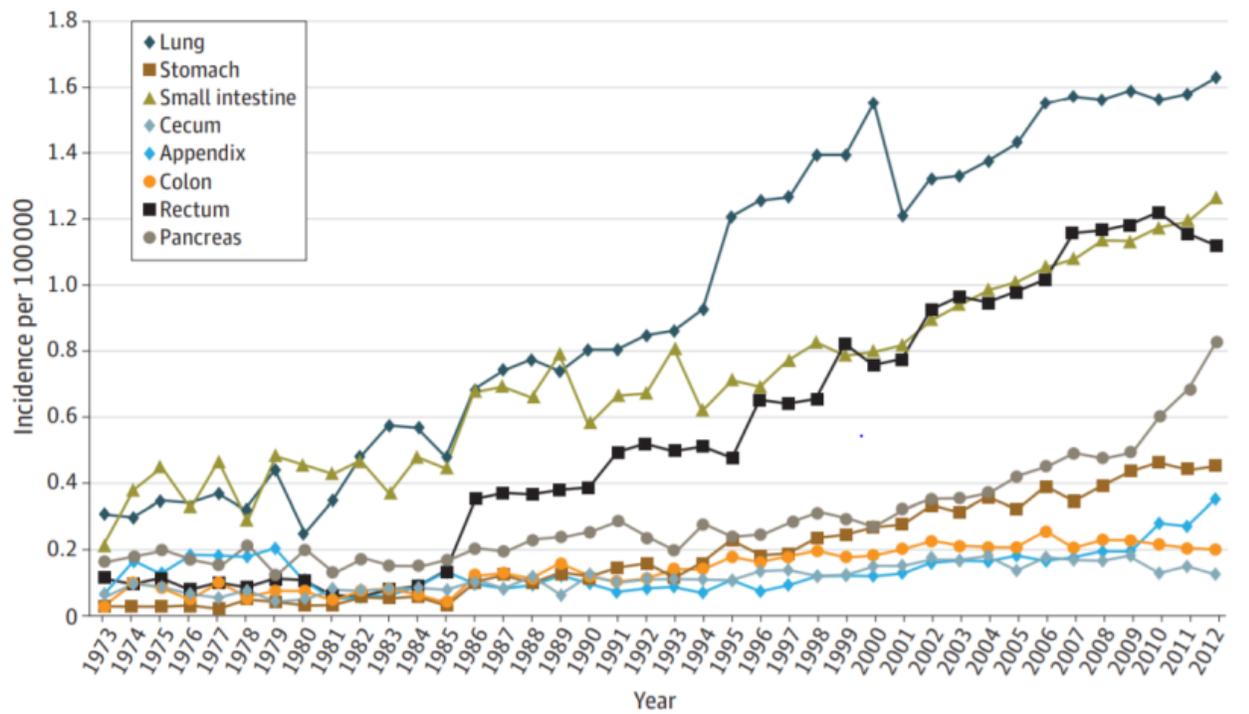Gr: Grade; HG: High grade

- Prognosis:
  - WD-Gr1/2 NET: Years (Median ~12 years)
  - PD-NEC: <12 months
  - WD-Gr 3 NET: In between the above

- WD-Gr3 NET mutational profiles more similar to WD-Gr1/2 NET
  - NET: MEN1, DAXX, ATRX
  - **NEC: TP53, RB1 (akin to SCLC, can be used to differentiate WD-Gr3 from NEC)**

- WD-Gr3 NET less responsive to platinum/etoposide compared to PD-NEC

- Differentiating WD-Gr3 from PD-NEC is important for prognostic and treatment considerations

Epidemiology of GEP-NET

A — All NETs and malignant neoplasms

B — NETs by site
- Lung
- Stomach
- Small intestine
- Cecum
- Appendix
- Colon
- Rectum
- Pancreas

- Incidence of NETs
- Incidence of all malignant neoplasms

Multiple factors likely contributing to increased incidence but most likely due to increased awareness/diagnosis

Dasari A, et al. JAMA Oncol. 2017;3(10):1335-1342

8

Hereditary Syndromes Associated with GEP-NET

- Most cases of GEP-NET don't have an obvious risk factor
- **~10-20% of pNET are associated with hereditary syndrome**
- Hereditary associated pNETs tend to more indolent
- **Importance of screening for other cancers in these patients!!**

Inherited disorders associated with pancreatic neuroendocrine tumors

Syndrome	Associated clinical features	Chromosomal location	Pancreatic neuroendocrine tumor type	Lifetime Risk
MEN1	Primary hyperparathyroidism Pituitary tumors Less commonly ■ Adrenocortical tumors ■ Carcinoid tumors ■ Nonmedullary thyroid tumors	11q13	Nonfunctional Gastrinoma Insulinoma Various	80-100%
Von Hippel-Lindau disease (VHL)	Pheochromocytoma (often bilateral) Retinal and cerebellar hemangioblastomas Renal cell carcinoma	3p25-26	Nonfunctional Various, including cystic tumors	~20%
Neurofibromatosis 1 (von Recklinghausen disease)	Neurofibromas Café au lait spots Pheochromocytoma	17q11.2		~10%
Tuberous sclerosis	Cardiac rhabdomyomas Renal cysts Angiomyolipomas	9q33.34 and 16p13.3		~1%

Symptoms of Hormonal Excess in GEP-NET

- GEP-NET may produce and secrete hormones & neuromodulators causing symptoms

- Classified as functional vs. non-functional

- Symptoms do not correlate with tumor burden

- Treatment of hormone excess: somatostatin analogue (SSA), except insulinoma

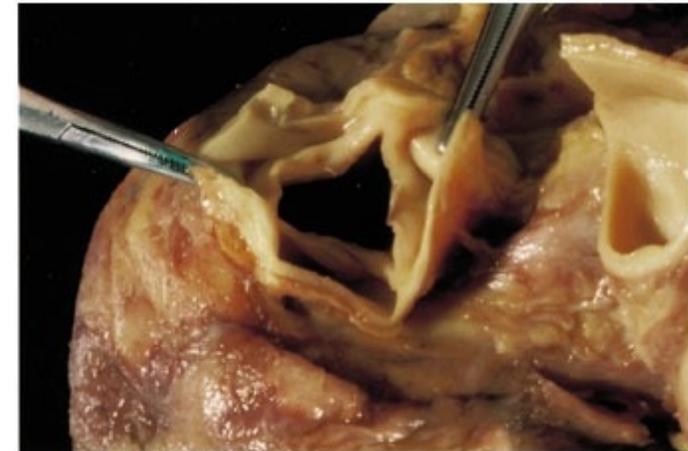- **Based on prevalence below, many patients have non-functional tumors (ie often asymptomatic)**
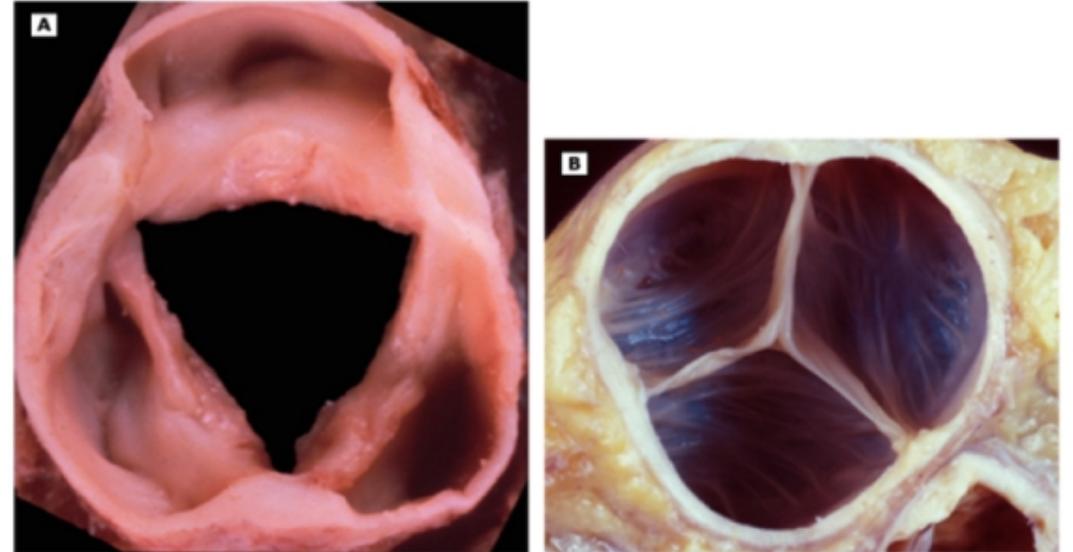
NOTE: Carcinoid Syndrome is less common in pNETs (i.e. hormone excess is not always "Carcinoid Syndrome")

Carcinoids (WD Gr1/2 midgut NET) (8-35% functional)	pNETs (10-40% functional)
- Carcinoid syndrome → flushing, diarrhea, bronchoconstriction, carcinoid heart dx - Due to excess serotonin, tachykinins, or histamine - Typically associated with midgut NETs and in the setting of liver metastases	- *Insulin (insulinoma) → hypoglycemia - *Gastrin (gastrinoma) → peptic ulcer disease - Vasoactive intestinal peptide (VIPoma) → diarrhea, hypokalemia - Glucagon (glucagonoma) → flushing, diarrhea, hyperglycemia

1. Choti et al. J Clin Oncol 2012;30:suppl abstr 4126. 2. Soga et al. J Exp Clin Cancer Res 1999;18:133. 3. Oberg K. Semin Oncol 2010;37:594. 4. Halfdanarson et al. Ann Oncol 2008;19:1727.

Clinical Symptoms of GEP-NET: Carcinoid Heart Disease

- ~1/3 of carcinoid syndrome-related deaths

- 20-65% of pts with carcinoid syndrome develop valvular pathology

- High serotonin and tachykinin levels released by carcinoid tumor cells → valvulitis and fibroblast proliferation

- Plaque-like fibrous thickening involving classically right heart valves (ie tricuspid)

- Treatment of carcinoid syndrome and management of heart failure

- **Valvular replacement needed if severe**

- **Need to screen for this if clinical concern (e.g. murmur, cardiac symptoms) and conduct surveillance echocardiogram if found**

1. Druce et al. Nat Rev Endorcinol 2009;5:276. 2. Pellikka et al. Circulation 1993;87:1188. 3. Kulke and Mayer. NEJM 1999;340:858l.

Clinical Symptoms of NET: Fibrosis/Desmoplastic Reaction

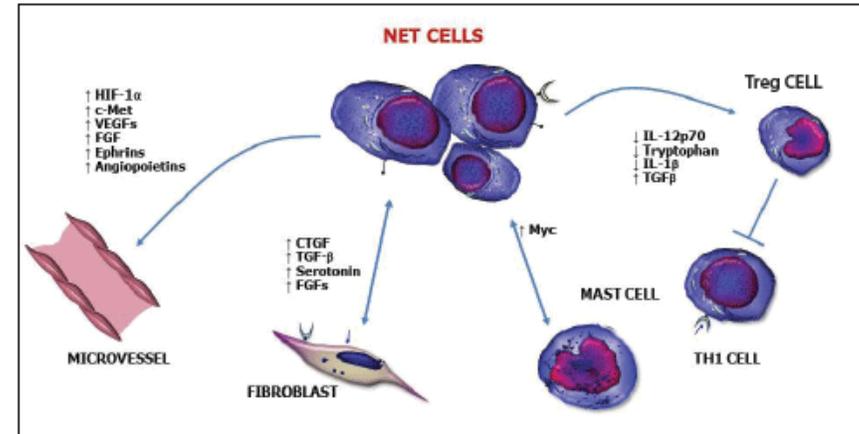Daskalakis K et al. Br J Surg, 2017: 104(1).

Figure: Role of the Microenvironment in the Pathogenesis of Neuroendocrine Tumors (NETs)—NET cells mutually interact with their microenvironment, prompting angiogenesis through cytokine secretion; inhibiting T-cell function by T-regulatory cell (Treg) dysregulation; promoting infiltration of mast cells via Myc upregulation; and driving fibroblast activation, which in turn enhances NET cell proliferation. CTGF = connective tissue growth factor; FGF = fibroblast growth factor; HIF-1α = hypoxia inducible factor alpha; IL = interleukin; TGF = transforming growth factor; TH1 = T helper type 1 cell; VEGF = vascular endothelial growth factor. Information from References 19, 22, 23, and 81.

Cives M & Strosberg J. Oncology (Williston Park) 2014; Sep 28(9): 749-56, 758

- Excess hormone production can lead to a fibrotic/desmoplastic reaction

- Tethers nearby bowel and place patients at risk of bowel obstruction

- Need to monitor closely for symptoms of bowel obstruction (e.g. pain, cramping, difficulty BM's, N/V, etc)

- Palliative resection of primary tumor (even if metastatic disease) often considered to avoid future risk of bowel obstruction

Workup and Staging of GEP-NEN

Workup of GI NET

- **Goals of workup**
  - Assess primary site and stage
  - Characterize aggressiveness (grade, differentiation) – need tissue
  - Establish functionality

- **Testing modalities**
  - Imaging
    - Multiphase CT scan or MRI
    - Somatostatin receptor-based imaging: ^{68}Ga Dotatate-PET scan or ^{64}Cu Dotatate-PET scan
  - Endoscopy
  - Biochemical evaluation as clinically indicated (if suspicious symptoms present)

Importance of Multiphase CT Imaging

© 2020 UpToDate, Inc. and/or its affiliates. All Rights Reserved.

CT of neuroendocrine tumor liver metastases

In patient A (top two images), the hypervascular liver metastases are more clearly observed on the arterial phase (left) compared to the portal venous phase (right); whereas in patient B (lower two images), the liver metastases are not as hypervascular and more clearly delineated on the portal venous phase (right) compared to the arterial phase (left).

