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Clinical Trials 101

NET Patient Conference
1.19.14

Division of Hematology and Oncology

Department of Medicine

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What is a clinical trial?

- **Research study involving people**
- **Differ by type of trial and phase of trial**
- **Each clinical trial follows a set of strict scientific guidelines called a protocol.**

http://www.cancer.gov/clinicaltrials/learningabout/basicworkbook/

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Clinical Trials…

- the final step in a long research process
- translate basic scientific research results into better ways to prevent, diagnose, or treat cancer
- lead to advances in cancer care
- today's cancer treatments are based on previous study results

http://www.cancer.gov/clinicaltrials/learningabout/basicworkbook/

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Clinical Trials…

- **The more people who participate in clinical trials, the faster critical research questions can be answered**
  - >60% of US children participate in clinical trials
  - only 3 percent of U.S. adults with cancer participate in clinical trials➔ Many barriers exist

http://www.cancer.gov/clinicaltrials/learningabout/basicworkbook/page3

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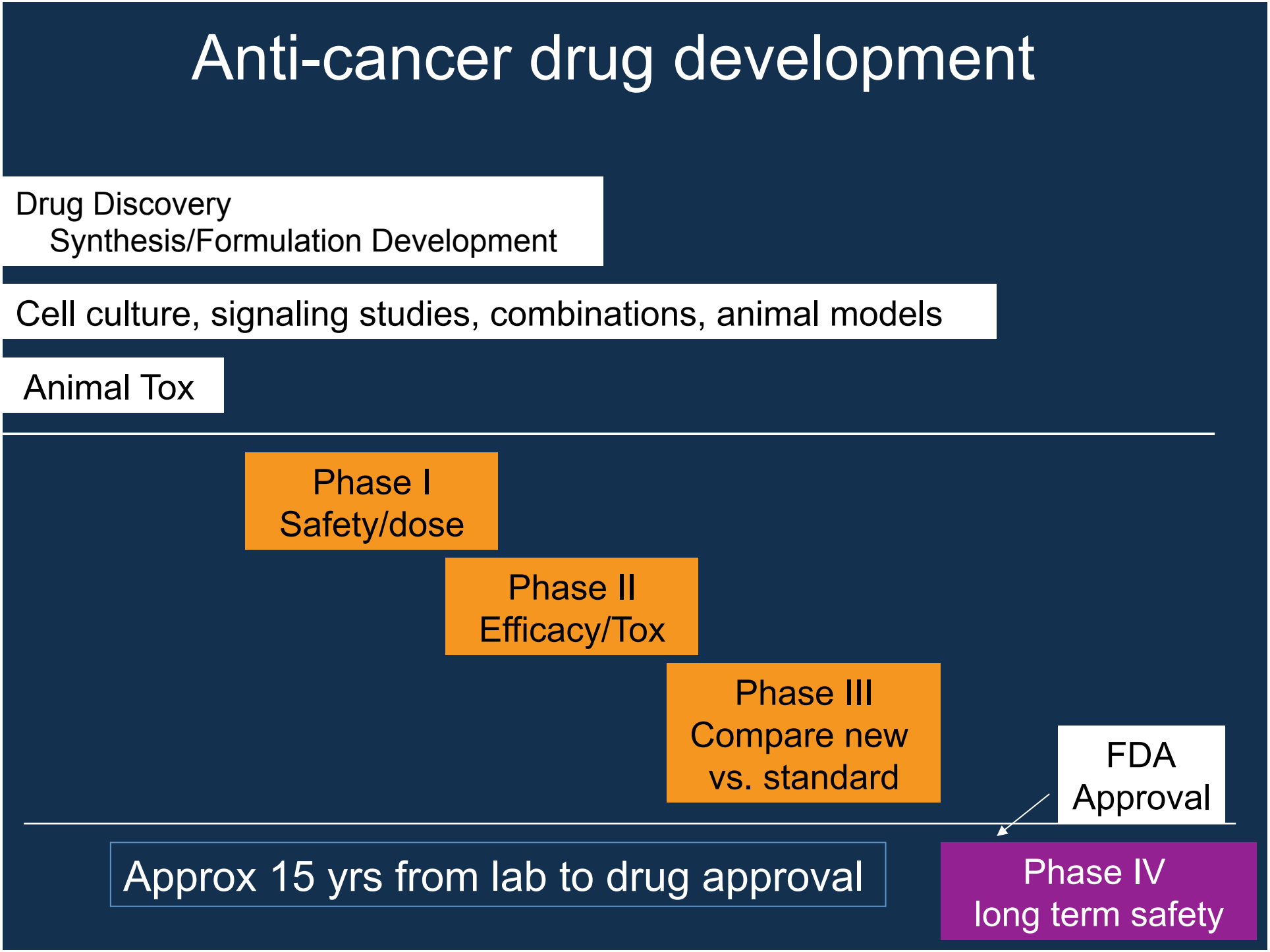
Types of cancer clinical trials

- Treatment trials
- Prevention trials
- Early detection/screening trials
- Diagnostic trials
- Quality of life/supportive care trials

http://www.cancer.gov/clinicaltrials/learningabout/basicworkbook/

Anti-cancer drug development



Phases of Clinical Trials

	Phase I	Phase 2	Phase 3	Phase 4
Number of participants	15-30	<100	100's-1000's	Several hundred to several thousand
Purpose	•To find a safe dosage •To decide how the agent should be given •To observe how the agent/ intervention affects the human body	•To determine if the agent or intervention has an effect on a particular cancer •To observe how the agent/ intervention affects the human body	To compare the new agent or intervention (or new use of a treatment) with the current standard	To further evaluate the long-term safety and effectiveness of a new treatment

http://www.cancer.gov/clinicaltrials/learningabout/basicworkbook/page3

Phases of cancer drug clinical trials:

Characteristics	Phase I	Phase II	Phase III
Time to complete trial	≈2 yr	≈3-4 yr	≈4-5 yr
Randomization	No	+/-	Yes
# Centers	1-5	1-several	many
Goals	Dose escalation; initial Safety & PK	Proof of concept (Efficacy signal) Toxicity	Efficacy (establish new standard)
Disease-specific	+/-	Yes	Yes

Investigator-initiated (smaller trials, often single institution)
Industry-sponsored ----------
Cooperative group (NIH/NCI sponsored)----------

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Biomarkers:

- **Potential to expedite process**
- **Use to enrich for patients likely to benefit and/or to provide evidence that the drug is inhibiting its target**
  - Glassman and Ratain. Clin Pharm and Ther, 2009

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The Research Protocol

- Background/Objectives: What are we trying to learn?
- Patient Eligibility: What group are we studying?
- Treatment Plan: What agent, dose schedule? What tests will be required?
- Statistical Methods: How many patients needed to draw valid conclusion? What information will be tracked (e.g. harmful effects of the drug, overall survival, tumor response)?
- Study Monitoring: How can we be sure the study data are reliable? How can we be sure its safe?

http://www.cancer.gov/clinicaltrials/learningabout/basicworkbook/

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What determines eligibility?

