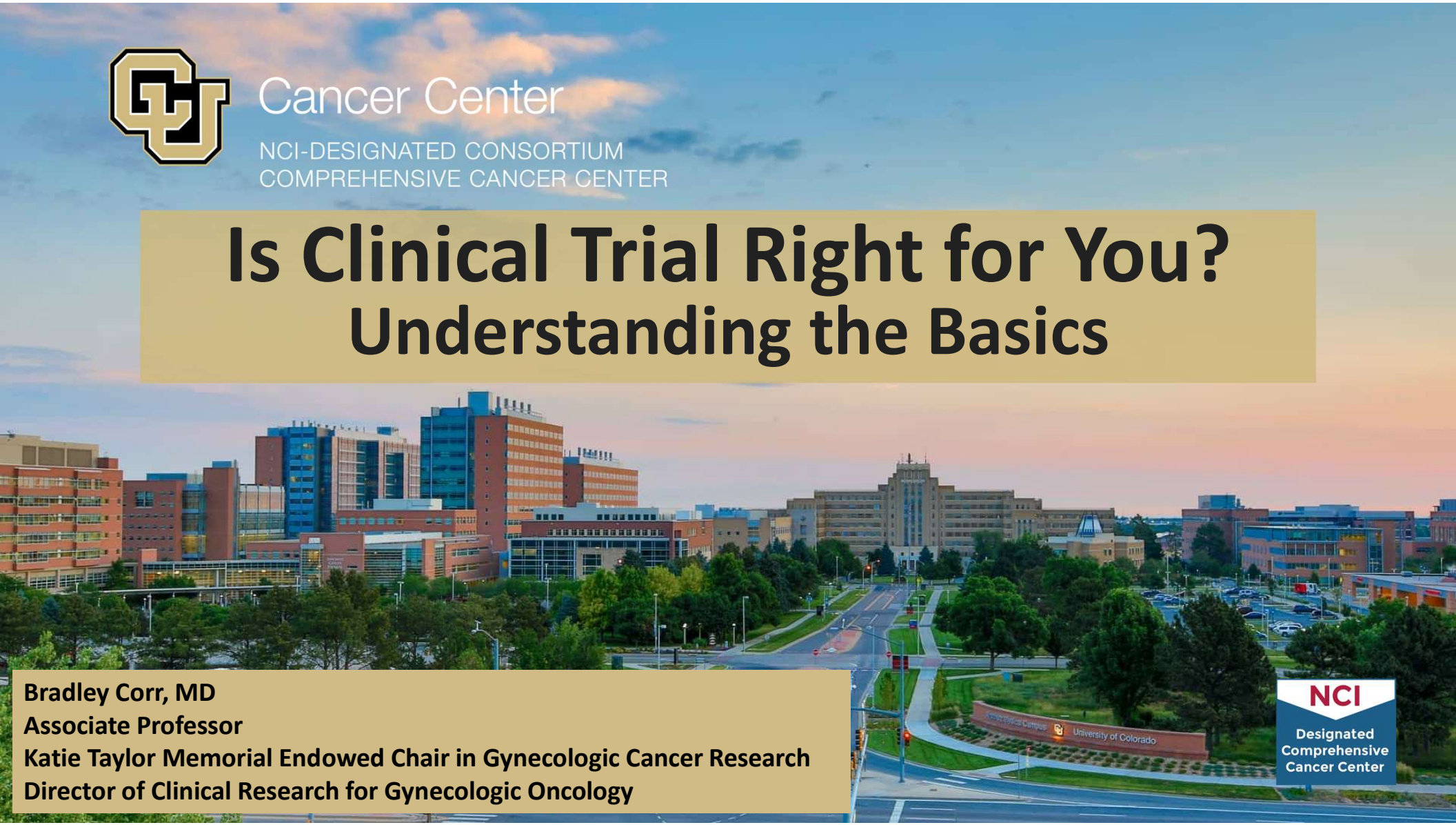


Is Clinical Trial Right for You?
Understanding the Basics

Bradley Corr, MD
Associate Professor
Katie Taylor Memorial Endowed Chair in Gynecologic Cancer Research
Director of Clinical Research for Gynecologic Oncology

Conflict of Interest:

- Advisory Board (s): GSK, Gilead, Immunogen, Zentalis, Merck, Corcept, Immunogen/Abbvie, AstraZeneca
- Research funding: Immunogen/Abbvie, NCI
- Educational speaker: Targeted Oncology

Common Misconceptions

- Big Bad Pharma
- All trials have placebo’s
- I don’t want to be a Guinee Pig
- The government has to give me these drugs regardless

