

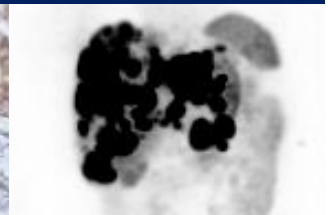
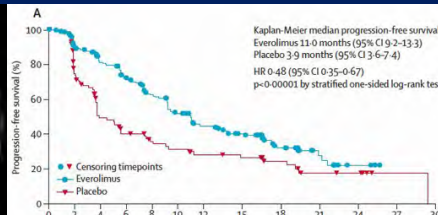
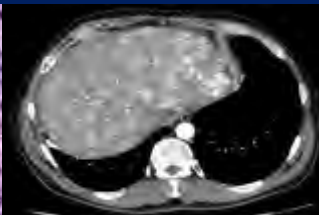
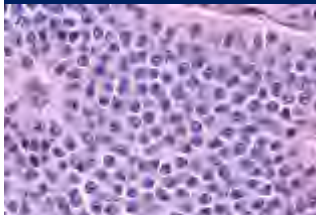
2015: Year in Review Results of Recent Trials

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Director, Stanford NET Program

Stanford University School of Medicine



Disclosures

- Research Funding: Advanced Accelerator Applications, Esanex, Genentech, Lexicon, Merck, Oxigene
- Advisory Boards: Ipsen, Novartis, Lexicon
- Stock: Guardant Health

Outline

- Clinical trial basics
- Interpreting recent trials
 - Lanreotide, Everolimus, Telotristat
- Trials on the horizon
- How you can 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?
 - Safety

Sources of clinical trials

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

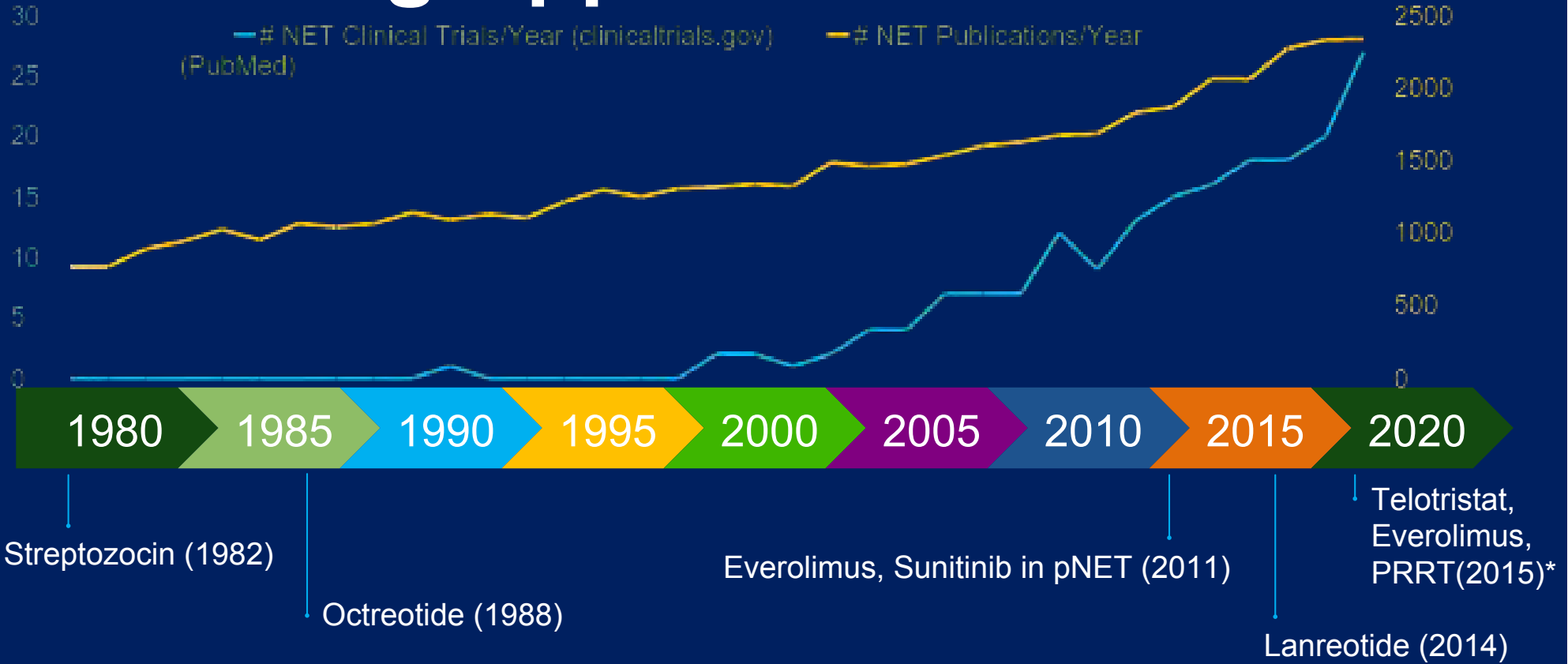
Why are clinical trials important?