Arterial Phase
- ~20 sec post-contrast injection
- Most NET seen better on this phase

Portal venous phase
- ~70 sec post-contrast injection
- Better for adenocarcinoma & some NET

Basics of Somatostatin Receptor (SSTR) Imaging

linker
(chelator)

radionuclide — peptide — target

^{111}In-DTPA-octreotide SPECT/CT:
^{111}In — DTPA — Octreotide   SSTR subtype 3-5

DOTATATE (GaTate) PET/CT:
^{68}Ga — DOTA — Octreotate   SSTR subtype 2
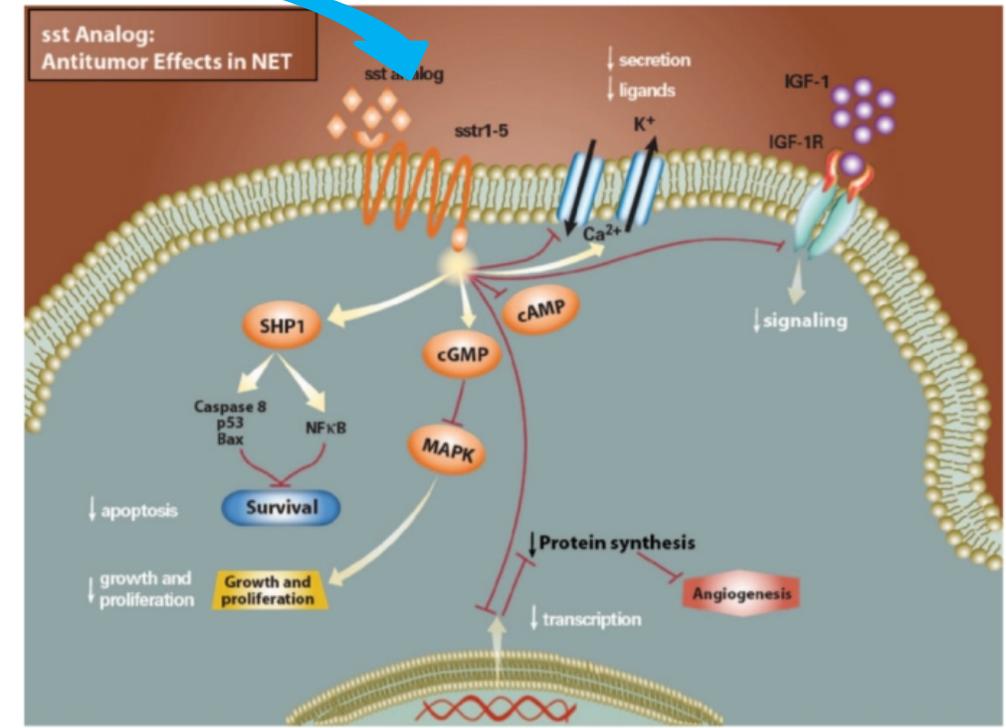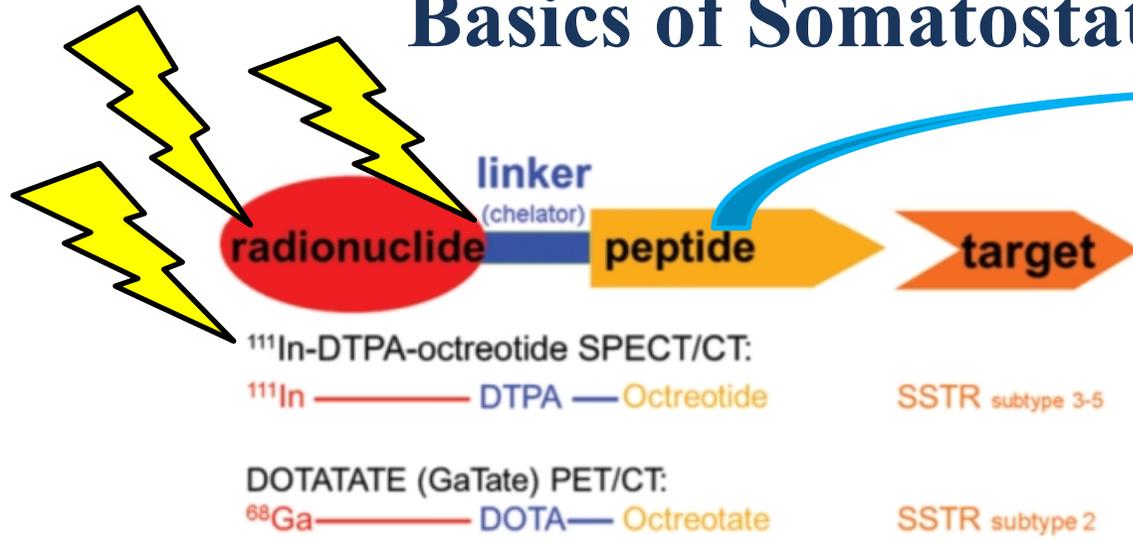
Table 1: Somatostatin Analogs Currently in Use for SSTR PET/CT

Compound	Abbreviation	Receptor Subtypes
^{68}Ga-DOTA-Tyr^3-octreotate	^{68}Ga-DOTATATE (GaTate)	SSTR 2
^{68}Ga-DOTA-NaI^3-octreotide	^{68}Ga-DOTANOC (GaNoc)	SSTR 3, SSTR 5
^{68}Ga-DOTA-TyI^3-octreotide	^{68}Ga-DOTATOC (GaToc)	SSTR 5

sst Analog: Antitumor Effects in NET

Hofman MS, Lau WFE, Hicks RJ. RadioGraphics 2015; 35:500–516

Sideris L, Dube P, Rinke A. The Oncologist 2012; 17: 747-755

- NET often express SSTR on the surface of NET cells
- There are 5 isoforms of SSTR (ie SSTR 1-5); most relevant in NET SSTR 2 (i.e. dotaTATE)
- Take advantage of this by developing a radiolabel that bind to SSTR on NET cell surface

SSTR Imaging: ^{68}Ga Dotatate is Standard

Anterior ^{68}Ga-DOTATATE   Posterior ^{68}Ga-DOTATATE   Anterior Octreoscan   Posterior Octreoscan
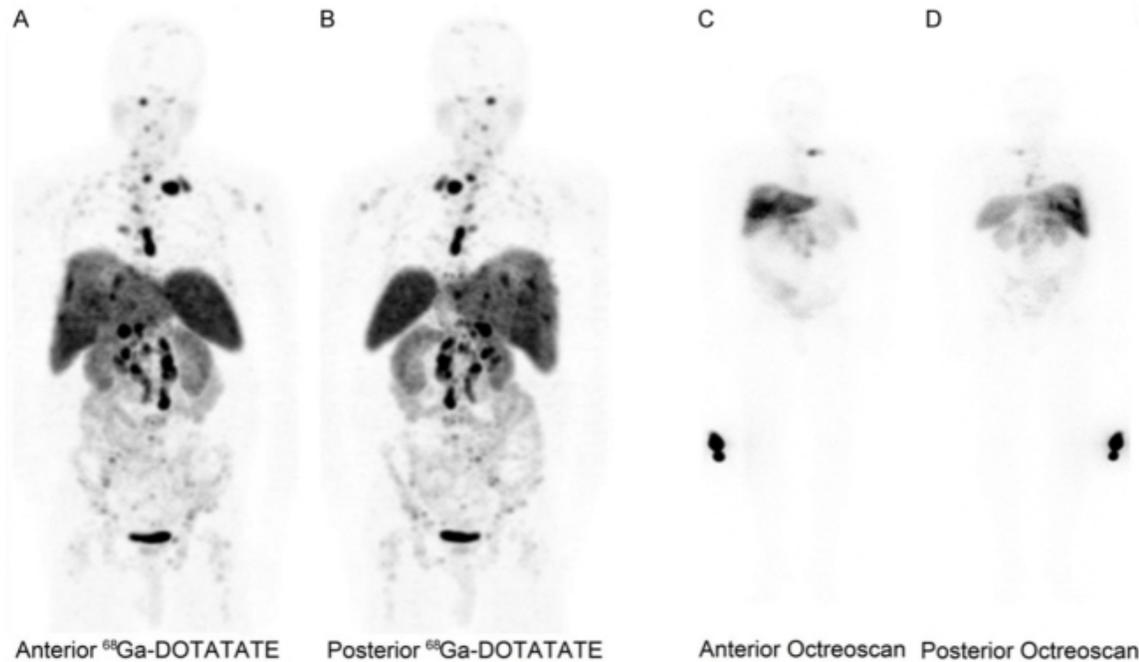
- Old standard was OctreoScan (^{111}Indium pentotreotdie radiolabel)

- ^{68}Ga-DOTATATE has increased sensitivity and more convenient

- Combined with PET/CT scans allow for better imaging visualization

- ^{68}Ga-DOTATATE FDA approved 2016 and

- Dotatate-PET scans are standard of care (and superior to OctreoScan)

^{64}Cu-dotatate PET scan

- Limitations of ^{68}Ga dotatate

  - Short half-life (1.1 hr)

  - Needs to be locally produced via a generator

  - Thus needs to given close to time of scan (Potentially limiting scan availability)

- ^{64}Cu dotatate has a longer half life (12.7 hr), eliminating need for a generator and increase scan availability

- Studies show same quality and safety as ^{68}Ga dotatate PET scans

- FDA approved in 9/2020

- While either 68Ga dotatate and 64Cu dotatate can be used interchangeably, consistency of use of one modality helps with radiology interpretations

Johnbeck CB et al. J Nucl Med. 2017;58:451–457.
Delpassand ES et al. J Nucl Med 2020; 61:890–896

Differentiation and Somatostatin Receptor Expression

- **WD-lower grade NET**
  - $+^{68}$Ga-dotatate PET avid (express SSTR)
  - Negative on FDG-PET

- **High grade NET/PD-NEC**
  - Often neg ^{68}Ga-dotatate PET (little to no expression of SSTR)
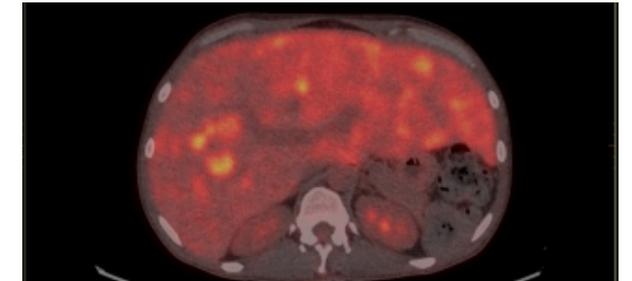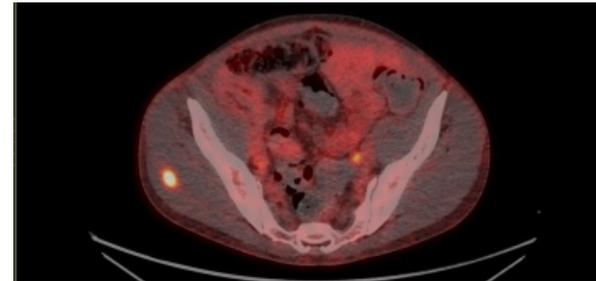 - Positive on FDG-PET

- **In some instances, both FDG-PET scan and ^{68}Ga- dotatate PET scan can be helpful**
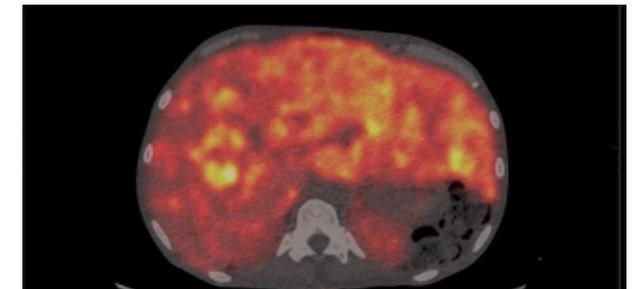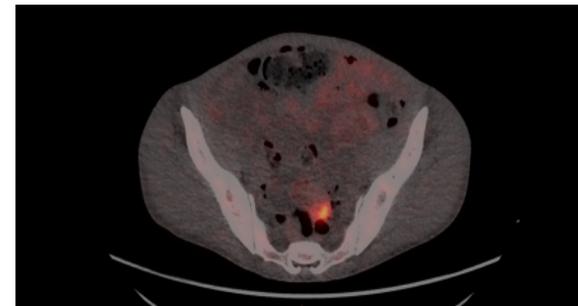 - Determine NET de-differentiation (ie to higher grade status)
  - Guide treatment options

WD-G1 NET rectal primary seen only on dotatate-PET

Mixed FDG avid and dotatate avid lesions in liver
(Mixed PD-NEC and WD-G2 NET)

F-18 FDG PET

^{68}Ga Dotatate PET

*Images from patient with mixed WD-Gr1 NET of the rectum and mixed WD-NET and PD-NEC in liver

Biochemical Testing

NCCN Guidelines Version 1.2023
Neuroendocrine and Adrenal Tumors

PRINCIPLES OF BIOCHEMICAL TESTING[1-10]

- Some NETs can secrete specific neuroendocrine hormones. Hormonal workup should be guided by the presence of symptoms of the excess hormone. Screening for hormones in individuals with asymptomatic disease is not routinely required.
  ‣ Patients with functional tumors have clinical symptoms related to tumor-associated hormone excess.
- PPIs, other drugs, some medical conditions, and certain foods are known to cause false elevations in serum gastrin and chromogranin A. To confirm diagnosis, serum gastrin should ideally be checked when fasting and off PPI for >1 week. However, PPI should be continued in patients with overt clinical symptoms of gastrinoma and/or risks of complications.
- If MEN2 is suspected, then patients should be evaluated for pheochromocytoma/paraganglioma prior to any procedures.[9]

Syndrome	Location	Clinical Signs or Symptoms	Testing
Carcinoid syndrome (NETs of Gastrointestinal Tract)	Primary tumors in small bowel and appendix; rarely in rectum	• Primary tumors in the GI tract usually are not associated with symptoms of hormone hypersecretion unless extensive metastasis. • Symptoms of hormone secretion may include flushing, diarrhea, cardiac valvular fibrosis, and bronchoconstriction	• 24-hour urine or plasma 5-HIAA ‣ Foods to avoid for 48 hours prior to and during testing: avocados, bananas, cantaloupe, eggplant, pineapples, plums, tomatoes, hickory nuts/pecans, plantains, kiwi, dates, grapefruit, honeydew, or walnuts
Carcinoid syndrome (NETs of Lung and Thymus)	Primary tumors in lung or thymus	• Bronchial/thymic tumors may be associated with classic carcinoid syndrome as well as hypercortisolemia (± Cushing's syndrome)	• 24-hour urine or plasma 5-HIAA ‣ Foods to avoid for 48 hours prior to and during testing: avocados, bananas, cantaloupe, eggplant, pineapples, plums, tomatoes, hickory nuts/pecans, plantains, kiwi, dates, grapefruit, honeydew, or walnuts • Test for hypercortisolemia (± Cushing's syndrome) (NE-C 2 of 4)
Insulinoma	Pancreas	Hypoglycemia	• While hypoglycemic: ‣ Serum insulin ‣ Pro-insulin ‣ C-peptide • See Workup for insulinoma (PanNET-5)
VIPoma	Most common in pancreas, rarely extra pancreatic	Severe watery diarrhea, hypokalemia	Serum VIP
Glucagonoma	Pancreas	Flushing, diarrhea, hyperglycemia, dermatitis, hypercoagulable state	Serum glucagon
Gastrinoma	Pancreas or duodenum	Gastric ulcers, duodenal ulcers, diarrhea	Serum gastrin[a]
Somatostatinoma	Pancreas or duodenum	Hyperglycemia, cholelithiasis, diarrhea/steatorrhea	Serum somatostatin

Footnotes on NE-C 3 of 4

NE-C 1 OF 4

Note: 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.

