Gastroenteropancreatic Neuroendocrine Tumors

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Fred Hutch · Seattle Children's · UW Medicine

Disclosures

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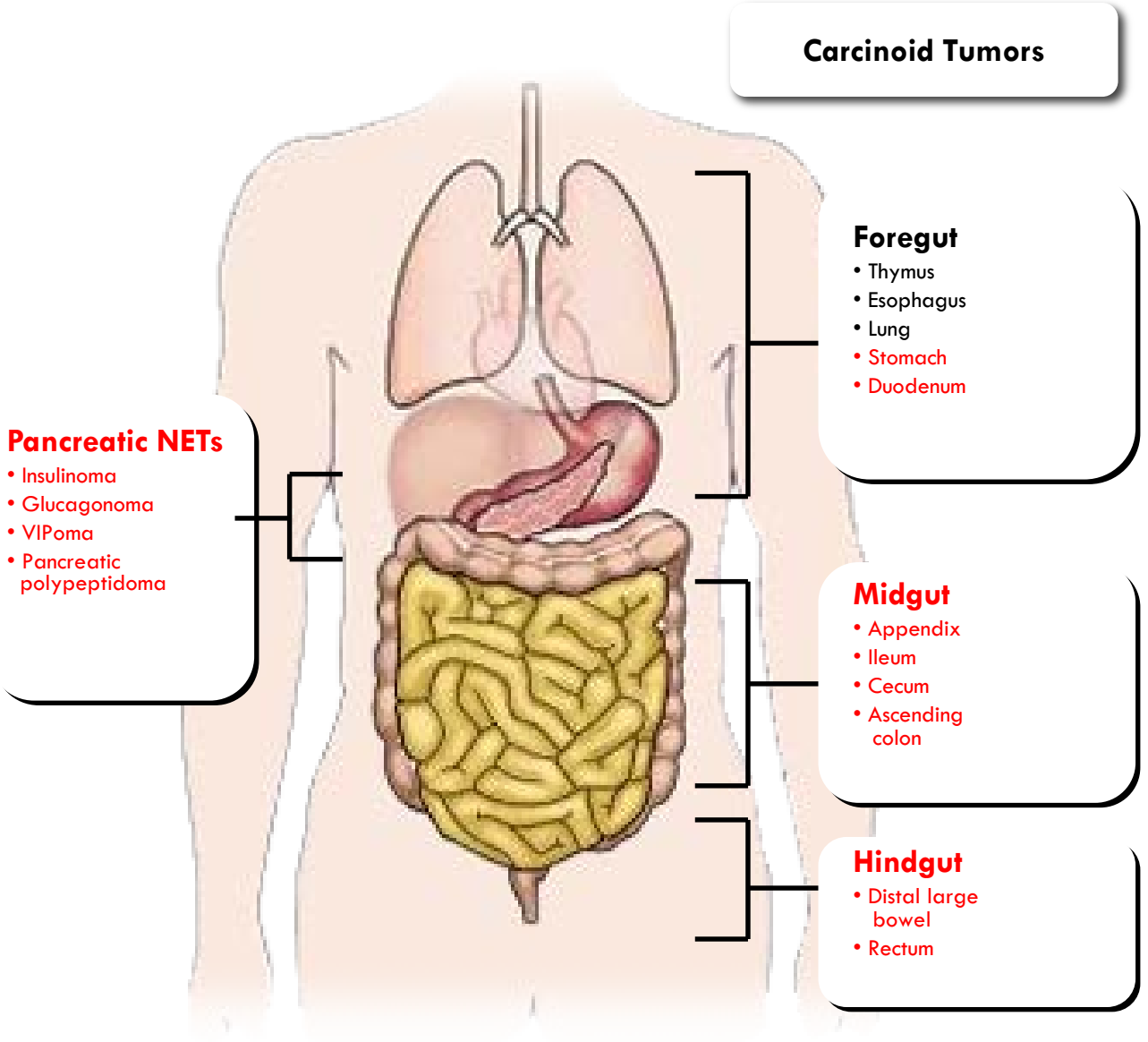
- Advisory board: HalioDx

Abbreviations

- NET = neuroendocrine tumor
- PNET = pancreatic neuroendocrine tumor
- GEP NET = gastroenteropancreatic neuroendocrine tumor = neuroendocrine tumor of GI tract and pancreas

Sites of NETs



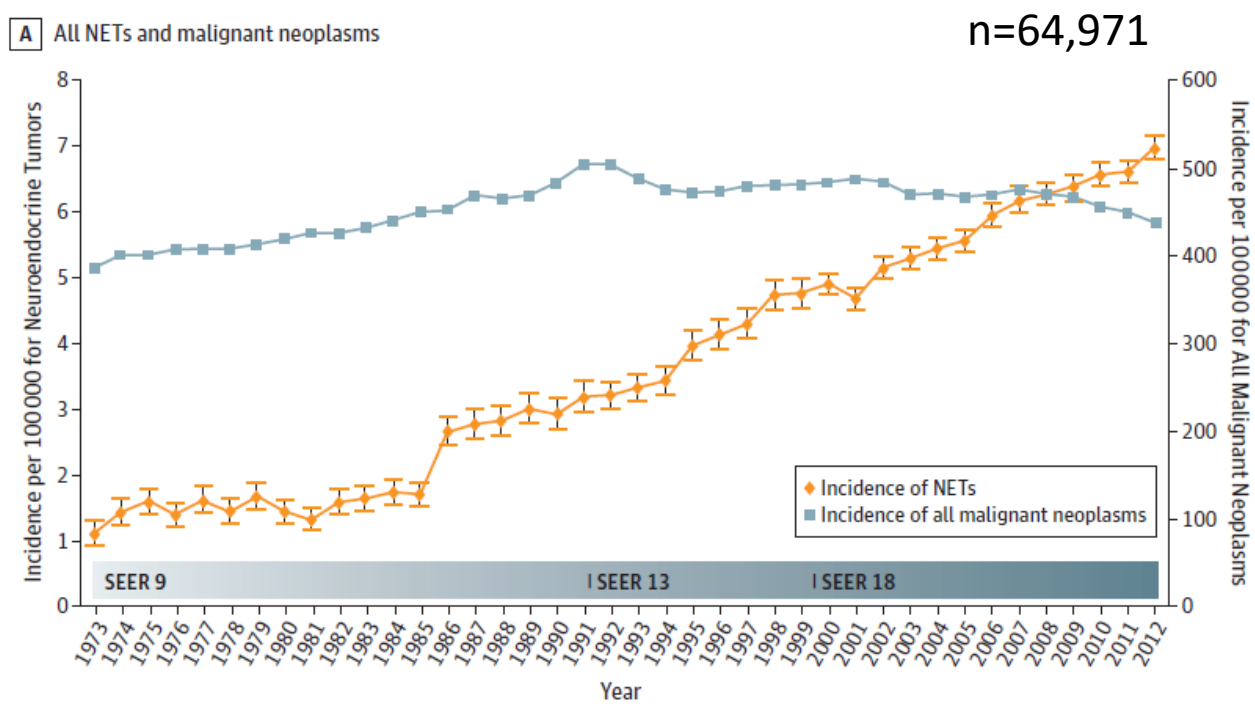
- Neuroendocrine cells found at various body sites
- Produce hormones and peptides with biological activity
- NETs can arise in different organs
- GI tract and pancreas are common sites of origin for NETs
- Some cases of unknown primary

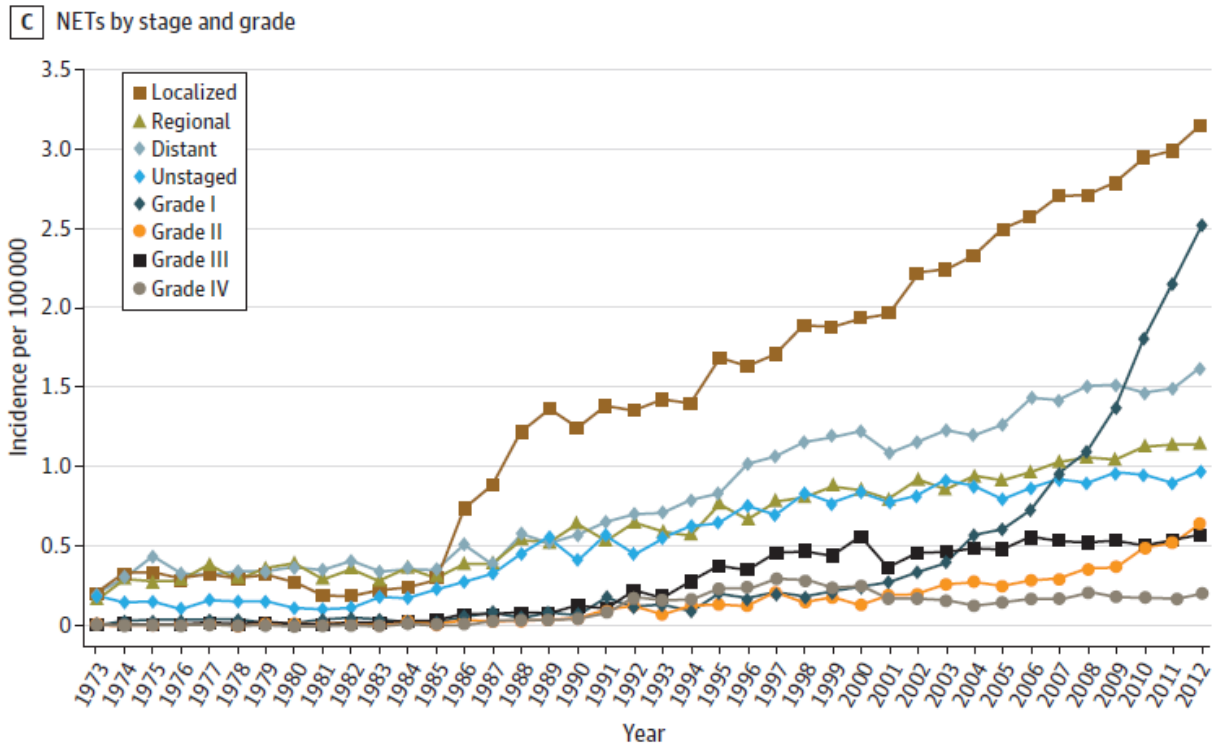
Epidemiology – SEER data

6.4-fold increase in incidence of all NETs from 1973 to 2012

Increased incidence of earlier stage disease

Figure 1. Incidence Trends of Neuroendocrine Tumors (NETs) From 1973 to 2012

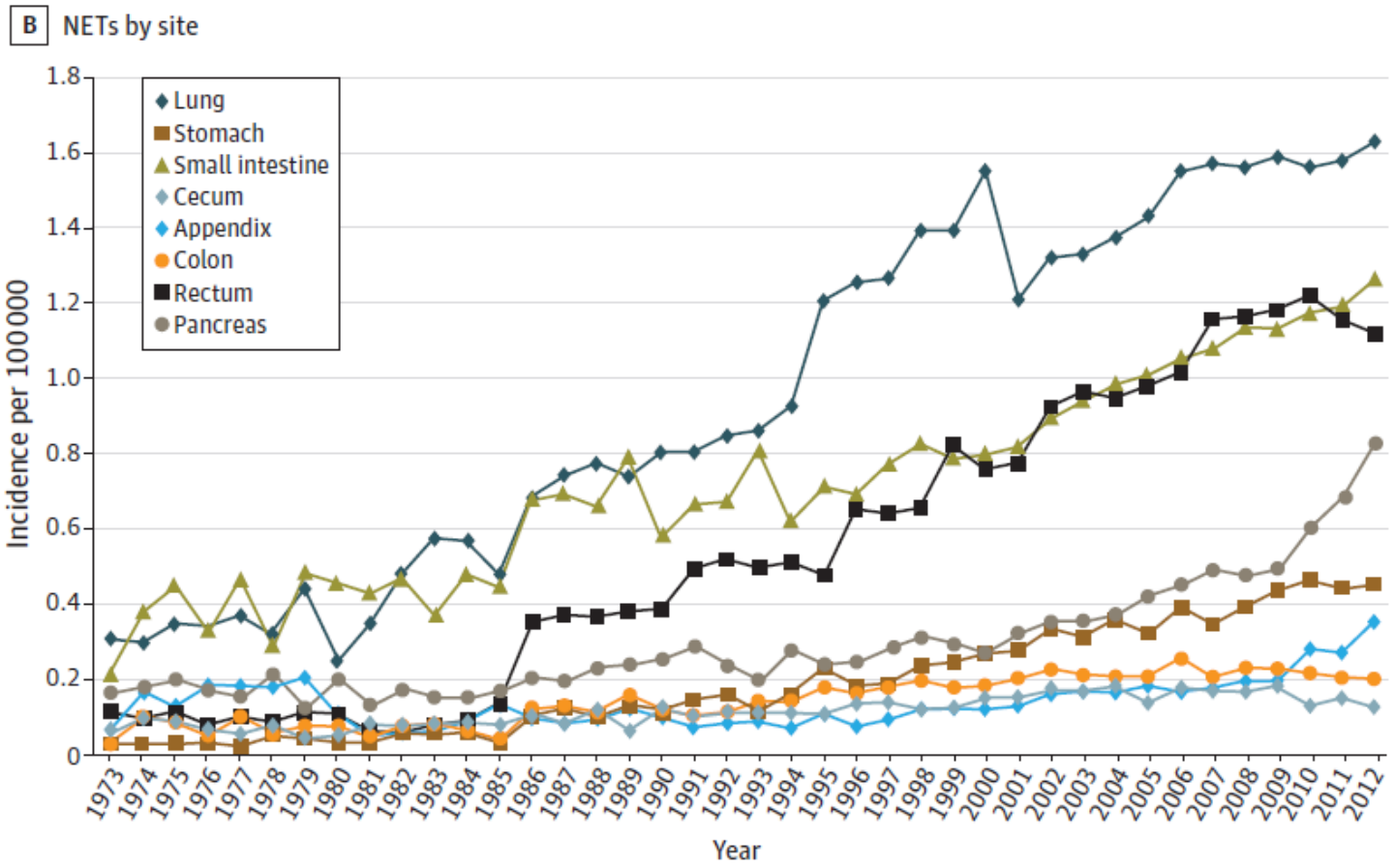




Trends may be related to improved diagnostic tests and more awareness of disease

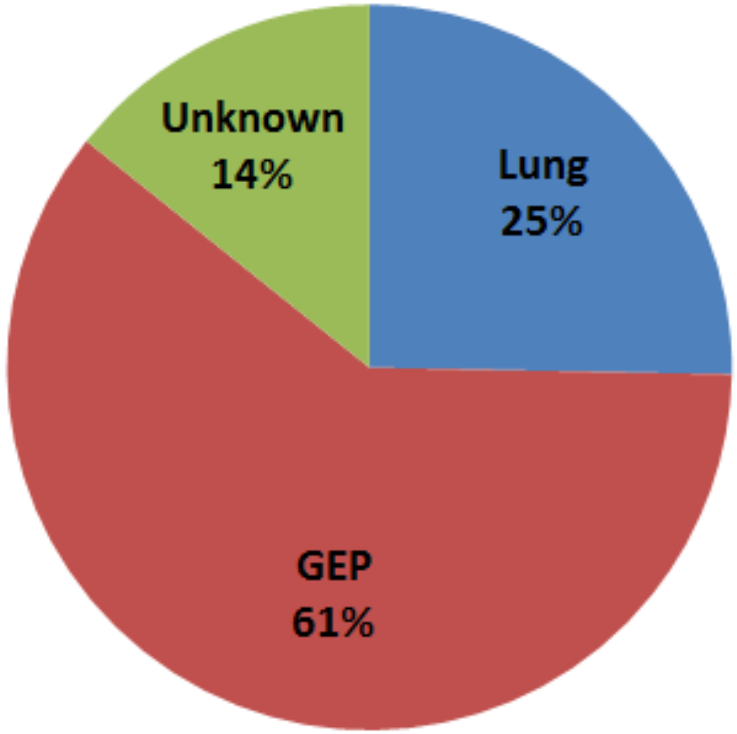
Dasari et al. JAMA Oncol. 2017;3:1335.