- 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

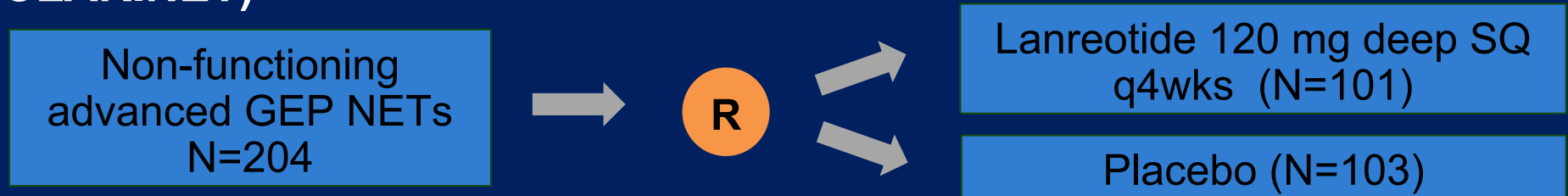
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NET Drug Approvals



*not currently FDA-Approved

Ph III Lanreotide in GEP NET (CLARINET)



- Eligibility:

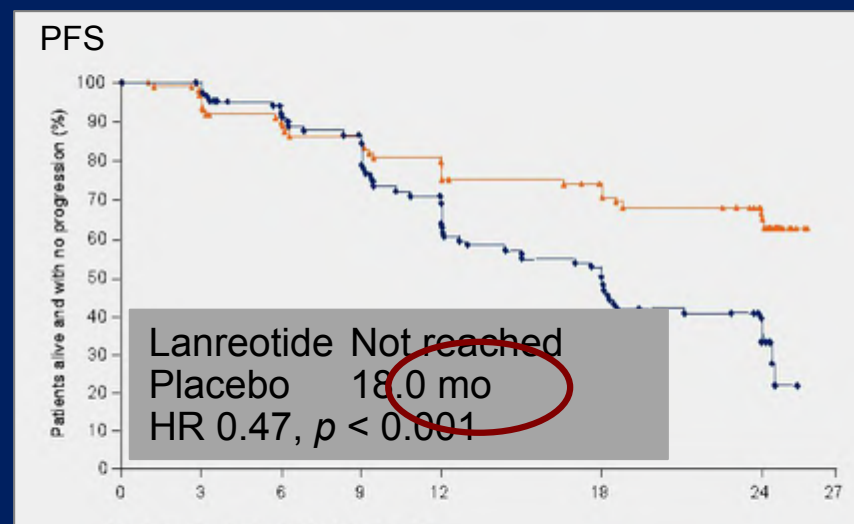
- Well or moderately differentiated
- Ki 67 < 10%
- Pancreas, midgut, hindgut, unknown
- Non-functional

- Design:

- 96 wk, randomized, double blind, placebo-controlled
- Primary EP: PFS
- Europe, UK, Ireland
- Crossover allowed on ext study

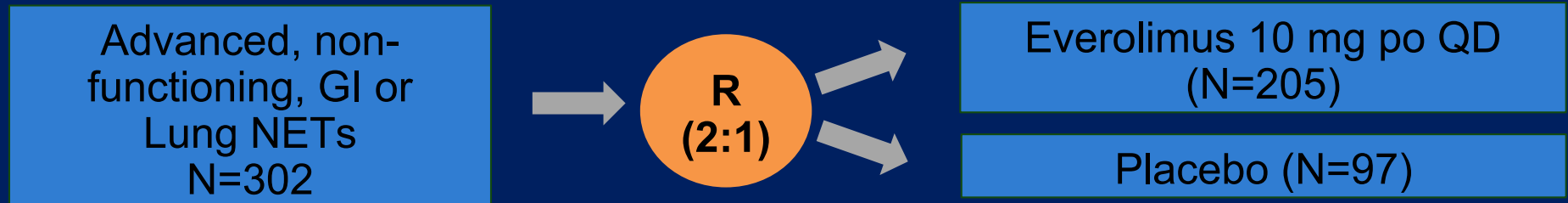
Ph III Lanreotide in GEP NET (CLARINET)

Baseline Characteristics		
Variable	Lanreotide	Placebo
Male - n(%)	53 (52)	54 (52)
Age - yr	63.3	62.2
Time since diagnosis (median, mo)	13.2	16.5
Origin – n (%)		
Pancreas	42 (42)	49 (48)
Midgut	33 (33)	40 (39)
Hindgut	11 (11)	3 (3)
Unknown/Other	15 (15)	11 (11)
Tumor Progression – n(%)	4 (4)	5 (5)