- Generally workup is guided by symptoms

- For most asymptomatic patients, hormone levels don't change management

- Often use as biomarkers for response (e.g. Chromogranin A), but remember they can fluctuate due to other factors

- Some exceptions for asymptomatic patients (e.g. screening for Cushing's syndrome/pituitary tumors in setting of MEN1)

- **Assessment of response and treatment should be based on the entire clinical picture (not just biochemical testing)**

Updates to AJCC v9 Staging for GEP-NET

Critical updates in neuroendocrine tumors: Version 9 American Joint Committee on Cancer staging system for gastroenteropancreatic neuroendocrine tumors

Aman Chauhan MD[1] | Kelley Chan MD[2] | Thorvardur R. Halfdanarson MD[3] | Andrew M. Bellizzi MD[4] | Guido Rindi MD, PhD[5,6] | Dermot O'Toole MD[7] | Phillip S. Ge MD[8] | Dhanpat Jain MD[9] | Arvind Dasari MD[10] | Daniel A. Anaya MD, MSHCT[11] | Emily Bergsland MD[12] | Erik Mittra MD, PhD[13] | Alice C. Wei MD[14] | Thomas A. Hope MD[15] | Ayse T. Kendi MD[16] | Samantha M. Thomas MS[17] | Sherlonda Flem BS, CTR[18] | James Brierley MB[19] | Elliot A. Asare MD, MS[20] | Kay Washington MD, PhD[21] | Chanjuan Shi MD, PhD[22]

Summary of Three Notable Changes

1) Recommend **AGAINST the use of chromogranin A** for diagnosis and for treatment response

2) Incorporation of WHO grading of GEP-NET in staging, prognosis, and treatment decisions

3) Evolution of Stage 1 disease and role for endoscopic resection for NET of the stomach, duodenum, and colorectum

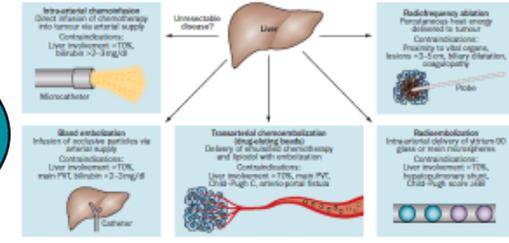Chauhan A et al. Ca Cancer J Clin 2024; 74: 359-367

Treatments for GEP-NET

Types of Treatments for GI NET

Surgery
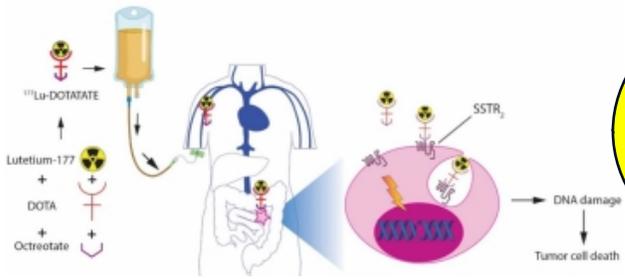
Catheter-based liver directed therapy

Habib A et al. Nat Rev Clin Oncol 2015.

Peptide Receptor Radionuclide Therapy (PRRT)/Radioligand Therapy (RLT)

Becx MN et al. Cancers 2022.

Medical (Systemic) Therapies
- Targeted agents
- Chemotherapy options

- Surgery preferred if can remove all disease; others mainly control disease

- Surgery can still be used even if disease can't be all removed (e.g. debulking liver surgery, resecting the primary tumor, etc)

- Treatments may be used separately, but sometimes can be used to compliment each other

- Each person's situation is different, and a multidisciplinary discussion is important

Localized GI NET: Primary Organ Site Influences Management

NET of small intestine (jejunum, ileum, colon)
- Bowel resection + lymph node resection

Pancreatic NET
- Pancreaticoduodenectomy (Whipple's)
- Observation (for smaller, stable tumors)

Gastric NET

Type 1 (~70-80%)	Type 2 (~5-10%)	Type 3 (~5-10%, Sporadic)	Type 4
• Occurs with autoimmune atrophic gastritis (stomach parietal cells can't make acid)	• Occurs in context of Zollinger-Ellison Syndrome	• Not Type 1 or Type 2	• Chronic proton pump inhibitors (PPI's)/antacids cause a similar physiology to Type 1
• **Low** acid in stomach -> **high gastrin** -> growth of neuroendocrine cells	• Tumor makes **high gastrin** -> **high** acid	• Single, large tumor of the stomach with high chance for spread	• **Low** acid in stomach -> **high gastrin** -> growth of neuroendocrine cells
• Causes small, benign polyps (low chance of spread)	• Medical treatment for acid secretion + resection tumor/stomach	• **Normal gastrin**	• Often indolent and can be monitored with endoscopies
• **Monitor with endoscopies (i.e. no surgery or medical treatment)**		• Surgery + lymph node removal	

Appendiceal
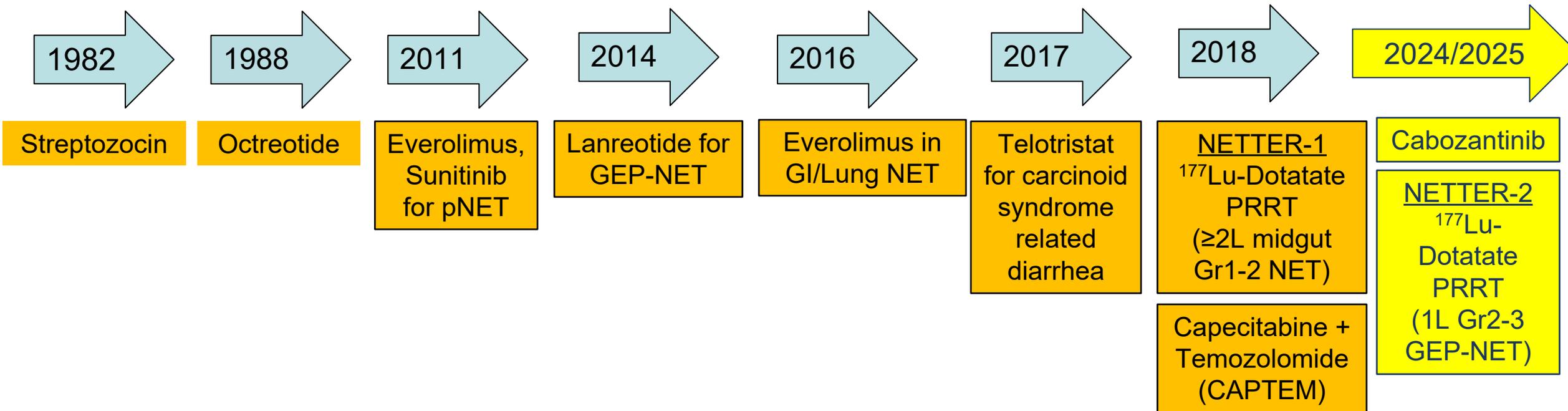- Simple appendectomy (<2 cm tumor)
- Right colon removal (hemicolectomy) + Lymph nodes (>2 cm)
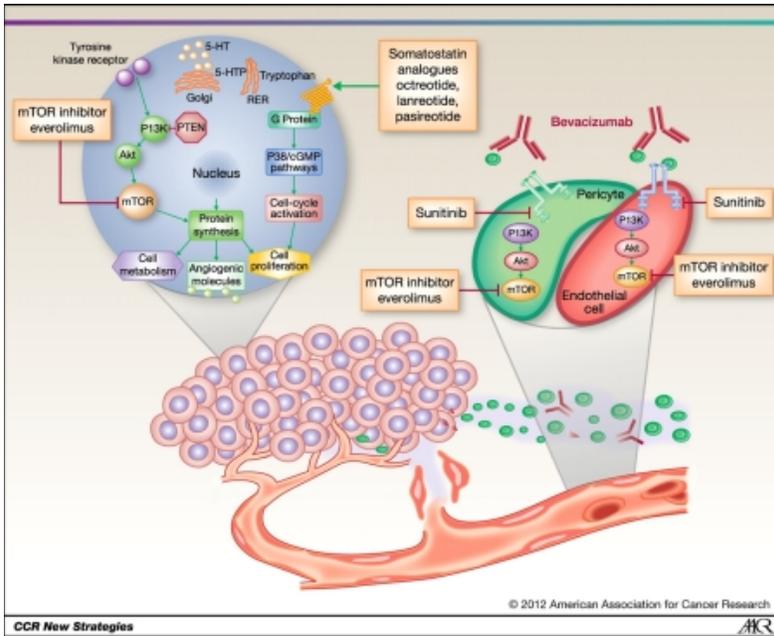- Debate over 1-2 cm tumors

Rectum
- Endoscopic resection if small tumors (up to 2 cm, if possible)
- Full rectal surgery + lymph nodes for larger tumors and/or abnormal lymph nodes on scans/biopsies

Fred Hutchinson Cancer Center

24

Extrapolated from NCCN and NANETS Guidelines

Therapies in GEP-NET

1982 → Streptozocin

1988 → Octreotide

2011 → Everolimus, Sunitinib for pNET

2014 → Lanreotide for GEP-NET

2016 → Everolimus in GI/Lung NET

2017 → Telotristat for carcinoid syndrome related diarrhea

2018 →
NETTER-1
^{177}Lu-Dotatate PRRT
(≥2L midgut Gr1-2 NET)

Capecitabine + Temozolomide (CAPTEM)

2024/2025 →
Cabozantinib

NETTER-2
^{177}Lu-Dotatate PRRT
(1L Gr2-3 GEP-NET)

Systemic Therapies for GEP-NET

Dong M, Phan AT, Yao JC.
Clin Cancer Res, 2012; 18(7): 1830-6.

Pancreatic NET (pNET)

- Somatostatin analogs (SSAs) (octreotide LAR, lanreotide)
- PRRT/^{177}Lutetium (^{177}Lu)-dotatate
- Everolimus
- Capecitabine/Temozolomide (CAPTEM)
- Sunitinib
- Belzutifan (germline *VHL* only)
- *Teloristat ethyl (for refractory carcinoid syndrome diarrhea)

Other GI NET

- SSAs (octreotide LAR, lanreotide)
- PRRT/^{177}Lutetium (^{177}Lu)-dotatate
- Everolimus
- *Teloristat ethyl (for refractory carcinoid syndrome diarrhea)

- For symptom and tumor control
- Observation may be appropriate for patients with low grade/indolent disease
- **Based on current data, there is no established sequence of therapies**

# Summary of Clinical Outcomes of GEP-NET Systemic Therapies

Objective response rate (ORR)	2-3%	• pNET: 5 • Other GI NET: 2%	9.3%	• pNET: 40% • Other GI NET: ? (~4-50%)	20-40% (↑ for higher grade disease and pNET)	18-50% (↑ in pNET)	pNET: 19% Non-pNET: 5%
Progression Free Survival (PFS, months)	Rate of 2 yr-PFS: 50-65%	• pNET: 11.4 • Other GI NET: 11-14	11.4	• pNET: 22.7 • Other GI NET: ? (>30)	>30	>30	pNET: 13.4 Non-pNET: 8.4
Overall Survival (OS, months)	Median not reached (NR)	Median NR	Median NR	pNET: 58.7 Other GI NET: ? (>20-30)	20-40	50-60	pNET: 40 Non-pNET: 22
Common Toxicities	Diarrhea, abdominal discomfort, gallstones	Mouth sores, diarrhea, fatigue, rash, hyperglycemia, potential pneumonitis	Diarrhea, nausea, fatigue, hand-foot syndrome	Cytopenias, nausea, diarrhea, fatigue, potential risk of MDS with long term temozolomide use	Cytopenias, nausea, fatigue, peripheral neuropathy	Nausea, fatigue, cytopenias, ~1.5% risk MDS/AML	Diarrhea, hypertension, hand-foot syndrome, blood clots

[1]Rinke A, et al. J Clin Oncol, 2009. [2]Caplin ME et al. N Eng J Med 2014. [3]Yao JC, et al. N Eng J Med 2011. [4]Yao JC et al, Lancet 2016. [5]Raymond E, et al. N Eng J Med 2011.
[6]Kunz P, et al. Abstract 4004, ASCO 2022 Annual Meeting [7]Fine RL et al. Abstract 179, GI ASCO 2014 [8]Thomas K et al. Cancers 2020. [9]Al-Toubah T et al. Curr Oncol 2022.
[10]Das S, et al. Cancers 2021. [11]Brabander T et al. Clin Cancer Res 2017. [12]Strosberg J et al. N Eng J Med 2017. [13]Strosberg J et al. Abstract 4112. ASCO 2021.[14]Chan JA et al. N Engl J Med 2024

Systemic Therapy Considerations for GEP-NET

Goals of Therapy

Disease Biology

Patient goals and Preferences

Efficacy of Treatments

Logistical Considerations of Treatment

Toxicities of Treatment (short-term and long-term)
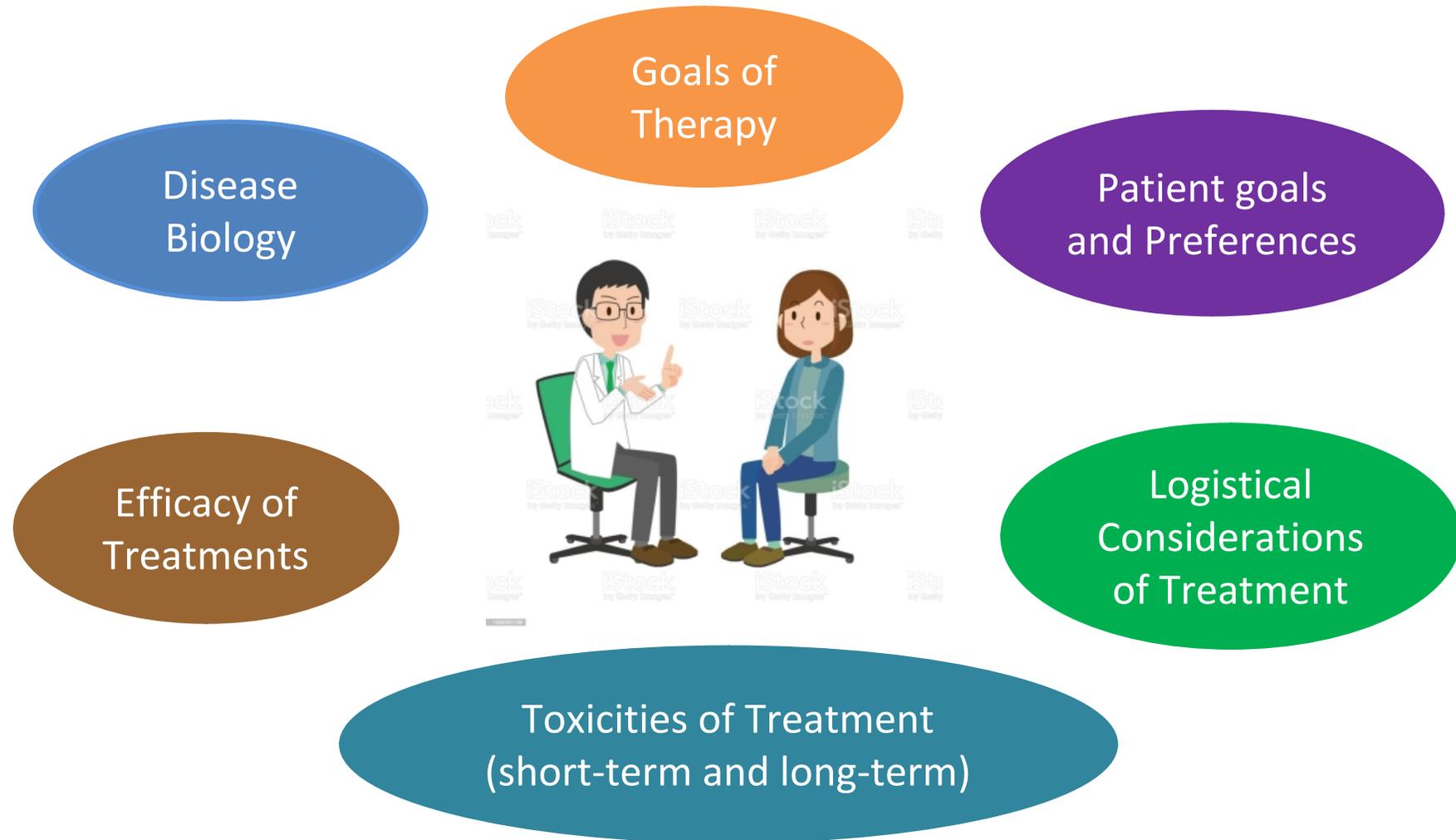
- No one size fits all with regards to treatment approach
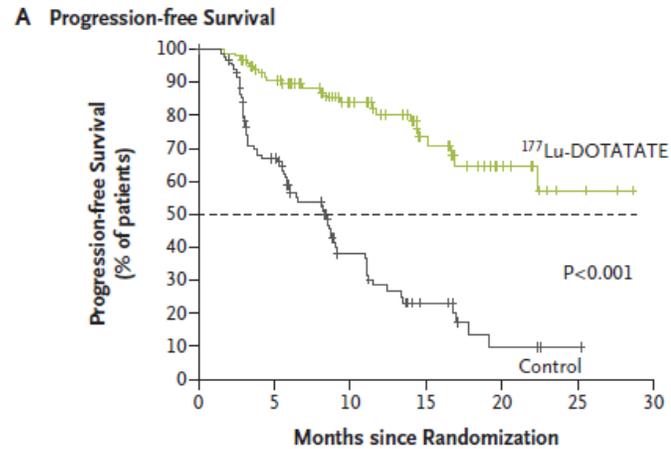- Multidisciplinary discussion important

