Recent Clinical Trials and Implications for Therapy of Neuroendocrine Tumors

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Metastatic Neuroendocrine Tumors: What are the Treatment Options?

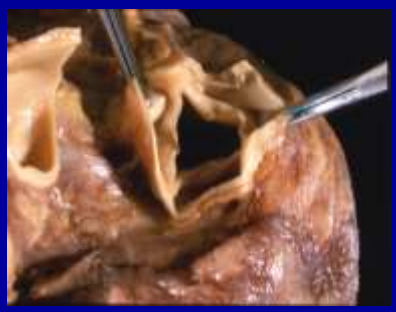
- Somatostatin analogs
- Treatment of Liver Metastases
- Cytotoxic Chemotherapy
- "Targeted" Therapies

Carcinoid Syndrome

- Caused by secretion of serotonin and other neuropeptides into systemic circulation
- Manifested by episodic flushing, diarrhea, and eventual right sided valvular heart disease
- Treated with somatostatin analogs

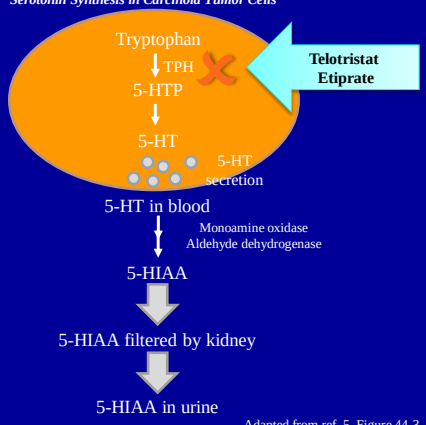
Flushing associated with carcinoid syndrome

Carcinoid Heart Disease: Tricuspid valve is fibrotic and leaflets retracted



Telotristat Etiprate
A Tryptophan Hydroxylase (TPH) Inhibitor

Serotonin Synthesis in Carcinoid Tumor Cells



Adapted from ref. 5, Figure 44-3

- Telotristat etiprate is a novel oral inhibitor of TPH, the rate-limiting enzyme in serotonin biosynthesis[1]
- Two early-stage clinical studies demonstrated the safety and evidence of clinical activity in carcinoid syndrome[2,3]
- Both preclinical and clinical studies suggested that telotristat etiprate is associated with minimal CNS activity[1-3]
- Granted Fast Track Status and Orphan Drug Designation[4]

5-HIAA, 5-hydroxyindoleacetic acid; **5-HT**, serotonin; **5-HTP**, hydroxytryptophan; **CNS**, central nervous system; **TPH**, tryptophan hydroxylase.

1.Liu Q, Yang Q, Sun W, *et al. J Pharmacol Exp Ther* 2008; 325:47–55. 2. Kulke MH, O'Dorisio T, Phan A, *et al. Endocr Relat Cancer* 2014;21:705–714. 3. Pavel M, Horsch D, Caplin M, *et al. J Clin Endocrinol Metab* 2015;100:1511–1519. 4. FDA Orphan Drug Designations. Available at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index. Accessed September 2015. 5. Kronenberg HM, Melmed S, Polonsky KS, *et al. Williams Textbook of Endocrinology*, 11th edn. 2008:1823–1824.

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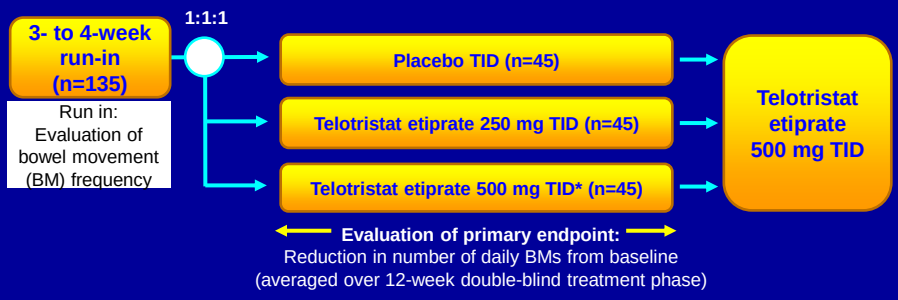
TELESTAR
Phase 3 Study Design

*Kulke et al, presented at ECCO/ESMO, 2015



All patients required to be on SSA at enrollment and continue SSA therapy throughout study period

*Including a blinded titration step of one week of 250 mg TID.
BM, bowel movement; **SSA**, somatostatin analog; **TID**, three times daily.
ClinicalTrials.gov. NCT01677910 TELESTAR. Available at: https://clinicaltrials.gov/ct2/show/NCT01677910. Accessed September 2015.

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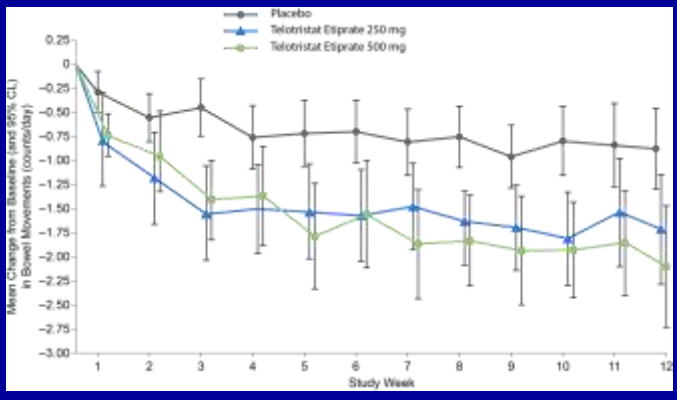
TELESTAR: Reduction in Daily Bowel Movement Frequency Averaged Over Double-Blind Treatment Phase



- Hodges–Lehmann estimator of treatment differences showed a median reduction versus placebo of
  - –0.81 BMs daily for telotristat etiprate 250 mg dose (*P*<0.001)
  - –0.69 for telotristat etiprate 500 mg dose (*P*<0.001)

BM, bowel movement.

