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Advances in NET treatment: Medical Oncology Perspective

Emily Bergsland

Stanford-CRCF Patient Education Conference

3.1.15

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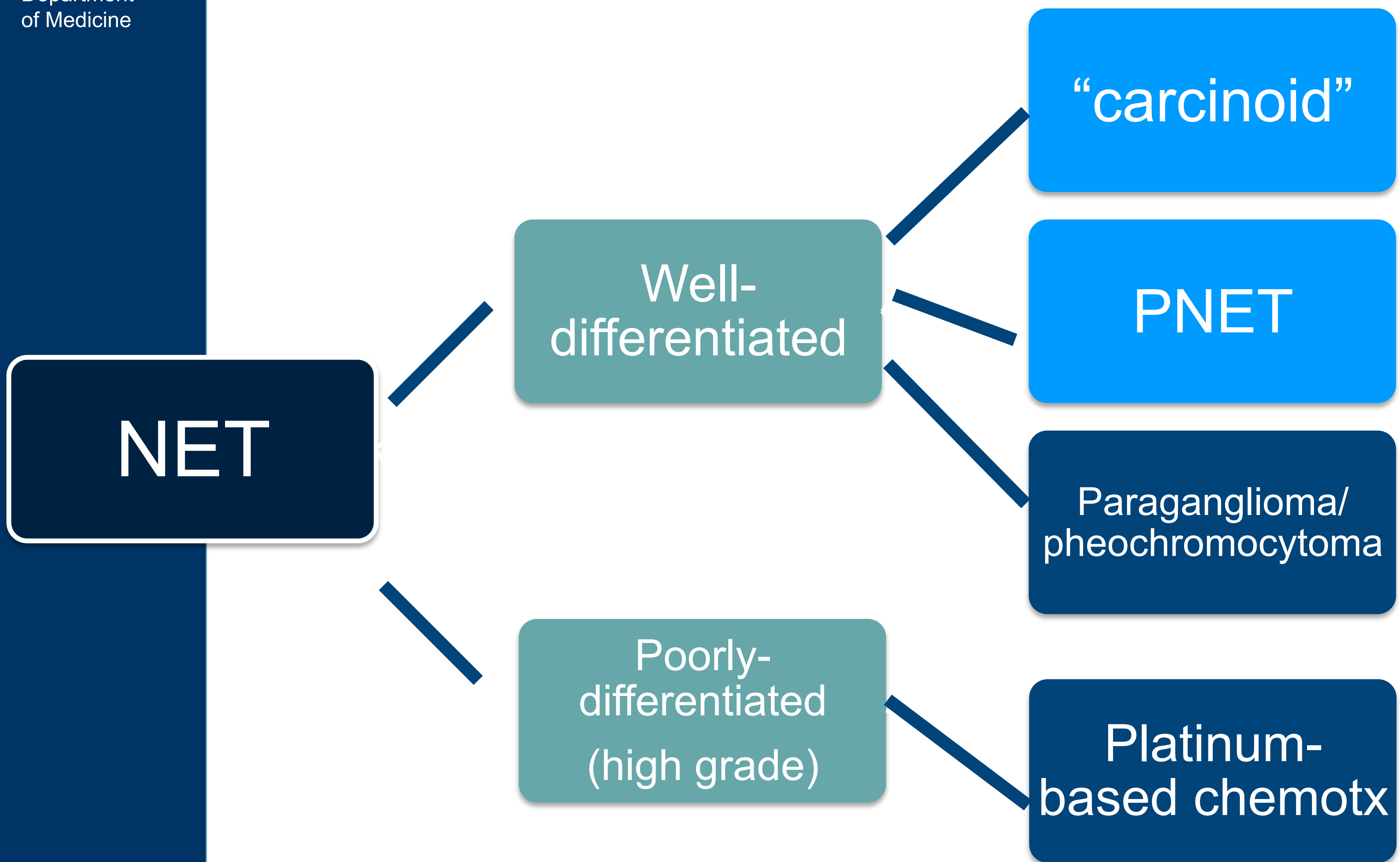
Decision Tree: NET



Advanced Disease: Indications for therapy

Well-differentiated NET

Ability to resect all known disease

Control of hormone-mediated symptoms

Progressive disease (need for anti-tumor effect)

Patient selection is key!

Survival measured in years

Somatostatin analogs (SSTa) and NETs

- SSTa indicated for the treatment of hormone-mediated sx[1]: reduces glandular /exocrine secretions, antiproliferative

- Octreotide (SQ)/Octreotide LAR (IM q mo)
  - Sandostatin®, Sandostatin LAR®
  - Approved for acromegaly and carcinoid syndrome

- Lanreotide (SQ q 14d)/Lanreotide autogel (SQ q mo)
  - Approved for acromegaly (Somatuline) and well differentiated GEP-NET

- sstr 2, 5 (high) >sstr 3>sstr 1,4 (low)
- Both afford ≈70% symptomatic response rate

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

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Unanswered questions

- Value of lanreotide for symptom control after failing octreotide?
- Value of octreotide after failing lanreotide?
- Value of high dose octreotide (e.g. 60 mg/mo)?
  - Phase II study pending (Strosberg, PI)
    - 1°EP symptoms
- Value of high dose lanreotide (>120 mg/mo)?