Incidence of NETs by anatomic site



Incidence per 100,000 persons (SEER 18, 2000-2012 data):

- Lung: 1.49
- GEP NETs: 3.56
- Unknown primary: 0.48



Among GEP NETs:
Small intestine: 29%
Rectum: 29%
Pancreas: 13%

Dasari et al. JAMA Oncol. 2017;3:1335.

Pathologic classification

- GEP NETs are characterized by strong immunohistochemical staining of synaptophysin and chromogranin
- Very heterogeneous group of tumors with different biology and behavior
- WHO classification – based on degree of proliferation (Ki67 index, mitotic count)

2010 WHO classification for gastrointestinal tract NETs (carcinoid tumors)

		GEP NETs[7]		
Differentiation	Grade	NET	Proliferative Rate	
Well-differentiated	G1 (low grade)	NET	< 2 mitoses/10 hpf AND < 3% Ki-67 index	**Neuroendocrine tumor**
	G2 (intermediate grade)	NET	2-20 mitoses/10 hpf OR 3%-20% Ki-67 index	
Poorly differentiated	G3 (high grade)	Neuroendocrine carcinoma small-cell type; neuroendocrine carcinoma large-cell type	> 20 mitoses/10 hpf OR > 20% Ki-67 index	**Neuroendocrine carcinoma**

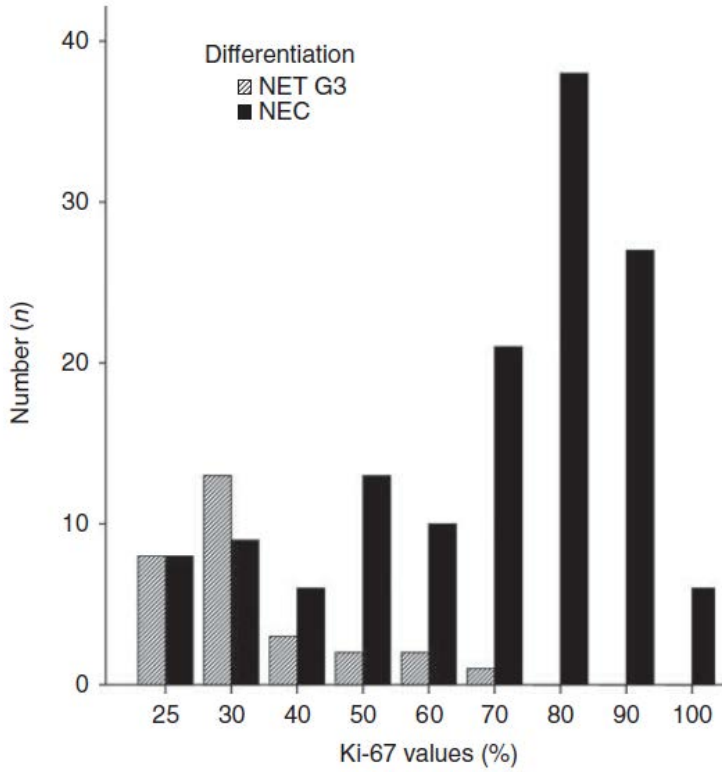
Abbreviations: GEP, gastroenteropancreatic; hpf, high-powered field; NET, neuroendocrine tumor.

1. Modlin et al. Lancet Oncol 2008;9:61. 2. Bosman et al. WHO Classification of Tumours of the Digestive System (ed 4), 2010.

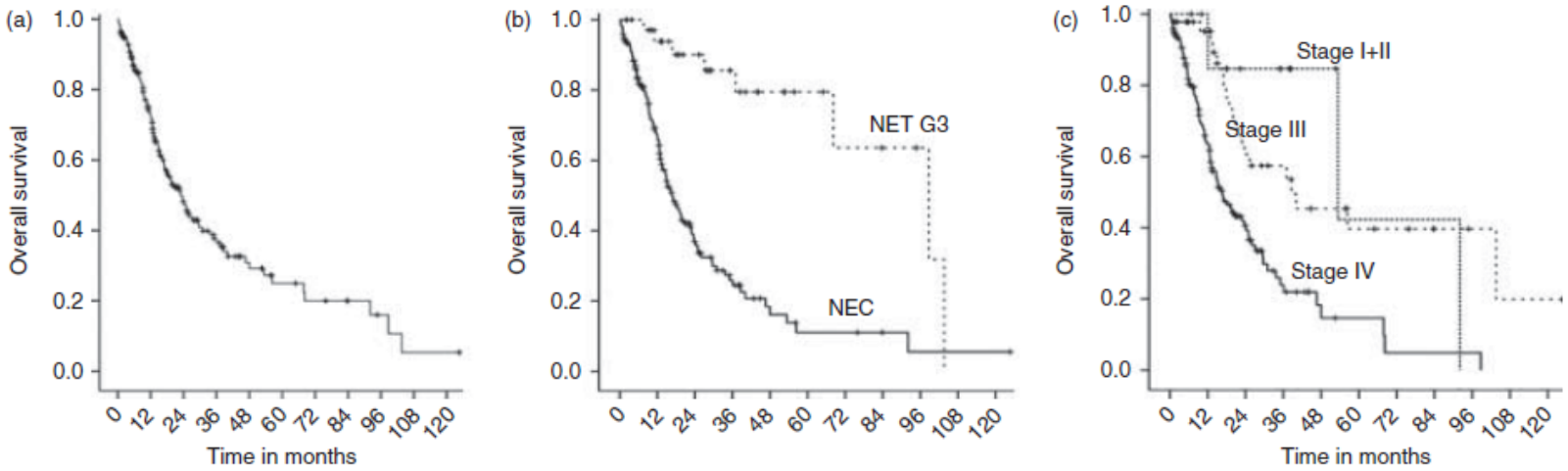
Grade 3 well-differentiated NETs (WD NETs)

- Distinct group of tumors from grade 3 poorly differentiated neuroendocrine carcinomas (PD NECs)
- Compared to PD NECs, the grade 3 WD NETs are more likely to:
  - Be diagnosed at earlier age and be functional
  - Have lower Ki67 (typically 21-55%)
  - Have +ve somatostatin receptor imaging
  - Carry mutations associated with low/intermediate grade NETs (i.e. mutations in DAXX, ATRX, MEN1)
  - Have longer overall survival (i.e. median OS 98.7 months for WD NETs vs. 17.0 months for PD NECs, $p<0.001$)

Heefeld et al. Endocr Relat Cancer 2015;22:657.



WD G3 NETs have lower Ki67



Cell differentiation and TNM stage are independent prognostic factors for grade 3 neuroendocrine neoplasms

Heefeld et al. Endocr Relat Cancer 2015;22:657.

2017 WHO classification for PNET

Neoplasm				Proliferation	
Type	Differentiation Status	Definition	Grade	Ki67 (% of ≥500 cells)	Mitotic Count (2 mm^2)
NEN	Well differentiated	NET	G1	<3	<2
			G2	3–20	2–20
			G3	>20	>20
	Poorly differentiated	NEC	(default G3)	>20	>20
		Small cell type			
		Large cell type			
MiNEN[a]	Well/poorly differentiated	*NET or NEC*	*G1-G3*	See above	See above
		ADC[b] or SCC	*G1-G3*	See Ref.[11]	See Ref.[11]

- Takes into account the heterogeneity of PNETs
- Grade 3 includes both well-differentiated PNET (PanNET G3) and poorly differentiated pancreatic NEC (PanNECs G3)
- Cell differentiation distinguishes between NET and NEC, not Ki67 value
- Therapy for the well-differentiated G3 tumors needs to be further studied

Inzani et al. Endocrinol Metab Clin N Am 2018;47:463.

Prognosis

- Wide range of prognosis based on:
  - Stage at diagnosis (localized > regional > distant)
    - By AJCC TNM staging system (stages 1-4)
  - Grade (well diff > poor diff)
  - Age at diagnosis (younger > older)
  - Primary site
  - Time of diagnosis (2000-2004 < 2005-2008 < 2008-2012)
    - Greater improvement in survival for advanced GEP NETs (especially carcinoids) due to better therapies

Dasari et al. JAMA Oncol. 2017;3:1335.

Functionality

- GEP NETs may produce and secrete bioactive amines and peptides (hormones, neuromodulators) causing clinical symptoms
- Classified as functional vs. non-functional
- Symptoms do not correlate with tumor burden
- Treatment of clinical syndromes of hormone excess: somatostatin analogue (SSA), except insulinoma

Carcinoids (8-35% functional)	PNETs (10-40% functional)
- Carcinoid syndrome → flushing, diarrhea, right sided valvular fibrosis, bronchoconstriction - Typically associated with serotonin and midgut NETs in the setting of liver metastases	Secretion of: - *Insulin (insulinoma) → hypoglycemia - *Gastrin (gastrinoma) → PUD - Vasoactive intestinal peptide (VIPoma) → diarrhea, hypoK - 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.

Characteristics of carcinoid tumors by location

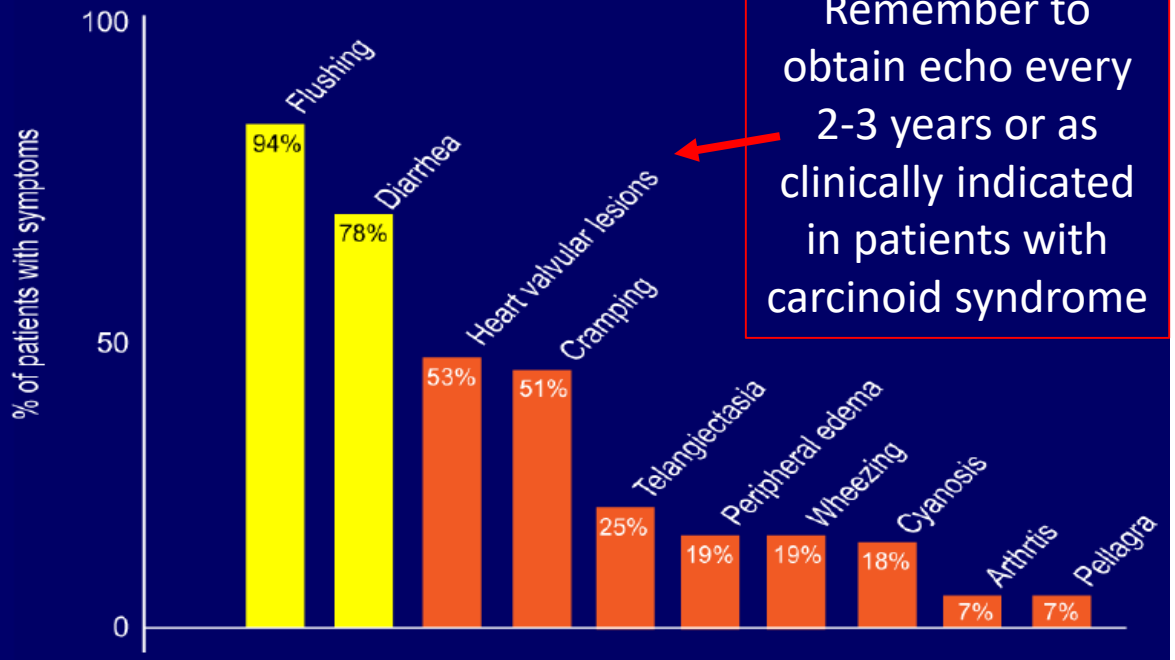
	Foregut	Midgut	Hindgut
Localization	Stomach, duodenum, bronchus, thymus	Jejunum, ileum, appendix, ascending colon	Transverse, descending, and sigmoid colon, rectum, genitourinary
Secretory products	5-hydroxytryptophan, histamine, multiple polypeptides	Serotonin prostaglandins, polypeptides	Variable
Carcinoid syndrome	Rare, and atypical when it happens (angioedema, hive-like pink flushing, rash)	**Classic** (flushing, diarrhea, wheezing due to bronchoconstriction, R valvular involvement)	Rare (usually found on lower GI endoscopy, patients may present with obstructive symptoms)

1. Loughrey et al. Endocrinol Metab Clin N Am 2018;47:557. 2. UptoDate.

Carcinoid syndrome

- Occurs in approximately 8% to 35% of patients with NETs and occurs mostly in cases of patients with hepatic metastases[1]
- Consequence of vasoactive peptides such as serotonin, histamine, or tachykinins released into the circulation[2,3]
- Manifested by episodic flushing, wheezing, diarrhea, and, potentially, the eventual development of carcinoid heart disease[2,3]

Percentage of patients with symptoms of carcinoid syndrome[4]



Remember to obtain echo every 2-3 years or as clinically indicated in patients with carcinoid syndrome

1. Rorstad O. *J Surg Oncol*. 2005; 89:151-60.
2. Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD. *Gastroenterology*. 2005;128:1717-1751.
3. Vinik A, Moattari AR. *Dig Dis Sci*. 1989;34(3 Suppl):14S-27S.
4. Creutzfeldt W. *World J Surg*. 1996;20:126-131.

