# Neuroendocrine Tumours

## A primer for Primary Care Physicians

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# Disclosures

- Honoraria: Incyte, Pfizer
- Advisory board: Astellas, Ipsen

# Objectives

Foundations of Neuroendocrine Tumors (NETs)

Recognize signs and symptoms suggestive a NET

Understand current standards of care (SOC) in the diagnostic work-up

Review the treatment landscape and recent advances in management

# What is a NEN? What is a NET? What is a NEC?

Neuroendocrine neoplasias (NENs): a heterogeneous group of cancers arising from the body's neuroendocrine system.

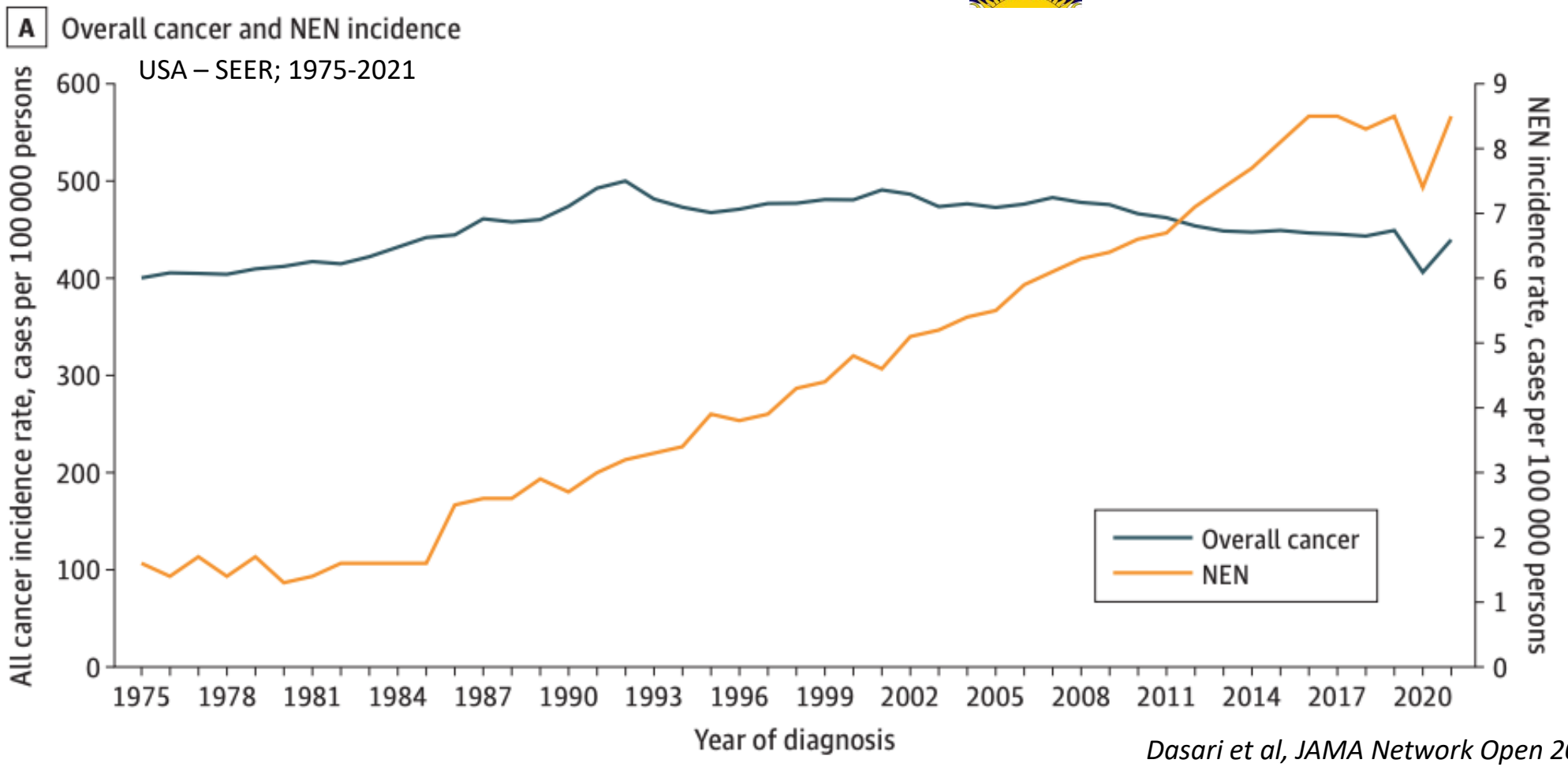
| Terminology | Differentiation | Grade | Mitotic Count Mitoses/2 mm$^{2a}$ | Ki-67 Index$^{b}$ |
|---|---|---|---|---|
| G1 NET | Well differentiated | Low | <2 | <3% |
| G2 NET | | Intermediate | 2-20 | 3%-20% |
| G3 NET | | High | >20 | >20% |
| Small-cell NEC | Poorly differentiated | High | >20 | >20% |
| Large cell NEC | | | >20 | >20% |
| MiNEN | Well or poorly differentiated | Variable | Variable | Variable |

Abbreviations: G, grade; MiNEN, mixed neuroendocrine-non-neuroendocrine neoplasm; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.
[a]Mitotic counts are to be expressed as the number of mitoses/2 mm$^2$ (equaling 10 high-power fields) at 40× magnification evaluated in areas of highest mitotic density.
[b]The Ki-67 proliferation index value is determined by counting at least 500 cells in hot spots.

*Riechelmann et al, ASCO Ed. Book 2023*

# Not rare, uncommon and on the rise…

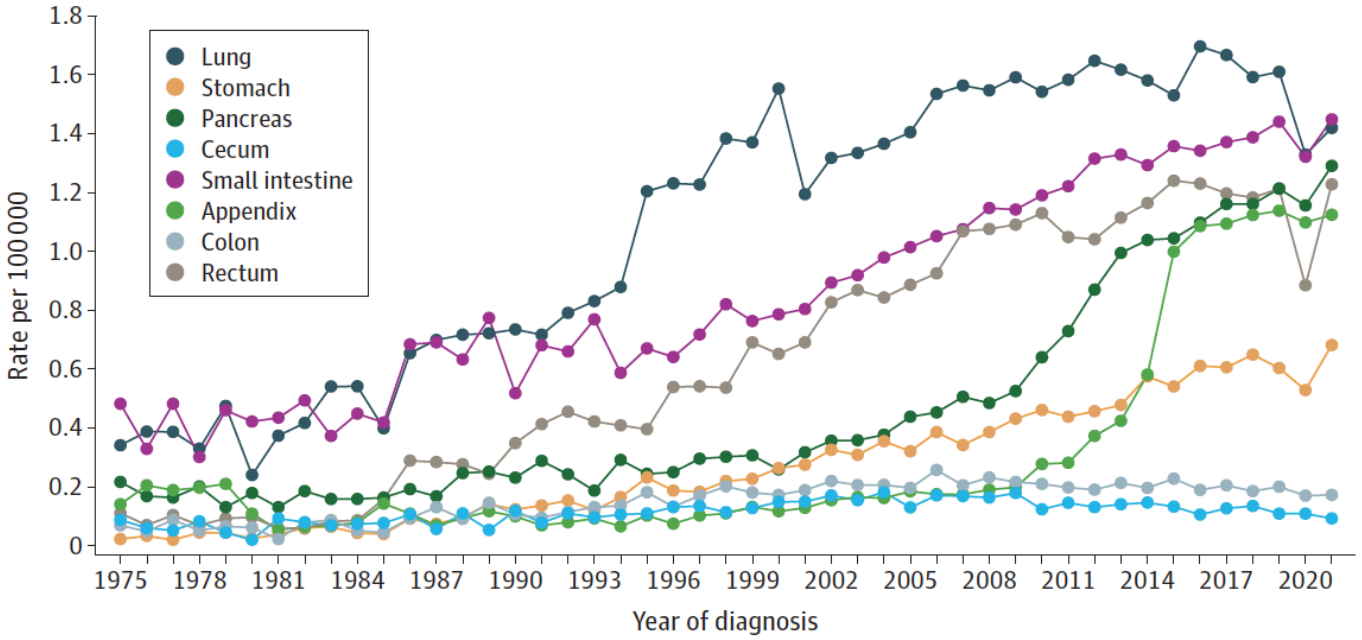
**BC ~200/300 GI cases/year**



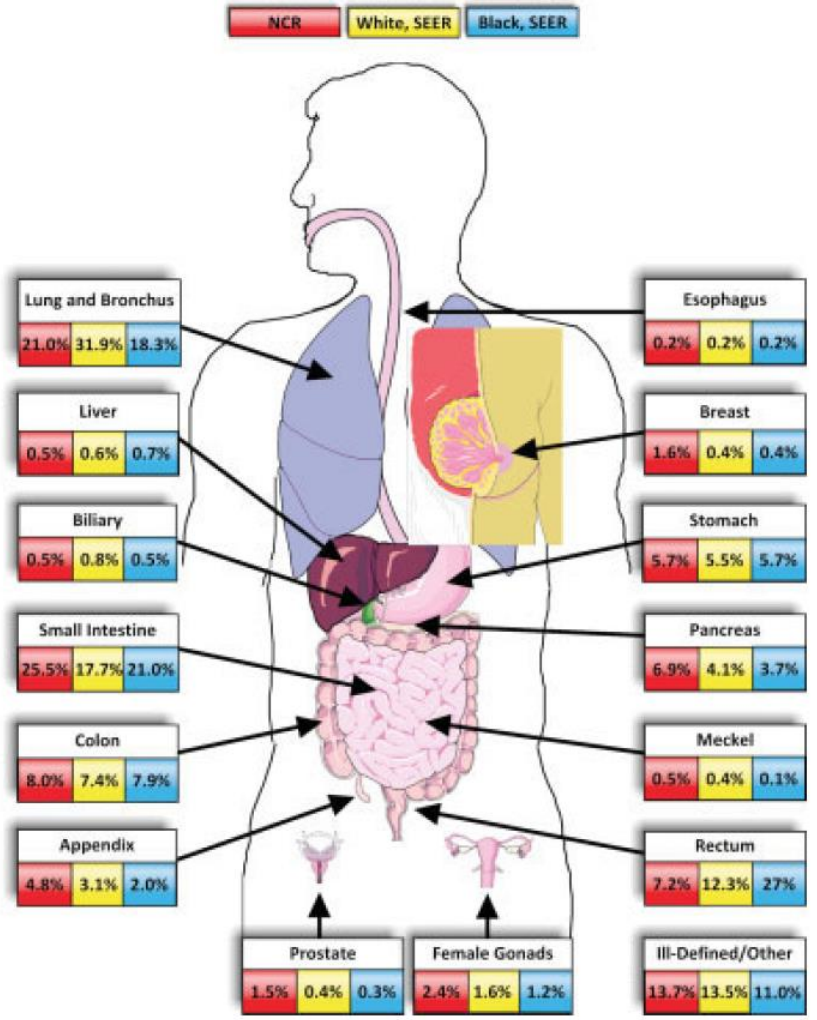

*Dasari et al, JAMA Network Open 2025*

# The diffuse neuroendocrine system means almost all sites can be affected.

Incidence by site
USA – SEER; 1975-2021




*Dasari et al, JAMA Network Open 2025*




*Huse et al, Cancer 2008*

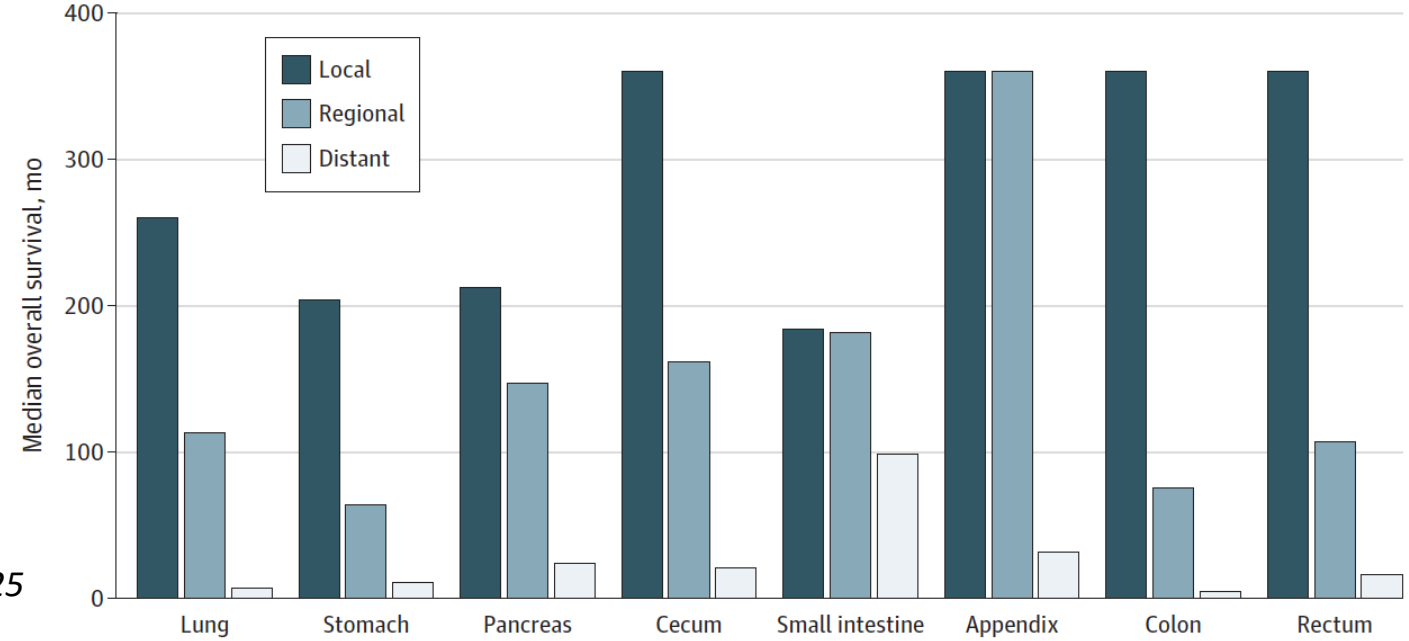
# Commonly present as localized disease with a good prognosis.

USA – SEER; 2012

| Localisation | Incidence/100 000 |
|---|---|
| All NENs | 7 |
| All localised NENs | 3.1 |
| All regional NENs | 1.1 |
| All distant NENs | 1.7 |
| Unstaged NENs | 1.1 |

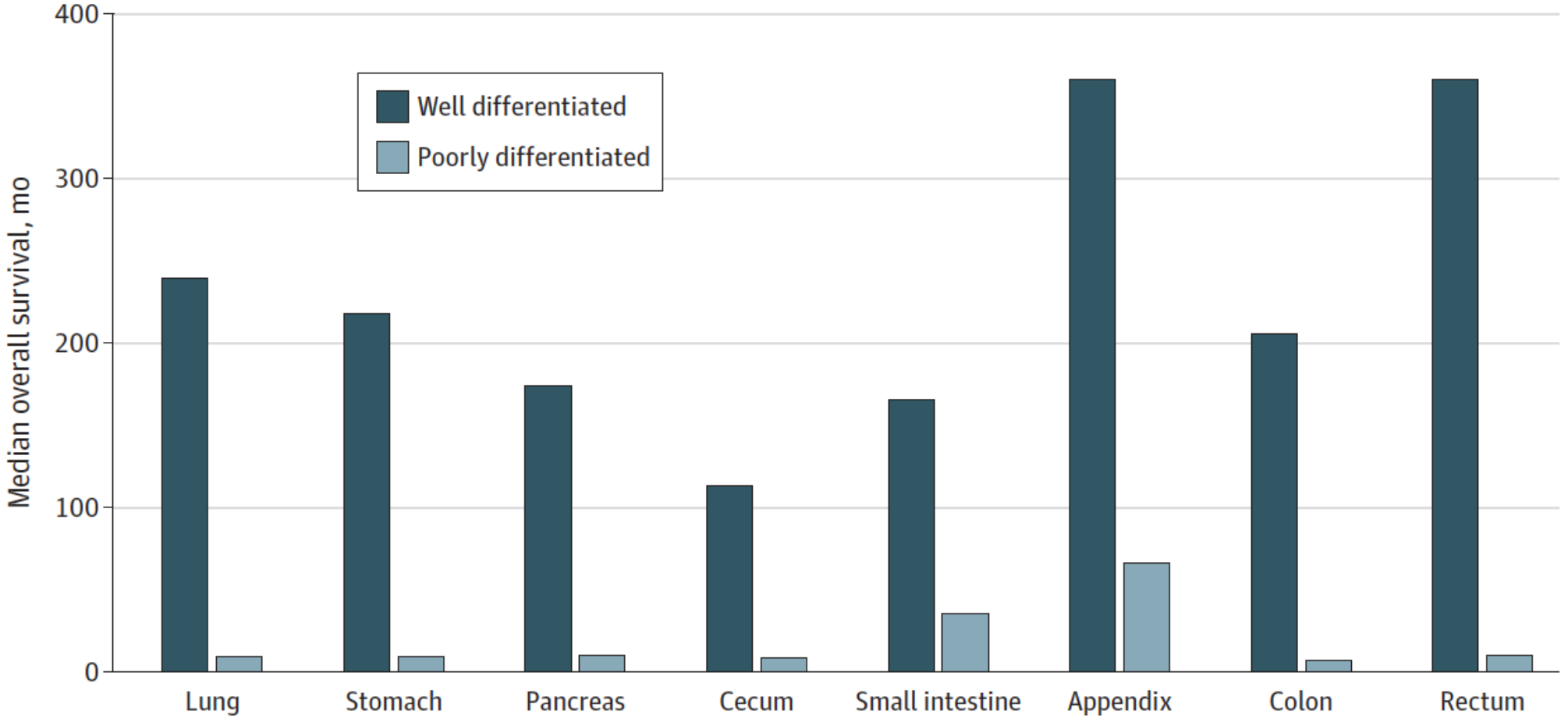
*Pavel et al, Annals of Oncology 2020*

Survival by stage and site at diagnosis
USA – SEER; 1975-2021




*Dasari et al, JAMA Network Open 2025*

# NET (Well-differentiated NENs) usually have a prolonged survival in all sites…




*Dasari et al, JAMA Network Open 2025*

# The challenge of diagnosis and the need to have a high suspicious index

Median times ranging from 24-53 months from symptom onset to a diagnosis

29% of small bowel NET patients initially misdiagnosed with irritable bowel syndrome

Patients typically see their primary care physician 5 times over 18 months before diagnosis

31% diagnosed following unplanned emergency admission

*Basuroy et al, Neuroendocrinology 2018*
*Basuroy et al, BMC Cancer 2018*

# Common presenting symptoms of NETs

Symptoms  vary significantly based on whether the tumor is functional (hormone-secreting) or nonfunctional, as well as the tumor location.