- **Disease (e.g. high grade vs low-intermediate grade; PNET vs carcinoid)**
  - Site of origin (e.g.midgut, foregut, hindgut)
  - Ki67
- **Stage (e.g. early vs metastatic disease)**
- **Stable disease vs progressive disease**
  - Functional v nonfunctional tumor
- **Prior therapy**
- **Current medication**
- **Other medical problems, etc.**

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Participant protection in clinical trials

- **Informed consent**
  - Process by which participant learns about risks/benefits
- **2 review panels:**
  - Scientific review
  - Institutional Review Board (IRB)-oversees clinical research at the local institution)
- **Monitoring (throughout the study)**
  - IRB-monitors patient safety
  - Data and safety monitoring boards (Phase III trials; periodic reviews of study conduct and participant safety)
  - Required reports to Federal agencies

http://www.cancer.gov/clinicaltrials/learningabout/basicworkbook/

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How can you find out about clinical trials?

- Ask your doctor
- Call the NCI's Cancer Information Service (1-800-4-CANCER (1-800-422-6237))
- Log on to NIH website (US government and industry-sponsored trials): www.clinicaltrials.gov
- Local cancer center website
- Foundations (e.g. Caring for Carcinoid)

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Is a trial right for you?

- Why is the study being done?
- What kinds of tests and treatments are involved?
- What are the possible side effects or risks of the new treatment? How do they compare to my other options?
- What are the possible benefits?
- How could the trial affect my daily life?
- Will I have to travel long distances?
- Will I have to pay for any of the treatments or tests?

http://www.cancer.gov/clinicaltrials/learningabout/basicworkbook

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CURRENT CLINICAL TRIALS

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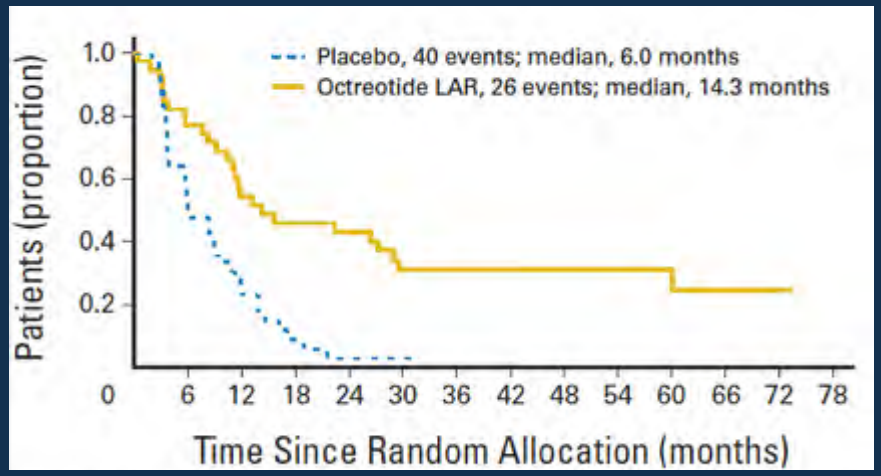
Clinical Trials

CARCINOID

CARCINOID

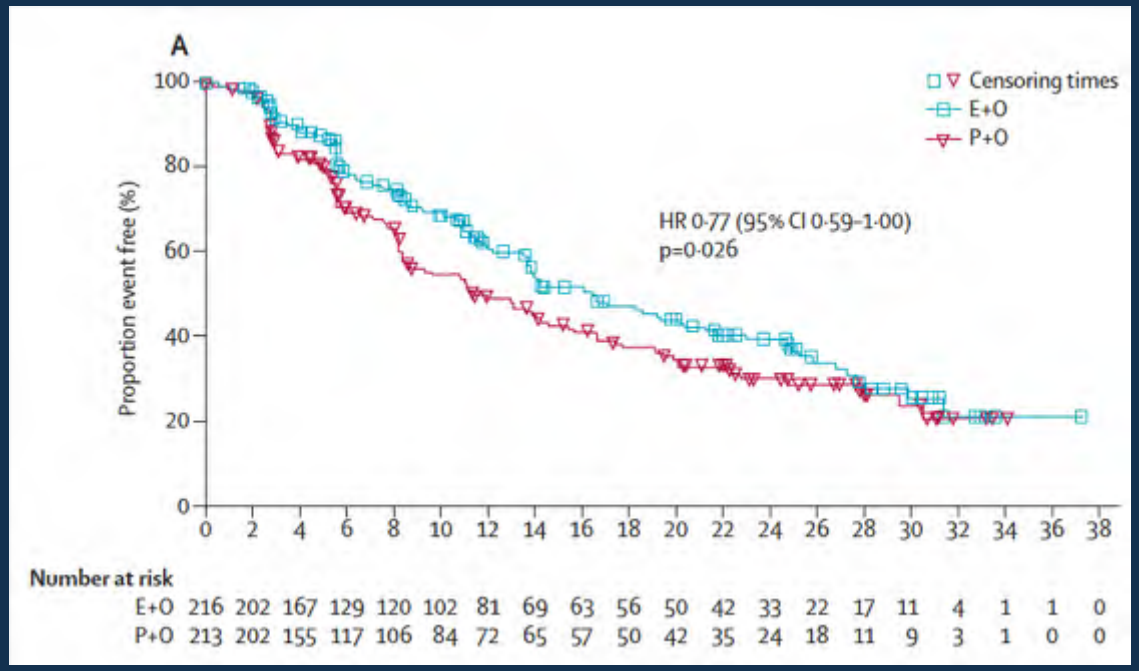
- Octreotide is approved for symptom control in patients with functional tumors
  - Octreotide delays tumor progression in mid-gut tumors (PROMID study; Rinke et al. 2009. Intermin analysis, 85 pt)



- Lanreotide delays progression in nonfunctional well-diff NET (but not yet FDA approved for this) (CLARINET study; Phan et al. NANETS, 2013) median PFS 18 mo placebo (21 mo midgut, 12 mo PNET) vs Not reached; 204 pt
- Role of PRRT uncertain in US

