Demystifying Clinical Trials

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I SNIFF THE SAME SPOT UNTIL MY SISTER JOINS ME: THEN I PEE ON HER HEAD

I STILL FALL FOR THAT TRICK AFTER 10+ YEARS

WHY CLINICAL TRIALS?

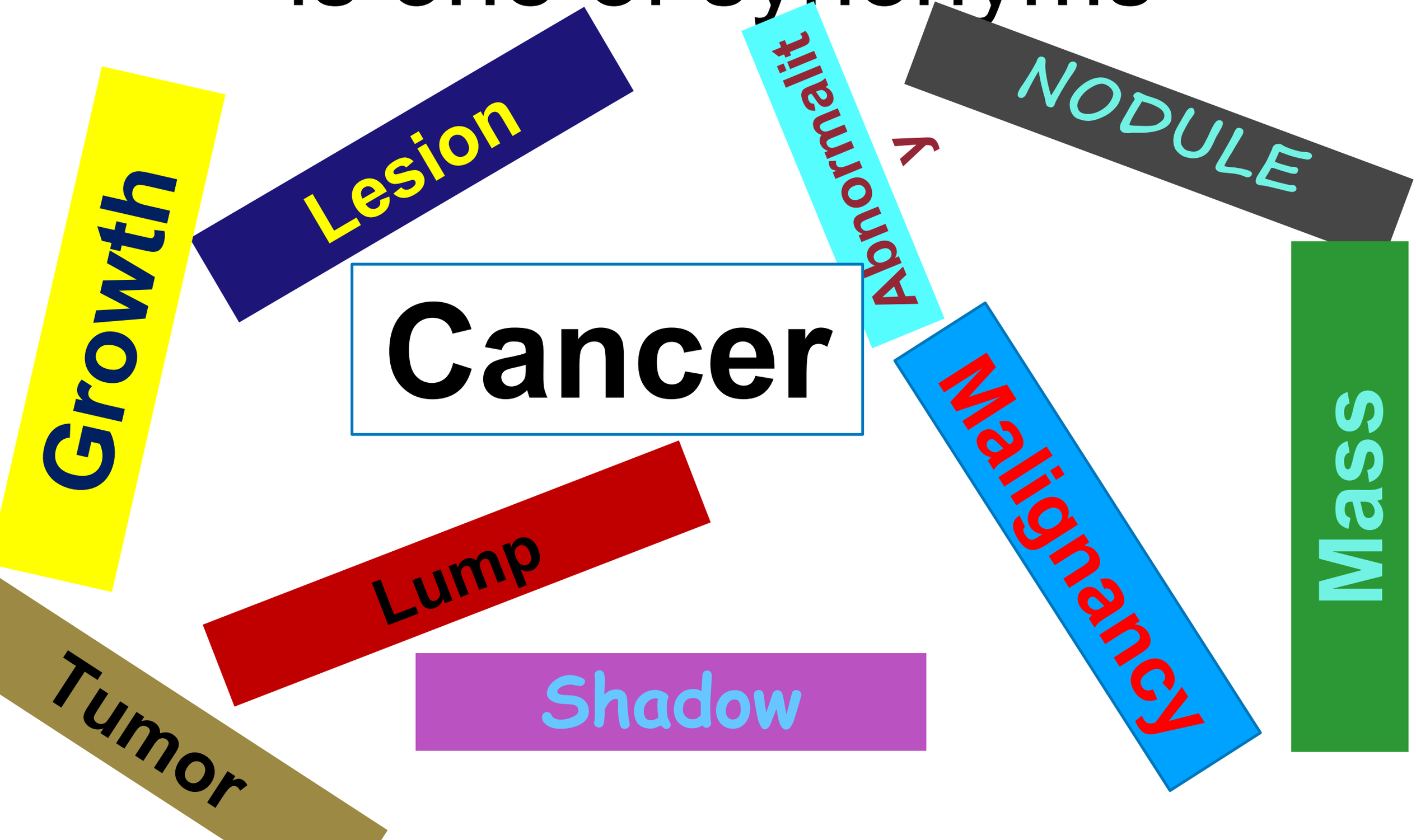
What is in it for me?

