

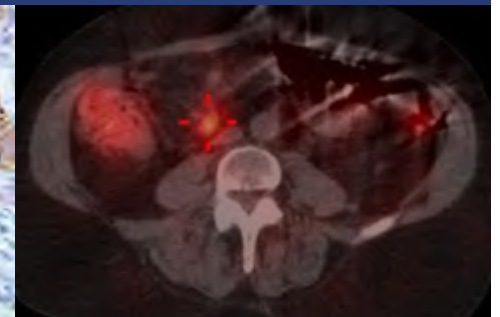
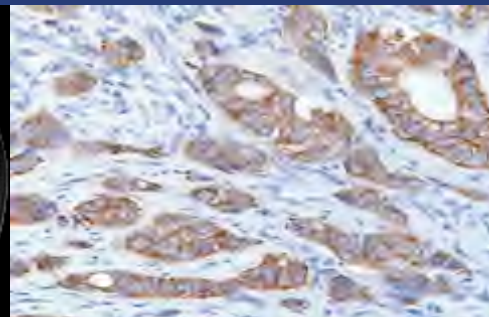
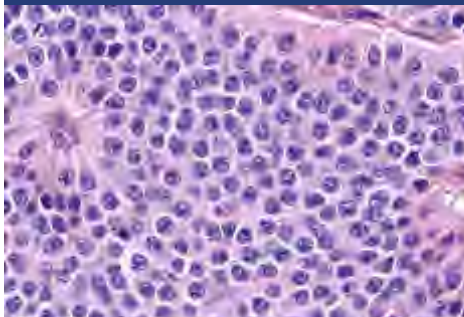
# An Immunotherapy Clinical Trial for NETs

Pamela L. Kunz, MD

Assistant Professor of Medicine / Oncology

Stanford Cancer Institute

March 1, 2015



# Outline

- Clinical trial basics
- What have we learned from recent NET trials?
- The Stanford Immunotherapy Trial in NETs
- How can you learn about clinical trials?

# What are clinical trials?

- *“Clinical trials are research studies that explore whether a medical strategy, treatment, or device is safe and effective for humans.”*

# Types of clinical trials

- Preclinical: Works in mouse tumors...
- Phase I = tests safety (hope for efficacy)
  - Often any type of tumor eligible
  - Usually 15-25 patients
  - Defines sides effects; “best” dose
- Phase II = preliminary test of efficacy
  - Limited to specific tumor type
  - Usually 25-50 patients
- Phase III = tests efficacy compared to “standard”
  - Limited to specific tumor type; sometimes placebo “control”
  - Usually 200-500 patients
  - Essential to assess survival differences

# Design and interpretation of clinical trials

- Eligibility Criteria
  - Which NETs?
  - Well vs. poorly differentiated?
  - Site of origin?
  - Growing (or not)
  - Prior treatment (or not)
- Measures of Success
  - Response Rate (RR)
    - How much does the tumor shrink?
  - Progression Free Survival (PFS)
    - How long does it take for the tumor to grow?
  - Overall Survival (OS)
    - How long do patients live?

# Sources of clinical trials

<b>Investigator Initiated</b>	<b>Industry Initiated</b>	<b>Cooperative Group</b>
<ul style="list-style-type: none"><li>• Often smaller Ph I/II</li><li>• Usually available at a single academic institution</li><li>• Idea is initiated by academic MD</li><li>• Funding and/or drug supply from industry</li></ul>	<ul style="list-style-type: none"><li>• Ph I, II or III</li><li>• Usually involves many sites and sometimes international</li><li>• Idea is initiated by industry</li><li>• Funding from pharmaceutical company</li></ul>	<ul style="list-style-type: none"><li>• Ph I, II or III</li><li>• Sponsored by NIH / National Cancer Institute</li><li>• Open at centers participating in a cooperative group (i.e. ECOG, SWOG, ALLIANCE)</li><li>• Funding is federal</li></ul>

