

Update on Neuroendocrine Tumors

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Neuroendocrine (NE) tumors of the GI tract Epidemiology

- Increasing incidence of carcinoid tumors over past 25 years
 - ~4 cases per 100,000 per year in U.S.
- Majority (55-68%) of carcinoid tumors arise in GI tract
- NE tumors of the pancreas
 - 0.2 to 0.4 per 100,000 per year
- Prevalence relatively high due to prolonged survival

Modlin et al. Cancer 2003; Maggard et al. Ann Surg 2004; Ramage et al. Gut 2005.

Neuroendocrine Tumors (NET): A Diverse Group of Malignancies

- Characterized by:
 - site of origin
 - ability to make biologically active peptides
 - histological grade
- Express somatostatin receptors and neuroendocrine markers (CGA, NSE)

References: 1. Dorland's Medical Dictionary Web site. Available at: <http://www.dorlands.com>. Accessed November 10, 2008. 2. Modlin IM, Kidd M, Latch I, Zikusoka MN, Shapiro MD. Current status of gastrointestinal carcinoids. Gastroenterology. 2005;128:1717-1731.

Neuroendocrine (NE) tumors of the GI tract: Classification

- **Functioning:** clinical syndrome due to hormone (~10%)
 - serotonin, substance P, gastrin, insulin, glucagon, somatostatin, vasoactive intestinal peptide, growth hormone-releasing factor, adrenocorticotrophic hormone
- **Nonfunctioning:** no specific symptoms
 - may also secrete hormones (pancreatic polypeptide)

Neuroendocrine (NE) tumors of the GI tract Genetics

- Most tumors sporadic
 - DAXX/ATRX (43%), MEN1 (44%), and mTOR (14%) pathway genes are frequently altered in PNET
 - Jiao, et al. Science, 2011
- Familial syndrome:
 - MEN1 (Werner's)
 - Von Hippel-Lindau
 - Neurofibromatosis type 1 (Von Recklinghausen's)
 - Tuberous sclerosis



Yao, Best Practice & Research Clinical Endocrinology & Metabolism, 2007; 21: 163-172
Nakamura and Bergsland. Hematol Oncol Clin North Am 2007.

Histological Classification of Neuroendocrine Tumors

Differentiation	Grade	Mitotic Count	KI-67 index (%)	Traditional Classification	ENETS, WHO Classification
Well-differentiated	Low (G1)	< 2 per 10 HPF	≤ 2	Carcinoid, islet cell, pancreatic neuroendocrine tumor	Neuroendocrine tumor, grade 1
	Intermediate (G2)	2-20 per 10 HPF > 20 per 10 HPF	3-20	Carcinoid, atypical carcinoid, islet cell, pancreatic neuroendocrine tumor	Neuroendocrine tumor, grade 2
Poorly differentiated	High (G3)	> 20 per 10 HPF	> 20	Small cell carcinoma Large cell neuroendocrine carcinoma	Neuroendocrine carcinoma, grade 3, small cell Neuroendocrine carcinoma, grade 3, large cell

ENETS, European Neuroendocrine Tumor Society; WHO, World Health Organization; HPF, high-power fields

- ### Summary
- NETs are malignancies that arise in cells whose normal function is to secrete peptides
 - Vast majority are low-intermediate grade (well-differentiated NET)
 - Majority express NET markers and SSTRa receptors
 - Incidence of NETs has increased 5-fold in the last 30 yrs
 - Exact reasons are unknown, but may include increased awareness, detection, and/or environmental factors
 - Most NETs arise in the digestive tract
 - GEP NET are 2nd most prevalent GI malignancy (2x PDAC)
 - PNET and carcinoid
 - Optimal therapy for patients with advanced disease is unknown—New treatment options are needed