Nonfunctional NETs:

- Incidental findings

- Weight loss; Fatigue
- Pain and symptoms related to tumor bulk
- GI symptoms: change in bowel habit; obstruction
- Respiratory symptoms: SOB, wheezing, repeated infection

*Basuroy et al, Neuroendocrinology 2018*
*Cuthbertson et al, Clinical Medicine 2023*

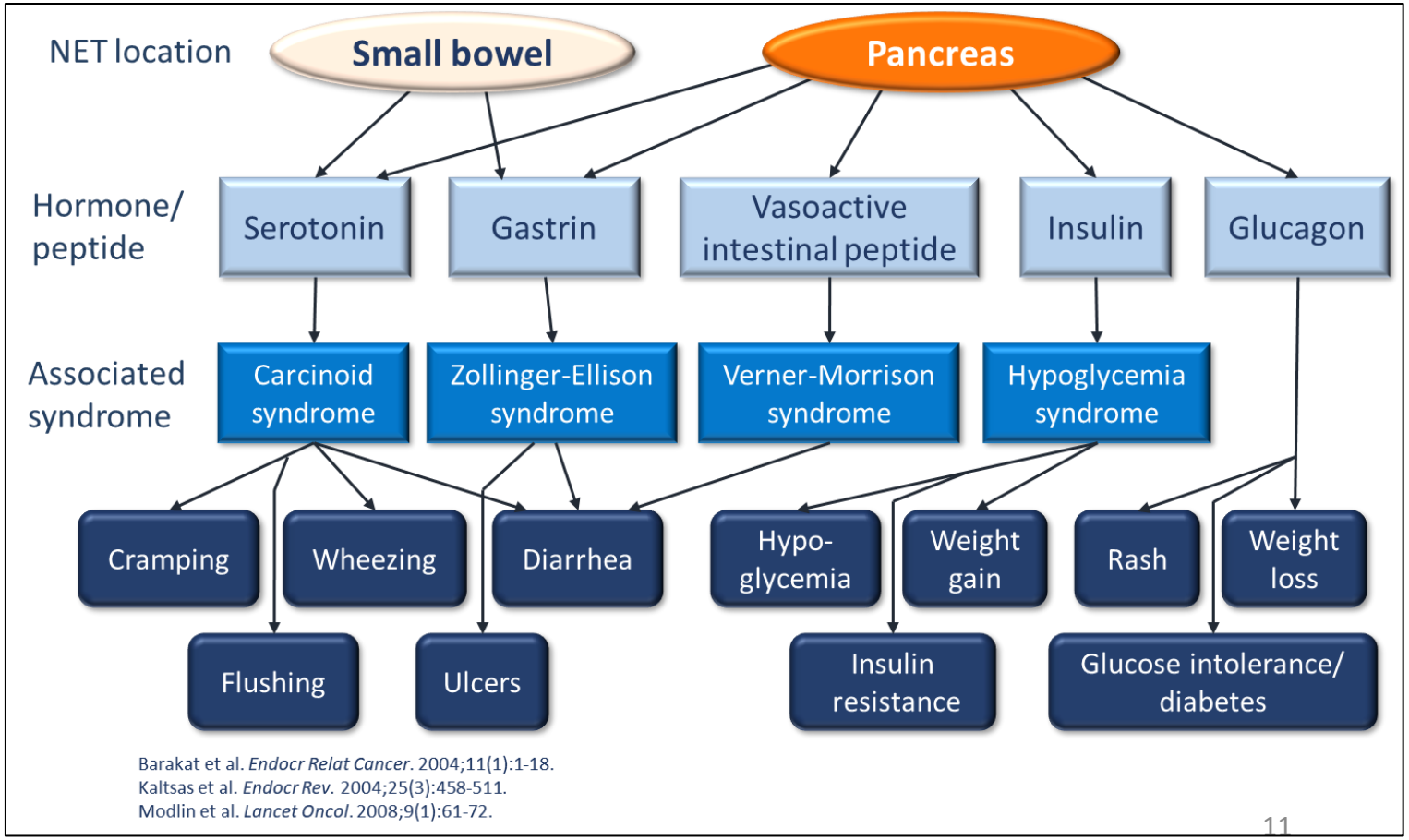
# Functional NETs
# Hormone hypersecretion syndromes

~20% of localized small bowel NETs have syndrome and up to 56% with distant disease[1]

pNETs usually non-functional but if functional get more “weird” hormones

**Characteristics of gastroenteropancreatic neuroendocrine tumors**

| | Foregut | Midgut | Hindgut |
|---|---|---|---|
| **Localization** | Stomach, duodenum, bronchus, thymus | Jejunum, ileum, appendix, ascending colon | Transverse, descending, and sigmoid colon, rectum, genitourinary |
| **Secretory products** | 5-hydroxytryptophan, histamine, multiple polypeptides | Serotonin prostaglandins, polypeptides | Variable |
| **Carcinoid syndrome** | Rare, and atypical when it happens | Classic | Rare |




[1]Halperin et al. *Lancet Oncology* (2017)
UpToDate, accessed Feb 10 2026

**Slide adapted from Dr. Jonathan M. Loree**

# Definitions - Carcinoid

- Carcinoid syndrome
  - Wheeze
  - Flushing
  - Diarrhea
  - Heart Failure
  - *Worsen with the 5Es = emotion, epinephrine, EtOH, eating MAOI, exercise*
- Serotonin causes GI symptoms and valvular issues while bradykinin causes flushing
- Tryptophan needed for serotonin production so patients can have niacin deficiency
- Atypical carcinoid = more histamine related symptoms and usually with foregut tumors

Condreon et al, Surgery (2016)

# Carcinoid syndrome complications

**Carcinoid crisis**

Massive release of vasoactive substances

Sudden onset of hemodynamic instability +/- classical symptoms of carcinoid syndrome

Can occur in up to 30% of cases

Usually associated with surgery, but has been described after PRRT and spontaneously

Very little evidence to guide management

- Prophylactic administration of SSA.
- Vasopressors, antihypertensives, beta blocker

# Carcinoid syndrome complications

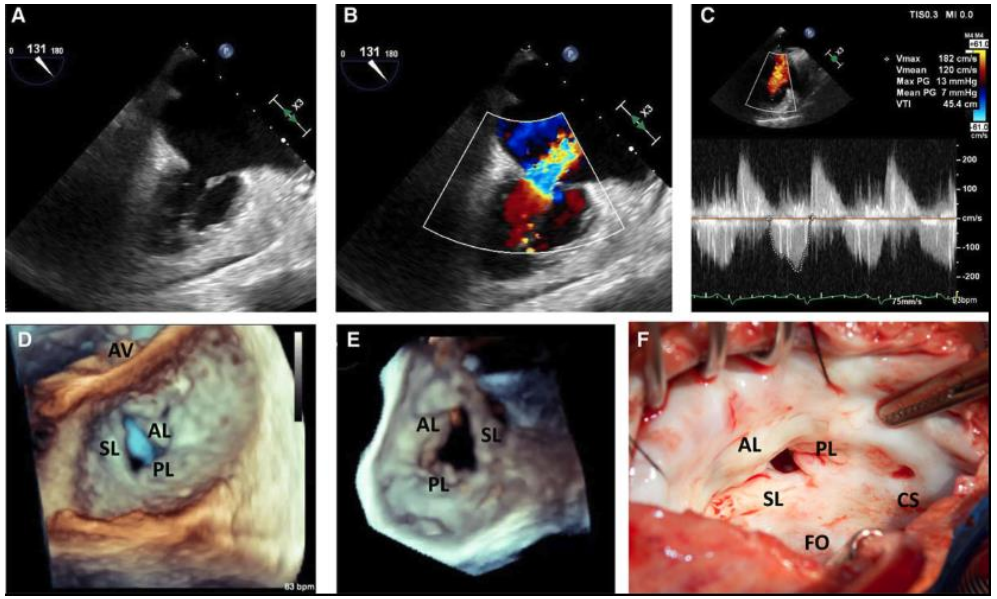
## Carcinoid heart disease

Plaque-like fibrous endocardial thickening of mostly the right heart valves

Caused partially by chronically elevated levels of circulating serotonin

Independent negative prognostic factor

- Serial BNP; Echocardiogram baseline and q1-2 years for surveillance.
- Surgical intervention is the primary treatment once stablished.




Myasaka, et al. Circulation 2019

# Mesenteric fibrosis

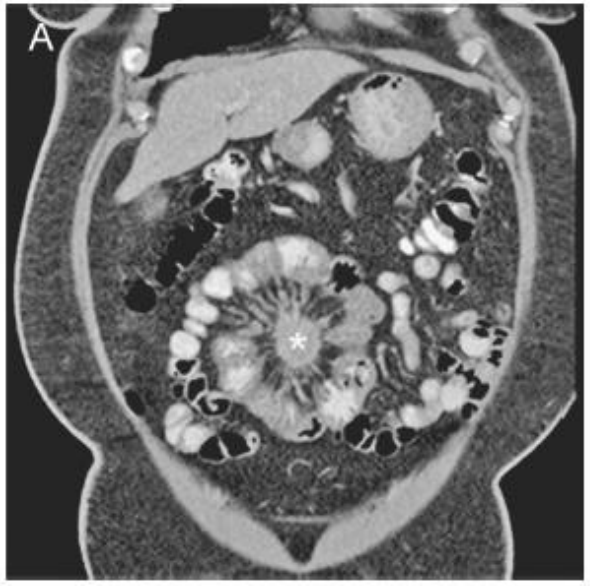
Hallmark of SB-NETS

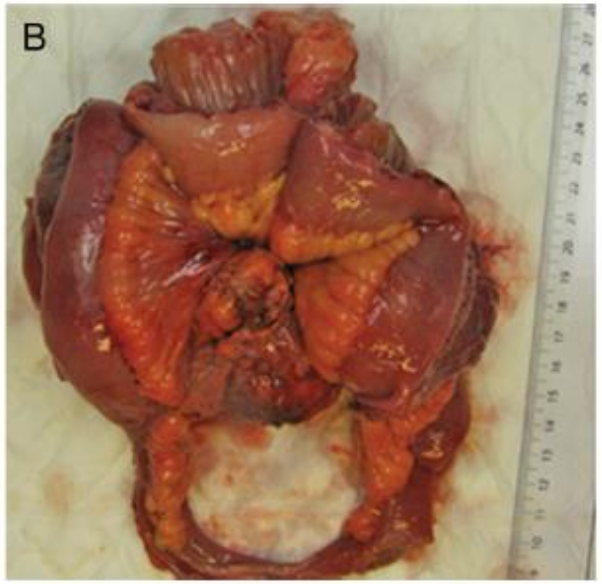
Frequently associated with significant morbidity: intestinal obstruction, ischemia, and cachexia.

Pathogenesis remains poorly understood

Mesenteric mass with radiating strands of soft-tissue on CT imaging is a pathognomonic.

Surgery to treat complications; SSA and growth control could delay progression?




Blažević, et al. ERC 2018

# The NET Checklist – All you need (and would like) to know if you can when you see a NET. And why?

Sex, Gender, Race, SDOH
Primary Site
Stage
Histology, Differentiation, WHO Grade
Functional Status
Disease Burden
SSTR status and DOTA uptake
FDG avidity*
Germline mutations*
Somatic mutations*


*AI-generated figure, Chat GPT V5.0*

*Useful in specific situations

# Core Diagnostic Workup Components

**Pathology**

- Tissue sample with assessment of differentiation and grade
- Comprehensive genomic profile for specific situations

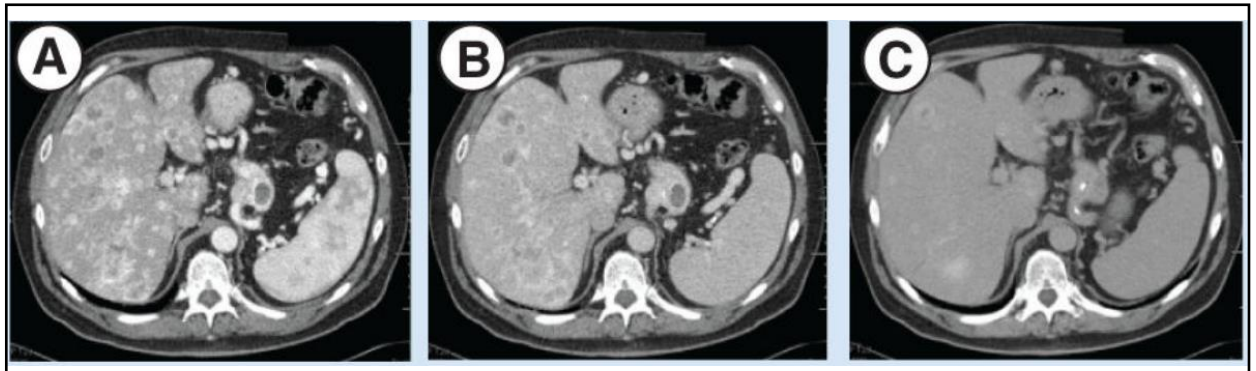
**Biochemical testing**

- Hormonal work up guided by symptoms
- Chromogranin A (Sen 60-90%; Spec < 50%)
- 24-hour urine/plasma 5-HIAA: For carcinoid syndrome (requires dietary restrictions)
- Syndrome-specific hormones: Insulin, gastrin, VIP, glucagon

# Core Diagnostic Workup Components

**Anatomical Imaging**

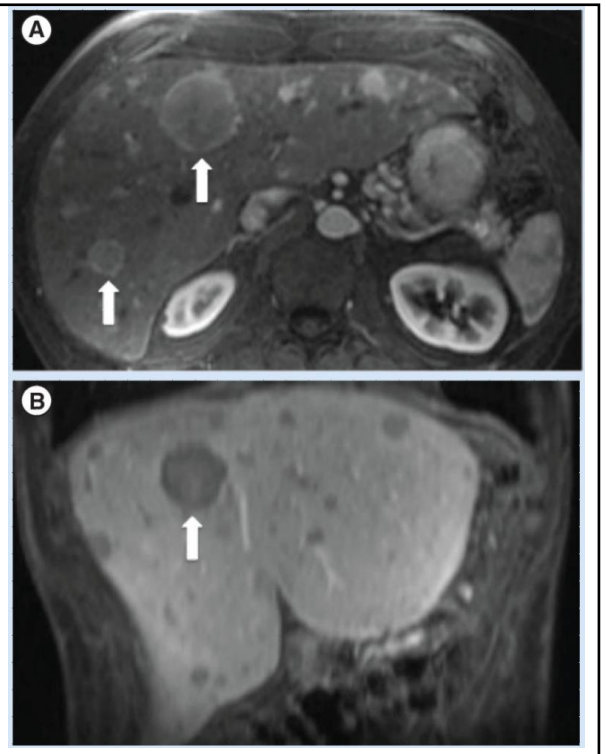
Multiphasic CT or MRI is the foundation of anatomic imaging




**Arterial phase** **Venous phase** **Equilibrium phase**

Multiphasic (dual-phase) contrast-enhanced imaging with arterial and portal venous phases is critical because NETs are often hypervascular and enhance in the arterial phase

Hepatobiliary-phase MRI with diffusion-weighted sequences is more sensitive than CT for detecting small hepatic metastases



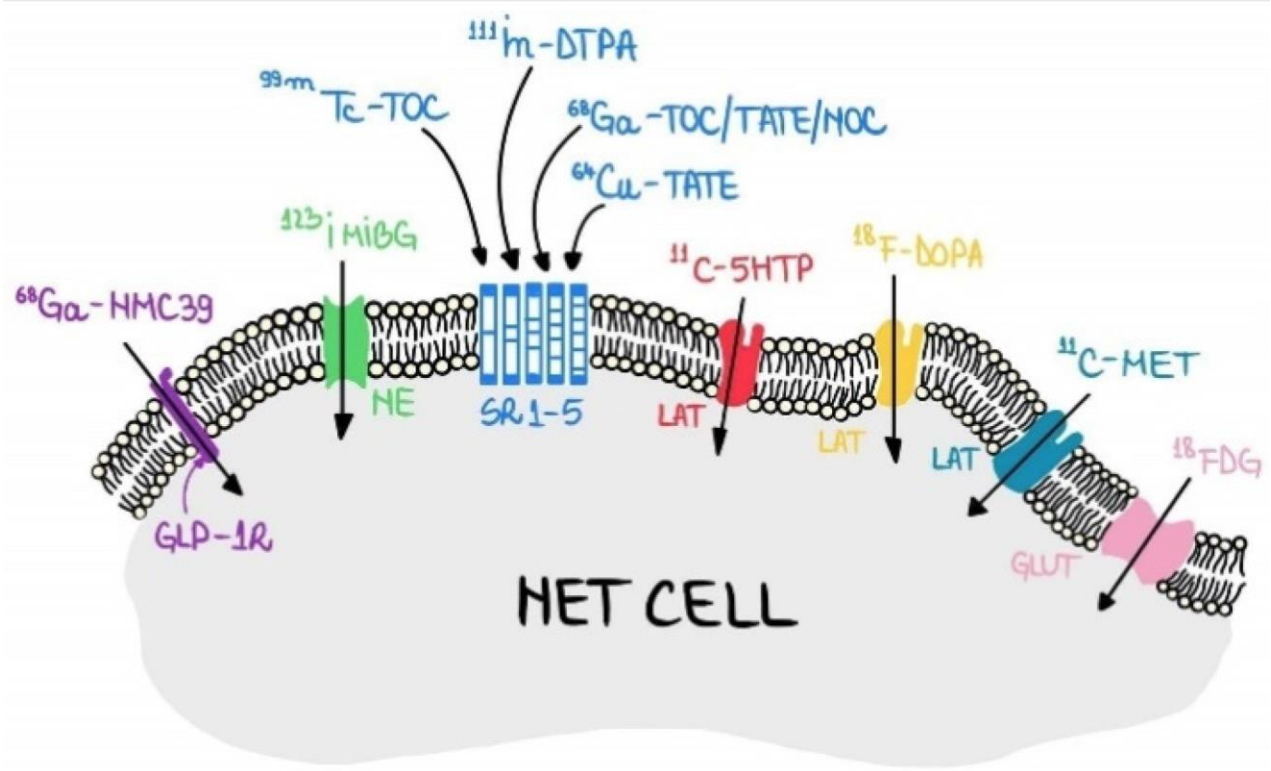

*Maxwell, et al. Int J Endocr Oncol. 2015*

# Core Diagnostic Workup Components

**Functional Imaging**

85-90% of well-differentiated gastroenteropancreatic NETs express somatostatin receptor

SSTR expression is critical for determining eligibility for SSTR-directed therapies (SSA; PRRT) and as a good prognostic marker

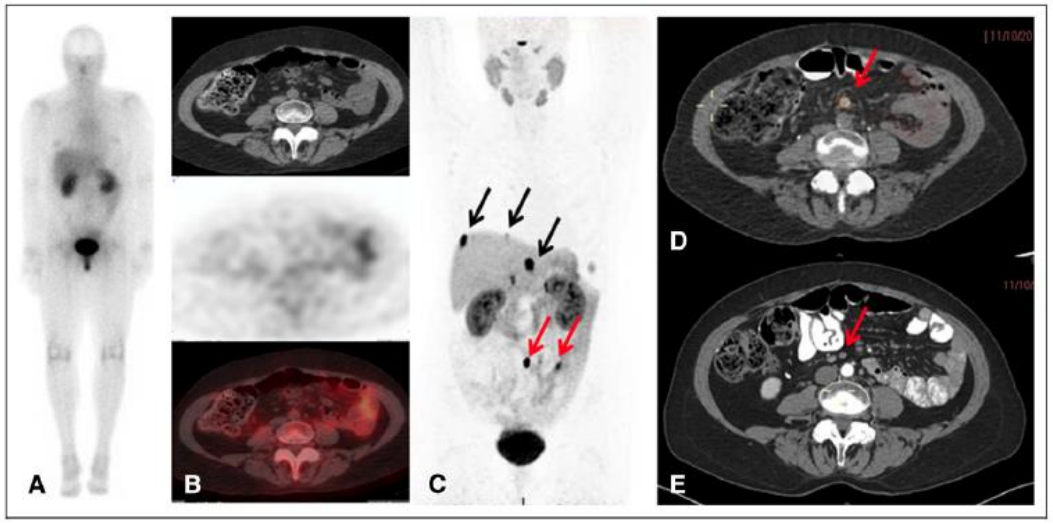



*Stolniceanu, et al. J. Pers. Med. 2021*

# Core Diagnostic Workup Components
# The role of functional imaging

SSTR PET has superior accuracy over Octreoscan and traditional cross-sectional imaging

Is the standard of care for patients with NETs




*A patient with known liver metastases and previously unknown primary lesion. (a)Octreoscan; (b) CT, Octreoscan, SPECT/CT; (c) 68Ga-DOTATATE PET; (d) Arterial phase CT