Workup

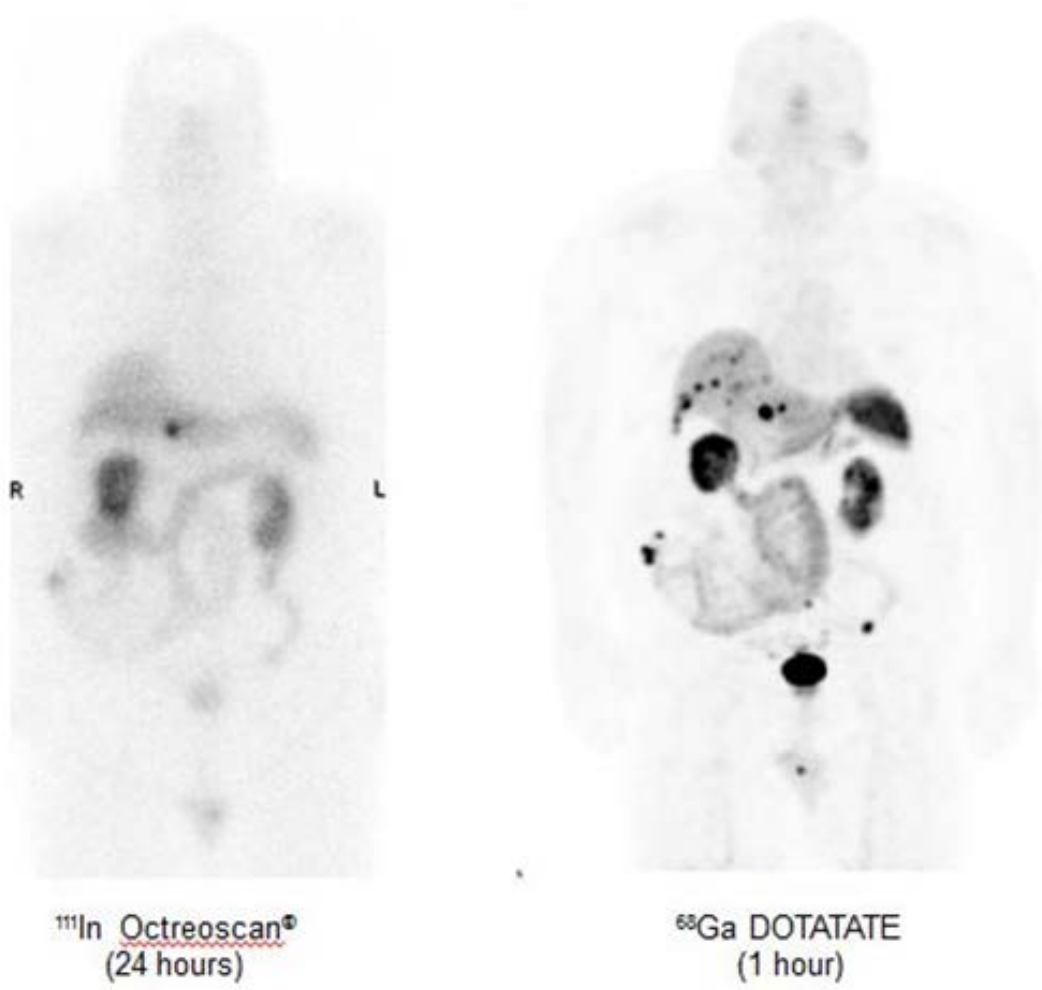
- Goals of workup
  - Assess primary site and stage
  - Characterize aggressiveness (grade, differentiation) – need tissue
  - Establish functionality
- NCCN guidelines (v2.2020)
  - Recommend: multiphasic CT or MRI abdomen/pelvis
  - As appropriate:
    - CT chest with or without contrast
    - Somatostatin receptor-based imaging (Ga68 dotatate PET/CT preferred, or Octreoscan)
    - Endoscopy
    - Biochemical evaluation as clinically indicated (if suspicious symptoms present)

NCCN Practice Guidelines (Neuroendocrine Tumors). https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

Somatostatin receptor-based imaging

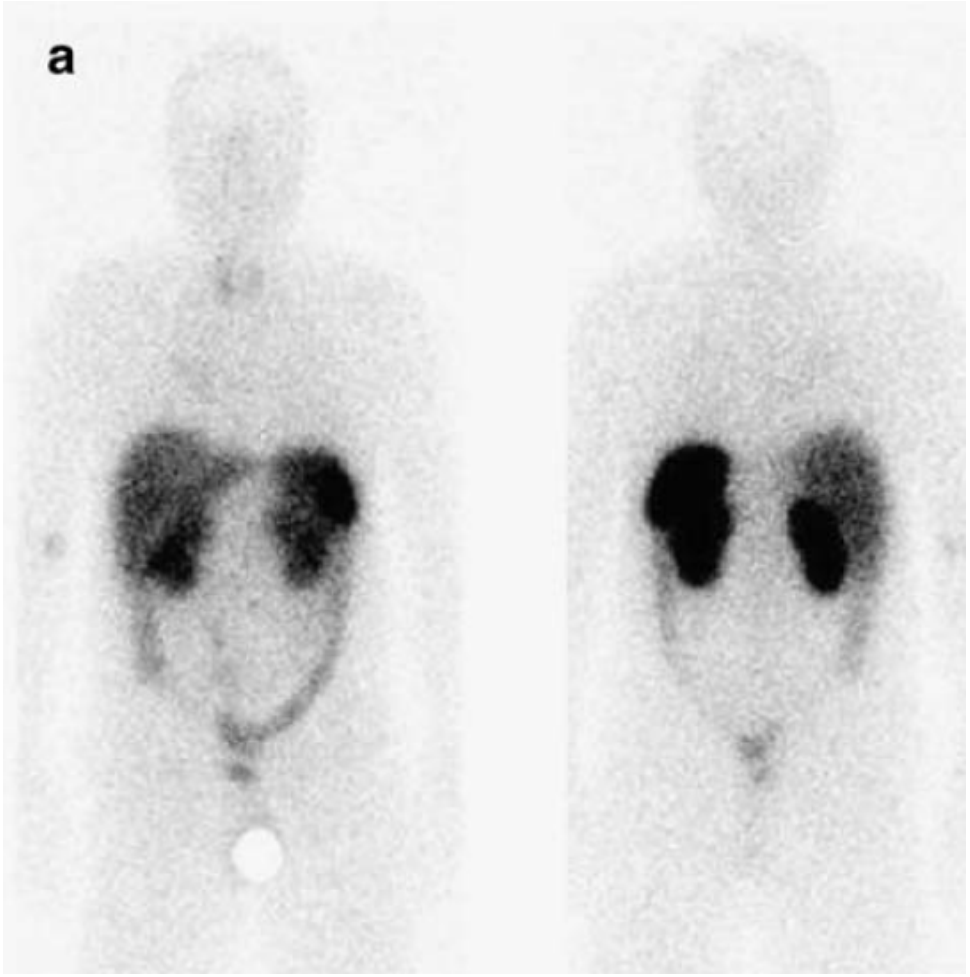
- >90% well-differentiated GEP NETs express variable levels of SSTR
- Imaging using radiolabelled SSAs
  - Bind to SSTR2 and 5 on NET cells
  - OctreoScan (Indium-111 pentetreotide)
  - Functional PET imaging (68Ga DOTATATE PET/CT) – more sensitive for detecting small lesions, shorter time (30-60 min)

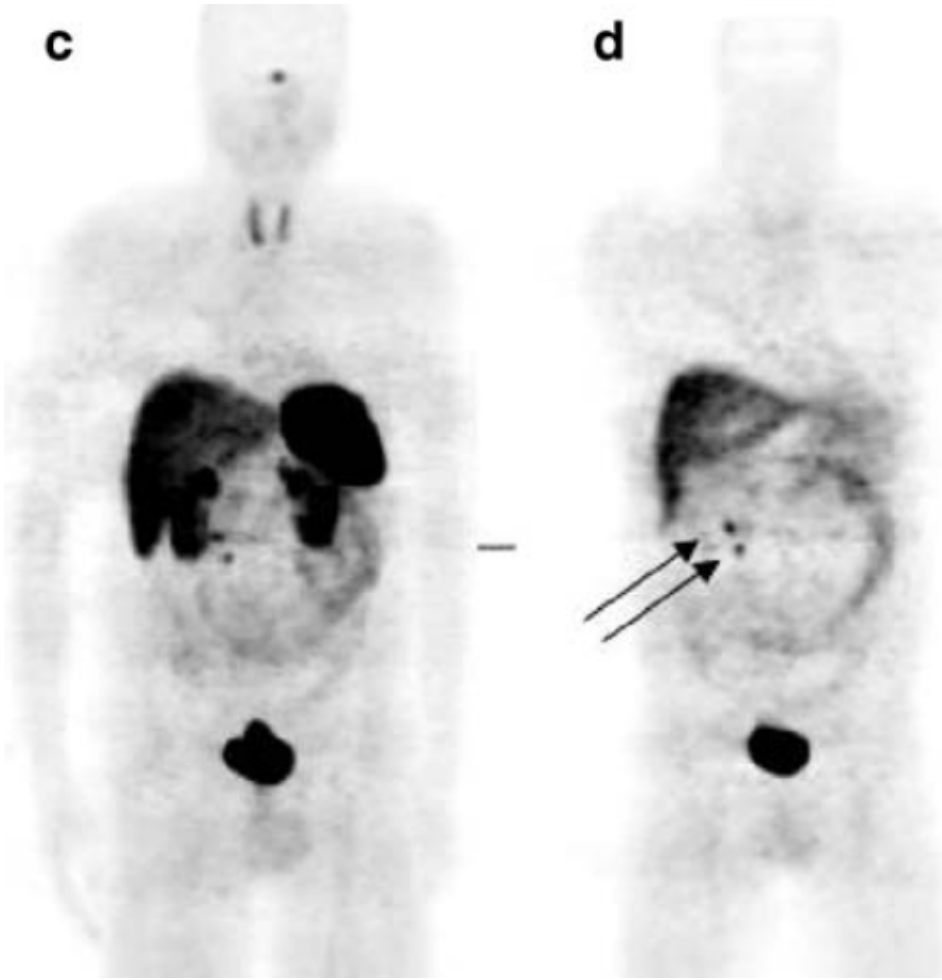
- **Should stop short-acting SSA 24 hours and long-acting SSA 5-6 weeks before imaging**
- **NOT recommended for routine surveillance**



http://www.carcinoid.org/2014/06/30/carcinoid-cancer-foundation-awards-grant-to-stanford-university/.

Kidd et al. Nat Rev Clin Oncol 2016;13:691.





111-In-DTPAOC SPECT

68-Ga-DOTATOC PET

Buchmann et al. Eur J Nucl Med Mol Imaging 2007;34:1617.

Biochemical testing (NCCN v2.2020)

	Location	Clinical Symptoms	Testing
NETs of Gastrointestinal Tract, Lung, and Thymus	Primary tumors in GI tract (ileum, appendix, rectum), lung, or thymus	• Primary tumors in the GI tract usually are not associated with symptoms of hormone secretion unless extensive metastasis. • Symptoms of hormone secretion may include flushing, diarrhea, cardiac valvular fibrosis, and bronchoconstriction. • Bronchial/thymic tumors may be associated with classic carcinoid syndrome as well as Cushing's syndrome.	• Chromogranin A (category 3) • 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 Cushing's syndrome (NE-C, 2 of 3)
PanNET (see subtypes below)	Pancreas	Depends on hormone secreted, can be clinically silent	• Serum pancreatic polypeptide (category 3) • Chromogranin A (category 3)
Insulinoma	Pancreas	Hypoglycemia	• While hypoglycemic: ▸ Serum insulin ▸ Pro-insulin ▸ C-peptide • See Workup for insulinoma (PanNET-3)
VIPoma	Most common in pancreas, can be extra pancreatic	Diarrhea, hypokalemia	Serum VIP
Glucagonoma	Pancreas	Flushing, diarrhea, hyperglycemia, dermatitis, hypercoaguable state	Serum glucagon
Gastrinoma	Pancreas or duodenum	Gastric ulcers, duodenal ulcers, diarrhea	Serum gastrin[a]

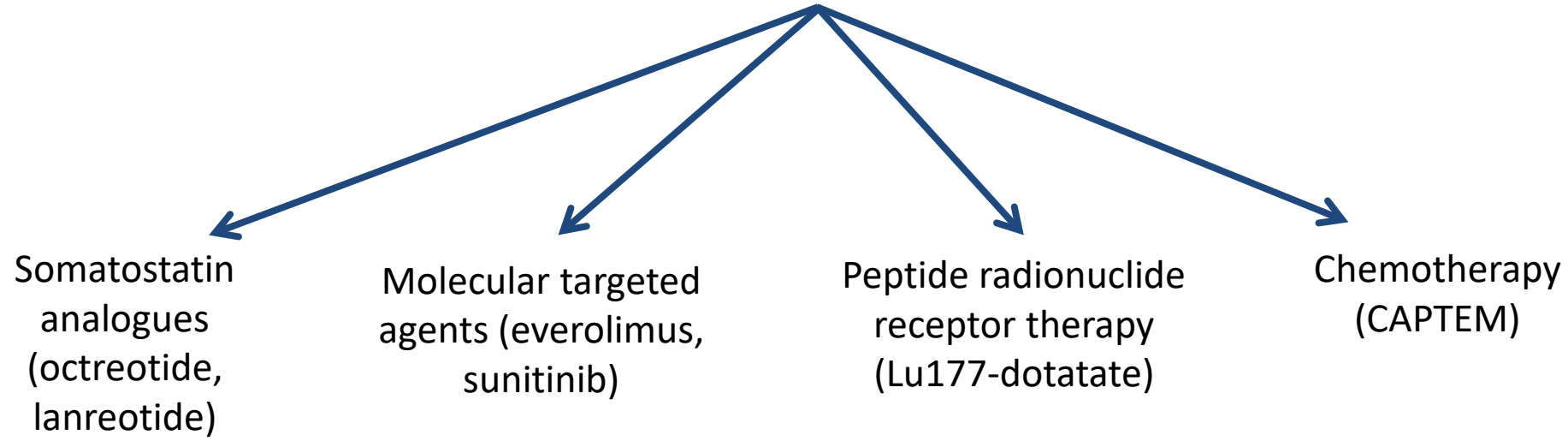
- Chromogranin A
  - Ubiquitous distribution in neuroendocrine tissues, stored in secretory granules and secreted with modified amines
  - Sensitive, but non-specific
  - Trend is more important

