Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NEN)

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Disclosures

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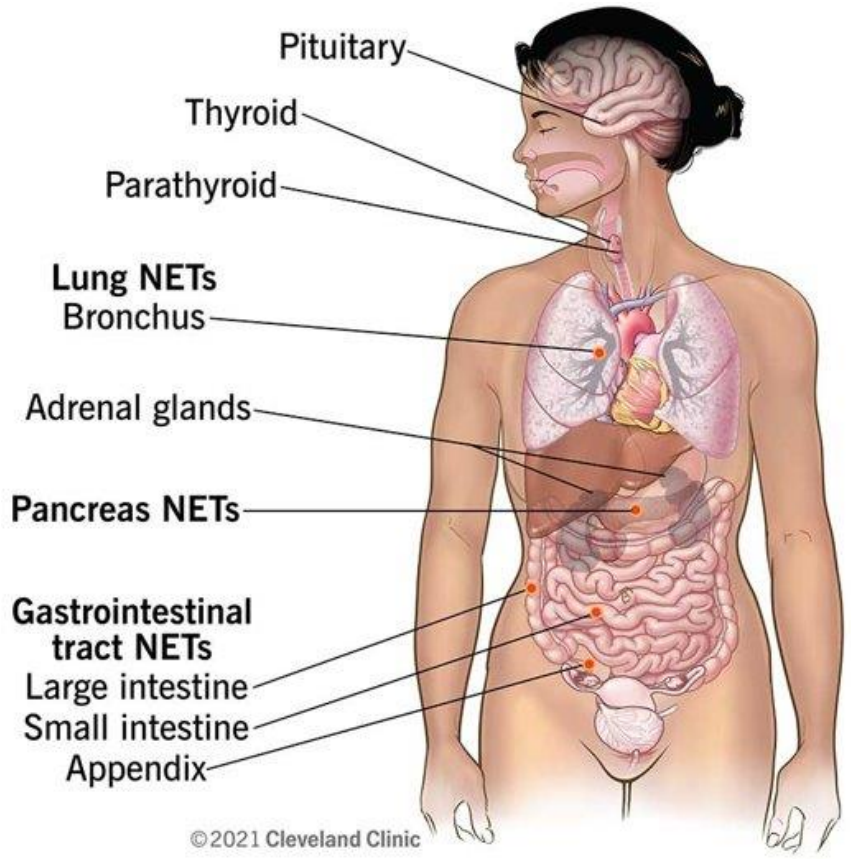
Outline

- Overview and Clinical Symptoms of GEP-NEN
- Workup and Staging of GEP-NEN
- Systemic Therapies for GEP-NET
- Systemic Therapies for GEP-NEC

Overview and Clinical Presentations of GEP-NEN

Neuroendocrine Neoplasms (NEN)



- 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)

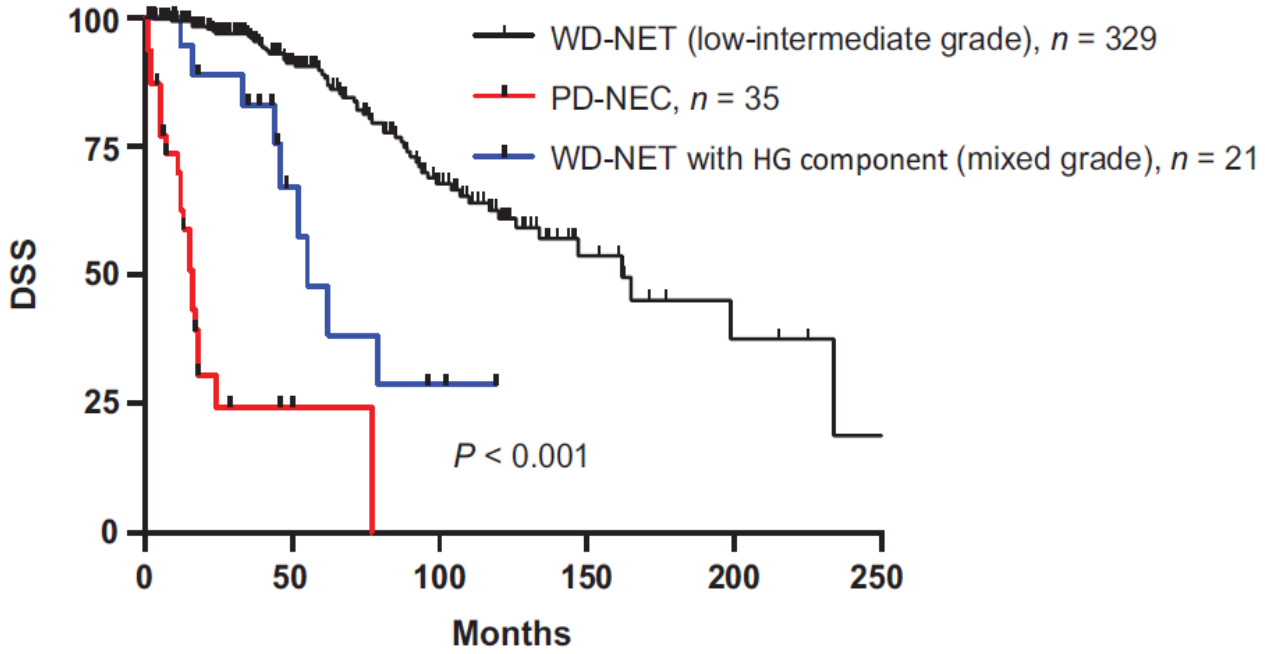
https://my.clevelandclinic.org/health/diseases/22006-neuroendocrine-tumors-net

2019 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
New category compared to prior WHO classifications	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

Adapted from Rindi G et al. *Mod. Pathol.* 2018; **31**; 1770 – 1786.

Relevance of 2019 WHO Pathological Criteria

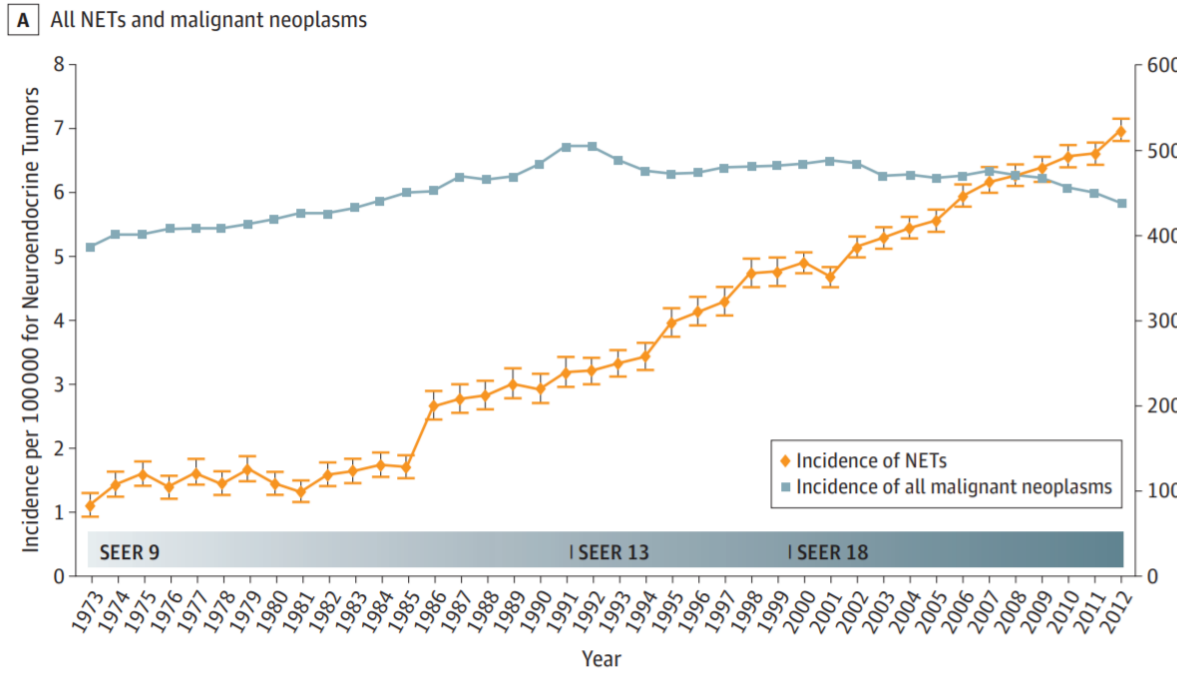


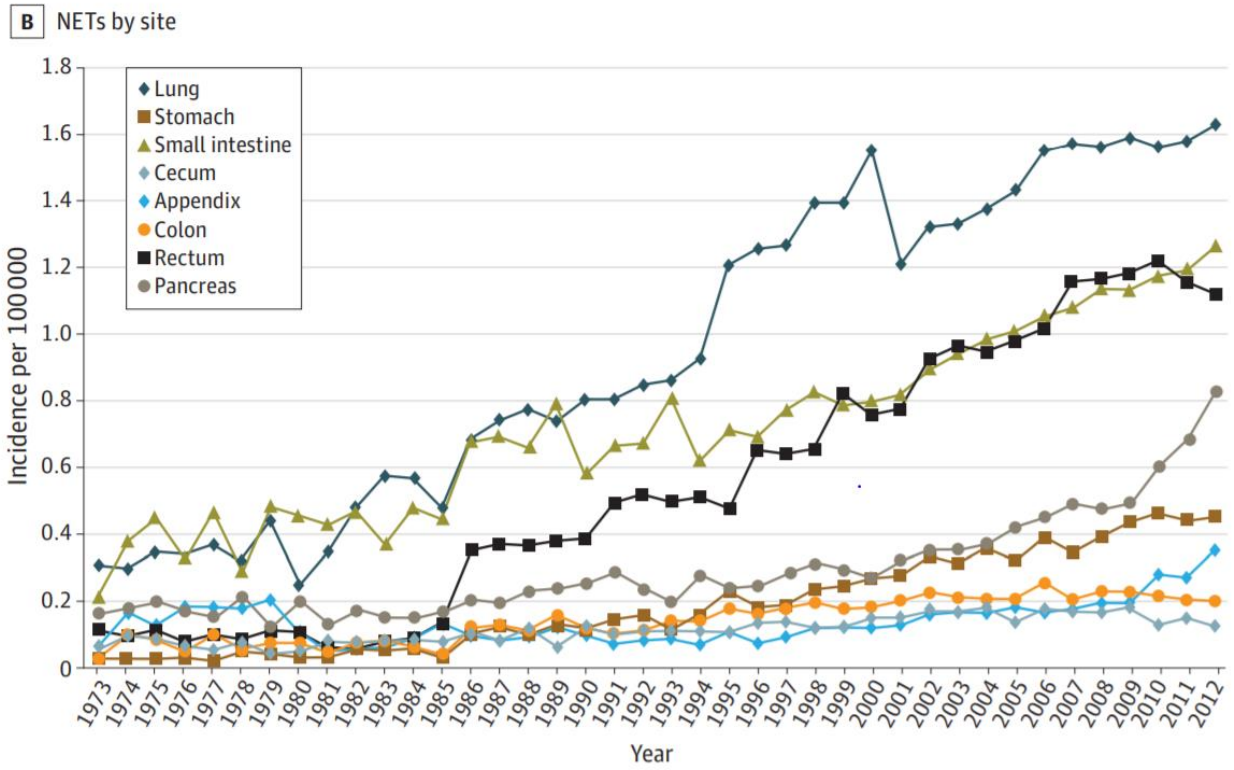
Tang et al. Clin Cancer Res 2015; 22:1011.

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
- 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





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

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
MEN1	Primary hyperparathyroidism Pituitary tumors Less commonly ▪ Adrenocortical tumors ▪ Carcinoid tumors ▪ Nonmedullary thyroid tumors	11q13	Nonfunctional Gastrinoma Insulinoma Various
Von Hippel-Lindau disease (VHL)	Pheochromocytoma (often bilateral) Retinal and cerebellar hemangioblastomas Renal cell carcinoma	3p25-26	Nonfunctional Various, including cystic tumors
Neurofibromatosis 1 (von Recklinghausen disease)	Neurofibromas Café au lait spots Pheochromocytoma	17q11.2	
Tuberous sclerosis	Cardiac rhabdomyomas Renal cysts Angiomyolipomas	9q33.34 and 16p13.3	

Lifetime Risk

80-100%

~20%

~10%

~1%

Reproduced with permission from: Milan S, Yeo CJ. Neuroendocrine tumors of the pancreas. Curr Opin Oncol 2012; 24:46. Copyright © 2012 Lippincott Williams & Wilkins.