PNET vs Carcinoid

- ### Pancreatic NET (PNET)
- Incidence has increased over last several decades
 - 0.2 to 0.4 per 100,000 per year
 - ≈1.5% pancreatic cancers (≈400-1200 cases/yr)
 - Increases with age; peaks in 7th decade, median age ≈60
 - Prevalence relatively high due to prolonged survival
 - 10% of all pancreatic cancers by prevalence
 - Arise from islets of Langerhans (usually well-differentiated)
 - head 29%, body 10%, tail 21%, unknown 34%*
 - Most are nonfunctional
 - Functional: gastrinoma > insulinoma > glucagonomas > VIPomas
 - Pancreatic polypeptide production sometimes occur (nonfunctional)
- Halldanarson et al. Annals of Oncology, 2008; 19: 1727-33; Yao et al. JCO, 2008; 26: 3063; Yao et al. Ann Surg Oncol, 2007; 14: 3492-3500

PNET: Prognosis

OS correlates with stage at diagnosis and grade

- 55-70% metastatic at diagnosis

Despite reputation for being indolent, surgery is the only curative treatment option

- Incurable once unresectable disease

Much better than PDAC, “pancreatic cancer”

- Median OS stage IV 2-6 years

Halldanarson et al. Annals of Oncology, 2008; 19: 1727-33; Yao et al. JCO, 2008; 26: 3063; Strosberg et al. Pancreas 2009; 38: 255-58

Classification of Carcinoid Tumors

Origin	Organ	Clinical syndrome*	Behavior when metastatic
Foregut (33%)	Thymus Respiratory tract	Carcinoid syndrome, wheezing, rarely Cushing's syndrome or acromegaly	Relatively aggressive
	Stomach Duodenum	Flushing, gastrin hypersecretion, diarrhea, and Cushing's syndrome (5HIAA often normal)	
Midgut (34%)	Jejunum Ileum Appendix Cecum	Carcinoid syndrome Carcinoid syndrome Rare Carcinoid syndrome	Relatively indolent (+/-Obstruction from 1 st , mesenteric fibrosis/ischemia)
Hindgut (14%)	Descending colon	Rare	Relatively aggressive
	Rectum	Rare	

*From 5-HIAA, ACTH, histamine, 5-HTP, substance P, ACTH, etc.

Boudreaux et al. Pancreas, 2010; 39: 753-766; Phan et al. Pancreas 2010; 39: 784-798; Kulke et al. Pancreas, 2010; 39: 735-752

Hormone production: Carcinoid Syndrome

- Caused by secretion of serotonin and other neuropeptides into systemic circulation
- Abdominal pain
- Flushing
- Diarrhea
- Wheezing
- Palpitations
- Right-sided valvular heart disease
- Symptoms often controlled with somatostatin analog=SSTa (e.g. octreotide)

Somatostatin (SST)

- Bioactive neuropeptide
 - Prepro→SST-14 and SST-28 (Short t ½)
- Produced and acts locally:
 - ↓Glandular and exocrine secretions:
 - Inhibits GH/ACTH/TSH release
 - Pan-inhibitor of GI tract hormone release (insulin, glucagon)
 - Inhibits release of gastric acid, amylase
 - Antiproliferative
- Mediates inhibitory effects thru 5 GCPR (SSTR 1-5)
 - Expressed throughout CNS, GI tract, endocrine/exocrine glands, & immune/inflammatory cells

Schmid et al. *Mol Cell Endocrinol* 2008;286:69–74;

Somatostatin analogs (SSTa) and NETs

SSTa indicated for the treatment of hormone-mediated sx¹:

Octreotide (SQ)/Octreotide LAR (IM q mo)

- sstr 2, 5 (high) >sstr 3>sstr 1,4 (low)
- SMS201-995
- Approved for acromegaly and carcinoid syndrome

Lanreotide (SQ q 14d)/Lanreotide autogel (SQ q mo)

- sstr 2, 5 (high) >sstr 3>sstr 1,4 (low)
- Approved for acromegaly (Somatuline)

Pooled data suggests similar efficacy in NET ²	Symptom RR	Biochemical response
Octreotide LAR	74% (62%-93%)	51% (28-77%)
Lanreotide autogel	68% (40-100%)	39% (18-58%)