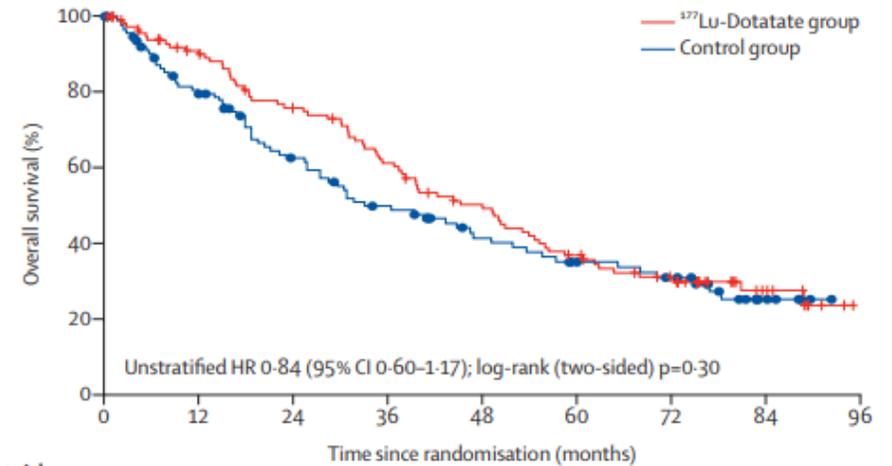# Peptide receptor radionuclide therapy (PRRT): Revolutionized Treatment in GEP-NET
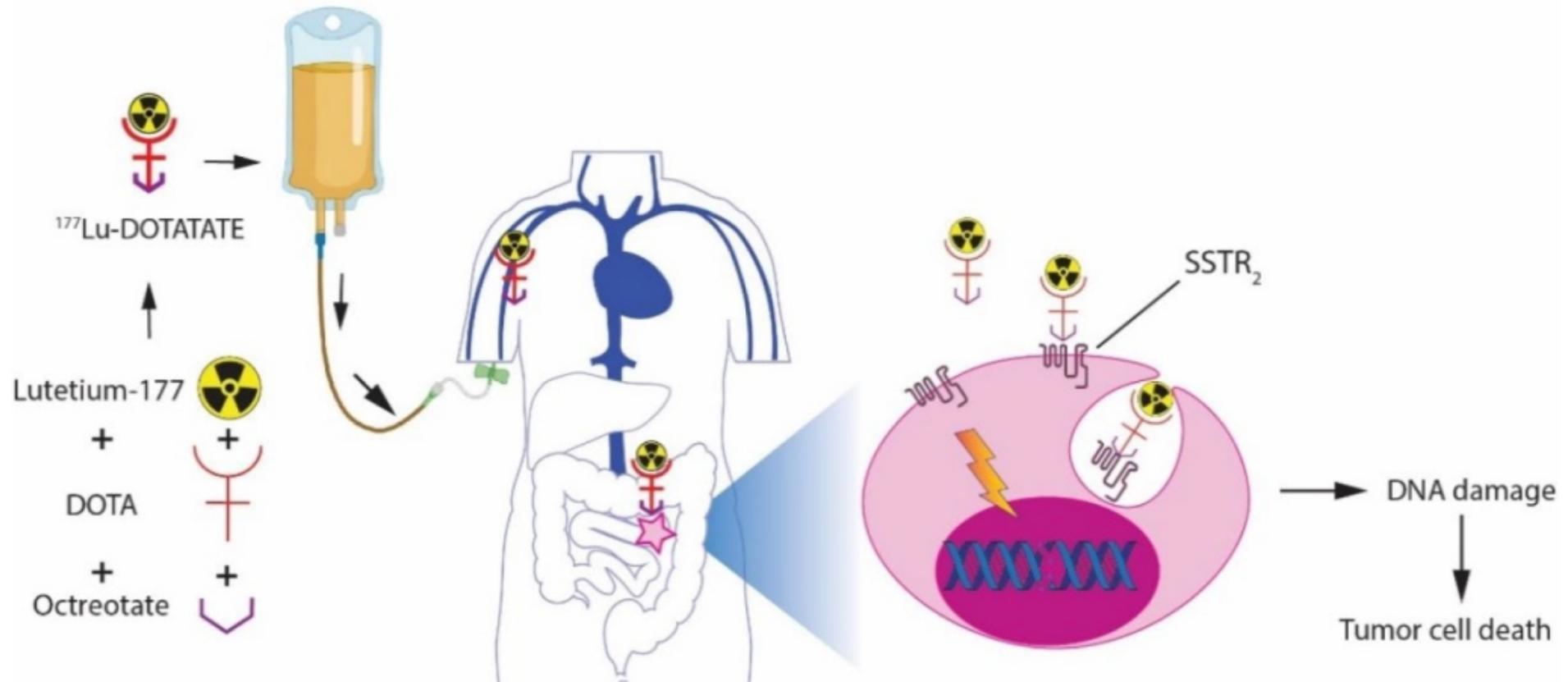
Becx MN et al. Cancers 2022; 14; 5792.

NETTER-1:
Improved PFS in Previously Treated WD-Gr 1/2 Midgut NET

A Progression-free Survival

No. at Risk

177Lu-DOTATATE group	116	97	76	59	42	28	19	12	3	2	0
Control group	113	80	47	28	17	10	4	3	1	0	0

Unstratified HR 0·84 (95% CI 0·60–1·17); log-rank (two-sided) p=0·30

Number at risk (number censored)

177Lu-Dotatate group	117 (0)	98 (9)	79 (12)	63 (13)	48 (16)	35 (17)	25 (22)	10 (35)	0 (44)
Control group	114 (0)	84 (8)	61 (14)	45 (18)	33 (23)	25 (26)	21 (27)	6 (39)	0 (45)

- ORR 18% vs 3%

- No OS benefit at final analysis, but 36% of pts on controlled arm received 177Lu-dotatate at time of progression

- Median OS of 48.0 months in the 177Lu-Dotatate group and 36.3 months (25·9–51·7) in the control group (HR 0·84 [95% CI 0.60–1.17]; two-sided p=0.30).

- Led to FDA approval in Feb 2018 for GEP-NET progressed on somatostatin analogs

- Data on non-midgut NET and higher grade disease lacking

Strosberg J et al. N Engl J Med 2017; 376: 125-35
Strosberg JR et al. Lancet Oncol 2021; 22: 1752–63

NETTER-2: Improved PFS in 1L WD-Gr 2/3 GEP-NET
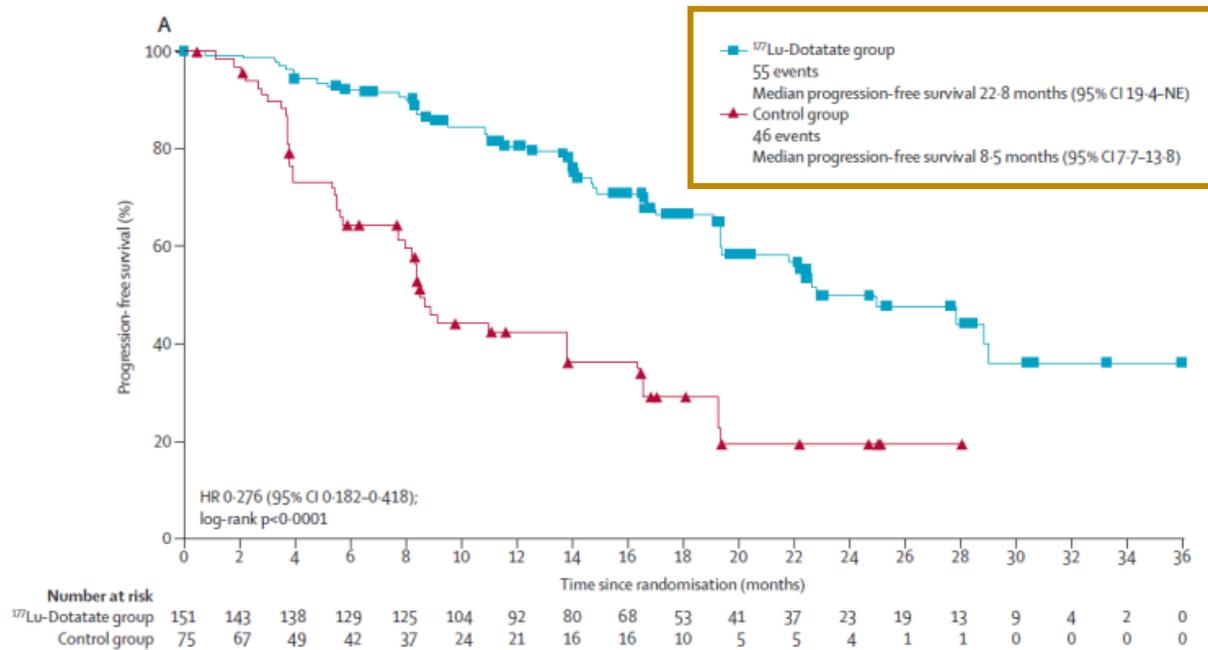
- First study demonstrating benefit of ^{177}Lu-dotatate in 1L treatment of GEP-NET, including WD-Gr2/3 NET and for pancreatic NET
- ORR 43% vs 9.3%, with higher ORR in pancreas vs small bowel NET (51.2% vs 26.7%)
- Most common AE's are low grade diarrhea, abdominal pain, nausea
- ~1% risk of MDS/AML, which can occur within first 2 years
- Questions remain:
  - 1) Do all patients need 1L Lutathera?
  - 2) Is high dose octreotide LAR a fair comparator in higher grade disease?

Sequencing of Radioligand Therapy in GEP-NET

OCCULORANDOM STUDY
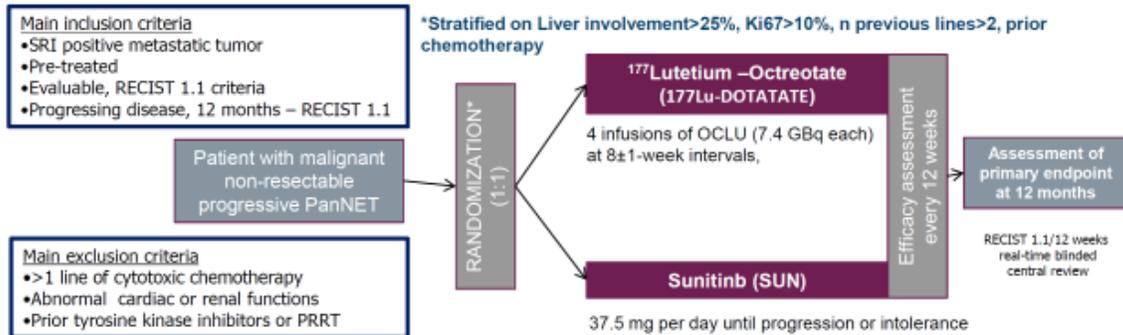
Baudin E et al. Abstract 8870. ESMO Congress 2022

COMPETE STUDY
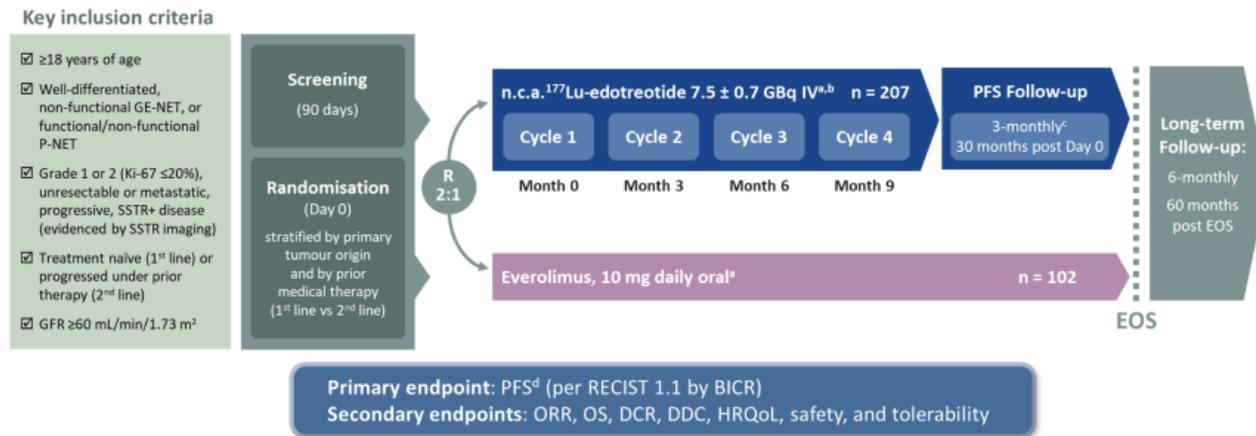
Capdevila J E et al. ENETS 2025