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)**

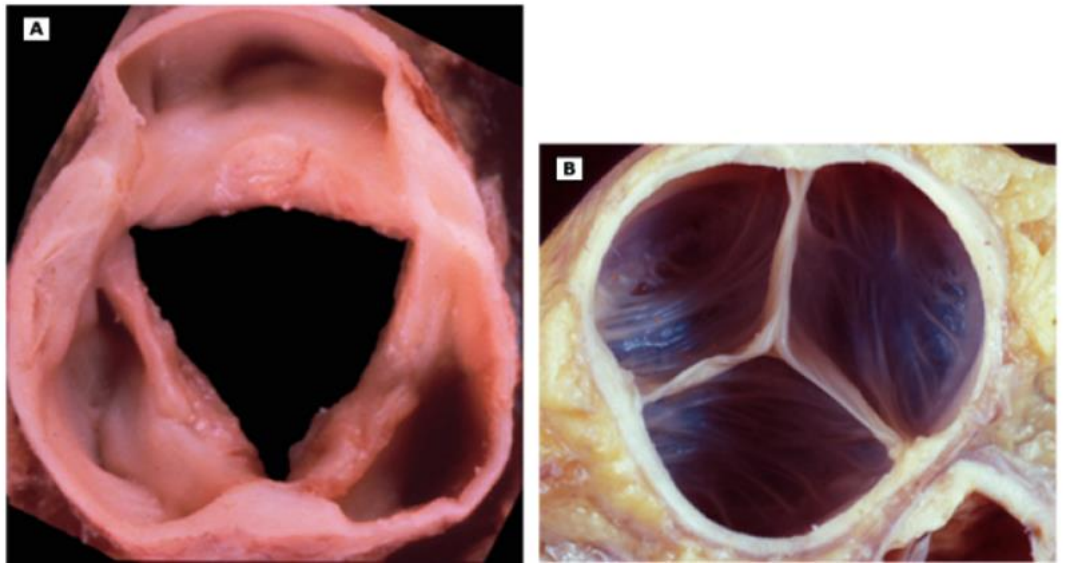
NOTE: Carcinoid Syndrome is less common in pNETs (i.e. hormone excess is not always "Carcinoid Syndrome")

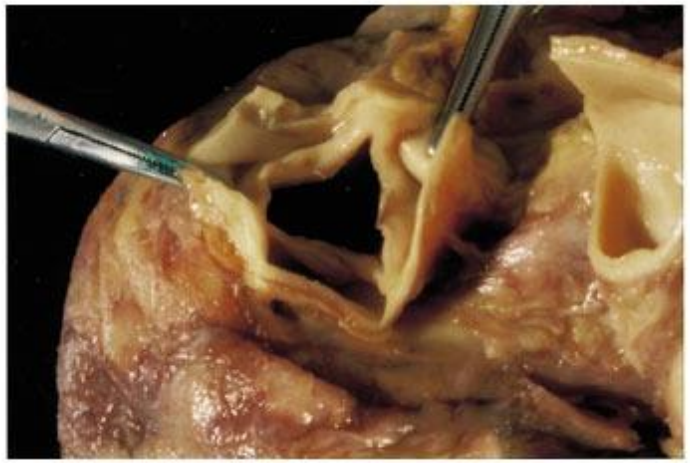
Carcinoids (WD Gr1/2 midgut NET) (8-35% functional)	pNETs (10-40% functional)
- Carcinoid syndrome → flushing, diarrhea, bronchoconstriction, carcinoid heart dx - Due to excess serotonin, tachykinins, or histamine - Typically associated with midgut NETs and in the setting of liver metastases	- *Insulin (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

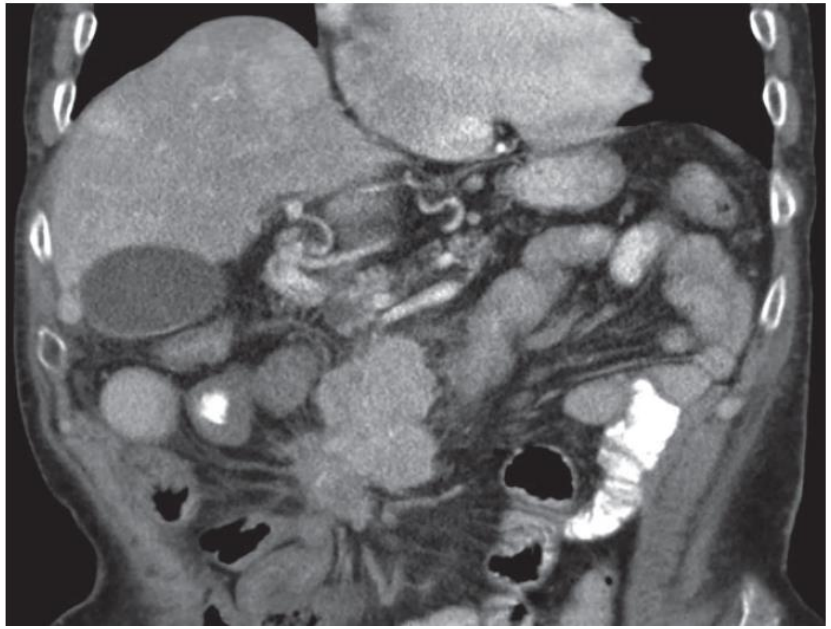
- ~1/3 of carcinoid syndrome-related deaths
- 20-65% of pts with carcinoid syndrome develop valvular pathology
- High serotonin and tachykinin levels released by carcinoid tumor cells → valvulitis and fibroblast proliferation
- Plaque-like fibrous thickening involving classically right heart valves (ie 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).

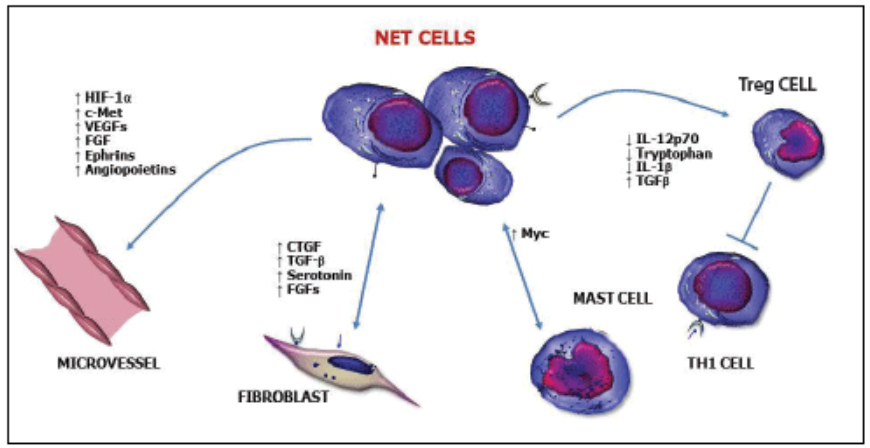


Figure: Role of the Microenvironment in the Pathogenesis of Neuroendocrine Tumors (NETs)—NET cells mutually interact with their microenvironment, prompting angiogenesis through cytokine secretion; inhibiting T-cell function by T-regulatory cell (Treg) dysregulation; promoting infiltration of mast cells 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

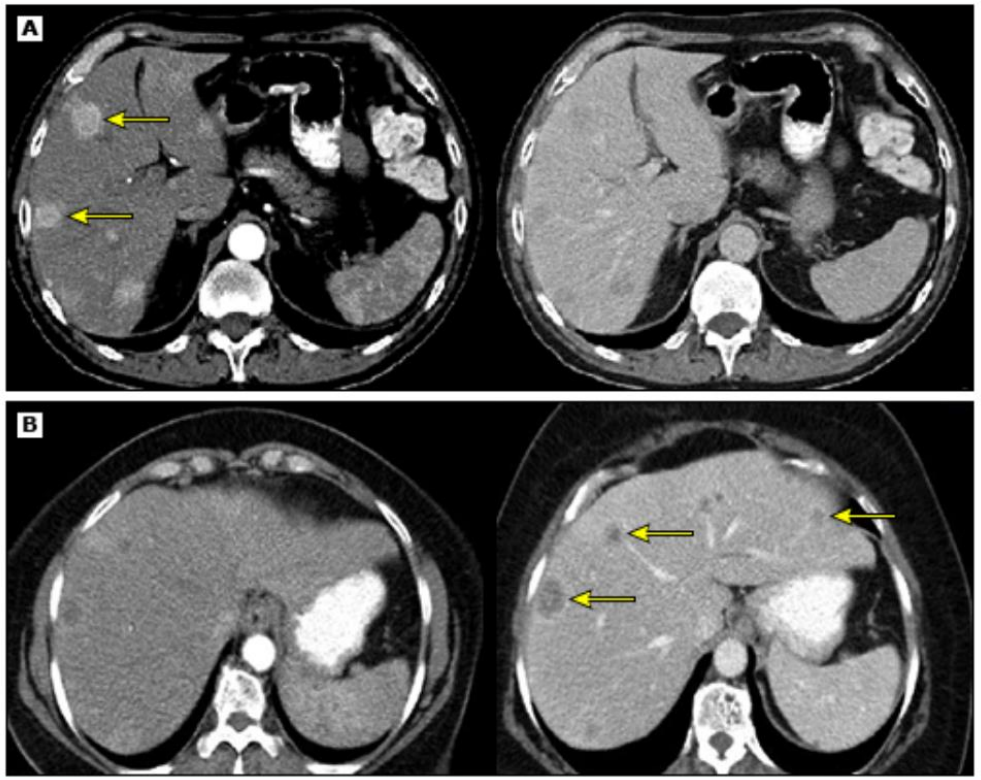
Arterial Phase

- ~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

CT of neuroendocrine tumor liver metastases

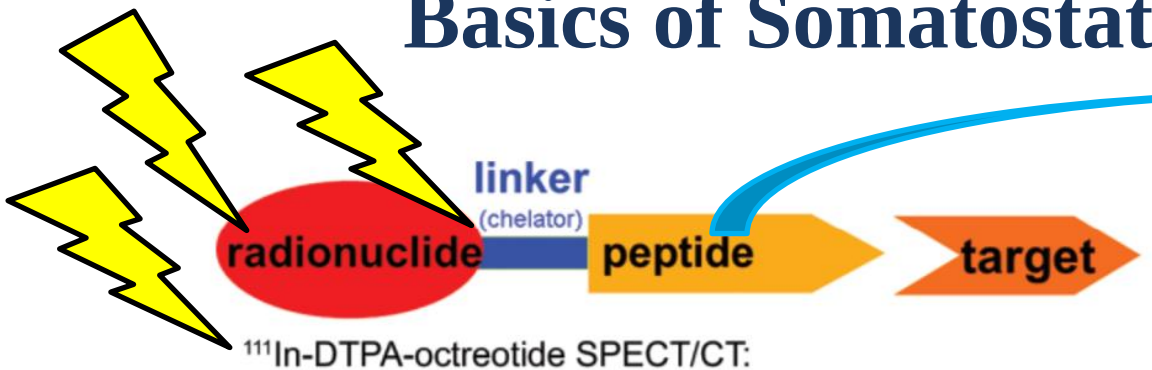


In patient A (top two images), the hypervascular liver metastases are more clearly observed on the arterial phase (left) compared to the portal venous phase (right); whereas in patient B (lower two images), the liver metastases are not as hypervascular and more clearly delineated on the portal venous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

Up to Date, 2020.

Legmann P et al. AJR Am J Roentgenol 1998;170(5):1315.