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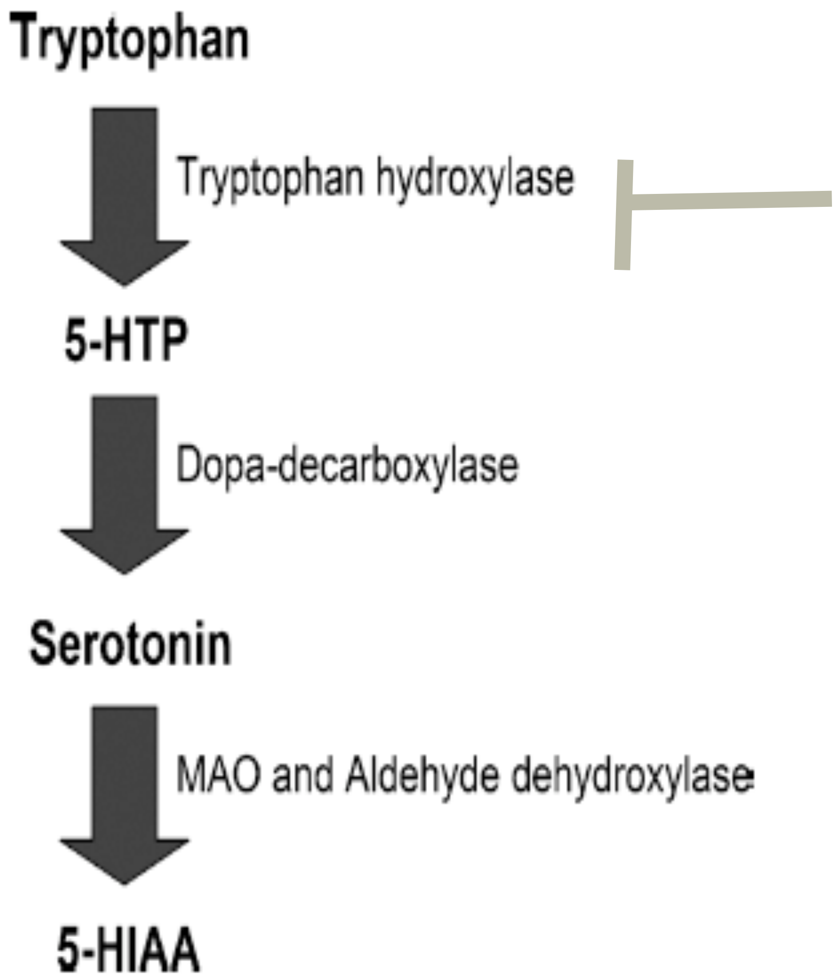
Synthesis of 5-HIAA



Telotristat

Oral Tryptophan hydroxylase inhibitor)

Vinik, et al. Pancreas, 2009

O-Toole, et al. Neuroendocrinology, 2009

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Phase 3 Study : Telotristat Etiprate in carcinoid (TELESTAR) -open

Stable dose SSTA
Minimum
octreotide 30 mg / 4wk or lanreotide 120 mg/28d
or MTD

Carcinoid syndrome
4-12 BM/d

N=105
(Lexicon)

