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CLINICAL TRIALS 101

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11.2.16



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DRUG DEVELOPMENT

- 2015:
 - 586 cancer compounds in late stage development
 - Median time from patent filing to FDA approval 9.5 yr (as fast as 4 years)
 - 15 cancer drugs approved

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.

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 the results of previous clinical trials

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 % of U.S. adults with cancer participate in clinical trials → Many barriers exist

TYPES OF CANCER CLINICAL TRIALS

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

Anti-cancer drug development

Drug Discovery

Synthesis/Formulation Development

Cell culture, signaling studies, combinations, animal models

Assessment of Toxicity in animals

IND
application

Phase I
Safety/dose

Phase II
Efficacy/Tox

Phase III
Compare new
vs. standard

NDA-FDA
Approval

Approx 10 yrs from lab to drug approval

Phase IV
long term safety

PHASES OF CLINICAL TRIALS

	Phase 1	Phase 2	Phase 3	Phase 4
Number of participants	20-80	35-300	200-3000	Several hundred to several thousand
Purpose	<ul style="list-style-type: none"> •To find a safe dosage •To decide how the agent should be given •To observe how the agent/intervention affects the human body •Determine how metabolized/excreted 	<ul style="list-style-type: none"> •To determine if the agent or intervention has an effect on a particular cancer •To observe how the agent/intervention affects the human body •Collect safety information 	<p>To compare the new agent or intervention (or new use of a treatment) with the current standard (or placebo) in a specific population</p> <p>Collect more safety info</p>	<p>To further evaluate the long-term safety and effectiveness of a new treatment (after FDA approval)</p> <p>Assess optimal use</p>

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 & pharmacokinetics	Proof of concept (Efficacy signal) Toxicity	Efficacy (establish new standard)
Disease-specific	Varies	Yes	Yes

FDA APPROVAL

- NDA (new drug application) submitted to FDA
- FDA has 60 days to decide if acceptable for review
- FDA typically provides decision within 6 mo
 - Facility inspection
 - Drug labeling
 - Drug approval

8-9 mo

- *Accelerated approval (earlier approval based on surrogate endpoint—biomarker, scan)*
- *Fast Track program (rolling submission as info becomes available)*

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

The Research Protocol: Contents

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: What endpoints must occur in how many patients over what period of time 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?

WHAT FACTORS DETERMINE IF A PATIENT IS ELIGIBLE?

- Disease (e.g. high grade vs low-intermediate grade; PNET vs carcinoid)
- Stage (e.g. early vs metastatic disease)
- Stable disease vs progressive disease
- Prior therapy
- Current medication
- Other medical problems, etc.

WHAT PROCESSES ARE IN PLACE TO PROTECT PATIENTS ENROLLED ON 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

HOW CAN YOU FIND OUT ABOUT CLINICAL TRIALS?

- Ask your doctor
- Local cancer center website
- NET foundation/support group websites
- 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

THINGS TO THINK ABOUT IF YOU ARE CONSIDERING ENROLLING IN A CLINICAL TRIAL?

- 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?

INTERPRETING DATA FROM CLINICAL TRIALS

INTERPRETING DATA FROM CLINICAL TRIALS: WHAT INFORMATION DO WE NEED?

Background: Rationale, context

- Is the therapy new? Does it fill an unmet need? Does it have activity in other diseases? Has it previously shown preliminary activity in NETs? Has the target been shown to be expressed in NETs?)

Methods: Trial design, eligibility, treatment plan, endpoints, analysis plan

Results: Safety? Efficacy? (Survival? Scan results? Biomarker?)

Discussion: Interpretation of data, limitations, future directions

INTERPRETING DATA FROM CLINICAL TRIALS: PITFALLS

- ***Know the patient group under study***
 - untreated vs previously treated
 - carcinoid vs pancreatic NET
 - well diff NET vs poorly differentiated NEC
 - functional or nonfunctional
 - Progressing vs stable at study entry

Do the results apply to you?