CARCINOID

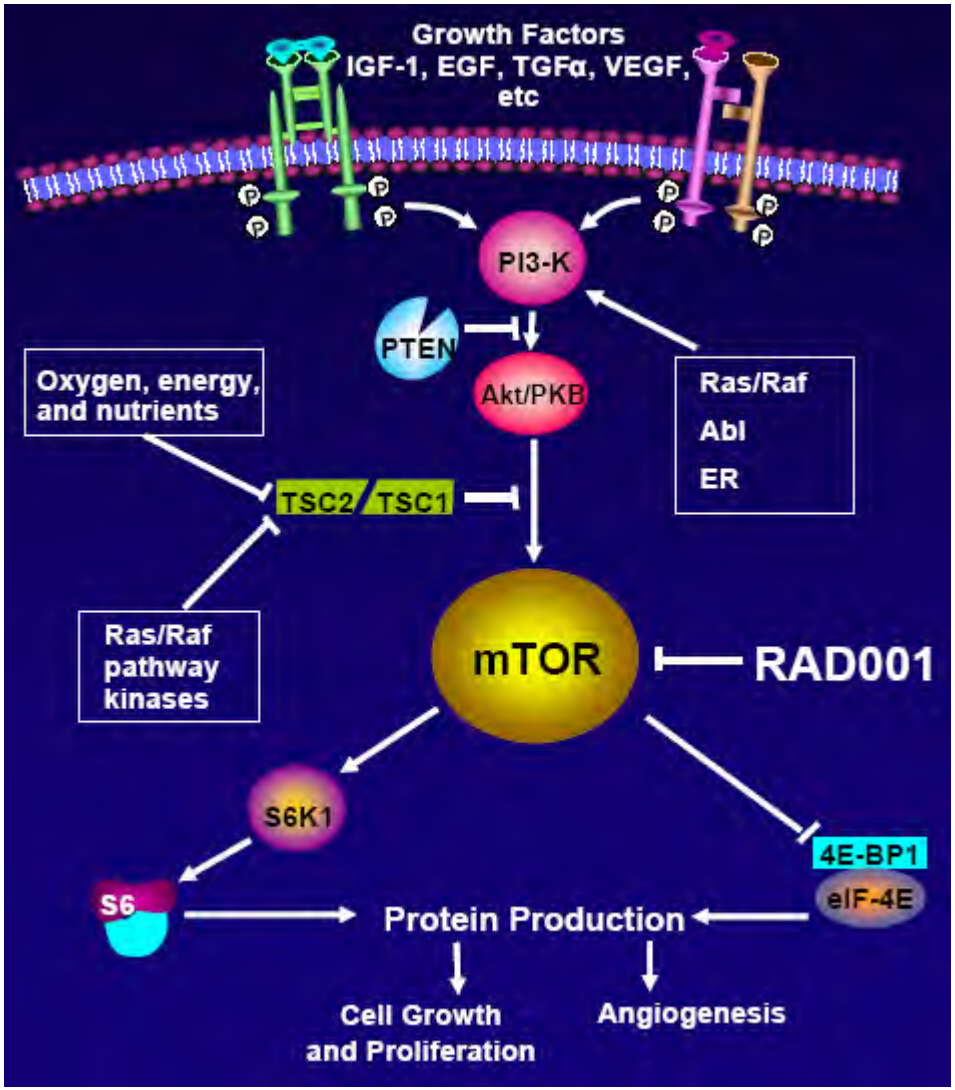
- Liver-directed therapies often employed (SIRT, HAE, HACE)
- Chemotherapy not routinely used
- Everolimus (mTOR inhibitor): category 3 per NCCN guidelines (i.e. *not FDA approved* for carcinoid)
  - RADIANT-2 (Pavel, et al. 2011)-progressive functional tumors



Everolimus	16.4 mo
Placebo	11.3 mo

NO SIGNIFICANT DIFF
(statistically)