1:1:1

Placebo TID + SSTa

Telotristat 250 mg TID + SSTa

Telotristat 500 mg TID + SSTa

Double blind treatment
Phase x 12 wk

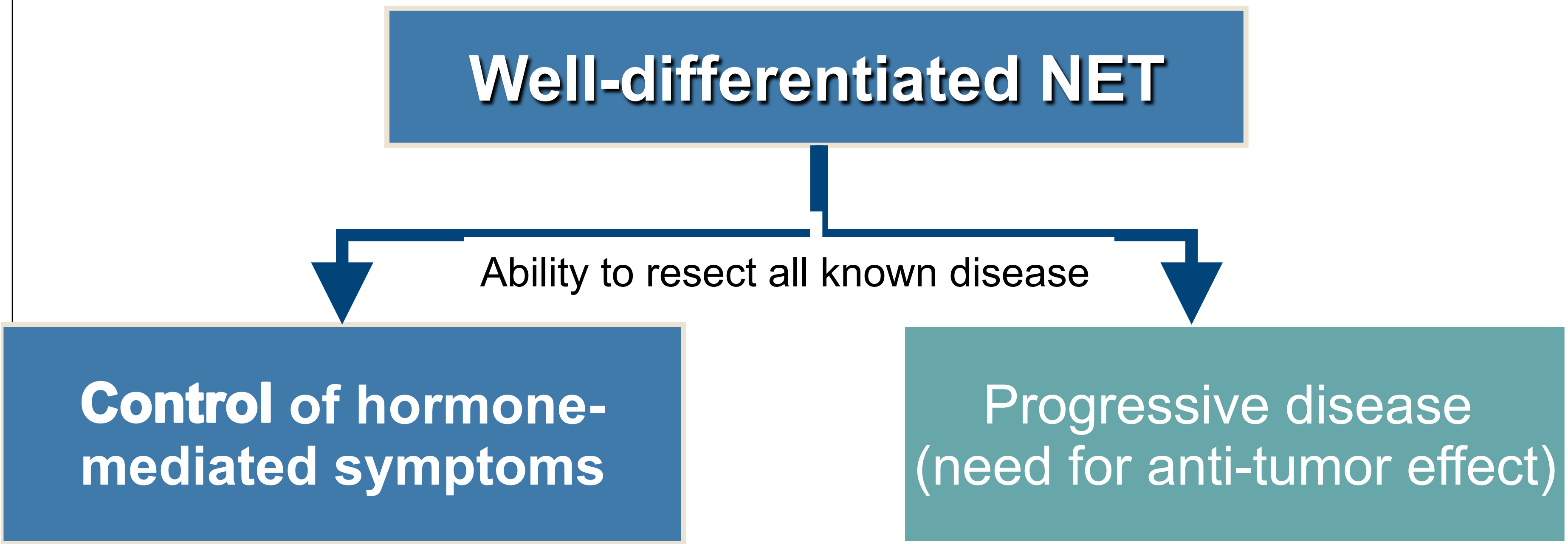
1°EP: safety, **#BM/D**

2° EP: #flushing/d
Abdominal pain,
change 24 hr 5HIAA (12 wk)

Telotristat 500 mg TID + SSTa

Open label extension phase

Advanced Disease: Indications for therapy



Patient selection is key!

Survival measured in years

Treatment Options-Systemic therapy

- Somatostatin analogs
- PRRT
- Interferon
- Chemotherapy
- VEGF inhibitors
- mTOR inibitors

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Antitumor activity: Somatostatin analogs

- **PROMID study: Octreotide LAR treatment delays progression in treatment-naïve well-diff mid-gut carcinoids (6 v 14 mo)**
  - Rinke, et al. 2009. J Clin Onc

- **CLARINET study: Lanreotide delays progression in non-functioning well-mod diff (Ki67<10%) GI and pancreatic NET (16.6 mo v NR)**
  - Serious side effects rare; Mild diarrhea, abdominal pain, gall stones most common
  - Cross-over allowed
  - FDA approved 12/2014
  - Caplin, et al. NEJM 2014

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Unanswered questions

- Is one better than the other for tumor control?
- Optimal timing of therapy?
- Are there certain patients who stand to better the most? The least?
- What is the optimal treatment for tumors arising in less common sites (e.g. rectum? Lung?)
- Does either agent have antitumor activity after failure of the first SSTa?
- Are there “better” SSTa?

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Pasireotide LAR

- Binds sstr1,2,3,5 with high affinity (not sstr4); 30-, 5- and 40x greater affinity for $sstr_{1,3,5}$ and slightly less affinity for $sstr_2$ than octreotide

- Phase 3 study v octreotide LAR negative (symptom control)
  - More hyperglycemia w pasireotide
  - Pasireotide LAR ↑PFS by 5 months
    - Suggests potential for anti-tumor activity
    - Phase II trial in SB NET pending (Strosberg)
      - Moffitt and Stanford

. Bruns C *et al. Eur J Endocrinol* 2002;2. Schmid *et al. Mol Cell Endocrinol* 2008 3. Ono K *et al. Anticancer Res* 2007 4. Kvols et al. J Clin Oncol, 2006;24:198s

Wolin et al. Abstract 4031: poster presented at ASCO; May 31-June 4, 2013; Chicago, IL.

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Treatment Options: Systemic Therapy

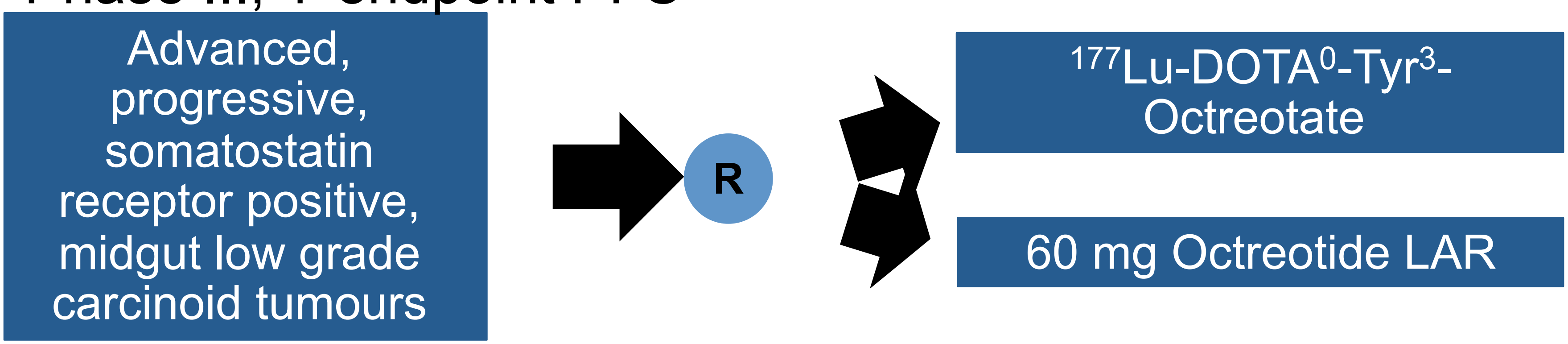
Peptide receptor radiotherapy (PRRT)