# Why are clinical trials important?

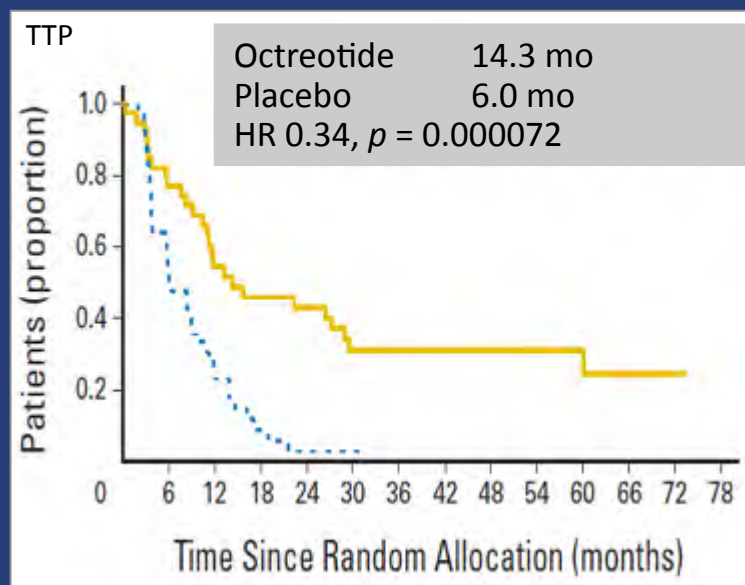
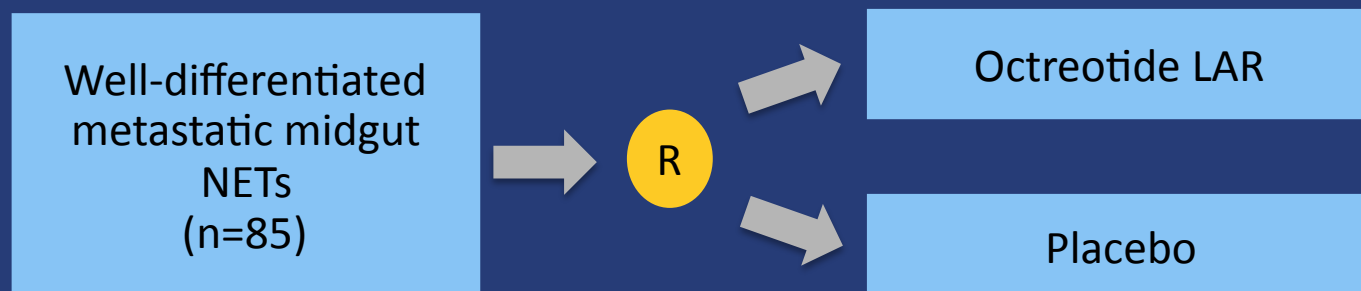
- Clinical trials are a key research tool for advancing medical knowledge and patient care.
- Clinical research is done to learn:
  - Whether a new approach is safe and effective
  - Which treatments or strategies work best for certain illnesses or groups of people
- Yet...only 3% of U.S. adults with cancer participate in clinical trials!

# Outline

- Clinical trial basics
- What have we learned from recent NET trials?
- The Stanford Immunotherapy Trial in NETs
- How can you learn about clinical trials?

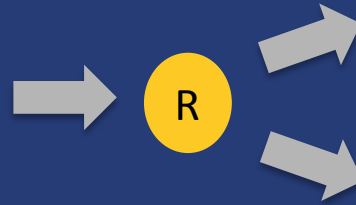


# Somatostatin Analogue: Phase III Octreotide (PROMID)



# Somatostatin Analogue: Phase III Lanreotide (CLARINET)

Non-functioning  
advanced NETs  
(n=204)