Outline

- Who Runs clinical trials?
- What are these phases I keep hearing about?
- Trial design
  - Phase 1/2/3
  - Eligibility
  - Randomization
  - Biomarkers
  - Trial assessment
  - Trial endpoints

Who Runs Clinical Trials

- Government
- Industry
- Investigators

Who Runs Clinical Trials

- Government

Who Runs Clinical Trials

- Cancer Therapy Evaluation Program (CTEP)
  - Mission: to improve the lives of cancer patients by finding better ways to treat, control and cure cancer
  - Attempt to forge broad collaborations within the research community and works extensively with the pharmaceutical/biotechnology industry to effectively develop new cancer treatments

Who Runs Clinical Trials

Who Runs Clinical Trials

- Industry

Prevent and conquer cancer. **Together**.

Who Runs Clinical Trials

- Investigators:
  - IIT's (Investigator Initiated Trial)

Who Runs Clinical Trials

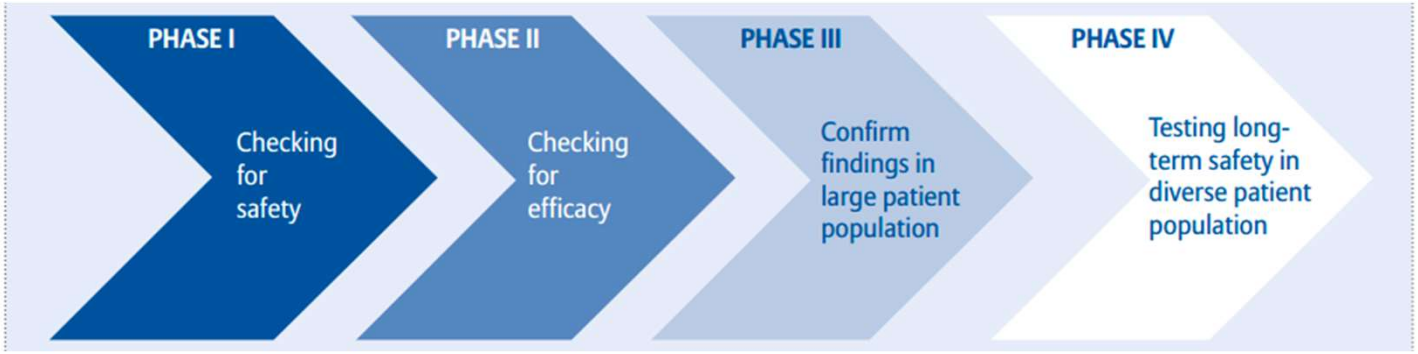
Who Pays for Clinical Trials?

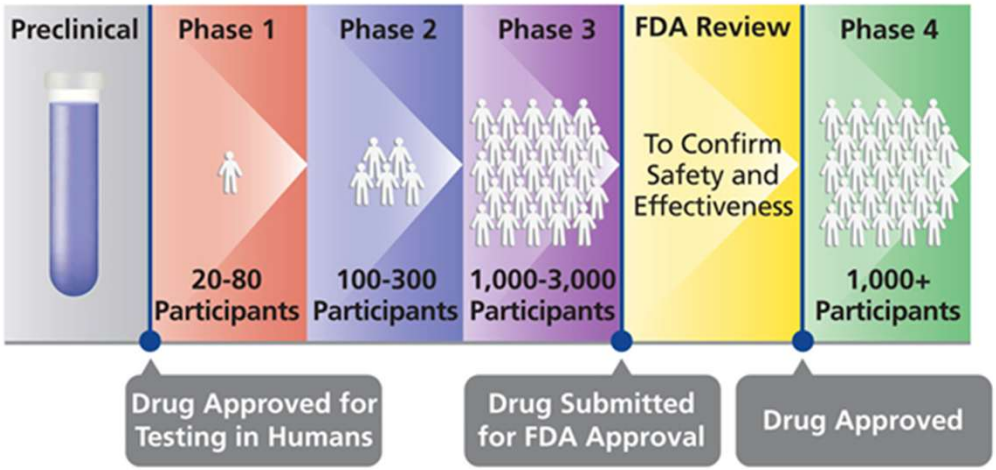
- Patient Protection and Affordable Care Act (ACA)
  - Health plans ***CANNOT***
    - Deny participation in clinical trials;
    - Deny or limit coverage of routine patient costs, subject to the plan's out-of-network coverage policy; and/or
    - Discriminate against the individual on the basis of participation in a trial.

Who Pays for Clinical Trials?