- Median PFS in extension study 32 mo
- No difference seen in OS ($p = 0.88$)
- RR 2%
- Well-tolerated

Ph III Everolimus in GI and Lung NETs (RADIANT-4)



- Eligibility:

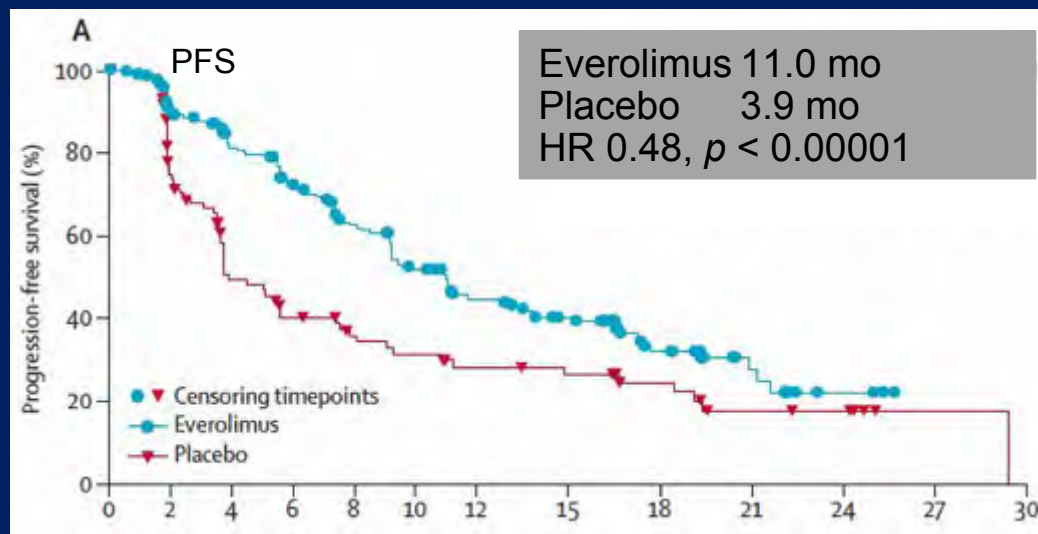
- Well or moderately differentiated
- WHO Grade 1 or 2 (Ki 67 <20%)
- Non-functional
- Lung, GI tract (pancreas excluded)
- Progression within 6 months

- Design:

- Randomized, double blind, placebo-controlled
- Primary EP: PFS
- US, UK, Europe, Asia
- No crossover allowed

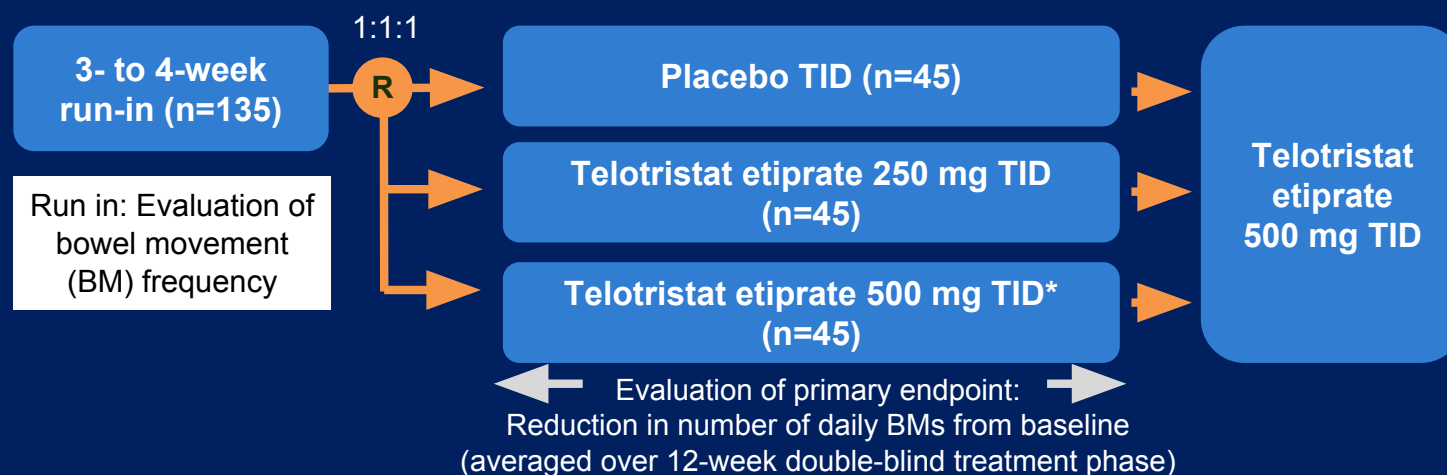
Ph III Everolimus in GI and Lung NETs (RADIANT-4)