1. Oberg et al. 2004. *Ann Oncol*; 15: 966–973
2. Modlin et al. *Alimentary Pharmacology & Therapeutics*, 2009

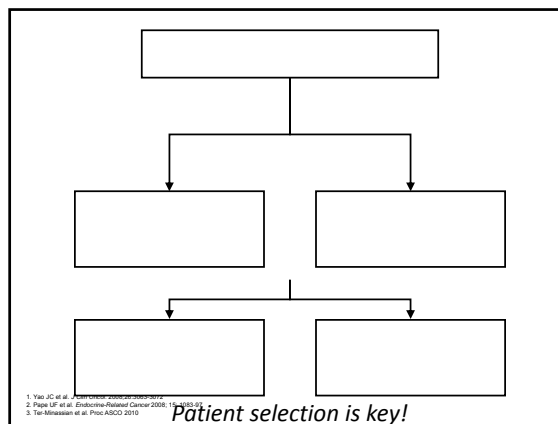
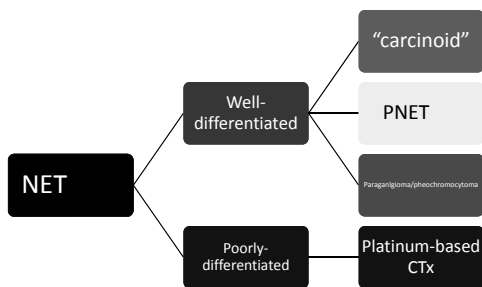
Future Directions:

Control of hormone-mediated symptoms

- New delivery systems (e.g. octreotide implant)
- Other sstr2,5 agonists and pan-receptor agonists
- Subtype-specific SSTa
- Bi-specific SST analogs
- Hybrid SST/dopamine compounds (dopastatins)
 - D2R is often expressed in low grade NET
- Non-peptide analogs
 - Orally bioavailable? Longer t_{1/2}? Less immunogenicity?
- Serotonin synthesis inhibitors: Tryptophan hydroxylase (TPH) inhibitors (Lexicon)

Modlin et al. *Alimentary Pharmacology & Therapeutics*, 2009

Treatment Options



Treatment: Localized and/or liver-dominant disease (no RCT)

- Resection of known disease if possible
 - 5 yr OS 80-100% if early stage
 - Prolonged survival if R0 resection of liver metastases
 - Mayo, et al. Ann Surg Onc, 2010;17: 3129-36
- Liver-directed therapy (Liver-dominant)
 - Surgical debulking (if >90% resected) and/or ablation
 - Hepatic artery (chemo)embolization
 - SIRT
 - (Liver transplant?)

Kulke, et al. JCO, 2010;29: 934-943. Oberg, et al. Annals of Oncology, 2010; 21 (Suppl 5)

Do SST analogs have a true antiproliferative effect on NET?

PROMID Study: Phase III randomized, double blind, placebo-controlled study

N=162

- Treatment-naïve
- Metastatic or LA inoperable well-diff mid-gut NET
- Functional or non-functional

RANDOMIZE

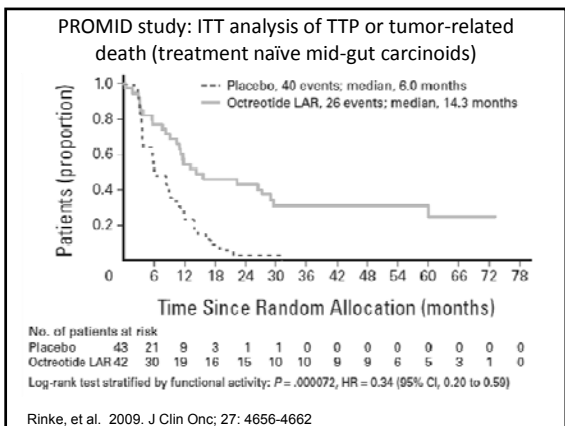
Placebo
(IM q mo until PD or death)

Octreotide LAR
(30 mg IM q mo until PD or death)

1° EP TTP
(blinded central)

Interim analysis: Trial stopped early (N=85)

Rinke, et al. 2009. J Clin Onc; 27: 4656-4662.