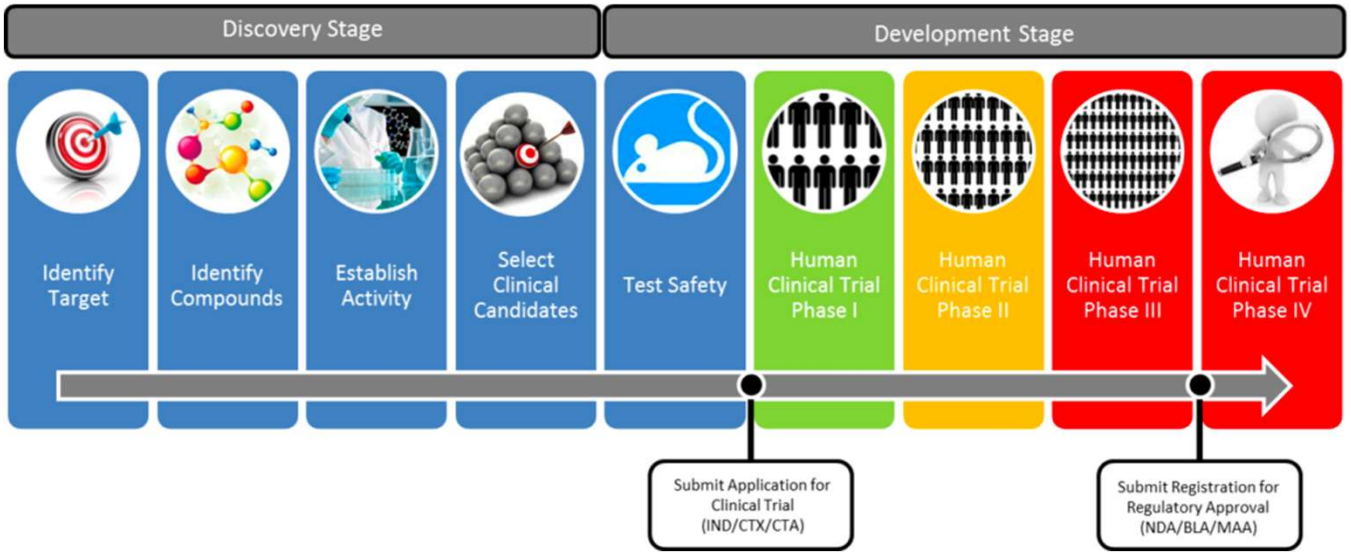
- Right to Try Act
  - Eligibility
    - Have a life-threatening disease or condition
    - Have exhausted all approved treatment options
    - Be unable to participate in a clinical trial involving the drug
    - Provide written informed consent
  - Eligible drugs
    - Have completed a phase 1 clinical trial
    - Be in active development or production
    - Not be approved by the FDA for any use
    - Be the subject of an investigational new drug application filed with the FDA