NCCN Practice Guidelines (Neuroendocrine Tumors). https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

False elevations

- Chromogranin A
  - Proton pump inhibitors (should be discontinued at least 2 weeks before)
  - Other disorders: endocrine, GI, cardiac, inflammatory diseases, renal impairment, other non-GI cancers
- 24h urinary 5-HIAA (5-hydroxyindoleacetic acid)
  - Ingestion of tryptophan/serotonin-rich foods
  - Avoid for 48h before measurement: avocado, banana, cantaloupe, eggplant, pineapple, plum, tomato, hickory nut/pecan, plantain, kiwi, date, grapefruit, honeydew, walnut
  - Malabsorption syndromes

Systemic therapy for metastatic GEP NETs



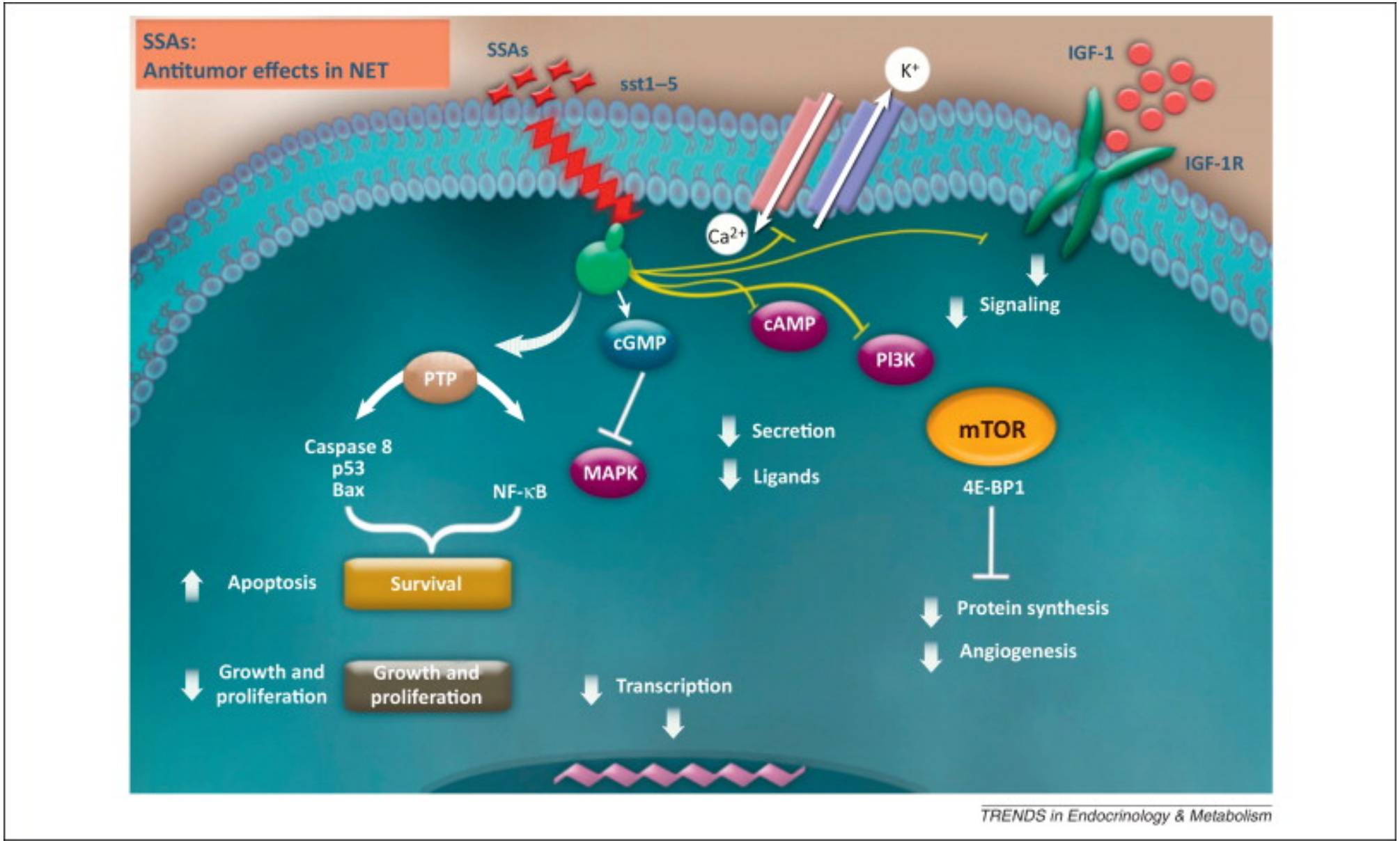
- For symptom (if present) and tumor control
- Multidisciplinary approach if appropriate
- Therapy selection depends on:
  - Carcinoid vs. PNET, grade and cell differentiation, SSTR expression, symptoms, tumor burden, rate of growth

Systemic therapy for symptoms

- Clinical symptoms associated with hormone secretion
- SSA is mainstay of treatment
  - Octreotide
    - Highest affinity for SSTR2
    - Short-acting and long-acting formulations
    - Recommend short-acting for 2-3 weeks until steady levels of octreotide LAR are reached
  - Lanreotide (SSTR2) and pasireotide (SSTR1,2,3,5)
    - Equally effective as octreotide in controlling carcinoid syndrome
- Telotristat – for refractory carcinoid syndrome-related diarrhea
  - Tryptophan hydroxylase inhibitor in serotonin synthesis pathway
- Consider octreotide during surgery to avoid carcinoid crisis

1. Strosberg et al. J Clin Oncol 2014;19:930. 2. O'Toole et al. Cancer 2000;88:770. 3. Wolin et al. J Clin Oncol 2013;31:suppl 15s;abst 4031.

SSAs have anti-tumor activity against GEP NETs and inhibit growth factors



Chalabi et al. Trends in Endocrinology & Metabolism 2014;25:115.

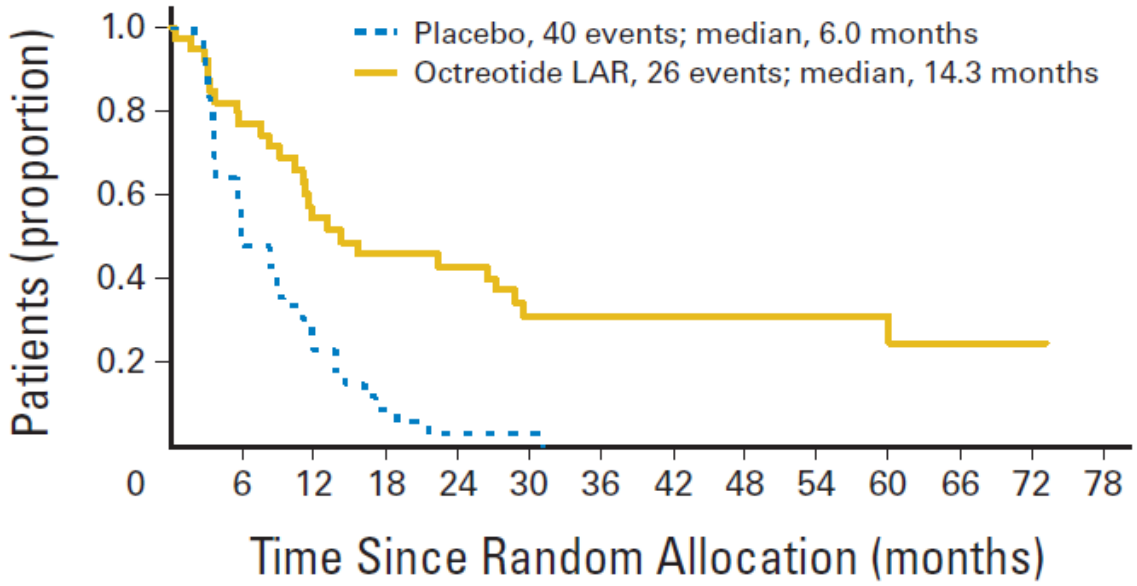
Octreotide

PROMID trial

Patients with metastatic well-differentiated midgut NETs, treatment naïve

- Octreotide LAR 30 mg IM every month (n=42)
- Placebo (n=43)

A



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

Log-rank test stratified by functional activity: $P = .000072$, HR = 0.34 (95% CI, 0.20 to 0.59)

- Improvement in median time to progression (HR 0.34, 95% CI 0.2-0.59, p=0.000072)
- Stable disease: 67% vs. 37% (at 6m)
- No improvement in overall survival
- Both functional and non-functional tumors responded
- Most common adverse events related to GI tract (diarrhea, flatulence)

Rinke et al. J Clin Oncol 2009;27:4656.

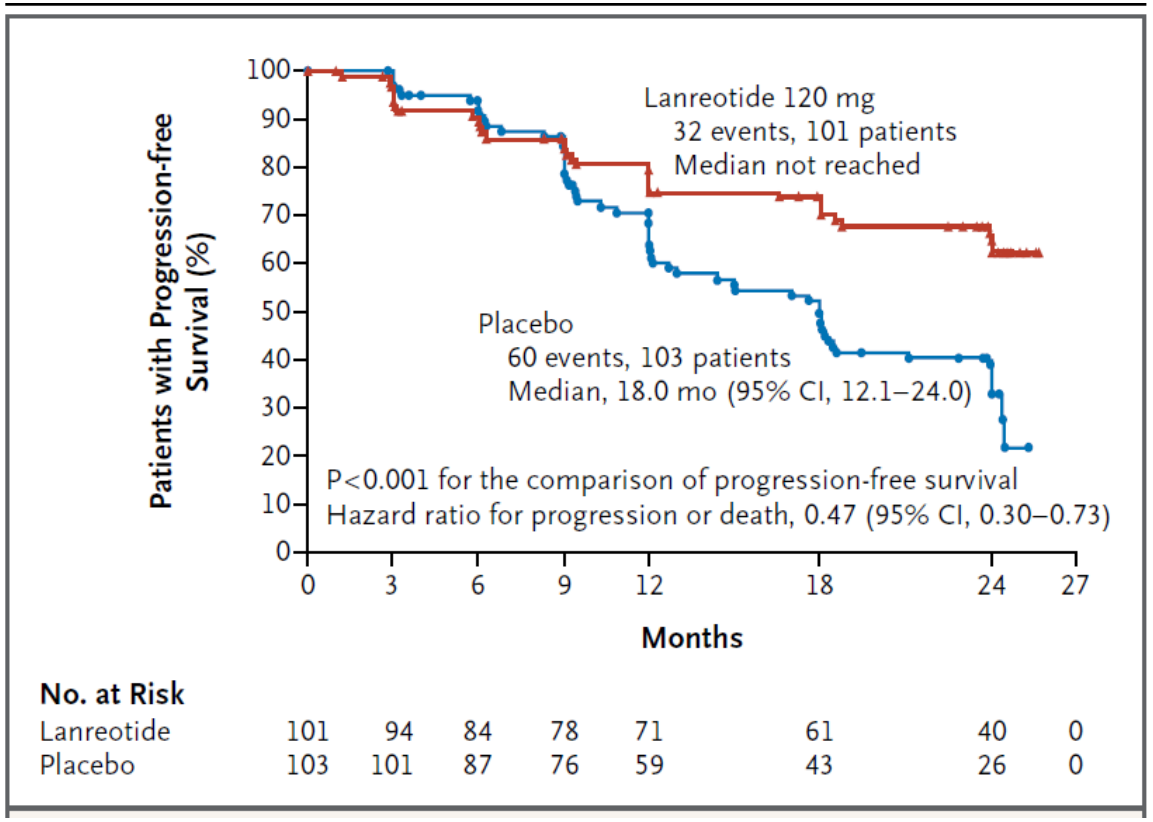
Lanreotide

CLARINET trial

- Patients with metastatic well differentiated NETs
  - PNET, mid/hindgut, unknown origin
    - SSTR positive, non-functioning

→ Lanreotide 120 mg deep SC every 28 days (n=101)

→ Placebo (n=103)



- Improvement in median progression-free survival
- PFS (at 24m): 65% vs. 33%
- Greater rate of reduction in chromogranin A by >50%
- No improvement in overall survival or quality of life
- Most common side effect: diarrhea (26% vs. 9%)

Caplin et al. N Engl J Med 2014;371:224.