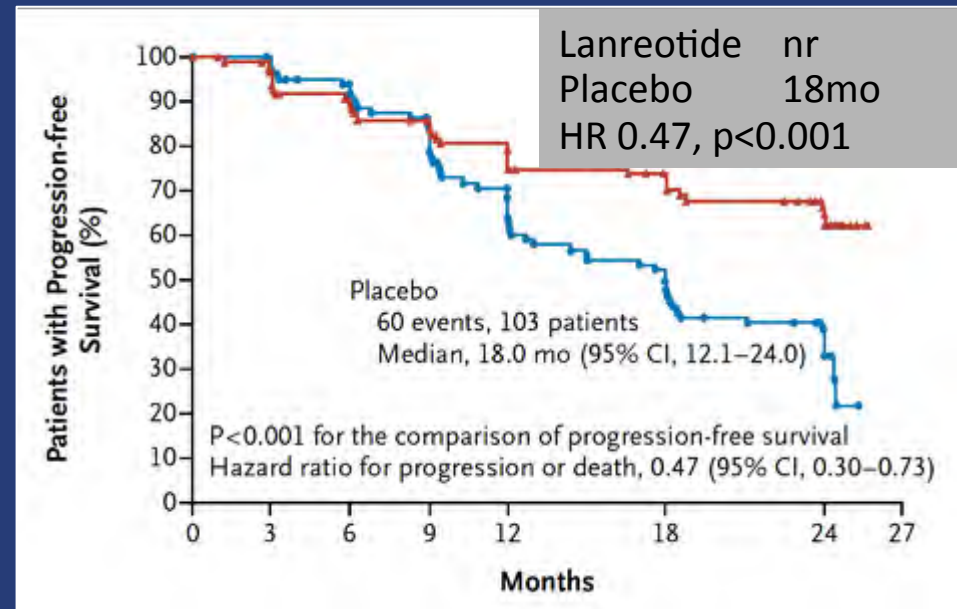


Lanreotide

Placebo

Primary site	%
Pancreas	45
Midgut	36
Hindgut	7
Unknown	13

FDA approved for  
GI-NETs



# mTOR Inhibitors: Phase III Everolimus (RADIANT 3)

Advanced pancreatic  
NETs  
(n=410)

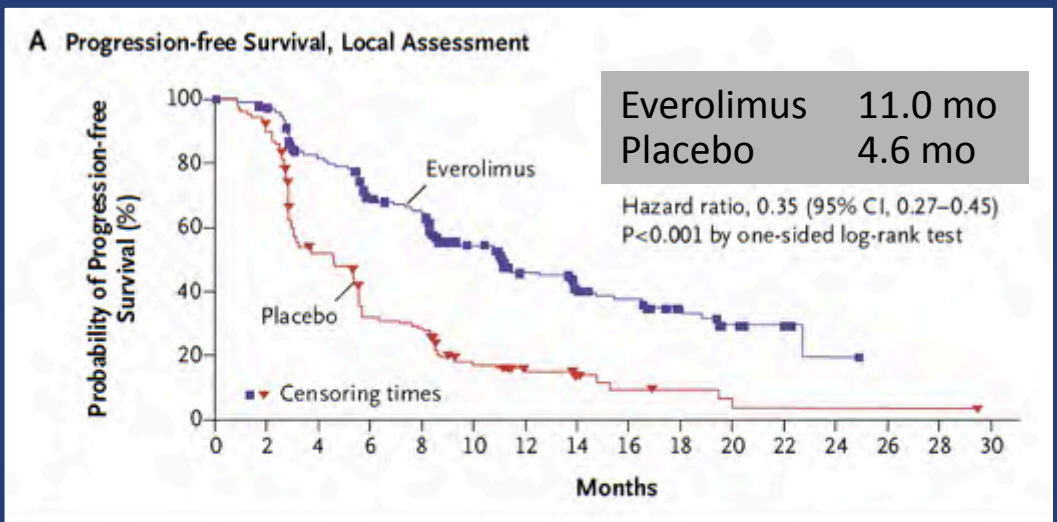


R



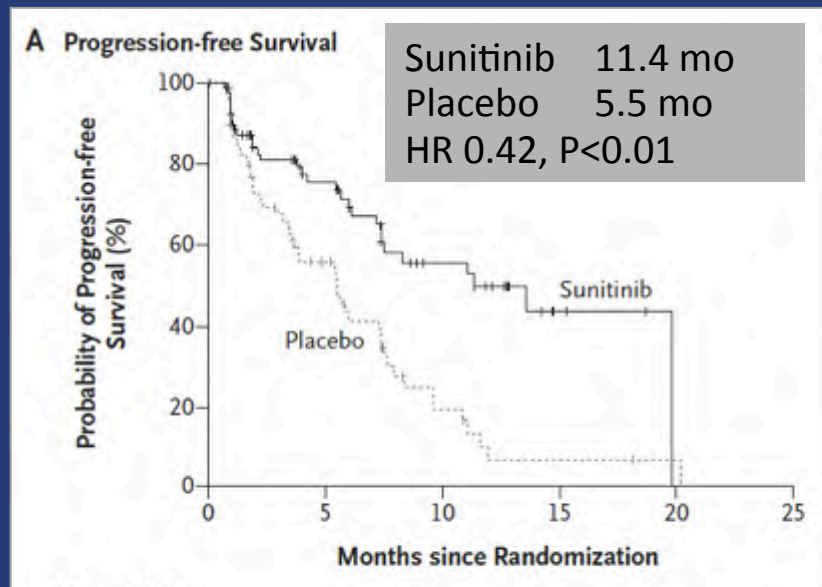
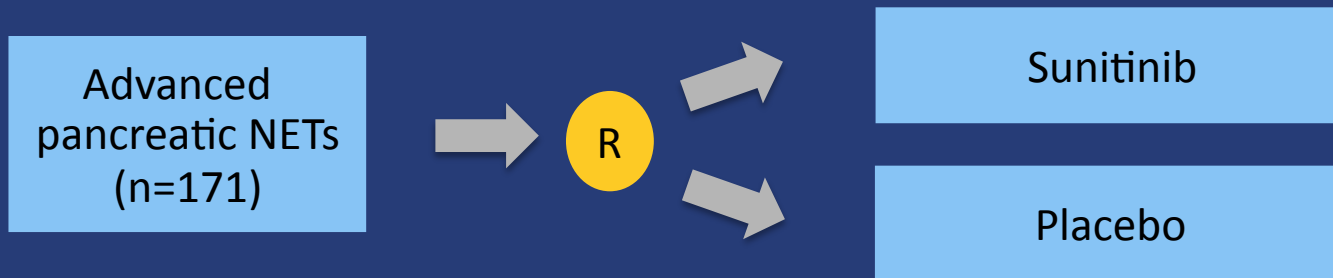
Everolimus