Clinical Trial Phases



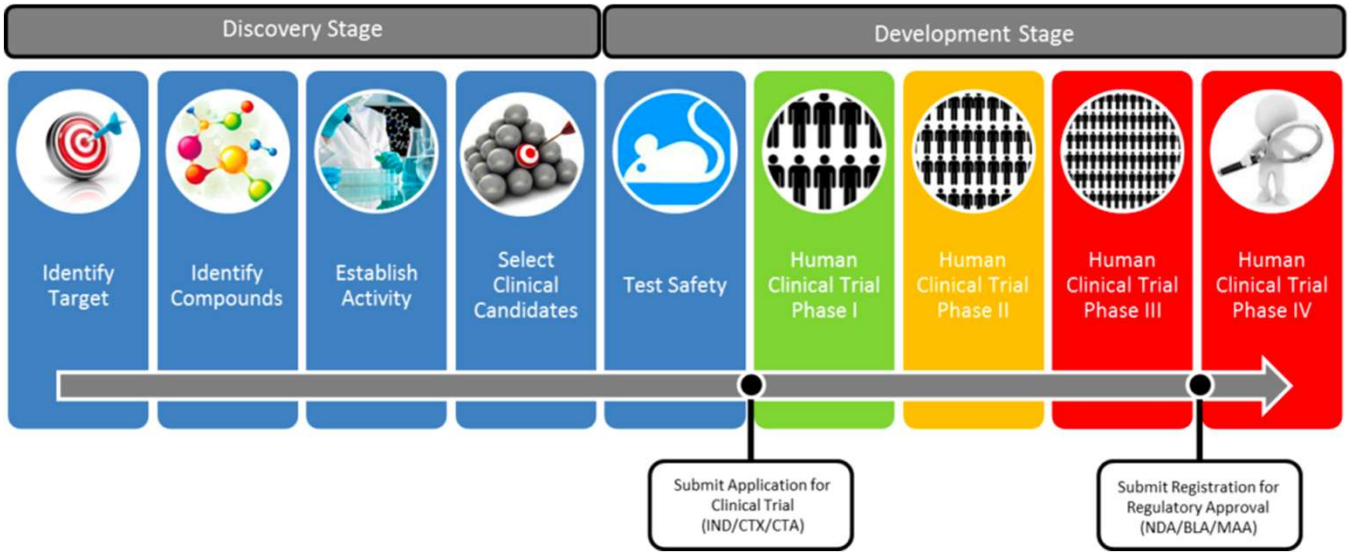


Trial Design



time → time → more time

Trial Design



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time → time → more time

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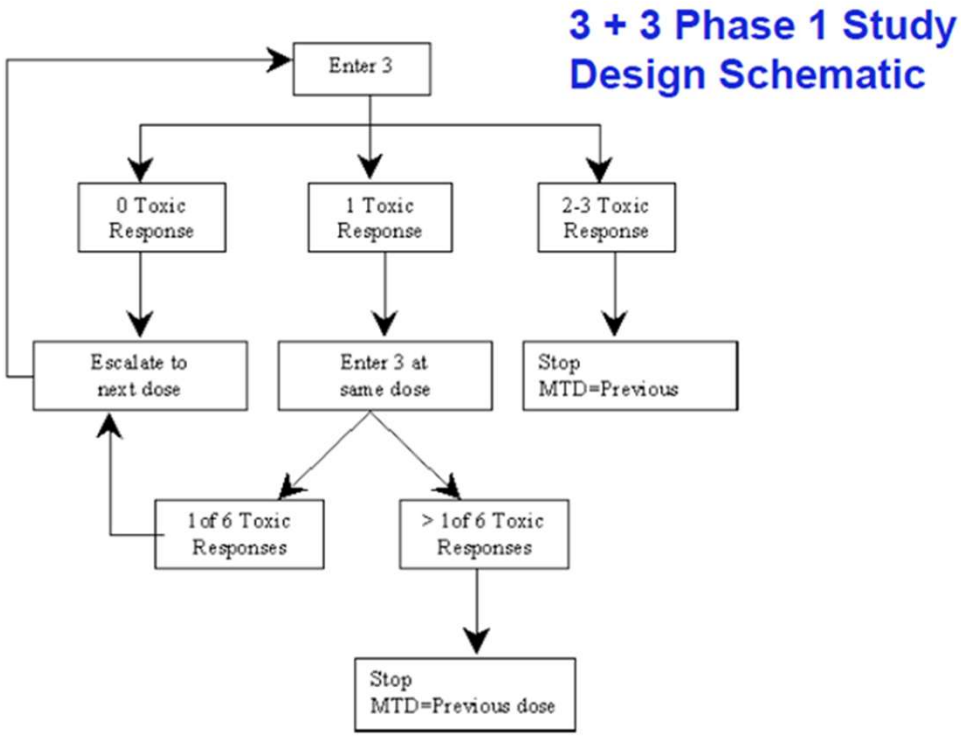
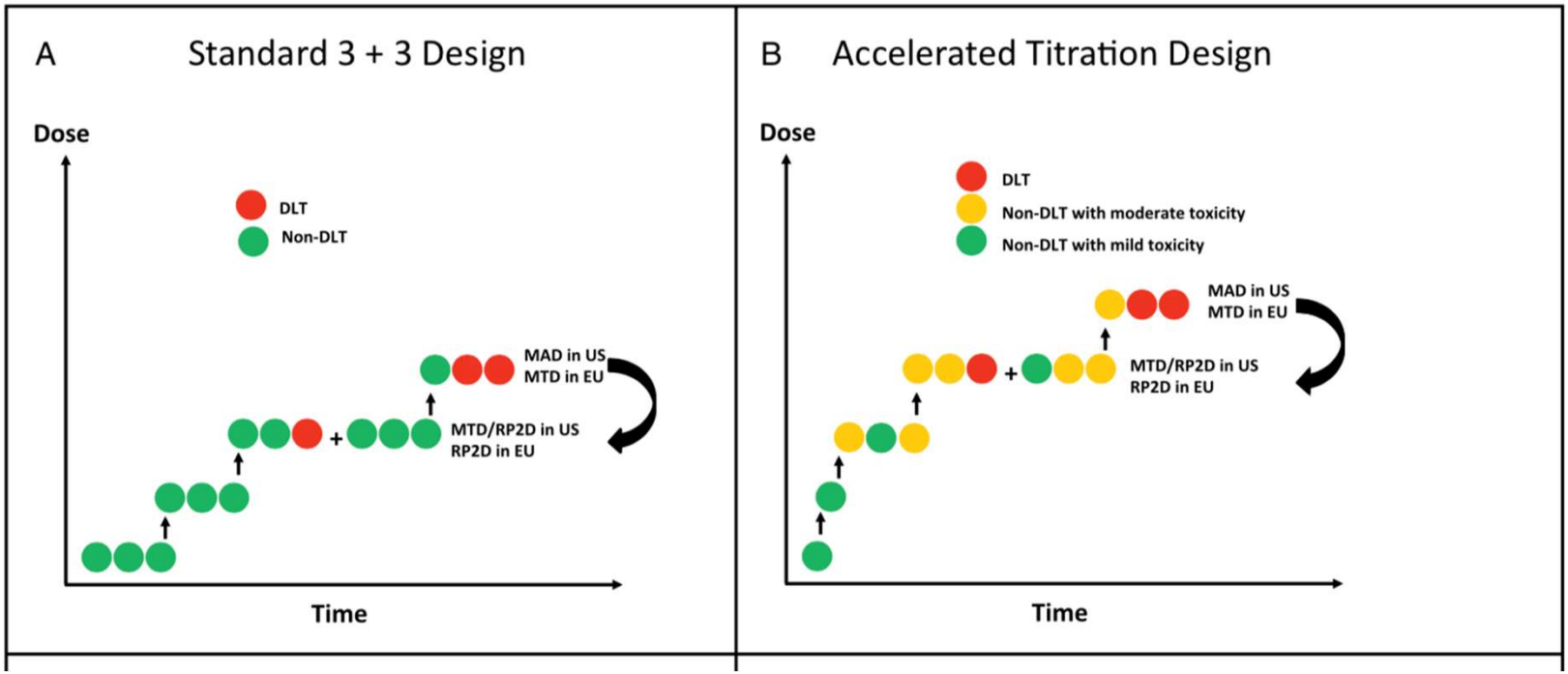
Trial Design – Phase I