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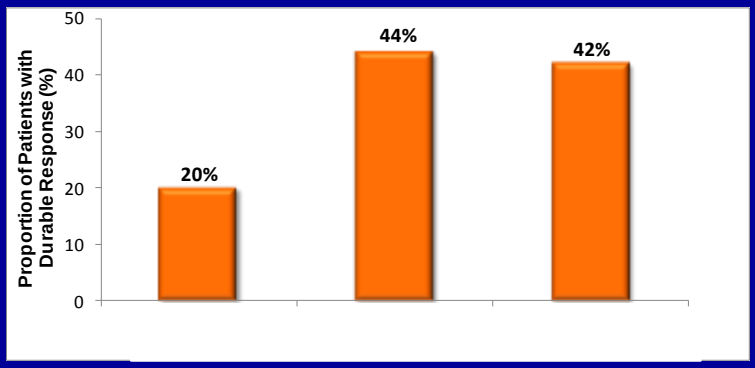
TELESTAR
Proportion of Patients with Durable Response



	Placebo (n=45)	Telotristat etiprate 250 mg (n=45)	Telotristat etiprate 500 mg (n=45)
Odds ratio, telotristat etiprate to placebo (95% CI)	–	3.49 (1.33–9.16)	3.11 (1.20–8.10)
P value		0.011	0.020

All patients continue SSA therapy throughout study period.

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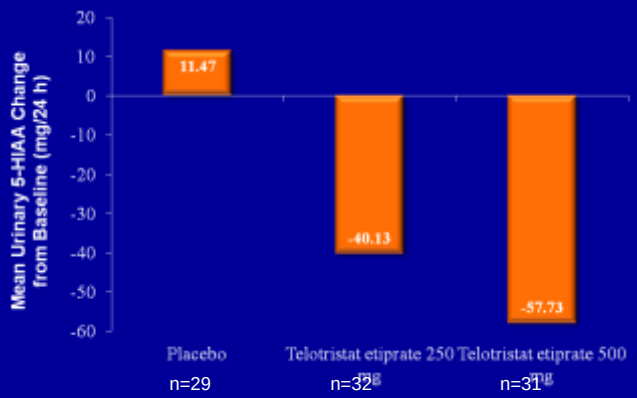
TELESTAR: Mean Absolute Change in Urinary 5-HIAA (mg/24 h) from Baseline to Week 12



All patients continue SSA therapy throughout study period. Data include only patients for whom both baseline and Week 12 assessments were available.

- Wilcoxon rank-sum test showed significant differences for each telotristat etiprate dose vs. placebo ($p<0.001$)
- Baseline 5-HIAA levels across treatment arms ranged from 80.96-92.65 mg/24 h

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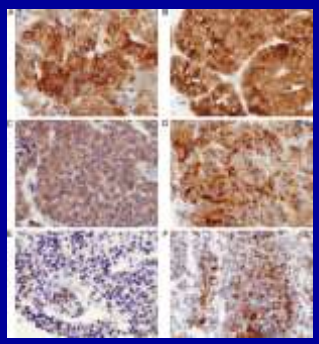
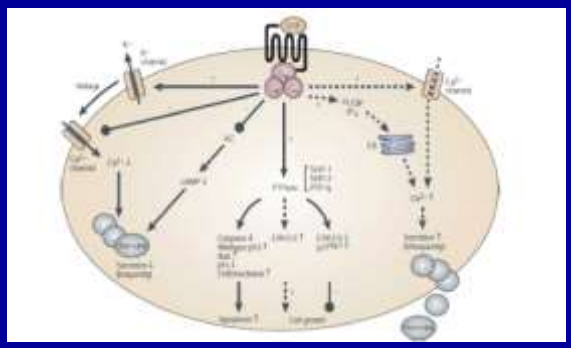
Somatostatin Receptors in Neuroendocrine Tumors



Expression of SSTR 1, 2A, 2B, 3, 4 and 5 in Pulmonary NET

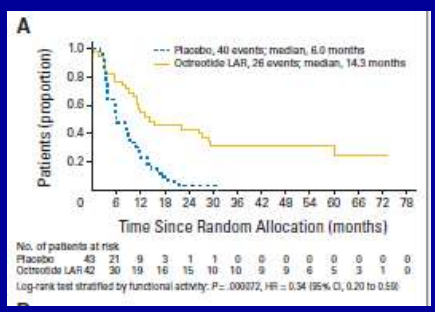
(Tsuta et al, Path Res Pract 2012; 208: 470-4)



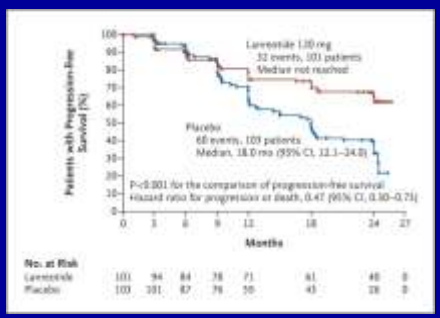
Somatostatin receptor signaling pathways

(Colao et al, Endocrine Rev 2011; 32: 247-71)