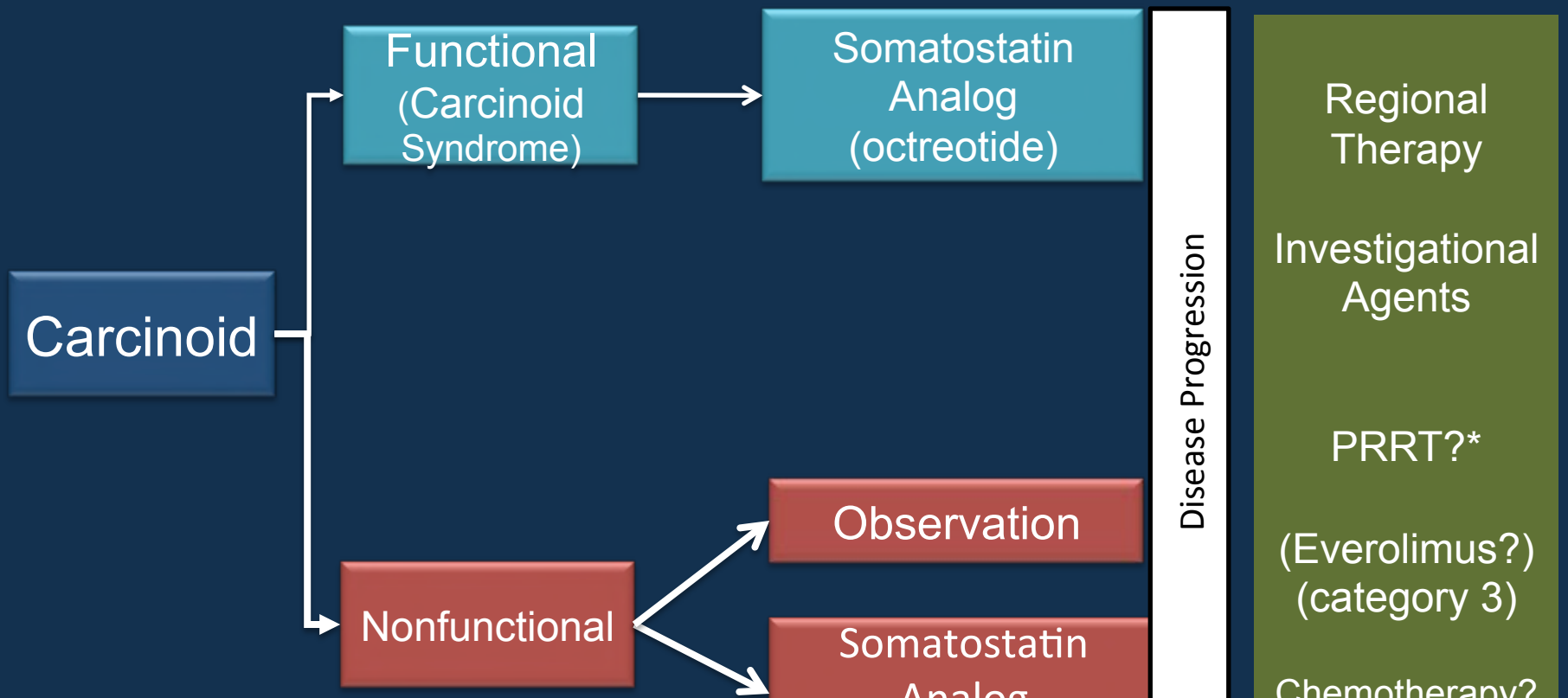
Everolimus inhibits mTOR pathway



- Patients with inherited problems of mTOR inhibition (TSC1/2) develop NETs ‡§
- Whole genome sequencing in pNET-15% w/ mutations in mTOR pathway†
- **Everolimus** (RAD001) inhibits mTOR signaling -FDA approved for pNET in April 2011
- Whole genome sequencing in small bowel NETs also (+) mutations in mTOR pathway

*Van Gompel et al. *Surgery*. 2004;136:1297-1302
†Jiao e al. *Science* 2011;60:4573-4581
‡Bank, JNCI, 2013

Medical Treatment Outlook for Unresectable Advanced Carcinoid in 2014



*Octreotide scan positive tumors- investigational in US

**Not yet FDA approved for CARC

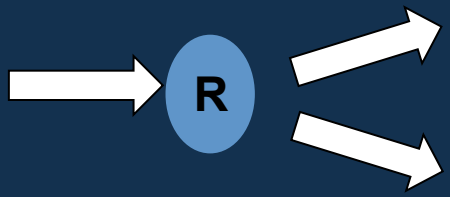
Adapted from D. Riedy-Lagunes

RECENT/CURRENT RANDOMIZED TRIALS IN CARCINOID			
SWOG 0518 BEV/LAR vs IFN/LAR	Advanced progressive carcinoid	Phase III	Accrual completed, results pending
RADIANT-4: Everolimus v placebo	Progressive, nonfunctional NETS of GI and Lung origin;	Phase III	Accrual completed Results pending
NETTER-1 177Lu-DOTA0-Tyr3-Octreotate v Octreotide LAR	Progressive SSTR (+) midgut, low grade carcinoid tumors	Phase III	OPEN
ALLIANCE 81102 Pazopanib v placebo	Progressive well diff NET (nonpancreatic; prior progression on LAR required for mid-gut)	Phase II	OPEN
TELESTAR Telotrastat v placebo	Inadequately controlled carcinoid syndrome	Phase III	OPEN (symptom control)

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

1°endpoint PFS

- Low grade; Ki67<20%
- Progressive SSTR(+) midgut CARC (by RECIST w/i 3 yr)
- On 20-30mg/mo LAR q 3-4 wk

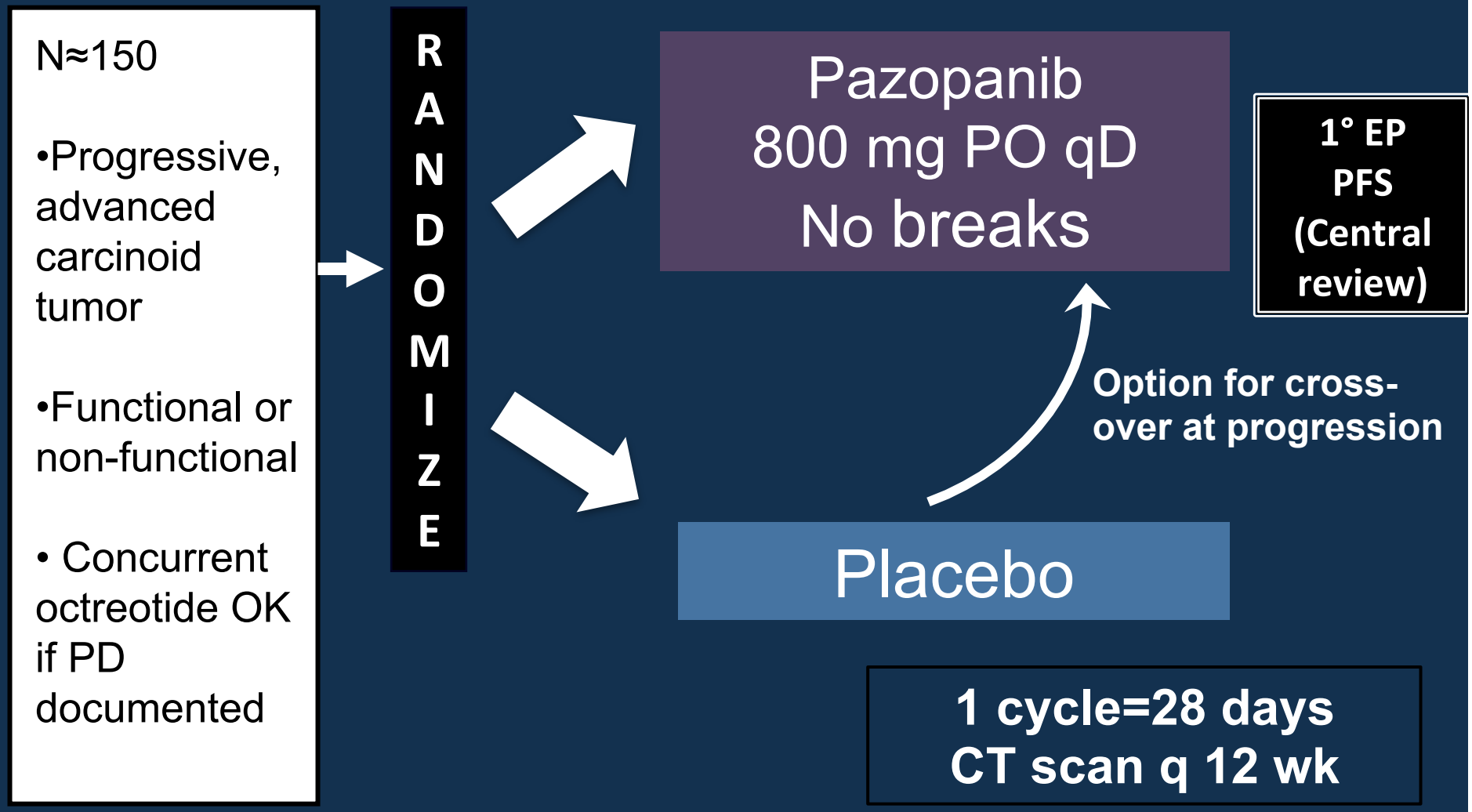


^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate x 4+ 30 mg octreotide LAR/mo