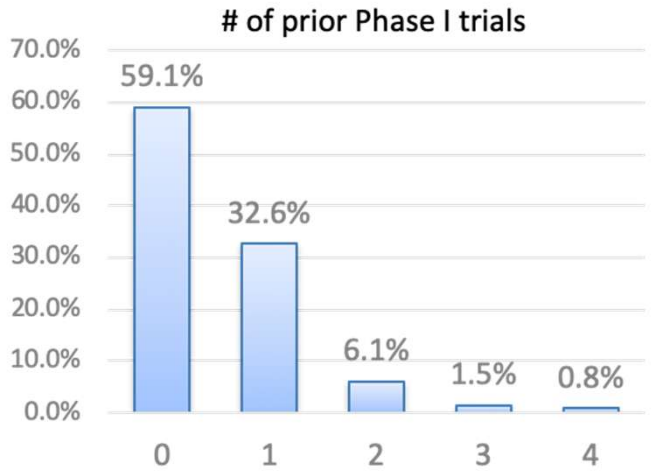


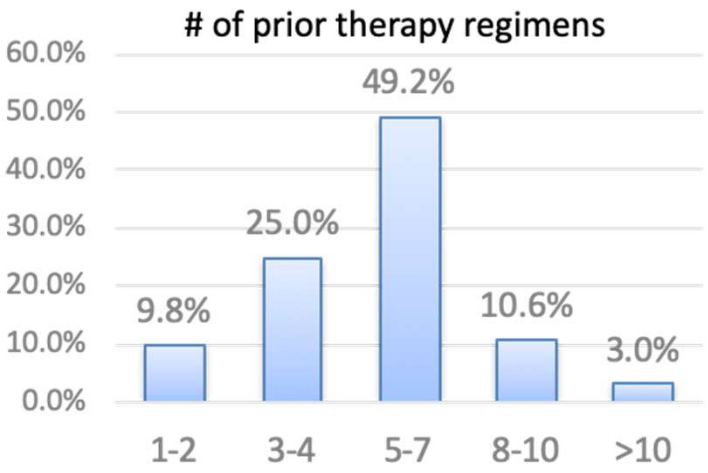
Trial Design – Phase I



Trial Design – Phase I

- Survival and clinical outcomes of ovarian cancer patients enrolled in Phase I clinical trials
  - 132 patients over 10 years





Corr et al. Cancer. 2020 126(19).