Clinical Scenarios for SSTR PET

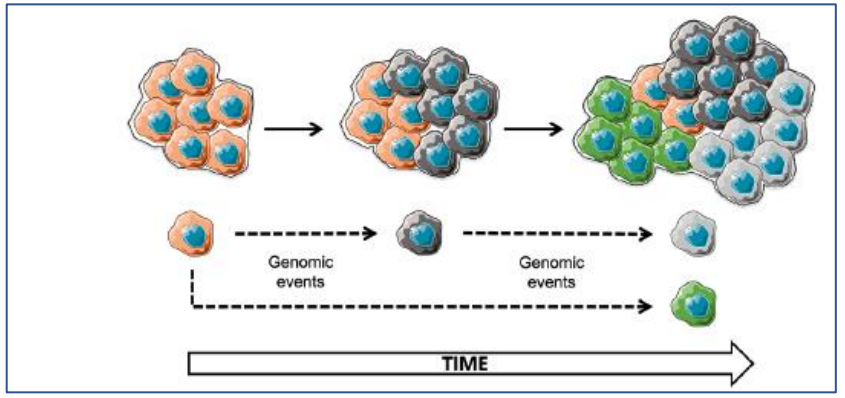
| Scenario no. | Description | Appropriateness | Score |
|---|---|---|---|
| 1 | Initial staging after histologic diagnosis of NETs | Appropriate | 9 |
| 2 | Localization of primary tumor in patients with known metastatic disease but unknown primary | Appropriate | 9 |
| 3 | Selection of patients for 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 | Evaluation of patients with biochemical evidence and symptoms of NET without evidence on CI and without prior histologic diagnosis of NET | Appropriate | 7 |
| 8 | Restaging at time of clinical or laboratory progression without progression on CI | Appropriate | 7 |
| 9 | New indeterminate lesion on CI, with unclear progression | Appropriate | 7 |
| 10 | Restaging of patients with NETs at initial follow-up after resection with curative intent | May be appropriate | 6 |
| 11 | Selection of patients with nonfunctional NETs for SSA treatment | May be appropriate | 6 |
| 12 | 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 |

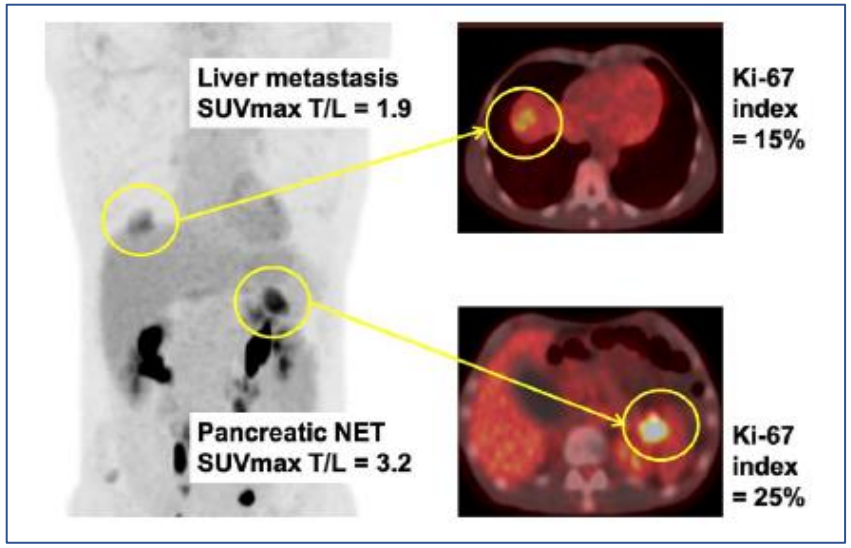
Sadowski et al, *JCO* (2015)
Hope et al, *J. Nucl. Med.* (2018)

# Neuroendocrine tumors (NETs) can be highly heterogeneous

| Issues | Proposals |
|---|---|
| **Inter-tumor heterogeneity (Ki-67, grade, hormone staining, SSTR)**<br>- ≈30% between primary tumors and metastases (usually higher grade)<br>- ≈30% between metastases<br>- higher for metastases sized >4 cm | - Prioritize sampling of metastatic lesions whenever possible<br>- Prioritize sampling of largest metastases if possible<br>- Use both $^{18}$F-FDG and $^{68}$Ga-DOTA PET to target the best lesion to biopsy |
| **Intra-tumor heterogeneity (Ki-67, grade, hormone staining, SSTR)**<br>- ⩾30% within tumors<br>- Higher for tumors sized >2 cm<br>- Higher for tumors with Ki-67 >10% | - Use core-needle biopsy (rather than fine-needle biopsy)<br>- Consider rebiopsy if discordance with clinical behavior and/or uptake on $^{18}$F-FDG PET<br>- Assess the Ki-67 index on at least 2000 cells (or 500 cells in case of biopsies)<br>- On resected specimen, assess Ki-67 each 2 cm, or in case of heterogeneous morphology<br>- Assess Ki-67 on each resected metastasis if multiple |
| **Temporal heterogeneity (Ki-67, grade)**<br>- 30–60% between metachronous lesions<br>- Can be revealed by metachronous hormonal syndrome and/or morphological progression<br>- Especially in patients heavily pretreated (including alkylating agents) | - Systematic sampling of metachronous NET metastases at relapse or unexpected progression<br>- Use both $^{18}$F-FDG and $^{68}$Ga-DOTA PET to target the best lesion to (re)-biopsy |

$^{18}$F-FDG PET, Fluorine-18 fluorodeoxyglucose positron emission tomography; NENs, neuroendocrine neoplasms; SSTR, somatostatin receptor.

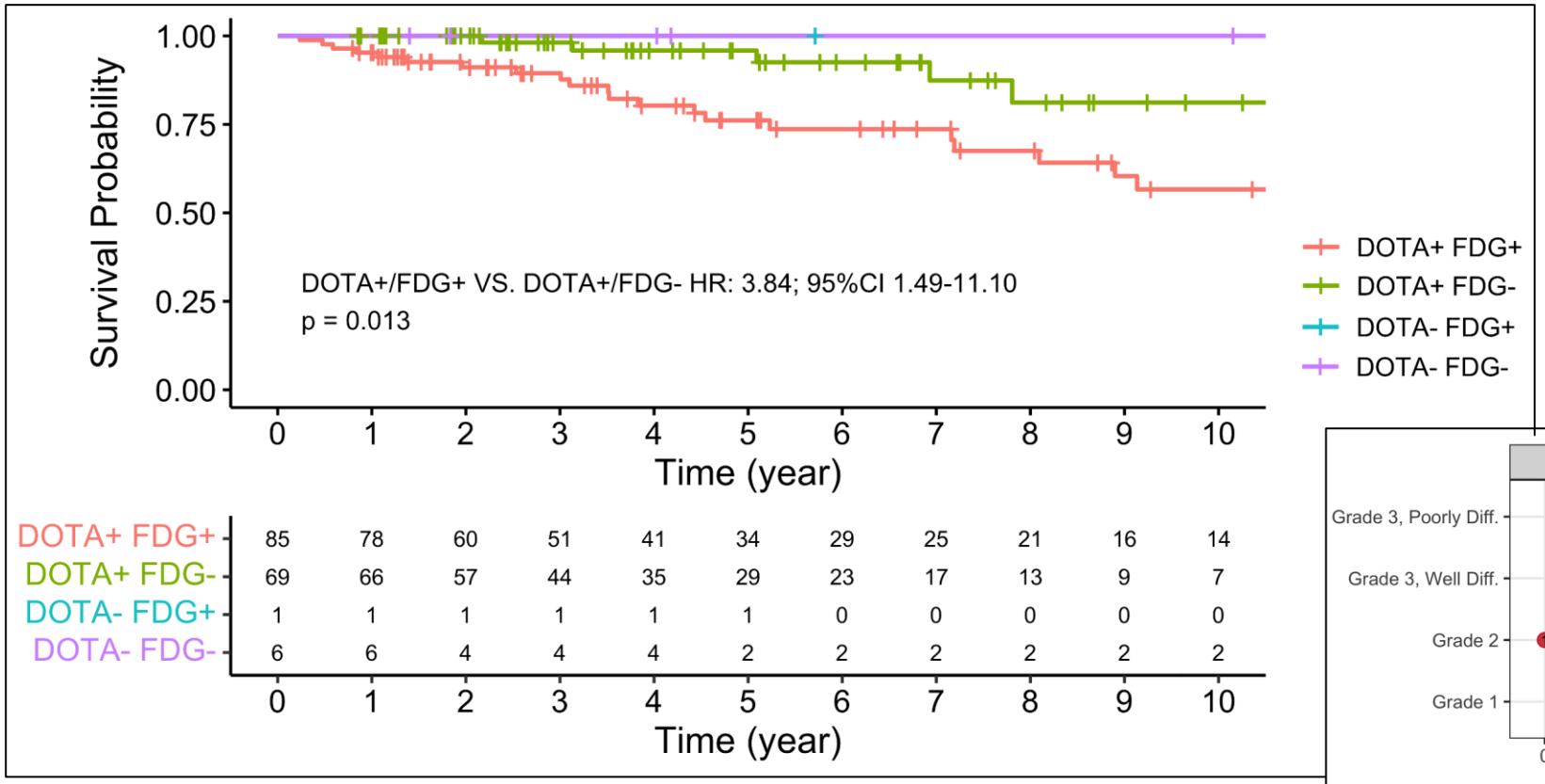


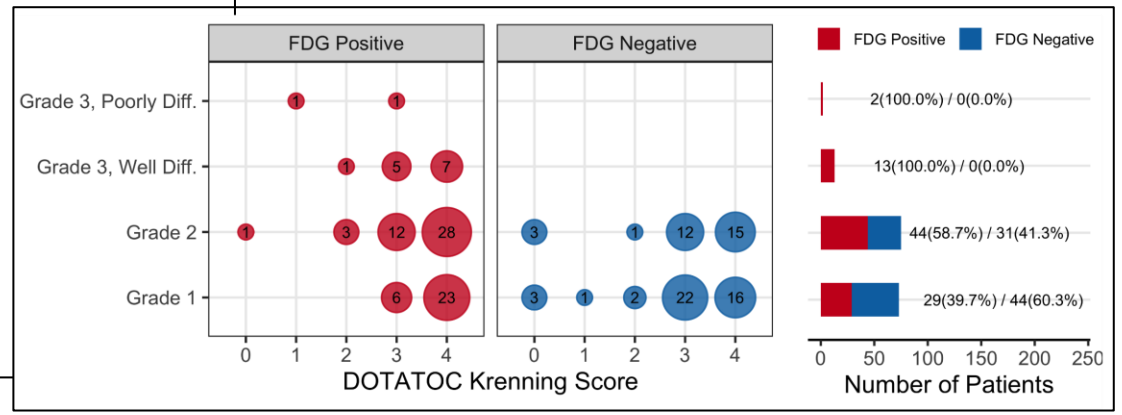




Bourdeleau et al, *Ther Adv Med Oncol* (2023)

# The role of functional imaging

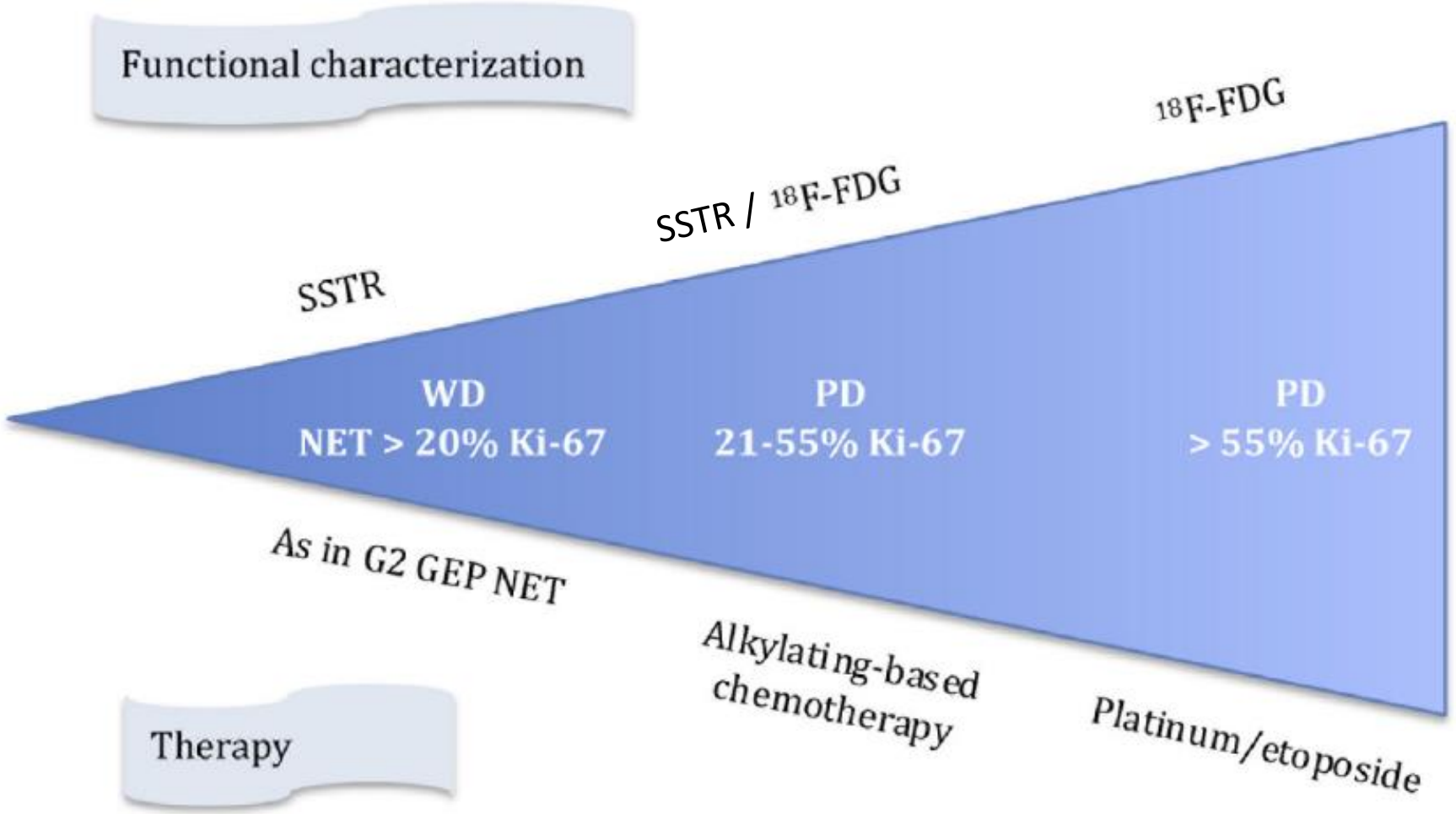
## FDG prognostic in GEP-NENS




Vasconcelos et al, ASCO Annual Meeting (2023)

# Concurrent FDG Pet? Why?




Fazio et al, *Cancer Treatment Reviews* (2016)

# Principles of treatment

# Think (again and again) about locoregional treatment. They can be used at any point during a patient's disease course.

For a curative attempt in early/locally advanced disease.

For symptomatic tumor bulk, hormone hypersecretion, or a threat to critical structures.

As a treatment line (near total debulking has been associated with improvement in survival).

Surgery (primary/metastasis); Liver directed therapy (many options); liver transplant (selected patients)

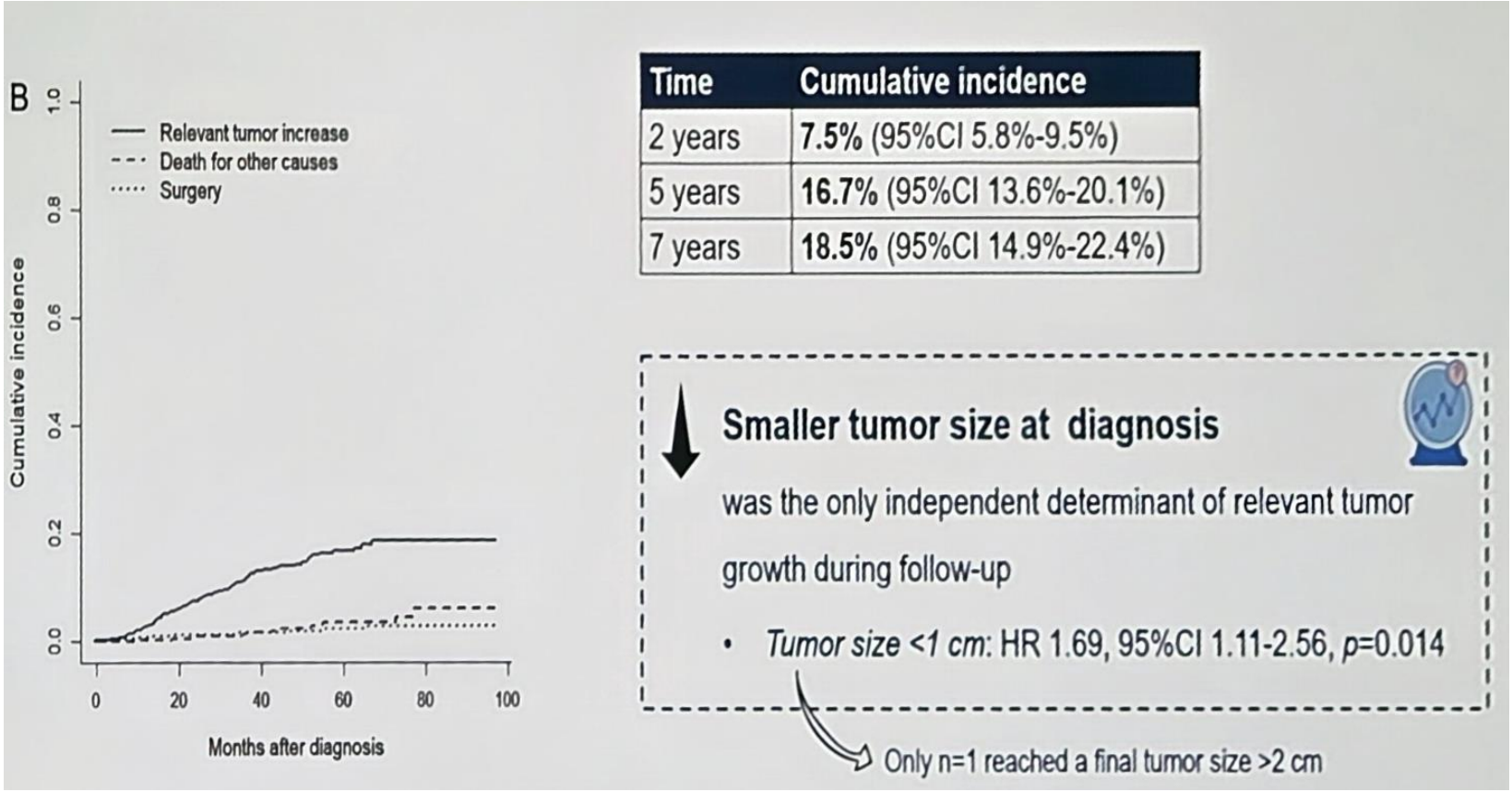
# When surgery might not be needed in early stage: asymptomatic, sporadic, Non-functional p-NET, < 2cm

**ASPEN STUDY**

Prospective multicentre observational cohort.