Side effects of SSAs

- Injection site pain (8-10%)
- Nausea (9-30%)
- Abdominal cramps (4-44%), diarrhea (7-58%), steatorrhea (0-4%), flatulence (0.5-13%)
- Hyperglycemia (15%)
- Cholelithiasis/biliary sludge (52-62%)
  - Consider prophylactic cholecystectomy if anticipate long-term use
  - Assess with ultrasound of gallbladder and bile ducts every 6-12 months
  - Gallstones may be treated with ursodiol

1. Narayanan and Kunz. J Natl Compr Canc Netw 2015;13:109. 2. BC Cancer Agency Drug Manual.

Everolimus

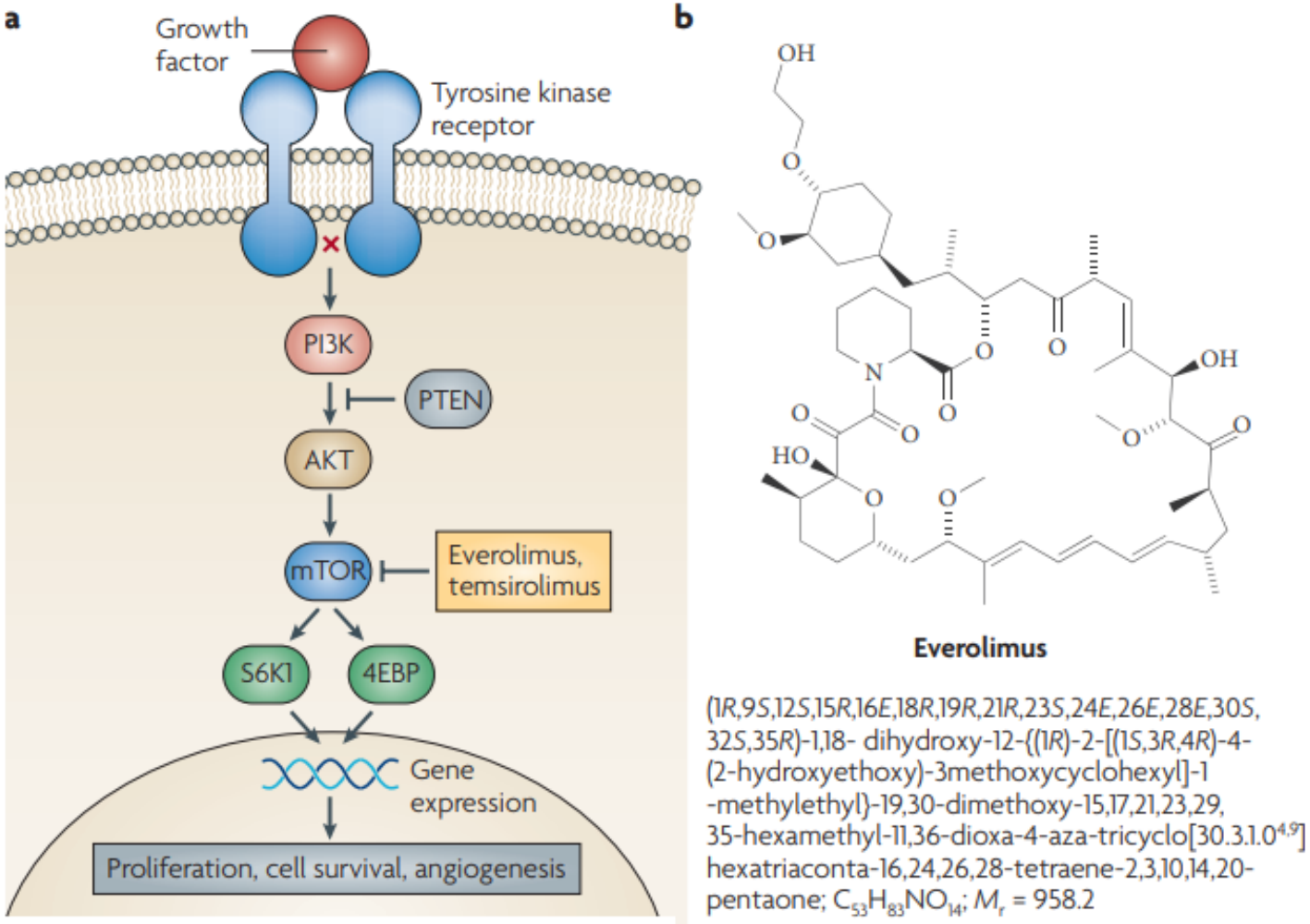


Figure 1 | **Selected signalling pathways and drugs for RCC. a** | A simplified overview of the PI3K–AKT–mTOR pathway, together with points of action of drugs for RCC. **b** | Everolimus.

Atkins et al. Nat Rev Drug Discov 2009;8:535.

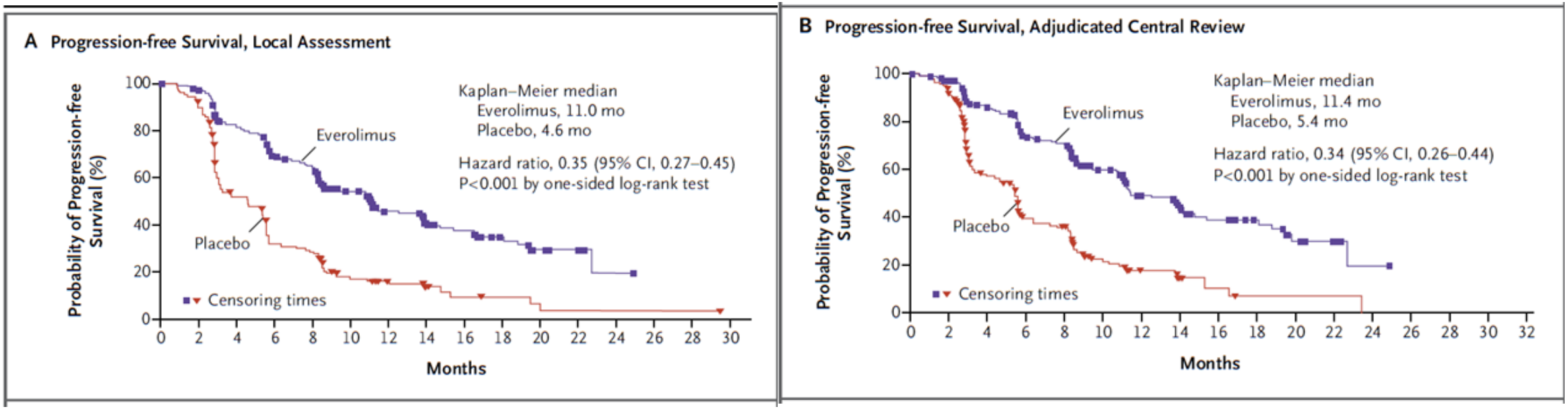
Everolimus – RADIANT3

- Patients with metastatic well-differentiated PNETs
- Disease progression in last 12 months
  - Any # and type of prior therapy

→ Everolimus 10 mg daily (n=207)

→ Placebo (n=203)

ORR: 5% vs. 2%
SD: 73% vs. 51%



Yao et al. N Engl J Med 2011;364:514.

Everolimus – RADIANT4

- Patients with metastatic well-differentiated NETs of GI or lung
- Non-functioning

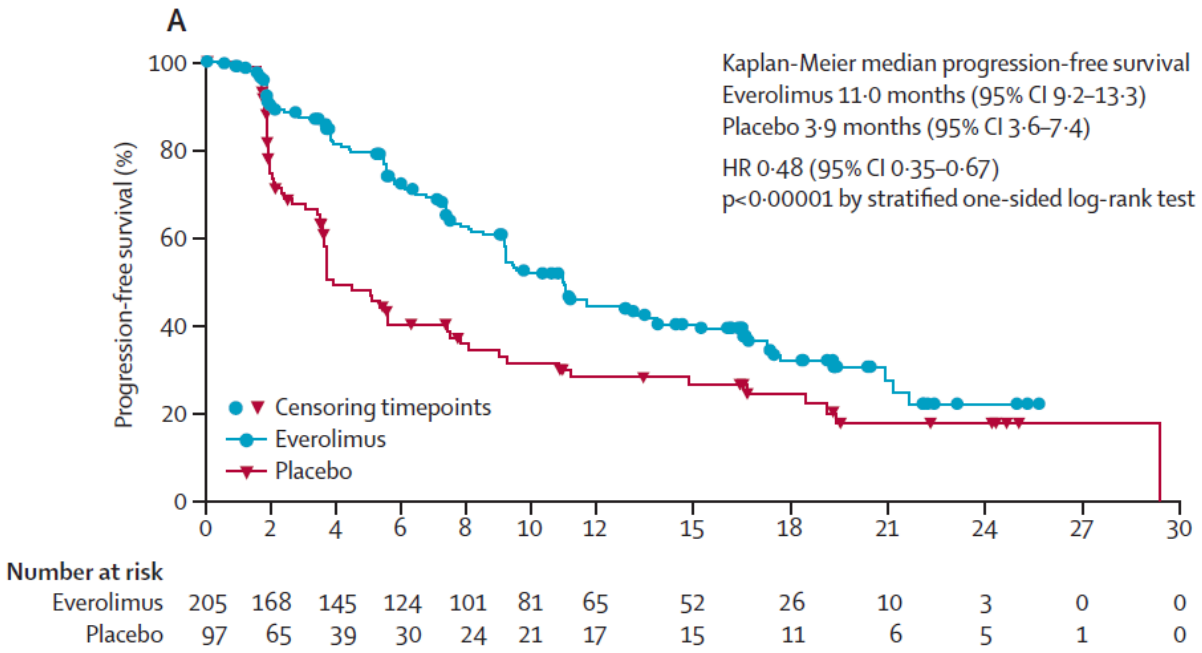
2:1

Everolimus 10 mg daily (n=205)

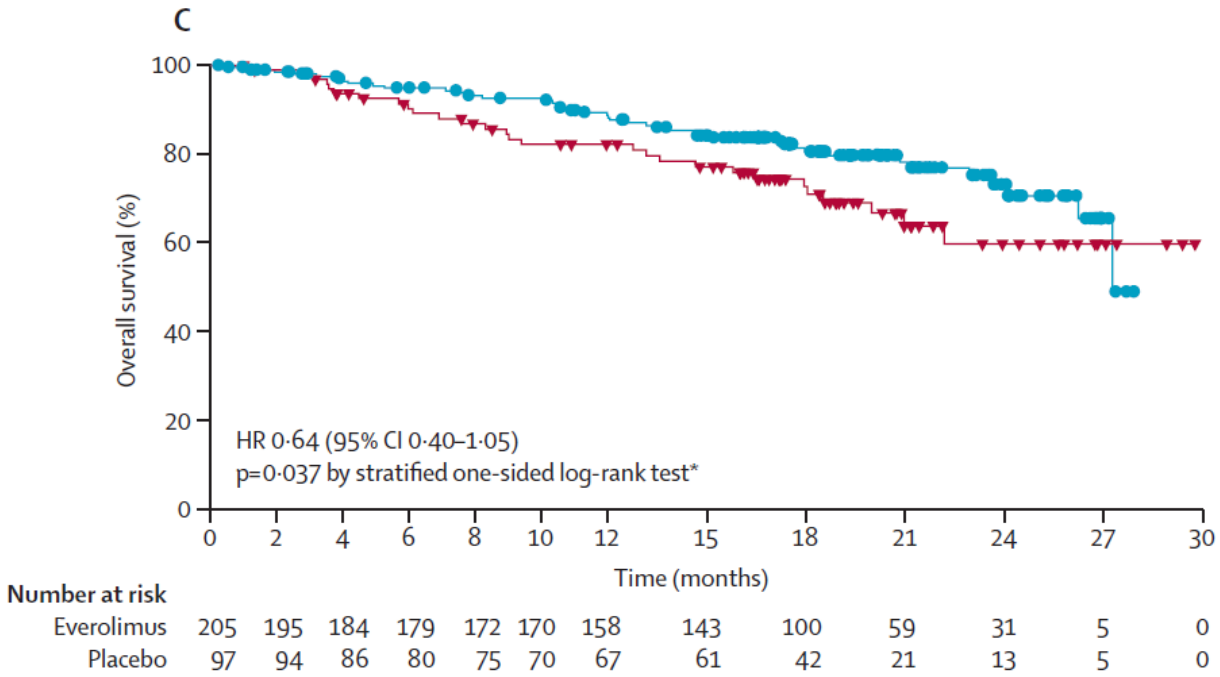
Crossover NOT allowed

Placebo (n=97)

ORR: 2% vs. 1%
SD: 81% vs. 64%



PFS by central review



OS

Yao et al. Lancet 2016;387:968.

	Everolimus (n=202)					Placebo (n=98)				
	All grades	Grade 1	Grade 2	Grade 3	Grade 4	All grades	Grade 1	Grade 2	Grade 3	Grade 4
Stomatitis*	127 (63%)	72 (36%)	37 (18%)	18 (9%)	0	19 (19%)	17 (17%)	2 (2%)	0	0
Diarrhoea	63 (31%)	30 (15%)	18 (9%)	13 (6%)	2 (1%)	16 (16%)	10 (10%)	4 (4%)	2 (2%)	0
Fatigue	62 (31%)	35 (17%)	20 (10%)	5 (2%)	2 (1%)	24 (24%)	17 (17%)	6 (6%)	1 (1%)	0
Infections†	59 (29%)	12 (6%)	33 (16%)	10 (5%)	4 (2%)	4 (4%)	1 (1%)	3 (3%)	0	0
Rash	55 (27%)	42 (21%)	12 (6%)	1 (<1%)	0	8 (8%)	6 (6%)	2 (2%)	0	0
Peripheral oedema	52 (26%)	30 (15%)	18 (9%)	4 (2%)	0	4 (4%)	2 (2%)	1 (1%)	1 (1%)	0
Nausea	35 (17%)	26 (13%)	6 (3%)	2 (1%)	1 (<1%)	10 (10%)	7 (7%)	3 (3%)	0	0
Asthenia	33 (16%)	8 (4%)	22 (11%)	2 (1%)	1 (<1%)	5 (5%)	4 (4%)	1 (1%)	0	0
Anaemia	33 (16%)	5 (2%)	20 (10%)	8 (4%)	0	2 (2%)	0	1 (1%)	1 (1%)	0
Decreased appetite	32 (16%)	22 (11%)	9 (4%)	1 (<1%)	0	6 (6%)	2 (2%)	4 (4%)	0	0
Non-infectious pneumonitis‡	32 (16%)	5 (2%)	24 (12%)	3 (1%)	0	1 (1%)	0	1 (1%)	0	0
Dysgeusia	30 (15%)	26 (13%)	3 (1%)	1 (<1%)	0	4 (4%)	4 (4%)	0	0	0
Pruritus	26 (13%)	19 (9%)	6 (3%)	1 (<1%)	0	4 (4%)	4 (4%)	0	0	0
Cough	26 (13%)	18 (9%)	8 (4%)	0	0	3 (3%)	3 (3%)	0	0	0
Pyrexia	22 (11%)	14 (7%)	4 (2%)	2 (1%)	2 (1%)	5 (5%)	4 (4%)	1 (1)	0	0
Hyperglycaemia	21 (10%)	5 (2%)	9 (4%)	7 (3%)	0	2 (2%)	2 (2%)	0	0	0
Dyspnoea	21 (10%)	4 (2%)	15 (7%)	2 (1%)	0	4 (4%)	2 (2%)	1 (1)	0	1 (1)

