Management of Advanced GI and Pancreatic NET

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- Stock: Merck

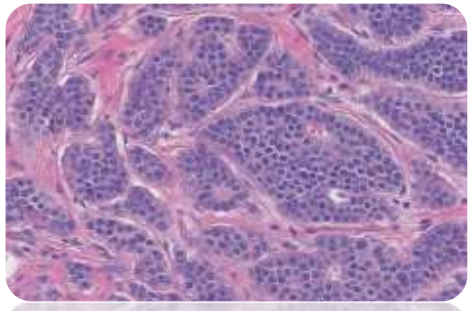
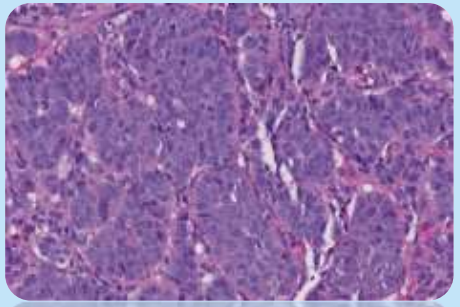
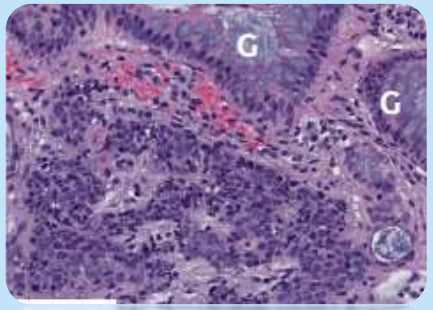
Objectives

1. To identify factors impacting treatment decisions for patients with advanced GI and pancreatic NET

2. To review treatment options to control carcinoid syndrome

3. To review treatment options to slow progression or achieve objective response in patients with advanced GI and pancreatic NET

WHO Classification of Neuroendocrine Neoplasms

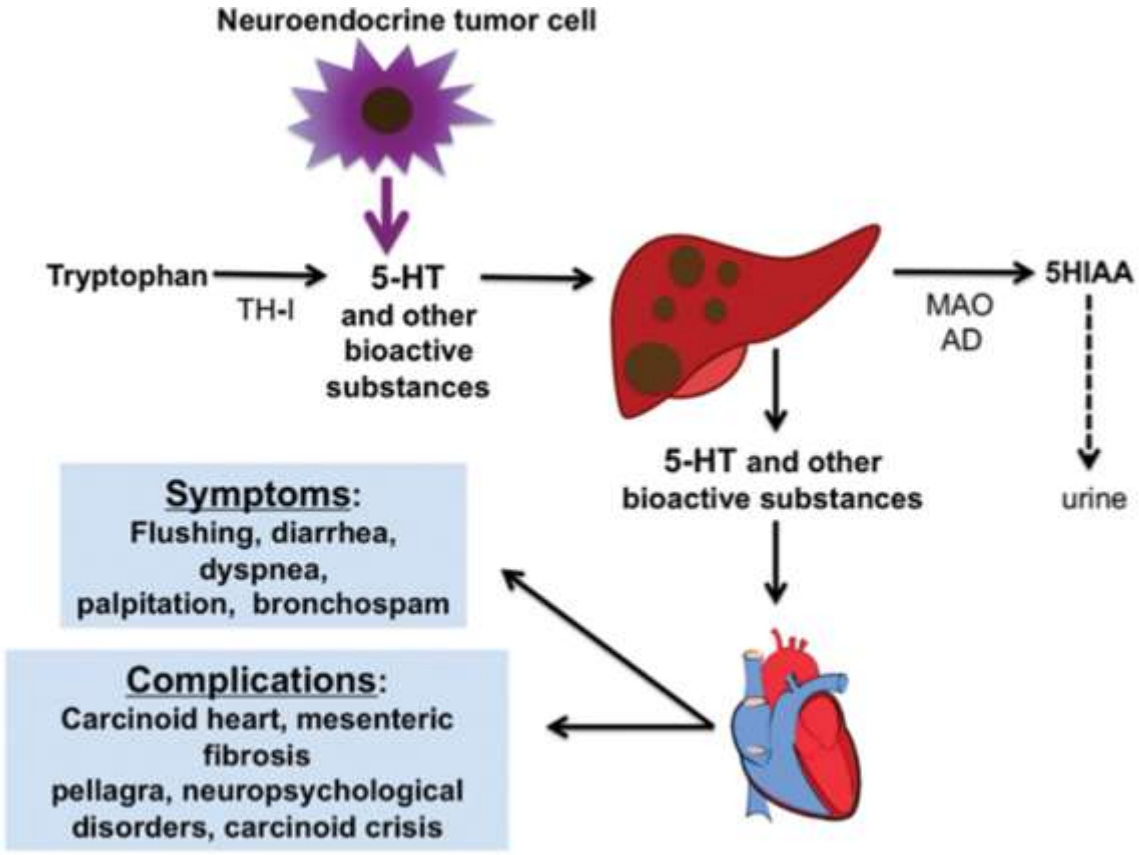
Tumor category	Neuroendocrine Neoplasia		
Family/class	Well-differentiated NEN	Poorly differentiated NEN	
Type	Neuroendocrine Tumor (NET)	Neuroendocrine Carcinoma (NEC)	
Subtype	Variable, depending on site	Large cell NEC	Small cell NEC
Grade	G1,G2,G3	High grade (by definition)	
			

Rindi et al., *Endocrine Pathology*, 2022. Kawasaki et al., Nat Rev Clin Oncol, 2023

Principles of Management of NET

- Resection of localized and limited metastatic disease
- Advanced disease
  - Improve symptoms due to hormone excess for functional tumors
  - Control tumor growth
  - Reduce disease burden, particularly if high volume disease or symptoms related to disease

Carcinoid Syndrome

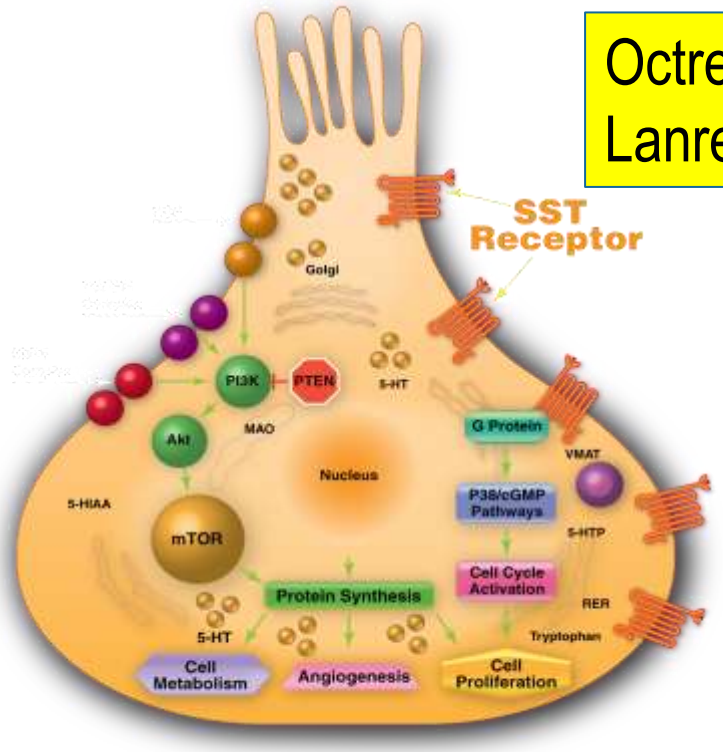


Abbreviations: 5-HT: serotonin; TH-I: tryptophan hydroxilase I; MAO: monoamine oxidase; AD: aldehyde dehydrogenase

- ~ 20-30% of patients have carcinoid syndrome related to secretion of serotonin and other vasoactive peptides
- Most common in patients with metastatic midgut (jejunum, ileum, cecum) NET with liver metastases

Loughrey et al, Endocrinol Metab Clin N Am, 2018
Ferrari,AC et al., *Clinics*(2018), 73 (Suppl 1)

Somatostatin Analogs for Carcinoid Syndrome



Octreotide
Lanreotide

- First-line therapy for carcinoid syndrome
- Bind to somatostatin receptors (SSTR) that are highly expressed by NET
- Improve hormone-mediated symptoms by reducing hormone secretion