Octreotide and Lanreotide for the Treatment of Advanced NET

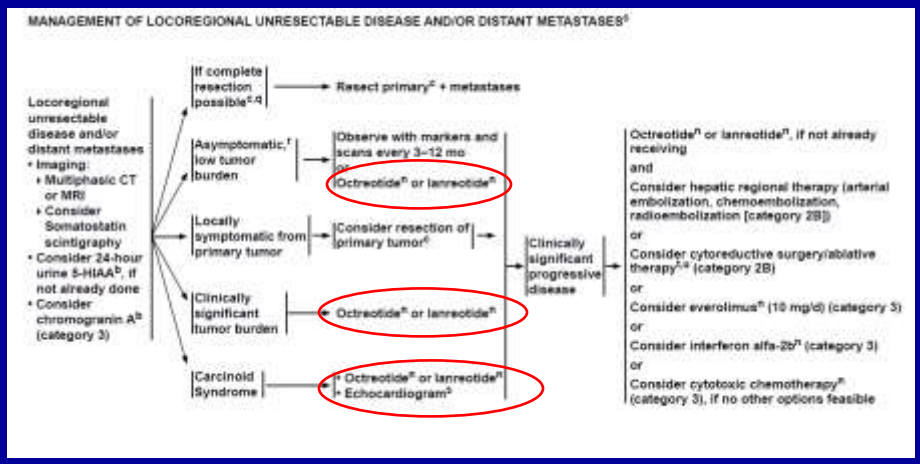


PROMID: Rinke A et al, J Clin Oncol 2009; 27: 4656-63

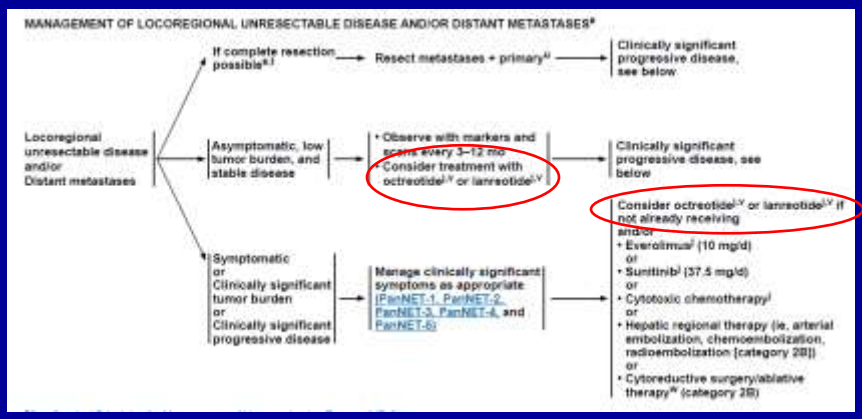


CLARINET: Caplin ME et al. N Engl J Med 2014;371:224-233.

2015 NCCN Guidelines: Role of SSAs in Advanced Carcinoid Tumor



2015 NCCN Guidelines: Role of SSAs in Advanced Pancreatic NET



Streptozocin-based Therapy for Pancreatic NET

- Streptozocin approved for pancreatic NET in 1982
- Streptozocin/doxorubicin associated with survival benefit compared to streptozocin/5-FU (2.2 vs. 1.5 years)
- Response rates 30-40% in retrospective series

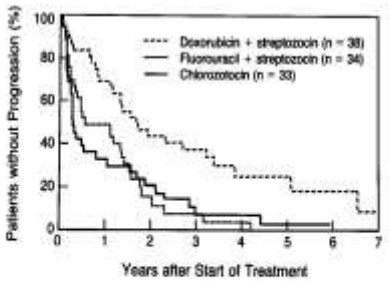


Figure 2. Length of Time to Disease Progression, According to Treatment Group.

P<0.001 for the comparison between doxorubicin plus streptozocin and fluorouracil plus streptozocin; P<0.001 for the comparison between doxorubicin plus streptozocin and chlorozotocin.

CG Moertel et al, N Engl J Med 1992; 326: 519-23

Kouvaraki et al, J Clin Oncol 2004; 22: 4762-71

Temozolomide-Based Therapy in Pancreatic NET

	Regimen	N	Response Rate
Retrospective Series			
	Tem (single agent)	12	8%
	Tem/capecitabine	30	70%
	Tem (various)	53	34%
Prospective Trials			
	Tem/Thalidomide	11	45%
	Tem/Everolimus	40	40%
	Tem/Bevacizumab	15	33%
	Tem/Bevacizumab	15	64%

1. Ekeblad et al, Clin Cancer Res 2007; 2986-91 2. Strosberg et al Cancer 2011; 117: 268-75 3. Kulke et al, Clin Cancer Res 2009; 15: 338-45 4. Kulke et al, J Clin Onco l2006; 24: 401-6 5. Kulke et al J Clin Oncol 2006; 24(18S) A4044; 6. Chan et al, Cancer 2013; 119: 3212-18. 7. Koumarianou et al, Endoc Rel Cancer 2012; 19: L1-4.