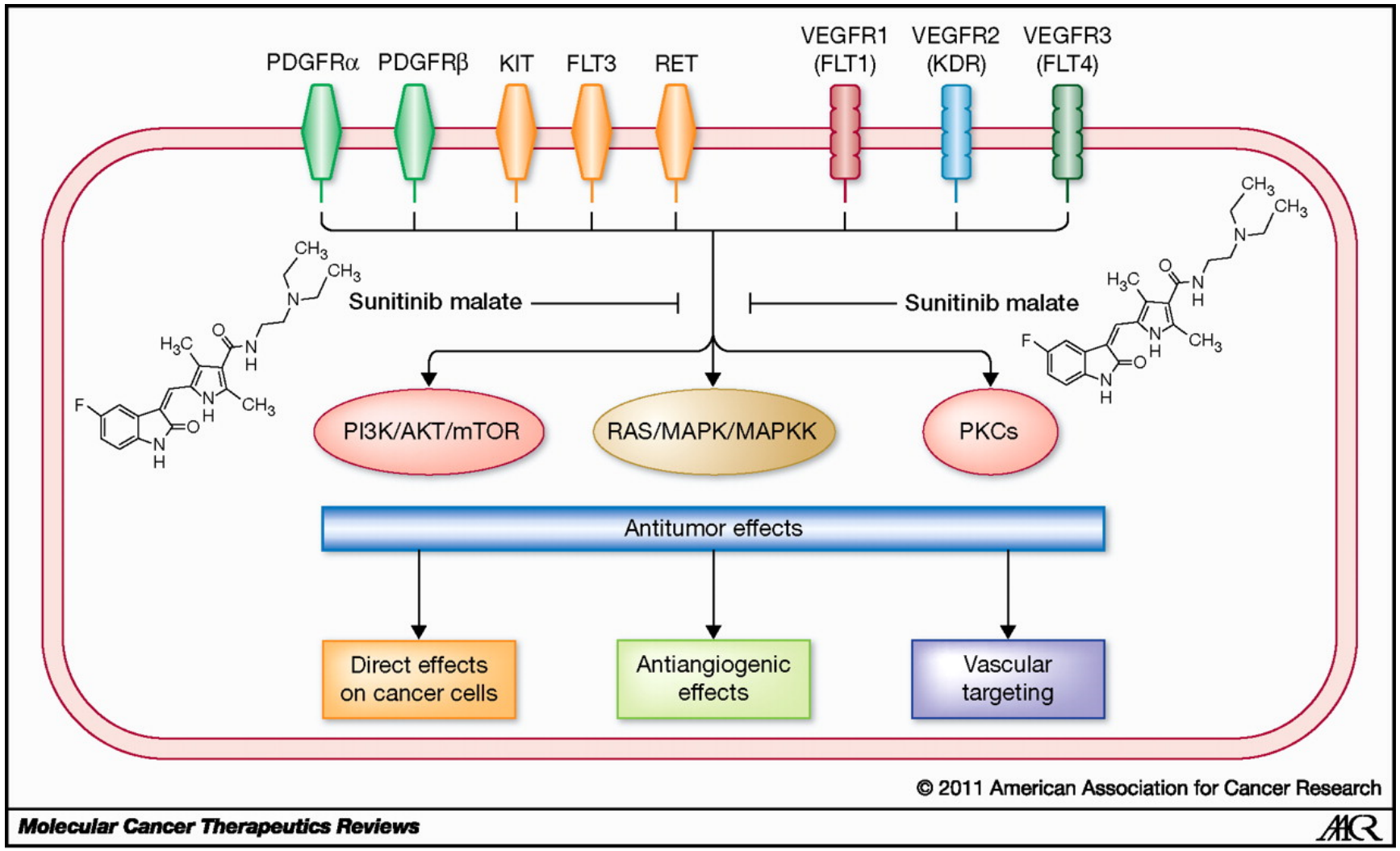
*Included in this category are stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration. †All types of infections are included. ‡Included in this category are pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis.

Table 3: Treatment-related adverse events reported in at least 10% of patients (safety population)

Most significant toxicities: stomatitis, diarrhea, fatigue, infections, rash
Possible hyperglycemia and pneumonitis

Yao et al. Lancet 2016;387:968.

Sunitinib



Aparicio-Gallego et al. Mol Cancer Ther 2011;10:2215.

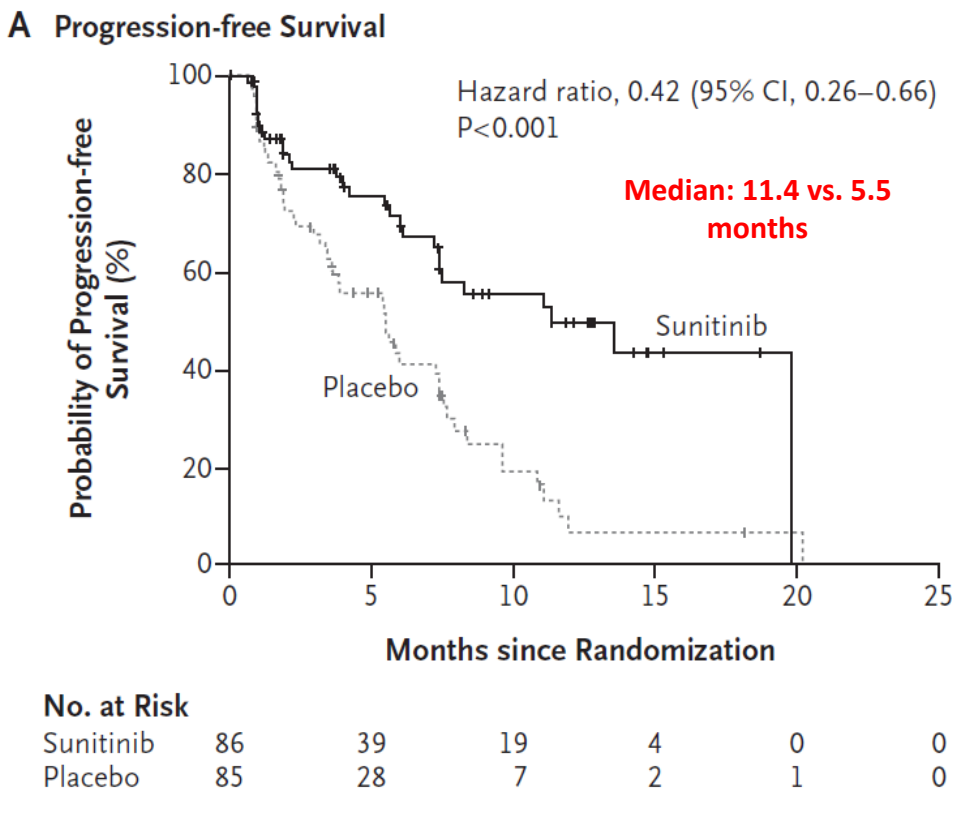
Sunitinib

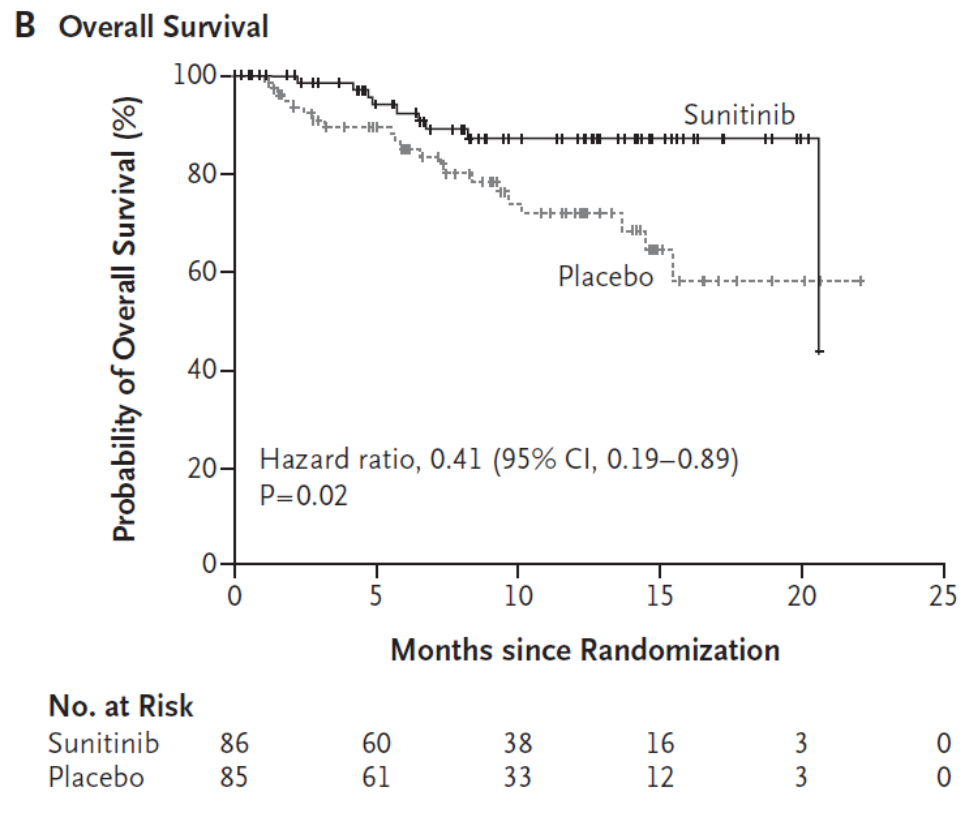
- Patients with metastatic well-differentiated PNET
- Progressed in last 12 months

→ Sunitinib 37.5 mg daily (n=86)

→ Placebo (n=85)

ORR: 9.3% vs. 0%





Benefit observed across subgroups

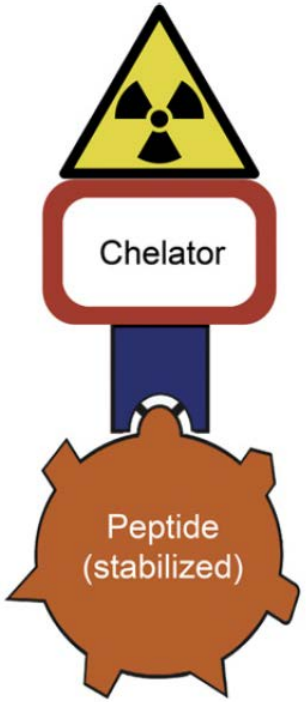
Raymond et al. N Engl J Med 2011;304:501.

Table 3. Common Adverse Events in the Safety Population.*

Event	Sunitinib (N=83)			Placebo (N=82)		
	All Grades	Grade 1 or 2	Grade 3 or 4	All Grades	Grade 1 or 2	Grade 3 or 4
	number of patients (percent)					
Diarrhea	49 (59)	45 (54)	4 (5)	32 (39)	30 (37)	2 (2)
Nausea	37 (45)	36 (43)	1 (1)	24 (29)	23 (28)	1 (1)
Asthenia	28 (34)	24 (29)	4 (5)	22 (27)	19 (23)	3 (4)
Vomiting	28 (34)	28 (34)	0	25 (30)	23 (28)	2 (2)
Fatigue	27 (32)	23 (28)	4 (5)	22 (27)	15 (18)	7 (8)
Hair-color changes	24 (29)	23 (28)	1 (1)	1 (1)	1 (1)	0
Neutropenia	24 (29)	14 (17)	10 (12)	3 (4)	3 (4)	0
Abdominal pain	23 (28)	19 (23)	4 (5)	26 (32)	18 (22)	8 (10)
Hypertension	22 (26)	14 (17)	8 (10)	4 (5)	3 (4)	1 (1)
Palmar–plantar erythrodysesthesia	19 (23)	14 (17)	5 (6)	2 (2)	2 (2)	0
Anorexia	18 (22)	16 (19)	2 (2)	17 (21)	16 (20)	1 (1)
Stomatitis	18 (22)	15 (18)	3 (4)	2 (2)	2 (2)	0
Dysgeusia	17 (20)	17 (20)	0	4 (5)	4 (5)	0
Epistaxis	17 (20)	16 (19)	1 (1)	4 (5)	4 (5)	0
Headache	15 (18)	15 (18)	0	11 (13)	10 (12)	1 (1)
Insomnia	15 (18)	15 (18)	0	10 (12)	10 (12)	0
Rash	15 (18)	15 (18)	0	4 (5)	4 (5)	0
Thrombocytopenia	14 (17)	11 (13)	3 (4)	4 (5)	4 (5)	0
Mucosal inflammation	13 (16)	12 (14)	1 (1)	6 (7)	6 (7)	0
Weight loss	13 (16)	12 (14)	1 (1)	9 (11)	9 (11)	0
Constipation	12 (14)	12 (14)	0	16 (20)	15 (18)	1 (1)
Back pain	10 (12)	10 (12)	0	14 (17)	10 (12)	4 (5)

Raymond et al. N Engl J Med 2011;304:501.