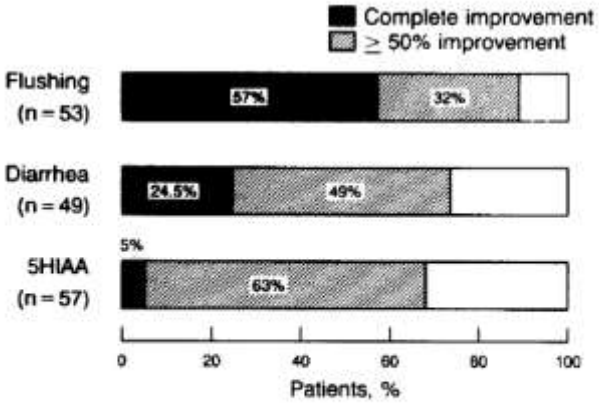
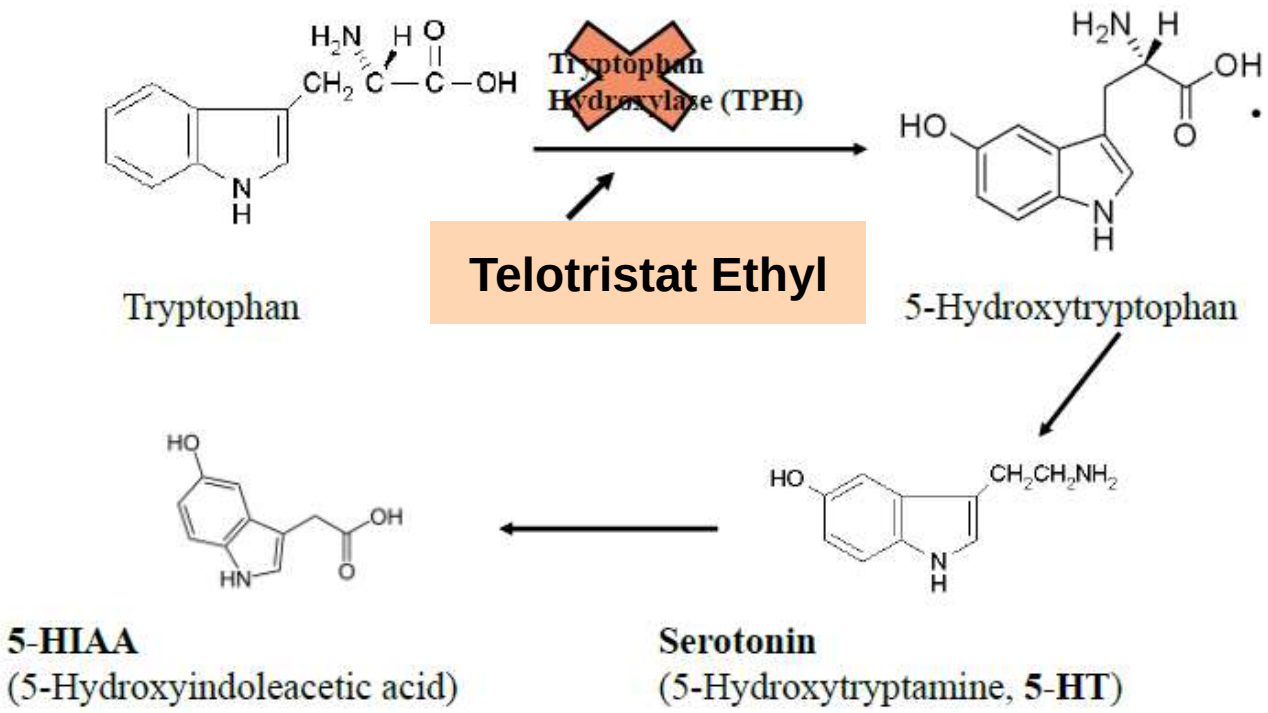


Fig 5. Clinical and 5HIAA response to therapy of the malignant carcinoid syndrome with somatostatin analogue.

Kvols *et al., NEJM*, 1986; Rubin *et al.*, *J Clin Oncol*, 1999;
Khan *et al.*, *Aliment Pharmacol Ther*, 2011; Vinik *et al.*, *Endocr Pract* 2016

Moertel CG. *J Clin Oncol*. 1987.

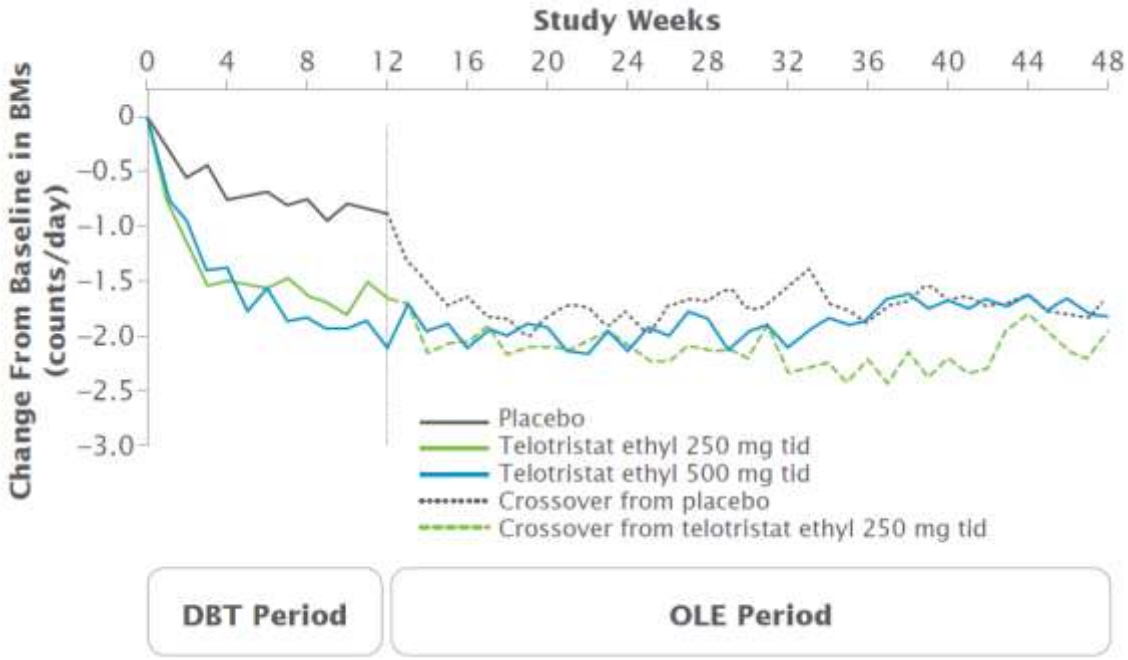
Carcinoid Syndrome: Targeting Serotonin Synthesis

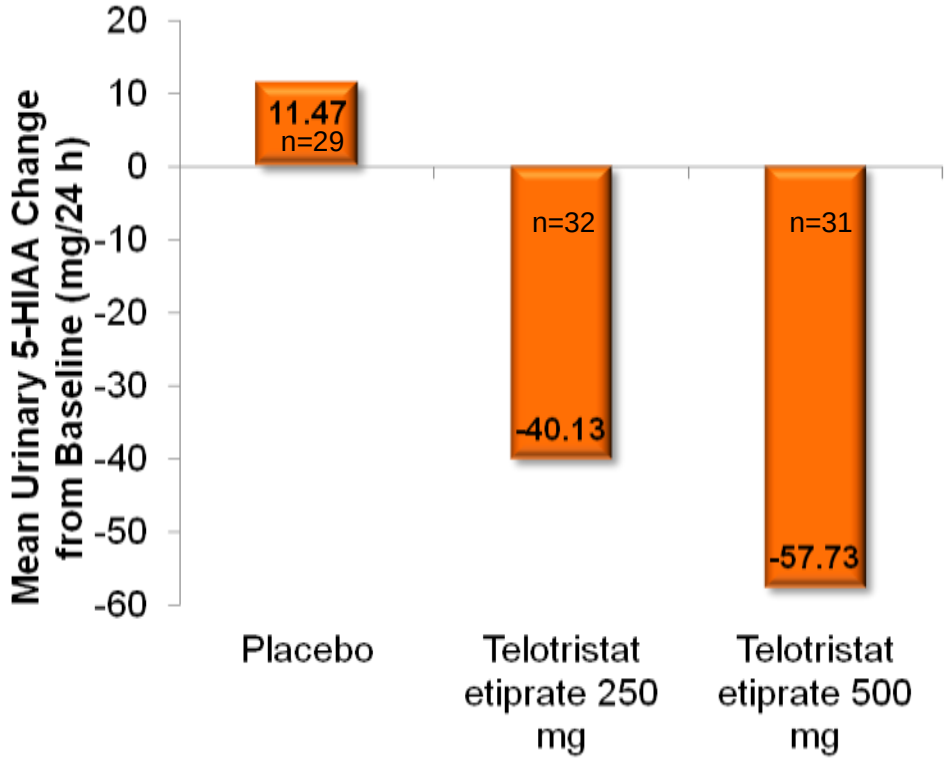


- Treatment with somatostatin analogs (SSAs) is associated with improved symptom control, but patients may not maintain adequate control of symptoms.
- **Telotristat ethyl** is an oral inhibitor of TPH, the rate-limiting enzyme in serotonin biosynthesis.