Sequencing of Radioligand Therapy (RLT) in GEP-NET

OCCULORANDOM STUDY

Baudin E et al. Abstract 8870. ESMO Congress 2022

COMPETE STUDY
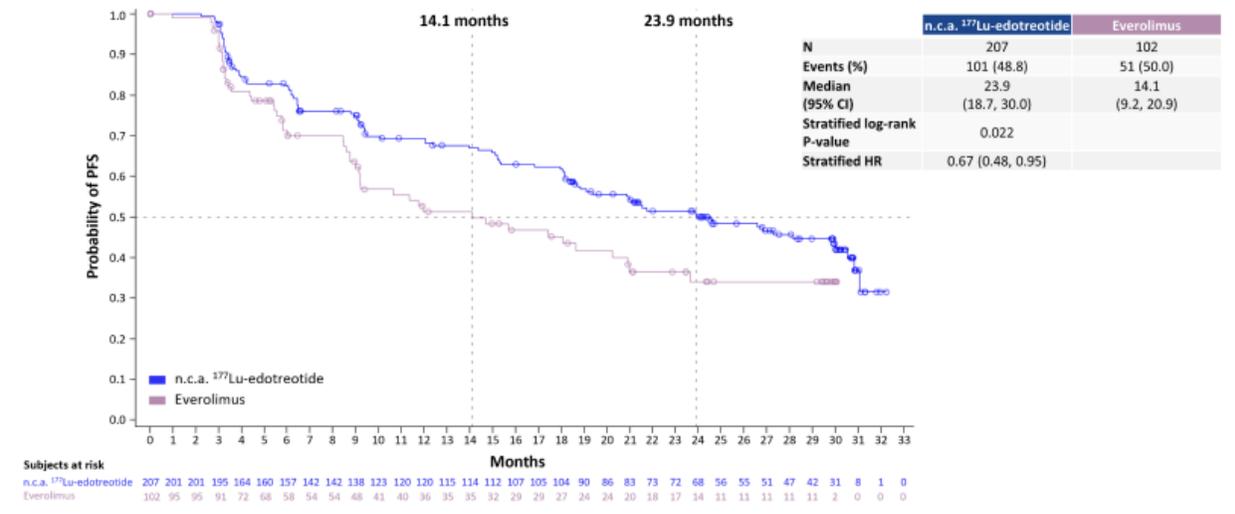
Capdevila J E et al. ENETS 2025

- OCULORANDOM and COMPETE suggest that earlier treatment with RLT is better (at least compared to sunitinib for pNET and everolimus for GEP-NET)

- Ongoing studies will address RLT compared to other systemic treatments (e.g. CAPTEM/FOLFOX) in higher-grade GEP-NET

Alpha-emitter PRRT: Evolving treatment in GEP-NET
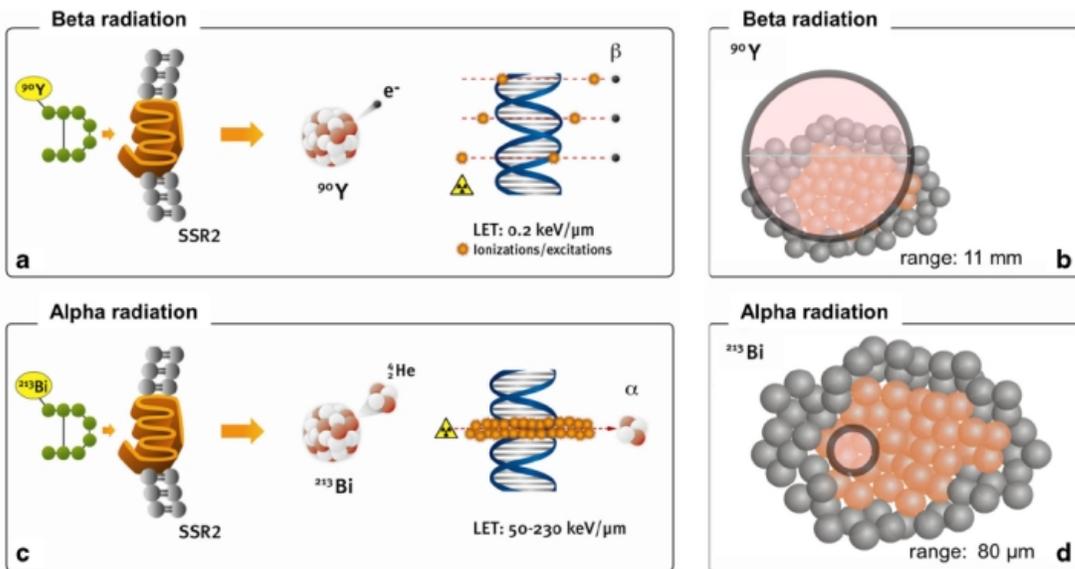
Eur J Nucl Med Mol Imaging (2014) 41:2106–2119
DOI 10.1007/s00259-014-2857-9

Targeted Alpha-Emitter Therapy With ^{212}Pb-DOTAMTATE for the Treatment of Metastatic SSTR-Expressing Neuroendocrine Tumors: First-in-Human, Dose-Escalation Clinical Trial

Ebrahim S Delpassand, Izabela Tworowska, Rouzbeh Esfandiari, Julien Torgue, Jason Hurt, Afshin Shafie and Rodolfo Núñez
Journal of Nuclear Medicine January 2022, jnumed.121.263230; DOI: https://doi.org/10.2967/jnumed.121.263230
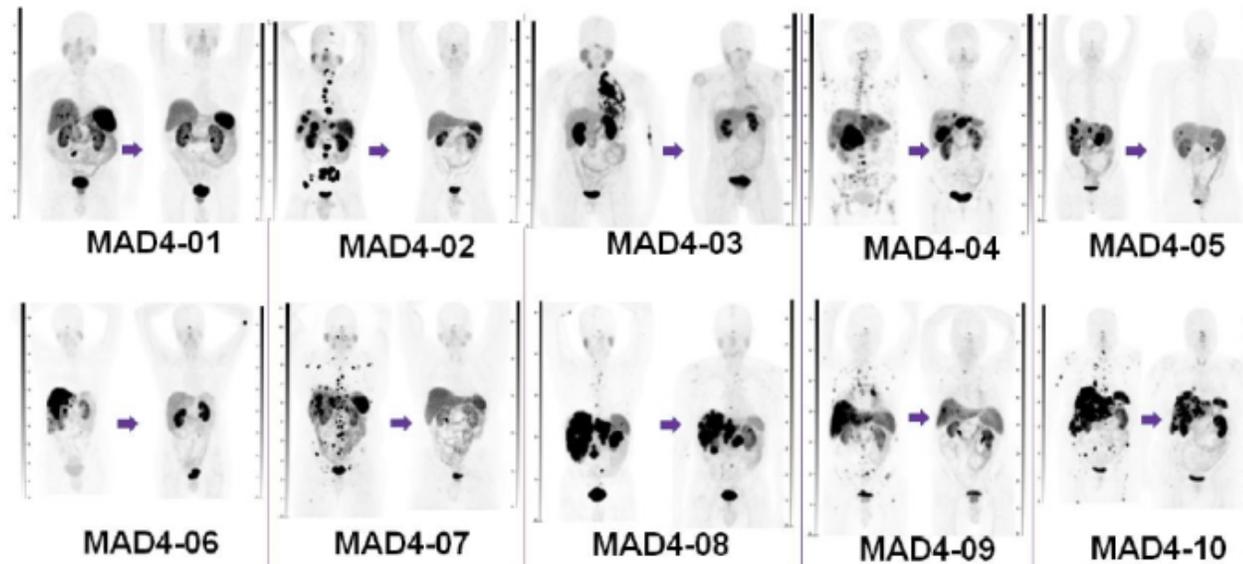
- Current PRRT treatments consists of beta-radiation
- Alpha-radiation particles penetrate cell with less scatter and increase chance for double stranded DNA breaks
- Preliminary studies suggest active even in patients who have received prior beta-emitter PRRT
- Phase 3 ACTION-1 Study ongoing against other systemic treatments (NCT05477576)

Tyrosine Kinase Inhibitors/Angiogenesis Inhibition in GEP-NET

- Tyrosine kinase inhibitors (TKI) target various pathways, particularly with respect to angiogenesis

- VEGF/VEGFR pathway is primary target but most TKI's target other pathways (e.g. c-KIT, PDGFR, others)

- New TKI's inhibit other pathways (e.g FGFR, CSF1-R, MET, AXL) which may be able to overcome resistance after progression on prior treatments

- Sunitinib only approved TKI (for pNET)
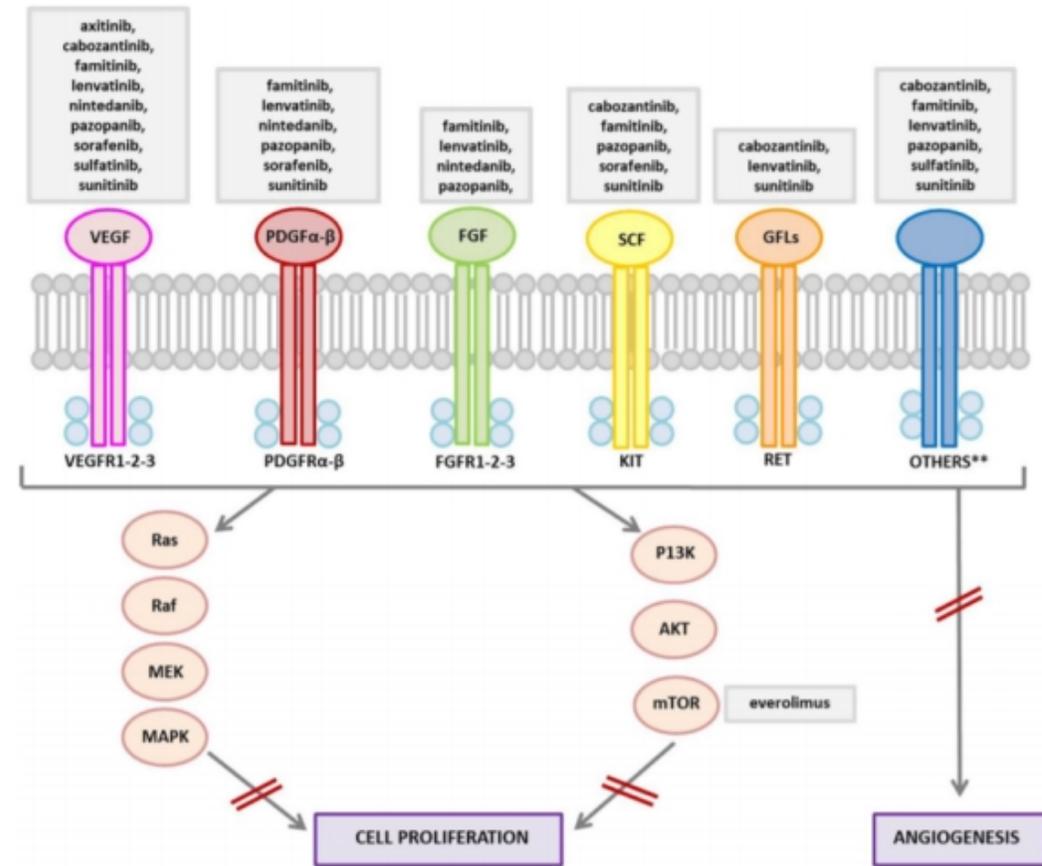
Grillo F et al. Endocrine-Related Cancer, 2018; 25: R405–R418

Studies of Other Tyrosine Kinase Inhibitors
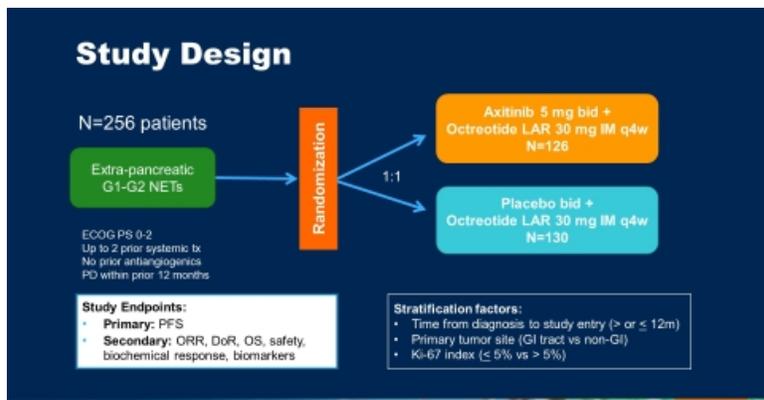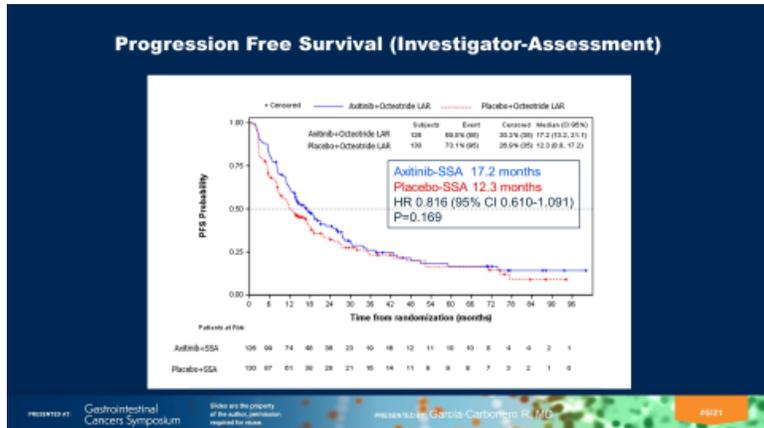
Garcia-Carbonero R et al. Abstract 360, ASCO GI 2019
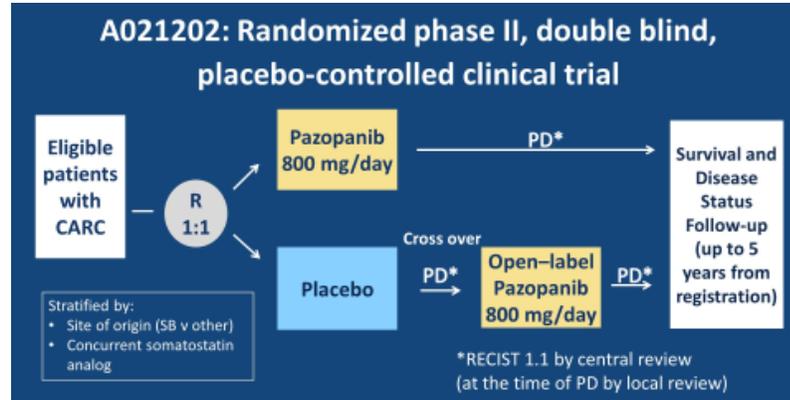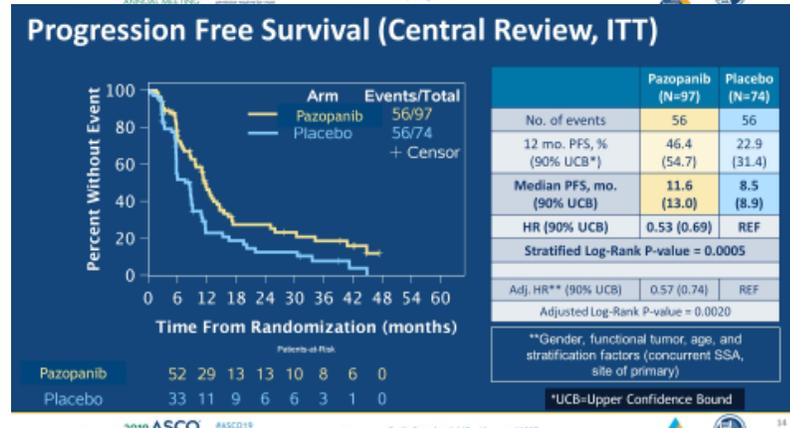
Bergsland EK et al. Abstract 4005, ASCO 2019

Lenvatinib
Capdevila J et al. J Clin Oncol 2021;39: 2304-2312.
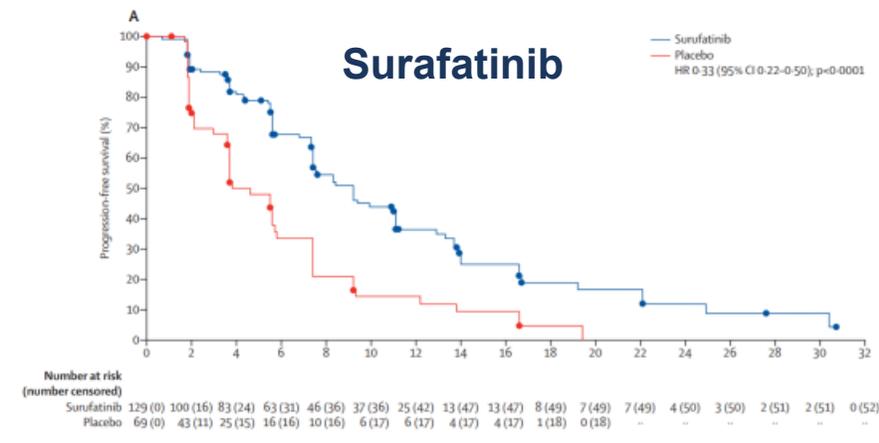
Surafatinib
Xiu J et al. Lancet Oncol 2020; 21: 1500–12.
Paulson S et al. Abstract 4114, ASCO 2021.