Basics of Somatostatin Receptor (SSTR) Imaging



^{111}In-DTPA-octreotide SPECT/CT:

^{111}In — DTPA — Octreotide SSTR subtype 3-5

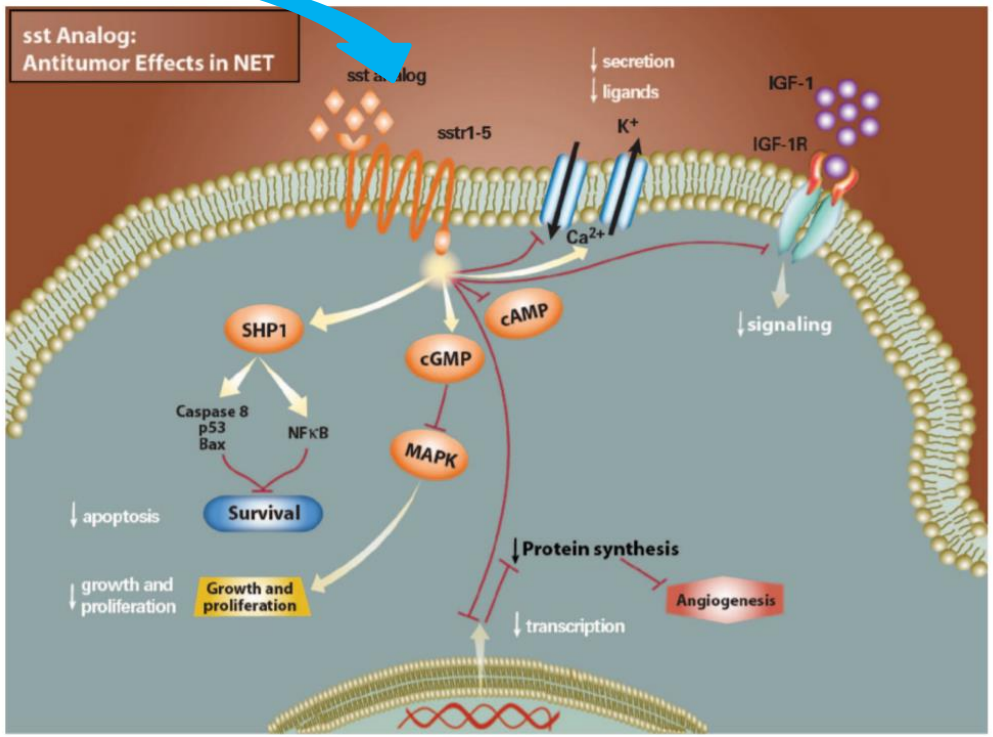
DOTATATE (GaTate) PET/CT:

^{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

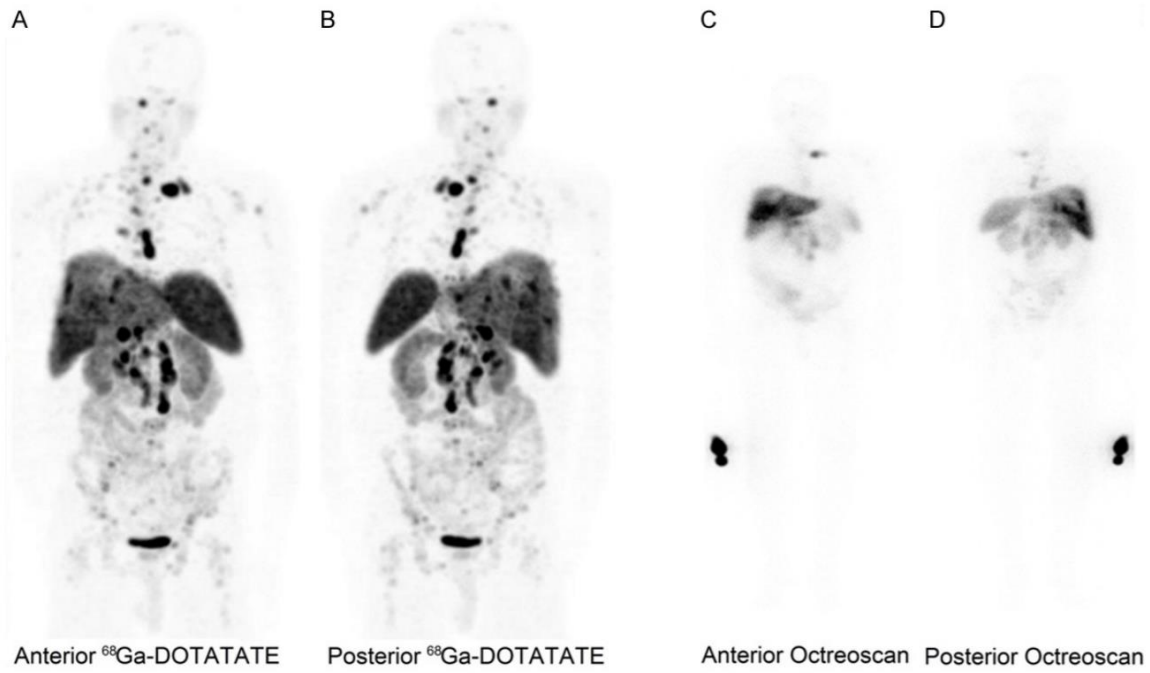
Hofman MS, Lau WFE, Hicks RJ. RadioGraphics 2015; 35:500–516



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



- 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)

Mojtahedi A et al. Am J Nucl Med Mol Imaging 2014;4(5):426-434

^{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

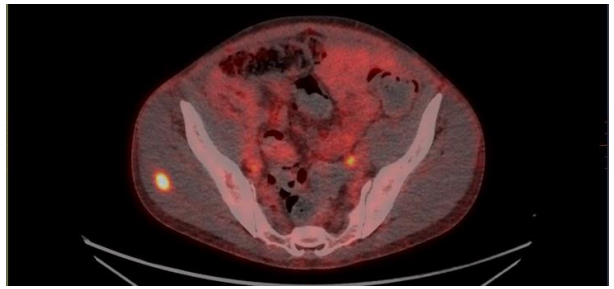
Differentiation and Somatostatin Receptor Expression

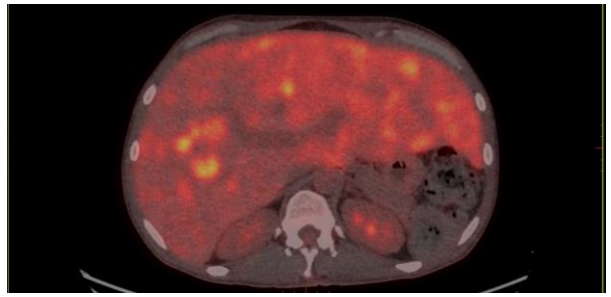
- **WD-lower grade NET**
  - +^{68}Ga-dotatate PET avid (express SSTR)
  - Negative on FDG-PET
- **High grade NET/PD-NEC**
  - Often neg ^{68}Ga-dotatate PET (little to no expression of SSTR)
  - Positive on FDG-PET
- **In some instances, both FDG-PET scan and ^{68}Ga- dotatate PET scan can be helpful**
  - Determine NET de-differentiation (ie to higher grade status)
  - Guide treatment options

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

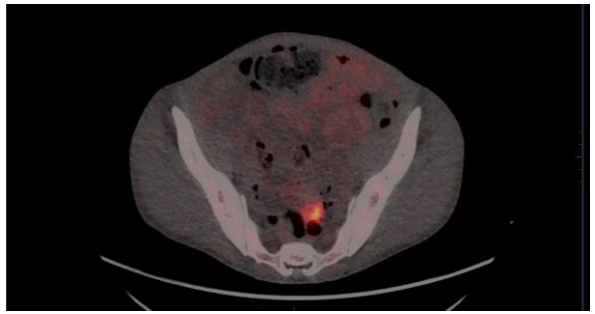
Mixed FDG avid and dotatate avid lesions in liver (Mixed PD-NEC and WD-G2 NET)

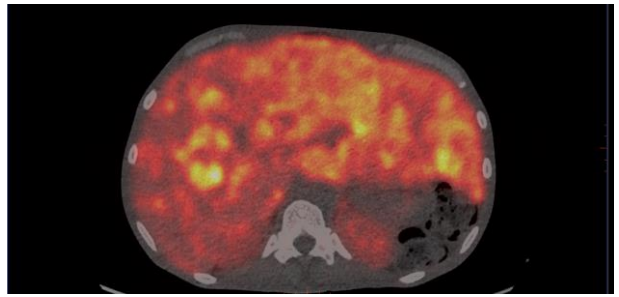
F-18 FDG PET





^{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

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Neuroendocrine and Adrenal Tumors

NCCN Guidelines Index
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Discussion

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

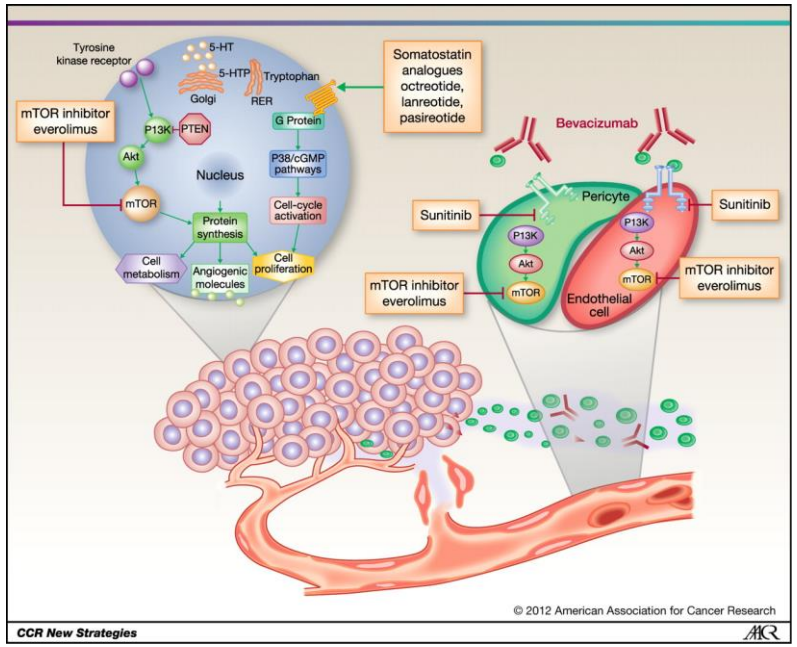
References on NE-C 4 of 4

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)**

Systemic Therapies for 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

	Somatostatin Analogs[1,2] (Octreotide LAR, Lanreotide)	Everolimus[3,4]	Sunitinib[5] (for pNET only)	CAPTEM[6-9]	IV Chemo (e.g. streptozocin, FOLFOX)[10]	177Lu-dotatate (PRRT)[11-13]
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)
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
Overall Survival (OS, months)	Median not reached (NR)	Median NR	Median NR	pNET: 58.7 Other GI NET: ? (>20-30)	20-40	50-60
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

[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.

Systemic Therapy Considerations for GEP-NET

Goals of Therapy

Disease Biology

Patient goals and Preferences

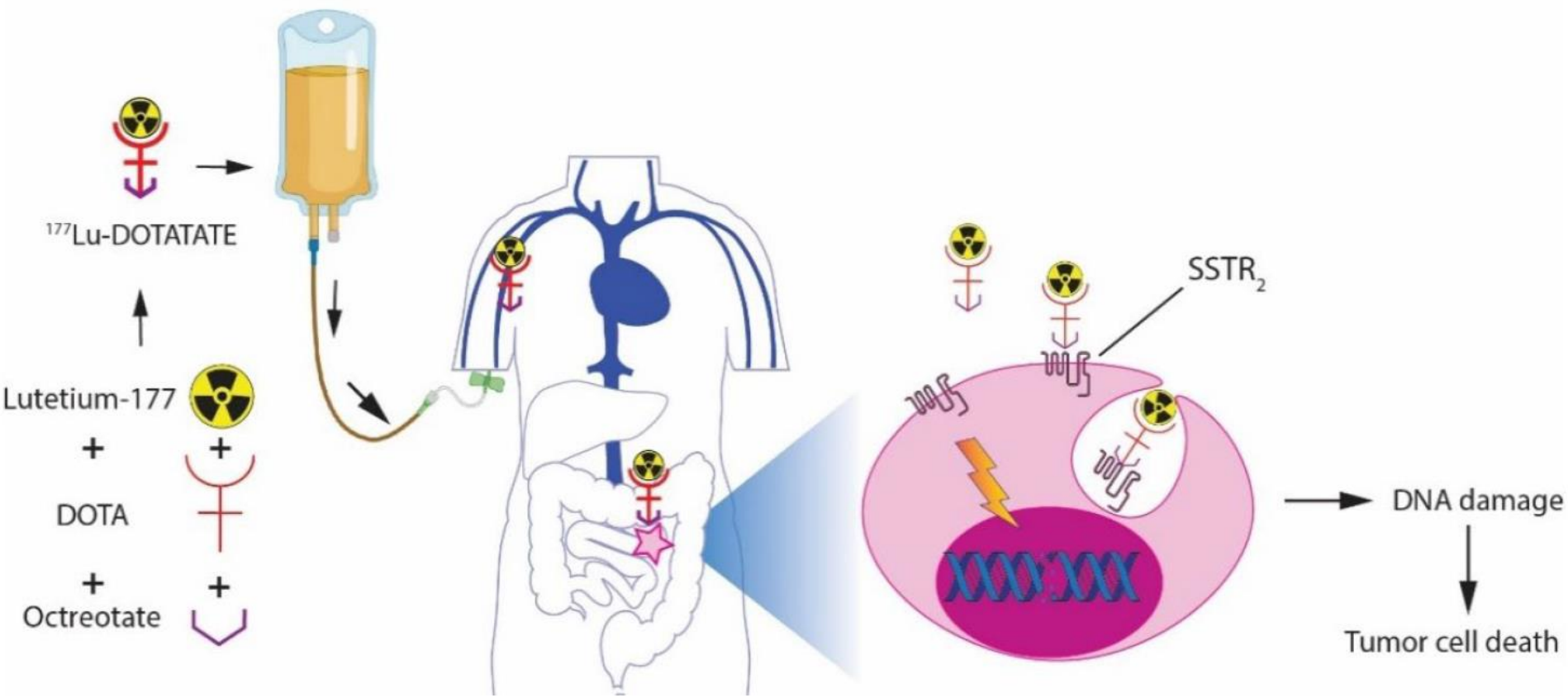
Efficacy of Treatments

Logistical Considerations of Treatment

Toxicities of Treatment (short-term and long-term)