Liu *et al. J Pharmacol Exp Ther* 2008; 325:47–55.
Kulke *et al. Endocr Relat Cancer* 2014;21:705–714.
Pavel *et al. J Clin Endocrinol Metab* 2015;100:1511–1519.

TELESTAR Trial Results





Telotristat decreases daily bowel movement frequency and 24-hr urine 5-HIAA in patients with carcinoid syndrome diarrhea not controlled with SSA.

Kulke *et al., J Clin Oncol* 2017

Management of Poorly Controlled Carcinoid Syndrome

Factors to consider
- Status of disease
- Nature and impact of symptoms (diarrhea vs. other symptoms)
- Dose/schedule of SSA
- Timing of symptoms

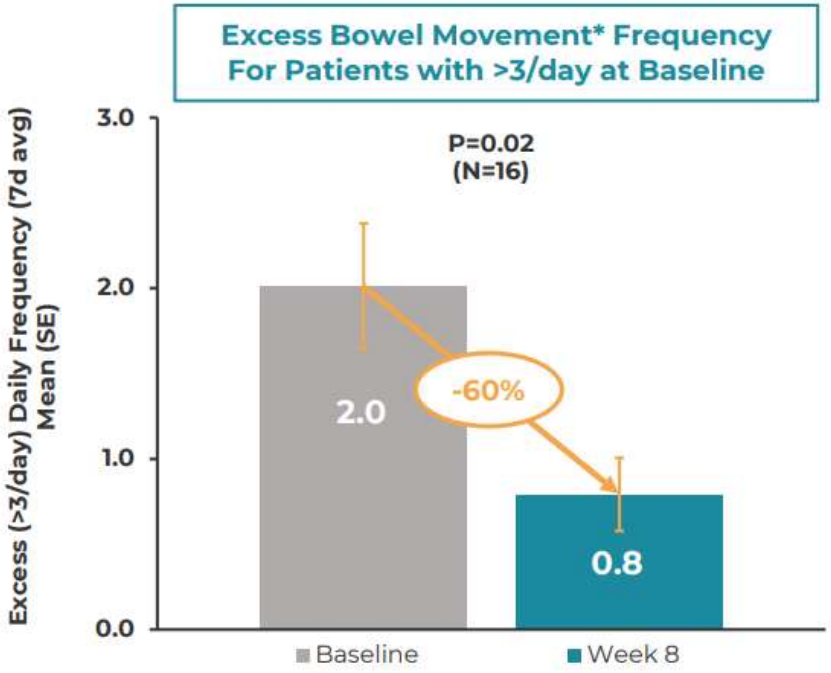
Exclude other causes of symptoms

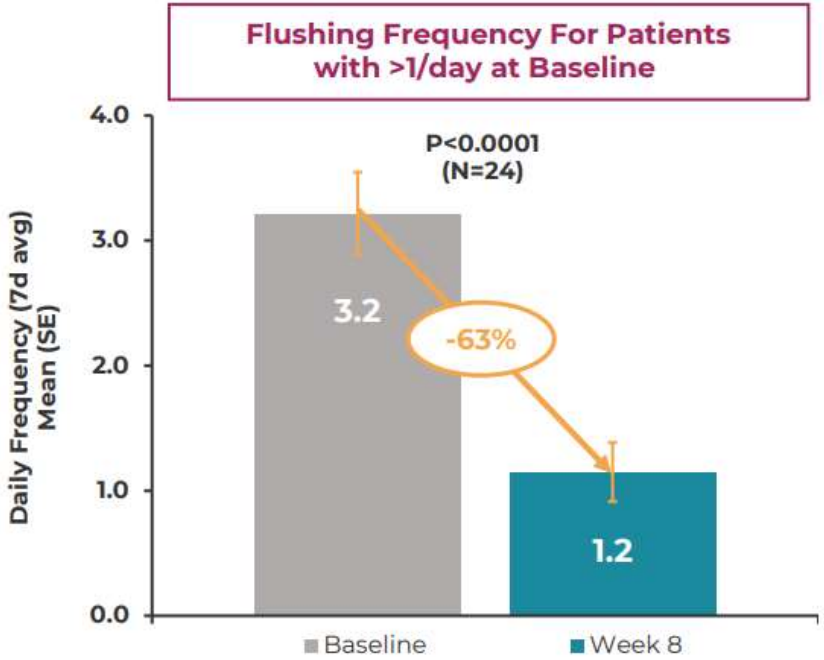
Stable disease
- Optimize dosing of SSA with higher or more frequent dosing
- Breakthrough sc octreotide
- Telotristat ethyl
- Liver-directed therapy with hepatic artery embolization or cytoreductive liver surgery

Progressive disease
- Liver-directed therapy (liver predominant disease)
- PRRT
- Other systemic options for disease control

Phase 2 Trial of Paltusotine in Carcinoid Syndrome

- Paltusotine: Oral non-peptide, highly selective SSTR2 agonist
- Evaluated in Phase 2 trial of patients with SSTR positive G1-2 NET and carcinoid syndrome
- Paltusotine reduced frequency of excess bowel movements and flushing