Placebo



FDA approved for  
Pancreatic NETs

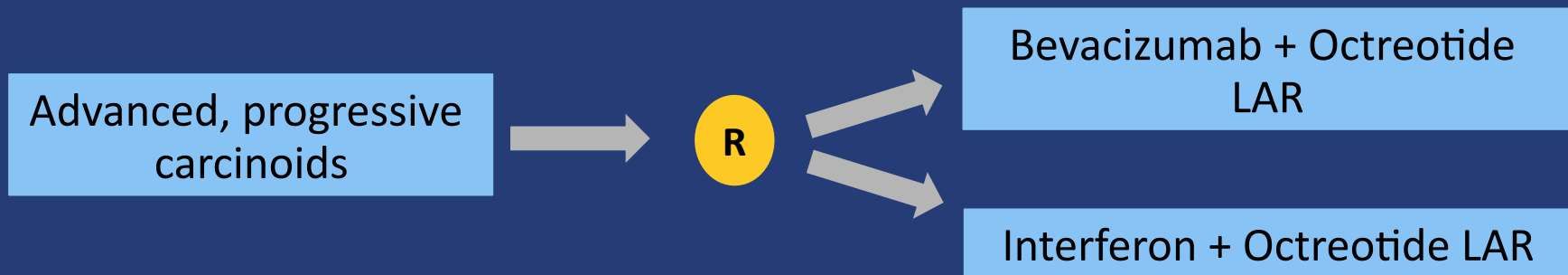
# Angiogenesis Inhibitors: Phase III Sunitinib



FDA approved for  
Pancreatic NETs

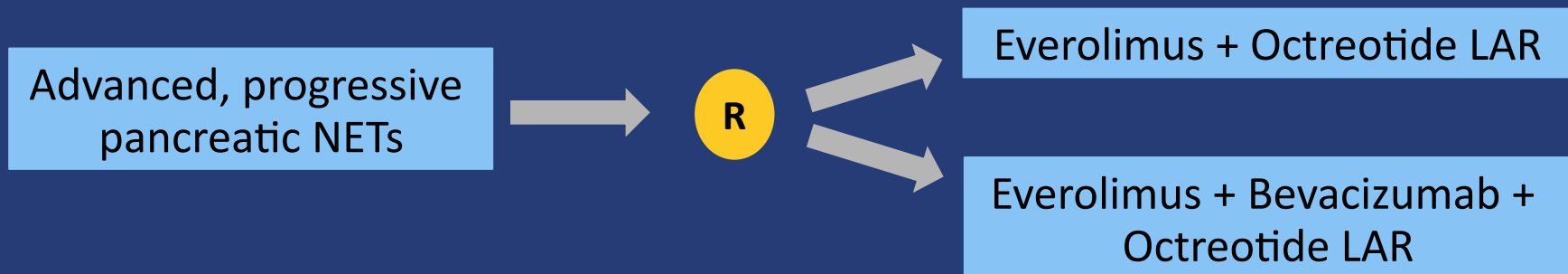
# Recently completed trials (eagerly awaiting results!)