Octreotide LAR 60 mg/mo

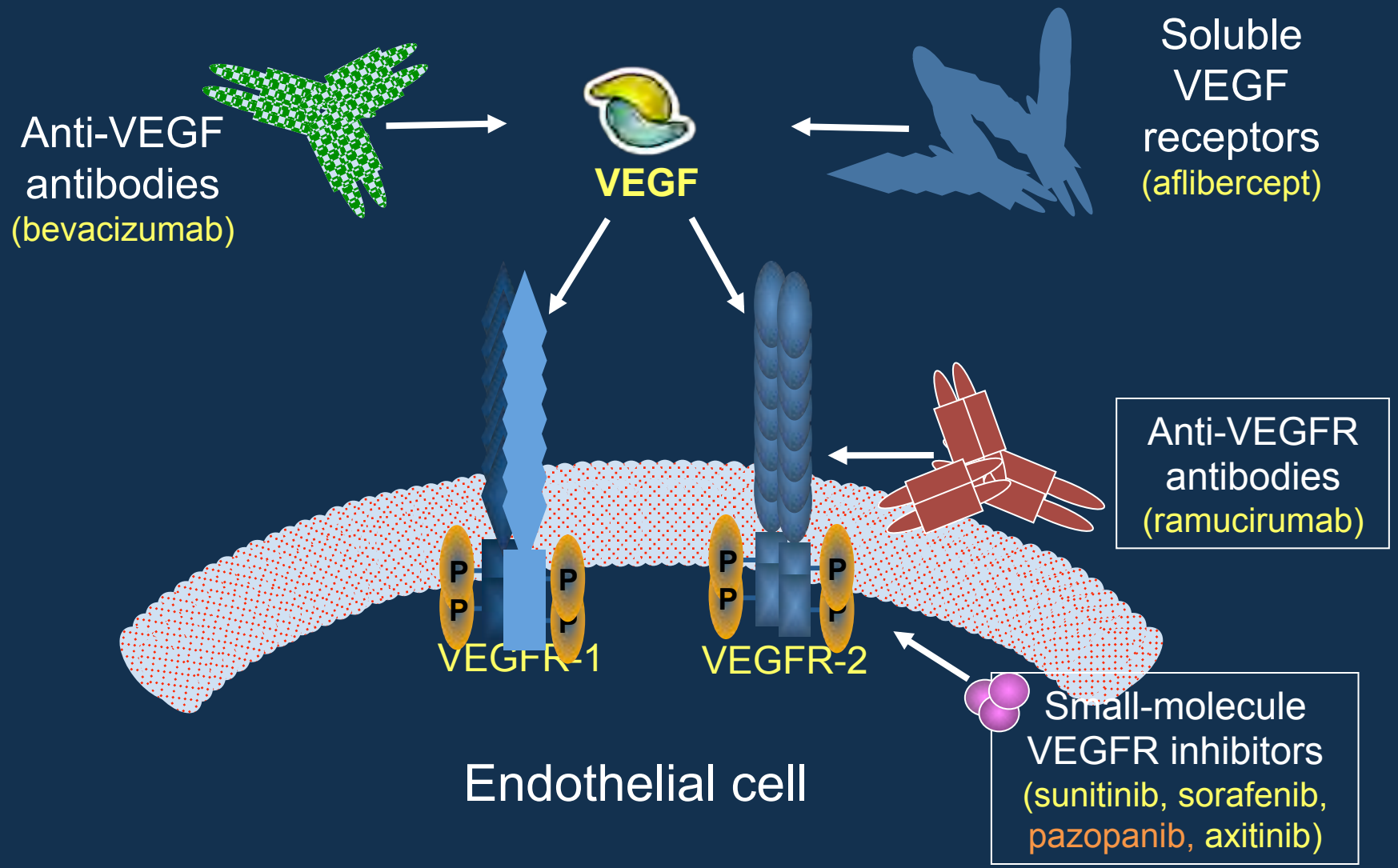
Sponsor: Advanced Accelerator Applications, France