N= 1000 pNET< 2cm
87% AS; 13% upfront Sx

OS NS (p=0.53); Liver mets 0.3%; NNT=289; NNH=6




| Time | Cumulative incidence |
|---|---|
| 2 years | **7.5%** (95%CI 5.8%-9.5%) |
| 5 years | **16.7%** (95%CI 13.6%-20.1%) |
| 7 years | **18.5%** (95%CI 14.9%-22.4%) |

**Smaller tumor size at diagnosis**

was the only independent determinant of relevant tumor growth during follow-up

- *Tumor size <1 cm*: HR 1.69, 95%CI 1.11-2.56, *p*=0.014

Only n=1 reached a final tumor size >2 cm

*Partelli et al, ESMO 2025*

# Management of hormone hypersecretion in a nutshell. Treat the hormone and the cancer!

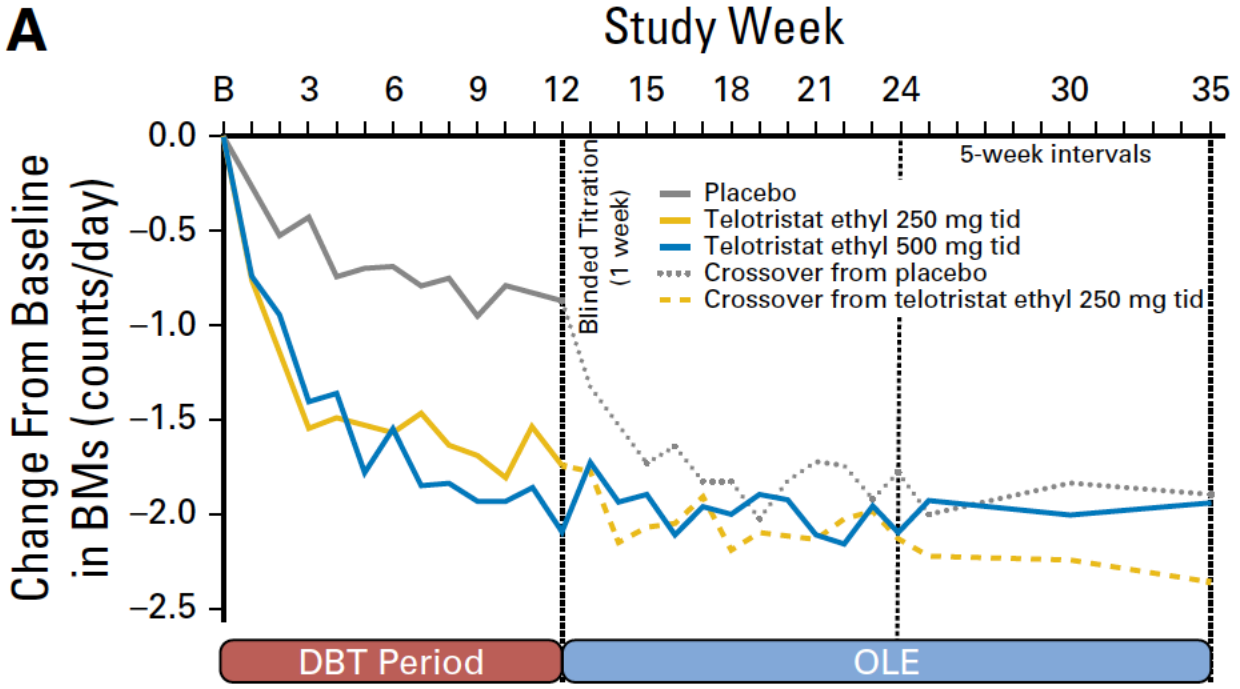
| Therapy line | Carcinoid syndrome | | Functioning Pancreatic NEN | |
|---|---|---|---|---|
| | **Indolent tumors** | **Aggressive tumors[a]** | **Indolent tumors** | **Aggressive tumors[a]** |
| **First** | SSA[b] | SSA[b] | SSA[c] | SSA[c] + chemotherapy (eg, CAPTEM) |
| **Second** | Increase SSA dose and/or shorten injections intervals | Increase SSA dose and/or shorten injections intervals + Hepatic embolization[d] +/- telotristat ethyl[e] | Everolimus, sunitinib or Hepatic embolization[d] | Switch chemotherapy (eg, to oxaliplatin-based) |
| **Later lines** | Add telotristat ethyl[e] or Hepatic embolization[d] or Lutetium$^{177}$ | Lutetium$^{177}$[d] | Lutetium$^{177}$ or CAPTEM | Palliative surgical debulking or Hepatic embolization[d] |
| **Other options** | Everolimus or Alpha-interferon | Chemotherapy | Palliative surgical debulking | Everolimus or Sunitinib |

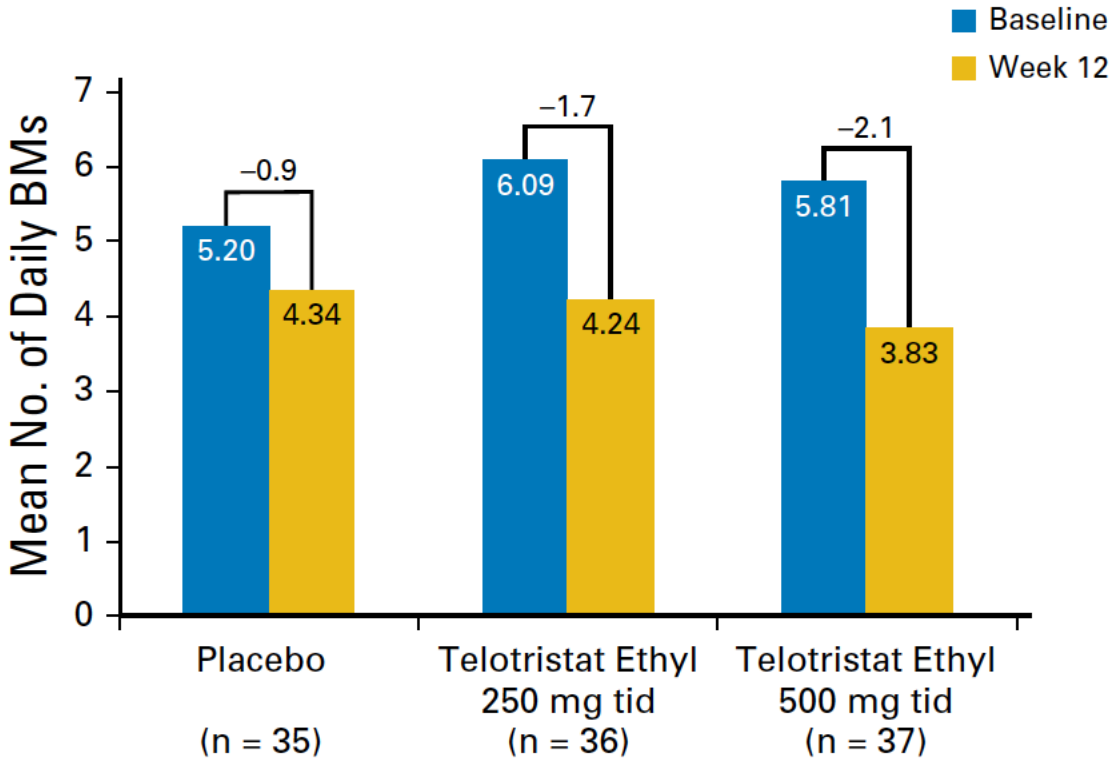
[C] SSA should be used carefully in insulinomas (SSTR+ only) due to the risk of worsening hypoglycemia; [e]For uncontrolled diarrrhea

*Riechelmann et al, ASCO Ed. Book 2023*

# Telotristat approved for SSA refractory carcinoid syndrome related diarrhea based on TELESTAR trial results

**Approved dose 250 mg TID (better tolerated less nausea)**



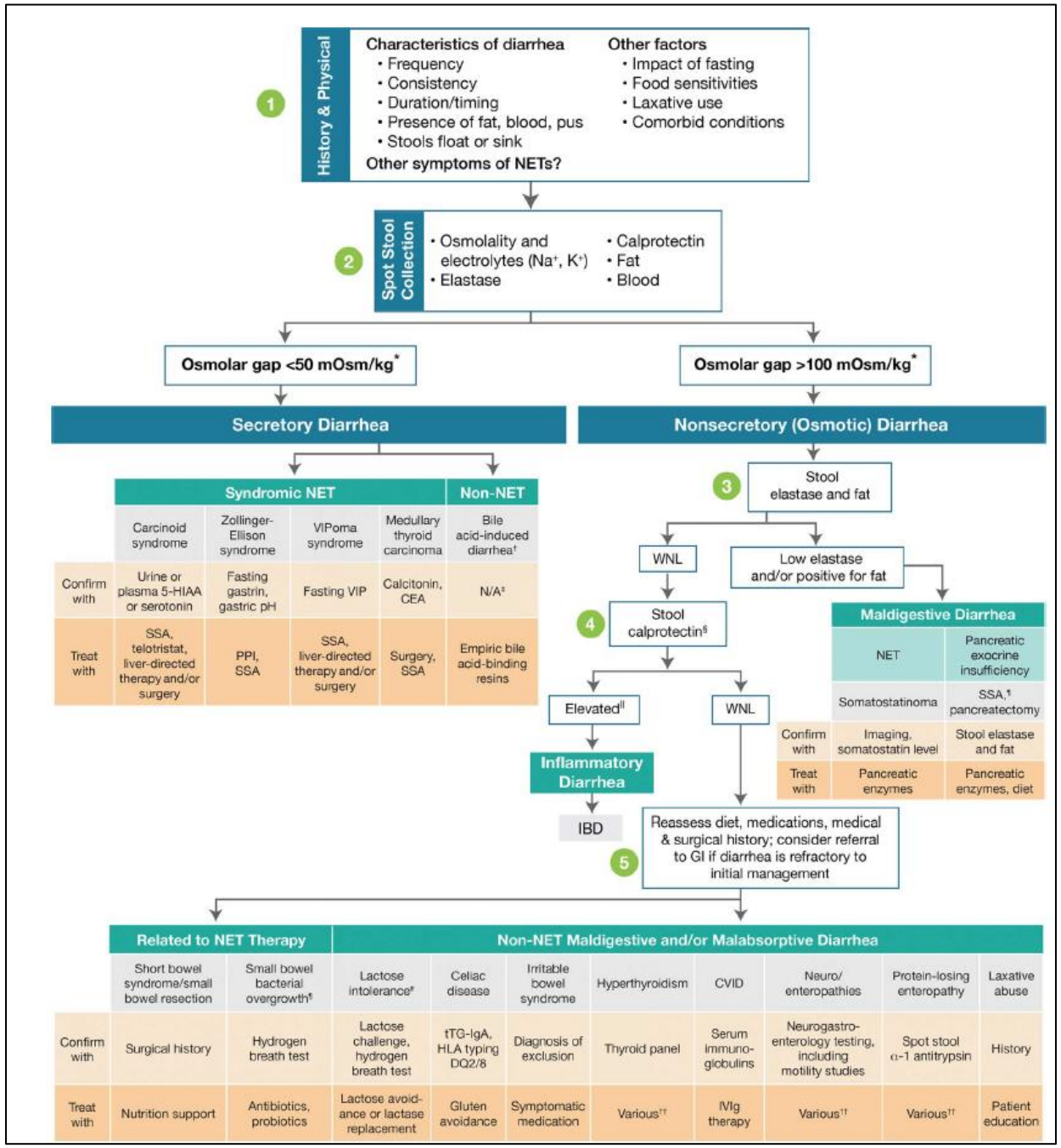

**Also, a significant reduction on urinary levels of 5HIAA.**
**Underpowered for flushing and abdominal pain assessment.**

Kulke MH, et al. J Clin Oncol. 2017

# Managing refractory diarrhea

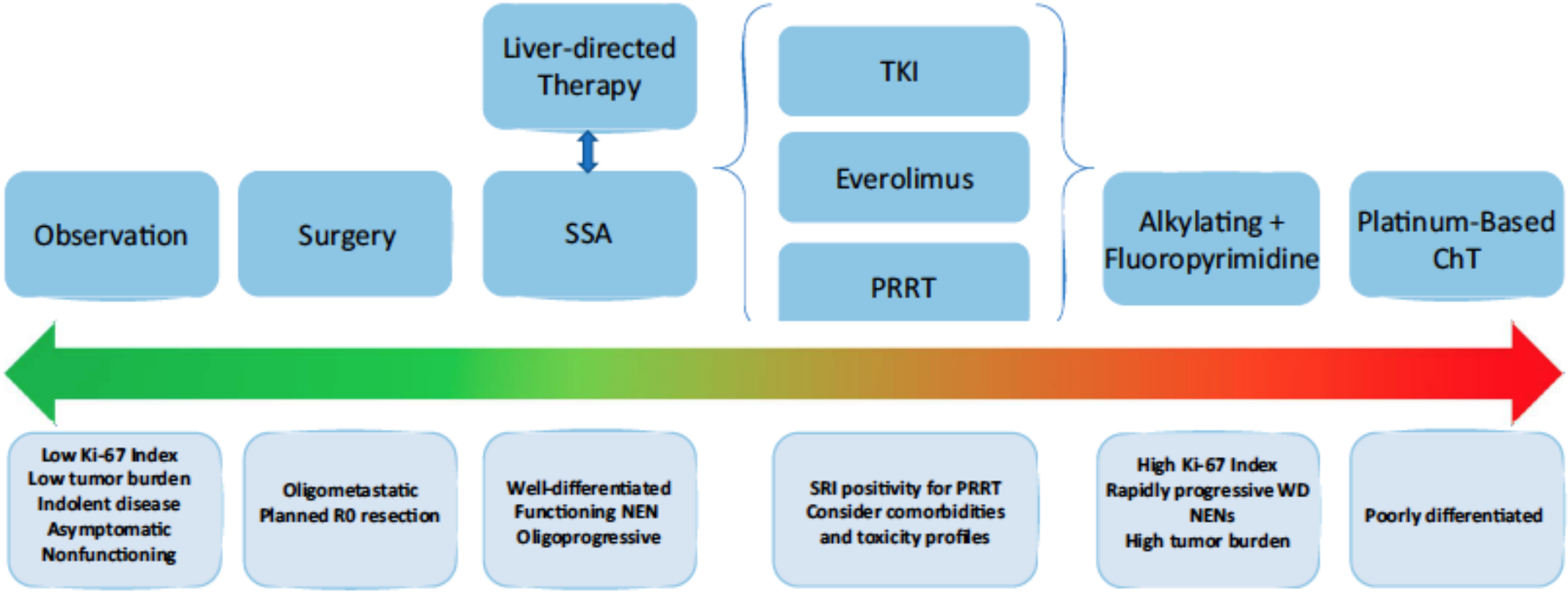
Think about the differentials…

- Pancreatic exocrine insufficiency
- Bile-acid induced diarrhea
- Short bowel syndrome
- SBO




Eads et al, *pancreas* (2020).

# Many options for growth control
# Best therapy sequencing remains unknown



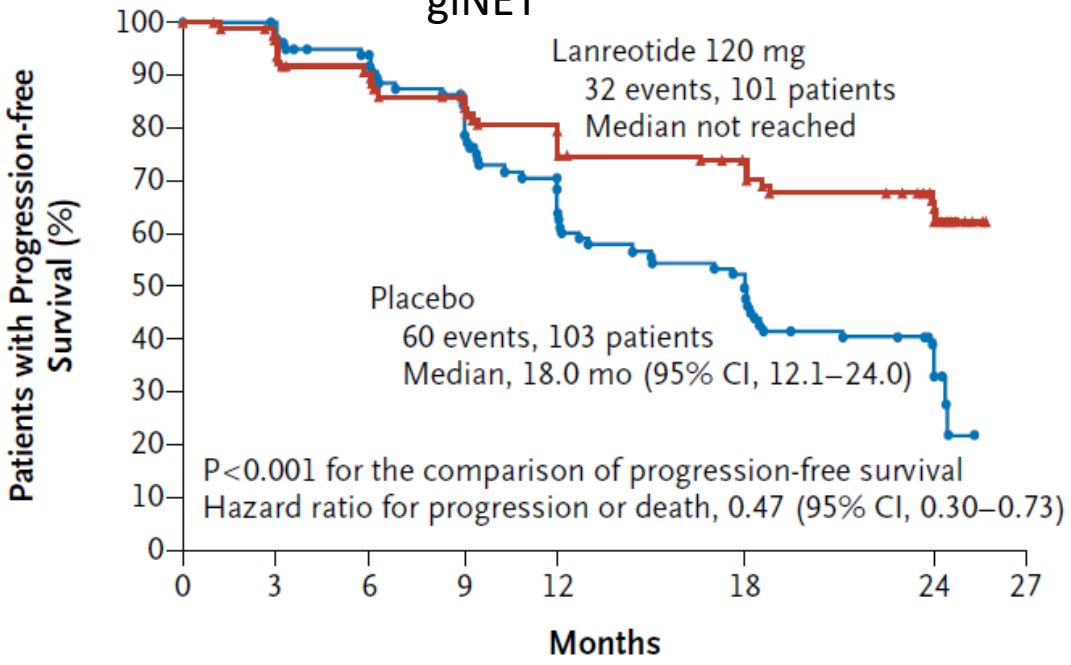

*Riechelmann et al, ASCO Ed. Book 2023*

# Observation is often the preferred approach for G1/G2, non-functional, asymptomatic, stable and low burden

**6-18 months of disease stabilization**

**CLARINET TRIAL**

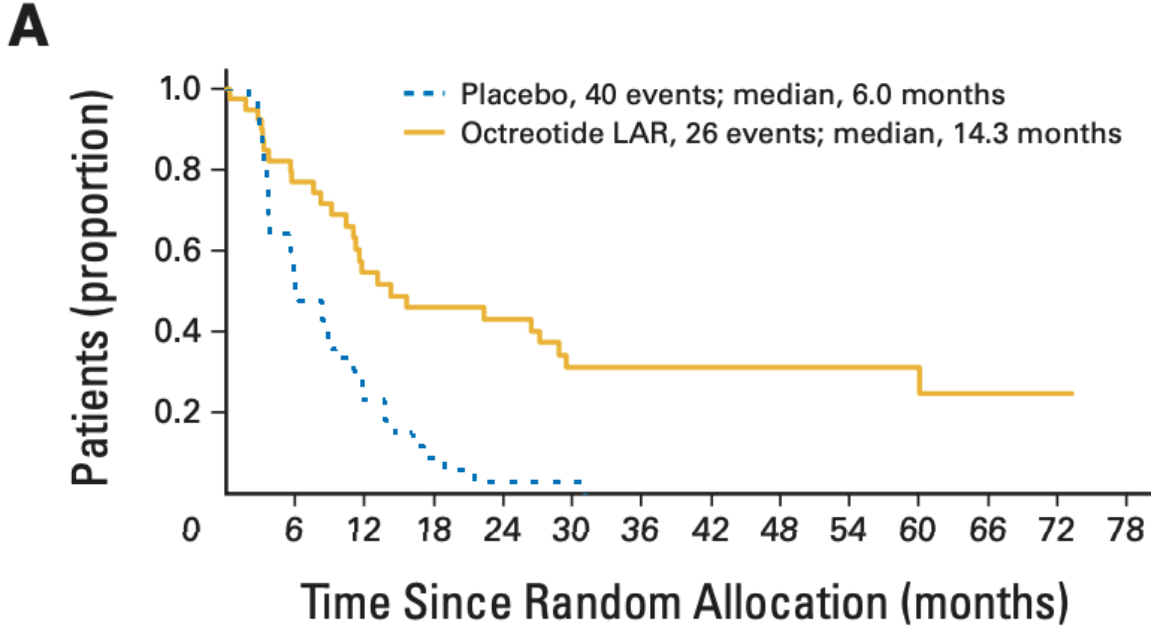
1st line, non-fuctional, G1-G2 (ki 67<10%); SSTR+, giNET




| No. at Risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Lanreotide | 101 | 94 | 84 | 78 | 71 | 61 | 40 | 0 |
| Placebo | 103 | 101 | 87 | 76 | 59 | 43 | 26 | 0 |

**PROMID**

1st line, functional and fuctional, G1 (95%); midgut NET




| No. of patients at risk | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 43 | 21 | 9 | 3 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Octreotide LAR | 42 | 30 | 19 | 16 | 15 | 10 | 10 | 9 | 9 | 6 | 5 | 3 | 1 | 0 |

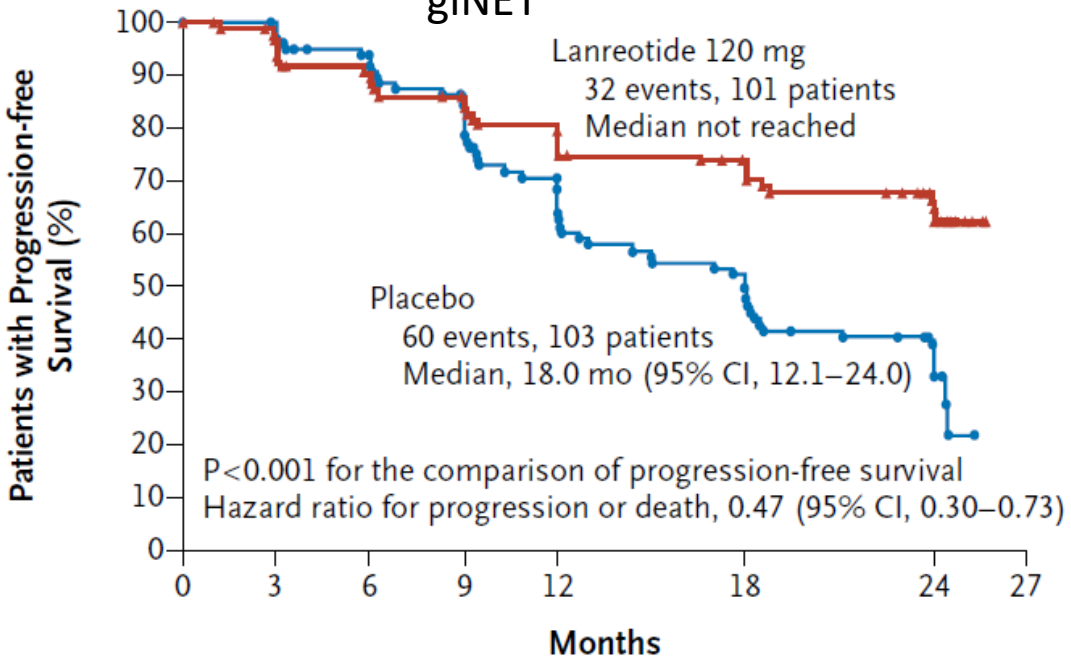
# Somatostatin analogs

**Negligible tumor responses (2%)**

Well tolerated, most common adverse events: pain, injection site reaction, diarrhea, disglycemia, and cholelithiasis.