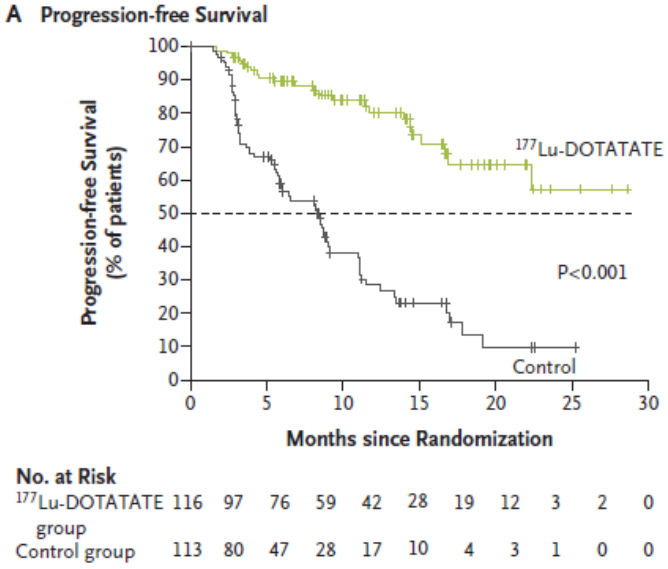
- No one size fits all with regards to treatment approach
- Multidisciplinary discussion important

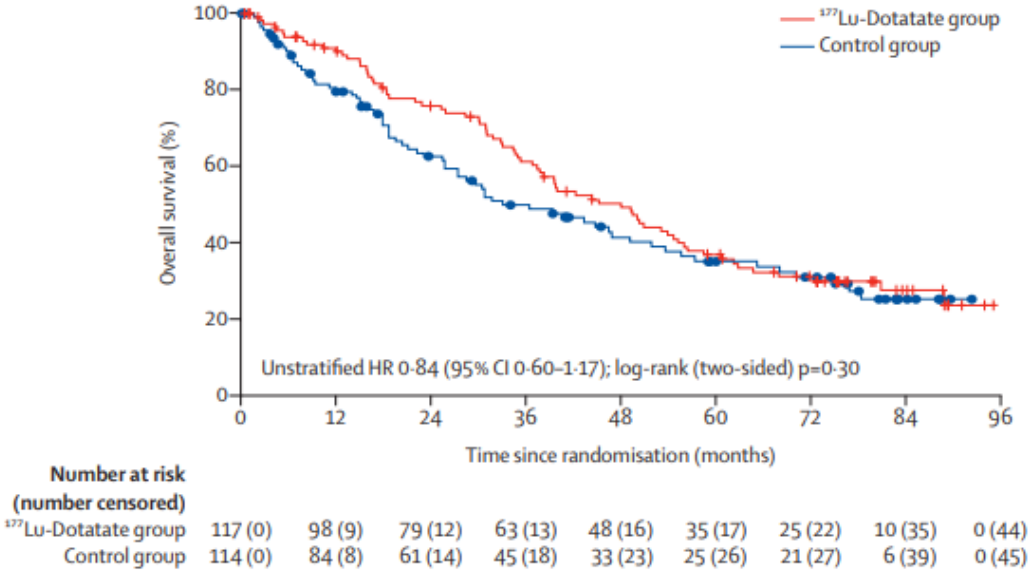
Peptide receptor radionuclide therapy (PRRT): Revolutionized Treatment in GEP-NET



Becx MN et al. Cancers 2022; 14; 5792.

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

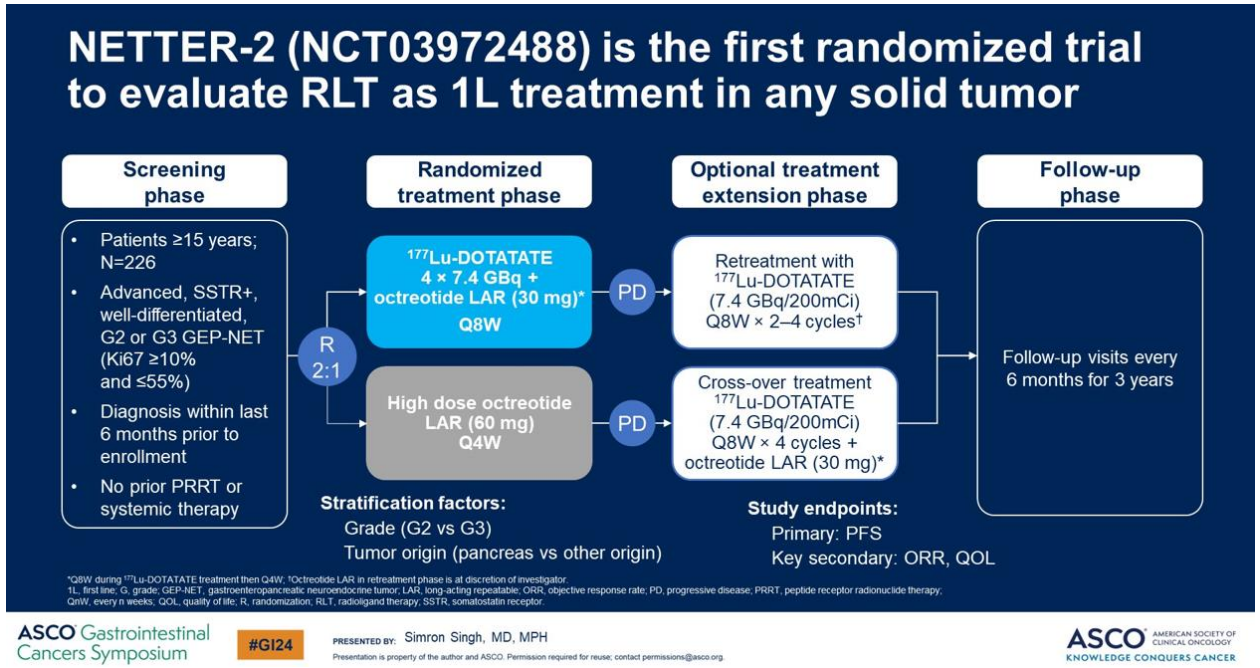


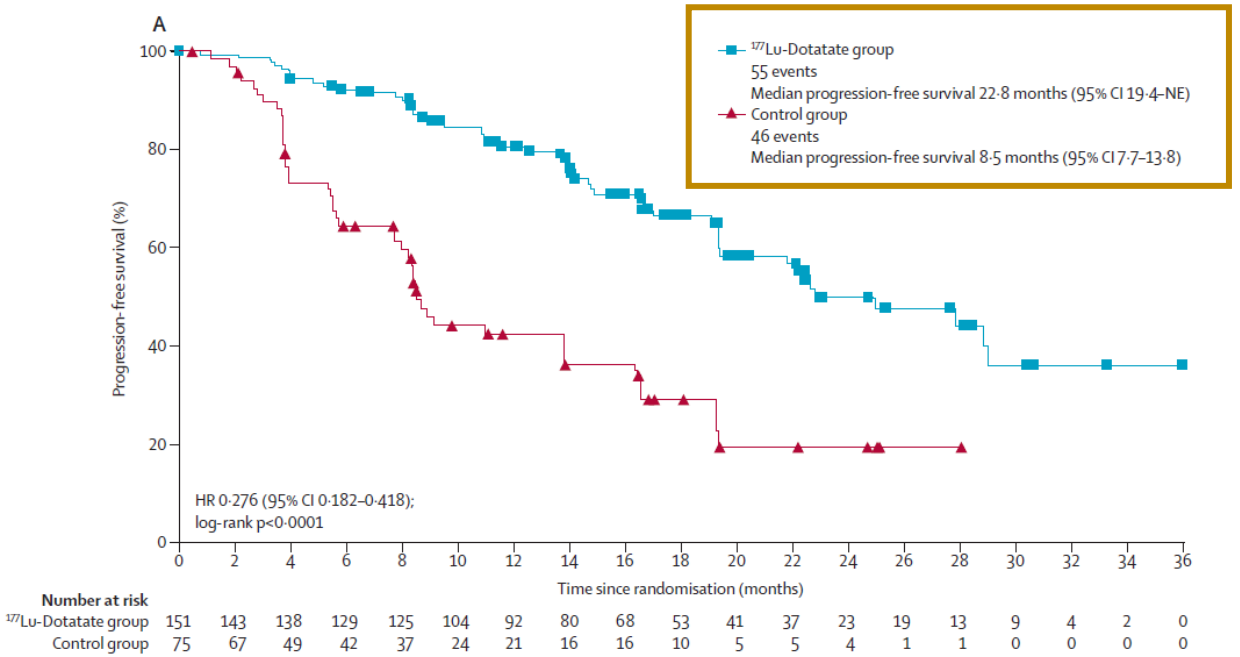


- ORR 18% vs 3%
- No OS benefit at final analysis, but 36% of pts on controlled arm received ^{177}Lu-dotatate at time of progression
- Median OS of 48.0 months in the ^{177}Lu-Dotatate group and 36.3 months (25·9–51·7) in the control group (HR 0·84 [95% CI 0.60–1.17]; two-sided p=0.30).
- Led to FDA 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?

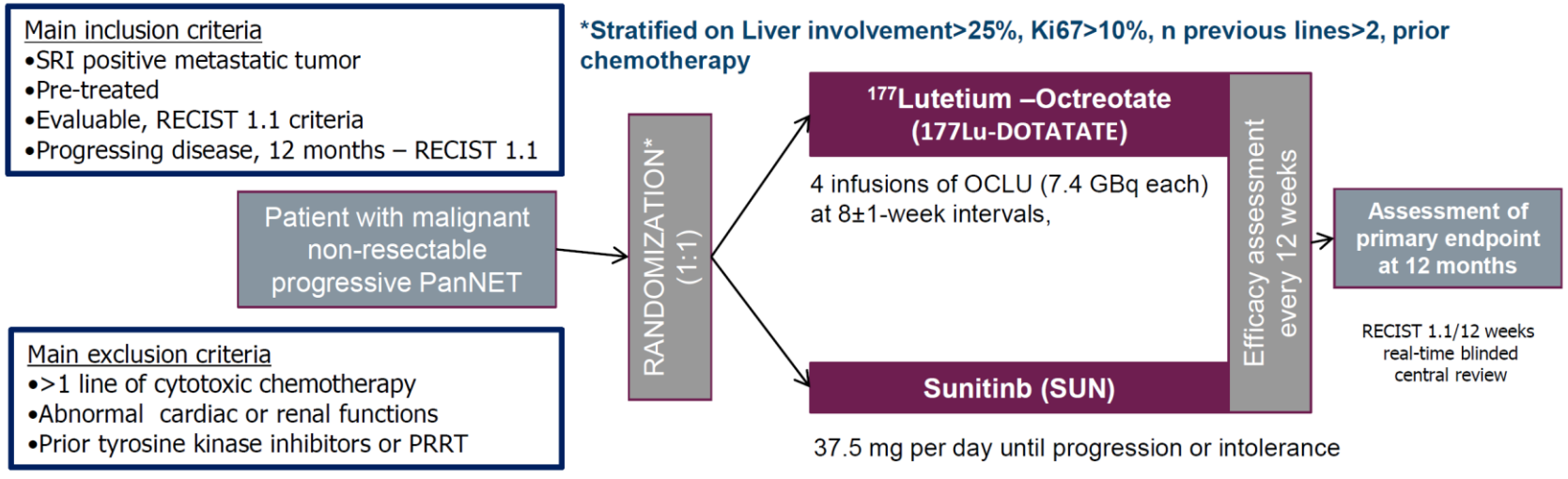
Singh S et al. ASCO GI 2024, Abstract LBA588
Singh S et al. Lancet 2024; https://doi.org/10.1016/S0140-6736(24)00701-3
Singh S et al. ESMO-GI 2024, Abstract 211MO

OCULORANDOM Study

Academic randomized phase II trial in advanced progressive PanNET (well differentiated)