Baseline Characteristics		
Variable	Everolimus	Placebo
Male - n(%)	89 (43)	53 (55)
Age - yr	65	60
Time since diagnosis (median, mo)	29.9	28.9
Origin – n (%)		
Lung	63 (31)	27 (28)
Midgut	72 (35)	32 (32)
Hindgut	34 (17)	19 (20)
Unknown/Other	36 (18)	19 (20)



- Trend towards OS difference (HR 0.64, [95% CI 0.40-1.05], $p = 0.037$)
- RR 2% on everolimus
- AEs were as expected

Ph III Telotristat in Carcinoid Syndrome (TELESTAR)



Ph III Telotristat in Carcinoid Syndrome (TELESTAR)

Key Eligibility Criteria

- Well-differentiated metastatic NET
- Documented Carcinoid Syndrome (CS) with ≥ 4 BMs/day
- Currently receiving stable-dose (≥ 3 months) SSA therapy
- Exclude diarrhea not related to CS or history of short gut syndrome
- Exclude >12 BMs/day associated with volume depletion, dehydration

Study Design

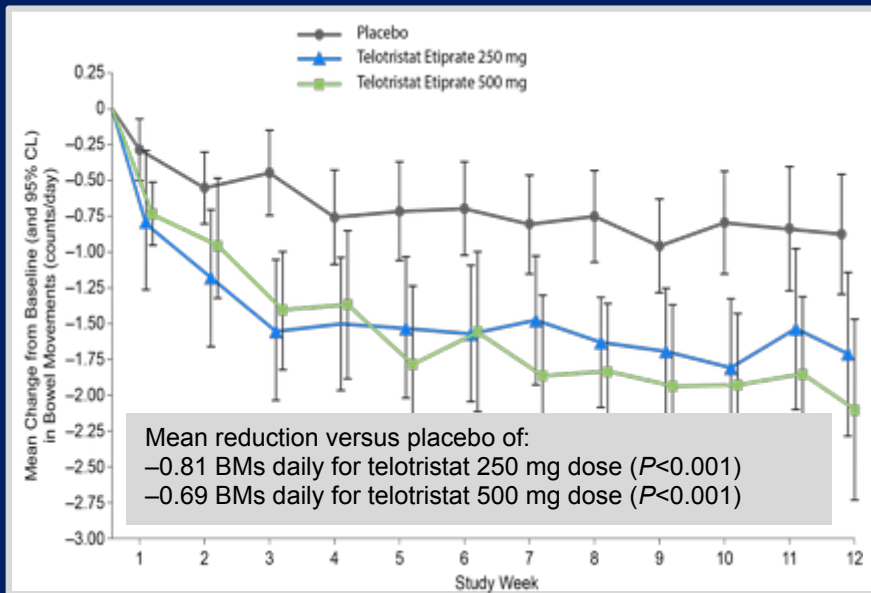
- Randomized, double blind, placebo controlled
- Primary EP: Daily BM frequency averaged over 12-week, double-blind treatment phase

Ph III Telotristat in Carcinoid Syndrome (TELESTAR)