**CLARINET TRIAL**

1st line, non-fuctional, G1-G2 (ki 67<10%); SSTR+, giNET

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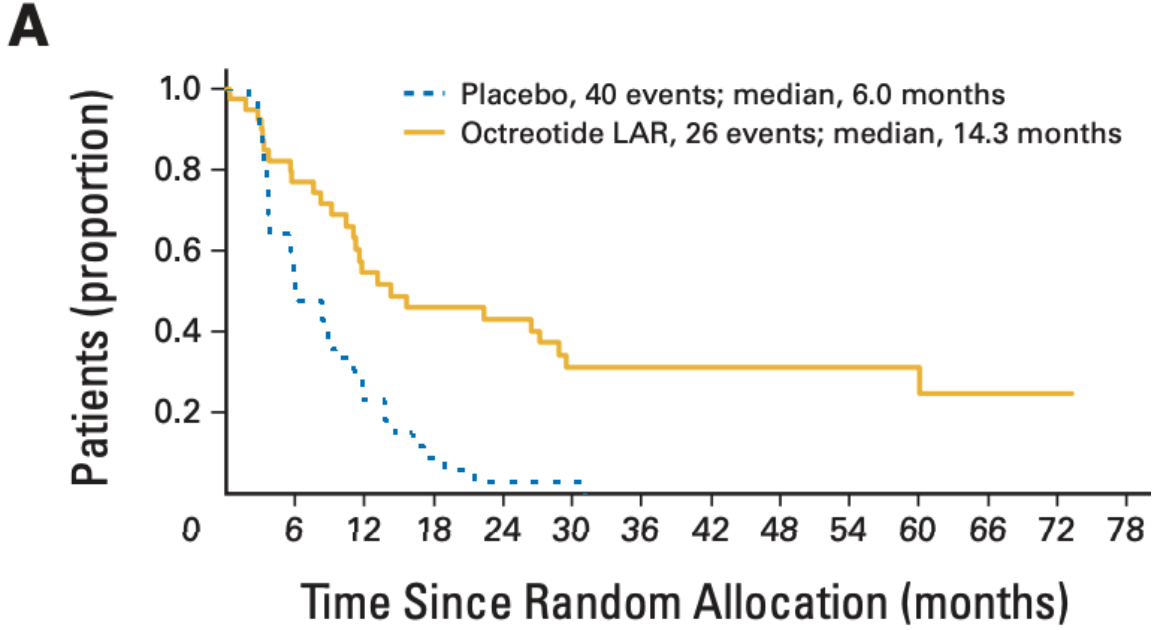
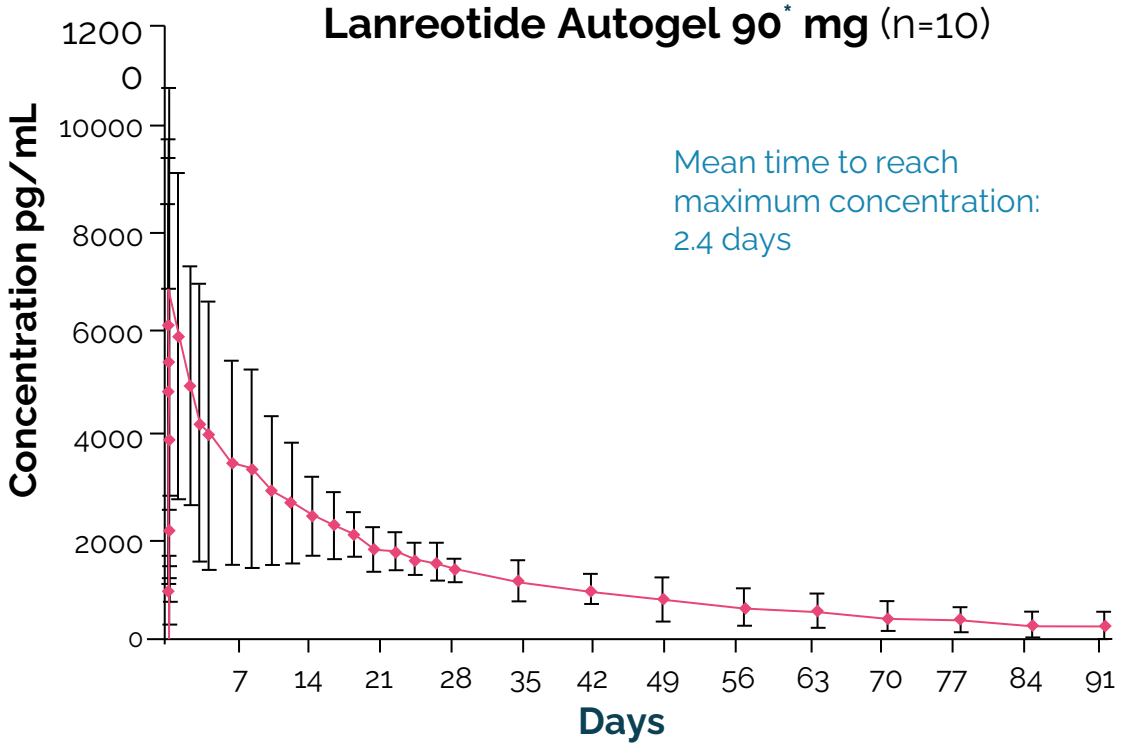
1st line, functional and fuctional, G1 (95%) and G2; midgut NET

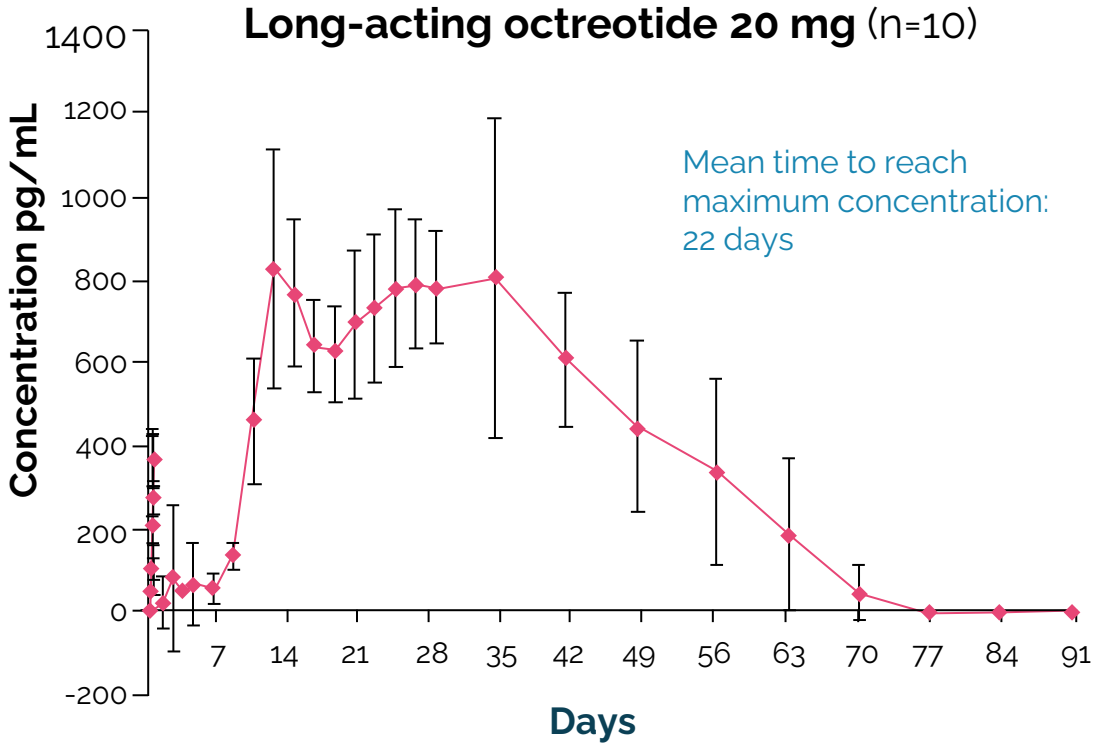



| No. of patients at risk | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 43 | 21 | 9 | 3 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Octreotide LAR | 42 | 30 | 19 | 16 | 15 | 10 | 10 | 9 | 9 | 6 | 5 | 3 | 1 | 0 |

# Pharmacokinetics: Lanreotide and Octreotide LAR




**Reported mean times to reach maximum concentration for lanreotide 120 mg:[1,2] 7 hours to 1.1 days**




**Reported mean time to reach maximum concentration for octreotide LAR 30 mg:[3] 14.0 days**

- Graphs are not directly comparable. Concentrations were measured using immunoassays specific to either octreotide LAR or lanreotide, and different scales were used.

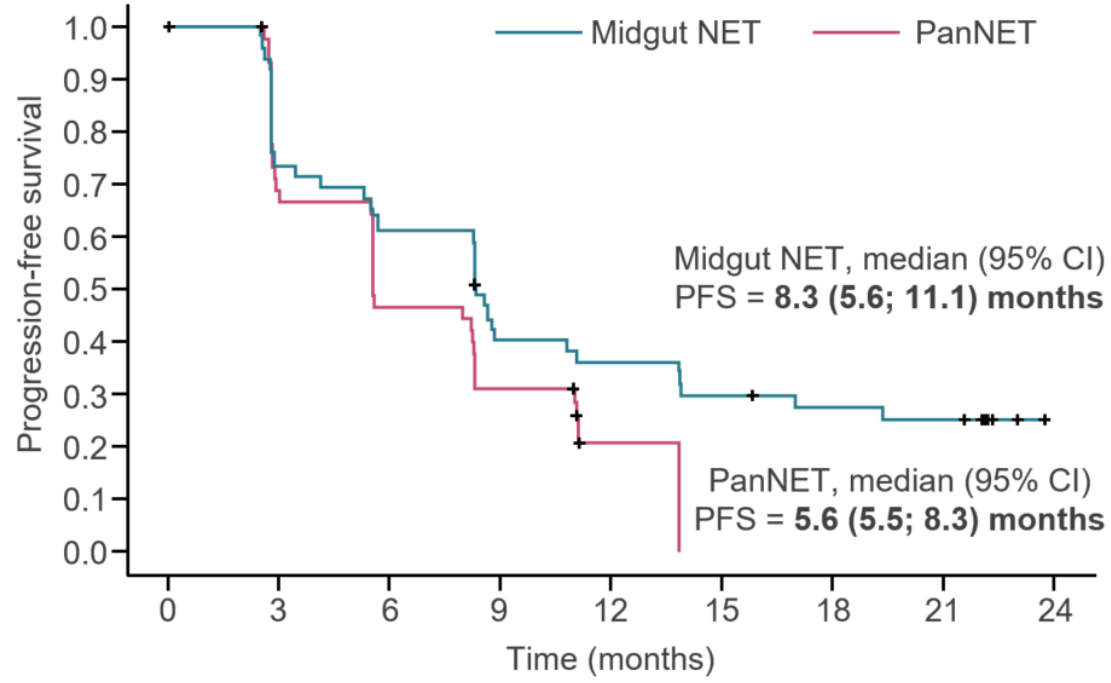
*Not the approved dose for enteropancreatic NETs or carcinoid syndrome.
NET, neuroendocrine tumour; SD, standard deviation.

1. Astruc B, et al. J Clin Pharmacol 2005;45:836-844;
2. Wolin EM et al. J Gastrointest Canc 2016;47:366-374;
3. Tiberg F et al. Br J Clin Pharmacol 2015;80:460-72.

# LAN 120 mg every 14 days resulted in promising PFS and DCR outcomes

## PFS (primary endpoint)

But no randomization and this is RECIST progression…




## Secondary efficacy endpoints

| Endpoint | PanNET, n=48 | Midgut NET, n=51 |
|---|---|---|
| **Best overall response***, % (95% CI) | | |
| **Partial response** | 0 | 3.9 (0.5; 13.5) |
| **Stable disease** | 66.7 (51.6; 79.6) | 68.6 (54.1; 80.9) |
| **Progressive disease** | 31.3 (18.7; 46.3) | 23.5 (12.8; 37.5) |
| **DCR† at Week 24,** % (95% CI) | 43.8 (29.5; 58.8) | 58.8 (44.2; 72.4) |
| **DCR† at Week 48,** % (95% CI) | 22.9 (12.0; 37.3) | 33.3 (20.8; 47.9) |

## Post-hoc efficacy endpoints

| Endpoint | PanNET | Midgut NET |
|---|---|---|
| **PFS by Ki67‡**, median (95% CI), months | | |
| **Ki67 ≤10%** (n=43; n=47) | 8.0 (5.6; 8.3) | 8.6 (5.6; 13.8) |
| **Ki67 >10%** (n=5; n=4) | 2.8 (2.8; 2.9) | 5.5 (2.6; NC) |



*Best overall response was defined as the best response recorded from the initiation of treatment until disease progression; one patient in the midgut NET cohort has 'not evaluable' as best overall response. †DCR was defined as the proportion of patients with complete response, partial response or stable disease. ‡Post hoc analysis by Ki67 index. CI, confidence interval; DCR, disease control rate; LAN, lanreotide autogel; NC, not calculable; NET, neuroendocrine tumour; panNET, pancreatic NET; PFS, progression-free survival

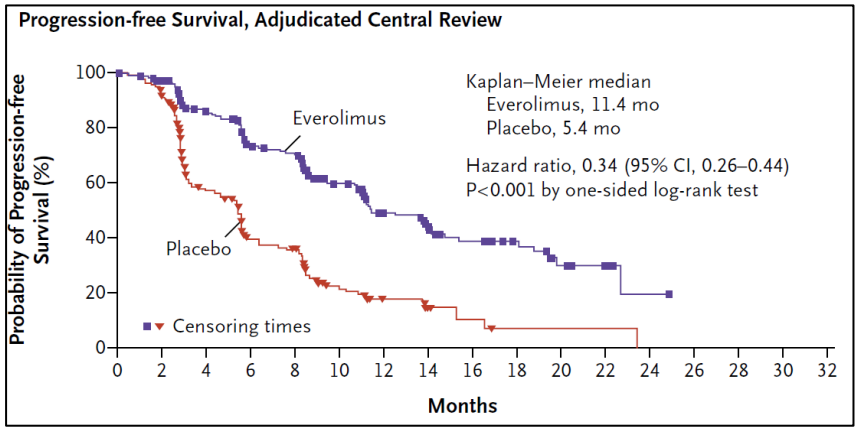
# Targeted Agents

# Everolimus- pNET and non-functional GI-NETs

## RADIANT 3

**Patients with well-differentiated (G1/G2), advanced, progressive, pancreatic neuroendocrine tumors (n = 410)**

- Radiographic progression within prior 12 months
- Pathologically confirmed advanced disease

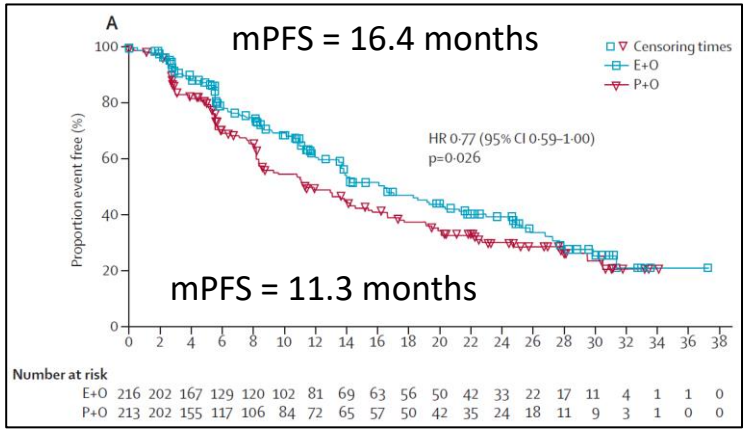



Yao et al, *NEJM* (2011)

## RADIANT 2

**Patients with well-differentiated (G1/G2), advanced, progressive, neuroendocrine tumors (n = 429)**

- Patients required secretory symptoms (carcinoid)
- Pathologically confirmed advanced disease
- Disease progression within prior 12 months

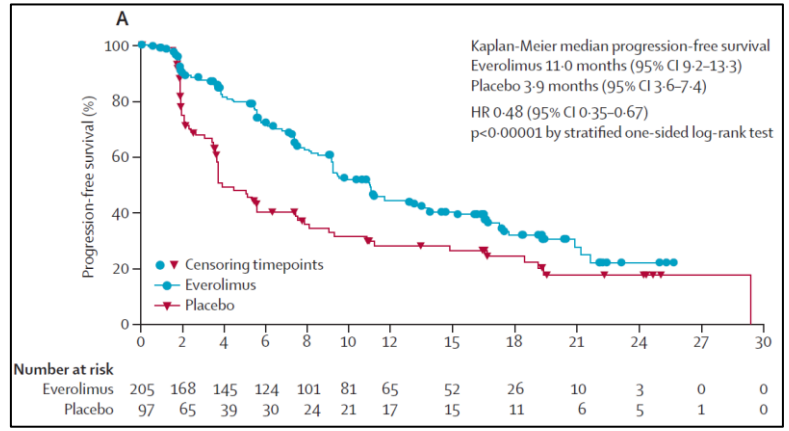



Pavel et al, *Lancet* (2011)

## RADIANT 4

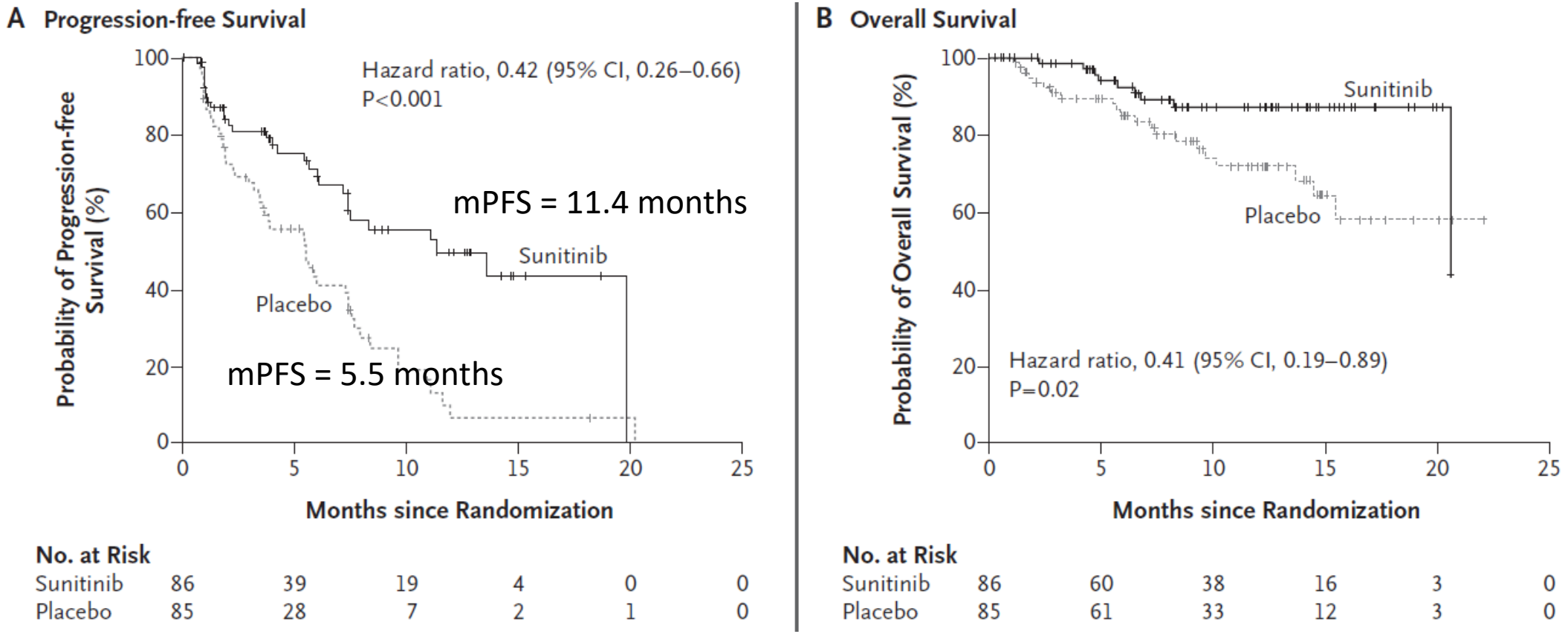
**Patients with well-differentiated (G1/G2), advanced, progressive, non-functional NET of lung or GI origin (n = 302)**