- Potential value (e.g. [^{177} Lu-DOTA 0,Tyr3]octreotate or ^{90}Y-DOTATOC) in pt with high tumor uptake on somatostatin receptor scintigraphy
- Symptom control, SD, and/or radiographic responses (4-30%) have been reported
- No prospective RCT evaluating toxicity/anti-tumor efficacy
  - DJ Kwekkeboom et al, J Clin Onc 2008; D Bushnell et al, J Clin Onc 2010

Boudreaux, et al. Pancreas, 2010; 39; 753-766.; Strosberg, et al. Cancer Control, 2011; 18: 127-137

A Study Comparing Treatment With 177Lu-DOTA0-Tyr3-Octreotate to Octreotide LAR in Patients With Inoperable, Progressive, Somatostatin Receptor Positive Midgut Carcinoid Tumours (NETTER-1)

Phase III, 1°endpoint PFS



Sponsor: Advanced Accelerator Applications, France

Trials in Carcinoid: PRRT	
Randomized phase III trial of 177Lu-octreotate versus interferon α-2b in non-pancreatic, SSTa resistent GI NET	Not yet open (Belgium)
Randomized phase II of PRRT vs high dose LAR in refractory SB NET	Open (PFS)
177Lutetium-DOTA-Octreotate Therapy in Somatostatin Receptor-Expressing Neuroendocrine Neoplasms, Phase II	Open (Excel Diagnostics)
Neo-adjuvant Peptide Receptor Mediated Radiotherapy With 177Lutetium in Front of Curative Intended Liver Transplantation in Patients With Hepatic Metastasis of Neuroendocrine Tumors (NEO-LEBE) Phase II	Open (Germany), tumor-free survival
A Multicenter Study Evaluating Efficacy and Safety of 177Lu-DOTA-TATE Based on Kidney-Dosimetry in Patients With Disseminated Neuroendocrine Tumors (ILUMINET) Phase II	Open, Sweden
177Lutetium-octreotate Treatment Prediction Using Multimodality Imaging in Refractory NETs (LUMEN)	Open, Brussels
Holmium-166-radioembolization in NET After Lutetium-177-dotatate; an Efficacy Study (HEPAR Plus)	Open, Netherlands

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Treatment Options: Systemic Therapy

- **Interferon**:
  RR rare (<5-12%)
  biochemical response ≈30%
  SD 25-60%
  - Potential benefit with SSTa plus IFN in patients resistant to either drug
  - Underpowered RCT preclude definitive recommendations
  - Given the toxicity, typically reserved for octreotide-refractory disease
  - Rarely used in US

Boudreaux, et al. Pancreas, 2010; 39; 753-766.; Strosberg, et al. Cancer Control, 2011; 18: 127-137

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Chemotherapy

- High grade/Anaplastic/poorly diff NEC: 50+% RR (platinum-based chemotherapy)
    - small cell v large cell treated the same
    - Tumors with Ki67<55% less responsive? (welin et al)

- Well-differentiated NET: No accepted standard treatment (G1/G2 bundled)
    - Carcinoids: RR<20%
    - PNET:
        - Inconsistent RR (6-40%) with streptozotocin-based therapy
        - 70% RR in 1st line PNET (retrospective, n=30) with capecitabine/temozolomide (Strosberg, et al. Cancer 2011)
        - Lower RR in prospective studies

ECOG 2211: Randomized phase II study of capecitabine/temozolomide vs temozolomide alone in Advanced, Progressive, Well-differentiated PNET (Kunz, PI)

Eligibility criteria:
- **Well-differentiated PNET**
- **Disease progression in past 12 months**
- **ECOG 0/1**