INTERPRETING DATA FROM CLINICAL TRIALS: PITFALLS

- ***Understand the significance of the results***
 - stability v shrinkage, impact on survival, safety/side effects
 - Preliminary analysis (e.g. interim analysis, abstract presentation, press release) vs. published, peer-reviewed manuscript (preferred)
 - Data from prospective, controlled study (preferred) vs retrospective series
 - Small, early phase study (I, II) vs phase III study (preferred)
 - Phase III studies potentially change standard of care

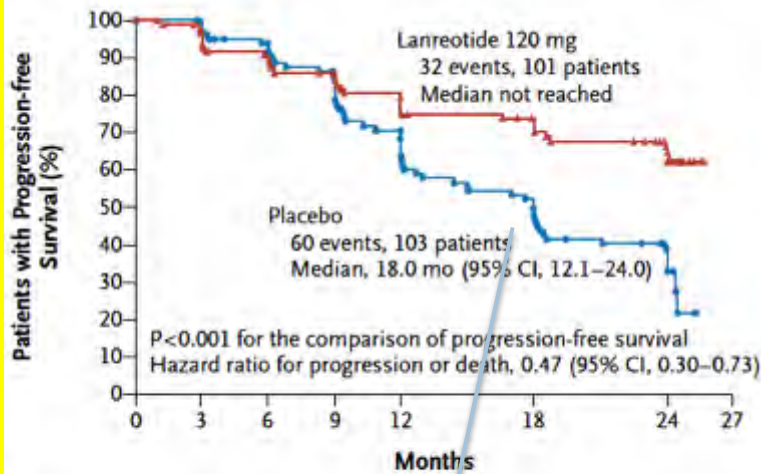
INTERPRETING DATA FROM CLINICAL TRIALS: PITFALLS

- ***Be careful with cross- study comparisons***
 - comparing outcomes in patients from one study to that of those enrolled in another study problematic (may have different eligibility, etc)

Progression-free survival (PFS)

CLARINET (LANREOTIDE)

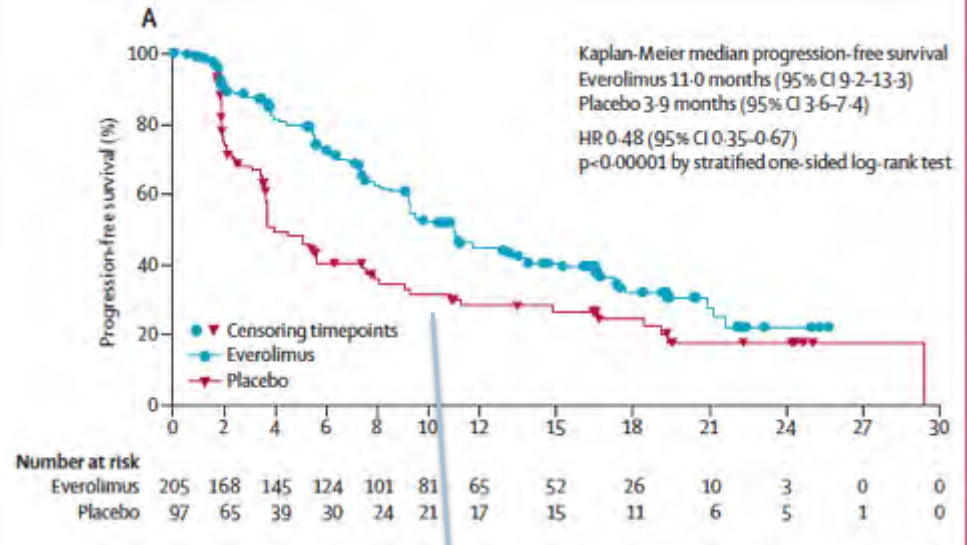
RADIANT-4 (EVEROLIMUS)



No. at Risk	0	3	6	9	12	18	24	27
Lanreotide	101	94	84	78	71	61	40	0
Placebo	103	101	87	76	59	43	26	0

**Median PFS
18 mo**

Caplin, et al.
NEJM, 2014



Median PFS 3.9 mo

Yao, et al.
Lancet, 2016

Randomized phase III studies in nonfunctional NET: outcome in placebo arms suggest patients with slower growing disease enrolled in CLARINET (GEP-NET) v RADIANT-4 (GI/Lung)