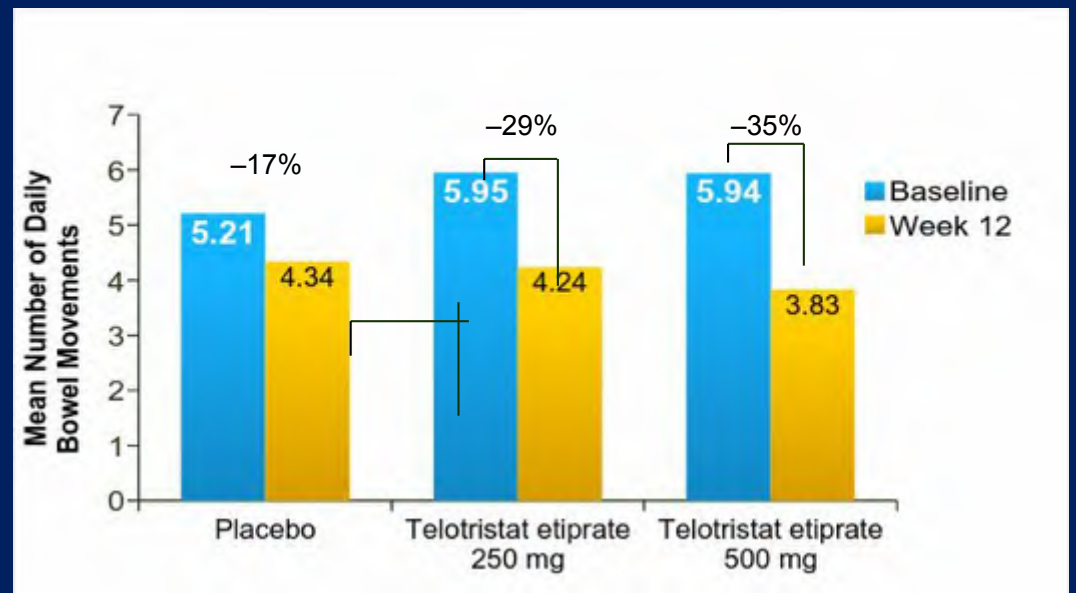
Baseline patient characteristics	Placebo (n=45)	Telotristat etiprate 250 mg (n=45)	Telotristat etiprate 500 mg (n=45)
Age, mean (SD)	63.3 (8.7)	62.4 (9.1)	64.9 (9.0)
Male sex, n (%)	24 (53.3)	21 (46.7)	25 (55.6)
Daily BM frequency, mean (SD)	5.2 (1.4)	6.1 (2.1)	5.8 (2.0)
SSA therapy at study entry, n (%)			
Octreotide	30 (66.7)	40 (88.9)	33 (73.3)
Lanreotide	15 (33.3)	5 (11.1)	12 (26.7)
Urinary 5-HIAA at randomization, n (%)			
≤ULN (≤0–15)	12 (26.7)	12 (26.7)	12 (26.7)
>ULN (>15)	26 (57.8)	26 (57.8)	26 (57.8)
Unknown	7 (15.6)	7 (15.6)	7 (15.6)

Slide courtesy of Dr. Matthew Kulke

Reduction in Bowel Movement Frequency



Reduction in BM frequency averaged over double blind period



Reduction in mean daily BM Frequency at baseline and Week 12

TELESTAR Interview Objectives

- Learn how baseline symptoms in TELESTAR affected patient lives
- Find out which symptoms changed the most during TELESTAR
- Assess patient satisfaction with telotristat etiprate in TELESTAR

Telotristat Clinically Meaningful Change

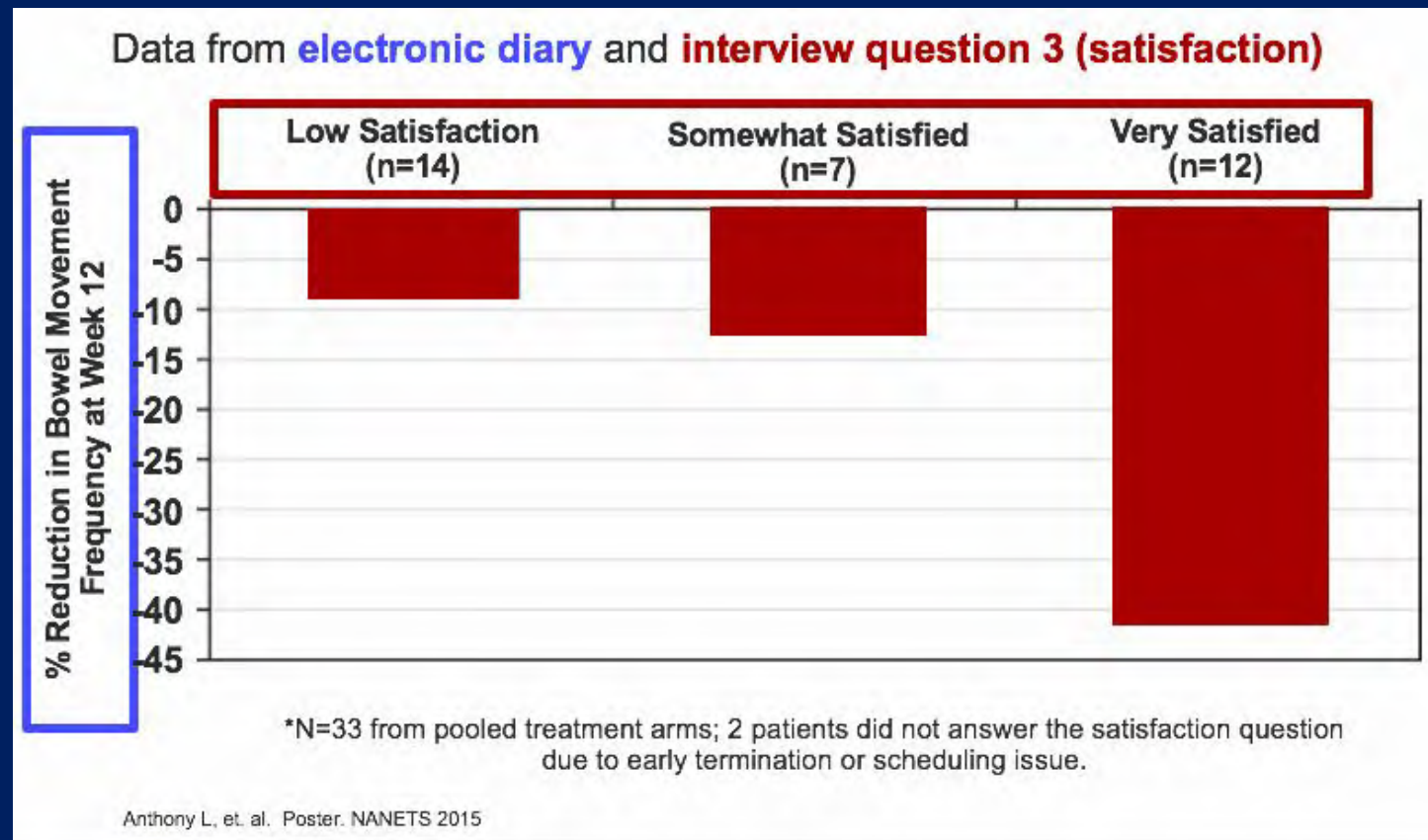
- 95% of participants who reported reductions in BM frequency noted that the reduction was meaningful to them.
- Participants described better enjoying life, leaving the house, and participating in social and other activities