N=145

Stratify:
Prior everolimus
Prior sunitinib
Concurrent octreotide

RANDOMIZATION

1:1

1°EP: PFS

Capecitabine/ temozolomide

Temozolomide

Up to 13 cycles

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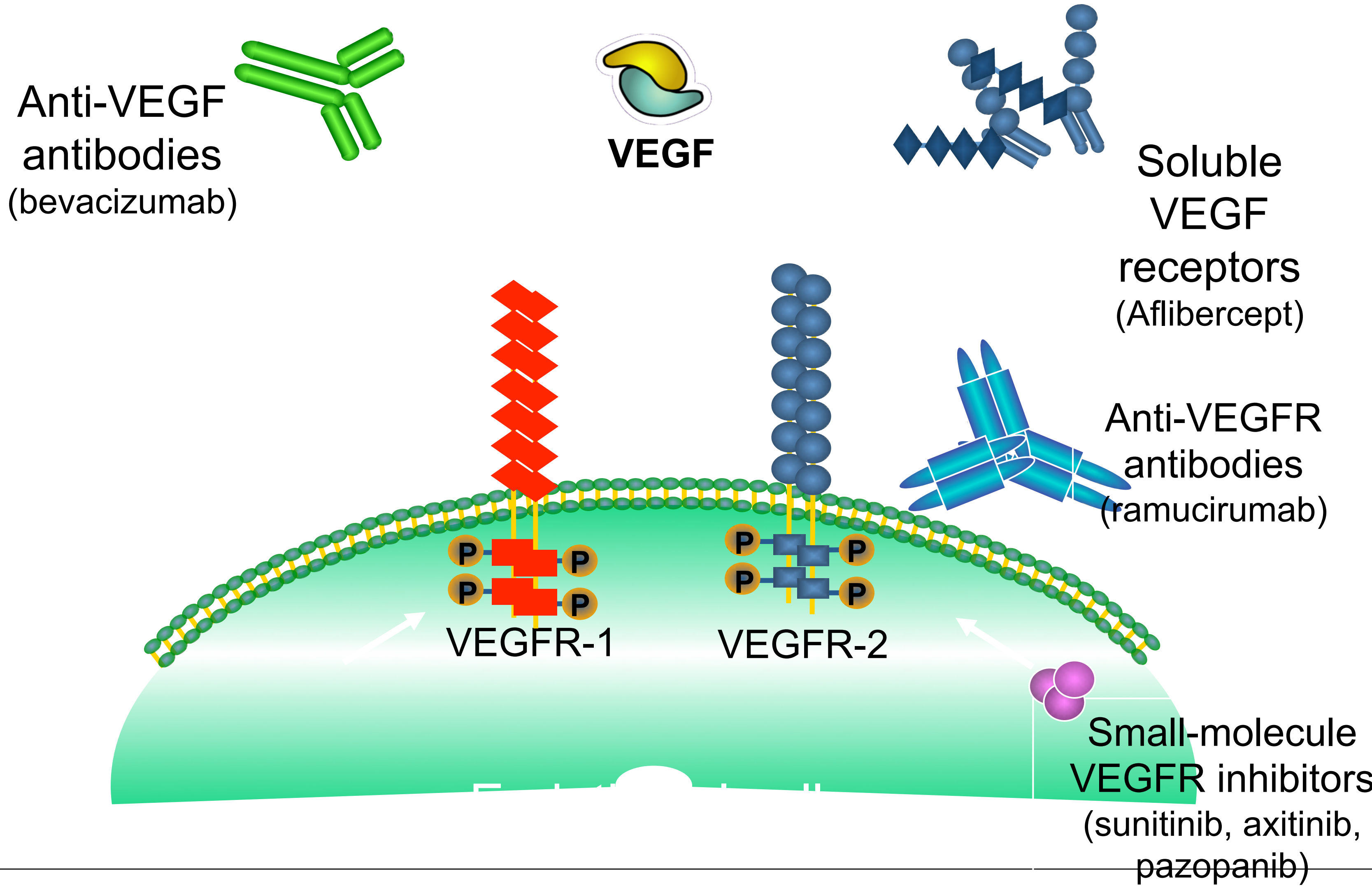
VEGF Inhibitors

Agents targeting the vascular endothelial growth factor (VEGF) signaling pathway: Designed to inhibit blood vessel growth



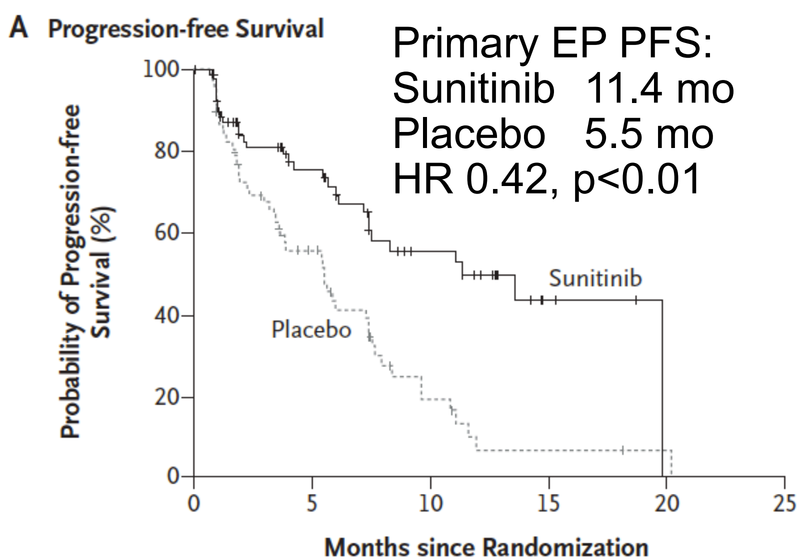
VEGF Inhibitors: Ph III Sunitinib in PanNETs

Advanced progressive pancreatic NETs
n=171

R

Sunitinib 37.5 mg daily
N=86

Placebo
N=85



Primary EP PFS:
Sunitinib 11.4 mo
Placebo 5.5 mo
HR 0.42, p<0.01

- Other key points:
  - Crossover allowed
  - Study terminated early (planned accrual 340)
  - OS not reached at time of initial report
  - RR low (9%)

Raymond. NEJM, 2011.

SWOG-0518: Phase III
BEV/LAR vs IFN/LAR in Poor Prognosis Carcinoid

1° EP PFS (central review, ACRIN)
CT q 9 wk (3 cycles)
1 Cycle=21 d
Central path review

Randomize

Octreotide LAR (20 ... 21 d) plus
Interfer ... MU TIW

http://Octreo.de

Accrual complete

Octreotide LAR plus
bevacizumab 15 mg/kg q 3 weeks

... risk/poor prognosis

- Progressive disease (per CT report within 6 mo of registration)
- Refractory carcinoid syndrome
- Atypical histology and more than 6 lesions
- Metastatic colorectal carcinoid
- Metastatic gastric carcinoid

Data presentation pending.