- New options
  - We are going to be looking for something better until we are curing every person of cancer with the least possible side effects
  - When we open clinical trials we are always hoping that our trial offers something new that will work better than what we have already
- Hope
  - We never underestimate the value of hope in helping our patients feel better/live longer/simply live
- Altruism
  - People are basically good but while people are hoping for something better more often than not they are hoping to also help other people going through the same situation

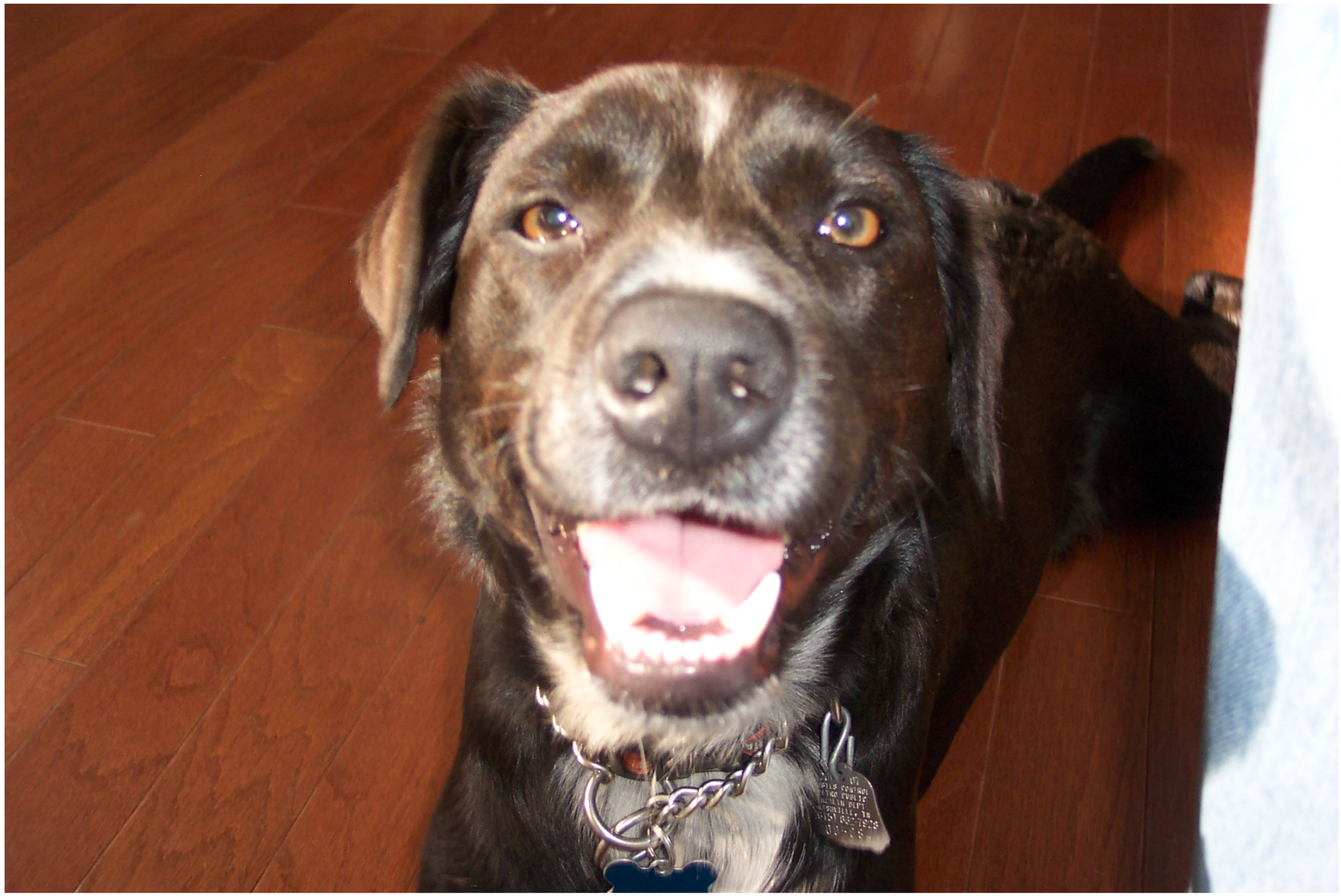
What comes from clinical trials

- **NO DRUG CURRENTLY IN USE TO TREAT CANCER WOULD BE AVAILABLE WITHOUT CLINICAL TRIALS**
- We learn how drugs are broken down in the body
  - Gives us an idea of what other drugs and/or radiation are safe or unsafe with the anticancer treatment
- We learn how effective the treatment is and in what diseases
- We learn the best way to give the drugs and/or radiation
- We learn how to manage the side effects

The problem with doctors is one of synonyms



Some Language



What is Standard Therapy?

- Standards include
  - Treatment standard: This is something we give to patients not treated on clinical trials
  - Clinical Trials standard: This is the “arm” that anything new must compare to in order to get FDA approval
  - The two are usually the same, but not always
    - In stomach cancer, the FDA used to use cisplatin and 5FU as a standard arm long after we had moved to less toxic treatments

How does a treatment become standard?

- Generally, it has to win (or beat something else)
  - This can be a comparison trial against a placebo (very tough in oncology)
- Or a comparison trial against the prior standard (more common)
- Or if there is something really good then a big single arm trial will do it
  - Example: GIST, a tumor with no drugs at all in 2000. We learned something in the lab and a new drug, imatinib, shrank the tumor in over 50% of patients and the shrinkage lasted. It got approved on one trial—so fast they didn't have time to find it a name!

Chemo vs other drugs

- Chemotherapy really refers to any chemical used to treat somebody, but in oncology world
  - Chemo = drugs that are geared to injure or kill dividing cells (DNA or things associated with DNA)
- We have newer drugs that aren't chemo
  - Biologic agents or targeted agents
    - These drugs block the action of a protein or some proteins that are different in some way in cancer cells and can drive cancer cell growth
  - Immune therapy
    - This one is the hot one
    - Lots of new ways to try to make the immune system recognize cancer cells and kill the cancer for us but really only two types FDA approved (many drugs hit same things)

Clinical Trial vs Study vs Protocol

- Clinical trial is always research
- Study is generally the same as clinical trial
- Protocol is tricky. It can be a clinical trial or study, but sometimes it is just the plan by which the doctor treats patients normally