- Absence of active or any history of carcinoid syndrome
- Pathologically confirmed advanced disease
- Enrolled within 6 months from radiologic progression




Yao et al, *Lancet* (2016)

# Sunitinib - pNET

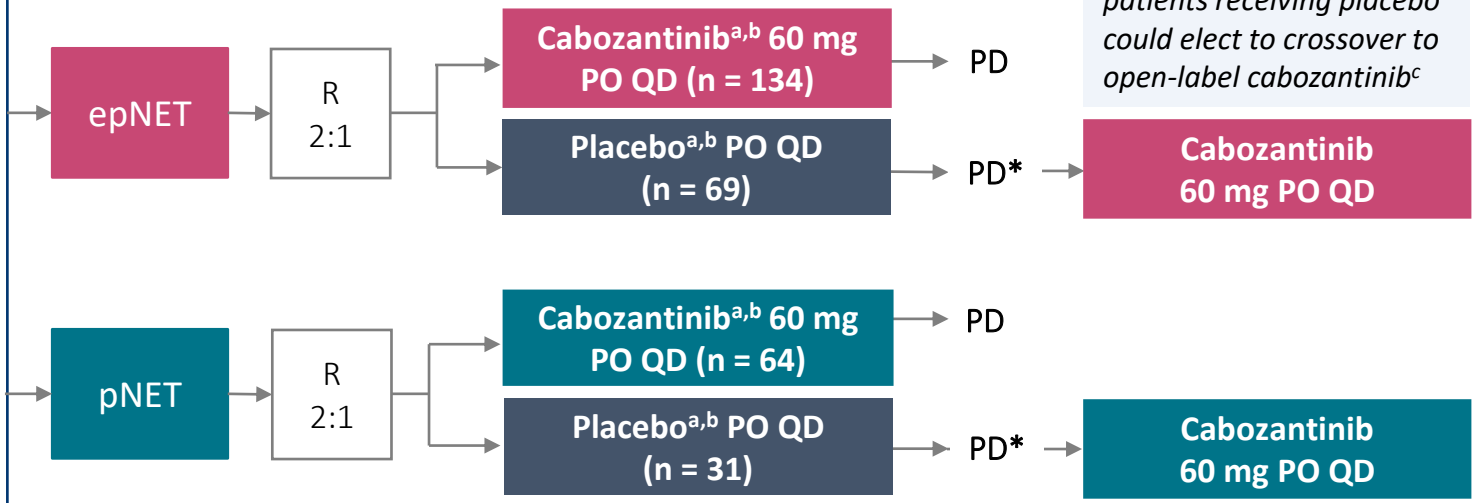



Raymond et al, *NEJM* (2011)

# CABINET – Cabozantinib after PD to at least 1 line of a non-SSA agent

## Key inclusion criteria

- Histologically confirmed locally advanced or metastatic well- or moderately differentiated epNET or pNET, WHO grade 1–3
- Disease progression by RECIST v1.1 within 12 months prior to enrollment
- Progression or intolerance, leading to discontinuation, of at least one prior FDA-approved systemic therapy, not including SSA
  - For pNET: everolimus, sunitinib, or $^{177}$Lu dotatate
  - For epNET (excluding lung NET): everolimus or $^{177}$Lu dotatate
  - For lung NET: everolimus
- Concurrent SSA allowed provided stable dose for ≥ 2 months




*After central confirmation of PD, patients receiving placebo could elect to crossover to open-label cabozantinib[c]

**Stratification factors**

- **epNET**: concurrent SSA and primary site (midgut GI/unknown vs non-midgut GI/lung/other)
- **pNET**: concurrent SSA and prior sunitinib

| | |
|---|---|
| **Primary endpoint** | PFS per RECIST v1.1 by retrospective BICR[d] |
| **Secondary endpoints** | Confirmed ORR[e] per RECIST v1.1, OS, safety |

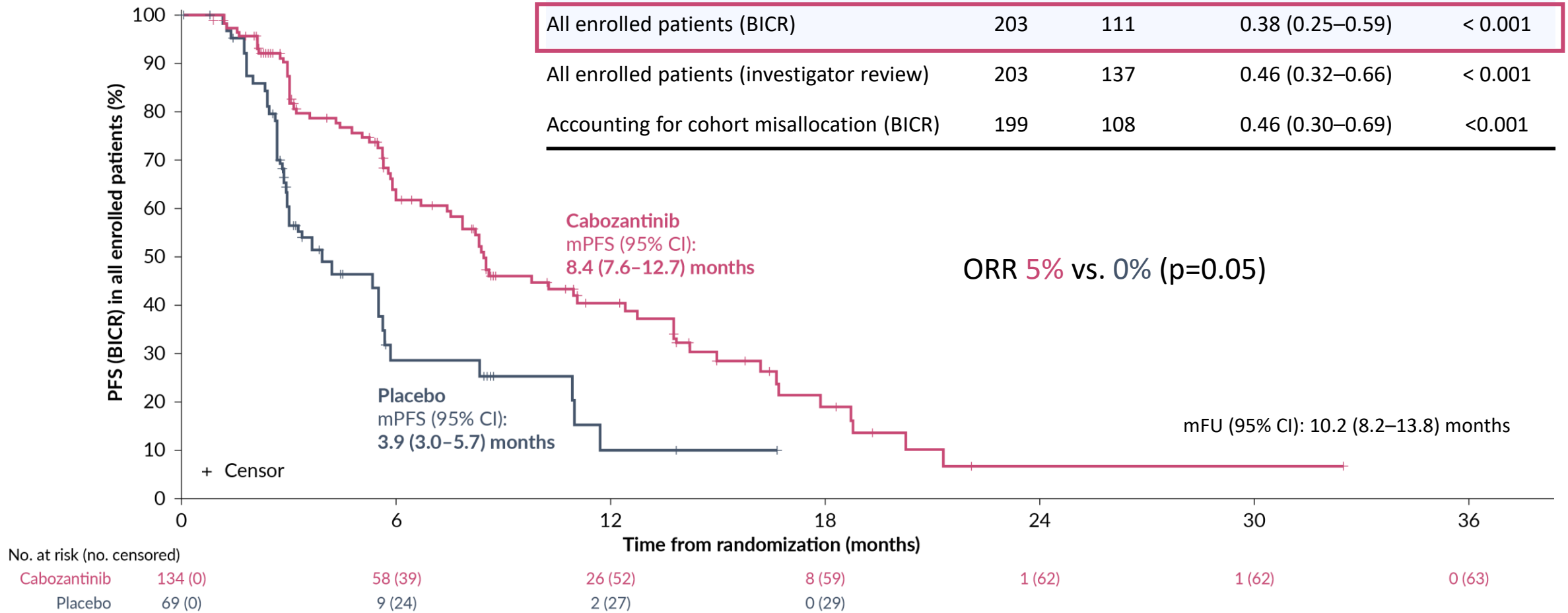
[a]Interruptions and dose reductions for cabozantinib (40 mg, then 20 mg) and placebo were specified for adverse event management; [b]Blinded treatment continued until PD, unacceptable toxicity or withdrawal of consent; [c]If investigator assessments of PD were confirmed by blinded real-time central review, patients were unblinded to treatment assignment; [d]Patients were evaluated every 12 weeks by radiographic imaging for tumor response and progression; [e]Defined as two consecutive scans showing complete or partial response by BICR.

$^{177}$Lu, lutetium 177; BICR, blinded independent central review; epNET, extra-pancreatic NET; FDA, Food and Drug Administration; GI, gastrointestinal; NET, neuroendocrine tumor; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; pNET, pancreatic NET; PO, oral; QD, once daily; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; SSA, somatostatin analog; WHO, World Health Organisation.

Chan J *et al*. *New Engl J Med* 2024;manuscript in press.

# PFS analyses: epNET cohort[a]

| PFS analysis | N | No. of events | Stratified HR (95% CI) | Log-rank *p* |
|---|---|---|---|---|
| All enrolled patients (BICR) | 203 | 111 | 0.38 (0.25–0.59) | < 0.001 |
| All enrolled patients (investigator review) | 203 | 137 | 0.46 (0.32–0.66) | < 0.001 |
| Accounting for cohort misallocation (BICR) | 199 | 108 | 0.46 (0.30–0.69) | <0.001 |



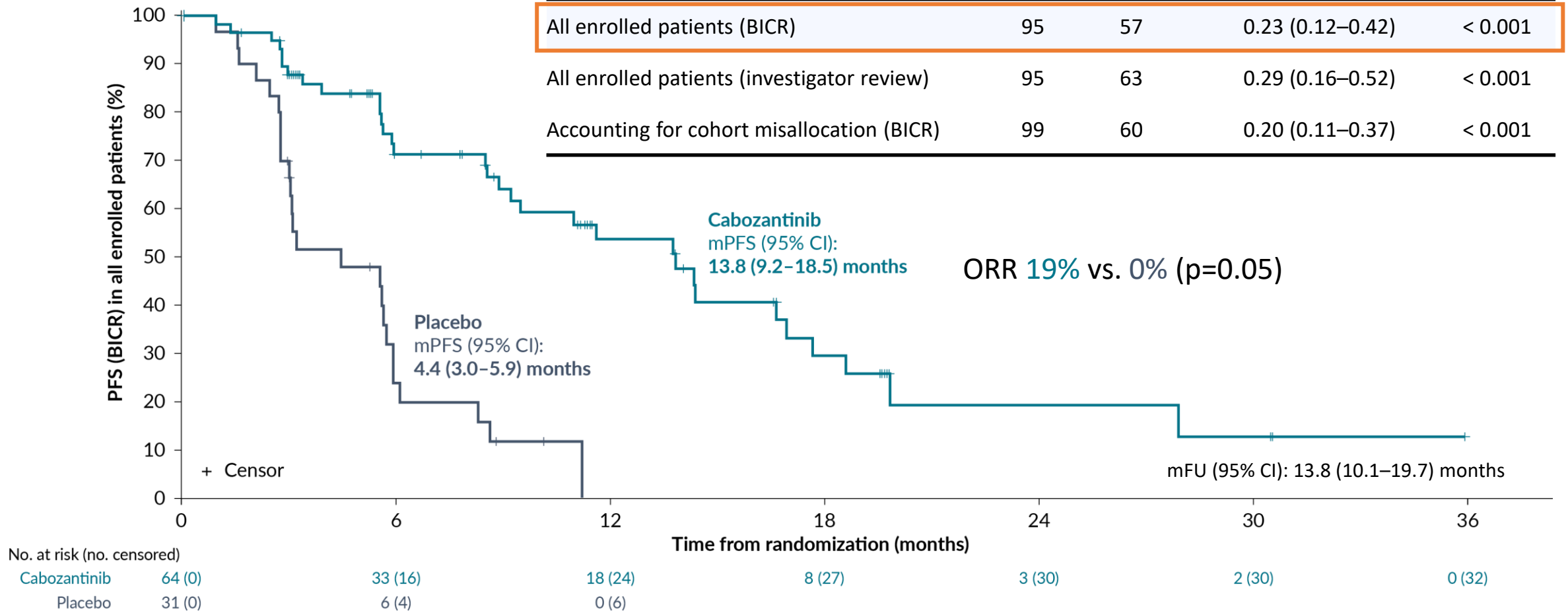

[a]Three patients with epNET were misallocated to the pNET cohort and seven patients with pNET were allocated to the epNET cohort. Data cutoff: 24 August 2024.

BICR, blinded independent central review; CI, confidence interval; epNET, extra-pancreatic neuroendocrine tumor; HR, hazard ratio; mFU, median follow-up; mPFS, median PFS; PFS, progression-free survival; pNET, pancreatic neuroendocrine tumor.

Chan J *et al. New Engl J Med* 2024;manuscript in press and Chan J *et al*. Abstract 1141O. Presented at ESMO 2024, 13–17 September 2024, Barcelona, Spain.

# PFS analyses: pNET cohort[a]

| PFS analysis | N | No. of events | Stratified HR (95% CI) | Log-rank *p* |
|---|---|---|---|---|
| All enrolled patients (BICR) | 95 | 57 | 0.23 (0.12–0.42) | < 0.001 |
| All enrolled patients (investigator review) | 95 | 63 | 0.29 (0.16–0.52) | < 0.001 |
| Accounting for cohort misallocation (BICR) | 99 | 60 | 0.20 (0.11–0.37) | < 0.001 |




[a]Three patients with epNET were misallocated to the pNET cohort and seven patients with pNET were allocated to the epNET cohort. Data cutoff: 24 August 2024.

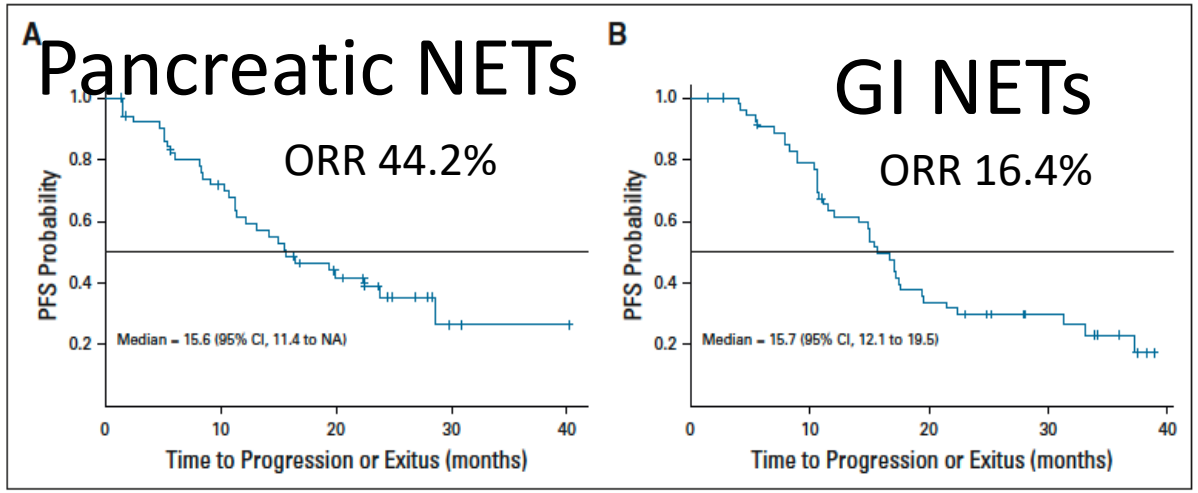
BICR, blinded independent central review; CI, confidence interval; epNET, extra-pancreatic neuroendocrine tumor; HR, hazard ratio; mFU, median follow-up; mPFS, median PFS; PFS, progression-free survival; pNET, pancreatic neuroendocrine tumor.

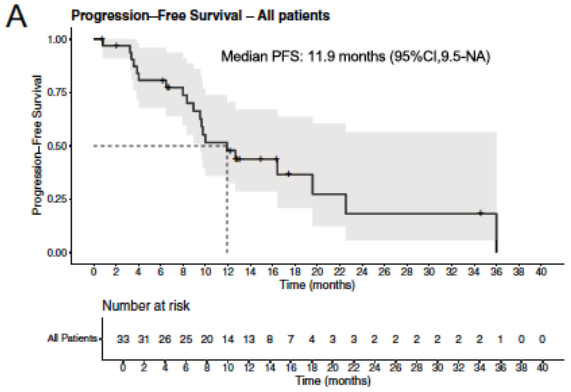
Chan J *et al. New Engl J Med* 2024;manuscript in press and Chan J *et al*. Abstract 1141O. Presented at ESMO 2024, 13–17 September 2024, Barcelona, Spain.

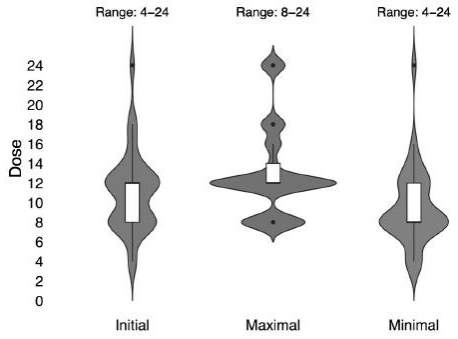
# Lenvatinib

**Lenvatinib in Patients With Advanced Grade 1/2 Pancreatic and Gastrointestinal Neuroendocrine Tumors: Results of the Phase II TALENT Trial (GETNE1509)**

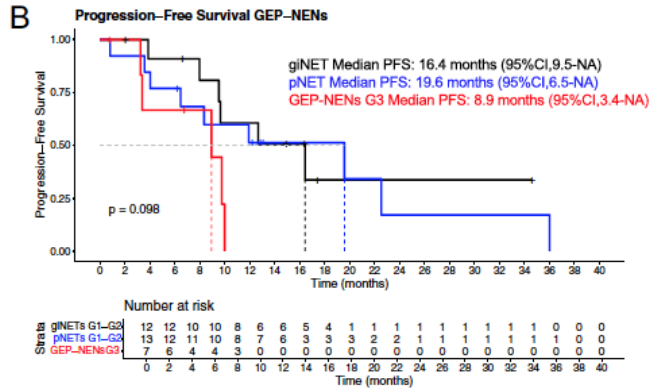
| Efficacy Parameter | panNETs (n = 55) | GI-NETs (n = 56) | Total (N = 111) |
|---|---|---|---|
| Patients with tumor assessment, No. (%) | 52 (94.6)[a] | 55 (98.2)[a] | 107 (96.4)[a] |
| Best overall response, No. (%) | | | |
| Complete response | 0 | 0 | 0 |
| Partial response | 23 (44.2) | 9 (16.4) | 32 (29.9) |
| Stable disease | 27 (51.9) | 42 (76.4) | 69 (64.5) |
| Progressive disease | 2 (3.9) | 1 (1.8) | 3 (2.8) |
| Not evaluable | 0 | 3 (5.5)[b] | 3 (2.8)[b] |
| Overall response rate (95% CI) | 44.2% (30.7 to 58.6) | 16.4% (8.2 to 29.3) | 29.9% (21.6 to 39.6) |
| Disease control rate | 96.2% (85.7 to 99.3) | 92.7% (81.6 to 97.6) | 94.4% (87.7 to 97.7) |
| Median duration of response, months (range) | 19.9 (8.4-30.8) | 33.9 (10.6-38.3) | 21.5 (8.4-38.3) |