SWOG 0518 (Yao PI): Phase III, opened 12/07, 1° endpoint PFS



---

CALGB 80701 (Kulke PI): Phase II, opened 10/10, 1° endpoint PFS



# Outline

- Clinical trial basics
- What have we learned from recent NET trials?
- The Stanford Immunotherapy Trial in NETs
- How can you learn about clinical trials?

# A Phase I/II Clinical Trial of Intratumoral Anti-CTLA-4 (Ipilimumab) and Anti-PD-L1 (MPDL3280A) in NETs

PL Kunz, H Kohrt, GA Fisher  
Stanford University

# Background (1)

- We need cancer therapies with less toxicity and more specific targeting of tumor cells.
- Antibody-based therapies can target specific protein receptors on the surface of tumor cells.
- The first generation of antibody-based therapies has transformed the standard of care:
  - Bevacizumab (Avastin<sup>®</sup>) – colon, lung, glioblastoma
  - Trastuzumab (Herceptin<sup>®</sup>) – breast, stomach



## Background (2)

- New therapies target “immunologic checkpoints” in the patient’s immune system to reverse tumor-induced immunosuppression
- These immunotherapies have been limited to immune-sensitive tumors like melanoma
- Immune related side effects are potentially serious (ie. inflammation of normal organs)

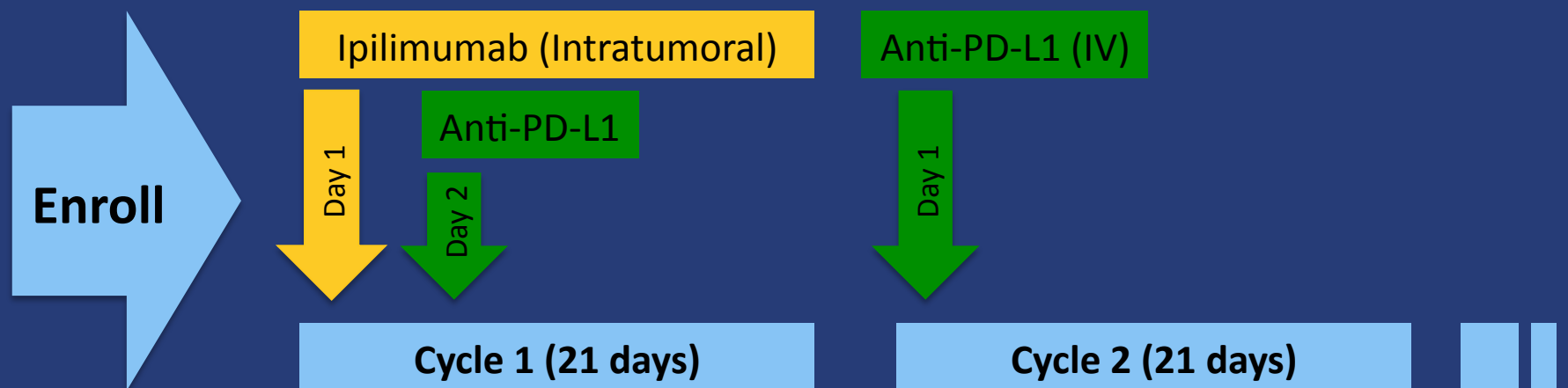
## Background (3)

- NETs have some rationale for using immunotherapies, though are not traditionally considered immune-sensitive
- Interferon alpha, a naturally occurring immune modulatory cytokine, controls carcinoid syndrome and slows tumor growth in some small bowel NETs

# The scientific questions

- Can we design a trial that:
  - ① has the potential to shift an immune-insensitive tumor, such as NET, to immune-sensitive and
  - ② limits the immune toxicities?

