Demystifying Clinical Trials: Focusing on Trials with Therapeutic Intent

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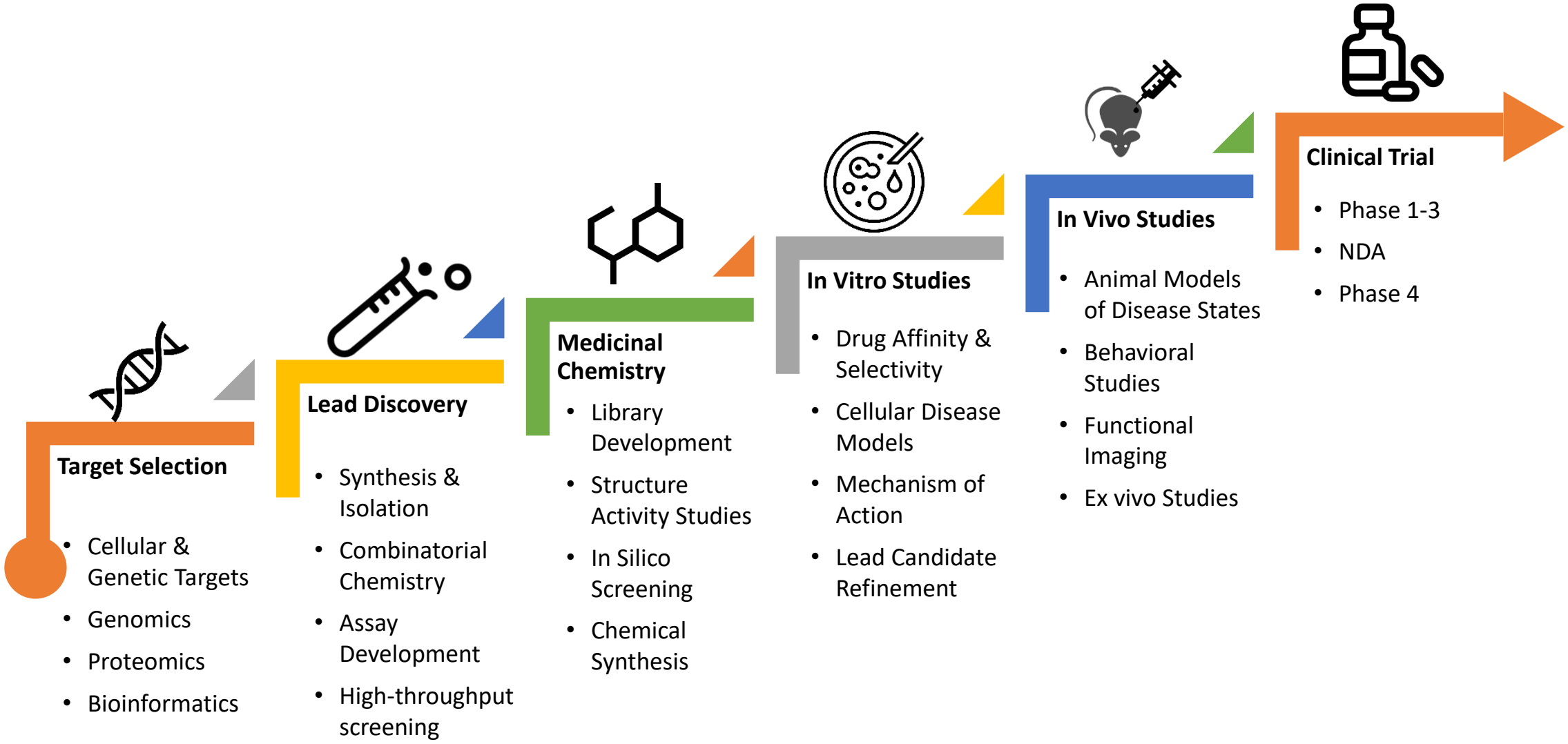
Objectives

1. Understand and define the different stages of drug development.
2. Define GCP (Good Clinical Practice) and its applications for patients and research.
3. Understand and define the principles of informed consent.
4. Identify common misconceptions in clinical trials.
5. Better understand the changing landscape of clinical trials by examples in prostate cancer

Drug Discovery Process



Development: Clinical Trial Stages

Average time is 12-14 years for a drug to go from pre-clinical laboratory testing to obtaining approval for human use

Drug Development: Clinical Trial Stages

Phase 1

1. Evaluates the safe dose, how often it should be given, side effects.
2. Enrolls a small number of patients (20-30)
3. Often not tumor specific but may be target specific.
4. Patients are often of more advanced stage heavily pre-treated.