E2211: A Randomized Study of Temozolomide or Temozolomide+Capecitabine in Patients with Advanced, Metastatic Pancreatic Neuroendocrine Tumors

PI: Pam Kunz, Activated

Advanced pNET; prior treatments allowed (no prior temozolomide)

RANDOMIZE

Arm 1: **Temozolomide 200 mg/m2/day d1-5**

28 day cycle; N=69

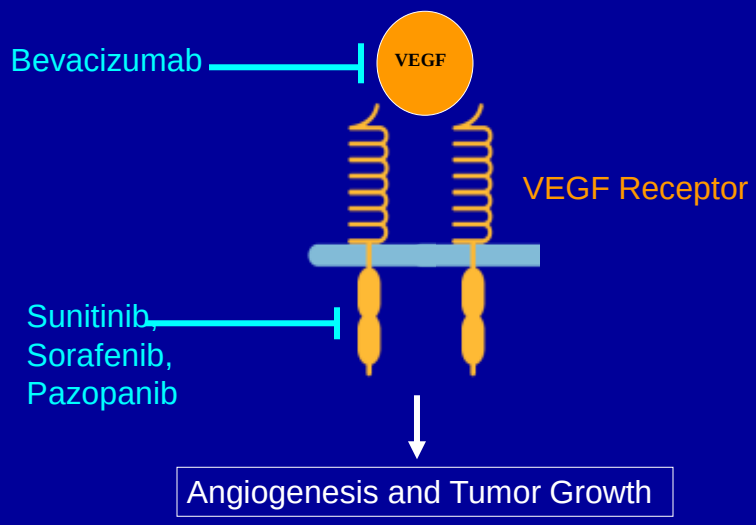
Arm 2: **Capecitabine 750 mg/m2 BID d 1-14**
Temozolomide 200 mg/m2 d 10-14

28 day cycle; N=69

Primary Endpoint: PFS

Correlates: MGMT IHC, promoter methylation

Targeting the VEGF Pathway in Neuroendocrine Tumors



Phase III, Randomized, Double-Blind Study of Sunitinib vs. Placebo in Patients with Advanced, Progressive, Well-Differentiated Pancreatic Neuroendocrine Tumors

Key Eligibility criteria

- Well-differentiated, malignant pancreatic endocrine tumor
- Disease progression in past 12 months

N=340 (planned)
N=171 (enrolled)

RANDOMIZATION

1:1

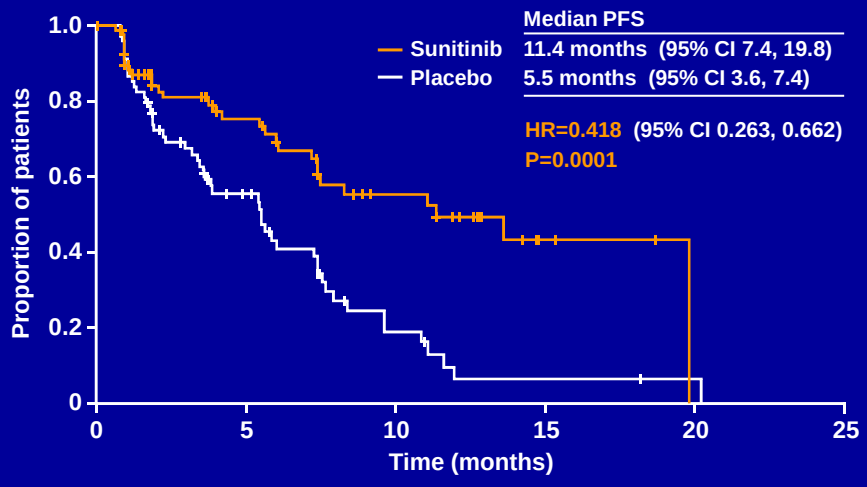
Arm A
Sunitinib 37.5 mg/day orally, continuous daily dosing (CDD)*

Arm B
Placebo*

Primary endpoint: PFS

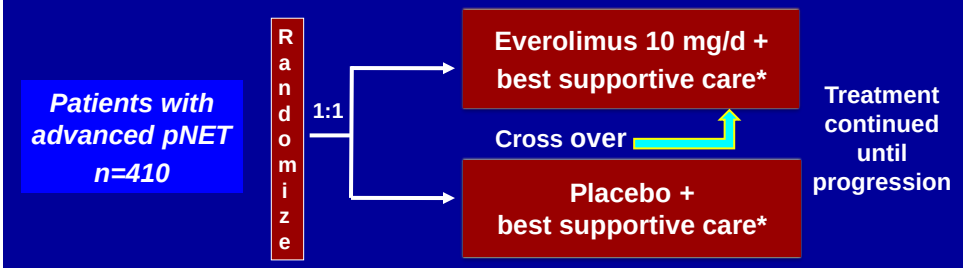
After trial closure patients became candidates for open-label sunitinib in trial NCT00443534 or NCT00428220

Sunitinib in Pancreatic NET: Investigator-Assessed Progression-Free Survival



Raymond et al, N Engl J Med 2011; 364: 501-13

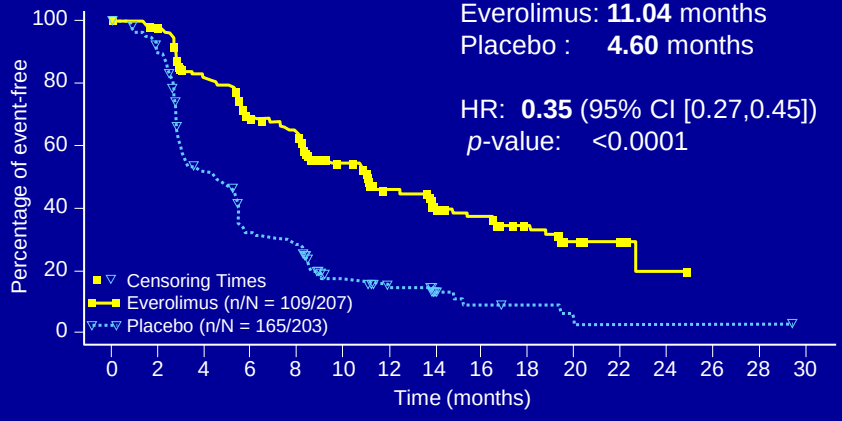
RADIANT-3: Everolimus vs. Placebo in Advanced Pancreatic NET