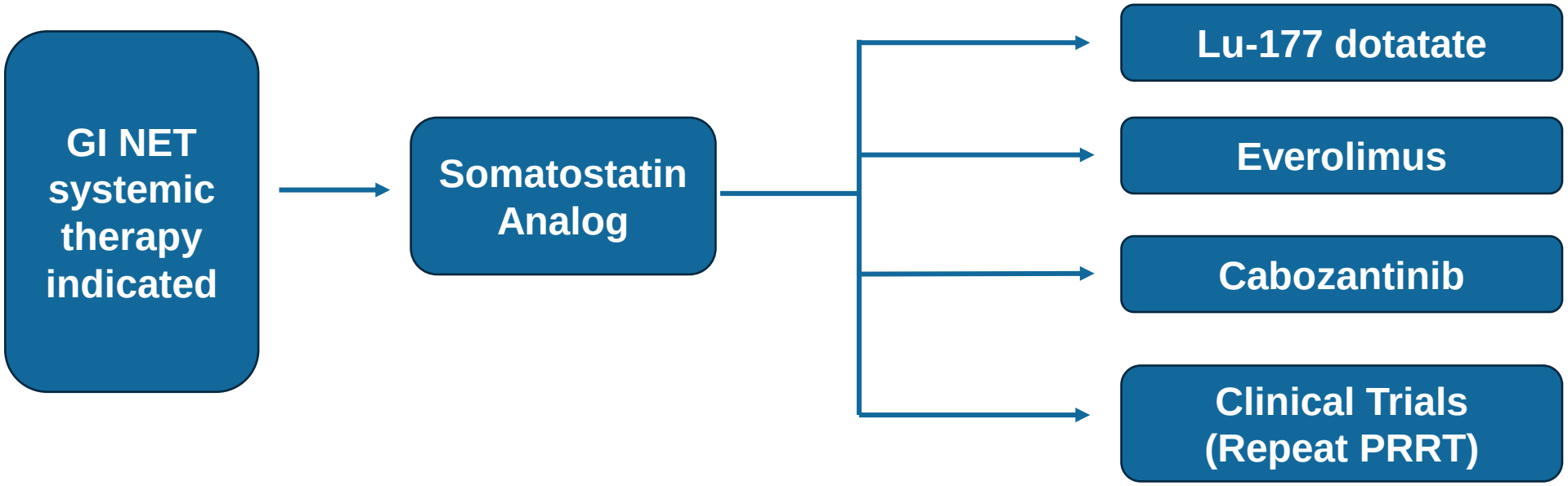




Chauhan et al., NANETS Symposium, 2024

Management of Advanced GI NET

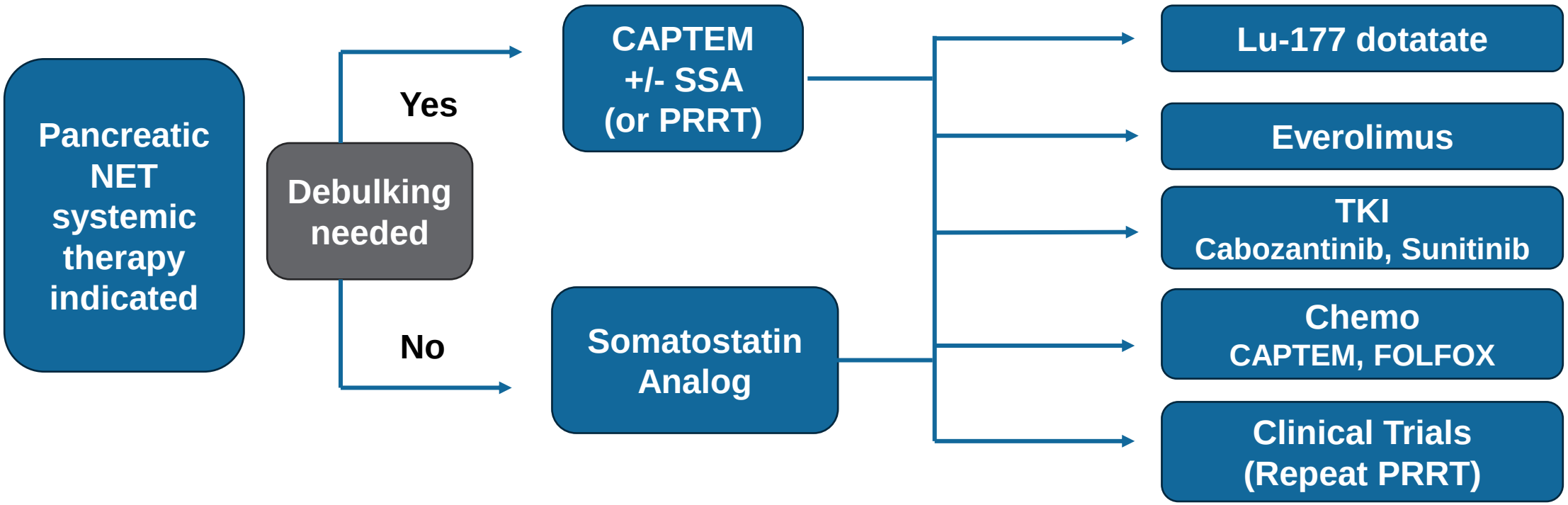
- Multidisciplinary evaluation
- Consider whether surgical resection is indicated (palliation of symptoms, cytoreduction)
- Consider whether regional therapy (hepatic artery embolization, ablation, RT) is indicated



- In select cases (high disease burden, high G2/G3 NET), it may be appropriate to use alternative front-line systemic therapy prior to or concurrently with SSA
- Chemo (CAPTEM or FOLFOX) not typically used, except if G3 or aggressive disease

Management of Advanced Pancreatic NET

- Multidisciplinary evaluation
- Consider whether surgical resection is indicated (palliation of symptoms, cytoreduction)
- Consider whether regional therapy (hepatic artery embolization, ablation, RT) is indicated



* In select cases (high disease burden, high G2/G3 NET), it may be appropriate to use alternative front-line systemic therapy prior to or concurrently with SSA

Somatostatin Analogs Improve PFS in GI and Pancreatic NET

	PROMID[1]	CLARINET[2]
Agent	Octreotide LAR 30 mg IM every 4 weeks (n=42) vs. placebo (n=43)	Lanreotide 120 mg deep sc every 4 weeks (n=101) vs. placebo (n=103)
Patient population	• Midgut NET • Functional and non-functional • Octreotide scan positive in 74% • Mostly Ki 67 < 2%	• GI and pancreatic NET • Non-functional • Positive octreotide scan • Ki 67 < 10%
Primary endpoint	Median TTP 14.3 mo vs. 6.0 mo HR 0.34 (95% CI, 0.20-0.59)	Median PFS not reached vs. 18 mo HR 0.47 (95% CI, 0.30-0.73)
Radiographic response rate	PR 2% vs. 2%	(low)

1. Rinke et al, *JCO*, 2009 2. Caplin et al, *NEJM*, 2014

Lu-177 Dotatate in Midgut NET
NETTER-1 Trial

Key Eligibility:

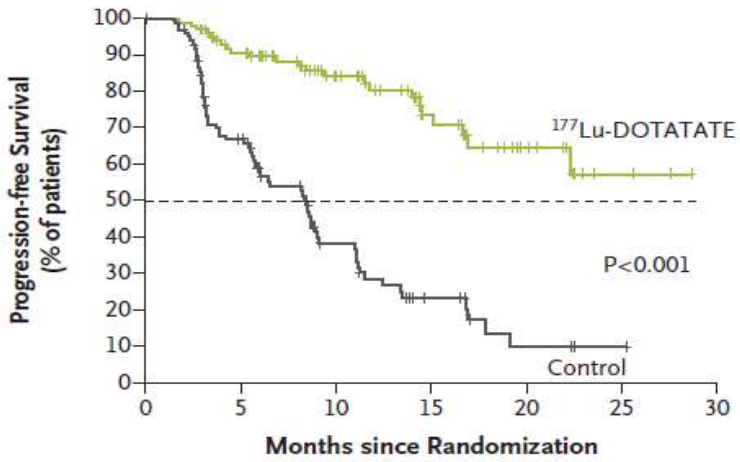
- Progressive SSTR+ advanced midgut NET
- Prior standard dose octreotide
- Low-intermediate grade

177 Lu-Dotatate (200 mCi) q 8 weeks x 4 + Octreotide LAR 30 mg after each treatment, then monthly (n= 115)

Octreotide LAR 60 mg every 4 weeks n=115

Primary Endpoint

Progression-Free Survival



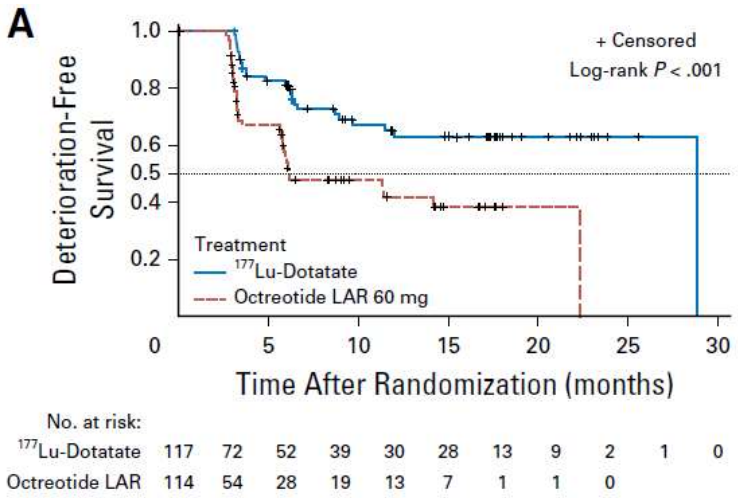
	Lu-177 dotatate	Octreotide LAR 60 mg
Median PFS	Not reached	8.4 mo
HR	0.21 (95% CI, 0.13-0.33)	
CR + PR / SD	18% / 66%	3% / 62%

Strosberg et al, *NEJM* 2017

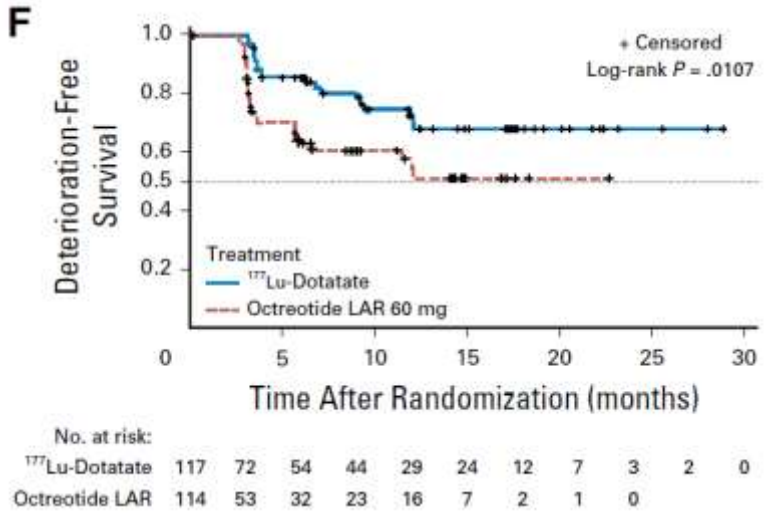
Lu-177 Dotatate Impact on QOL

^{177}Lu-Dotatate demonstrated significant benefit compared to high-dose octreotide in time to deterioration in global health status, physical functioning, role functioning, and symptoms including diarrhea.