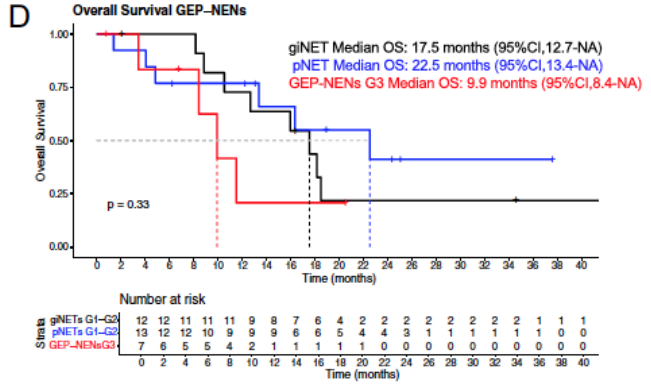






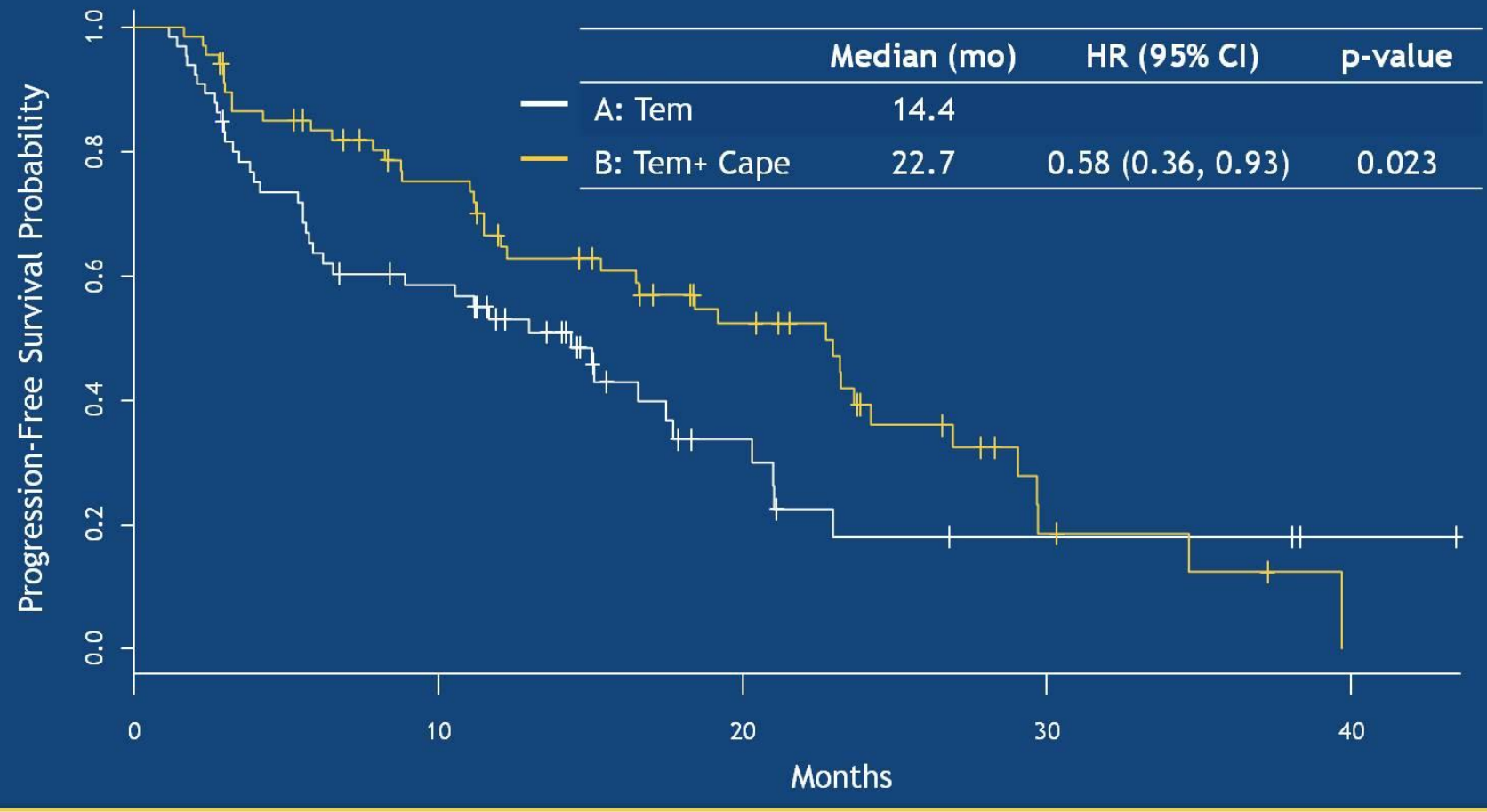

Capdevila et al, *JCO* (2021)
Solar Vasconcelos et al, ERC (2025)

*Lenvatinib does not currently have a Health Canada indication for neuroendocrine tumors

# Chemotherapy

# E2211- CAP-TEM - pNET

## Progression Free Survival




| | Median (mo) | HR (95% CI) | p-value |
|---|---|---|---|
| A: Tem | 14.4 | | |
| B: Tem+ Cape | 22.7 | 0.58 (0.36, 0.93) | 0.023 |

# Response Rates

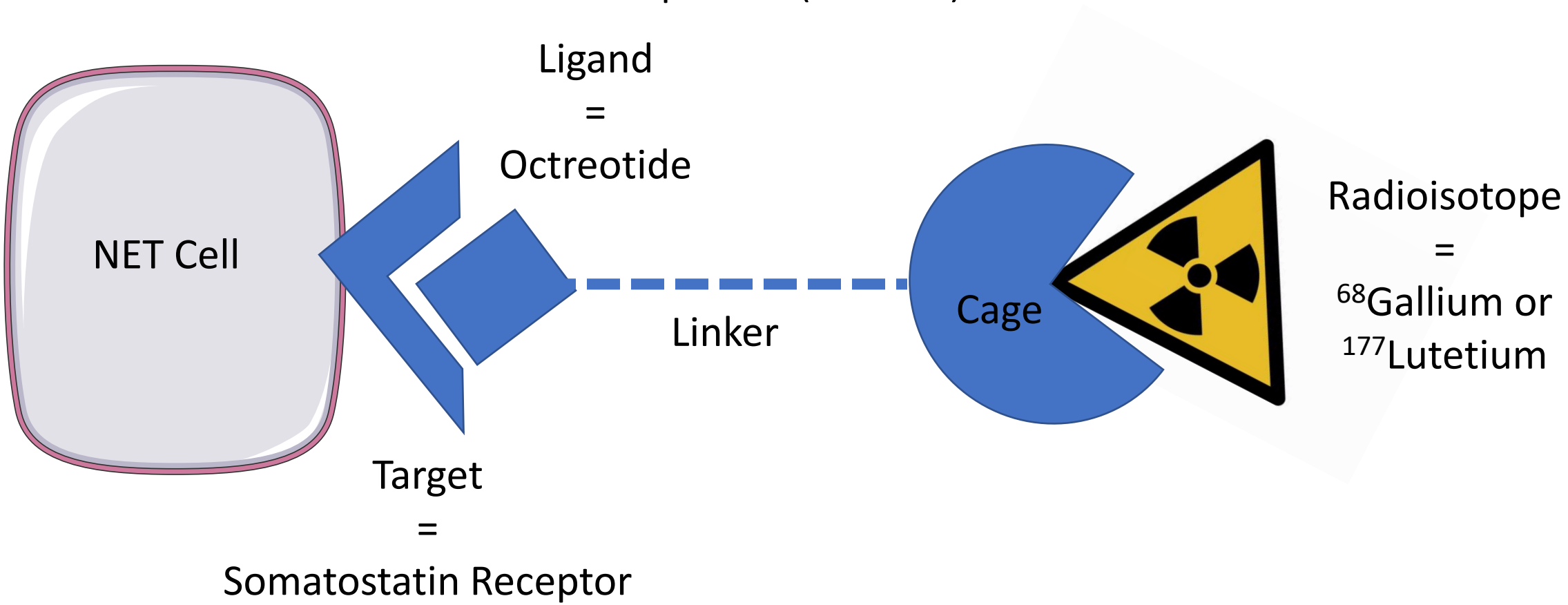
| | Temozolomide (N=72) | Temozolomide + Capecitabine (N=72) | p-value |
|---|---|---|---|
| Complete response | 2.8% | 0 | |
| Partial response | 25.0% | 33.3% | |
| Stable disease | 40.3% | 48.6% | |
| Progressive disease | 19.4% | 13.9% | |
| Unevaluable | 12.5% | 4.2% | |
| Objective Response Rate (CR+PR) | 27.8% | 33.3% | 0.47 |
| Disease Control Rate (CR+PR+SD) | 68.1% | 81.9% | |

| | | | |
|---|---|---|---|
| Response Duration (median) | 9.7 mo | 12.1 mo | |

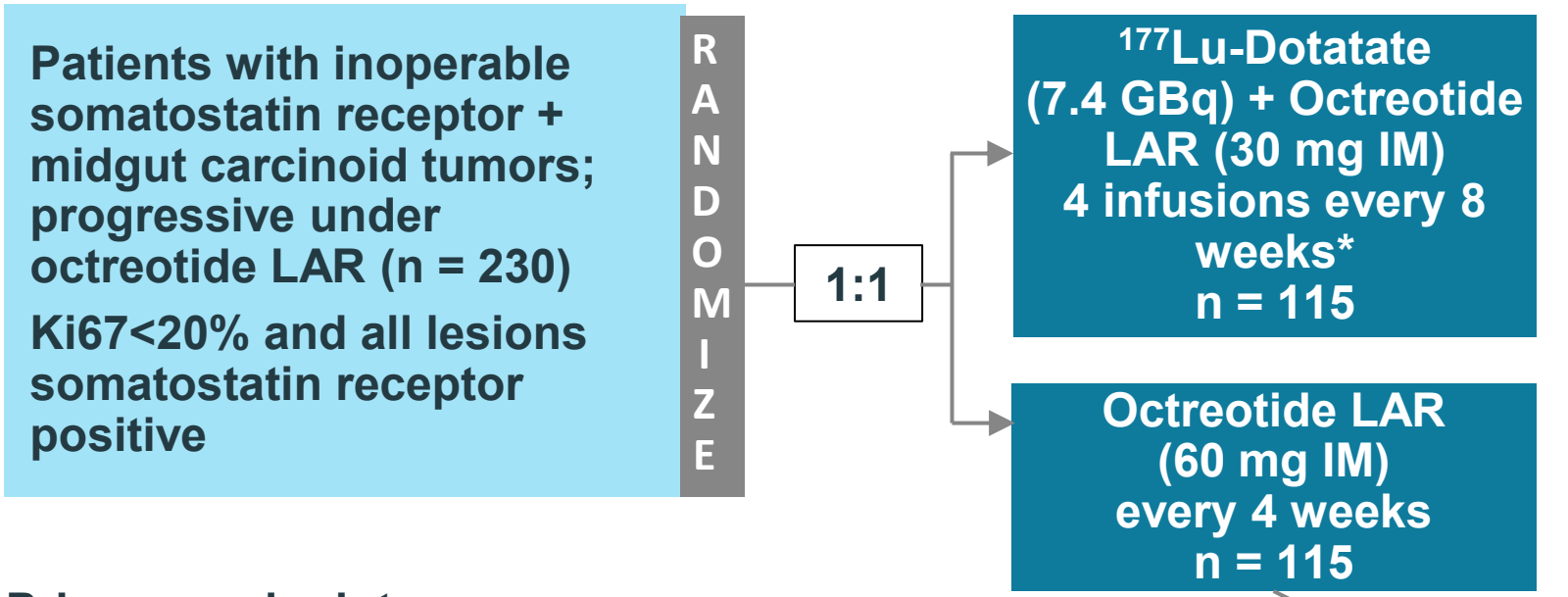
# Peptide receptor radionuclide therapy (PRRT)

# Theranostics

Targeted radiotherapy delivers cytotoxic radiation directly to tumor cells by using a radiolabeled somatostatin analogue that binds to somatostatin receptors (SSTRs)



# $^{177}$Lu-Dotatate – NETTER1 Phase 3 RCT




**Primary endpoints**

- PFS according to RECIST criteria (objective tumor response)

**Secondary endpoints**

- Safety and tolerability

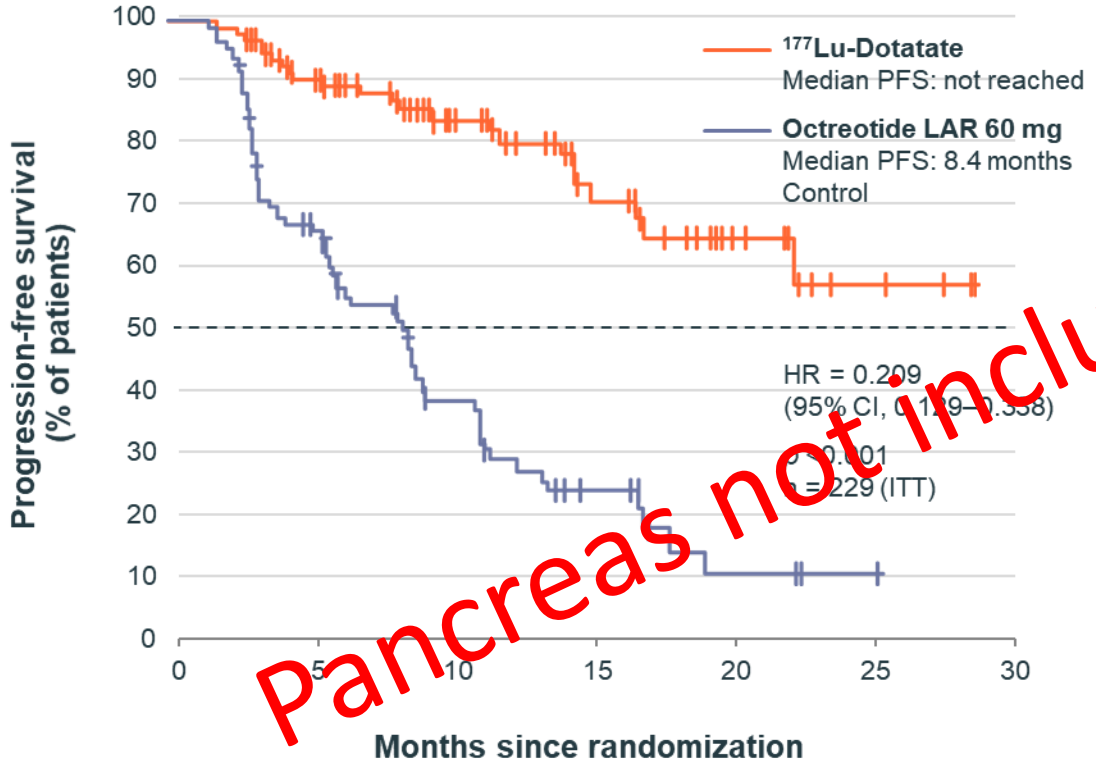
**Active control**

*Note: dose is higher than that approved in Canada*

Strosberg et al, *NEJM* (2017)

# $^{177}$Lu-Dotatate – NETTER1 Phase 3 RCT

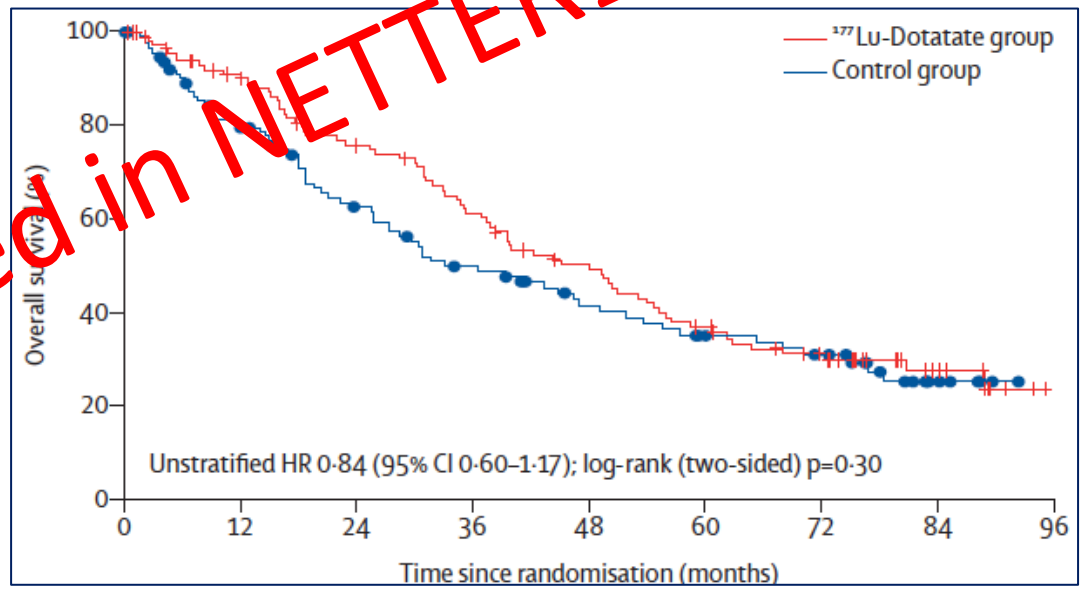
## Progression Free Survival




| No. at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $^{177}$Lu-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 |

Strosberg et al, *NEJM* (2017); *Strosberg et al. Lancet Oncol. 2021*

## Overall Survival




**OS (m): 48·0 (95% CI 37·4–55·2) vs. 36·3 months (25·9–51·7)**

- 36% crossover from control to PRRT
- 24% of patients received post protocol treatment
- Loss of power
  - -> 35% of patients with OS > 5 Year
  - -> OS analyzed with 142/152 planned events
  - -> 20% censored (consent withdraw; loss to follow up)

Pancreas not included in NETTER1!

# $^{177}$Lu-Dotatate – NETTER1 Phase 3 RCT

- $^{177}$Lu-DOTATATE – 6% (n=7) G3-5 toxicity
    - Half (3%, n=3) on long term follow up
        - 1 patient: G5 MDS
        - 1 patient: G3 respiratory infection; G3 refractory cytopenia with multilineage dysplasia
        - 1 patient: G2 breast cancer

- 2 patients (2%) treated with $^{177}$Lu-DOTATATE developed MDS

- Nephrotoxicity G3-5: $^{177}$Lu-DOTATATE 5% vs. 4% Control.
    - No significant change in creatinine clearence on follow up

*Strosberg et al. Lancet Oncol. 2021*

# NETTER-R

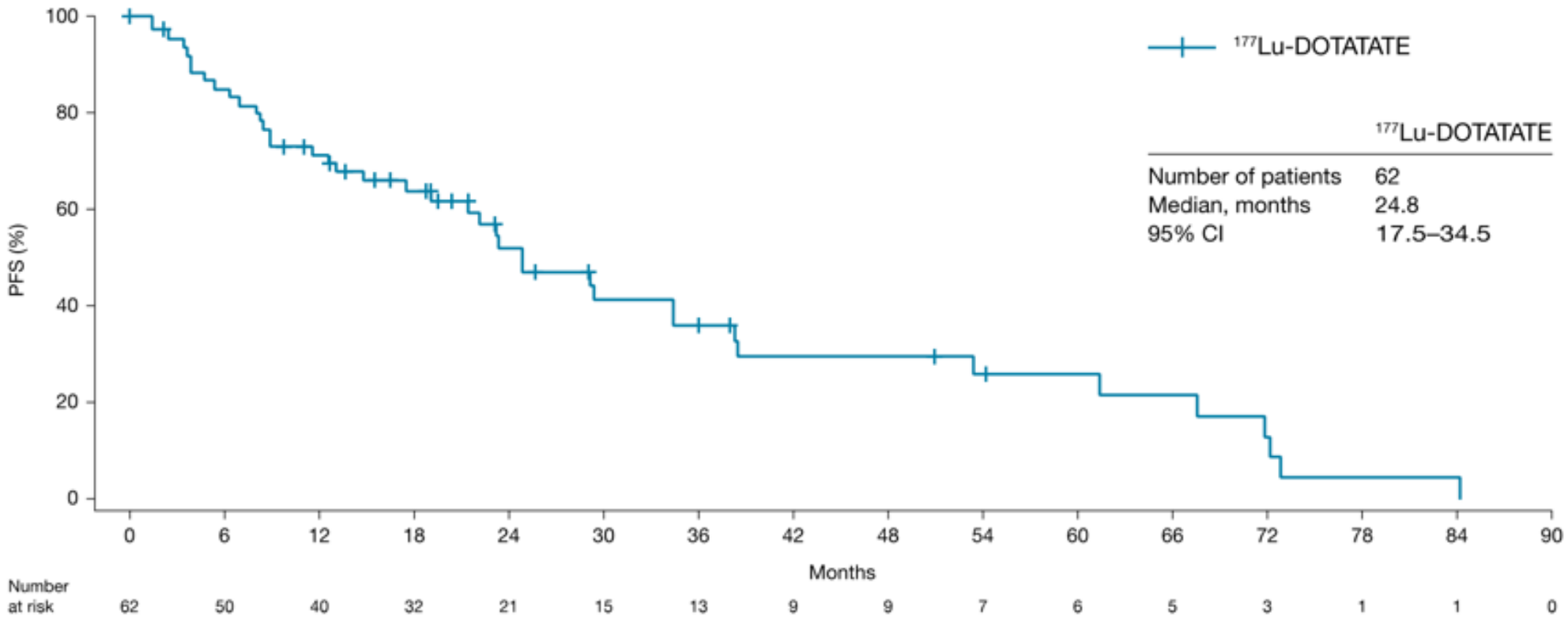



**Fig. 1** Kaplan–Meier analysis of PFS by RECIST v1.1. This analysis includes patients in the FAS where RECIST v1.1 data were available ($n = 62$). *CI*, confidence interval; *FAS*, full analysis set; *PFS*, progression-free survival; *RECIST v1.1*, Response Evaluation Criteria in Solid Tumors version 1.1

Clement et al, *Eur J Nuclear Med and Mol Imaging* (2022)

# Erasmus Retrospective Cohort

**Table 2.** Best response, PFS, TTP, and OS after therapy with $^{177}$Lu-DOTATATE

| Primary NET location | Total no of pts | CR No. of pts (%) | PR No. of pts (%) | SD No. of pts (%) | PD No. of pts (%) | NE No. of pts (%) | Median PFS (months) | Median TTP (months) | Median OS (months) |
|---|---|---|---|---|---|---|---|---|---|
| Midgut | 181 | 2 (1) | 55 (30) | 99 (55) | 16 (9) | 9 (5) | 30 | 42 | 60 |
| Non-PD | 32 | 0 (0) | 10 (31) | 18 (56) | 3 (9) | 1 (3) | 24 | 45 | 82 |
| PD | 94 | 1 (1) | 28 (30) | 50 (53) | 9 (10) | 6 (6) | 29 | 40 | 50 |
| Hindgut | 12 | 0 (0) | 4 (33) | 6 (50) | 1 (8) | 1 (8) | 29 | 29 | Not defined |
| Pancreatic | 133 | 6 (5) | 66 (50) | 40 (30) | 17 (13) | 4 (3) | 30 | 31 | 71 |
| Non-PD | 21 | 1 (5) | 9 (43) | 10 (48) | 1 (5) | 0 (0) | 31 | 31 | Not defined |
| PD | 66 | 2 (3) | 36 (55) | 15 (23) | 10 (15) | 3 (5) | 31 | 36 | 71 |
| Functional | 21 | 1 (5) | 12 (57) | 4 (19) | 3 (14) | 1 (5) | 30 | 33 | Not defined |
| Nonfunctional | 112 | 5 (4) | 54 (48) | 36 (32) | 14 (13) | 3 (3) | 30 | 31 | 69 |
| Bronchial | 23 | 0 (0) | 7 (30) | 7 (30) | 6 (26) | 3 (13) | 20 | 25 | 52 |
| Other foregut[a] | 12 | 1 (8) | 4 (33) | 5 (42) | 2 (17) | 0 (0) | 25 | Not defined | Not defined |
| Unknown | 82 | 0 (0) | 29 (35) | 35 (43) | 11 (13) | 7 (9) | 29 | 37 | 53 |
| Total | 443 | 9 (2) | 165 (37) | 192 (43) | 53 (12) | 24 (5) | 29 | 36 | 63 |

[a]Including five tumors of the stomach, five of the duodenum, and two of the thymus.