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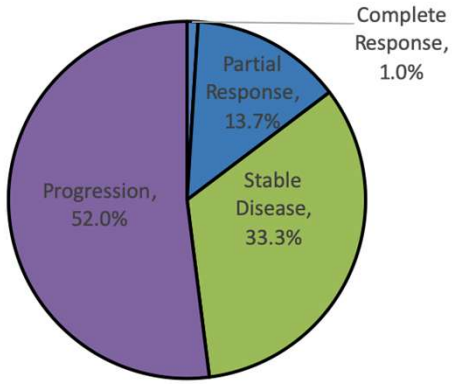
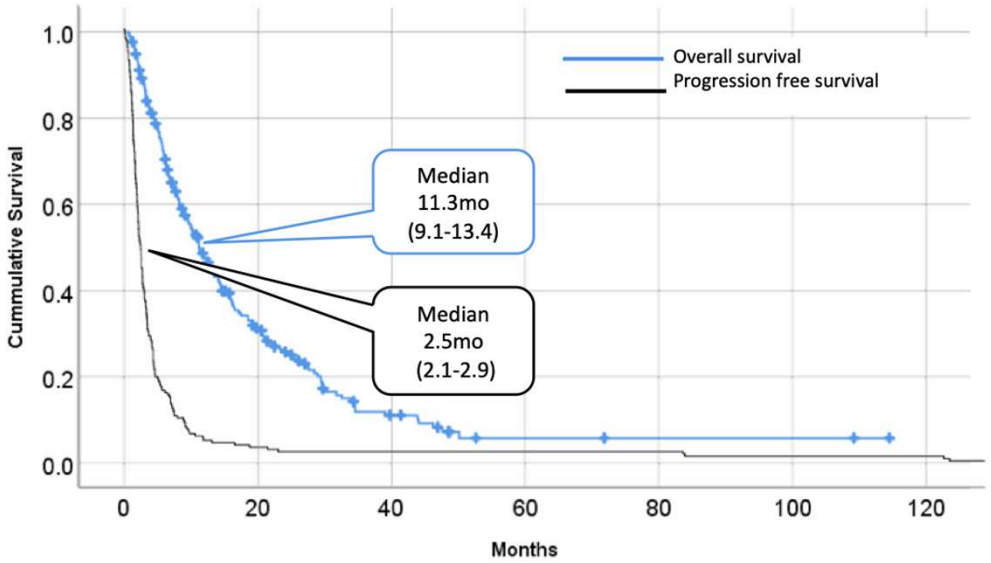
Trial Design – Phase I

- No patient died due to toxicity, 2 patients died on trial due to progression of disease
- ORR = 14.7%
- Clinical Benefit Rate = 48%





Corr et al. Cancer. 2020 126(19).

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Trial Design – Phase II

- With goals of efficacy still need a comparison
  - Compare to historical controls
  - Use of placebo