Conclusions: PROMID study

- Octreotide LAR inhibits tumor growth (↑ TTP) in well-differentiated mid-gut NETs
 - Prelim analysis: no OS benefit (post-study SSTa allowed)
 - Radiographic responses rare
- Functionally active/ inactive tumors responded similarly
- Best outcome in pts with with low (≤10%) hepatic tumor load (p=0.0023)
- Evidence for anti-tumor activity
 - Optimal timing of therapy (up-front vs delayed) ?
 - Benefits in PNET or non-midgut carcinoids?
 - Value of other SSTa (e.g. pasireotide, lanreotide)?

Current Clinical Trials: Phase III

Arms	Phase	Endpoint
lanreotide vs placebo carcinoid syndrome	III	Use of SQ octreotide to control symptoms during the DB phase of study
Pasireotide LAR vs octreotide LAR Uncontrolled carcinoid syndrome on SSTa	III	Symptom RR
Lanreotide Autogel vs placebo Non-functioning PNET or carcinoid (no prior SSTa)	III	PFS
Octreotide LAR +IFN vs Octreotide LAR+bevacizumab in high risk, low-intmed grade carcinoid (SWOG 0518)	III	PFS

Treatment Options

- Somatostatin Analogs (SSTa):
 - Cytostatic effect and/or control of hormone mediated symptoms
 - Radiographic responses rare
 - RCT with octreotide in SB carcinoid only; not FDA approved
 - Value of other SSTa (e.g. pasireotide?)
- Interferon: RR rare (<5%), biochemical response ≈30%
- Peptide receptor radiotherapy (PRRT)
 - Europe, x 3-4; no RCT

Yao, Best Practice & Research Clinical Endocrinology & Metabolism, 2007; 21: 163-172

Neuroendocrine (NE) tumors of the GI tract Chemotherapy

- No accepted standard treatment
- Anaplastic/poorly diff 50+% RR (platinum-based)
- Carcinoids: objective response rates less than 20%
- NE tumors of pancreas: inconsistent response rates 6-40% with streptozotocin-based therapy
- Treatment related toxicity often limiting

Nakamura et al. Surg Oncol Clin N Am (2007).

Temozolomide-based Chemotherapy: Summary

- Activity in NET
 - May be dose/schedule/partner-dependent
 - 3+ regimens under study
 - May be MGMT-dependent
 - Definition of high vs. low?
 - May be disease-dependent: PNET vs carcinoid
 - 70% RR in 30 PNET (retrospective) with capecitabine/temozolomide
 - Strosberg, et al. Cancer 2011
 - May be site-dependent (e.g. thymic vs bronchial vs SB)
- Toxicity may be schedule-dependent
- Utility of MGMT testing needs prospective validation
- *Prospective, randomized trials are needed!*
- *Not approved for this indication*

NCCN Guidelines: Systemic Chemotherapy

PNET: The following agents have been used:
streptozocin, doxorubicin, dacarbazine,
capecitabine, 5-FU, temozolomide

Carcinoid: Cytotoxic agents such as temozolomide, dacarbazine, capecitabine, and 5-FU can be used...*Objective responses are rare and no chemotherapy drug or regimen has been shown to have a PFS or OS benefit*

<http://www.nccn.org/index.asp>

VEGF Inhibitors

VEGF and NET

- NETs are highly vascular and express VEGF and its receptors
- VEGF expression correlates with metastases and decreased progression free survival (PFS)
- In preclinical models, VEGF is a valid target for therapy
 - Anti-VEGF Mab inhibits metastases orthotopic model of carcinoid
 - VEGF RTK inhibitors active in RIPTag model