Global health status



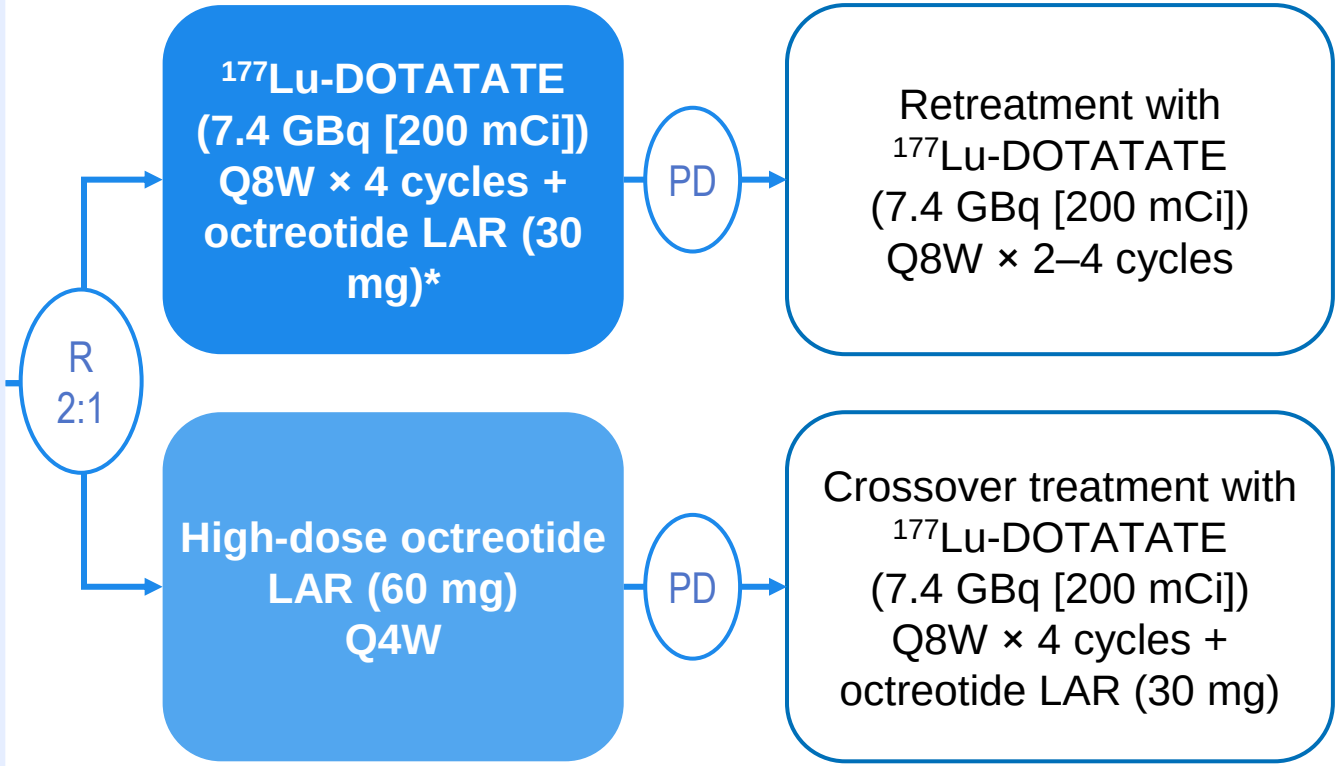
Diarrhea



Strosberg *et al., JCO*, 2018

Lu-177 Dotatate in High G2-G3 GEP- NET NETTER -2 Trial

- Patients ≥15 years (N=226)
- Advanced, well-differentiated, Grade 2 or 3 (Ki67 ≥10% and ≤55%), SSTR+ GEP-NETs
- Diagnosis within last 6 months before enrolment
- No prior PRRT or systemic therapy



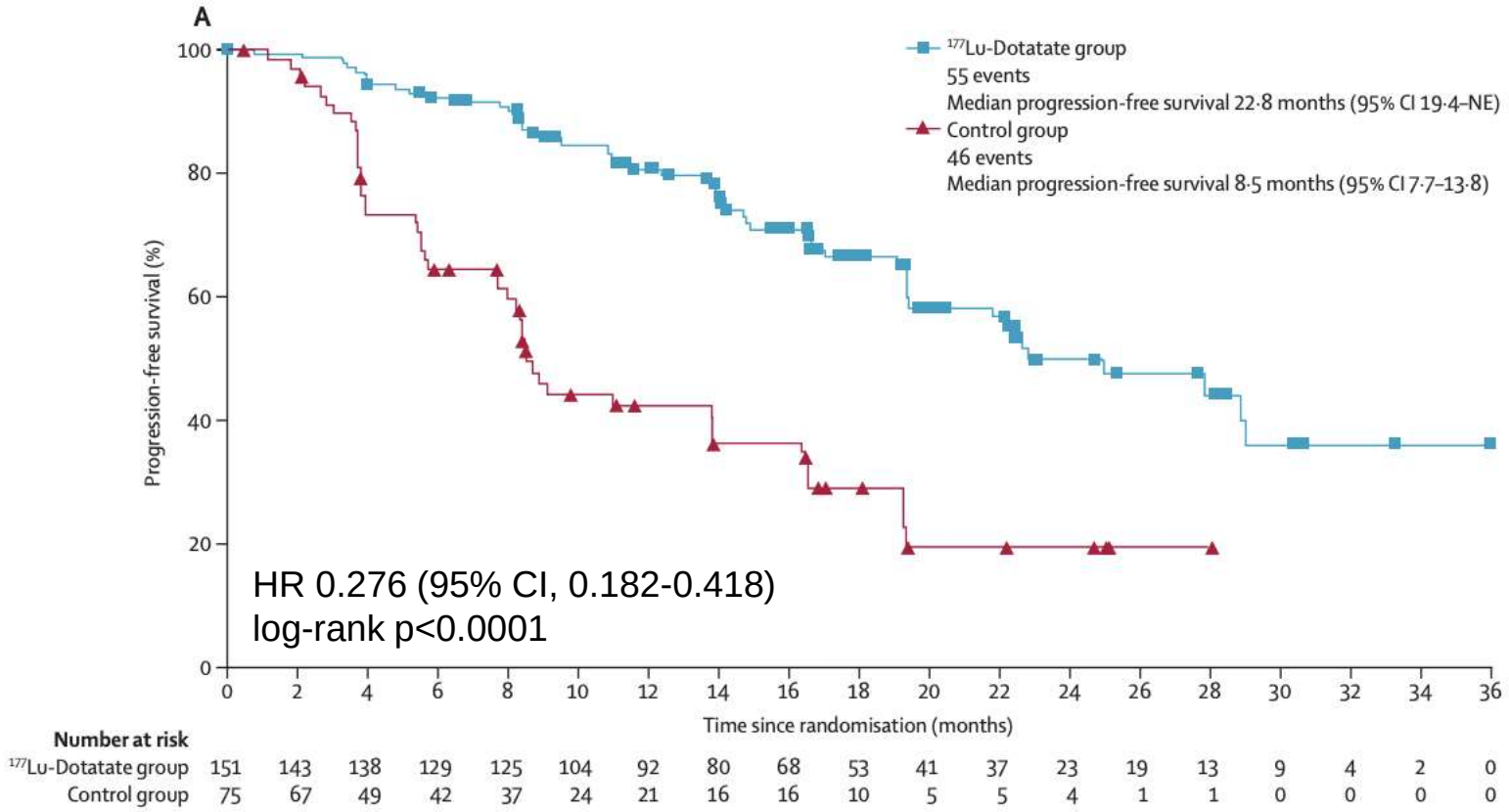
Study Endpoints

Primary: Progression-free Survival

Key Secondary: ORR, QOL

Singh et al. *Lancet.* 2024;403(10446):2807-2817.

Lu-177 Dotatate in High G2-G3 GEP- NET NETTER -2 Trial



Best overall response

	Lu-177 dotatate + octreotide LAR 30 mg (n=151)	High dose octreotide LAR 60 mg (n=75)
CR	8 (5%)	0
PR	57 (38%)	7 (9%)
SD	72 (48%)	42 (56%)
PD	8 (5%)	14 (19%)
Unknown	6 (4%)	11 (15%)