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Trial Design – Phase III

SUPERIORITY

- Is new treatment superior to standard treatment

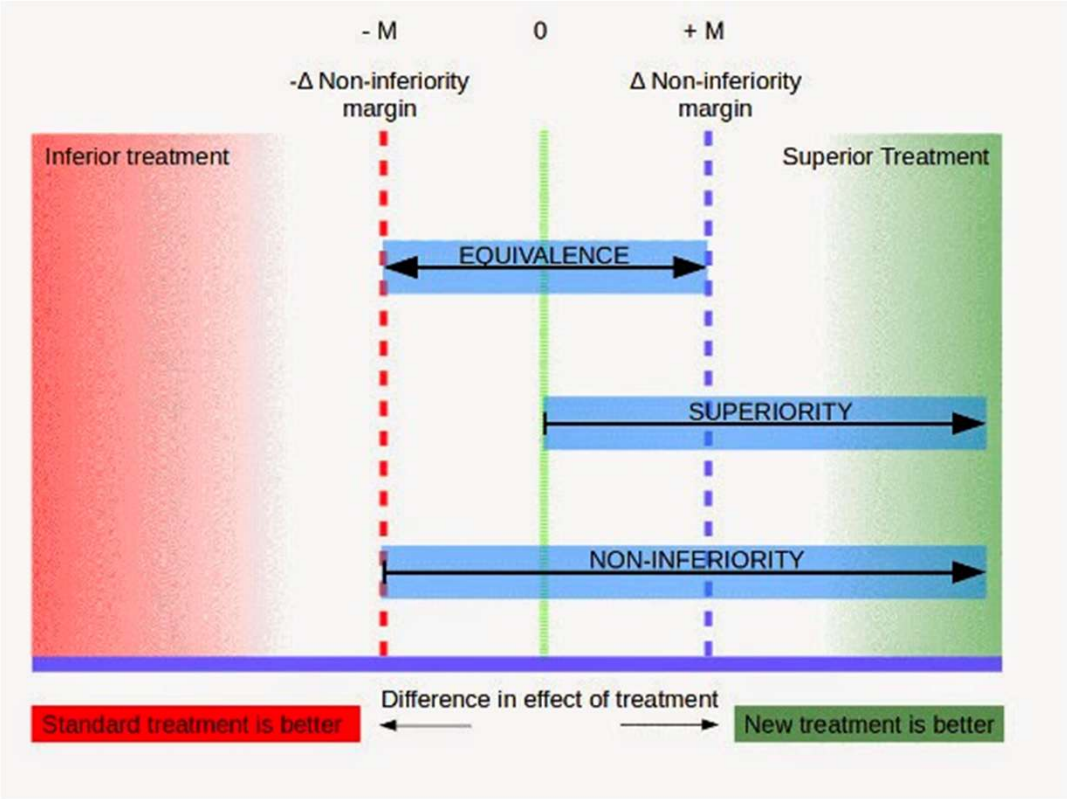
NON-INFERIORITY

- Is new treatment not worse than standard therapy
- Typically less toxic or less expensive

EQUIVALENCE

- Two treatments are not too different clinically
- Seldom used in oncology

Trial Design – Phase III

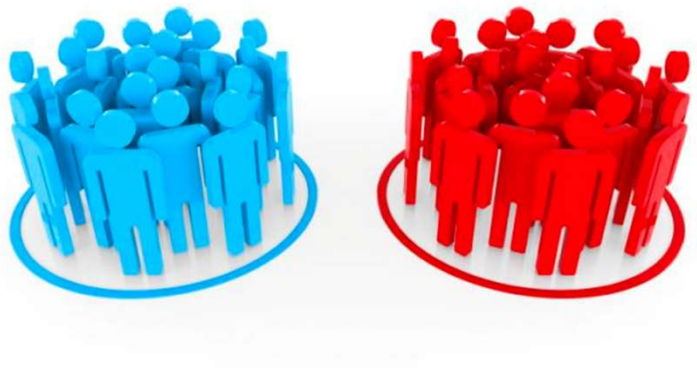


Trial Eligibility

- Screening
- Inclusion/Exclusion criteria
  - Validity vs feasibility

Randomization

- Removes bias (intentional or not)
- Eliminates systemic imbalances in populations
  - Stratification models