Phase 2

1. Continues to test the safety of the treatment and how well it works.
2. Usually focuses on a specific target, cancer type, or clinical scenario
3. Enrolls between 50-300 patients.

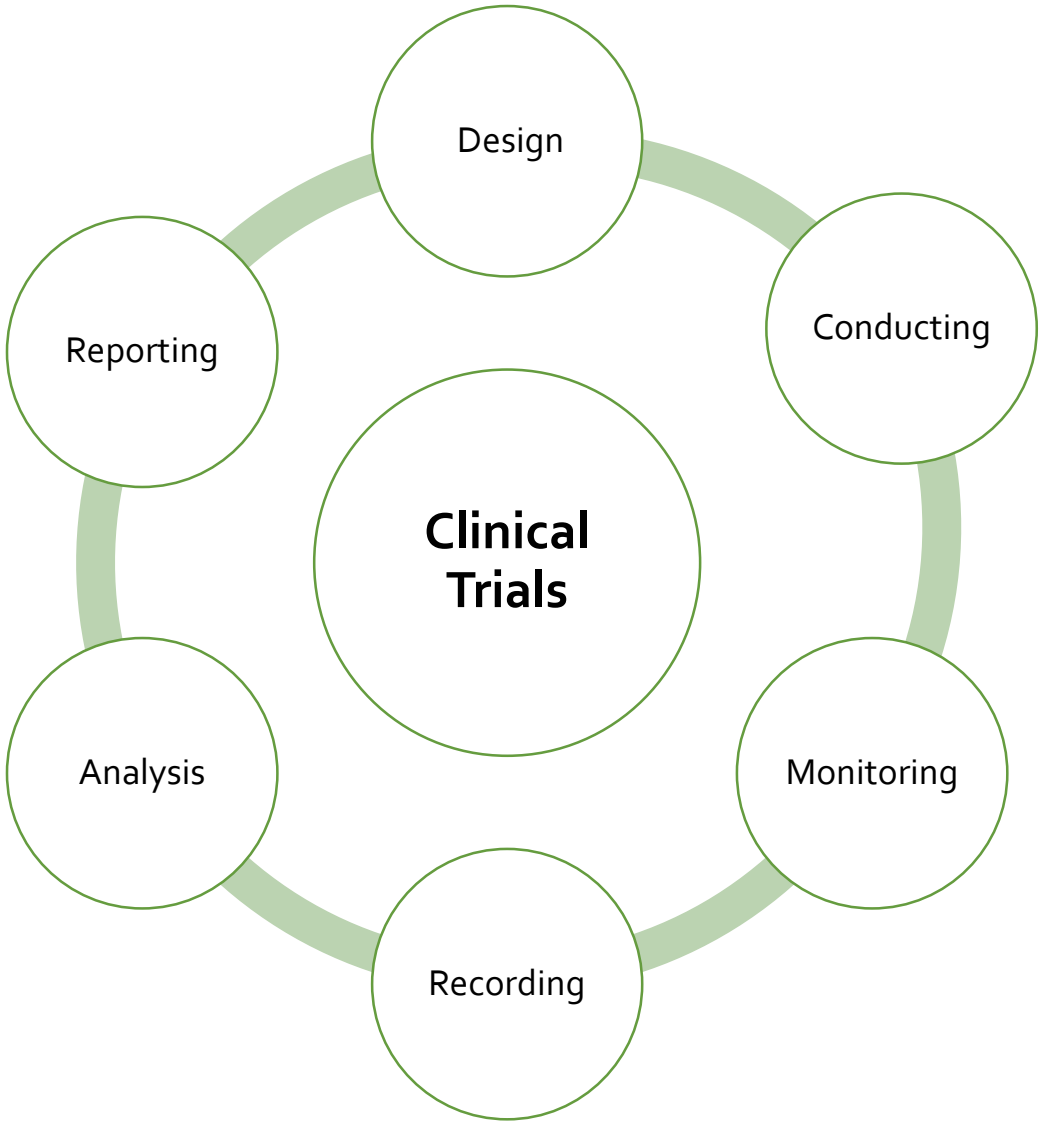
Phase 3

1. Tests the new drug in comparison to the standard therapy.
2. Usually involves a randomization.
3. Enrolls a large number of patients nationwide (thousands).
4. Often first line
5. Leads to a New Drug Application (NDA) with the FDA

Phase 4

1. Further evaluates the long term safety and effectiveness of a new treatment, after a drug approved for standard use.
2. Enrolls large numbers of patients nationwide (thousands).