Peptide receptor radionuclide therapy (PRRT)



Radionuclide — $[^{111}In\text{-}DTPA^{0}]Octreotide$

Chelator — $[^{90}Y\text{-}DOTA^{0},Tyr^{3}]Octreotide$

$[^{177}Lu\text{-}DOTA0,Tyr^{3}]Octreotide$

Cyclic Octapeptide — $[^{177}Lu\text{-}DOTA0,Tyr^{3}]Octreotate$

^{177}Lu-dotatate

- Delivers radionuclides directly to tumor cells via SSTR
- Used for SSTR-positive metastatic well-differentiated NETs in Europe since 1990s
- Lutetium-177 is a beta and gamma emitting radionuclide

Kunz PL. J Clin Oncol 2015;33:1855.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

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

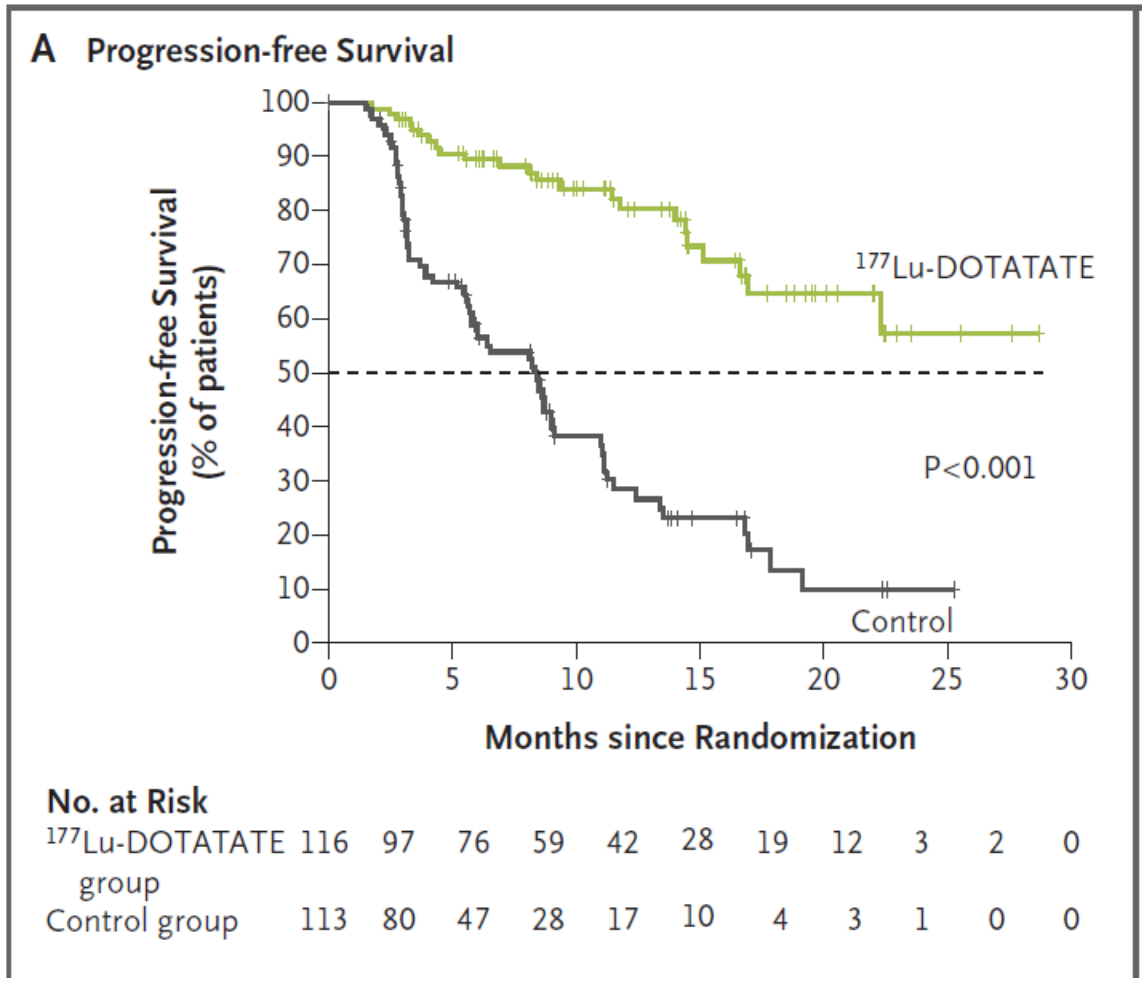
- Patients with metastatic well-differentiated midgut NETs
  - SSTR-positive
- Progressed during treatment with octreotide LAR for at least 12 wks prior to study

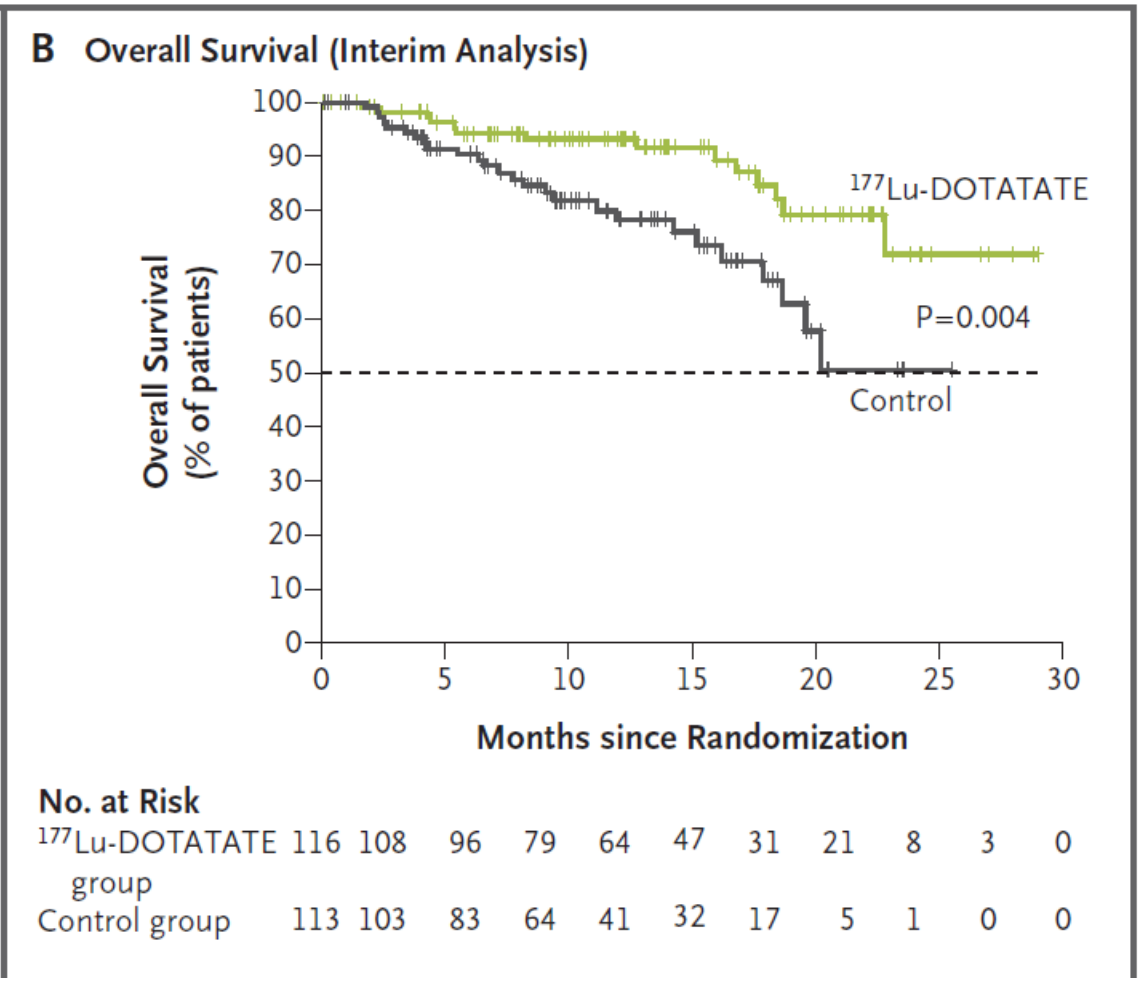
→ 177Lu-Dotatate 7.4 GBq/200mCi every 8 weeks x 4 + octreotide LAR 30 mg IM (n=116)

→ Octreotide LAR 60 mg IM every 4 weeks (n=113)

- For renal protection, IV amino acid solution (lysine, arginine) given concomitantly for at least 4 hours starting 30 min before infusion of 177Lu-Dotatate
- Octreotide LAR given 24 hours after each infusion of 177Lu-Dotatate, then monthly

Strosberg et al. N Engl J Med 2017;376:125.





Rate of progression-free survival at 20 months: 65% vs. 11%

Median PFS: not reached vs. 8.4 months (HR 0.21, 95% CI 0.13-0.33, p<0.001)

Interim analysis for overall survival: 14 vs. 26 deaths (p=0.004)

Strosberg et al. N Engl J Med 2017;376:125.

Table 2. Objective Tumor Response.*

Response Category	^{177}Lu-Dotatate Group (N = 101)	Control Group (N = 100)	P Value†
Complete response — no. (%)	1 (1)	0	
Partial response — no. (%)	17 (17)	3 (3)	
Objective response			
No. with response	18	3	
Rate — % (95% CI)	18 (10–25)	3 (0–6)	<0.001

Table 3. Overview of Adverse Events (Safety Population).*

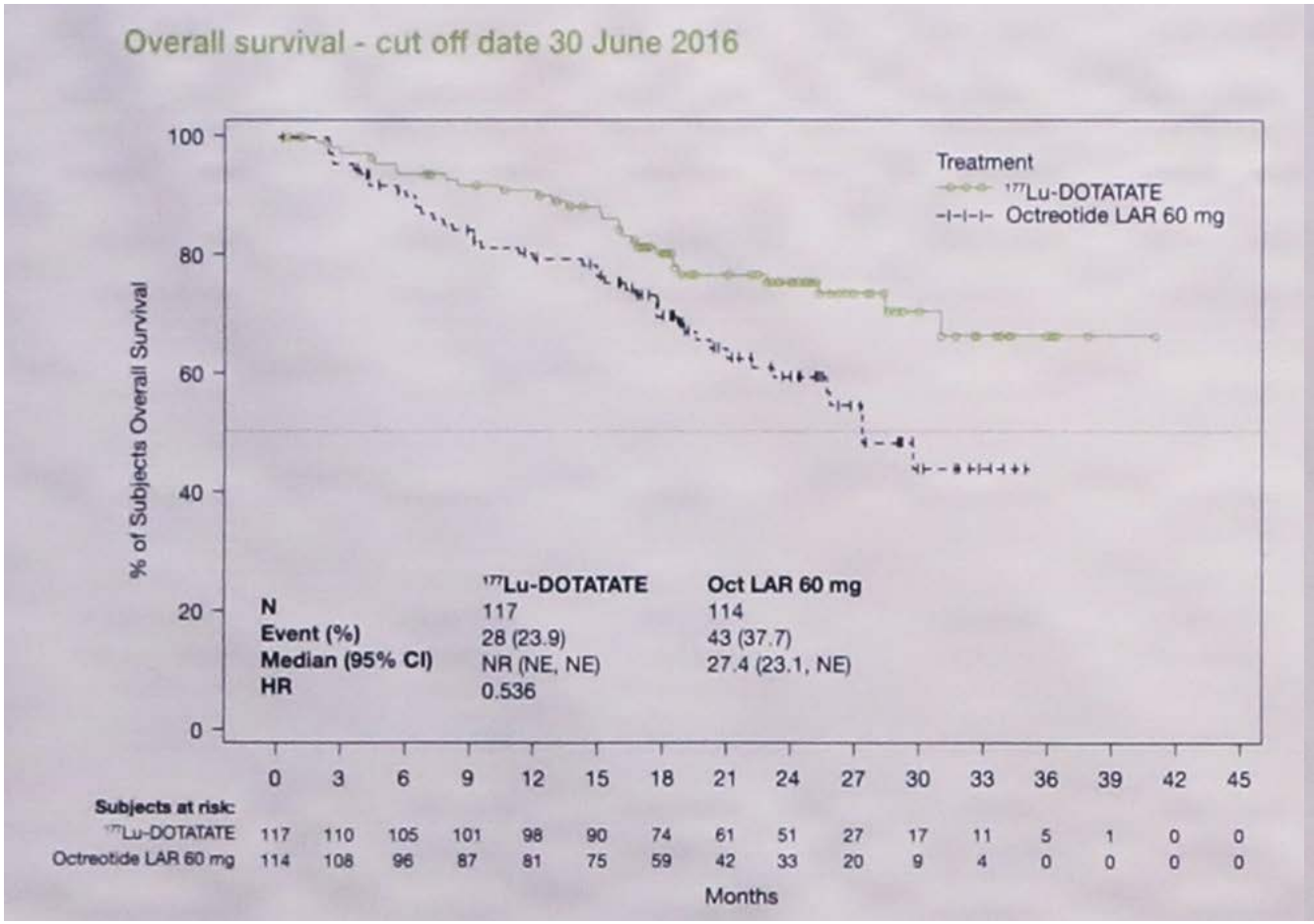
Event	^{177}Lu-Dotatate Group (N = 111)	Control Group (N = 110)	P Value†
	number of patients (percent)		
Adverse event			
Any	106 (95)	95 (86)	0.02
Related to treatment	95 (86)	34 (31)	<0.001
Serious adverse event			
Any	29 (26)	26 (24)	0.76
Related to treatment	10 (9)	1 (1)	0.01
Withdrawal from trial because of adverse event			
Because of any adverse event	7 (6)	10 (9)	0.46
Because of adverse event related to treatment	5 (5)	0	0.06

* The safety population included all patients who underwent randomization and received at least one dose of trial treatment.
† P values were calculated with the use of Fisher's exact text.

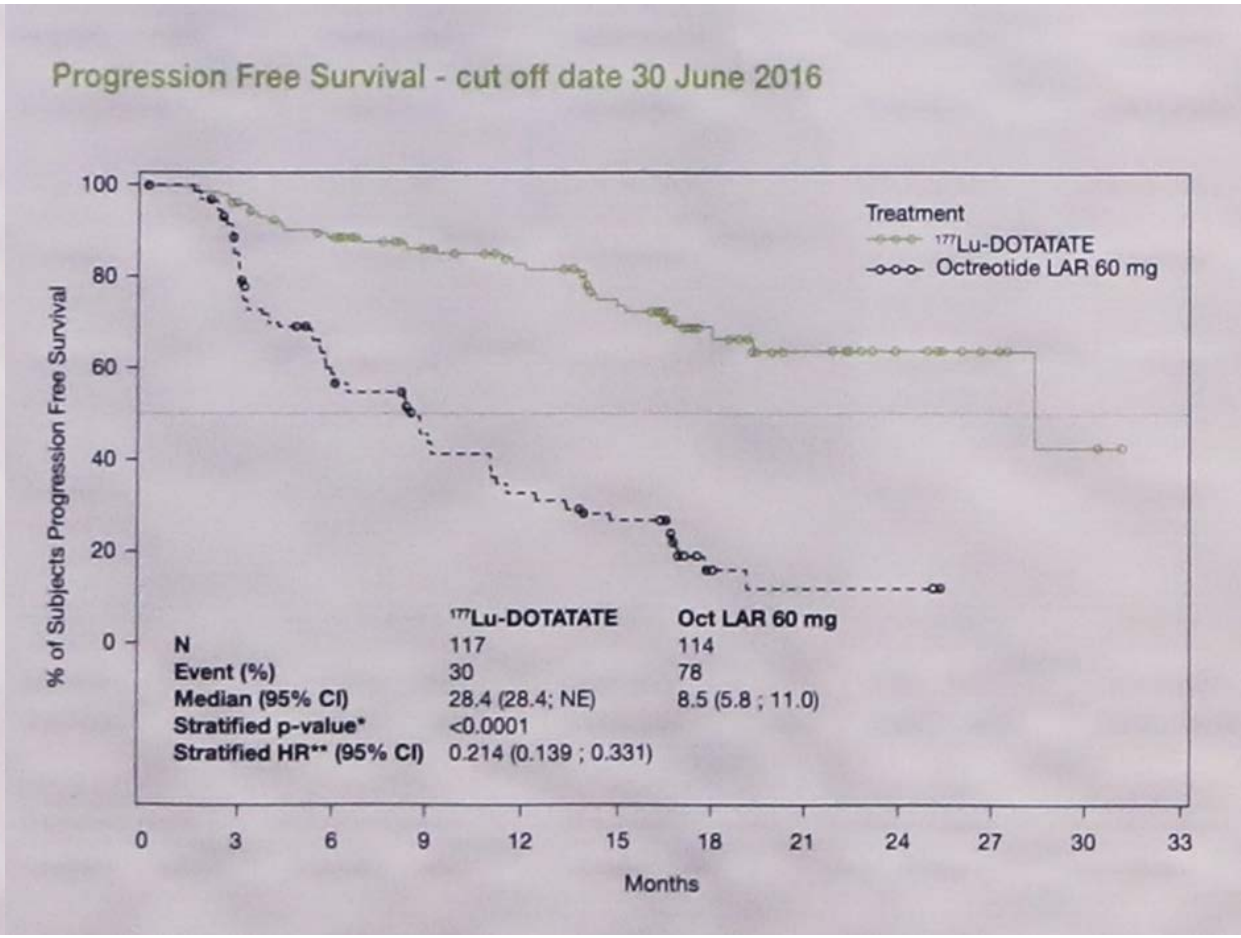
- **177Lu-Dotatate group:**
  - Nausea 59%, vomiting 47% (due to amino acid), fatigue/asthenia 40%
  - Grade 3 or 4: neutropenia 1%, thrombocytopenia 2%, lymphopenia 9% (none in control group)
- No renal toxicity observed at median follow-up duration of 14 months
- 1 patient developed myelodysplastic syndrome possibly related to PRRT

Strosberg et al. N Engl J Med 2017;376:125.