“I definitely feel like I'm not a prisoner in my house, staying 10 feet to the nearest bathroom. I can go out to activities...”

“But the biggest change is not having to run to the toilet constantly... You can't live going 20 times a day. I was able to go out more often...”

- Most participants reported that a BM frequency reduction of at least 30% would be considered meaningful.

Satisfaction and Observed Reduction in BM Frequency at Week 12



Reports of “Very Satisfied” in TELESTAR

	Low Satisfaction n (%)	Somewhat Satisfied n (%)	Very Satisfied n (%)
Placebo	6 (67%)	3 (33%)	0
<u>Telotristat*</u>	8 (33%)	4 (17%)	12 (50%)

*Note: Total 33 participants answered question on satisfaction [§].

Data were pooled from telotristat 250 mg tid and 500 mg tid:

“very satisfied” patients were 5 out of 9 on 250 mg tid and 7 out of 15 on 500 mg tid

[§] Of 35 participants, two did not answer the satisfaction question due to early termination or scheduling issue

Available drugs and comparison of endpoints

Agent	Study population	TTP or PFS*			RR	OS
		TTP or PFS	Delta	HR		
Octreotide	Midgut	TTP 14.3 mo vs. 6 mo	8.3	0.34	2%	Median not reached
Lanreotide	GI and pancreas	PFS not reached vs. 18 mo	-	0.47	2%	Median not reached
Sunitinib	Pancreas	PFS 11.4 vs. 5.5	5.9	0.42	9%	33 vs. 27 mo (HR 0.71, not signif)
Everolimus	Pancreas	PFS 11 vs 4.6 mo	6.4	0.35	5%	44 vs. 37.7 mo (HR 0.94, not signif)
Everolimus [#]	GI and Lung	PFS 11 vs. 3.9 mo	7.1	0.48	2%	Median not reached
¹⁷⁷ Lu-PRRT [#]	Midgut					