Terris B, Scoazec JY, Rubbia L, et al. Histopathology 21: 133-8, 1998
Houde M, Pflieger JM, Ferraris N, et al. Cancer Cell 1: 199-202, 2002
Zhang J, et al. Cancer, 2007;109: 1478-86.
Konno H, et al. Jpn J Cancer Res, 1998;89: 933-9

Antitumor Activity of Small Molecule TKIs in Carcinoid and Pancreatic NET

	Carcinoid		pNET	
	6m. PFS*	(ORR)	6m.PFS*	(ORR)
Sunitinib (phase II) ¹	73%	(2%)	70%	(16%)
Pazopanib ²	68%	(0%)	81%	(19%)
Sorafenib ³	40%	(7%)	61%	(11%)

*PFS= progression free survival rate at 6 months;
ORR=objective response rate

1.. Kulke M et al. JCO 2008 2. Phan A et al, ASCO 2010; 3. HobdayT et al. ASCO 2007

Phase 3, Randomized, Double-blind Study of Sunitinib vs Placebo in Patients With Advanced, Progressive, Well-differentiated PNET

Eligibility criteria:

- Well-differentiated PNET
- Disease progression in past 12 months
- ECOG 0/1

N=340 planned (171 actual) Closed early

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Sunitinib 37.5 mg PO Q day w/o breaks

1° EP: 1:1 PFS

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

Placebo*

*With best supportive care

Somatostatin analogs permitted in both arms

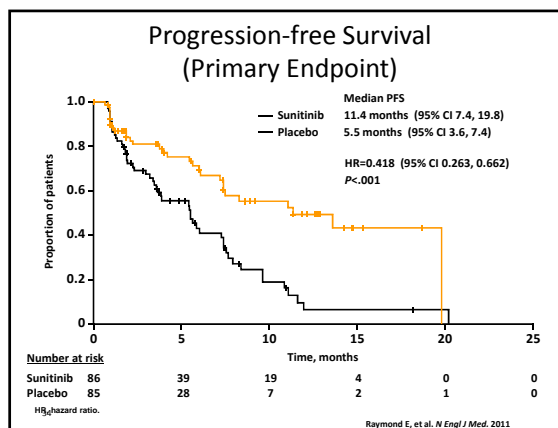
Raymond, et al. NEJM, 2011

Phase III study of sunitinib vs placebo in PNET: Results

	PFS	SD	PFS @ 6 mo	OS at 6 mo	Median OS	RR
Sunitinib (n=86)	11.4 mo	34.9%	71.3%	92.6%	NR	9.3%
Placebo (n=85)	5.5 mo	24.7%	43.2%	85.2%	NR	0%
	HR 0.418 P<0.001			HR 0.409 P=.0204*	Median f/u 10-11 mo	

* Data not mature. Median OS not reached; few events (9 vs 21); majority of pt censored

Raymond, et al. NEJM, 2011



Summary

- Sunitinib improves PFS in progressive, well-differentiated pNET
 - Benefit across subgroups (including on-study and prior SSA)
 - PR rate low (9%)
 - QOL preserved
 - Hypertension, fatigue, diarrhea, nausea
 - Overall survival data should be interpreted with caution (70% X-over)
 - Longer f/u needed
 - FDA-approved for PNET indication in May 11'
- Unanswered questions:
 - Optimal role/sequence in context of other “available” therapies (e.g. SIRT, everolimus, PRRT, chemotherapy) ?
 - Value in other low-grade NET (e.g. carcinoid)?