A021202 study Design: Randomized phase II trial in CARCINOID (PI-Bergsland) ACCRUAL ONGOING

N≈150

•Progressive, advanced carcinoid tumor

•Functional or non-functional

• Concurrent octreotide OK if PD documented

RANDOMIZE

Pazopanib
800 mg PO qD
No breaks

Option for cross-over at progression

1° EP
PFS
(Central review)

Placebo

1 cycle=28 days
CT scan q 12 wk

*Open 6/2014

Randomized Clinical Trials: NET

Trials in Carcinoid: VEGF Pathway Inhibitors	
Randomized phase II trial of sandostatin +/- axitinib in non-pancreatic NET	Open (Spain)
Randomized phase II lanreotide/sunitinib v lanreotide in mid-gut carcinoid	Open (GERCOR)
Phase II trial of capozantinib in advanced PNET/CARC	Open (DFCI/MGH), RR
Phase II trial of axitinib in PNET	Closed (Moffit/UCSF), PFS
Phase II trial of ziv-aflibercept in carcinoid	Closed (DFCI, MGH), PFS
Phase II trial of regorafenib in carcinoid/pnet	Pending (USC), PFS

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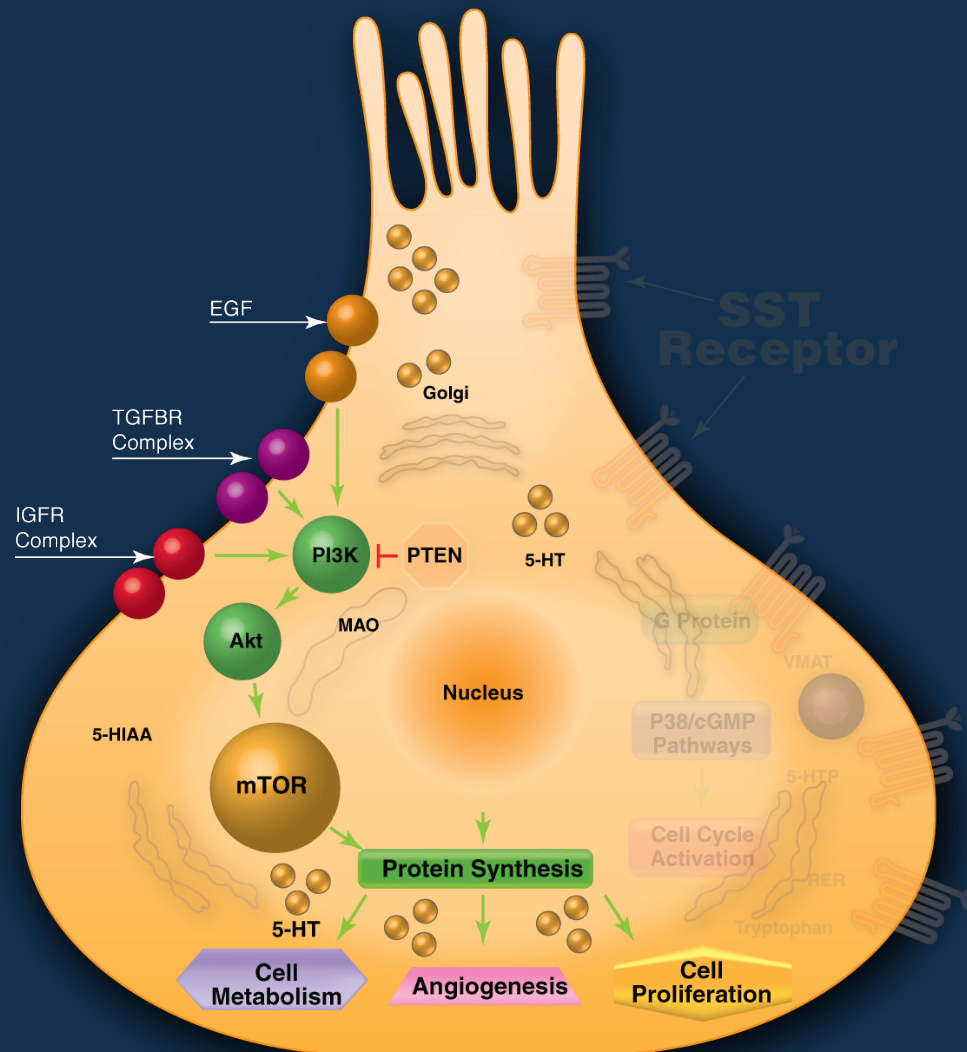
mTOR Pathway Inhibitors

mTOR pathway as a target for therapy in NET

- mTOR has a central role in a number of proliferation pathways[1]
- Abnormalities in the mTOR pathway are involved in the development of some NETs[2]
    - -TSC-2 is negative regulator of mTOR
- mTOR signaling promotes cell metabolism, angiogenesis, and cell proliferation[1,2]
    - mediator of VEGF and IGF-1 signaling



1. Bjornsti M-A, Houghton PJ. *Nature Rev Cancer*. 2004;4:335-348. **2.** von Wichert G, Jehle PM, Hoeflich A, et al. *Cancer Res*. 2000;60:4573-4581.