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

Inclusion between Feb 2015 – July 2020 in 10 French expert centers (GTE-RENATEN)



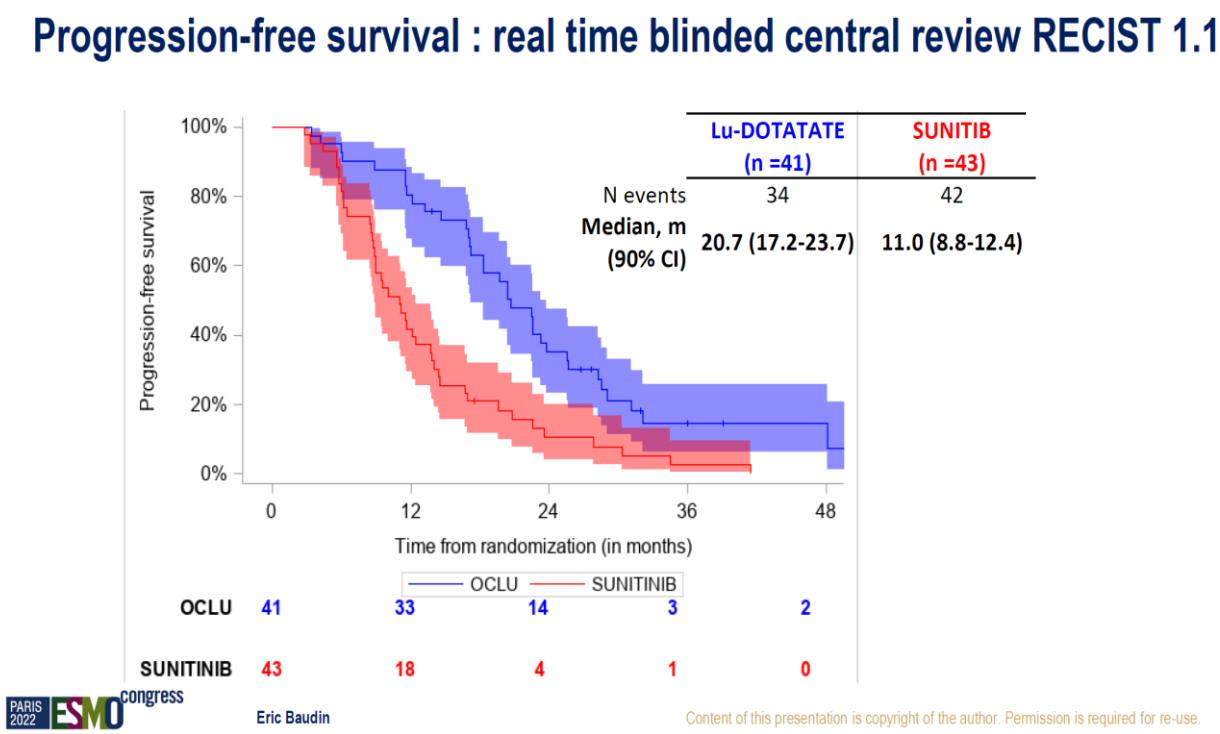
PARIS 2022 ESMO congress

Eric Baudin

- First randomized study directly comparing PRRT to another systemic treatment
- Obtain prospective data of benefit of PRRT in a pNET specific population (as NETTER-1 investigated mainly midgut NET)

Baudin E et al. Abstract 8870. ESMO Congress 2022

Sequencing of PRRT in GEP-NET



Baudin E et al. Abstract 8870. ESMO Congress 2022

Ongoing Studies Evaluating Sequencing of PRRT with Systemic Therapy

COMPETE (NCT03049189)

PRRT vs. everolimus for GEP NET (G1-2)

COMPOSE (NCT04919226)

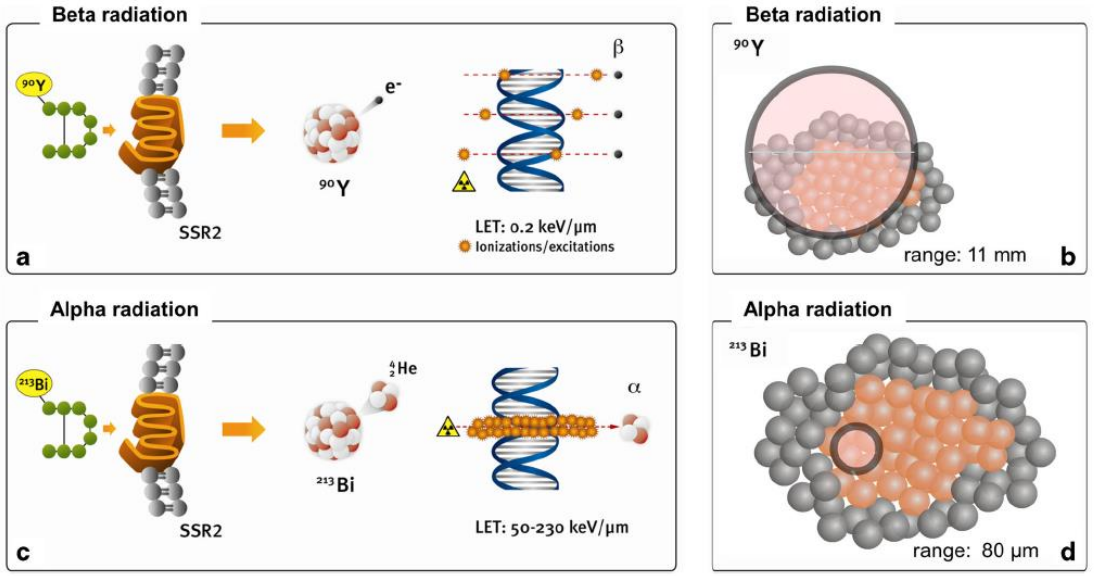
PRRT vs. everolimus/CAPTEM/FOLFOX for GEP NET (G2-3)

ComPareNET (NCT05247905)

PRRT vs. CAPTEM for PanNET (G1-3)

- OCULORANDOM suggests that earlier treatment with PRRT is better than using sunitinib earlier
- Ongoing studies will address PRRT compared to other systemic treatments and higher-grade GI NET
- Results of ongoing studies are important to better inform clinical practice and care of our patients

Alpha-emitter PRRT: Evolving treatment in GEP-NET

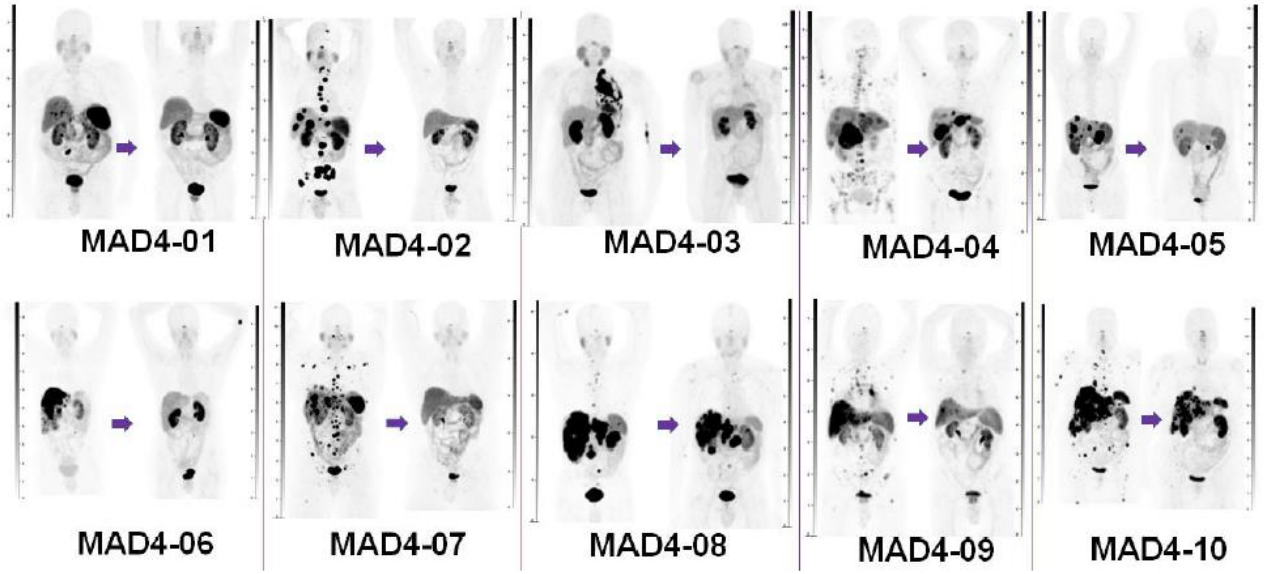


Eur J Nucl Med Mol Imaging (2014) 41:2106–2119
DOI 10.1007/s00259-014-2857-9

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

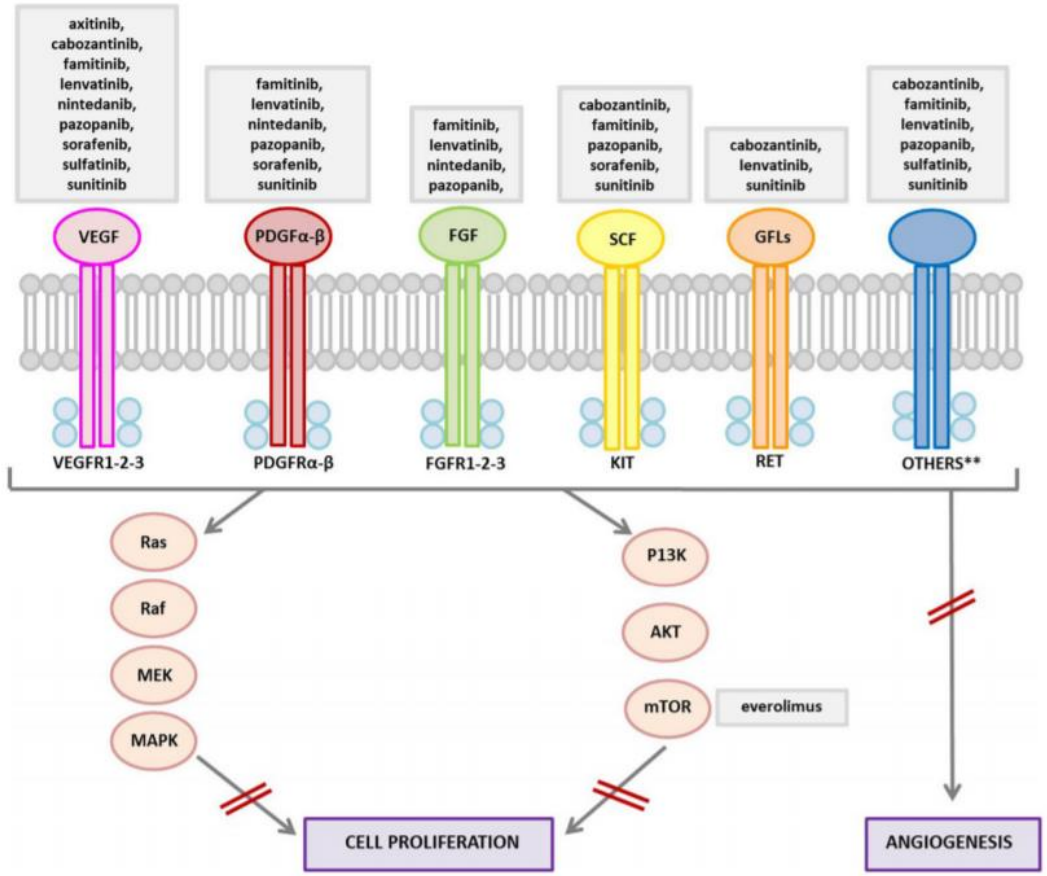
Journal of Nuclear Medicine January 2022, jnumed.121.263230; DOI: https://doi.org/10.2967/jnumed.121.263230



- 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)

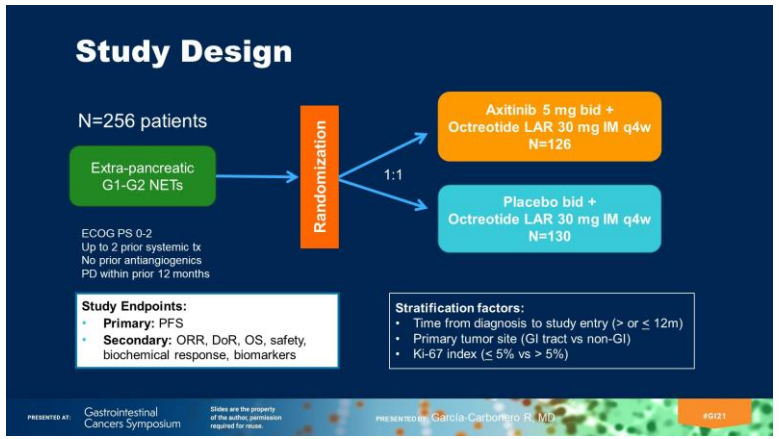
Tyrosine Kinase Inhibitors/Angiogenesis Inhibition in GEP-NET