Randomization Aug. 2007 – May. 2009

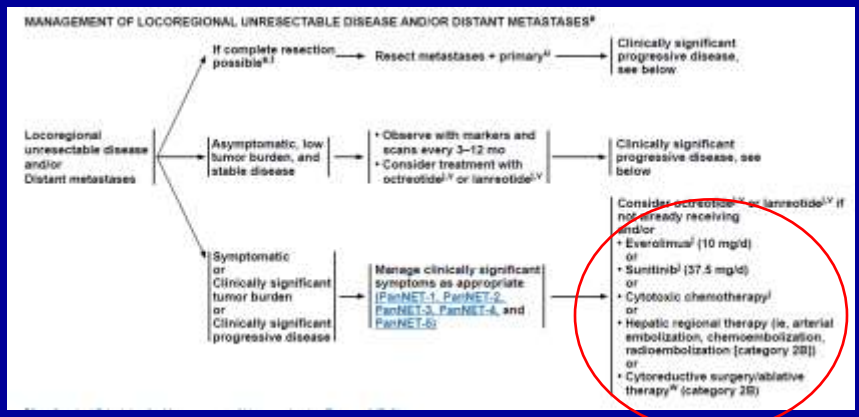
*concurrent somatostatin analogs allowed

RADIANT 3: Investigator-Assessed Progression-Free Survival



Yao et al, N Engl J Med 2011; 364: 514-23

2015 NCCN Guidelines: Systemic Options for Pancreatic NET



Streptozocin/5FU vs Doxorubicin/5FU in Advanced Carcinoid (E 1281)

249 Patients

Streptozocin/ 5FU

Doxorubicin/ 5FU

PFS: 5.3 mos

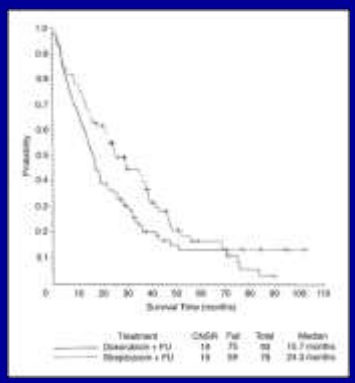
Response Rate: 16%

Renal Toxicity: 34.5%

PFS: 4.5 mos

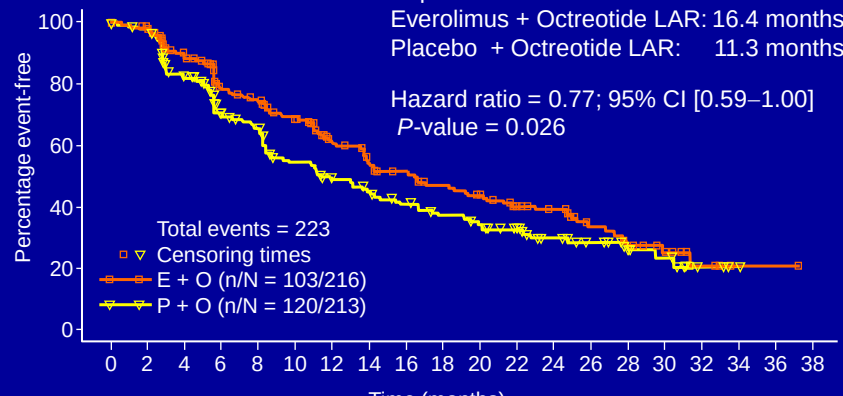
Response Rate: 15.9%

Overall Survival Probability



Sun et al, J Clin Oncol 2005; 23: 4897-4904

RADIANT 2: PFS by Central Review*



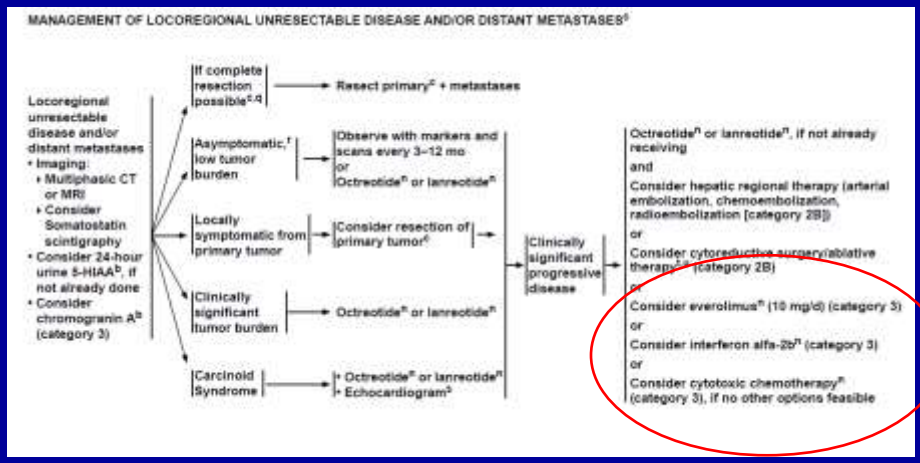
No. of patients still at risk

E + O	216	202	167	129	120	102	81	69	63	56	50	42	33	22	17	11	4	1	1	0
P + O	213	202	155	117	106	84	72	65	57	50	42	35	24	18	11	9	3	1	0	0

* Independent adjudicated central review committee
- *P*-value is obtained from the one-sided log rank test
- Hazard ratio is obtained from unadjusted Cox model