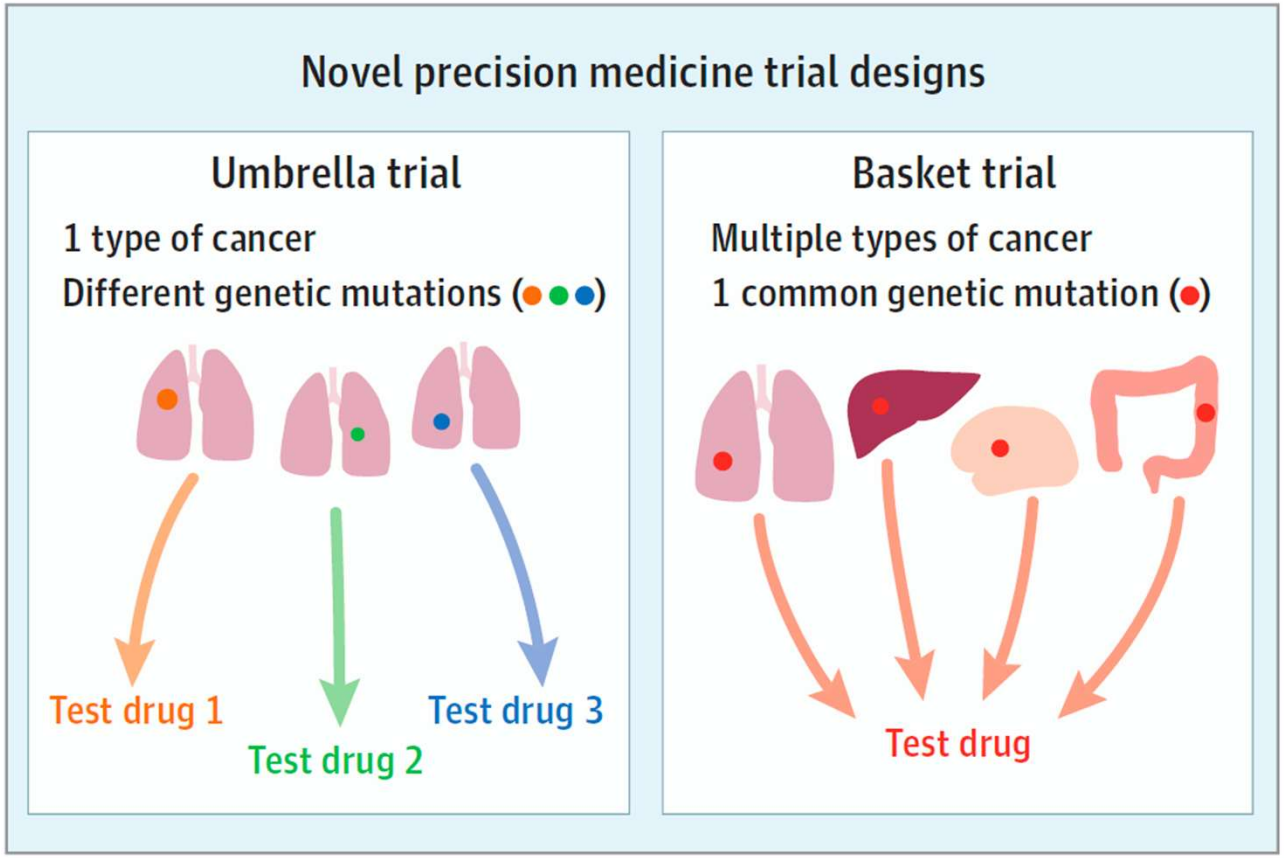


Biomarkers

- Prognostic: Provides information about prognosis or outcome
- Predictive: provides information about the likelihood that a patient will respond

- Integral: Required definition for trial enrollment
- Integrated: Used to test a trial hypothesis
- Exploratory: Used to develop new hypothesis

Biomarkers


Novel precision medicine trial designs
Umbrella trial
1 type of cancer
Different genetic mutations (●●●)
Test drug 1
Test drug 2
Test drug 3
Basket trial
Multiple types of cancer
1 common genetic mutation (●)
Test drug

Trial Assessment

- Imaging – RECIST
- Adverse Events - CTCAE

Trial Assessment - Imaging

- RECIST
  - Measurable lesions
    - 10mm in longest dimension
    - Lymph nodes: 15mm by short axis
  - Non measurable lesions
    - Lesions not meeting measurable criteria

  - Baseline Evaluation
    - Up to 5 target lesions (no more than 2 per organ system)
    - Identify all non-target lesions
    - Sum of diameter of target lesions

Trial Assessment - Imaging

- RECIST: Target response
  - Complete response (CR)
    - Disappearance of all target lesions
    - LN's must have reduction to < 10mm
  - Partial Response (PR)
    - At least 30% decrease in the sum of diameters
  - Progressive Disease (PD)
    - At least 20% increase in sum of diameters of target lesions
    - Any appearance of new lesions
  - Stable Disease (SD)
    - None of the above

Trial Assessment – Adverse Events

Common Terminology Criteria for Adverse Events (CTCAE)

Version 5.0

Published: November 27, 2017

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

The transformation is pretty bad, but the worst part is filling out the paperwork for the adverse events.

CartoonStock.com

Trial Assessment – Adverse Events

- **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2** Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental ADL.
- **Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
- **Grade 4** Life-threatening consequences; urgent intervention indicated.
- **Grade 5** Death related to AE.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability. **Navigational Note:** -					

Trial Endpoints

Endpoint	Definition	Advantages	Disadvantages
Response Rate	Assessed by RECIST or CA-125 criteria	Objective Quantifiable	Difficult to reproduce Not sufficient for Phase III
Time to progression	Time from entry into trial to progression of disease	Similar to PFS	Does not include deaths
Progression free survival	Time from entry into trial to progression of disease, death, or lost to follow up	Quicker results Avoids impact of post progression treatment	Requires blinded, placebo-controlled design Requires careful and symmetric assessment
Overall survival	Time from entry into trial to death or lost to follow up	Clear-cut endpoint	Longer time to results Affected by post progression treatment Influenced by crossover therapy
Patient reported outcomes	Symptom-based parameters	Direct clinical benefit as perceived and quantified by patients	Subjective and limited validation instruments Need randomized/blinded

Trial Endpoints

- FDA approval considerations

	Frontline	Platinum-sensitive	Platinum-resistant	Clear cell mucinous LG-serous
OS	Approve	Approve	Approve	Approve
PFS (statisticallysignificant) + other (QoL/PRO)	Approve	Approve	Consider	Consider
PFS (statistically significant) with clinically meaning MOE[a] (median difference)	Consider (MOE: 6 mos?)	Consider (MOE: 4 mos?)	Consider (MOE: 3 mos?)	Consider
Objective response rate (with supportive duration of response)	No	No	Consider	Consider

Herzog et al. Gynecol Onc. 147, 2017. 3-10.

Conclusions

- Clinical trials improve our ***knowledge*** about treatments, improve ***options*** for patients, improve ***outcomes*** for patients
- Clinical trials are excellent options for many patients
- Resources
  - Your care providers
  - Clinicaltrials.gov

THANK YOU

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