Other terms

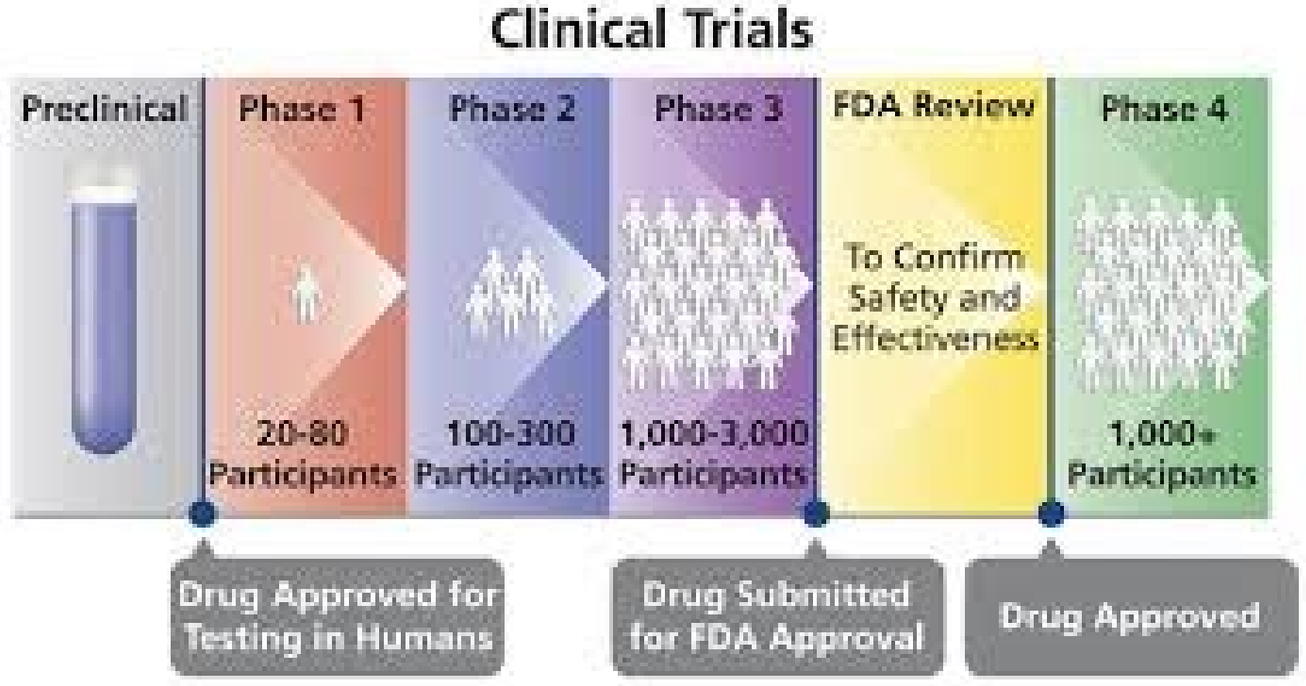
- Stage:
  - Classically 1-4, with a few extra letters in between. As the disease gets more advanced, the numbers and letters get higher
- Phase: I-III,
  - refers to clinical trials phases (there are 0 and 4 but we will ignore them)
- Adjuvant therapy
  - When all disease is removed, some cells may be hiding and can come back later. Adjuvant therapy is given to try to kill the hidden cells

Lines of therapy

- People with advanced cancer can go through several different treatments during their illness
- These are often considered “lines” of therapy
- Generally we try to start with our best treatments first but that is on average
- For some people the second line may work better than the first

WHAT ARE THE KINDS OF CLINICAL TRIALS?

Clinical Trials



- What are they?
  - We need to know about a drug to use it
  - We need to know:
    - The right dose
    - The side effects
    - Most importantly, does the drug help and how does it help?
      - Some drugs help shrink tumors more or less and some may not shrink the tumors but makes them stop growing, for example

What is the dose?

- Phase I trials
- Takes what we know from laboratories about a drug and chooses how to give it at a presumed safe starting dose
- Slowly, in 1-3 patients at a time, we try higher and higher doses to make sure it is safe
- Gives us hints of effectiveness and an idea of what side effects happen
- Very few patients treated at each dose

What is phase II?

- We get clues in phase I, but there are very few patients treated at each dose
- Phase II
  - One dose, one disease type
  - Gives us a “signal” of how effective it is, but
  - More information on side effects
  - And if the dose we found on phase I is really the safe dose in a larger group of patients

How effective is it?

- Phase II tells us this may or may not work, but not all phase II trials predict phase III accurately
- Phase III
  - Randomizes new drug or drugs against the standard
  - This proves if a drug is better or not and is definitive (we have been misled by all other methods so far)
  - Also, more info about toxicity

WHAT ARE THE ENDPOINTS?