Update of NETTER-1



Median OS: not reached vs. 27.4 months



Median PFS: 28.4 vs. 8.5 months
(HR 0.214, 95% CI 0.139-0.331, p<0.0001)

Strosberg et al. J Clin Oncol 2018;36:suppl abstr 4099.


U.S. Department of Health and Human Services

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FDA News Release

FDA approves new treatment for certain digestive tract cancers

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

For Immediate Release January 26, 2018

Release

The U.S. Food and Drug Administration today approved Lutathera (lutetium Lu 177 dotatate) for the treatment of a type of cancer that affects the pancreas or gastrointestinal tract called gastroenteropancreatic neuroendocrine tumors (GEP-NETs). This is the first time a radioactive drug, or radiopharmaceutical, has been approved for the treatment of GEP-NETs. Lutathera is indicated for adult patients with somatostatin receptor-positive GEP-NETs.

"GEP-NETs are a rare group of cancers with limited treatment options after initial therapy fails to keep the cancer from growing," said Richard Pazdur, M.D., director of the FDA's Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research. "This approval provides another treatment choice for patients with these rare cancers. It also demonstrates how the FDA may consider data from therapies that are used in an expanded access program to support approval for a new treatment."

PRRT approved for refractory SSTR-expressing well-differentiated GEP NETs

Pharmacokinetics:

- Half-life 6.71 days
- Poorly metabolized and mainly excreted renally as intact compound
  - 60% eliminated in urine within 24h; 65% within 48h

Use in patients with CKD:

- CrCl <30 mL/min: contraindicated
- CrCl <50 mL/min: not recommended
- Mild to moderate CKD with CrCl ≥50 mL/min: use with caution, consider dose reduction

1. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm594043.htm 2. Lutathera® monograph

Practical considerations for ^{177}Lu-Dotatate

- Interval between each infusion is 8 (+/-1) weeks, can be extended up to 16 weeks for toxicity
- May use half-dose (3.7 GBq) due to toxicity
- *No long-acting SSA within 4 weeks of treatment
- *No short-acting SSA within 24 hours of treatment
- Concomitant infusion of amino acid solution is required for renal protection (over 4 hours)
  - Composition: lysine 25g, arginine 25g in 1L NS

Lutathera® monograph

Chemotherapy

- Carcinoids
  - Generally do not respond well to chemotherapy
  - May be considered for progressive disease with no other standard or trial options
- PNETs
  - Activity has been shown with alkylating agents
  - May be initially considered for bulky, rapidly progressing, and/or symptomatic well-differentiated PNETs
    - Greater response rate
  - Synergistic activity of temozolomide and capecitabine in PNET in preclinical and early studies

A randomized phase II study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211)

Pamela L. Kunz[1], Paul J. Catalano[2,3], Halla S. Nimeiri[4], George A. Fisher Jr[1], Teri A. Longacre[1], Carlos J. Suarez[1], James C. Yao[5], Matthew H. Kulke[6], Andrew E. Hendifar[7], James C. Shanks[8], Manisha H. Shah[9], Mark M. Zalupski[10], Edmond Schmulbach[11], Diane L. Reidy-Lagunes[12], Jonathan R. Strosberg[13], Peter J. O'Dwyer[14], and Al B. Benson III[4] on behalf of the E2211 Study Team

[1]Stanford University, [2]Dana Farber Cancer Institute, [3]ECOG-ACRIN Biostatistics Center, [4]Northwestern University, [5]MD Anderson Cancer Center, [6]Boston University, [7]Cedars Sinai Medical Center, [8]Saint John's Hospital Healtheast, [9]Ohio State Comprehensive Cancer Center, [10]University of Michigan Comprehensive Cancer Center, [11]Kaiser Permanente South San Francisco, [12]Memorial Sloan Kettering Cancer Center, [13]Moffitt Cancer Center, [14]University of Pennsylvania

ECOG-ACRIN cancer research group
Reshaping the future of patient care

Presented By Pamela Kunz at 2018 ASCO Annual Meeting

E2211 Study Design

Progressive, G1/G2, metastatic pancreatic NETs

R 1:1

n=72

ARM A:
Temozolomide 200 mg/m^2 po QD days 1-5

n=72

ARM B:
Capecitabine 750 mg/m^2 po BID days 1-14
Temozolomide 200 mg/m^2 QD days 10-14

Cycle length = 28 days; max 13 cycles.
Imaging performed every 12 weeks (RECIST 1.1)

Stratified by:
- Prior everolimus
- Prior sunitinib
- Concurrent octreotide

Primary Endpoint:
- PFS (local review)

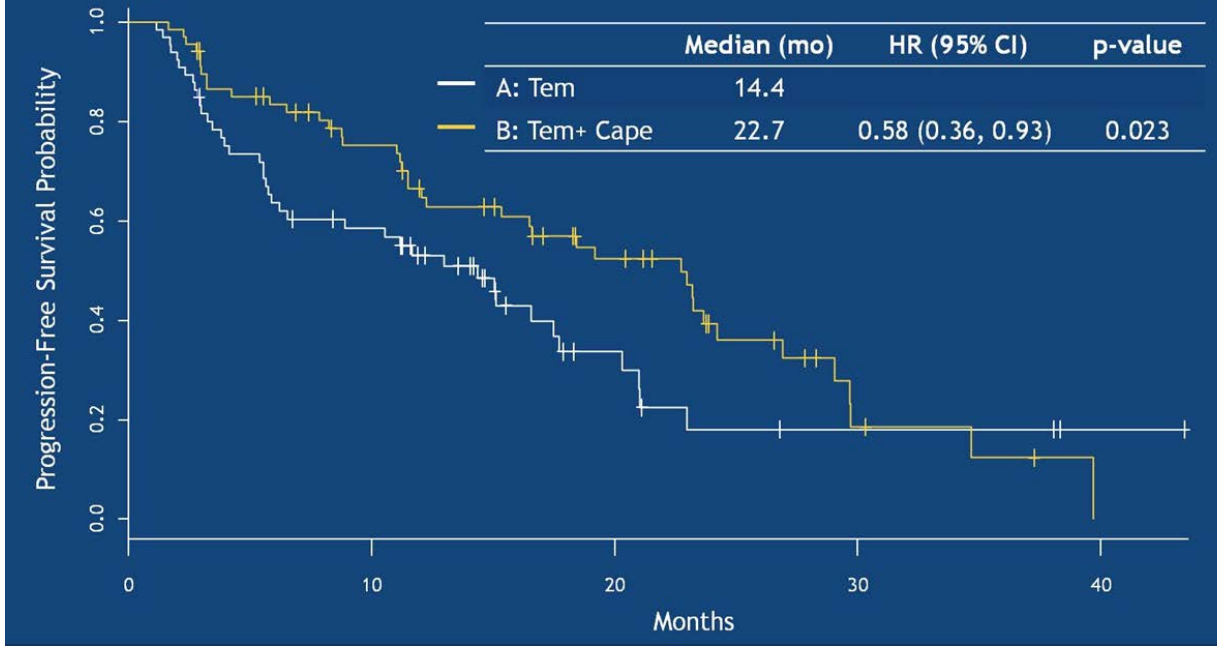
Secondary Endpoints:
- RR
- OS
- Toxicity

Correlative Endpoints:
- MGMT by IHC
- MGMT by promoter methylation

Concurrent SSAs allowed

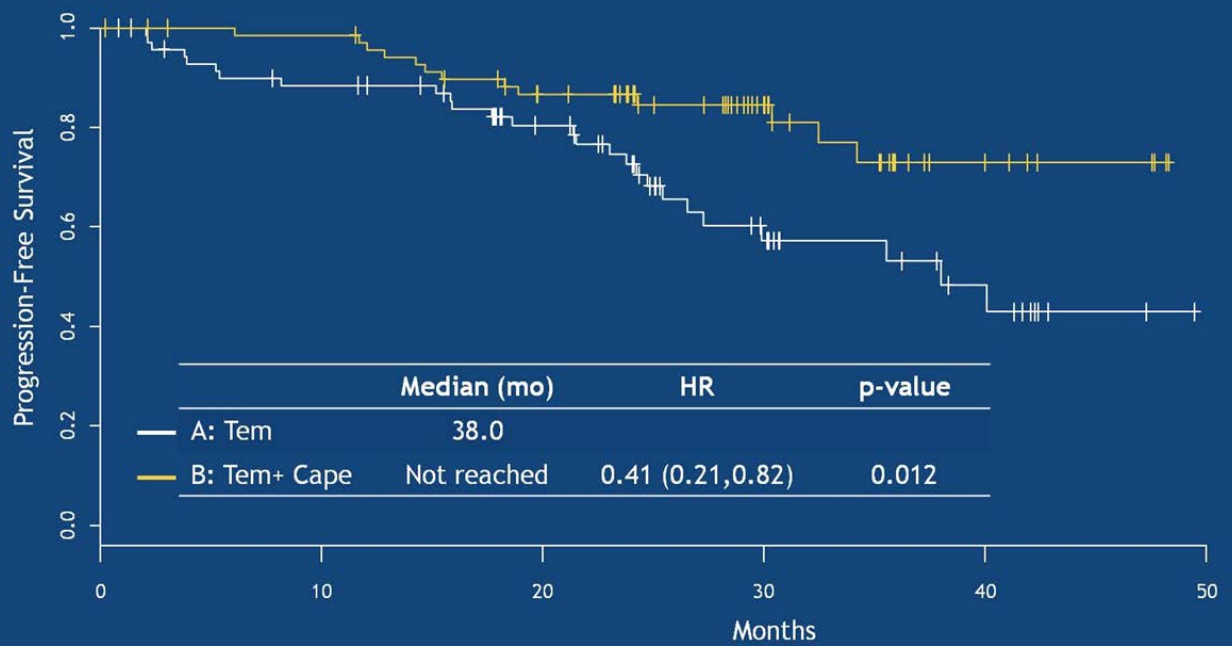
NCT01824875

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

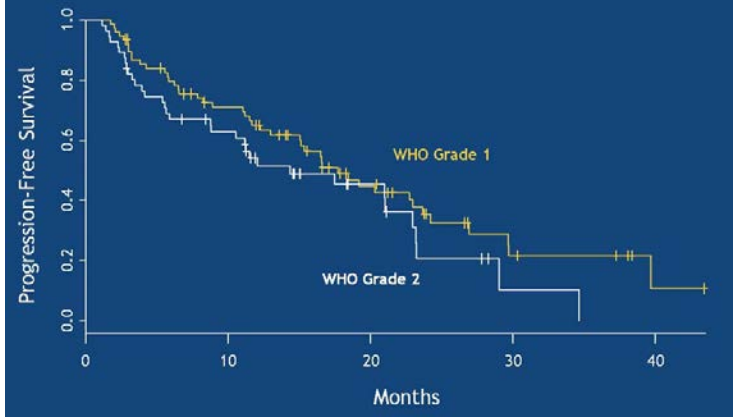
Overall Survival



	Median (mo)	HR	p-value
A: Tem	38.0		
B: Tem+ Cape	Not reached	0.41 (0.21,0.82)	0.012

	Temozolomide (N=72)	Temozolomide + Capecitabine (N=72)
Time from Diagnosis (months)	24.4 mo	34.0 mo
*WHO Grade		
Low (Grade 1)	45.1%	68.1%
Intermediate (Grade 2)	54.9%	31.9%

Survival by Grade



- Grade was not associated with PFS/OS
- PFS/OS benefits were observed after adjusting for grade

Kunz et al. J Clin Oncol 2018;36:suppl; abstr 4004.

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	

- Safety
  - Grade 3/4 treatment-related AEs: 44% vs. 22% (p=0.007)
  - Most common grade 3/4 AEs with CAPTEM – neutropenia (13%), thrombocytopenia (8%), nausea/vomiting (8%), diarrhea (8%), lymphopenia (5%), fatigue (5%)

Kunz et al. J Clin Oncol 2018;36:suppl; abstr 4004.

Summary of systemic therapy for unresectable or metastatic well-differentiated GEP NETs

Carcinoid tumor

- SSA (octreotide, lanreotide)
- PRRT
- Everolimus

PNET

- SSA (octreotide, lanreotide)
- PRRT
- Everolimus
- Sunitinib
- CAPTEM

Other cytotoxic chemotherapy regimens may be considered (less preferred) (for instance, FOLFOX or CAPOX)

No data to support a specific sequence of systemic therapy options
Consider clinical trials

Thank you for your attention!