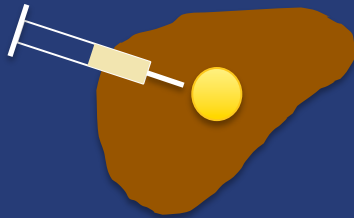
# Schema and Study Design



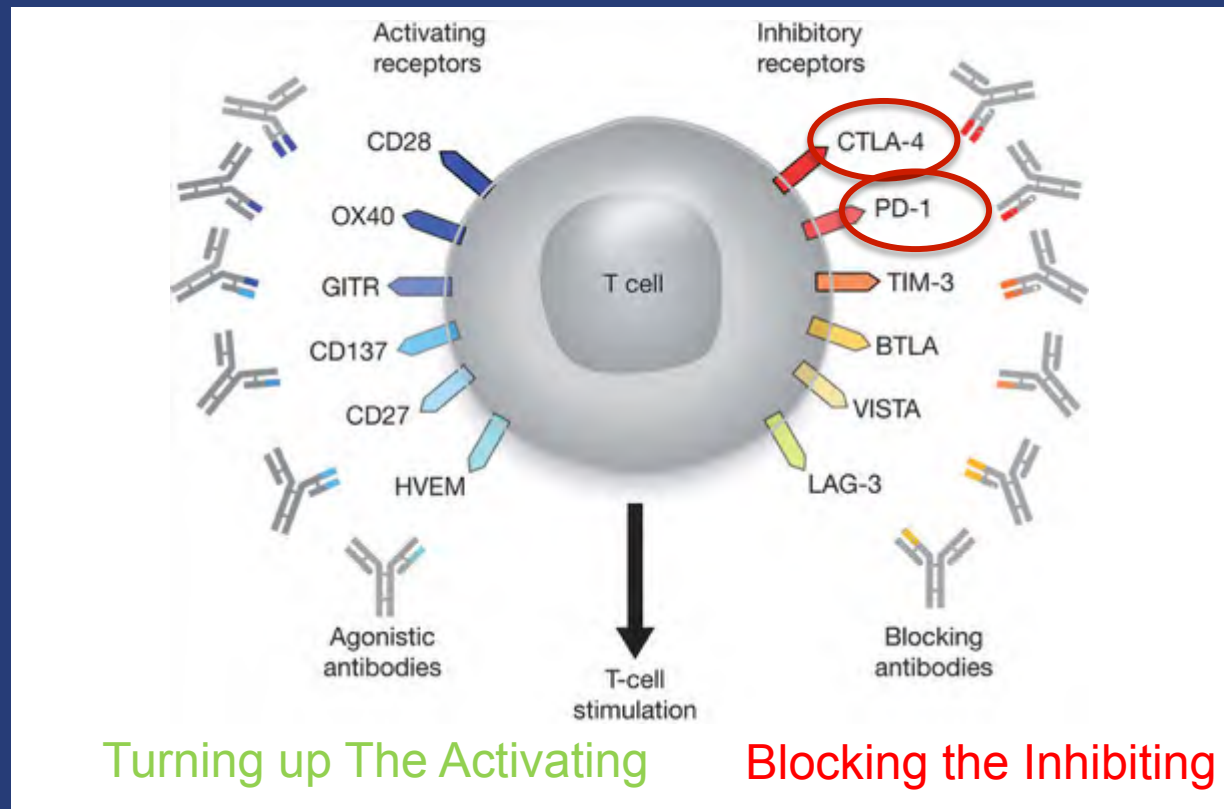
- Design: Single arm, Phase I/II, 20 patients enrolled in groups of 5 to allow early stopping for toxicity
- Primary Endpoints: To assess safety and efficacy
- Secondary Endpoints: To assess laboratory-based markers of immune response

# What are the drugs?

Anti-CTLA4 (Ipilimumab)



Anti PD-L1 (MPDL3280A)



# Key Eligibility Criteria

1. Metastatic NETs
  1. Pancreatic (10)
  2. Non-pancreatic (10)
2. All tumor grades with Ki-67  $\leq$  55%
3. ECOG Performance Status 0-2
4. Must have had at least 1 prior treatment
5. Must have had tumor growth on most recent treatment

# Correlative Studies

We will use four methods to identify immunologic biomarkers of tumor response:

1. Flow cytometry
2. Deep sequencing of T cell receptors,
3. Circulating tumor DNA
4. PD-L1 tumor immunostaining

# Frequently Asked Questions (1)

## 1. When does it start?

- Anticipated Summer 2015

## 2. How do I enroll?

- First, discuss the trial with your oncologist. If your oncologist thinks you would be a good candidate for the trial they can refer you to Dr. Kunz or Fisher.



## Frequently Asked Questions (2)

3. Are there certain treatments or characteristics that would make me ineligible?
  - Detailed inclusion and exclusion criteria will be available as soon as the trial is posted on [clinicaltrials.gov](https://clinicaltrials.gov).
4. How do I consult with an oncologist at the center where the clinical trial is being conducted?
  - To schedule a new patient evaluation with Drs. Kunz or Fisher, please call the Stanford Cancer Center 650-498-6000 and ask to speak with the GI Oncology new patient coordinators.