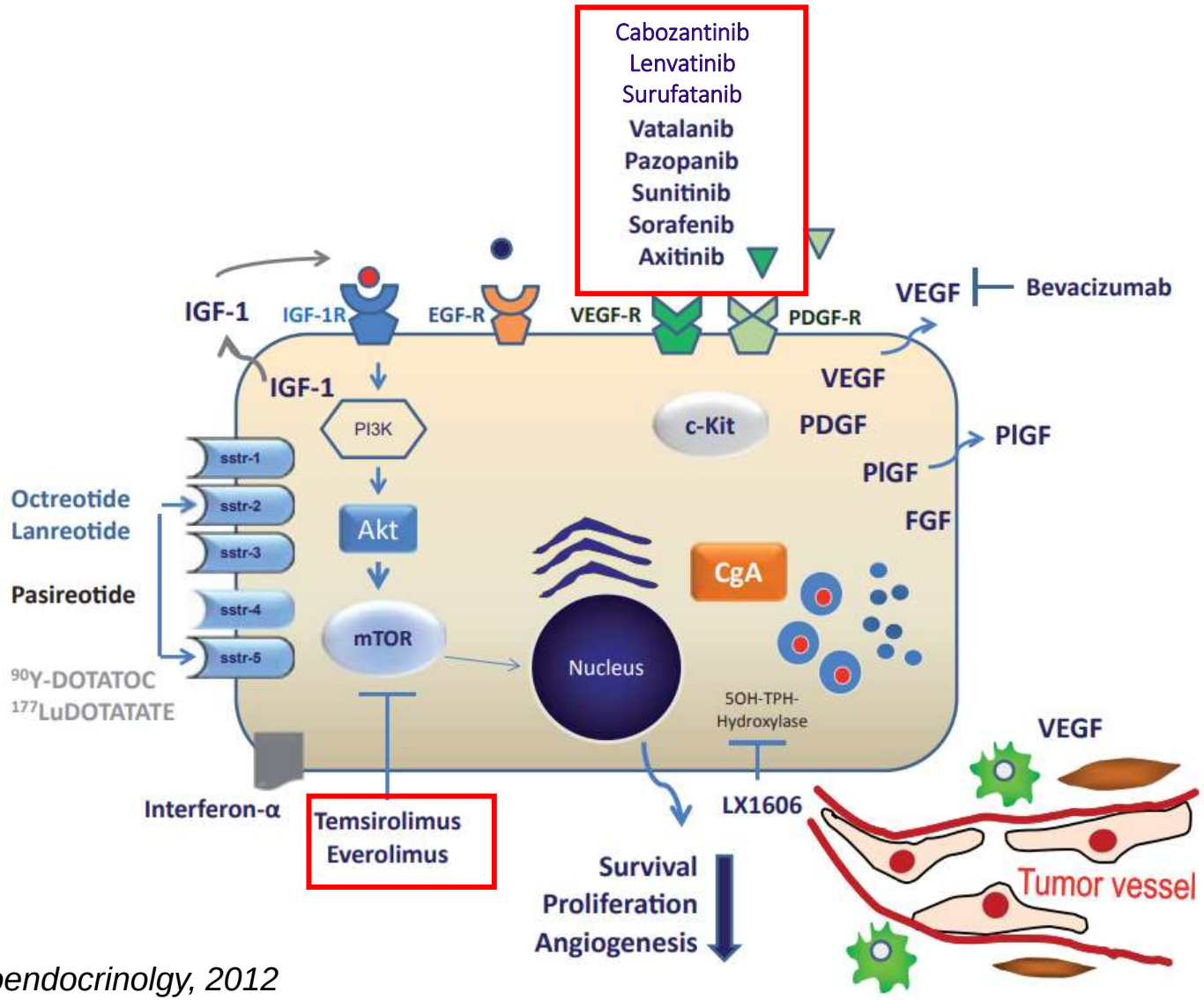
Singh et al. *Lancet.* 2024;403(10446):2807-2817.

NETTER-2: Other Key Results

- PFS benefit for Lu-177 dotatate was observed in pre-specified subgroups including grade and primary tumor site
- Subgroup analyses were presented at 2024 ESMO GI Congress
  - High G2 and G3 Subgroups: Median PFS was 29.0 (vs 13.8) and 22.2 (vs 5.6) months; ORR was 40.4% (vs 10.4%) and 48.1%,(vs 7.4%), respectively
  - Pancreas and Small Intestine Subgroups: Median PFS was 19.4 (vs 8.5) and 29.0 (vs 8.4) months; ORR was 51.2% (vs 12.2%) and 26.7% (vs 4.8%), respectively
- Time to deterioration in QOL was similar in both arms
- Safety findings were consistent with the known profile of Lu-177 dotatate
- Results support use of Lu-177 dotatate earlier in the disease course for some patients with high G2-G3 GEP-NET

Singh et al., Lancet. 2024 Jun 29;403(10446):2807-2817.
Singh et al., ESMO GI Cancers Congress, 2024.

Molecularly Targeted Agents in NET



Modified from
Pavel et al, Neuroendocrinolgy, 2012

Phase III Trials of Everolimus in NET

Trial	Treatment Arms	Disease	PFS (HR, median months)	ORR
RADIANT-2[1] (n=429)	Everolimus + Octreotide vs Placebo + Octreotide	NET with Carcinoid Syndrome	HR 0.77* 16.4 vs 11.3 mo	2% vs 2%
RADIANT-4[2] (n=302)	Everolimus vs Placebo	Nonfunctional GI and lung NET	HR 0.48 11.0 vs 3.9 mo	2% vs 1%
RADIANT-3[3] (n=410)	Everolimus vs Placebo	Panc NET	HR 0.35 11.0 vs 4.6 mo	5% vs 2%
STARTER-NET[4] (n=178)	Everolimus + Lanreotide vs Everolimus	Nonfunctinal GEP-NET (1st line, Grades 1-2)	HR 0.44 29.7 vs. 13.6	23% vs. 8%

* Did not meet primary endpoint

1. Pavel et al., Lancet, 2011. 2. Yao et al., Lancet, 2016. 3. Yao et al., NEJM, 2011. 4. Hijioka et al., ASCO GI Cancers Symposium, 2025.

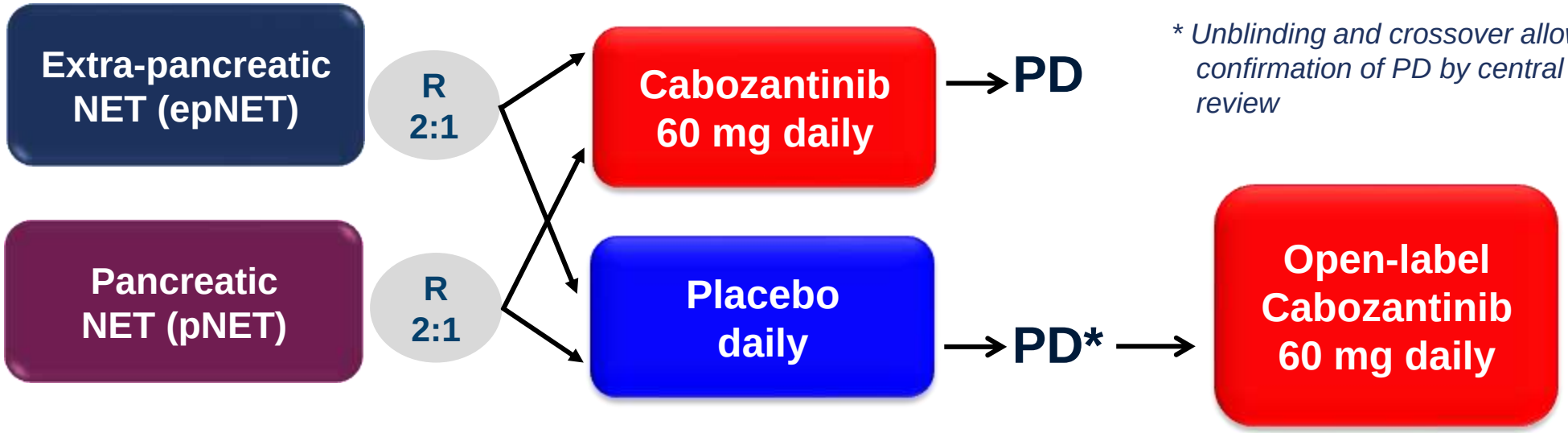
Phase III Trials of TKIs in NET

Trial	Treatment Arms	Disease	PFS (HR, median months)	ORR
AXINET[1] (n=256)	Axitinib + octreotide vs. Placebo + octreotide	Extra-panc NET	HR 0.82* 17.2 vs. 12.3	18% vs 4%
SANET-ep[2] (n=198)	Surufatinib vs Placebo	Extra-panc NET	HR 0.33 9.2 vs 3.8 mo	10% vs 0%
CABINET[3] (n=203)	Cabozantinib vs Placebo	Extra-panc NET	HR 0.38 8.4 vs. 3.9	5% vs 0%
SUN 1111[4] (n=171)	Sunitinib vs Placebo	Panc NET	HR 0.42 11.4 vs 5.5	9% vs. 0%
SANET-p[5] (n=172)	Surufatinib vs Placebo	Panc NET	HR 0.49 10.9 vs 3.7	19% vs 2%
CABINET[3] (n=95)	Cabozantinib vs Placebo	Panc NET	HR 0.23 13.8 vs 4.4	19% vs 0%

* Did not meet primary endpoint

1. Garcia-Carbonero et al, Presented at ASCO GI Cancers Symposium, 2021. 2. Xu et al. Lancet Oncol, 2020.
3. Chan et al., NEJM, 2024. 4. Xu et al. Lancet Oncol, 2020. 5. Raymond et al., NEJM 2011

Cabozantinib in Extra-pancreatic & Pancreatic NET
CABINET Trial



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

Key inclusion criteria:

- Well- to moderately differentiated NET, grades 1-3
- Disease progression by RECIST within 12 months prior to randomization
- Progression or intolerance of at least 1 prior FDA-approved systemic therapy, not including somatostatin analogs (SSA)
  - ➢ Includes everolimus, sunitinib, or Lu-177 dotatate for pNET
  - ➢ Includes everolimus for lung NET
  - ➢ Includes everolimus or Lu-177 dotatate for GI-NET
- Concurrent SSA allowed provided stable dose for ≥ 2 mo