- **Various TKI's (pazopanib, axinitinib, lenvatinib, surafatinib) have been evaluated**
- **New TKI's target other pathways (e.g. CSF-1R with surafatinib)**
- **No new approvals due to mixed results (pazopanib, axitinib), non-randomized & toxicities (lenvatinib), or need to be studied in other countries (surafatinib)**

36

Alliance A021602/CABINET Study:
Cabozantinib for Refractory GEP-NET and Pulmonary NET

CABINET Trial Study Design

Extra-pancreatic NET (epNET) → R 2:1 → Cabozantinib 60 mg daily → PD*

Pancreatic NET (pNET) → R 2:1 → Placebo daily → PD* → Open-label Cabozantinib 60 mg daily

* Unblinding and crossover allowed after confirmation of PD by central radiology review
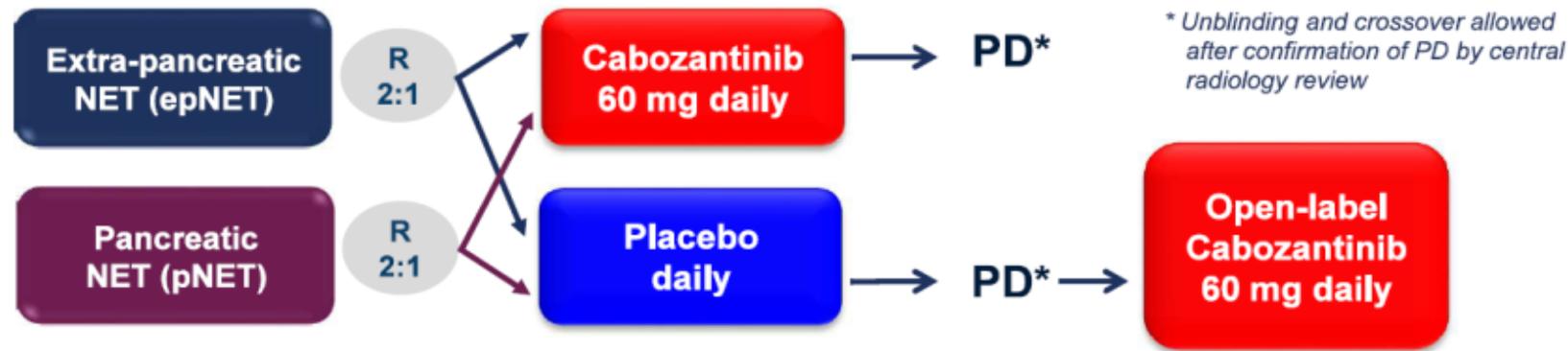
Stratification factors:
- epNET: Concurrent SSA & Primary site (midgut GI/unknown vs, non-midgut GI/lung/other)
- pNET: Concurrent SSA & Prior sunitinib

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

Chan JA et al. Abstract LBA53. ESMO Congress 2023

CABINET Trial Results

epNET Cohort: Progression-Free Survival (Local Review)

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)

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
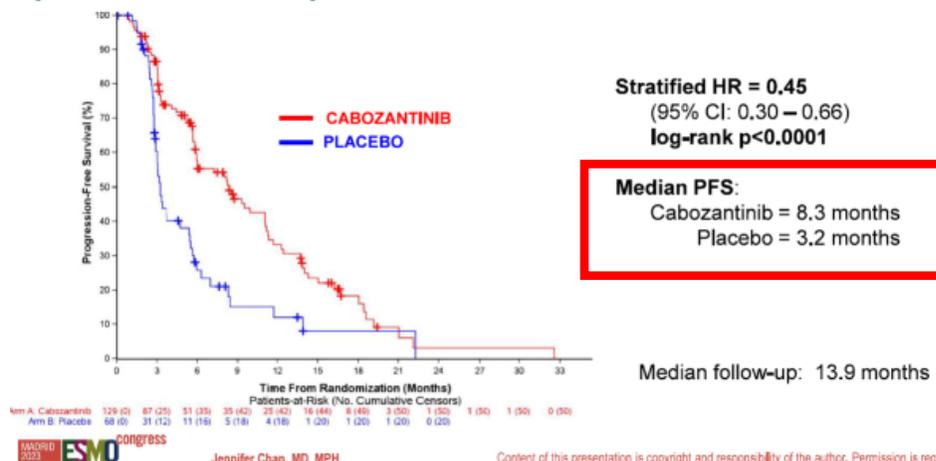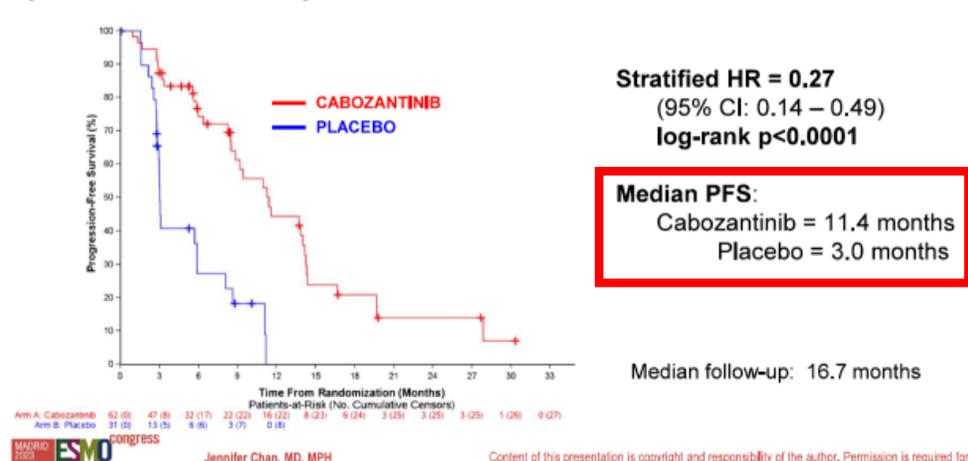
Best Overall Response (Local Review)

epNET Cohort

CABOZANTINIB — ORR 4%

PLACEBO — ORR 1%

Best response	CABO (N=129)	PLACEBO (N=68)
PR	5 (4%)	1 (1%)
SD	78 (60%)	26 (38%)
PD	21 (16%)	29 (43%)
Not Evaluable	25 (19%)	12 (18%)

pNET Cohort

CABOZANTINIB — ORR 18%

PLACEBO — ORR 6%

Best response	CABO (N=62)	PLACEBO (N=31)
PR	11 (18%)	2 (6%)
SD	36 (58%)	12 (39%)
PD	5 (8%)	14 (45%)
Not Evaluable	10 (16%)	3 (10%)

Overall Survival

epNET Cohort

Stratified HR = 0.90
(95% CI: 0.56 – 1.46)
log-rank p = 0.34

Median OS:
Cabozantinib = 21.9 months
Placebo = 22.4 months

pNET Cohort

Stratified HR = 0.77
(95% CI: 0.34 – 1.73)
log-rank p = 0.26

Median OS:
Cabozantinib = 43.5 months
Placebo = 31.0 months

Jennifer Chan, MD, MPH

Chan JA et al. Abstract LBA53. ESMO Congress 2023

Summary of CABINET Study Results

- Cabozantinib demonstrated significant improvement in PFS in previously treated GEP-NET

- Benefit seen in pancreas and small bowel NET, but benefit greater in pancreatic NET

- First study demonstrating benefit of an angiogenesis inhibitor in WD-Gr3 disease

- Notable AE's: Fatigue, diarrhea, hypertension, hand/foot syndrome

- Will be a new standard of care in previously treated GEP-NET (anticipated PDUFA date Apr 2025)

- Questions remain:

    - Optimal dose?: Recommended to start 60 mg po daily then dose-reduce as needed for toxicities

    - How best to sequence with other therapies? (e.g. pancreatic NET where there are more options)

Belzutifan in VHL-Associated Pancreatic NET (pNET)

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Belzutifan for Renal Cell Carcinoma in von Hippel–Lindau Disease

|	RCC (n=61)	Pancreatic Lesions (n=61)	pNET (n=22)	CNS Hemangioblastoma (n=50)
Objective Response Rate (ORR = CR + PR)	30 (49%)	47 (77%)	20 (91%)	15 (30%)
Complete response (CR)	0	6 (9.8%)	3 (13.6%)	3 (6.0%)
Partial response (PR)	30 (49%)	41 (67.2%)	17 (77.3%)	12 (24.0%)
Stable Disease (SD)	30 (49%)	12 (21.3%)	2 (9.1%)	31 (62.0%)
Median time to response	8.2 months	8.4 months	5.5 months	3.2 months
Median duration of response	Not reached	Not reached	Not reached	Not reached

- Belzutifan targets HIF-2$^\alpha$ which is upregulated in VHL associated cancers

- Secondary analysis of belzutifan in patients with VHL associated RCC who had concurrent pNET

- Belzutifan demonstrated ORR of pNET

- Listed in NCCN guidelines as an option for progressive VHL-associated pNET

- Remaining questions:
  - Most VHL pNET are indolent and localized disease --> when would Belzutifan be helpful?
  - Would this provide benefit in metastatic pNET (study excluded metastatic disease)?
  - Efficacy compared to other therapies for pNET? (i.e. sequencing)

Jonasch E, et al. N Engl J Med 2021; 385:2036-46.

Treatments for GEP-NEC

NEC Prevalence (SEER Database 1973-2012)
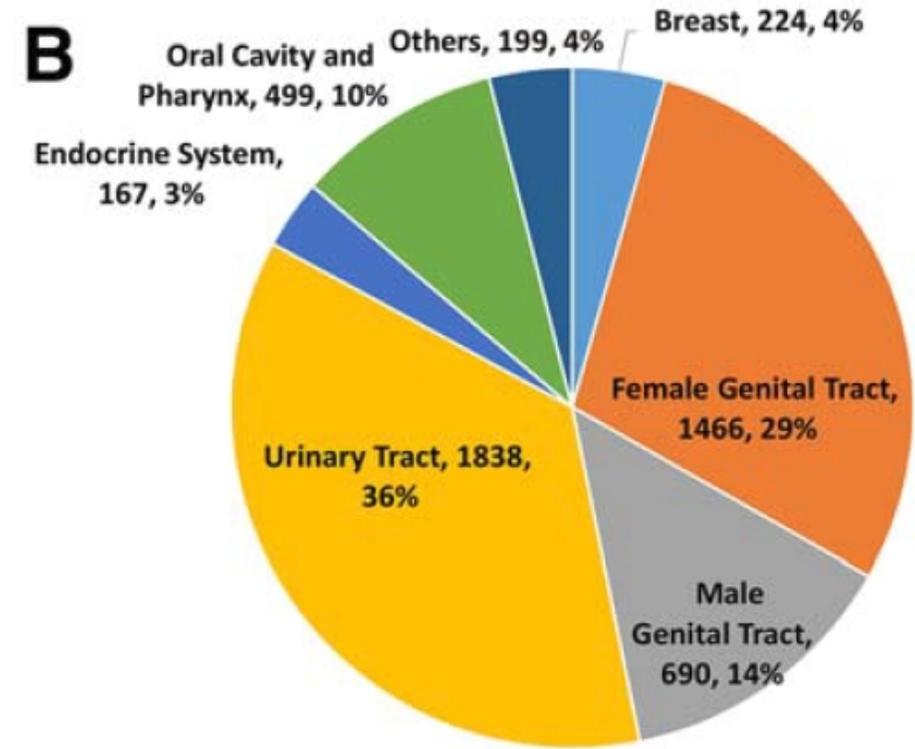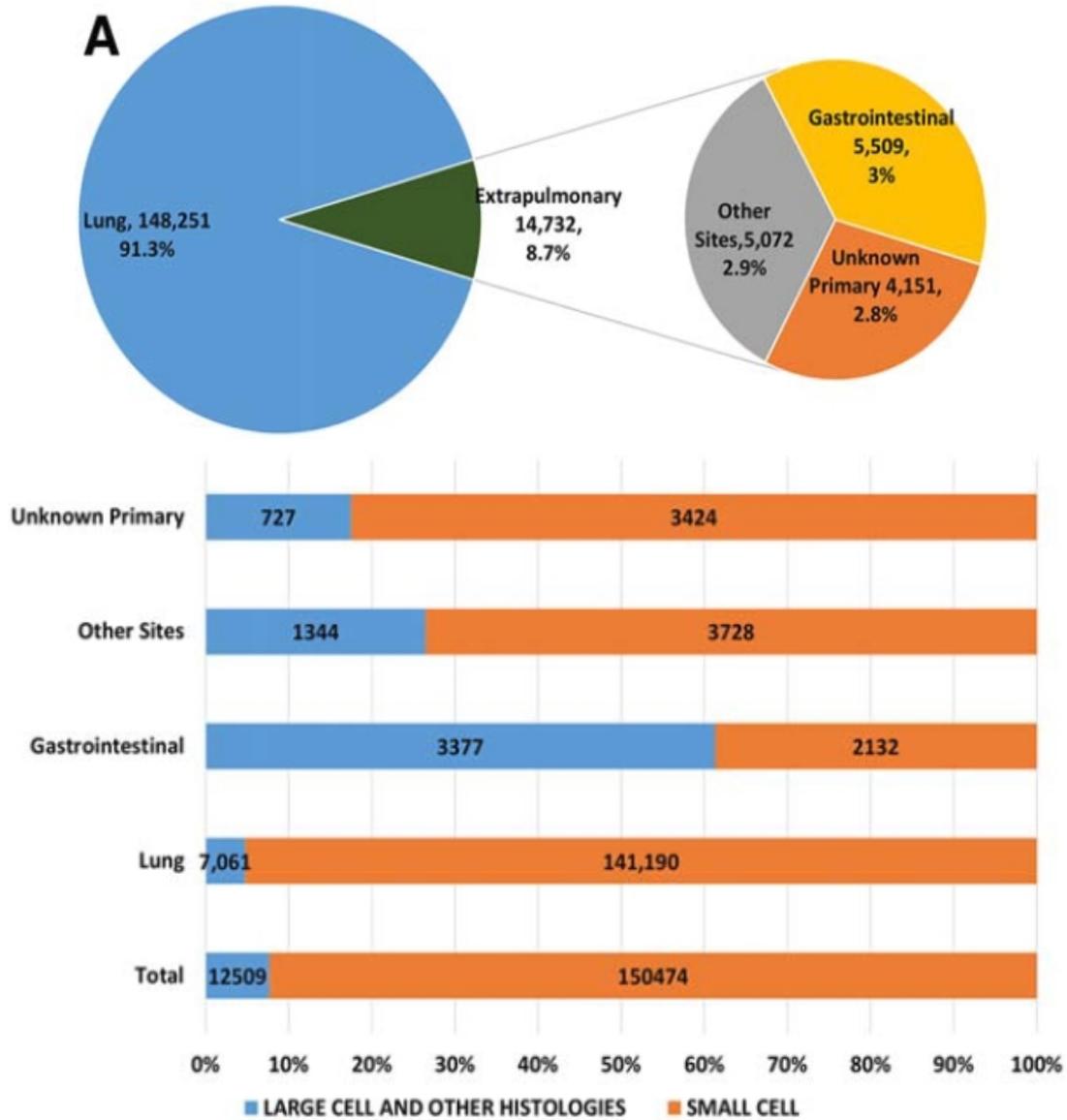
Dasari A et al. Cancer 2018