E + O = Everolimus + Octreotide LAR
P + O = Placebo + Octreotide LAR

2015 NCCN Guidelines: Systemic Options for Advanced Carcinoid Tumor



RADIANT-4 Study Design

* Yao et al, presented at ECCO/ESMO, 2015

Patients with well-differentiated (G1/G2), advanced, progressive, nonfunctional NET of lung or GI origin (N=302)

- Absence of active or any history of carcinoid syndrome
- Pathologically confirmed advanced disease
- Radiologic disease progression in ≤ 6 months

RANDOMIZE 2:1

Everolimus 10 mg/day N=205

Placebo N=97

Treated until PD, intolerable AE, or consent withdrawal

Endpoints:

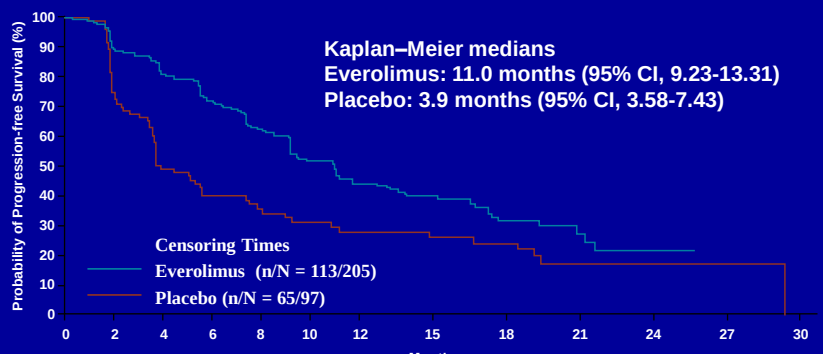
- Primary: PFS (central)
- Key Secondary: OS
- Secondary: ORR, DCR, safety, HRQoL (FACT-G), WHO PS, NSE/CgA, PK

Stratified by:

- Prior SSA treatment (yes vs. no)
- Tumor origin (stratum A vs. B)*
- WHO PS (0 vs. 1)

*Based on prognostic level, grouped as: Stratum A (better prognosis) – appendix, caecum, jejunum, ileum, duodenum, and NET of unknown primary. Stratum B (worst prognosis) – lung, stomach, rectum, and colon except caecum.
Crossover to open-label everolimus after progression in the placebo arm was not allowed prior to the primary analysis.

RADIANT 4: PFS by Central Review

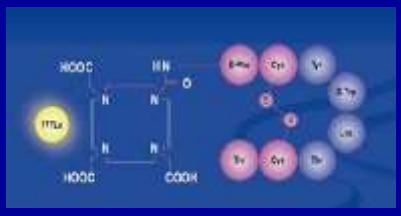


No.of patients still at risk

Everolimus	205	168	145	124	101	81	65	52	26	10	3	0	0
Placebo	97	65	39	30	24	21	17	15	11	6	5	1	0

P-value is obtained from the stratified one-sided log-rank test; Hazard ratio is obtained from stratified Cox model.
CI, confidence interval; HR, hazard ratio.

Peptide Receptor Radionuclide Therapy (PRRT)



From: Oberg, Theranostics 2012; 2: 448-58

NETTER-1: Phase III Study of ^{177}Lu-DOTA,Tyr^3-Octreotate vs. Octreotide LAR in Patients with Inoperable, Progressive, Somatostatin Receptor Positive Midgut Carcinoid Tumors

*Presented at ECCO/ESMO 2015

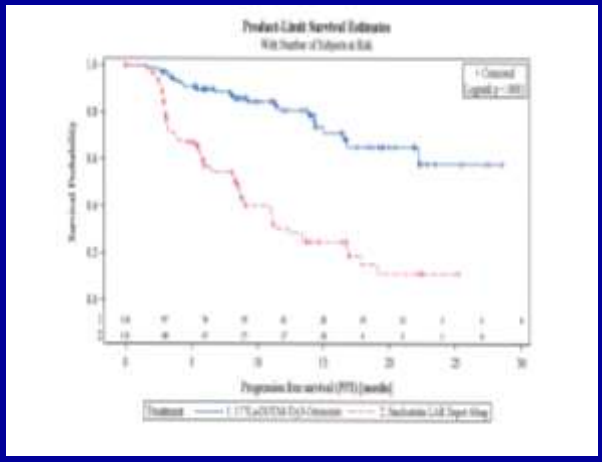
200 Patients with Midgut Carcinoid

- ^{177}Lu-DOTA-Tyr^3-Octreotate: 4 administrations of 200 mCI every 8-16 weeks
- High-dose Octreotide LAR: 60 mg IM every 4 weeks

Primary endpoint: Progression-Free Survival

Secondary endpoints: Response rate, TTP, Overall Survival

NETTER-1: Progression-Free Survival



Median PFS 8.4 mos vs. not reached (P<0.0001)

S0518: Study design

Study population
Advanced G1/2 NET with poor prognosis
- Progressive disease
- Refractory syndrome
- G2 with 6+ lesion
- Colorectal or gastric primary

RANDOMIZE

1:1

Bevacizumab 15 mg/kg q21 d
octreotide LAR 20 mg q21 d

Interferon α-2b 5 mu 3 d/wk
octreotide LAR 20 mg q21 d

Treatment until disease progression

Multiphasic CT or MRI performed every 9 wks

Primary endpoint:
- PFS (Central radiology review)