Study Endpoints

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

Chan et al., *NEJM*, 2024. Epub ahead of print

CABINET: Baseline Characteristics

	ep-NET		pNET	
	CABO (N=134)	PBO (N=69)	CABO (N= 64)	PBO (N=31)
Age, years, median (range)	66 (28-86)	66 (30-82)	60 (29-79)	64 (39-79)
Female, n (%)	74 (55)	31 (45)	27 (42)	13 (42)
ECOG PS, n (%)				
0	49 (37)	32 (46)	35 (55)	15 (48)
1	84 (63)	36 (52)	28 (44)	16 (52)
2	1 (1)	1 (1)	1 (2)	0
Primary tumor site, n (%)				
Gastrointestinal	70 (52)	46 (67)	2 (3)	1 (3)
Lung	27 (20)	12 (17)	-	-
Thymus	6 (4)	4 (6)	-	-
Unknown	22 (16)	2 (3)	-	-
Other	5 (4)	2 (3)	-	-
Pancreas*	4 (3)	3 (4)	62 (97)	30 (97)
Grade, n (%)				
G1	37 (28)	15 (22)	14 (22)	7 (22)
G2	86 (64)	48 (70)	39 (61)	19 (61)
G3	8 (6)	5 (7)	8 (12)	3 (10)
Unknown	3 (2)	1 (1)	3 (5)	2 (6)

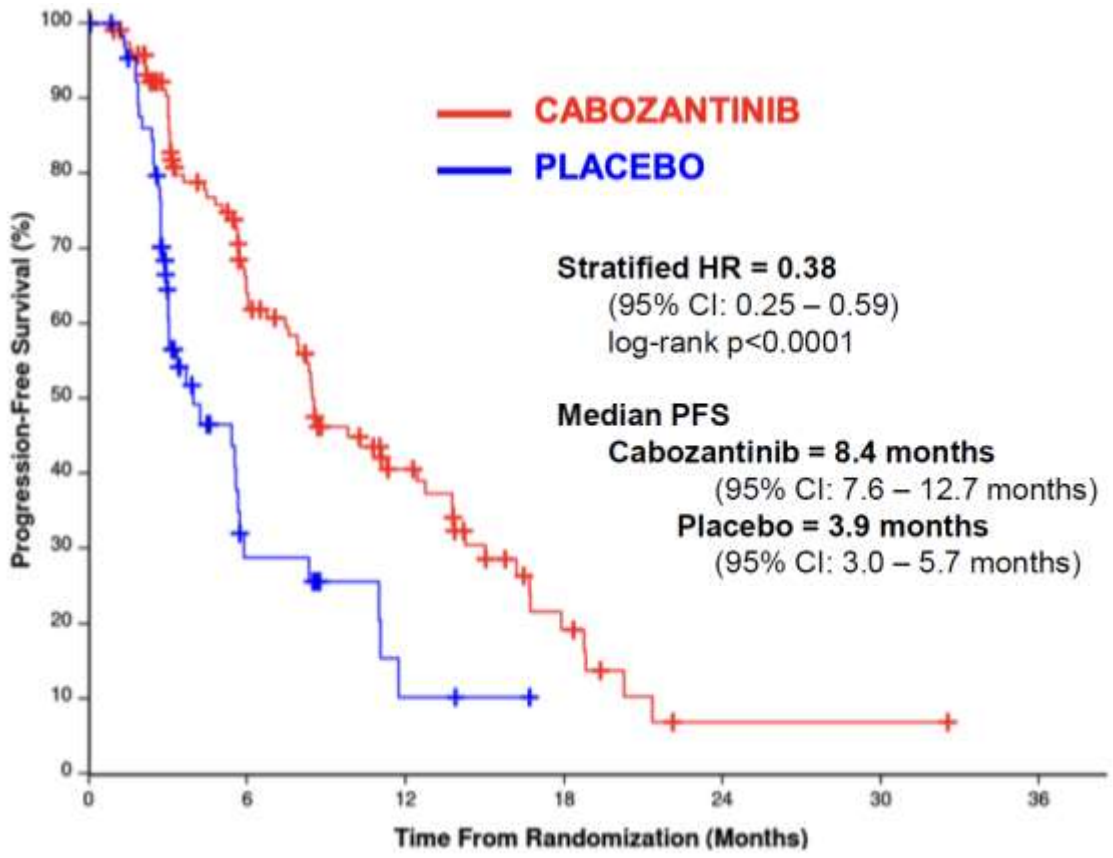
	ep-NET		pNET	
	CABO (N=134)	PBO (N=69)	CABO (N= 64)	PBO (N=31)
Hormone syndrome present, n (%)	41 (31)	25 (36)	11 (17)	5 (16)
Concurrent SSA, n (%)	92 (69)	48 (70)	35 (55)	17 (55)
Prior SSA, n (%)	125 (93)	64 (93)	63 (98)	30 (97)
Number of prior systemic therapies, median (range)	2 (1-6)	2 (1-6)	3 (1-9)	2 (1-7)
Prior systemic therapy, n (%)				
Lu-177 dotatate	80 (60)	41 (59)	38 (59)	18 (58)
Everolimus	96 (72)	44 (64)	51 (80)	25 (81)
Sunitinib	-	-	18 (28)	7 (22)
Temozolomide +/- capecitabine	43 (32)	20 (29)	43 (67)	16 (52)
Platinum + etoposide	11 (8)	8 (12)	-	-

Chan et al., *NEJM*, 2024. Epub ahead of print

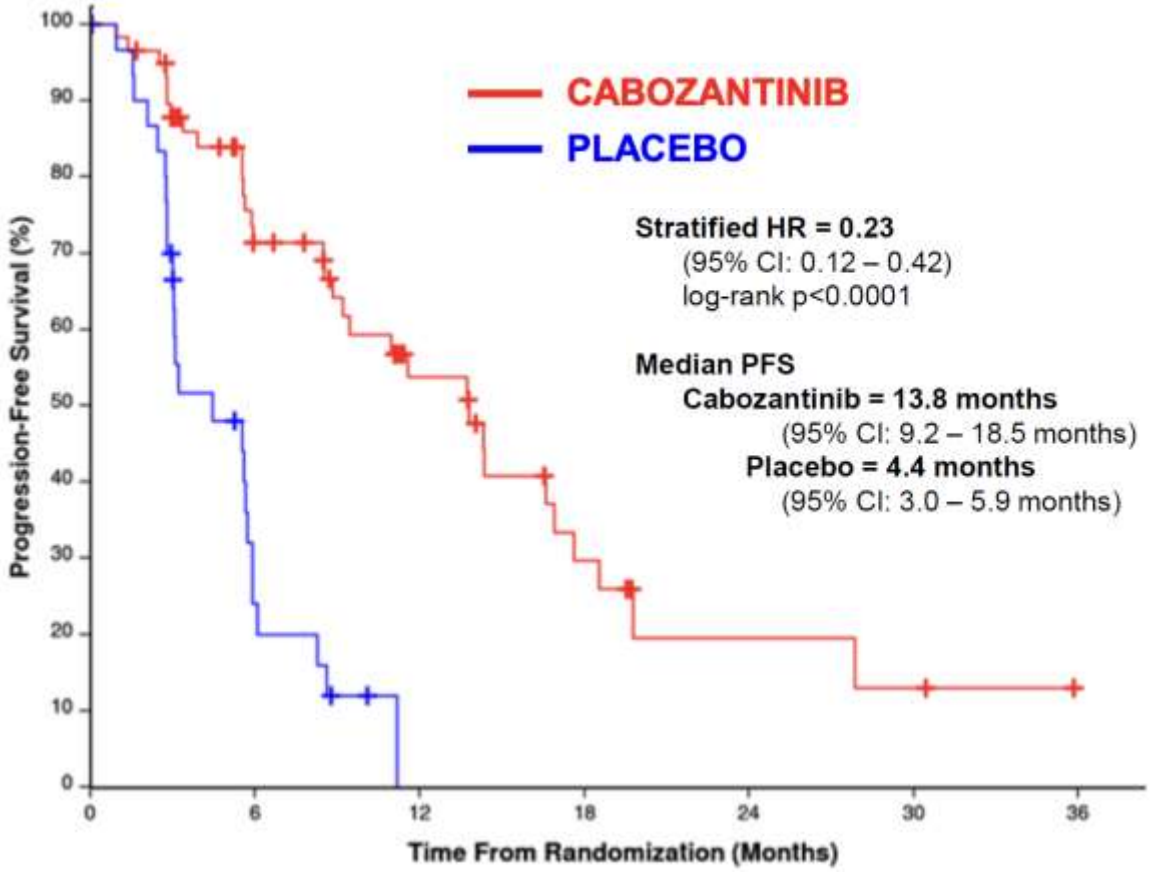
CABINET: Progression-Free Survival

Blinded Independent Central Review

epNET Cohort



pNET Cohort



Chan et al., *NEJM*, 2024. Epub ahead of print

CABINET – Other Key Results & Conclusions

- Subgroup analyses of PFS suggest benefits for cabozantinib across all clinical subgroups, including primary tumor site, grade, and prior anticancer therapy
- Confirmed ORR 5% for epNET and 19% for pNET vs 0% for placebo in both cohorts
- Adverse events are consistent with the known safety profile of cabozantinib
  - A majority of patients treated with cabozantinib required dose modifications or reductions to manage adverse events
- Overall Health-Related QoL, as measured by summary score of the EORTC QLQ-C30, remained stable over time and similar in both arms among those completing questionnaires
- Cabozantinib is an effective treatment option for patients with previously treated extra-pancreatic or pancreatic NET