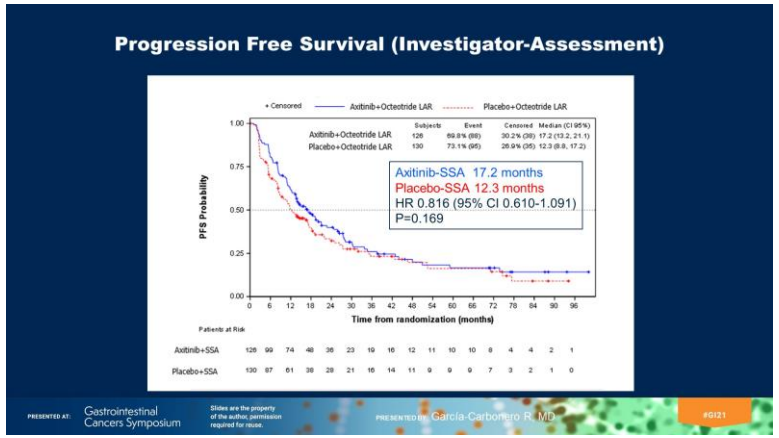
- Tyrosine kinase inhibitors (TKI) target various pathways, particularly with respect to angiogenesis
- VEGF/VEGFR pathway is primary target but most TKI's target other pathways (e.g. c-KIT, PDGFR, others)
- New TKI's inhibit other pathways (e.g FGFR, CSF1-R, MET, AXL) which may be able to overcome resistance after progression on prior treatments
- Sunitinib only approved TKI (for pNET)



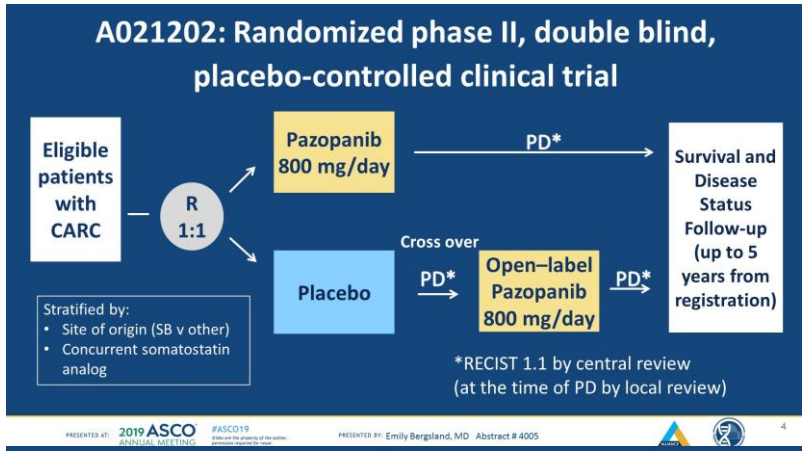
Grillo F et al. Endocrine-Related Cancer, 2018; 25: R405–R418

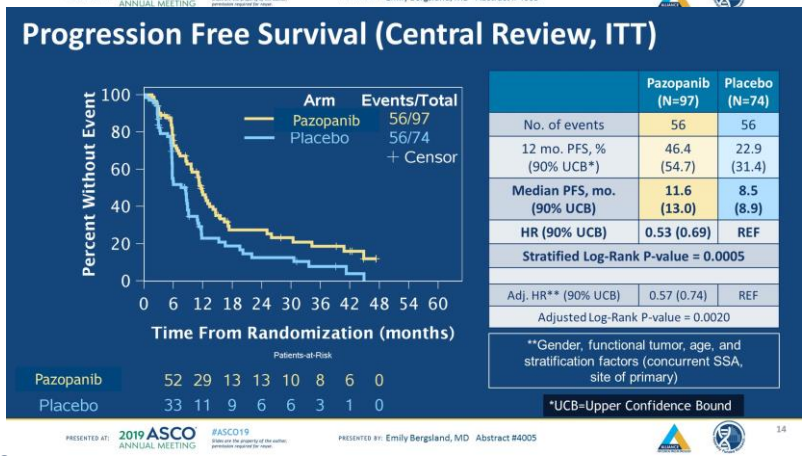
Studies of Other Tyrosine Kinase Inhibitors



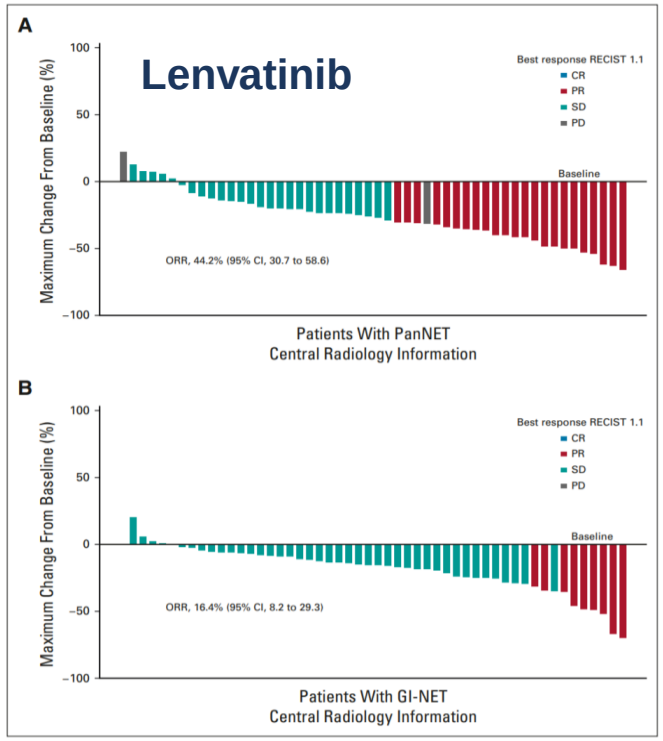


Garcia-Carbonero R et al. Abstract 360, ASCO GI 2019

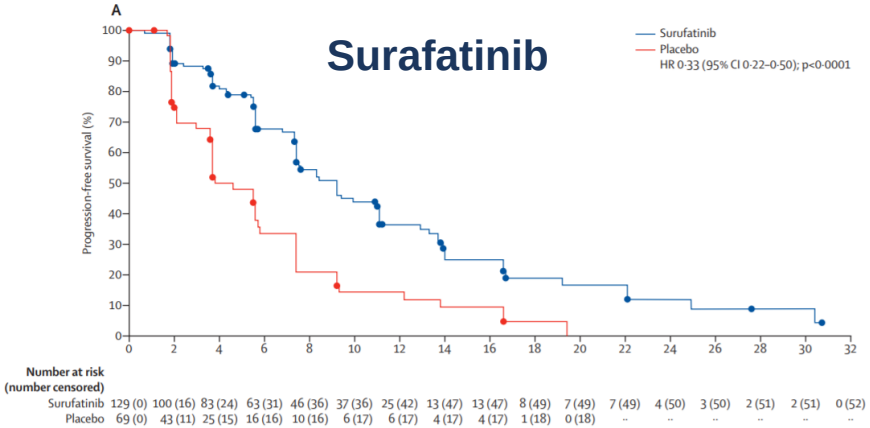




Bergsland EK et al. Abstract 4005, ASCO 2019



Capdevila J et al. J Clin Oncol 2021;39: 2304-2312.

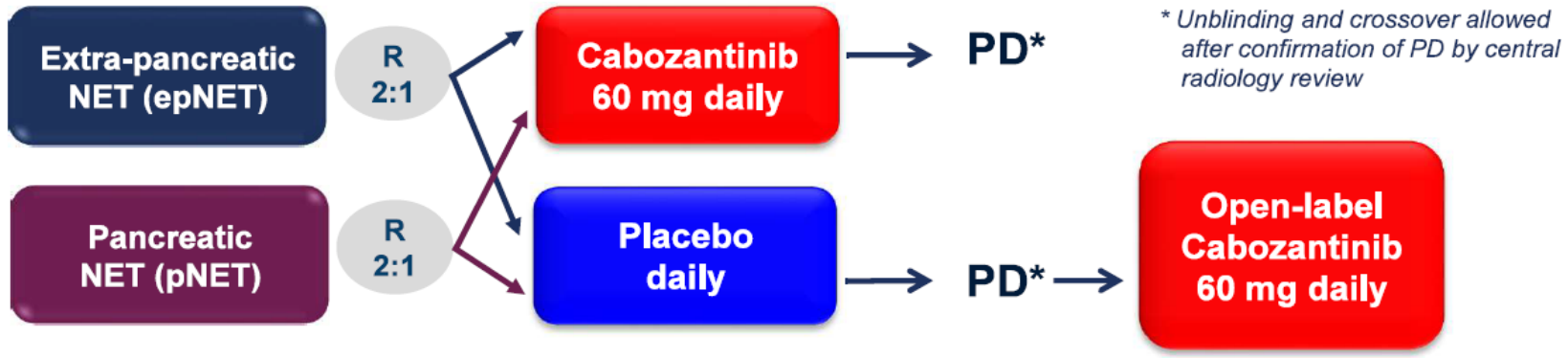


- **Various TKI's (pazopanib, axinitinib, lenvatinib, surafatinib) have been evaluated**
- **New TKI's target other pathways (e.g. CSF-1R with surafatinib)**
- **No new approvals due to mixed results (pazopanib, axitinib), non-randomized & toxicities (lenvatinib), or need to be studied in other countries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

Xiu J et al. Lancet Oncol 2020; 21: 1500–12.
Paulson S et al. Abstract 4114, ASCO 2021.

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

CABINET Trial Study Design



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

Stratification factors:

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

Study Endpoints:

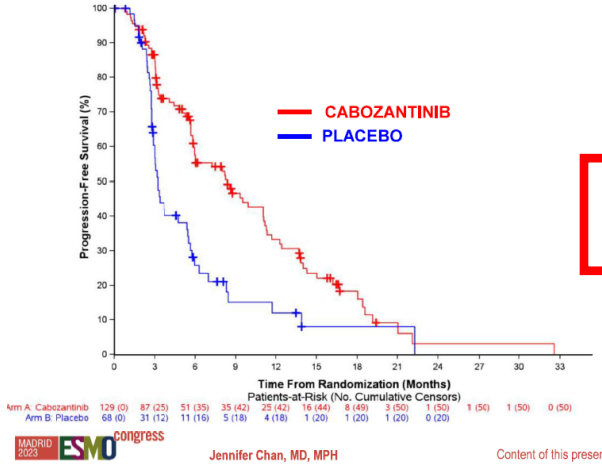
- **Primary Endpoint per cohort:**
  - **Progression-free survival (PFS) by blinded independent central review**
- **Secondary Endpoint per cohort:**
  - **Overall survival**
  - **Objective response rate**
  - **Safety and tolerability**

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Chan JA et al. Abstract LBA53. ESMO Congress 2023

CABINET Trial Results

epNET Cohort: Progression-Free Survival (Local Review)

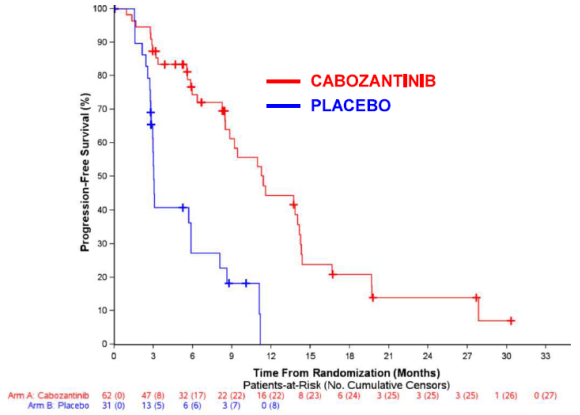


Stratified HR = 0.45
(95% CI: 0.30 – 0.66)
log-rank p<0.0001

Median PFS:
Cabozantinib = 8.3 months
Placebo = 3.2 months

Median follow-up: 13.9 months

pNET Cohort: Progression-Free Survival (Local Review)