*Primary Endpoint, [#]Not currently FDA-approved

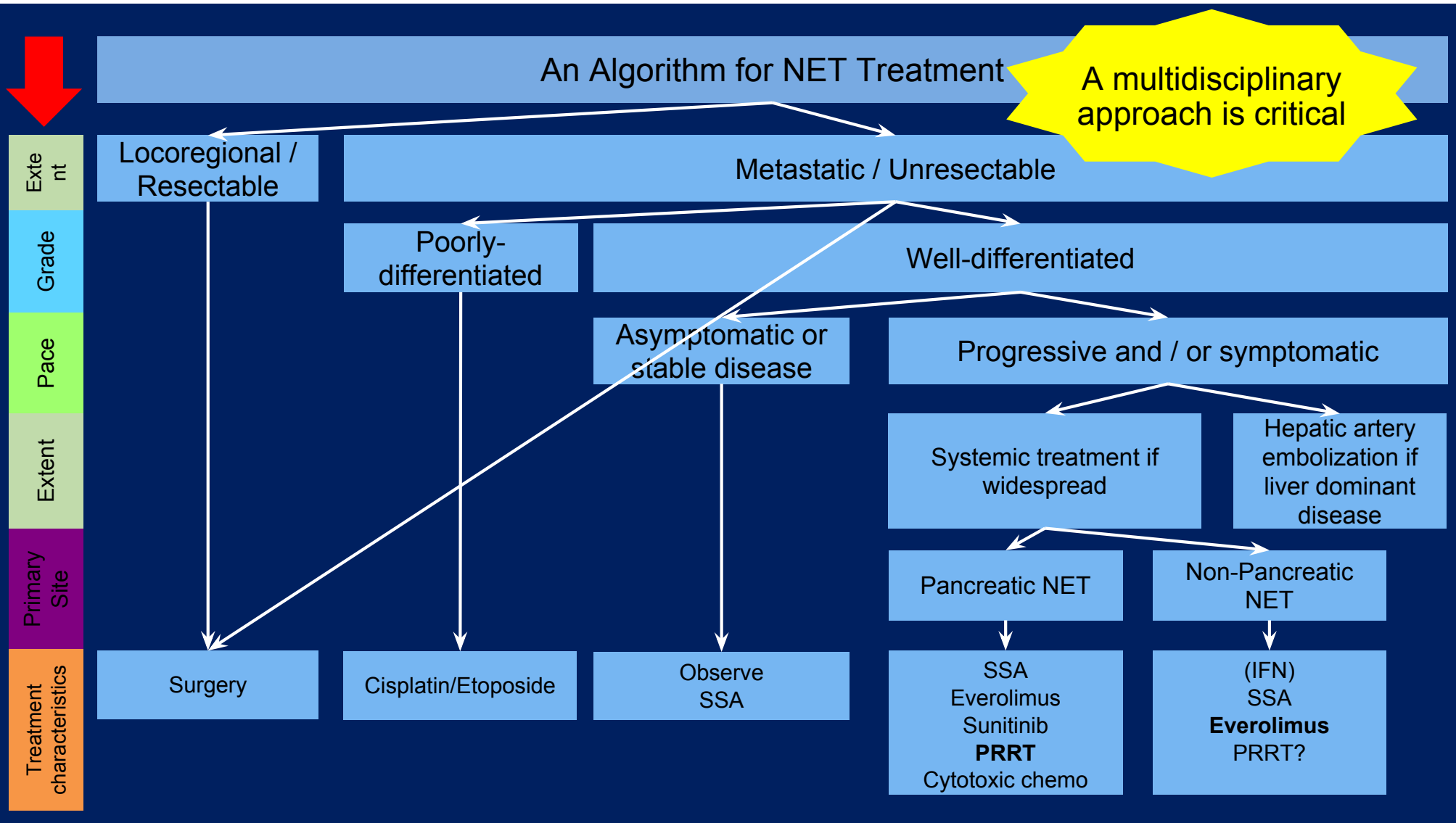
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¹⁷⁷ Lu-PRRT [#]	Midgut	☹️	☹️	☹️	☹️	☹️

*Primary Endpoint, [#]Not currently FDA-approved

An Algorithm for NET Treatment

A multidisciplinary approach is critical



Outline

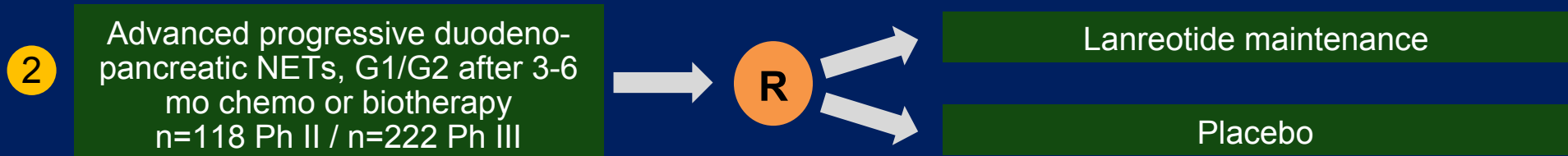
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Select ongoing pancreatic NET trials

ECOG/ACRIN 2211: Phase II (PI: Kunz; USA)



REMINET: Phase II/III (PI: Lepage; Germany and France)



SEQTOR: Phase III (PI: Salazar; Europe, UK)



Select ongoing non-pancreatic NET trials

ALLIANCE 021202: Phase II (PI: Bergsland; USA)

4

Advanced progressive non-pancreatic NETs, G1/G2
n=145



Pazopanib

Placebo

ECOG/ACRIN 2142: Phase II (PI: Eads; USA)

5

Advanced Grade 3, non-small cell
gastroenteropancreatic NECs
n=126



Temozolomide + Capecitabine

Platinum + Etoposide

SPINET: Ph III (PI: Reidy; USA)

6

Advanced progressive typical and
atypical lung NETs
n=201



Lanreotide

Placebo

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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](#).

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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"

Search Help

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

Locations of Recruiting Studies

Location	Percentage
Non-U.S. Only	50%
U.S. Only	43%
Both U.S. & Non-U.S.	6%

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

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How can you learn about clinical trials?