A021202 : Randomized phase II trial of pazopanib v placebo in CARCINOID

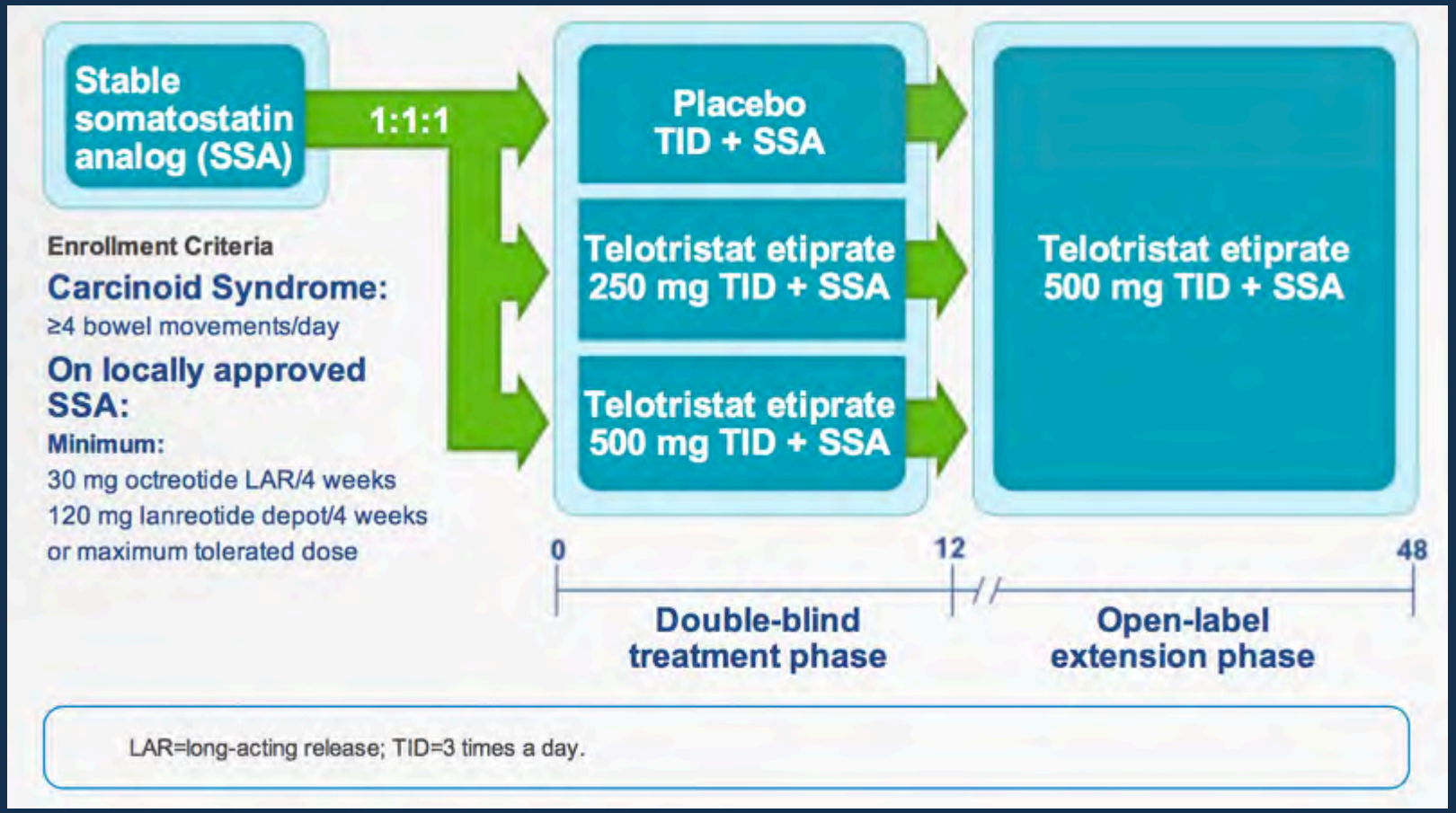


* Progression on octreotide required for midgut tumors

Agents Targeting the VEGF Pathway block tumor-associated blood vessel growth (angiogenesis)



TELESTAR Trial: Phase III trial of telotristat v placebo in patients with inadequately controlled carcinoid syndrome



1°EP: change in daily BM from baseline to wk 12

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PANCREATIC NET (PNET)

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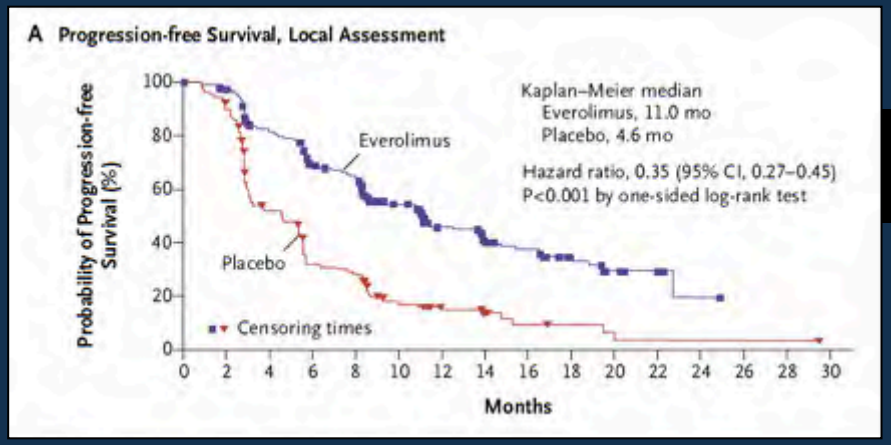
PNET

- Lanreotide delays progression in nonfunctional well-diff NET (not yet available)
- Liver-directed therapies often employed (SIRT, HAE, HACE)
- Role of PRRT uncertain in US
- Chemotherapy used in selected patients (streptozocin-based or temozolomide-based)

PNET

- Everolimus delays progression in patients with progressive PNET (Raymond, et al 2011)-FDA approved