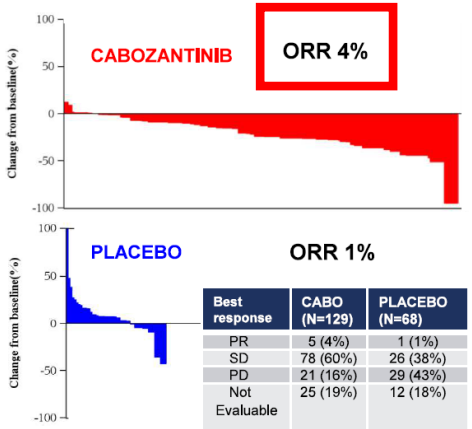
Stratified HR = 0.27
(95% CI: 0.14 – 0.49)
log-rank p<0.0001

Median PFS:
Cabozantinib = 11.4 months
Placebo = 3.0 months

Median follow-up: 16.7 months

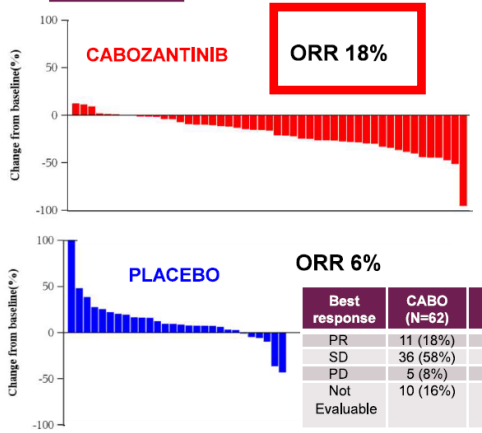
Best Overall Response (Local Review)

epNET Cohort



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%)

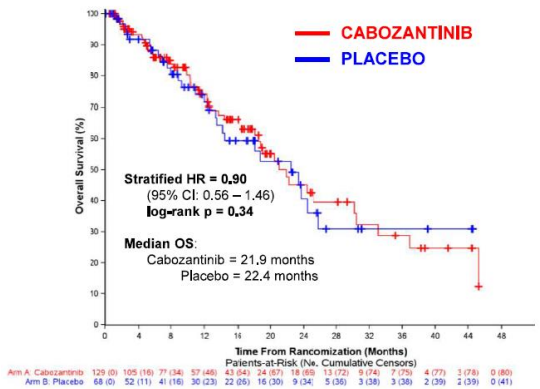
pNET Cohort



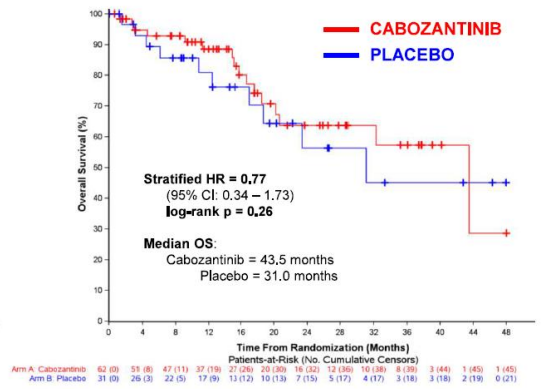
Best response	CABO (N=62)	PLACEBO (N=31)
PR	11 (18%)	2 (6%)
SD	36 (58%)	12 (39%)
PD	5 (8%)	14 (45%)
Not Evaluable	10 (16%)	3 (10%)

Overall Survival

epNET Cohort



pNET Cohort



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)
- <u>Questions remain:</u>
  - 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

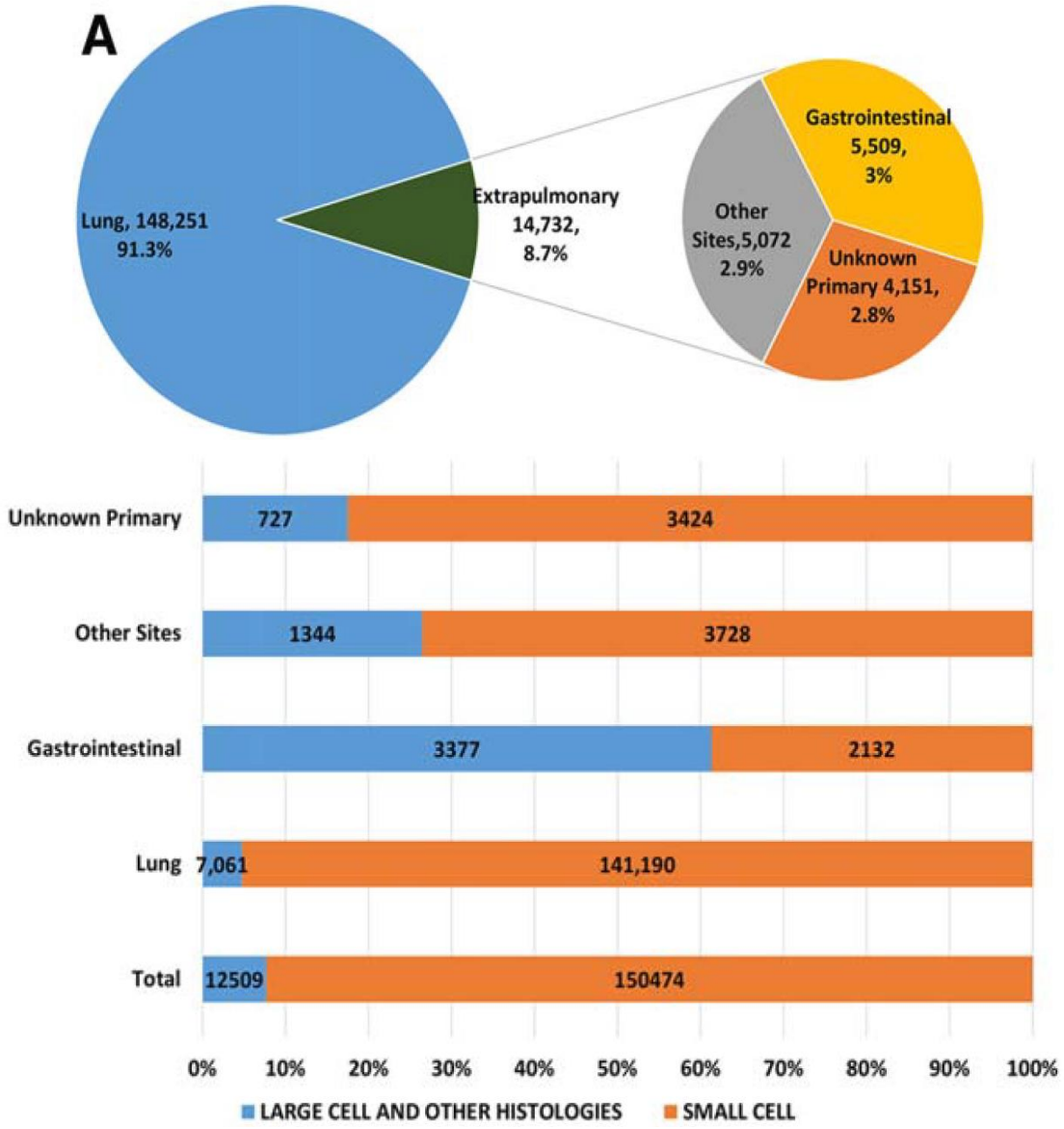
	RCC (n=61)	Pancreatic Lesions (n=61)	pNET (n=22)	CNS Hemangioblastoma (n=50)
Objective Response Rate (ORR = CR + PR)	30 (49%)	47 (77%)	20 (91%)	15 (30%)
Complete response (CR)	0	6 (9.8%)	3 (13.6%)	3 (6.0%)
Partial response (PR)	30 (49%)	41 (67.2%)	17 (77.3%)	12 (24.0%)
Stable Disease (SD)	30 (49%)	12 (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

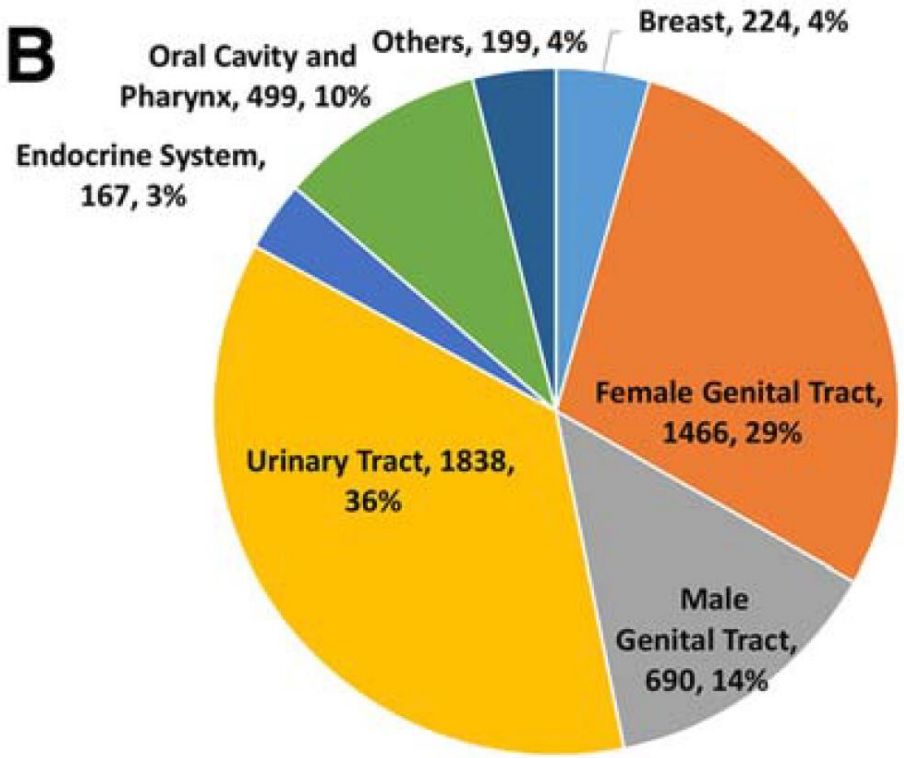
- Belzutifan targets HIF-2$^{\alpha}$ which is upregulated in VHL associated cancers
- Secondary analysis of belzutifan in patients with VHL associated RCC who had concurrent pNET
- Belzutifan demonstrated ORR of pNET
- Listed in NCCN guidelines as an option for progressive VHL-associated pNET
- Remaining 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.

Systemic Therapies 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%

[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

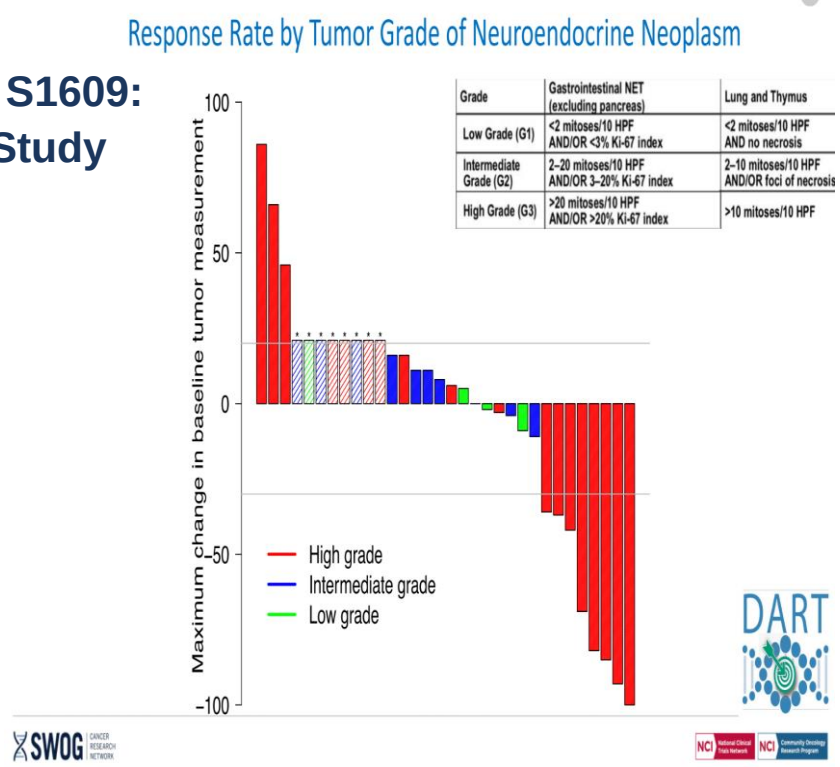
NEC
FOFLOX
FOLFIRI
FOLFIRINOX
Temozolomide +/- Capecitabine
Nivolumab + Ipilimumab
Pembrolizumab (if MSI-H or TMB ≥10)