The screenshot displays 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 'Clinical Trials' and 'Clinical Trials (List View)'. A central message thanks visitors for their interest and provides information about clinical trials, including links for more information, a PDF of current open Adult Interventional Trials, and contact details. A sidebar on the right offers options like 'Clinical Trials (List View)', 'Clinical Trials (PDF View)', 'Advanced Search', 'About Clinical Trials', 'For Referring Physicians', and 'Additional Resources'. A 'CONTACT US' section includes a phone icon and the number 877-827-3222. At the bottom, there is a section for 'Adult Cancers by Disease Site' with a list for 'Blood' (Malignant Hematology/Leukemias) including 'Lymphoid Leukemia' and 'Leukemia, other'. A note at the bottom right states 'For other types of clinical trials at UCSF'.

UCSF Helen Diller Family Comprehensive Cancer Center

PATIENT CARE CLINICAL TRIALS RESEARCH

Clinical Trials (List View)

Home Clinical Trials Clinical Trials (List View)

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.

> [More information about participating in a trial](#)
> A PDF of current open Adult Interventional Trials can be downloaded [here](#)
> For questions call us at 877-827-3222 or [email](#)

Pediatric Cancers are listed here: [Visual View](#) | [List View](#)

Adult Cancers by Disease Site:


Blood	(Malignant Hematology/Leukemias)
	<ul style="list-style-type: none">• Lymphoid Leukemia• Leukemia, other

Clinical Trials (List View)

- Clinical Trials (PDF View)
- Advanced Search
- About Clinical Trials
- For Referring Physicians
- Additional Resources

CONTACT US

Clinical trial availability changes frequently. **For information about any of our studies, contact us:**

 Call us at 877-827-3222
or [email us](#)

For other types of clinical trials at UCSF

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

UCSF NET Trials

- Open Trials
 - PNET: Ph II Temozolomide vs. Temozolomide + Capecitabine
- Coming Soon
 - ALL SOLID TUMORS (NET COHORT): Ph I Pembrolizumab (Anti-PD1)
 - ALL SOLID TUMORS: Ph I CB-5083 (inhibitor of p97)

How can you learn about clinical trials?

The screenshot shows the Stanford Cancer Institute website. The header includes the Stanford Medicine logo and the text 'Cancer Institute A NATIONAL CANCER INSTITUTE DESIGNATED CANCER CENTER'. A search bar is located in the top right. Below the header is a navigation menu with categories: Patient Resources, Diseases & Treatments, Understanding Cancer, Clinical Trials, Research, Training, Outreach, and About Us. The main content area is titled 'Find Cancer Clinical Trials' and includes a search bar, a 'Filter by One or More Trial Details' section with dropdown menus for Adult/Pediatric, Condition, Drug Used, Doctor, Trial ID, and Status, and a 'Search' button. A sidebar on the left lists various resources like 'Find Active Clinical Trials', 'Patient Resources', and 'MD Community Newsletter'.

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

The screenshot shows the Stanford Clinical Trials app interface. The top section is titled 'SCI Trials By Stanford University' and includes a 'View More by This Developer' link. Below this is a 'Description' section with a 'View in iTunes' button. The app is categorized as 'Medical' and is available for iOS and iPad. A 'Screenshots' section shows a preview of the app's interface, which includes a search bar and a 'CONTACT US' button. The app also features a 'What's New in Version 1.1' section and a 'Customer Ratings' section.

Stanford Clinical Trials App

Stanford NET Trials

- Open trials
 - PNET: Ph II Temozolomide, Cape, Bevacizumab
 - PNET: Ph II Temozolomide vs. Temozolomide + Capecitabine
 - GI and LUNG NET: Ph I Everolimus + SNX (HSP 90 inhibitor)
 - NET Registry
- Coming soon
 - GRADE 3 GI and PANC NEC: Ph II Temozolomide + Capecitabine vs. Cisplatin + Etoposide
 - PNET: Ph I Small Inhibitory RNA to MYC Oncogene
 - ALL NET (KI67 < 55%): Intratumoral Ipilimumab + AntiPDL1

Take home points

- We have more tools!
 - Telotristat lowers BMs and urine 5HIAA for carcinoid syndrome and increases patient satisfaction
 - SSAs (Octreotide and Lanreotide) prolong PFS in GI and pancreas NETs
 - Sunitinib prolongs PFS in pNETs
 - Everolimus prolongs PFS in GI, pancreas and lung NETs
 - PRRT...
- Patient and treatment characteristics inform the treatment algorithm
- Key questions remain around selecting 1st line treatment and sequence
- Novel and smart trial designs are imperative to move the field forward