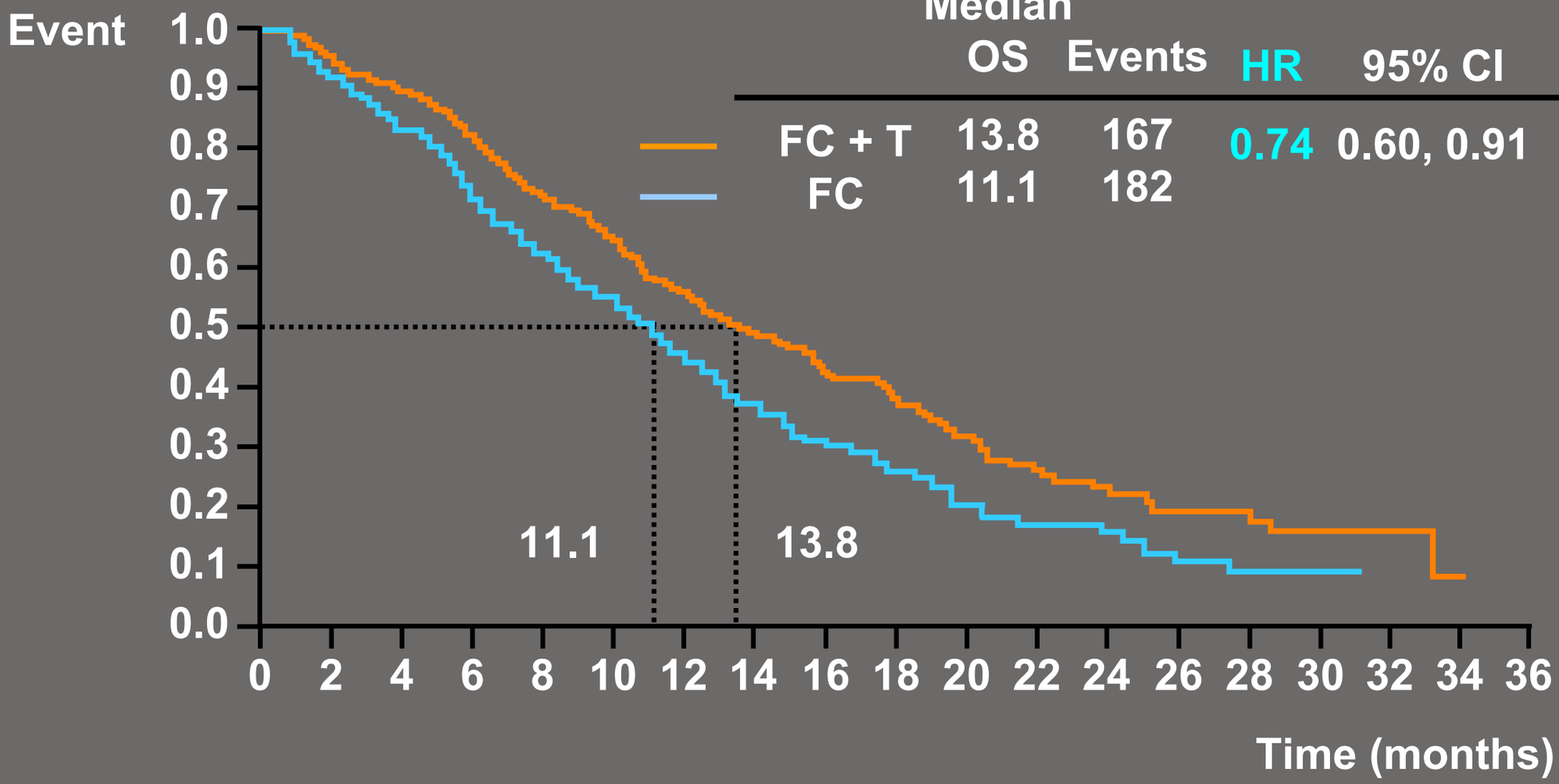
Endpoints (goals of the studies)

- Survival
- Disease-free survival or relapse-free survival
  - When we cut everything out, the time before the disease comes back (not all people have the disease come back)
- Progression-free survival
  - Time from start on treatment for a person until the disease is shown to grow
- Response Rate
  - Shrinkage has to be more than 30% to count as “response.” Less than 30% shrinkage is considered “stable.”

Median vs hazard ratio

- Median
  - Time when half the patients have had the event
    - Eg if the endpoint is PFS, the time when half had progression of disease
- Hazard ratio
  - Compares a line to a line. It tells you the odds something is going to happen compared to the control or standard arm

TOGA trial: Primary end point: OS



	Median OS	Events	HR	95% CI	p value
FC + T	13.8	167	0.74	0.60, 0.91	0.0046
FC	11.1	182			

No. at risk																			
FC + T	294	277	246	209	173	147	113	90	71	56	43	30	21	13	12	6	4	1	0
FC	290	266	223	185	143	117	90	64	47	32	24	16	14	7	6	5	0	0	0

T, trastuzumab


How have things changed
in recent years?