Adapted from NCCN Neuroendocrine Guidelines, v. Feb 2022

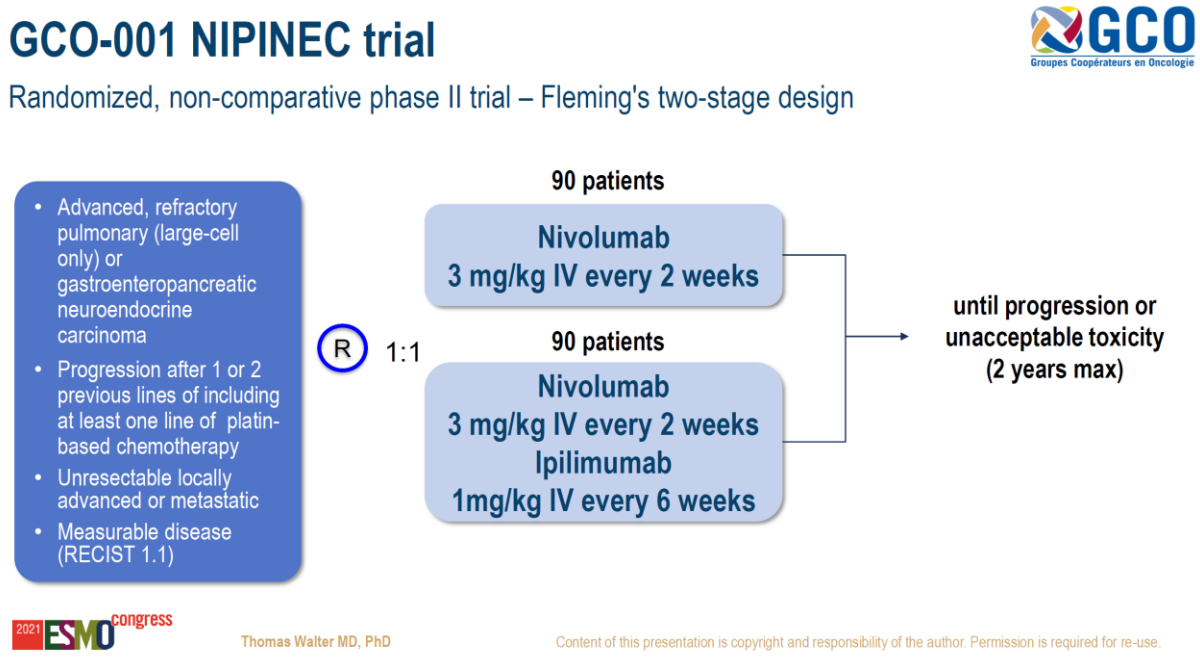
- No established standard for NEC after progression on platinum/etoposide
- Outcomes remain poor:
  - ORR: 20-30%
  - Median PFS ~3 months
  - Median OS 6-9 months
- Need more effective treatments

Nivolumab + Ipilimumab in Refractory Extrapulmonary NEC

SWOG S1609: DART Study



Patel SP et al. Clin Cancer Res 2020; 26: 2290-6



Walter T et al. Abstract LBA41. ESMO Congress 2021

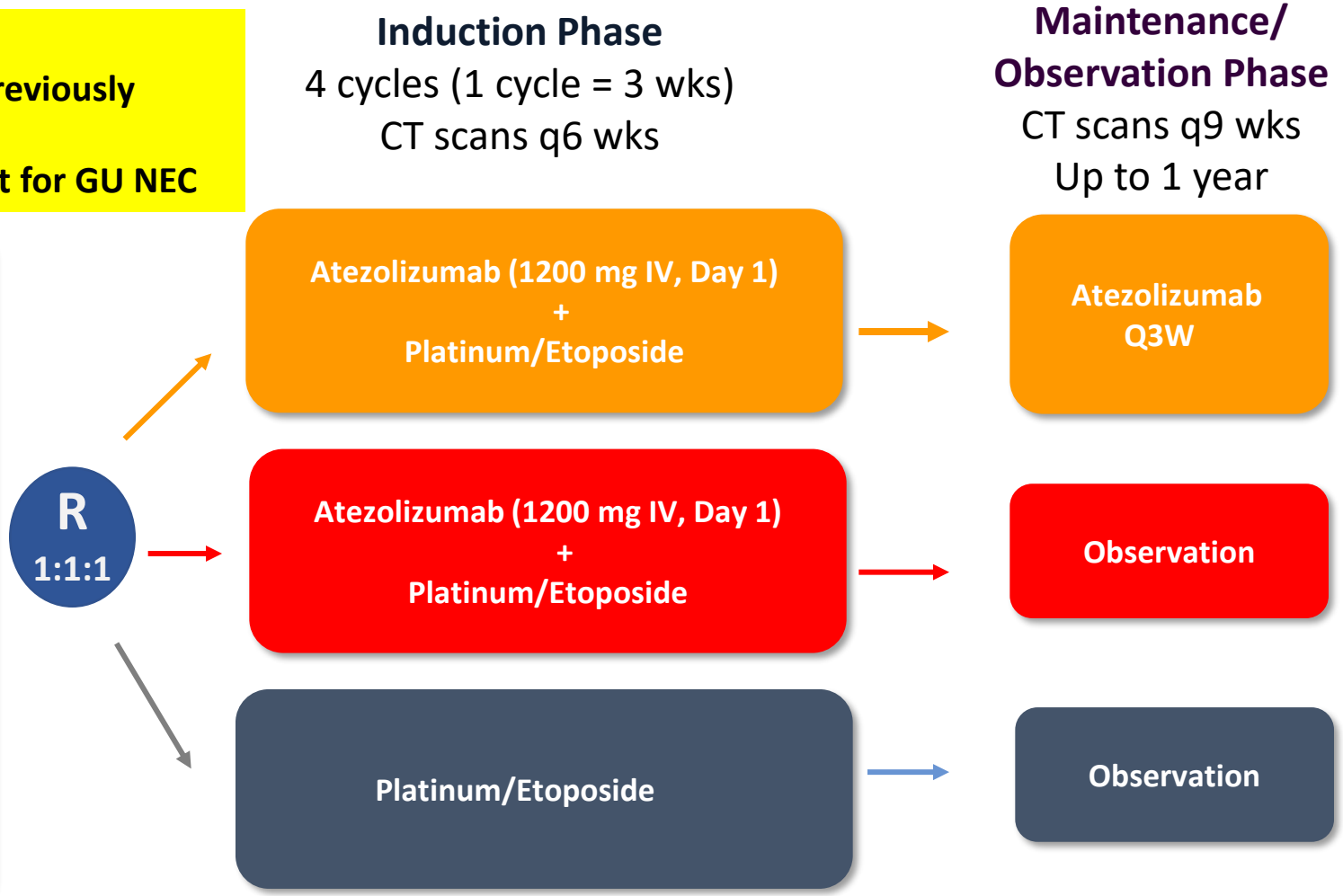
- Effective in high grade NEN/NEC (and not NET)
- Extrapumonary ORR: 10-25% (lower compared to lung NEC ~20-60%; nivolumab alone ORR: 7.1%)
- 6-month PFS: 20-30%; Median OS 6-11 months
- **Suggests that combination therapy is more effective than monotherapy**

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

- **Activated Dec 2, 2021**
- **Amended Jan 2023 to allow all NEC subtypes (previously restricted to small cell only)**
- **Amended Jan 2024 to remove Ki-67 requirement for GU NEC**

Key Eligibility: **(N=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



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

Death-like Ligand 3 (DLL-3): Emerging Target in NEC

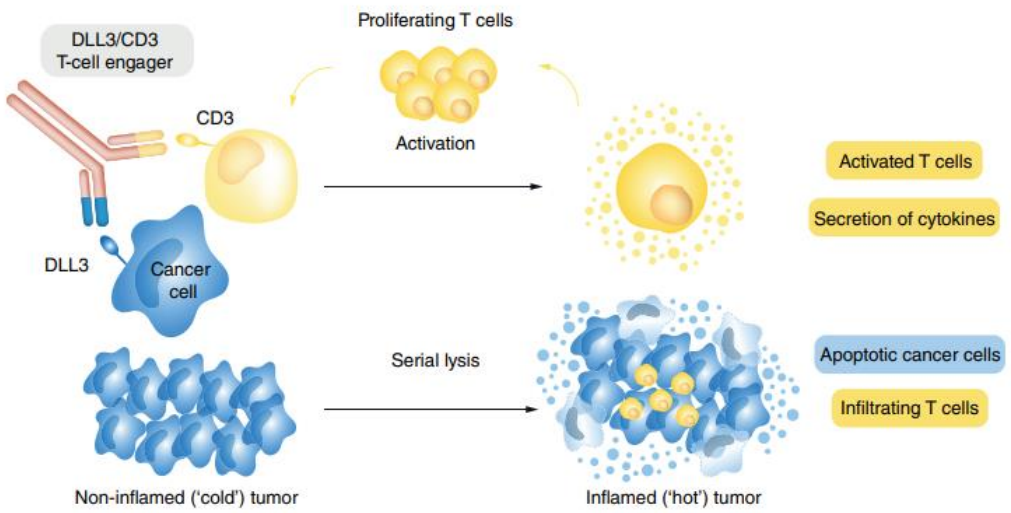
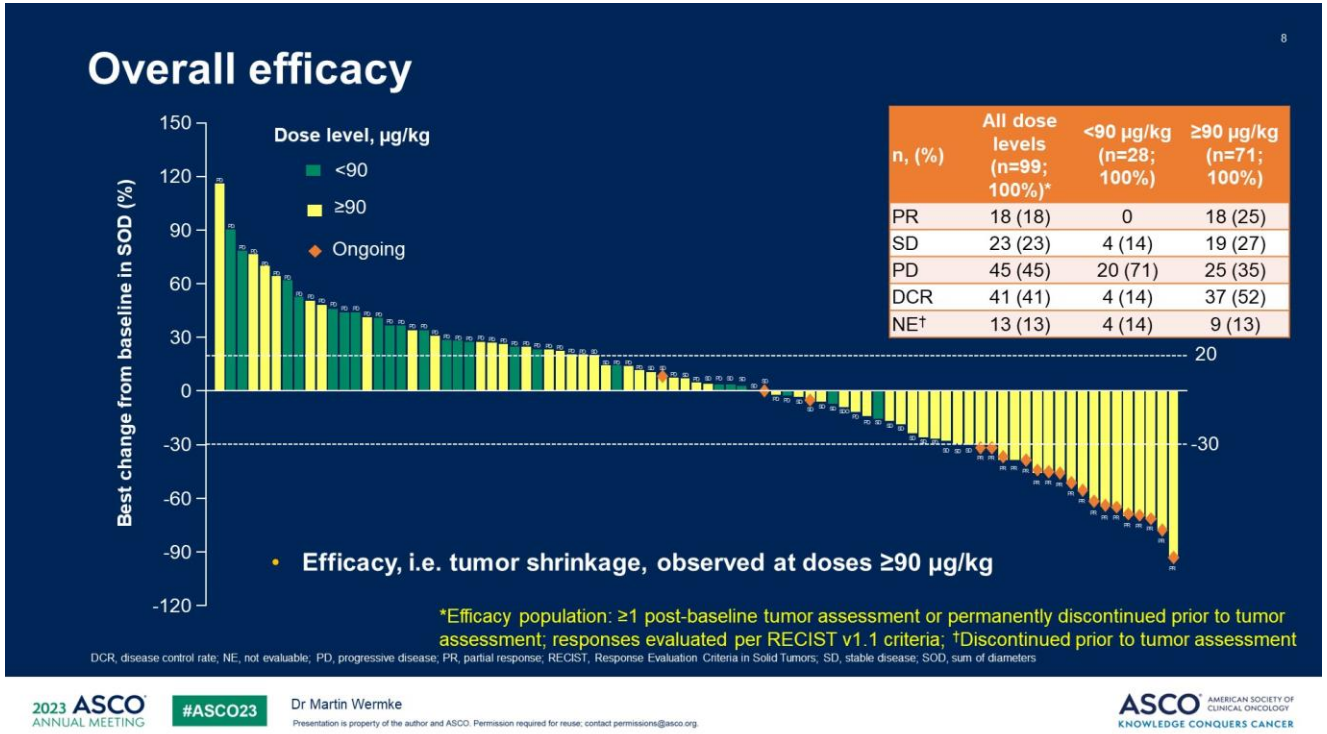


Figure 1. BI 764532 mechanism of action.

Wermke M, et al. Future Oncol 2022



Wermke M, et al. Abstract 8502. ASCO 2023

- Tarlatamab (BI 764532) is a bi-specific T-cell engager (BiTE) and approved for refractory SCLC[1]
- Promising early results in patients with previously treated NEC
- Efficacy may differ in small cell lung cancer vs extrapulmonary NEC (ORR 26% vs 19%)
- Need larger trials and longer term follow up to look at survival and side effects

[1]Ahn MJ et al. N Engl J Med 2023;389:2063-75.

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Cancer Center

Thank you

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