Ph III Trial of everolimus v placebo in progressive PanNETs (RADIANT 3)

Advanced pancreatic NETs
n=410

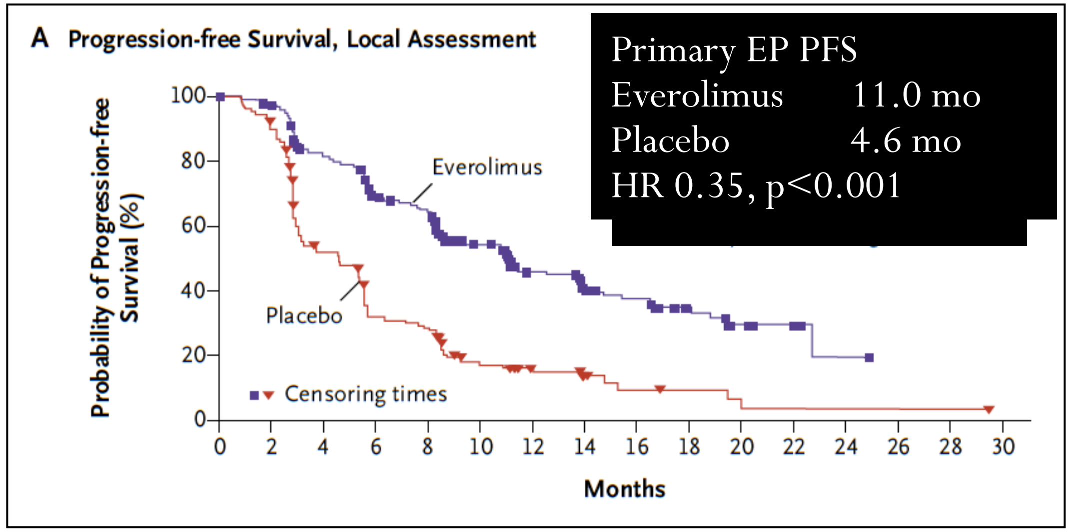
↓

R

↙ ↘

Everolimus 10 mg
N=207

Placebo
N=203



- Other key points:
  - Crossover allowed
  - OS not reached at time of initial report
  - RR low (5%)

Yao. NEJM, 2011.

Efficacy in Sunitinib or Everolimus NET Randomized Trials: Both FDA approved for PanNETs 5/2011

	Sunitinib (n=171)	Everolimus (n=410)
Median PFS	11.4 mos *(vs. 5.5 mos in placebo arm)*	11.0 mos *(vs 4.6 mos in placebo arm)*
Overall Response Rate (RECIST)	9.3%	5%
Partial Response or Stable Disease	72%	78%
Survival Advantage Demonstrated?	No*	No*
	GI sx, hypertension, fatigue	Mouth sores, rash, diarrhea, fatigue, high blood glucose

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

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

Combination mTOR inhibitor +VEGF inhibitor

Ph II Temsirolimus + bevacizumab in progressive PanNETs

Advanced, progressive G1/G2 pancreatic NETs (n=55) → Temsirolimus 25mg IV days 1, 8, 15, 22
Bevacizumab 10 mg/kg days 1, 15
Repeat Q28 days

Confirmed PR	23 (41%)
6-month PFS	79%
Med PFS	13.2 mo
12-month PFS	48%

Most common grade 3 to 4 adverse events: hypertension (21%), fatigue (16%), lymphopenia (14%), and hyperglycemia (14%).

Hobday. JCO 2014

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

RANDOMIZE

Arm 1: Everolimus 10 mg po qd + octreotide LAR

Arm 2: Everolimus 10 mg po qd + Bevacizumab 10 mg/kg IV q 2 wks + octreotide LAR

Primary Endpoint:

PFS

138 pts

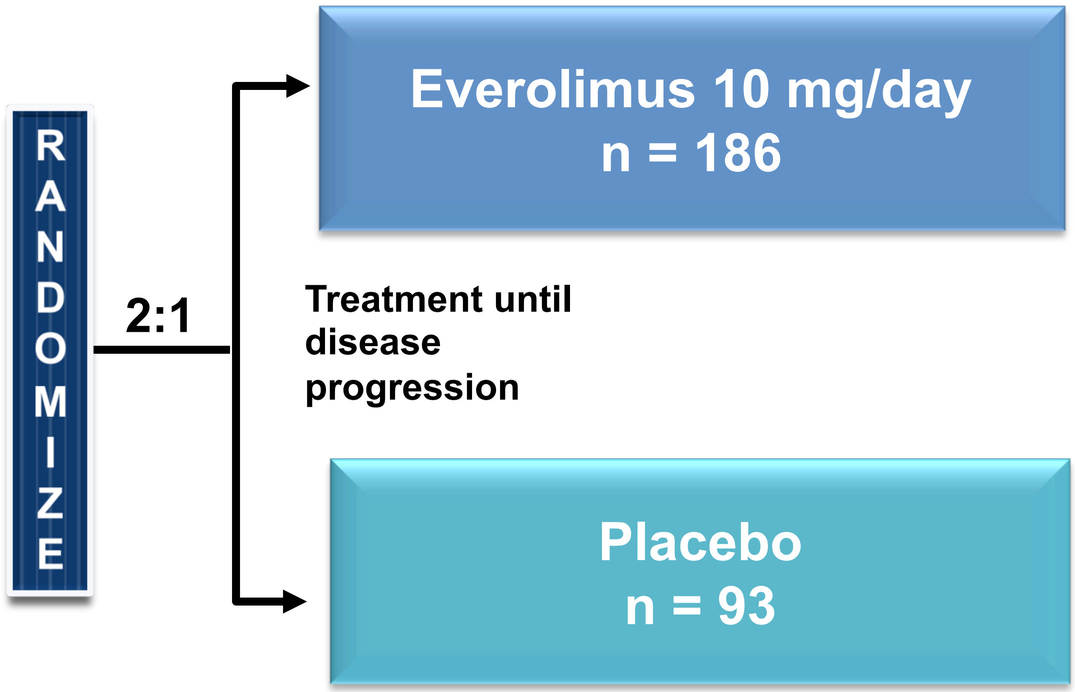
Opened: October 2010

Closed to accrual– results pending

RADIANT-4
Phase III study of everolimus versus placebo in nonfunctional NETs of GI or lung origin
ACCRUAL COMPLETED

Patients with advanced NET and no history of secretory symptoms
(N = 279)

- Advanced low- or intermediate-grade NET
- Radiologic progression
- Absence of carcinoid syndrome (flushing, diarrhea, or both)
- Presence of measurable disease (RECIST v1.0)
- Previous antitumor therapy allowed
- WHO PS ≤1



Primary endpoint: PFS (real-time central radiology review)

Phase II study of pasireotide LAR, everolimus Alone, or in Combination in Patients With Lung/Thymus NET - LUNA Trial

- Advanced typical and atypical carcinoid tumors lung and thymus

N=120
(Novartis)

1:1:1

Pasireotide LAR 60 mg IM q 28d

Everolimus 10 mg PO qD

Both

1°EP: 12 mo PFS

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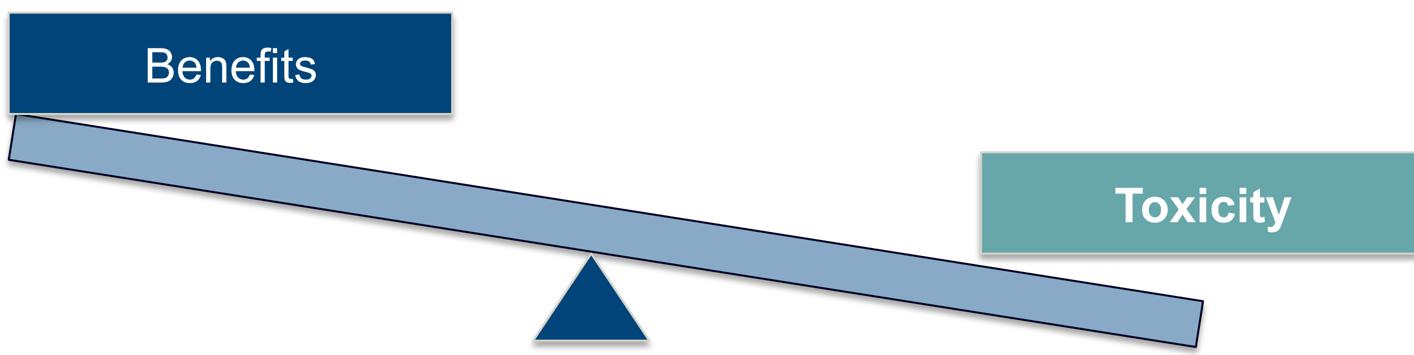
- **Major advances in understanding and treatment of NET in past 10 years**
- **Treatment needs to be individualized, weighing the risks of therapy vs potential benefit**
- **PanNETs ≠ Carcinoid**



Summary: Treatment of NETs

- Asymptomatic patients with stable G1/G2 unresectable disease and low tumor burden can be observed and monitored
- SSTa have documented antitumor activity in well diff NET
- Sequential therapy with targeted agents (everolimus or sunitinib) in patients with symptoms, clinically significant tumor burden, and/or progressive PanNETs
  - Stabilization >>> shrinkage
  - Optimal sequence unknown
- Chemotherapy standard for G3 tumors, and considered in PanNETs when tumor response required or when patients have failed targeted agents (optimal regimen unknown). Role of chemo in CARC unclear.
- Biomarkers needed

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Unanswered questions in well differentiated NETs

- **When should first line therapy be initiated?**
- **What is the optimal first line treatment?**
- **How should we sequence available agents in PanNET?**
  - SSTa, VEGF inhibitors, mTOR inhibitors, Chemotherapy, Liver directed, (PRRT)?
  - Novel agents?
- **Role of combination therapies?**
- **Role of adjuvant therapy (i.e. treatment to prevent recurrence after resection)**
  - ECOG 2212 (Everolimus v placebo in resected PanNET to liver)