We have moved beyond phase 1, 2 and 3

- There are phase Ib, randomized phase II and other subtitles
  - Phase Ib usually refers to new combinations of drugs while phase I is first-in-human
  - We usually don’t use these terms with our patients, just with the companies
  - Overall goals are the same: proper dose, side effects/safety
    - But sometimes we are not looking for the highest safe dose but a “Biologically effective dose.”

Dose Expansion Cohorts and Basket Trials

- These trials enroll a variety of different diseases into the trial
  - Each in its own “cohort”
  - More like a collection of phase II trials in one trial
  - This saves time and money for the companies and gets information on many signals at one time

Remember the “targeted” or “biologic” agents

- These agents block a specific protein that drives the growth of cancer generally
- Sometimes we can identify who will benefit from a targeted agent
  - Example: Trastuzumab or Herceptin
  - Example: Latroctenib, entrectinib
- Therefore, trials might require patients with stomach cancer and a certain gene mutation but not be available to other stomach cancer patients

FDA

- With more effective drugs, they are approving more drugs than ever without phase III trials
- It is often impossible to do a phase III trial in rare cancers or rare subsets of cancers but people with those diseases deserve treatments and trials too
- Also, some drugs are being approved for cancer based on a characteristic of the cancer rather than the disease type
  - Examples, MSI high, TRK fusion

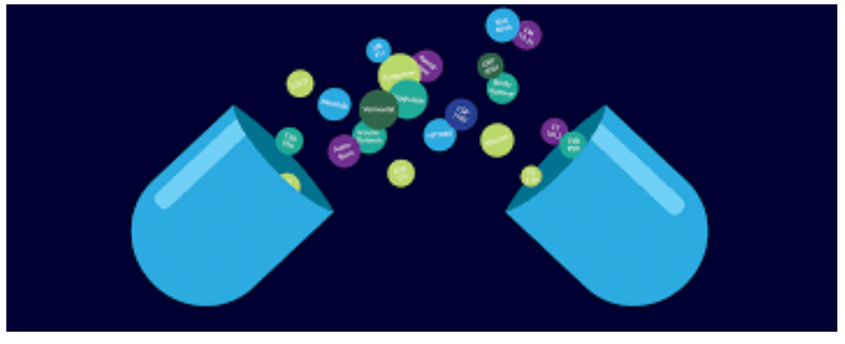
What is the process for getting onto a clinical trial?