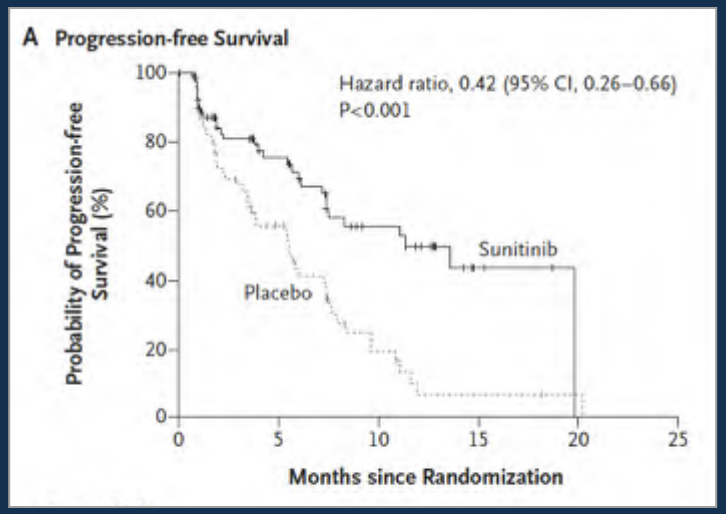


Everolimus	11.0 mo
Placebo	4.6 mo

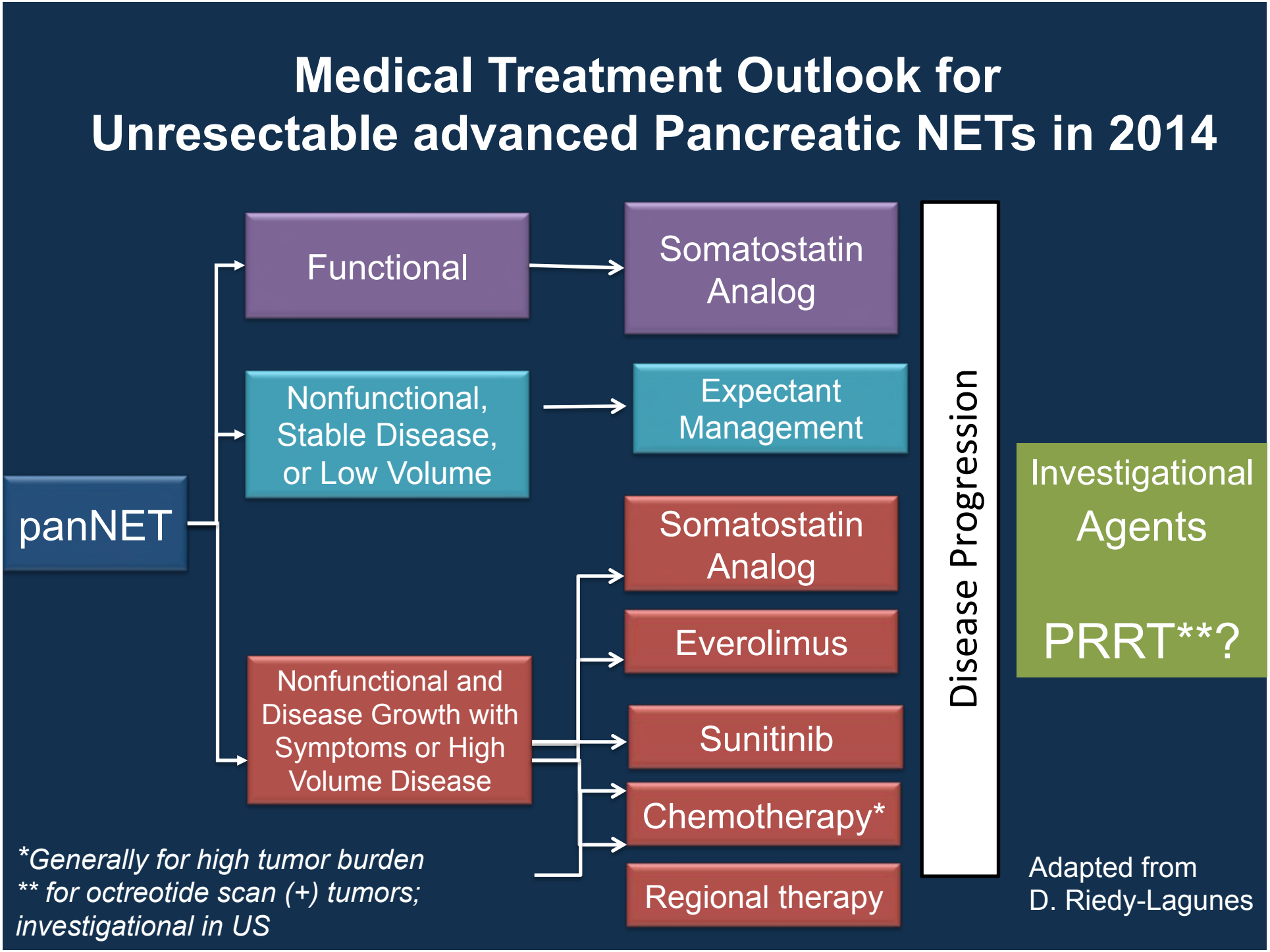
- Sunitinib delays progression in patients with progressive PNET (Yao, et al 2011):

FDA approved

Sunitinib	11.4 mo
Placebo	5.5 mo
HR 0.42, P<0.01	



Medical Treatment Outlook for Unresectable advanced Pancreatic NETs in 2014



Summary: streptozocin-based chemotherapy- pancreatic NETs

REGIMEN	N	AUTHOR	YEAR	RESPONSE RATE (%)
Streptozocin + fluorouracil[1]	95	Pavel	2014	43%
Streptozocin + doxorubicin[2]	38	Moertel	1992	69%
Streptozocin + doxorubicin[3]	16	Cheng	1999	6%
Streptozocin + doxorubicin + fluorouracil[4]	84	Kouvaraki	2004	39%

1. Pavel et al ASCO 2014 2. Moertel CG et al. *N Engl J Med* 1992;326:519-523; 3. Cheng PN and Saltz LB. *Cancer* 1999;86:944-948; 4. Kouvaraki MA et al. *J Clin Oncol* 2004;22:4762–4771

Temozolomide-based regimens

REGIMEN	N	AUTHOR	YEAR	RESPONSE RATE (%)
Temozolomide + thalidomide[1]	11*	Kulke	2006	45%
Temozolomide + bevacizumab[2]	15*	Chan	2012	33%
Temozolomide + capecitabine[3]	30	Strosberg	2010	70%
Temozolomide + capecitabine[4]	28	Fine	2014	43%**

*pancreatic NET cohort of trial

** MIX of tumors

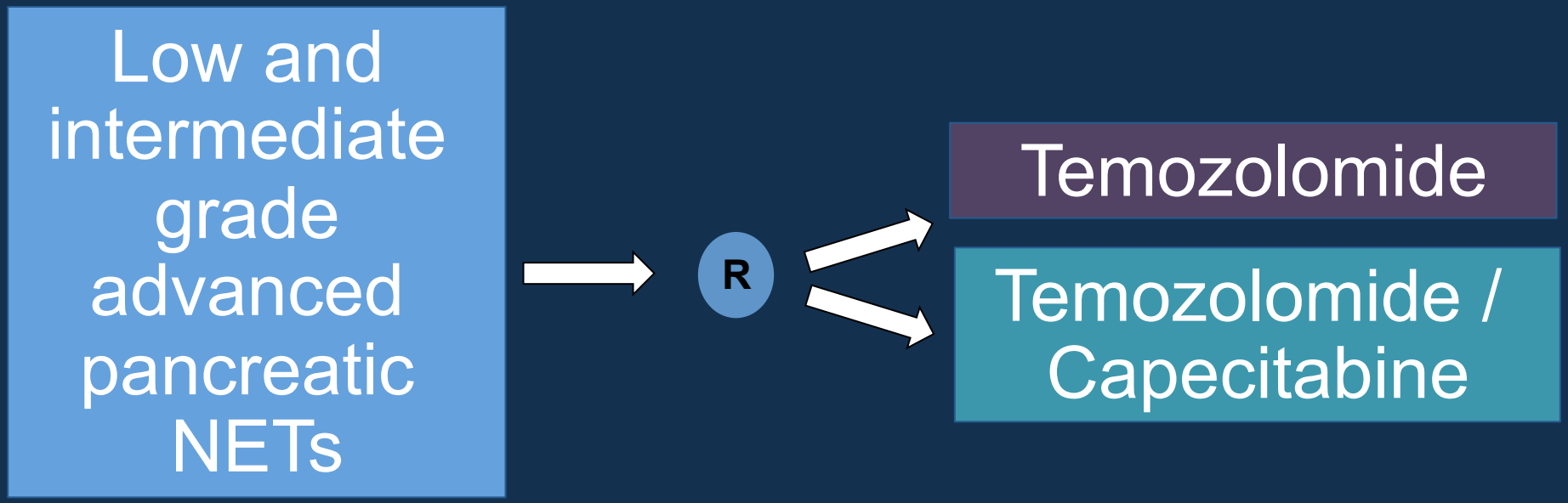
1. Kulke M et al. *J Clin Oncol* 2006;24:401–406; 2. Chan JA et al. *J Clin Oncol* 2012;30:2963–2968;
3. Strosberg J et al. *Cancer* 2011;117:268–275 4. Fine R et al ASCO GI 2014; interim analysis