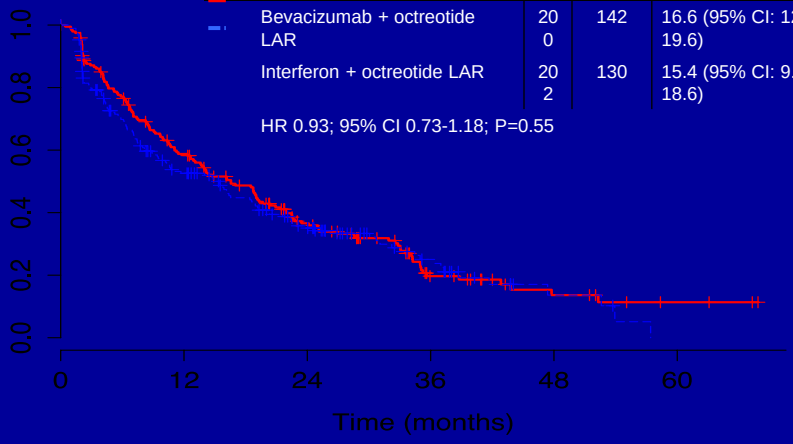
Stratification factors:
- Primary site: Midgut vs others
- RECIST PD since diagnosis
- Histologic grade: G1 vs G2
- Octreotide 2 months prior to registration

Yao et al, ASCO 2015

S0518: PFS by central review

Treatment arm	N	Events	Median PFS (months)
Bevacizumab + octreotide LAR	200	142	16.6 (95% CI: 12.9 – 19.6)
Interferon + octreotide LAR	202	130	15.4 (95% CI: 9.6 – 18.6)

HR 0.93; 95% CI 0.73-1.18; P=0.55



Yao et al, ASCO 2015

Alliance/CALGB 81103: Randomized Phase II Study of Pazopanib or Placebo in Patients with Advanced Carcinoid

PI: Emily Bergsland, Activated

Require:

- PD within 12 mos

Stratify:

- Concurrent octreotide
- PS

RANDOMIZE

Arm 1: Pazopanib 800 mg po qd

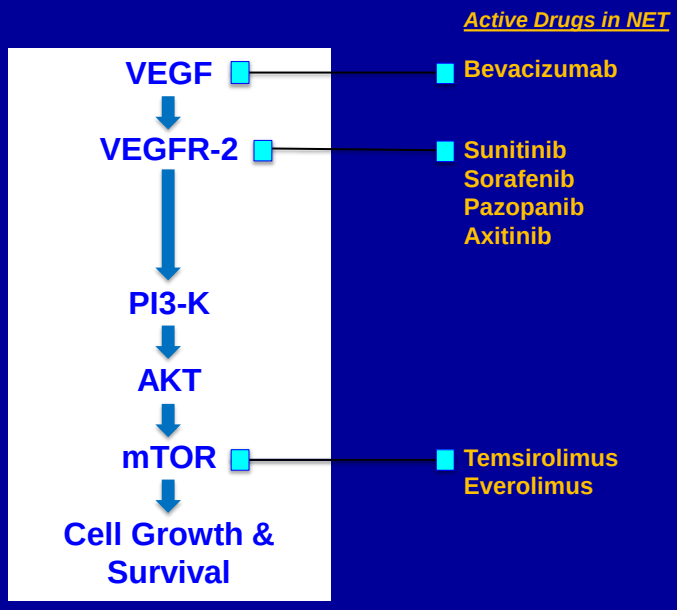
Crossover at progression

Arm 2: Placebo

Primary Endpoint: PFS

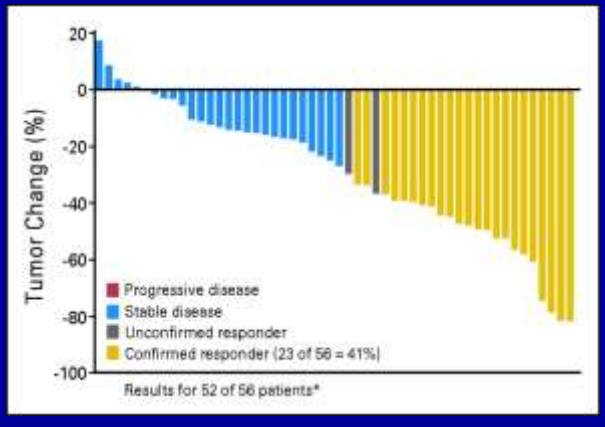
150 pts

Receptor Tyrosine Kinase/ AKT/ mTOR Pathway in NET



Multicenter Phase II Study of Temsirolimus + Bevacizumab in Advanced Pancreatic NET

- 56 patients with advanced pancreatic NET
- Received temsirolimus 25 mg IV weekly +bev 10 mg/kg q 2 wks
- Partial response rate 41%



Hobday et al, J Clin Oncol 2014 (epub ahead of print)

CALGB 80701: Schema

Key inclusion criteria:

- Advanced pancreatic NET
- Progression within 12 months
- No prior bevacizumab or mTOR inhibitor
- Prior treatment with SSA allowed

RANDOMIZE

1:1

Everolimus 10 mg po qd

(Octreotide LAR, institutional standard)

(Treatment until disease progression)