Current Treatment Paradigm in NEC

- Extrapolated from small cell lung cancer (SCLC) with use of platinum (cisplatin or carboplatin)/etoposide
- Data from restrospective series, except for 1 recent prospective study presented

Study	N	Histology (%)	Ki-67 Proportion	OS	PFS	RR
NORDIC-NEC[1] (GI)	305	Small Cell: 38% Non-small cell: 49% Unknown: 13%	**≥55%:** 54%	11 mo	4 mo	**Overall:** 31% **Ki-67 ≤ 55%:** 15% **Ki-67 ≥55%:** 42%
FFCD-GTE[2] (GI & unknown primary)	Total: 253 GI-NEC: 189	Small Cell: 39% Large Cell: 61%	**51-80%:** 47% **>80%:** 18%	11.6 mo	6.2 mo	50%
Mackey JR et al.[3] (GU)	Total 180 (106 bladder, 60 prostate, 8 renal, 6 ureter)	42.7% with mixed histology (adeno+ small cell);	Not reported	**Overall:** 10.5 mo Prostate: 7 mo Bladder: 13 mo	?	?
Margolis B et al.[4] (Cervix)	1,896	Not reported	Not reported	~10 mo	?	?
Morizane C et al. (GI, prospective)[5]	170	Small Cell: 48% Large Cell: 52%	Ki-67 ≥50%: 85%	12.5 mo	5.6 mo	54.5%

43

[1]Sorbye H et al. Ann Oncol 2013 [2]Walter T et al. Eur J Cancer 2017 [3]Mackey J et al. J Urol 1998 [4]Margolis B et al. Gynecol Oncol 2016 [5]Morizane C et al. JAMA Oncol 2022.

Systemic Therapies for Refractory NEC

NEC
FOFLOX
FOLFIRI
FOLFIRINOX
Temozolomide +/- Capecitabine
Nivolumab + Ipilimumab
Pembrolizumab (if MSI-H or TMB ≥10)

Adapted from NCCN Neuroendocrine Guidelines, v. Feb 2022

- No established standard for NEC after progression on platinum/etoposide

- Outcomes remain poor:
  - ORR: 20-30%
  - Median PFS ~3 months
  - Median OS 6-9 months

- Need more effective treatments

Nivolumab + Ipilimumab in Refractory Extrapulmonary NEC

**SWOG S1609:
DART Study**

Response Rate by Tumor Grade of Neuroendocrine Neoplasm
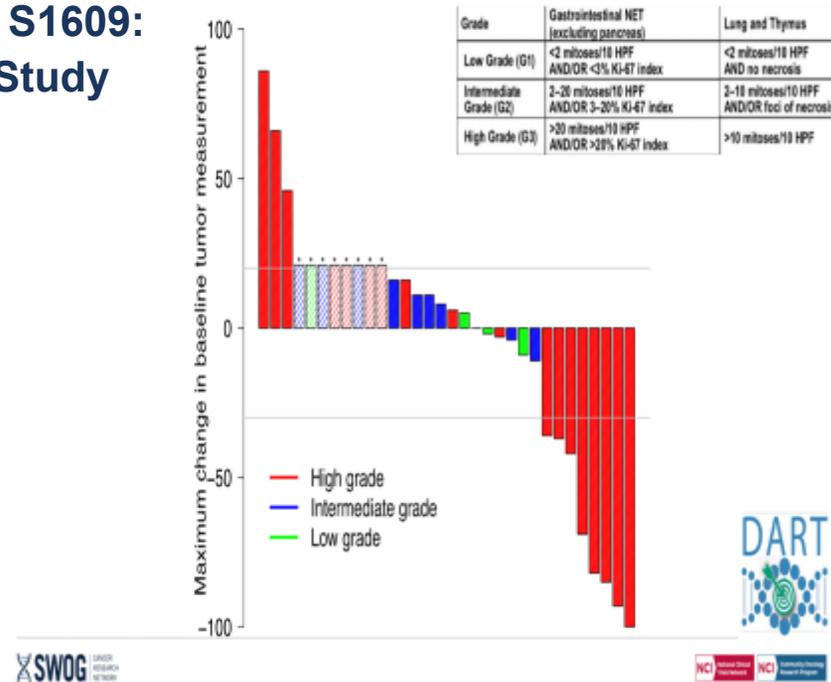
Patel SP et al. Clin Cancer Res 2020; 26: 2290-6

GCO-001 NIPINEC trial

Randomized, non-comparative phase II trial – Fleming's two-stage design
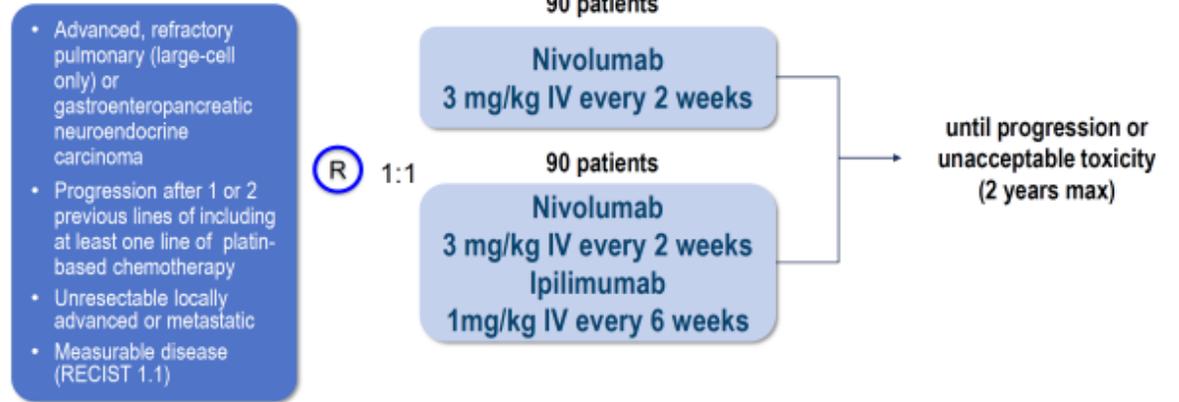
Walter T et al. Abstract LBA41. ESMO Congress 2021

- Effective in high grade NEN/NEC (and not NET)
- Extrapumonary ORR: 10-25% (lower compared to lung NEC ~20-60%; nivolumab alone ORR: 7.1%)
- 6-month PFS: 20-30%; Median OS 6-11 months
- **Suggests that combination therapy is more effective than monotherapy**

SWOG S2012: Randomized Phase 2/3 Trial of First Line Platinum/Etoposide +/- Atezolizumab for Extrapulmonary NEC

- **Activated Dec 2, 2021 (restricted to small cell NEC)**
- **Jan 2023: Amended to allow all NEC Subtypes**
- **Feb 2024: Amended to remove Ki-67 for GU NEC**
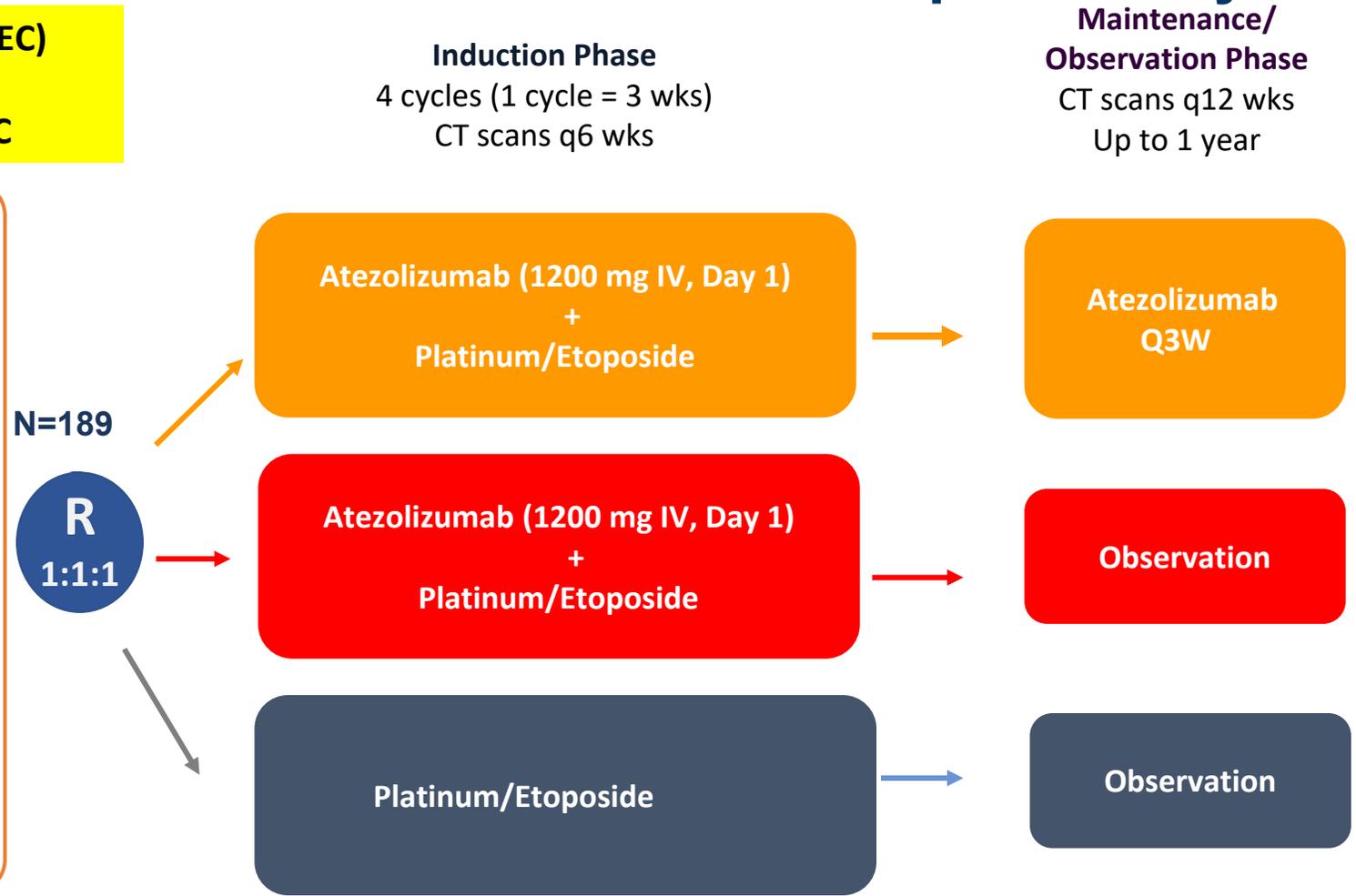
Induction Phase
4 cycles (1 cycle = 3 wks)
CT scans q6 wks

Maintenance/ Observation Phase
CT scans q12 wks
Up to 1 year

Key Eligibility: (N= 118/189)

- Metastatic poorly-differentiated extrapulmonary (i.e. exclude lung) NEC with Ki-67≥55%
- Evaluable, measurable and non-measurable disease
- Zubrod PS 0-2
- No prior treatment **EXCEPT one cycle of platinum/etoposide allowed**
- Asymptomatic brain metastases eligible
- **Stratification factors:**
  - ❏1) PS 0-1 vs 2
  - ❏2) Known prostate vs GI vs other origin

N=189

R
1:1:1

Atezolizumab (1200 mg IV, Day 1) + Platinum/Etoposide → **Atezolizumab Q3W**

Atezolizumab (1200 mg IV, Day 1) + Platinum/Etoposide → **Observation**
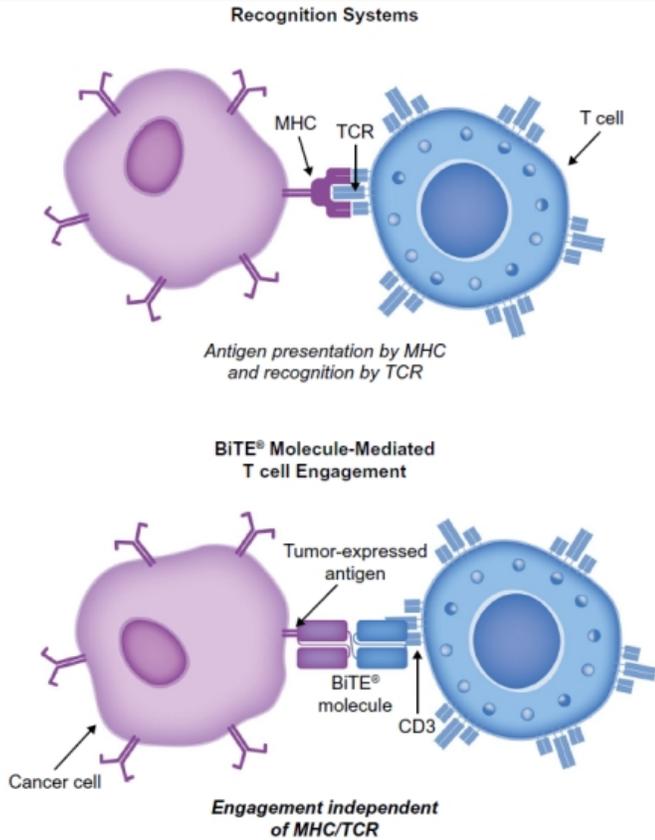
Platinum/Etoposide → **Observation**