Targeting the VEGF Pathway in Neuroendocrine Tumors

Bevacizumab — VEGF

Sunitinib, Sorafenib, Pazopanib — VEGF Receptor

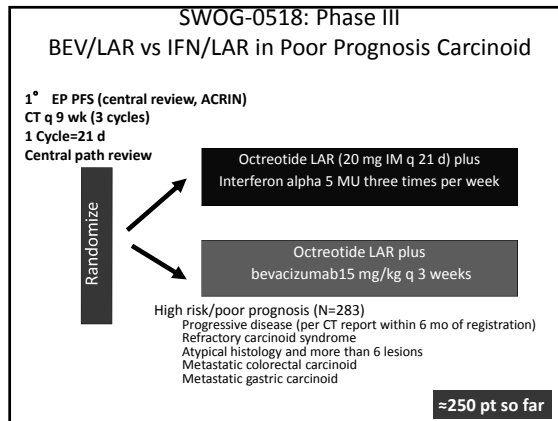
Bevacizumab: FDA approved for use in colorectal cancer, lung cancer, (breast cancer) and kidney cancer

Bevacizumab vs IFN in Carcinoid: Efficacy (RECIST)

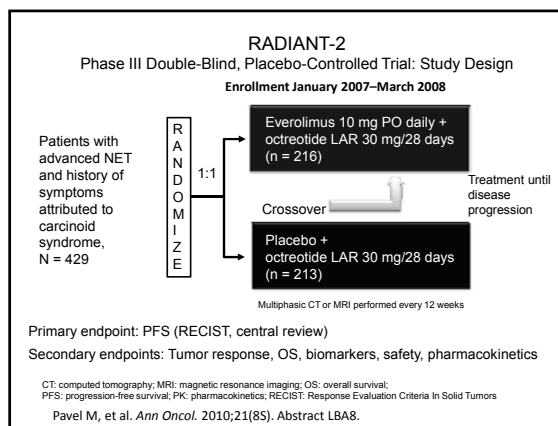
Best Response - intention to treat by assignment

	Bevacizumab (N = 22)	PEG interferon (N = 22)	Overall
PR (confirmed)	4	0	4
SD	17	16	33
PD	1	6	7
PFS @18wk	95%	68%	

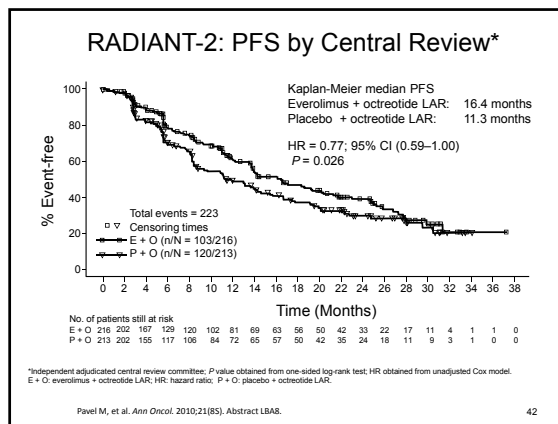
Yao et al. J Clin Onc, 2008; 26; 1316:

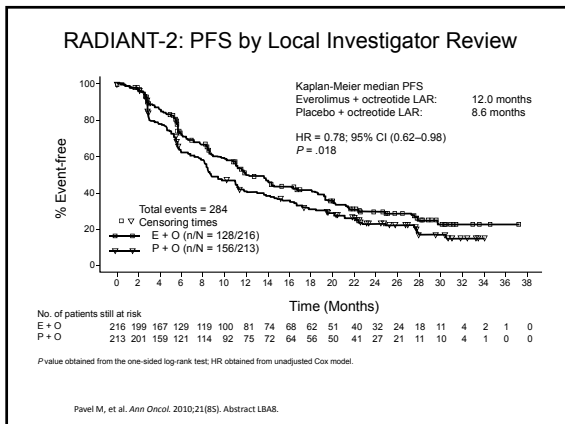


mTOR Pathway Inhibitors



- ### Key Eligibility Criteria
- Advanced low or intermediate grade NET
 - Radiologic disease progression within 12 months
 - Measurable disease per RECIST criteria
 - Multi-phasic computed tomography (CT) scan or MRI
 - History of symptoms attributed to carcinoid syndrome
 - Symptoms need not have been active at the time of enrollment
 - Prior anti-tumour therapy allowed
 - WHO PS ≤ 2, adequate blood counts and serum chemistry
- Pavel M, et al. ESMO 2010 Abstract LBA8