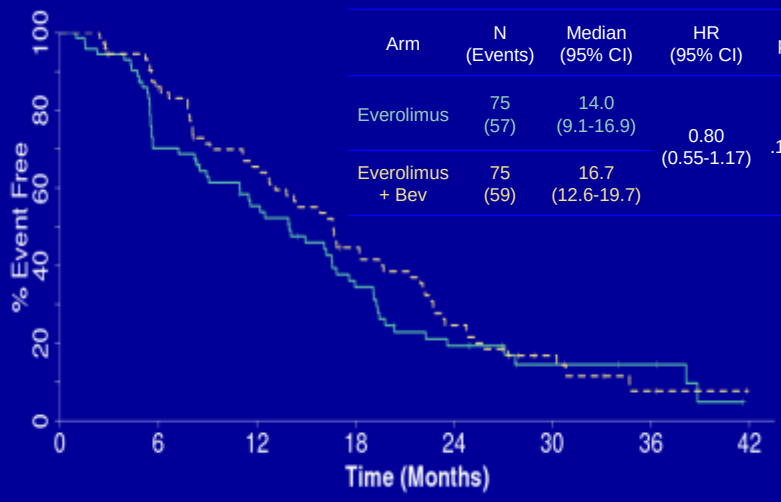
Everolimus 10 mg po qd

Bevacizumab 10 mg/kg IV q 2 weeks

(Octreotide LAR, institutional standard)

Stratification factors:
- Prior SSA
- Prior cytotoxic chemotherapy
- Prior sunitinib

CALGB 80701: Progression-Free Survival by Treatment Arm (Investigator-Assessed)



Arm	N (Events)	Median (95% CI)	HR (95% CI)	p
Everolimus	75 (57)	14.0 (9.1-16.9)	0.80 (0.55-1.17)	.12
Everolimus + Bev	75 (59)	16.7 (12.6-19.7)		

CALGB 80701: Efficacy Summary

	Everolimus (n=75)	Everolimus + Bev (n=75)	Estimate
Overall Response Rate	12%	31%	P=0.005
Median Progression-Free Survival	14.0 mos	16.7 mos	HR 0.80 (95% CI 0.55-1.17) P=0.12*
Median Overall Survival	35.0 mos	36.7 mos	HR 0.72 (95% CI 0.40-1.28) P=0.13
Median Time To Treatment Failure	12.2 mos	12.6 mos	HR 0.95 (95% CI 0.66-1.37) P=0.39

*Primary endpoint was PFS; potential superiority of everolimus + bevacizumab was assessed using a stratified log-rank test with 90% power (1-sided alpha=0.15 to detect a HR of 0.64)

Genomic Profiling of Pancreatic NETs

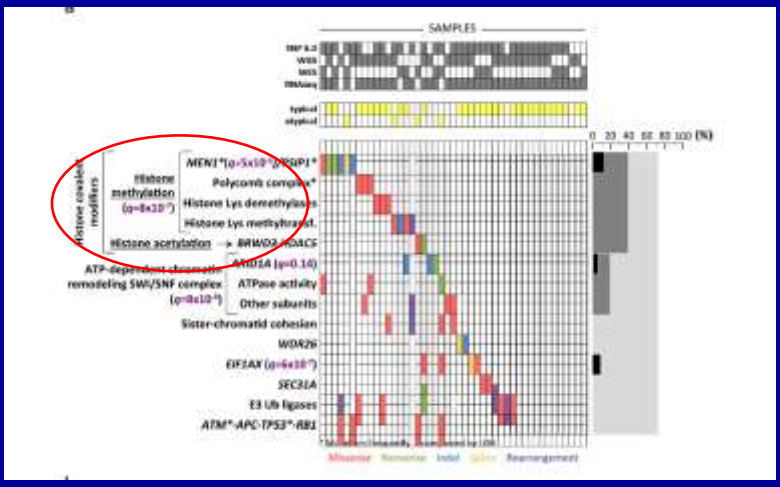
Table 1. Comparison of commonly mutated genes in PanNETs and PDAC, based on 68 PanNETs and 114 PDACs.

Genes*	PanNET	PDAC†
MEN1	44%	0%
DAXX, ATRX	43%	0%
Genes in mTOR pathway	15%	0.80%
TP53	3%	85%
KRAS	0%	100%
CDKN2A	0%	25%
TGFBR1, SMAD3, SMAD4	0%	38%

*Includes point mutations and indels.
†Data from Jones *et al.*, *Science* **321**, 1801 (2008).

Jiao et al, Science 2011; 331: 1199-203

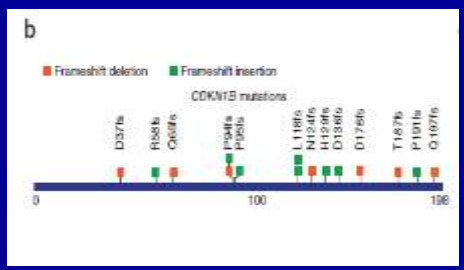
Mutations in Chromatin-Remodeling Genes in Pulmonary Neuroendocrine Tumors (N=44)



Fernandez-Cuesta et al, Nat Commun 2014; 5: 3518

Somatic Mutation of *CDKN1* in Small Intestine Carcinoid Tumors

- Profiled 55 tumors from 50 individuals using combination of whole genome and exome sequencing
- 5/50 individuals had mutations in *CDKN1B*
- Targeted sequencing in additional cases revealed overall incidence of *CDKN1B* mutations of 8% (14/180)



Mutational analysis of 31 primary and 19 metastatic small intestine NETs: schematic representation of frameshift mutations in CDKN1B

Francis et al, Nature Genetics 2013

NETS: Multiple Treatment Options

- Symptoms of Hormone Secretion:
  - SSA (octreotide, lanreotide)
  - Telotristat (?)
- Tumor Control (liver predominant disease)
  - Liver directed therapies
- Tumor Control (Systemic)

Pancreatic NET	Carcinoid
SSA (octreotide, lanreotide)	SSA (octreotide, lanreotide)
Everolimus	Everolimus
Sunitinib	PRRT
Temozolomide	

- *Future studies: combination therapy, molecular and genetic predictors of response, novel targets and agents*