Primary endpoint: OS (from time of randomization)
Secondary endpoints: OS (from time of maintenance/observation), PFS, ORR, DOR
Translational analyses: Banking tissue and blood for future biomarker analyses

Zhen DB, Chiorean EG, et al. Abstract TPS4201. ASCO 2024. NCT05058651

Novel Therapies for NEC

Bi-specific T-cell engagers (BiTE)[1]

Antibody Drug Conjugates (ADC)[2]
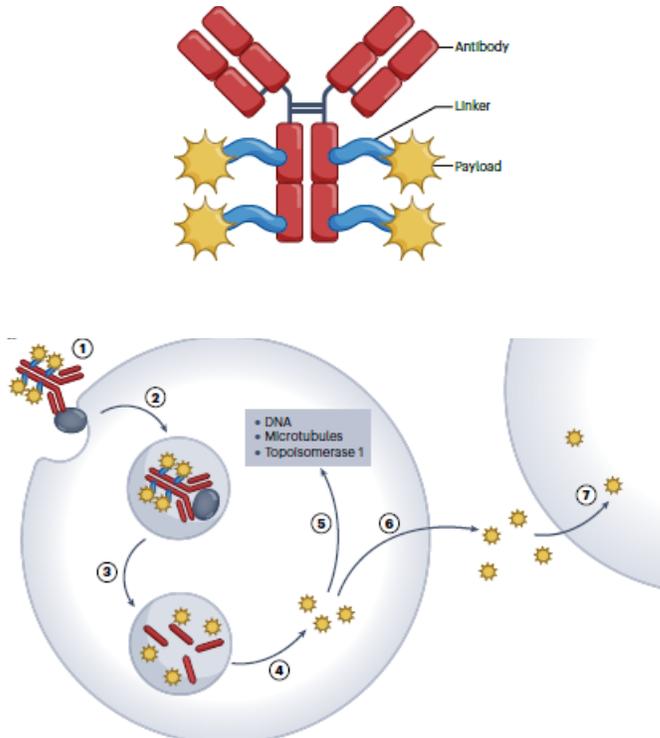
CAR-T[3]
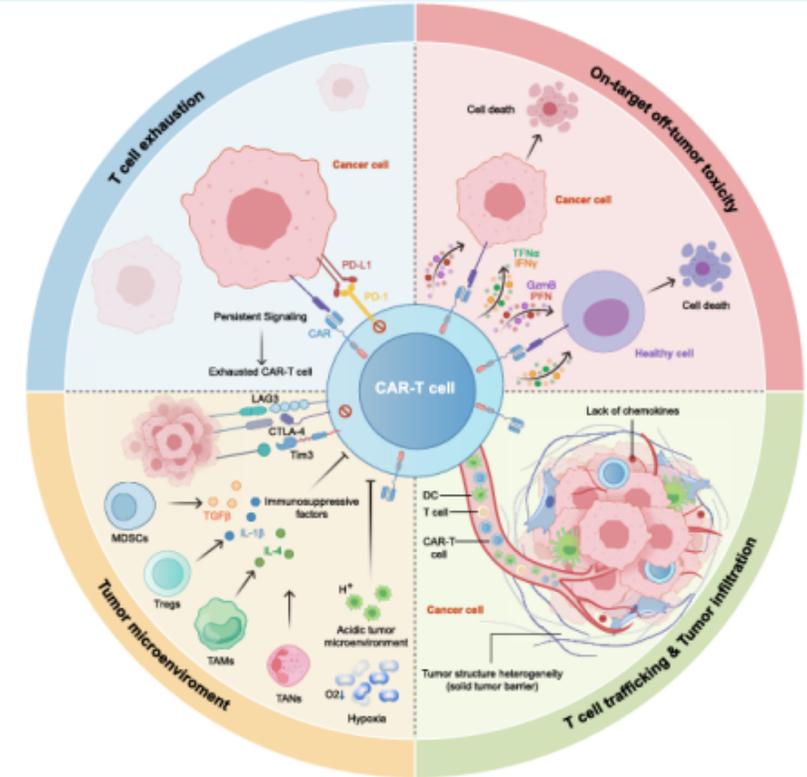
[1]Einsele H et al. Cancer 2020.
[2]Dumontet C et al. Nature Rev Drugs Disc. 2023: 22; 641-661
[3]Du B et al. Cancer Cell 2025: 43; 665-679

Death-like Ligand 3 (DLL-3) BiTE for NEC

Tarlatamab in Prostate NEC

Aggarwal R et al. Abstract 5012. ASCO 2024

Obrixtamig in Extrapulmonary NEC

Capdevila J et al. Abstract 3004. ASCO 2025

- Very promising BiTE targeting DLL-3 with impressive ORR in heavily pre-treated patients with NEC

- However, access to these drugs remains limited until further randomized studies completed (especially for GI)

- While some patients have significant responses, median DOR is still low and need to better understand mechanisms of response and resistance as well potentially moving therapies earlier in the disease course

- Need to monitor closely and manage cytokine release syndrome (CRS) (ie potential resource constraints in community setting)

Fred Hutchinson Cancer Center

SEZ6 is highly expressed in neuroendocrine neoplasms (NENs) and is the target of the ADC ABBV-706

- SEZ6 is a neuroendocrine lineage marker specifically expressed in SCLC and high-grade NENs[1]

- ABBV-706 is a first-in-class ADC composed of a potent Top1i attached via a stable linker to a SEZ6-directed monoclonal antibody, delivering the cytotoxic payload specifically to SEZ6-expressing tumor cells

- Preliminary data of ABBV-706 monotherapy showed manageable safety and promising activity in SCLC and NENs[2]

SEZ6 Gene Expression

*Data from public sources. ^Data from The Cancer Genome Atlas.
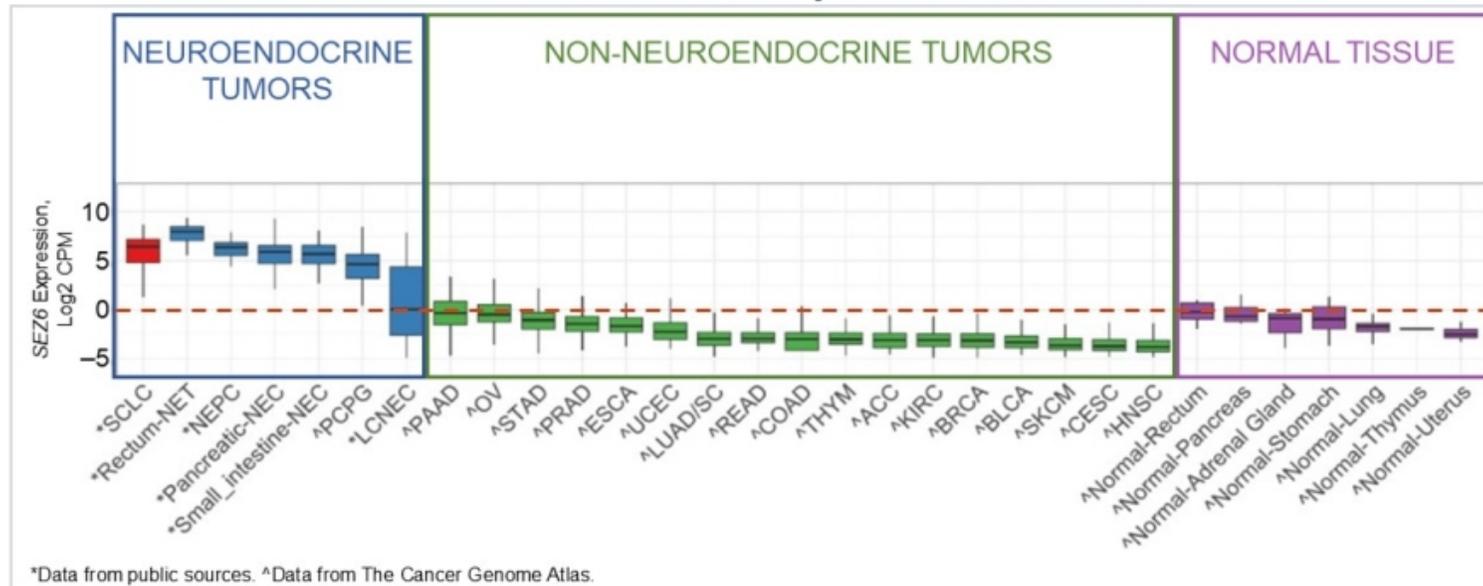
ABBV-706 Mechanism of Action
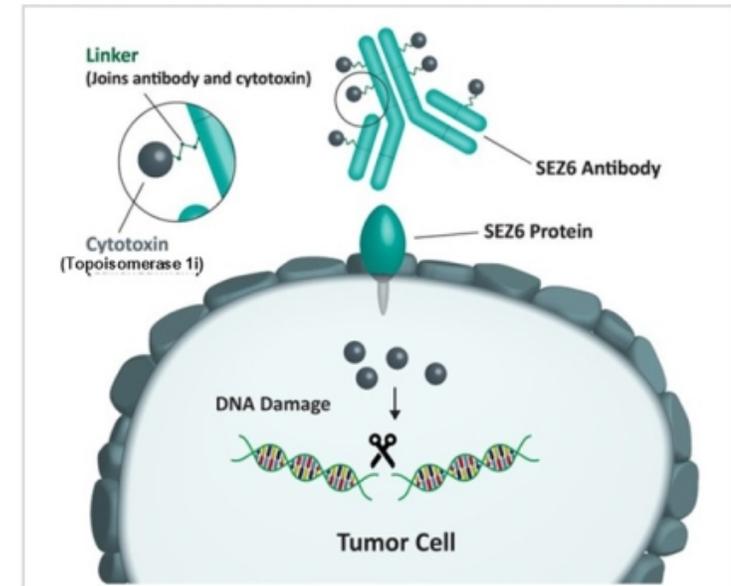
1. Wiedemeyer WR, et al. *Mol Cancer Ther*. 2022;21:986-998. 2. Chandana S, et al. ASCO 2024. Abstract 3001 (oral presentation).
ADC, antibody-drug conjugate; LCNEC, large cell NEC; NEC, neuroendocrine carcinoma; NEPC, neuroendocrine prostate cancer; NET, neuroendocrine tumor; SCLC, small cell lung cancer; SEZ6, seizure-related homolog protein 6; Top1i, topoisomerase 1 inhibitor.

Cooper A et al. Abstract 3085. ASCO 2025

ABBV-706 has promising antitumor activity in NENs

Change in Target Lesion Size by Dose (N=65)

ABBV-706 dose
- 1.8 mg/kg N=8
- 2.5 mg/kg N=49
- 3.0 mg/kg N=7
- 3.5 mg/kg N=1
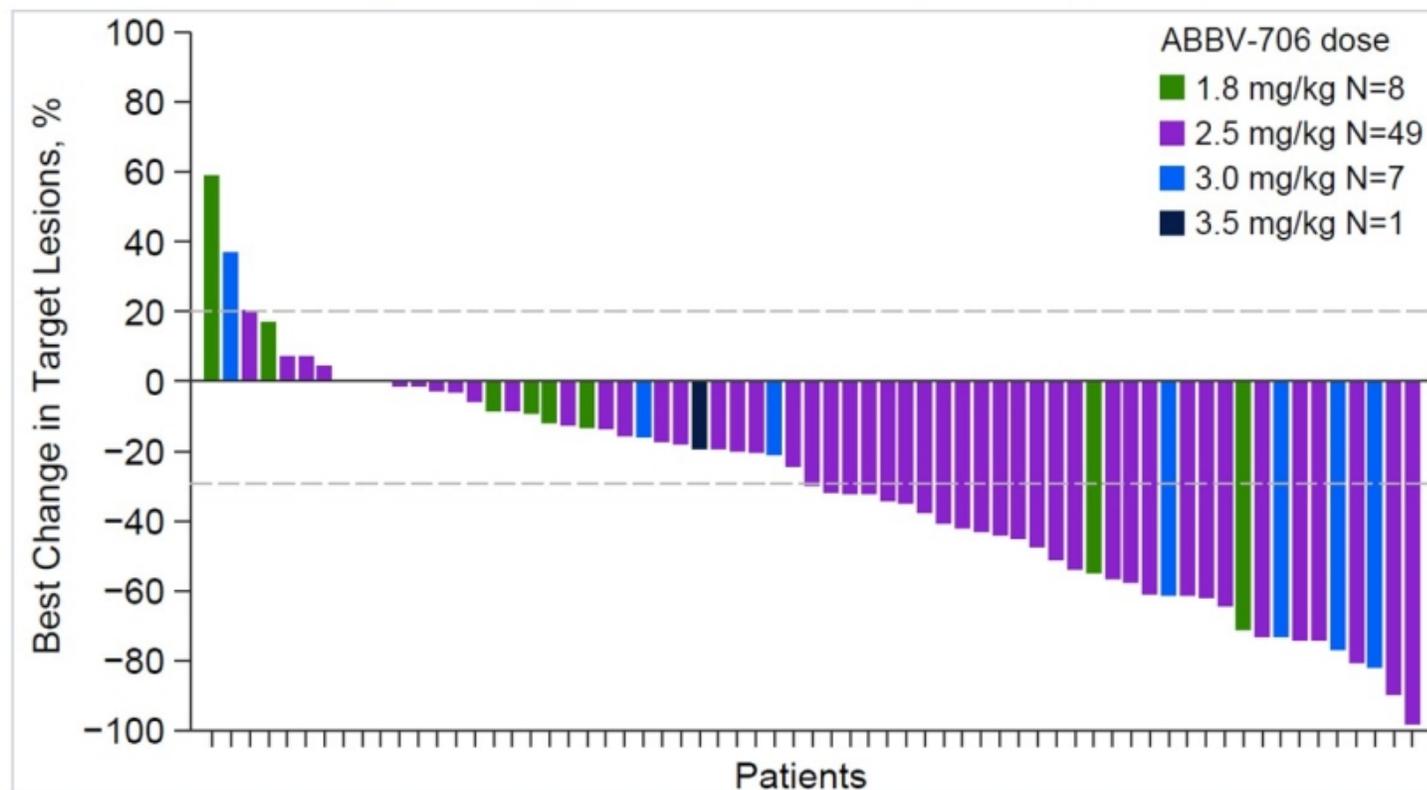
Outcome	Total NEN (N=65)[a,b]
ORR,[c] n (%) [95% exact CI]	**24 (36.9)** [25.3, 49.8]
Best response, n (%)	
CR	1 (1.5)
PR	23 (35.4)
SD	37 (56.9)
PD	4 (6.2)
Median DOR, months [95% CI]	6.37 [4.44, 9.46]
Median PFS, months [95% CI]	7.62 [5.52, 8.31]

- As of January 3, 2025, cutoff, 17/65 (26%) patients remain on treatment

- Median follow-up was 8.67 months for the 2.5-mg/kg cohort (n=49/65, 75%)

[a]Patients with response evaluation per RECIST v1.1. [b]49 of 65 (75%) patients received ABBV-706 at 2.5 mg/kg. [c]Requires a CR or PR confirmed ≥4 weeks later.
CI, confidence interval; CR, complete response; DOR, duration of response; NEN, neuroendocrine neoplasm; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Fred Hutch Cancer Center

Thank you

dbzhen@uw.edu