Getting onto a trial

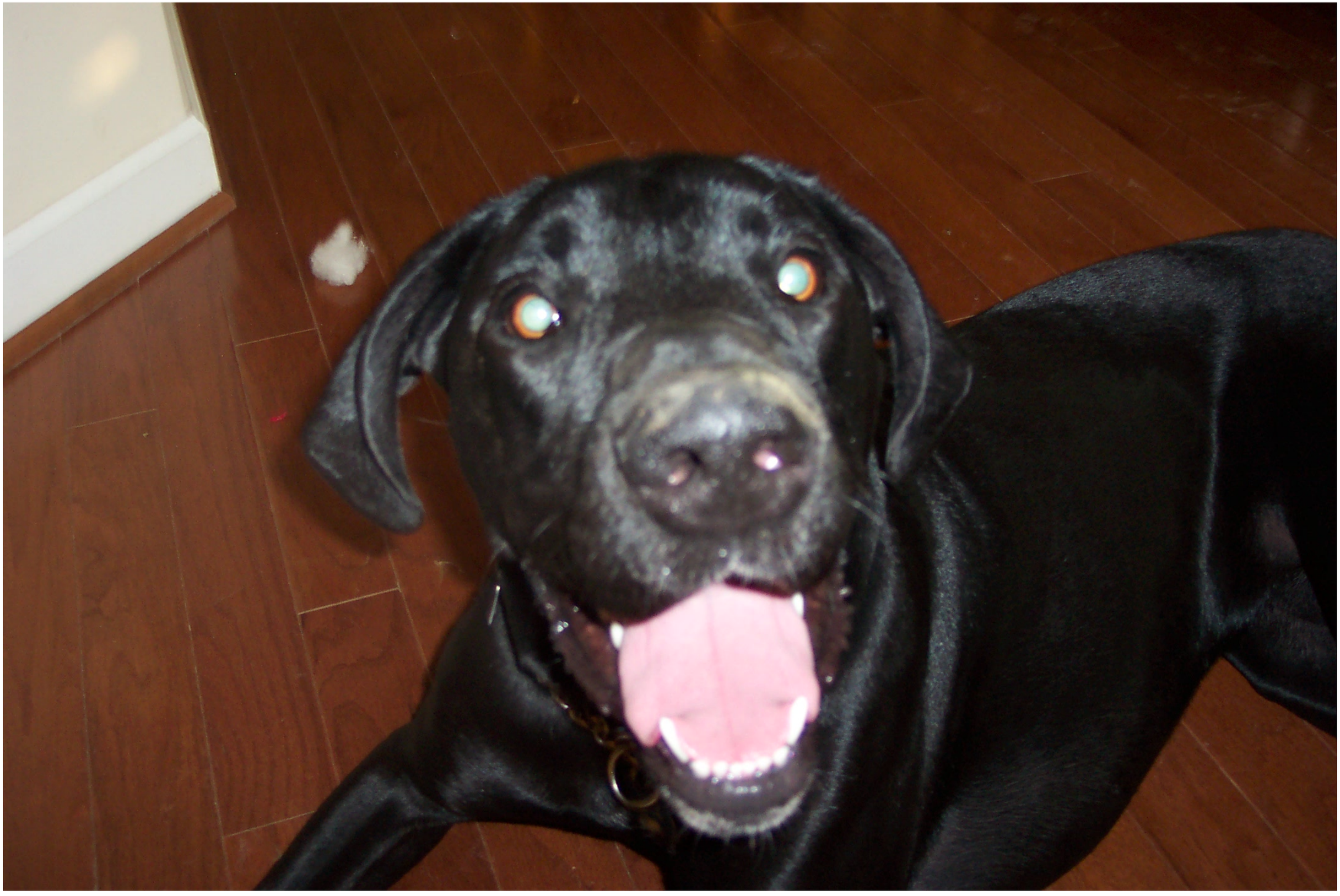
- Identify a trial
  - Generally up to your doctor to find the trials
  - But there is a NCI clinical trials finder
- Speak with study team to learn about the trial
- Review and sign consent form
- Screening
- Starting therapy

What are my rights on a trial?

- You give up no rights to be on a trial
- If you change your mind, you can stop the trial any time
  - Your doctor will treat you to the best of his/her ability regardless of whether or not you agree
- All trials have safety measures built in
  - This may include special tests or many more tests than you are used to taking
  - Some are for us to learn how your body uses the drug



Almost done !



Disclosures

- Advisory Boards since Jan 1, 2019
  - Eisai
  - Celgene (Steering Committee)
  - Taiho
  - FivePrime
  - EMD Serono (unpaid)
  - Armo (now owned by Lilly)
  - Astra Zeneca
  - Bayer
  - Rafael
  - Clovis
  - QED
  - Ipsen
  - Rafael
- Current Research Support
  - Novartis (Array) , Abbvie, Immunomedics, Taiho, Genentech/Roche, Bayer, Incyte, Pharmacyclics, FIvePrime, Loxo, EMD Serono, Boston Biomedical, Macrogenics, Karyopharm, Pfizer, I-Mab Biopharma, Dragonfly
- DSMB
  - Novocure, Pancreatic Cancer Action Network

Summary

- Clinical trials are options for people at all stages of disease
  - Not every doctor has a trial for your particular situation
  - Varies how far one might have to travel to find a trial
- Clinical trials are how we find new and better treatments
  - Better can be more effective, less toxic, easier to give (pills versus iv for example)

I hope I did not bite off more than I can chew