# Outline

- Clinical trial basics
- What have we learned from recent NET trials?
- The Stanford Immunotherapy Trial in NETs
- How can you learn about clinical trials?

# How can you learn about clinical trials?

## ClinicalTrials.gov

A service of the U.S. National Institutes of Health

*ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. Learn more [about clinical studies](#) and [about this site](#), including relevant [history](#), [policies](#), and [laws](#).*

[Find Studies](#) [About Clinical Studies](#) [Submit Studies](#) [Resources](#) [About This Site](#)

ClinicalTrials.gov currently lists **153,457 studies** with locations in all 50 states and in **185 countries**.

Text Size ▾

### Search for Studies

Example: "Heart attack" AND "Los Angeles"

[Advanced Search](#) | [See Studies by Topic](#)  
[See Studies on a Map](#)

### Search Help

- [How to search](#)
- [How to find results of studies](#)
- [How to read a study record](#)

### Locations of Recruiting Studies



Total N = 31,113 studies  
Data as of October 10, 2013

- [See more trends, charts, and maps](#)

### For Patients & Families

- [How to find studies](#)
- [See studies by topic](#)
- [Learn about clinical studies](#)
- [Learn more...](#)

### For Researchers

- [How to submit studies](#)
- [Download content for analysis](#)
- [About the results database](#)
- [Learn more...](#)

### For Study Record Managers

- [Why register?](#)
- [How to register study records](#)
- [FDAAA 801 Requirements](#)
- [Learn more...](#)

### Learn More

- [ClinicalTrials.gov Online Training](#)
- [Glossary of common site terms](#)

[For the Press](#)

[Using our RSS Feeds](#)

[HOME](#)

[RSS FEEDS](#)

[SITE MAP](#)

[TERMS AND CONDITIONS](#)

[DISCLAIMER](#)


[CONTACT NLM HELP DESK](#)

# How can you learn about clinical trials?

Clinical Trials Finder | Carcinoid and Pancreatic Neuroendocrine Cancer Research | CFCF

www.caringforcarcinoid.com/clinical\_trials

Most Visited | Getting Started | Latest Headlines




Dedicated to Discovering Cures for Carcinoid and Pancreatic Neuroendocrine Cancers

Log In | Blogs | CFCF Story | FAQs | Glossary | Contact Us

NEUROENDOCRINE CANCER | RESOURCES | JOIN US FOR A CURE | RESEARCH | ABOUT US

Make a Difference **DONATE NOW**



Newly Diagnosed

Carcinoid & Neuroendocrine Tumor Patient Community

Doctor Database

Clinical Trials

- Clinical Trials Finder
- About Clinical Trials
- Clinical Trials Updates

Educational Resources

News

Additional Resources

Home » Resources » Clinical Trials » Clinical Trials Finder

### Clinical Trials Finder

The Caring for Carcinoid Foundation offers its Clinical Trials Finder and Patient Resource. This resource will provide the neuroendocrine tumor community with the most up-to-date and comprehensive information on relevant clinical trials in the United States.

With this resource, patients and caregivers may learn about the availability and purpose of existing clinical trials, and access supplemental resources from the Food and Drug Administration, the American Cancer Society and the National Cancer Institute.

By using CFCF's Clinical Trials Finder, patients and caregivers can search our comprehensive neuroendocrine tumor database of clinical trials, which consists of all active clinical trials being conducted in the US for carcinoid, pancreatic neuroendocrine tumors and pheochromocytoma.

Visit our [About Clinical Trials](#) page to learn more. For additional information on clinical trials or help using this site, please contact CFCF at 617-948-2514 or [info@caringforcarcinoid.org](mailto:info@caringforcarcinoid.org).

**Conditions**

**Status**

**Phase**

**State (abbreviation)**

Title	Phase	Status	Conditions	State
<a href="#">131I-Metaiodobenzylguanidine (131I-MIBG) Therapy for Refractory Neuroblastoma and Pheochromocytoma</a>		Not Yet Recruiting	Pheochromocytoma	MN
			Carcinoid Tumor	
			Neuroendocrine Tumor	
<a href="#">177Lu-tetate-DOTA-Octreotate Therapy in Somatostatin Receptor-Expressing</a>	II	Enrolling	Pancreatic	TX

### Get the Facts on Pancreatic Neuroendocrine Cancer

Check out Lauren's Blog

### NET Survivors Tell your story

Submit and read other survivor stories.