Abbreviations: NE, not evaluable; Primary NET location "non-PD and PD" means "without PD and with PD" at start of therapy with $^{177}$Lu-DOTATATE.

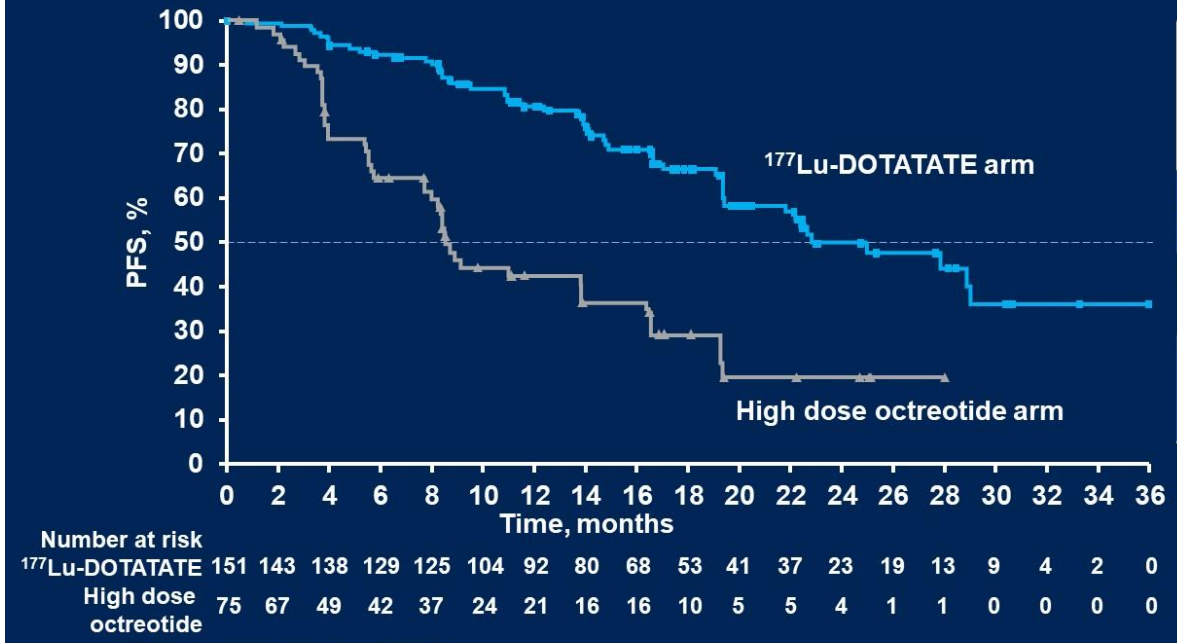
**0.7% Acute Leukemia; 1.5% MDS; 1% Renal Failure; No hepatic Failure**

Brabander et al, *Clinical Cancer Research* (2017)

# NETTER-2



## $^{177}$Lu-DOTATATE showed significant improvement in primary PFS endpoint



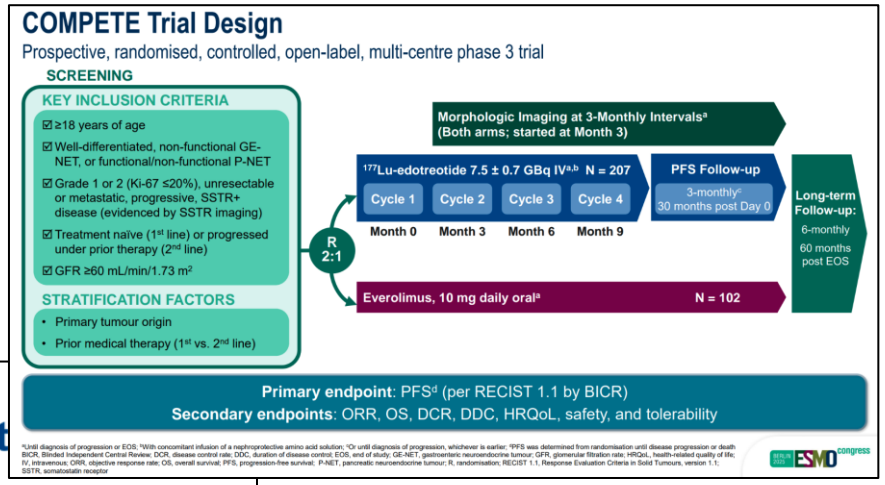

| | $^{177}$Lu-DOTATATE arm n=151 | High dose octreotide arm n=75 |
|---|---|---|
| PFS median, months (95% CI) | 22.8 (19.4, NE) | 8.5 (7.7, 13.8) |
| Stratified HR (95% CI) | 0.276 (0.182, 0.418) | |
| p-value | <0.0001 | |
| Number of events, n (%) | 55 (36) | 46 (61) |
| Progression | 47 (31) | 41 (55) |
| Death | 8 (5) | 5 (7) |

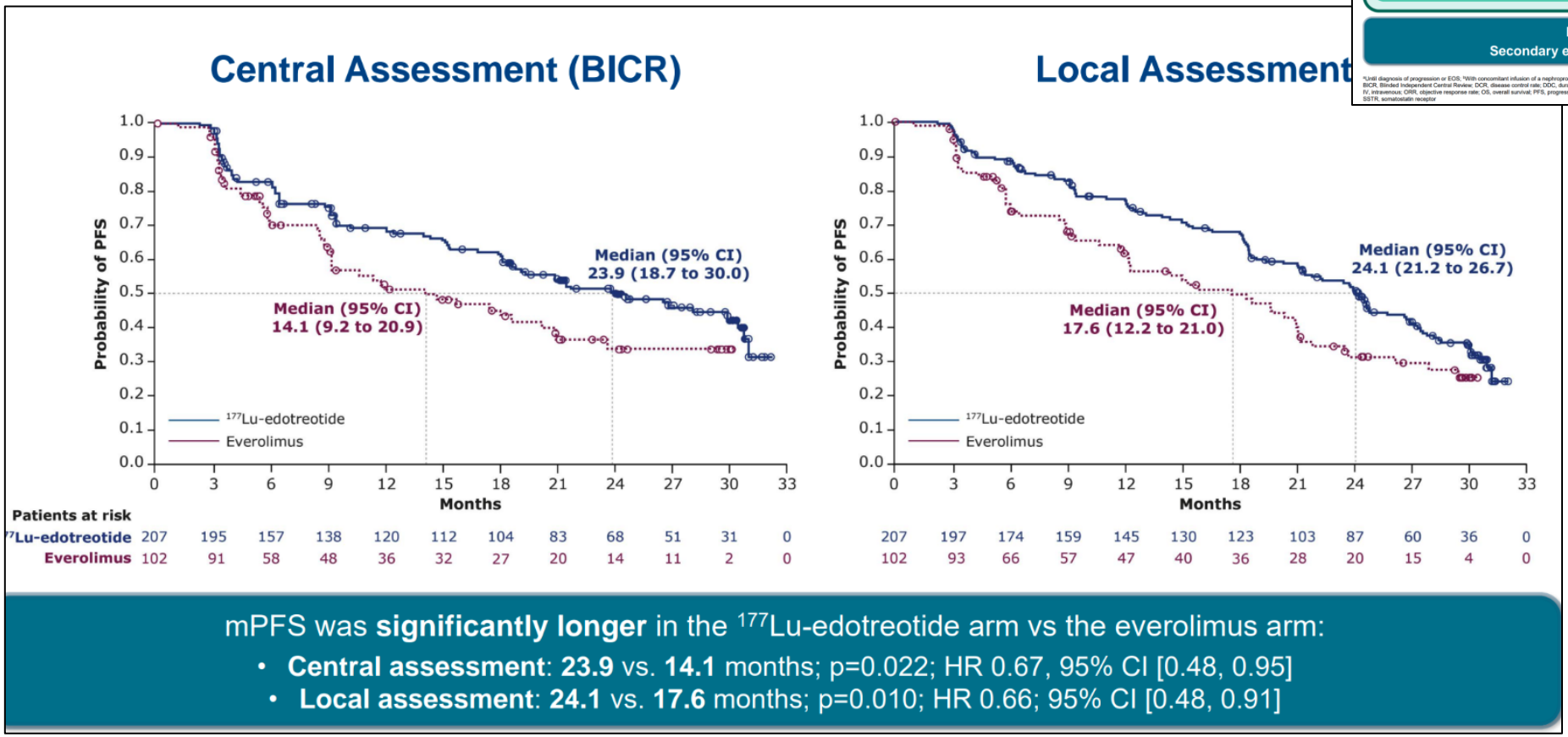
**72%** reduction in the risk of disease progression or death in the $^{177}$Lu-DOTATATE arm versus the high dose octreotide arm

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.


PRESENTED BY: Simron Singh, MD, MPH

# PRRT vs. Everolimus



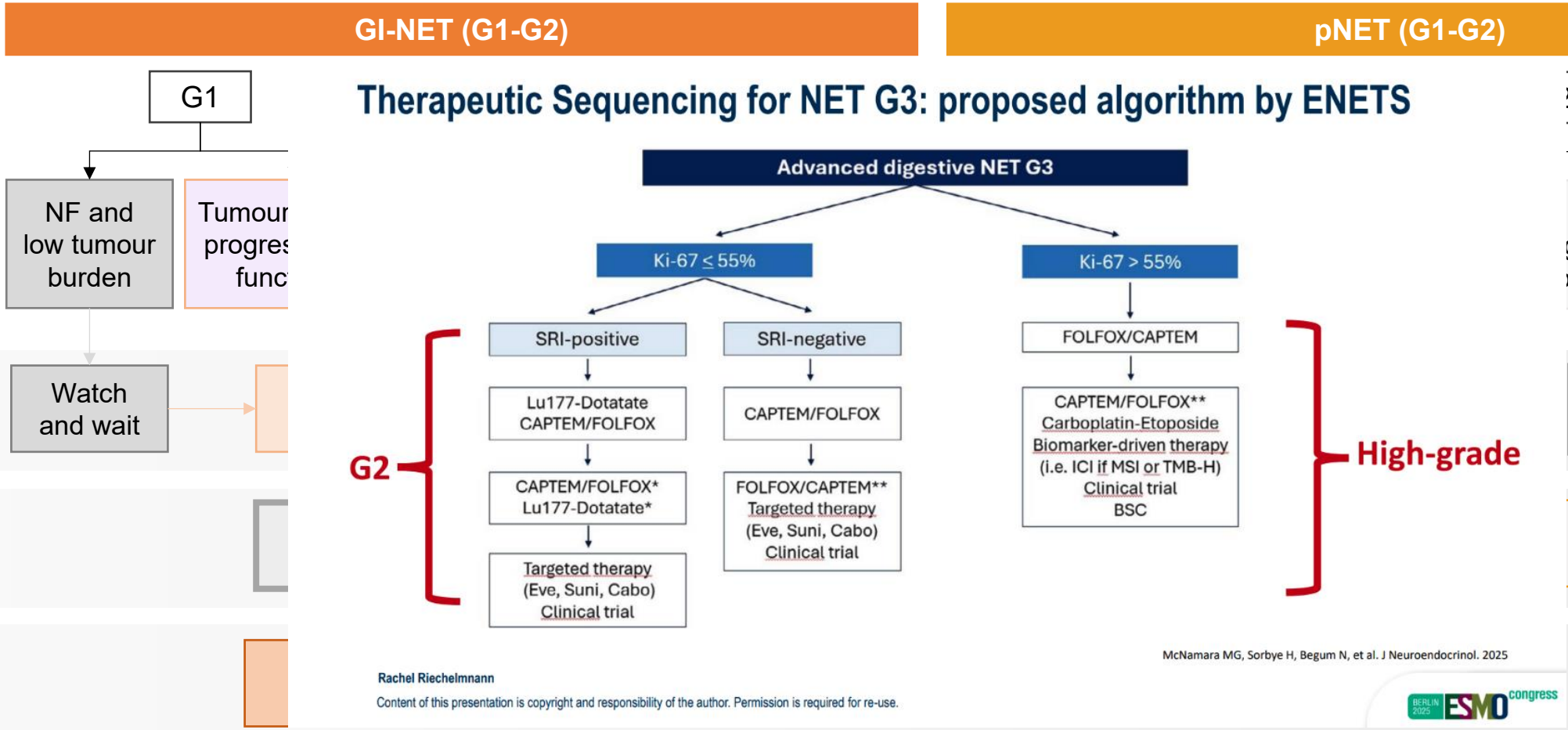




mPFS was **significantly longer** in the $^{177}$Lu-edotreotide arm vs the everolimus arm:

- **Central assessment**: **23.9** vs. **14.1** months; p=0.022; HR 0.67, 95% CI [0.48, 0.95]
- **Local assessment**: **24.1** vs. **17.6** months; p=0.010; HR 0.66; 95% CI [0.48, 0.91]

# Optimizing PRRT sequencing in NETs[1]

Proposed therapeutic algorithm of PRRT in advanced SSTR+ GEP-NETs presented at ENETS Conference 2025[2]



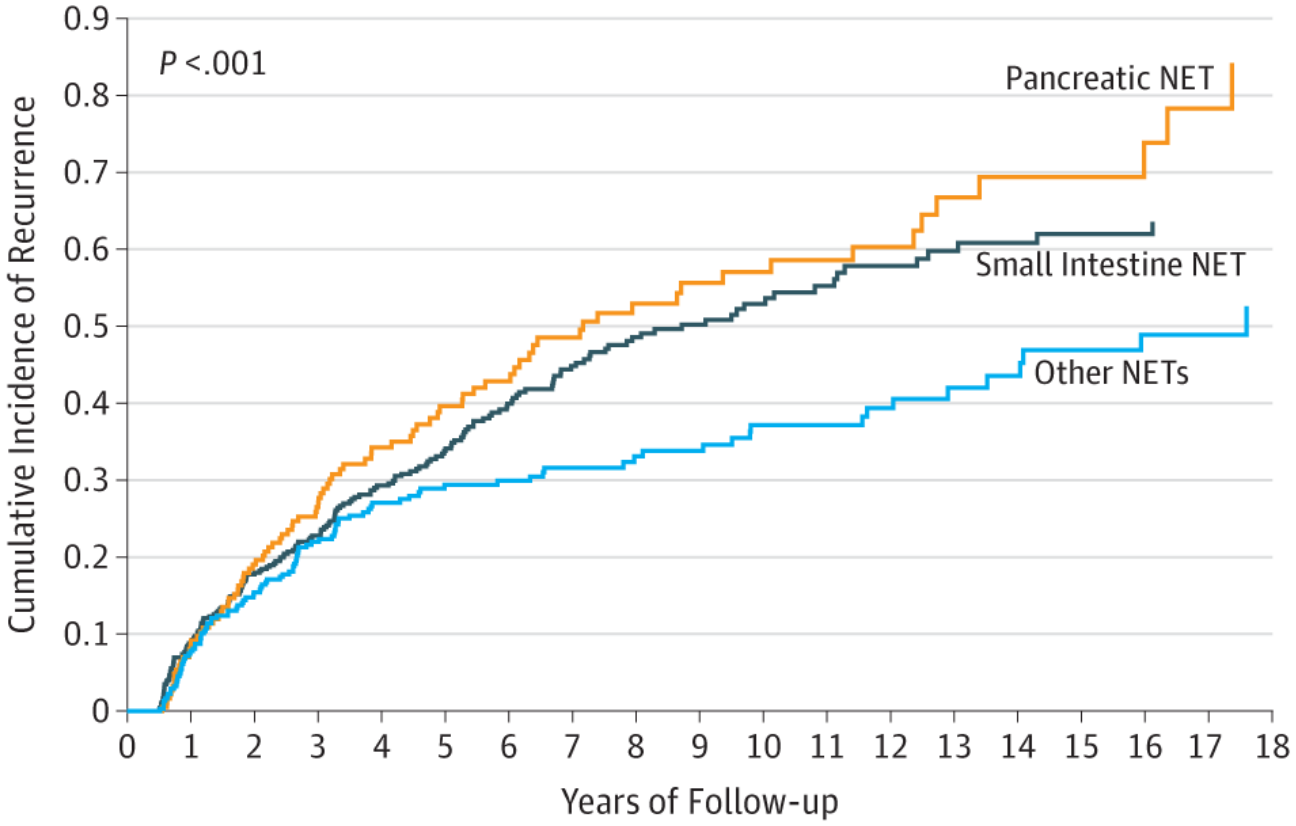

**Recent data from NETTER-2, NETTER-1 long-term follow-up, and OCLURANDOM support a potential shift toward earlier use of PRRT, especially in select high-risk or symptomatic patients.*

1L, first line; 2L, second line; 3L, third line; CAPTEM, capecitabine and temozolomide; ENETS, European Neuroendocrine Tumor Society; G, grade; GI, gastrointestinal; GEP, gastroenteropancreatic; NET, neuroendocrine tumour; NF, neurofibromatosis; pNET, pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue; SSTR, somatostatin receptor.

1. Kuiper J, et al. *J Neuroendocrinol* 2024 (Epub ahead of print); 2. Knigge U, et al. Oral presentation at 22nd Annual ENETS Conference; March 5–7, 2025.

# Surveillance after curative surgery

Surveillance after resection of NETs should continue for at least 10 years, with the decision to continue or cease surveillance beyond 10 years individualized based on recurrence risk and patient factors.




Singh et al, *JAMA Oncol* (2018)

# Questions?