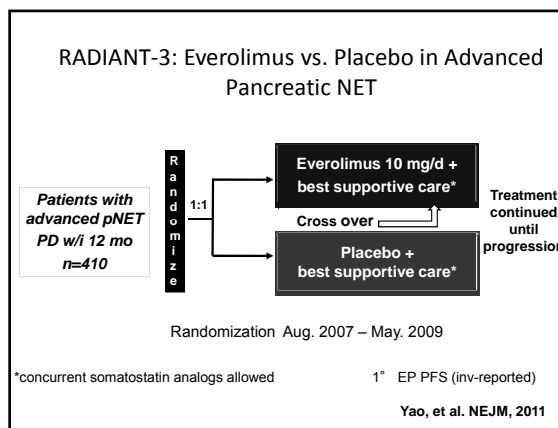
RADIANT-2 Treatment Related Adverse Events

Occurring in ≥ 10%	Everolimus + Octreotide LAR (n = 215)		Placebo + Octreotide LAR (n = 211)	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Stomatitis*	62	7	14	0
Rash	37	1	12	0
Fatigue	31	7	23	3
Diarrhea	27	6	16	2
Nausea	20	1	16	1
Infections*	20	5	6	1

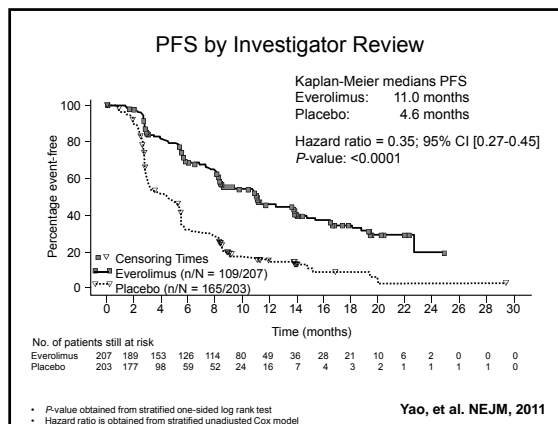
*Related toxicities grouped for calculation

Pavel M, et al. *Ann Oncol.* 2010;21(8S). Abstract LBAS.

- ### Summary: RADIANT-2
- Trend towards improved PFS (5.1 mo ↑) w/ RAD001+octreotide LAR (p=0.026) vs. placebo in pt with progressive carcinoid (w/ hx of syndrome), but this did not reach statistical significance (needed p=0.0246)
 - Local review suggests similar level of activity (p=0.018)
 - No OS benefit at the time of the analysis
 - Safety profile acceptable
 - FDA application withdrawn (spring 11')
 - RAD not approved for this indication
- Pavel, et al. ESMO, 2010, Abstr# LB



- ### Key Eligibility Criteria
- Advanced low or intermediate grade pancreatic NET
 - Radiologic disease progression within 12 months
 - Measurable disease per RECIST criteria
 - Multi-phasic computed tomography (CT) scan or MRI
 - Prior anti-tumour therapy allowed
 - WHO PS ≤ 2, adequate blood counts and serum chemistry



Summary: RAD001 in PNET

- Everolimus therapy resulted in a significant 6.4 month increase in median PFS
 - 4.6 months to 11.0 months
 - consistent benefit in all subgroups
 - No OS benefit
- Stability more common than significant shrinkage
 - 4.8% RR with RAD vs 2% with placebo
- Everolimus has an acceptable safety profile
 - Mouth sores, rash, hyperglycemia, hyperlipidemia, hypophosphatemia
- Approved by FDA for PNET in May 11'

Efficacy in Sunitinib or Everolimus NET Randomized Trials

	Sunitinib (n=171)	Everolimus (n=410)
Median PFS	11.4 mos <i>(vs. 5.5 mos in placebo arm)</i>	11.0 mos <i>(vs 4.6 mos in placebo arm)</i>
Overall Response Rate (RECIST)	9.3%	5%
Partial Response or Stable Disease	72%	78%
Survival Advantage Demonstrated?	No*	No*