Sign-up for our e-Newsletter.

Enter email to sign up


### Latest Video

Check out the CFCF video library.

### Lauren's Blog

Read the latest blog from CFCF's Director of Research.

Connect with CFCF online:



# How can you learn about clinical trials?

The screenshot shows the Stanford Cancer Institute website. At the top, there is a search bar and navigation links for "Patient Resources", "Diseases & Treatments", "Understanding Cancer", "Clinical Trials", "Research", "Training", "Outreach", and "About Us". The main heading is "Find Cancer Clinical Trials". Below this, there is a paragraph explaining that the clinician scientists are engaged in more than 250 clinical trials. A contact information box provides a phone number (650-498-7061) and an email address (cto-office@stanford.edu). A section titled "Filter by One or More Trial Details" includes input fields for Keyword, Adult/Pediatric (set to All), Condition (set to All), Drug Used, Doctor, Trial ID, and Status (set to Accepting Patients). A "Search" button is located at the bottom of the filter section.

<http://cancer.stanford.edu/trials/>

The screenshot shows the App Store page for the "SCI Trials" app by Stanford University. The app is described as a mobile app for finding clinical trials. It features a "Description" section, a "What's New in Version 1.1" section, and a "Screenshots" section. The "Screenshots" section shows a preview of the app's interface, which includes a search bar, a "CONTACT US" button, and a list of clinical trials. The app is available for free on both iPhone and iPad.

Stanford Clinical Trials App

# Stanford NET Trials

- PNET: Ph II Temozolomide, Cape, Bevacizumab
- PNET: Ph II Temozolomide vs. Temozolomide + Cape
- PNET after liver resection: Ph II Everolimus vs. Placebo
- CARC: Ph III  $^{177}\text{Lu}$ -DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate vs. Octreotide
- CARC: Ph II Pazopanib vs. Placebo
- CARC SYNDROME: Ph III Telotristat vs. Placebo
- GI NET: Ph II Fosbretabulin
- NET Registry

# How can you learn about clinical trials?

The screenshot shows the UCSF Helen Diller Family Comprehensive Cancer Center website. The top navigation bar includes 'PATIENT CARE', 'CLINICAL TRIALS', and 'RESEARCH'. The main heading is 'Clinical Trials (List View)'. A breadcrumb trail shows 'Home > Clinical Trials > Clinical Trials (List View)'. A central message reads: 'Thank you for your interest in clinical trials at UCSF. Research studies conducted with cancer patients are called clinical trials. As a cancer patient, you may take part in a clinical trial. Please see the links below for current open trials at UC San Francisco.' Below this are three links: '> [More information about participating in a trial](#)', '> A PDF of current open Adult Interventional Trials can be downloaded [here](#)', and '> For questions call us at 877-827-3222 or [email](#)'. A purple bar indicates 'Pediatric Cancers are listed here: [Visual View](#) | [List View](#)'. A section titled 'Adult Cancers by Disease Site:' lists 'Blood' with sub-items: '(Malignant Hematology/Leukemias)', 'Lymphoid Leukemia', and 'Leukemia, other'. On the right, a sidebar contains 'Clinical Trials (List View)', 'Clinical Trials (PDF View)', 'Advanced Search', 'About Clinical Trials', 'For Referring Physicians', and 'Additional Resources'. Below the sidebar is a 'CONTACT US' section with the text: 'Clinical trial availability changes frequently. For information about any of our studies, contact us: Call us at 877-827-3222 or [email us](#)'. At the bottom of the sidebar, it says 'For other types of clinical trials at UCSF'.

<http://cancer.ucsf.edu/clinical-trials>

# UCSF NET Trials

- PNET: Ph II Temozolomide vs. Temozolomide + Cape
- PNET after liver resection: Ph II Everolimus vs. Placebo
- CARC: Ph II Pazopanib vs. placebo
- CARC SYNDROME: Ph III Telotristat vs. placebo
- --
- ALL SOLID TUMORS: Ph IB MK-3475 (Anti-PD1)
- ALL SOLID TUMORS: Ph I CB-5083 (inhibitor of p97)



# Take home points

- There has been exponential growth of research in the field of NETs
- There are numerous active and developing clinical trials
- Clinical trial participation is essential to advance the field
- Immunotherapy holds promise