RANDOMIZED TRIALS IN PNET

CALGB 80701 Everolimus/LAR vs Everolimus +BEV/ LAR	Progressive PNET	Phase II	Accrual completed, results pending
E2211 capecitabine/tem vs tem	PNET	Phase II	OPEN
E2212 Everolimus v placebo after resection	PNET	Phase II	OPEN

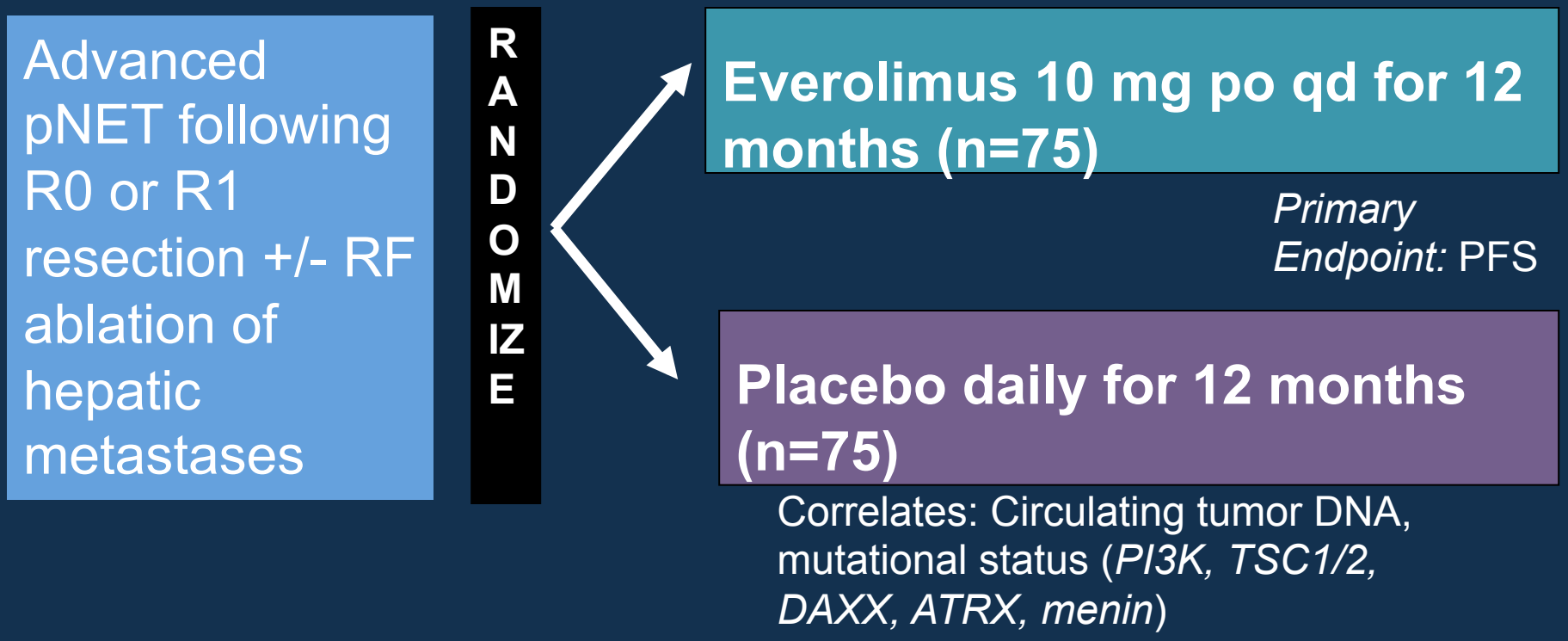
E2211 - A Randomized Study of Temozolomide or Temozolomide+Capecitabine in Patients with Advanced Pancreatic Neuroendocrine Tumors -OPEN

- 1°EP PFS



- Progression w/I 12 mo
- No prior 5-FU, cape, temozolomide or DTIC

E2212: Randomized Double-Blinded, Placebo-Controlled Phase II Study of Adjuvant Everolimus Following the Resection of Metastatic Pancreatic Neuroendocrine Tumors to the Liver



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HIGH GRADE NEUROENDOCRINE CARCINOMAS (NEC)

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High grade NEC

- **Typically treated like small cell lung cancer**
- **First line therapy typically platinum-based (e.g. cisplatin/etoposide)**
  - Recent data suggest that not all G3 tumor equally sensitive to chemotherapy (Sorbye, et al Ann Oncol 2013)
    - Ki67>55% 42% RR
    - Ki67<55% 15% RR (305 pt, P<0.001)
- **No standard second line and beyond**
  - Temozolomide-based chemotherapy appears to have activity in retrospective study of GI NEC (RR 33%; Welin, et al. 2011)
- **First line randomized trial in development**
- **Refractory patients: Phase I trials, small cell carcinoma etc. (Trials specifically for high grade NEC are relatively hard to find)**

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Clinical Trials: Bay Area

SUMMARY

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Bay Area NET Trials: Stanford

- PNET: Ph II Temozolomide, Cape, Bevacizumab
- PNET: Ph II Temozolomide vs. Temozolomide + Cape
- CARC: Ph III ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate vs. Octreotide
- CARC SYNDROME: Ph III Telotristat vs. Placebo
- NET Registry database

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Bay Area NET Trials: UCSF

- **CARC: Ph II Axitinib**
- **CARC: Ph II Pazopanib vs. placebo**
- **CARC SYNDROME: Ph III Telotristat vs. placebo**
- **PNET: Ph II Temozolomide vs. Temozolomide + Cape**
- ***PNET: Phase II oral TKI trial—open soon***
- **MIXED: Theraspheres for treatment of metastatic liver disease from primary NET**

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Unanswered Questions: Clinical Trials

- **Optimal timing and type of nonsurgical liver-directed treatment (HAE, SIRT, etc)?**
- **Relative efficacy and safety of PRRT in NET (and optimal timing of intervention)?**
- **Role of other systemic agents?**
  - Optimal chemotherapy regimen?
- **Can treatment be individualized to patient/tumor (biomarkers)?**
- **Are there new pathways/targets that should be targeted in NET?**
  - Mechanisms of resistance?