Chan et al., *NEJM*, 2024. Epub ahead of print

Capecitabine and Temozolomide in Panc NET ECOG 2211 Trial

Key Eligibility:

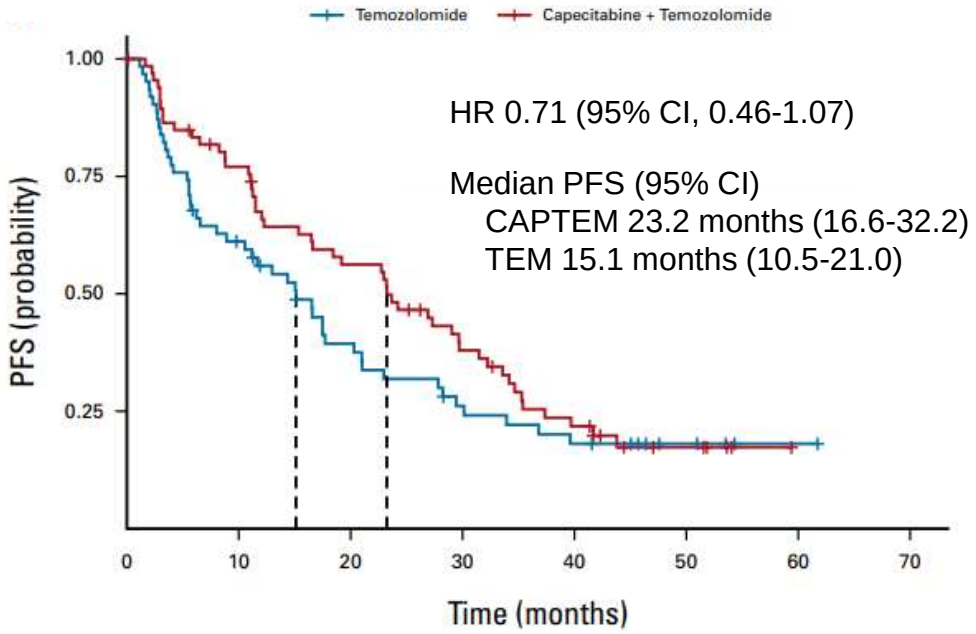
- **Well- Differentiated Pancreatic NET , G1-2**
- **Disease progression in prior 12 mo.**

Temozolomide 200 mg/m² po QD days 1-5
28 day cycle

Capecitabine 750 mg/m2 po BID days 1-14
Temozolomide 200 mg/m2 QD days 10-14
28 day cycle

Primary Endpoint

Progression-Free Survival



HR 0.71 (95% CI, 0.46-1.07)

Median PFS (95% CI)
CAPTEM 23.2 months (16.6-32.2)
TEM 15.1 months (10.5-21.0)

Response Category	Temozolomide (n = 65)	Temozolomide + Capecitabine (n = 68)	P[a]
CR	1 (1.5)	1 (1.5)	
PR	21 (32.3)	26 (38.2)	
Stable disease	26 (40.0)	30 (44.1)	
Progressive disease	12 (18.5)	9 (13.2)	
Unevaluable	5 (7.7)	2 (2.9)	
Response rate (CR + PR)	22 (33.8)	27 (39.7)	.59
Disease control rate (CR + PR + SD)	48 (73.8)	57 (83.8)	.20
Response duration (median)	12.6 months	16.6 months	.59

Kunz et al. *JCO*, 2022

Options for Tumor Control in Advanced NET

	Somatostatin Analogs	Targeted therapy	Peptide Receptor Radionuclide Therapy	Cytotoxic chemotherapy
Agents	**Octreotide Lanreotide**	**Everolimus TKIs: Cabozantinib, Sunitinib**	**Lu-177 dotatate**	**Alkylating agents (temozolomide- and streptozocin- based regimens)**
Primary tumor location	GI and pNET (SSTR+)	pNET (everolimus, cabozantinib, sunitinib) epNET (everolimus, cabozantinib)	GI and pNET (SSTR+)	pNET Lung NET
Treatment outcome	Stable disease	Stable disease	Moderate response	Moderate response
Side effects	Well tolerated Hyperglycemia, cholelithiasis, diarrhea, bloating, pancreatic exocrine insufficiency	Everolimus: hyperglycemia, stomatitis, edema, pneumonitis TKIs: hypertension, diarrhea, fatigue, stomatitis, PPE, transaminitis, thyroid dysfunction	Fatigue, diarrhea, nausea, thrombocytopenia, risk of MDS, leukemia Potential impact on tumor biology	Nausea, fatigue, vomiting, constipation, diarrhea, neutropenia, thrombocytopenia Potential impact on tumor biology

Choice of therapy with depend on goals of treatment and patient and tumor characteristics

- Individualize treatment decisions for each patient depending on comorbidities, treatment side-effects, preferences, features of disease (SSTR expression, disease burden and location, grade)
- Consider appropriate timing of therapy
- Multidisciplinary input is critical

Clinical situation	Treatment choices
If cytoreduction is needed (bulky disease, symptoms)	Liver-directed therapy CAPTEM Lu-177 dotatate
If disease is predominantly in the liver	Can consider liver-directed therapy
Progressive disease	Somatostatin analogs Everolimus Cabozantinib Sunitinib Plus options listed above

Recently Completed and Ongoing Trials in Advanced GEP-NET

Trial	Design	Population	Agents	Trial ID
OCCLURANDOM *Gustave Roussy*	Ph II	Panc NET G1-2, SSTR+	^{177}Lu-dotatate vs. sunitinib	NCT02230176
COMPETE *ITM*	Ph III	GEP-NET G1-2, SSTR+	^{177}Lu-edotreotide vs. everolimus	NCT03049189
COMPOSE *ITM*	Ph III	GEP-NET G2-3, SSTR+ 1st or 2nd line	^{177}Lu-edotreotide vs. SOC (CAPTEM or FOLFOX or everolimus)	NCT04919226
COMPARE NET *NCI*	Ph II	Panc NET G1-3, SSTR+	^{177}Lu-dotatate vs. CAPTEM	NCT05247905
ACTION-1 *RayzeBio*	Ph Ib/III	GEP-NET G1-2, SSTR+ Progression after prior ^{177}Lu-PRRT	^{225}Ac-dotatate vs. SOC (everolimus, sunitinib, high-dose SSA)	NCT05477576
NET RETREAT *NCI*	Ph II	Midgut NET G1-2, SSTR+ Progression after prior ^{177}Lu-dotatate	^{177}Lu-dotatate vs. everolimus	NCT05773274

Recently Completed and Ongoing Trials in Advanced GEP-NET

Trial	Design	Population	Agents	Trial ID
OCCLURANDOM *Gustave Roussy*	Ph II	Panc NET G1-2, SSTR+	^{177}Lu-dotatate vs. sunitinib	NCT02230176
COMPETE* *ITM*	Ph III	GEP-NET G1-2, SSTR+	^{177}Lu-edotreotide vs. everolimus	NCT03049189
NCI		G1-3, SSTR+		
ACTION-1 *RayzeBio*	Ph Ib/III	GEP-NET G1-2, SSTR+ Progression after prior ^{177}Lu-PRRT	^{225}Ac-dotatate vs. SOC (everolimus, sunitinib, high-dose SSA)	NCT05477576
NET RETREAT *NCI*	Ph II	Midgut NET G1-2, SSTR+ Progression after prior ^{177}Lu-dotatate	^{177}Lu-dotatate vs. everolimus	NCT05773274

* **ITM Press release 1/28/2025: COMPETE trial met its primary endpoint, demonstrating clinically relevant and statistically significant benefit in Progression-Free Survival (PFS) compared to everolimus**

Conclusions

- Multiple systemic therapy options exist to treat advanced NET including somatostatin analogs, targeted agents, chemotherapy, PRRT
- Patient, disease characteristics, and treatment goals should influence treatment choice. Multidisciplinary approach to care is critical
- Treatment options for patients with advanced NET are expanding
- Future studies to identify efficacy of novel agents, predictors of treatment response, and optimal sequencing are needed