*Pts receiving placebo in either study had opportunity to receive study drug following progression

Yao, et al. *NEJM*, 2011
Raymond, et al. *NEJM*, 2011

Adverse Events in Sunitinib and Everolimus PNET Phase III Trials

Event	SUNITINIB		Event	EVEROLIMUS	
	All Grades (%)	Grade 3-4 (%)		All Grades (%)	Grade 3-4 (%)
Diarrhea	59	5	Stomatitis	64	7
Nausea	45	1	Rash	49	1
Asthenia	34	5	Diarrhea	34	3
Vomiting	34	0	Fatigue	31	2
Fatigue	32	5	Infections	23	2
Hypertension	26	10	Pneumonitis	13	5

Yao, et al. *NEJM*, 2011
Raymond, et al. *NEJM*, 2011

CALGB 80701: Randomized Phase II Study of Everolimus Alone or in Combination with Bevacizumab, in Patients with Advanced Pancreatic NET (open 10/2010, Kulke, PI)

138 pts

Opened: October 2010
First site activated: January, 2011
Accrual 40/138

Primary Endpoint: INV-report PFS

Summary: Advanced pancreatic NET

- Asymptomatic patients with stable disease and low tumor burden can be observed and monitored
- Sequential therapy with targeted agents (everolimus or sunitinib) in patients with symptoms, clinically significant tumor burden, and/or progressive disease
 - Stabilization >>> shrinkage
 - Neither agent has been shown to improve overall survival
- Choice of targeted agent (everolimus or sunitinib) based on patient comorbidities and/or preference
- Streptozocin or temozolomide-based therapy can be considered where tumor response is required or where patients have failed targeted agents
- The anti-tumor activity of SSTa has not been established

Summary: Carcinoid

- Carcinoid ≠PNET
- Carcinoid tumors = heterogenous group of tumors
- Refractory carcinoid is an area of unmet need
- Octreotide is approved for control of hormone-mediated symptoms and delays TTP in advanced midgut carcinoids
- VEGF inhibitors are of unproven benefit in carcinoid
- RADIANT -2 (phase III) study suggests trend towards improved PFS with everolimus+octreotide LAR, but did not meet 1° EP and is not approved for carcinoid

Well-differentiated NET of GI Tract

	Carcinoid	PNET
Site of origin	Foregut, midgut, hindgut	Pancreas
Histology	Low- to intermediate grade NET (identical)	
Hormone production (when present)	Serotonin (+histamine, etc)	Insulin, glucagon, gastrin, VIP, PP, etc
Octreotide w/proven anti-tumor effect	YES-midgut	NO
Chemotherapy	Insensitive	Relatively sensitive
Sunitinib w/ proven anti-tumor effect	NO	YES
Everolimus w/ proven anti-tumor effect	NO (phase III fell short)	YES

Clinical Trials in NET

Study	Disease	Lead Site/sponsor
SWOG0518	High risk carcinoid	SWOG
BEV/LARvs IFN/LAR	Phase III	
RAD/LAR vs RAD/BEV/LAR (CALGB 80701)	Progressive PNET	CALGB
	Phase II	
BEV+LAR+capecitabine	phase II	Italy
	Progressive low-grade NET	
Sunitinib	Phase II, well diff NET	Pfizer/Japan
BEV+pertuzumab+LAR	Phase II	Sarah Cannon
	Progressive low-grade NET	
Temsirolimus/Bev	carcinoid, islet, and other tumors	Mayo Clinic
Everolimus +erlotinib	Phase II Carcinoid/PNET	UCSF
Sunitinib	Phase II in PD NET	
BEV/Strep/5-FU or BEV/Cape	Phase II in Carc and PNET	France/Hoffman-LaRoche

<http://www.cancer.gov/>