Good Clinical Practice (GCP)



1. International ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.

2. Provide a unified standard for the EU, Japan, and the United States to facilitate the mutual acceptance of clinical data by regulatory authorities.

3. Public assurance that the rights, safety and well being of trial participants are being protected.

Research: A Historical Perspective (US)

1. Nuremberg Code – 1946
2. Kefauver Amendments (thalidomide) – 1962
3. Declaration of Helsinki – 1962
4. National Research Act (Tuskegee Syphilis Study) - 1964
5. Belmont Report - 1979

The Nuremberg Code - 1946

Key points:

1. Experiments should yield fruitful results for the **good of society**
2. Experiments should be designed and **based on results of animal experimentation and a knowledge of the natural history or disease**
3. **Avoid** all unnecessary **physical and mental suffering** or injury
4. No reason to believe that death or disabling injury will occur
5. **Risk should never exceed benefits**
6. **Adequate protection** against even the remote possibility of injury, disability or death
7. Experiment should only be **conducted by scientifically qualified persons**
8. Subject has the **right to withdraw at any time**
9. Researcher must terminate experiment at any stage if continuation of experiment is likely to result in injury, disability or death.

Kefauver Amendment - 1962

1. "Drug Efficacy Amendment“
2. Drug manufacturers to provide proof of the effectiveness and safety
3. Drug advertising to disclose accurate information about side effects
4. **Stopped cheap generic drugs being marketed as expensive drugs under new trade names as new “breakthrough” medications.**

Declaration of Helsinki - 1964

- World Medical Association gathered in Helsinki to elaborate and revise ethical rules in Nuremberg Code
- Revised 6 times between 1964 and 2008
- Known cases of abuse to clinical research subjects in US between the 1948-1964

- **Concept of Informed consent established**
- **Establish IRBs**
- Require journals to refuse unethical studies
- Allowed legal guardians to give (proxy) consent
- Controls must be given the best supportive care
- Allow patients **continued access to the intervention at end of study if they benefit from it**
- Researchers must maintain privacy for subjects
- Unproven prescriptions are ok in controls if it offers them hope
- Placebo is ok only if there is no proven prescription or the disease is so mild that no harm will occur

National Research Act -1974

Tuskegee Syphilis Study (1932-1972)

- Investigators enrolled in the study a total of 600 impoverished, African-American sharecroppers from Macon County, Alabama.
- 399 had previously contracted syphilis before the study began, and 201 did not have the disease.
- The men were given free medical care, meals, and free burial insurance for participating in the study.
- Failed to treat patients appropriately after 1940s in order to validate penicillin

The New York Times

Syphilis Victims in U.S. Study Went Untreated for 40 Years

By JEAN HELLER
The Associated Press

WASHINGTON, July 25—For 40 years the United States Public Health Service has conducted a study in which human beings with syphilis, who were induced to serve as guinea pigs, have gone without medical treatment for the disease and a few have died of its late effects, even though an effective therapy was eventually discovered.

The study was conducted to determine from autopsies what the disease does to the human body.

Officials of the health service who initiated the experiment have long since retired. Current officials, who say they have serious doubts about the morality of the study, also say that it is too late to treat the syphilis in any surviving participants.

Doctors in the service say they are now rendering whatever other medical services they can give to the survivors while the study of the disease's effects continues.

Dr. Merlin K. DuVal, Assistant Secretary of Health, Education and Welfare for Health and Scientific Affairs, expressed shock on learning of the study. He said that he was making an immediate investigation.

The experiment, called the Tuskegee Study, began in 1932 with about 600 black men,

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

- Further developed guidelines for human subjects
- Regulate human experimentation
- **Formalized the IRB process**

The Belmont Report - 1979

1. **Respect for persons**
   - ✓ Protect autonomy of all people
   - ✓ Treat people with courtesy and respect
   - ✓ Allow for informed consent
   - ✓ Provide additional protections to those with limited autonomy

2. **Beneficence**
   - ✓ Maximize research project while minimizing risk to participants
   - ✓ Do no harm, prevent harm, and promote good

3. **Justice**
   - ✓ Fair distribution of costs and benefits to potential research participants
   - ✓ Distinguish procedural justice from distributive justice

Principles of Informed Consent

- IRB written approval of written informed consent
- Written informed consent should be provided to patient prior to time of signing consent
- Investigator/trial staff should not influence participation in trial
- No language in consent that waives legal right or releases investigator of liability
- Investigator/designee will fully inform patient of all aspects of trials in the written informed consent
- Language in oral written consent should be understandable
- Patient have ample time/opportunity to ask questions
- Signed and personally dated by patient
- If unable to read/legally acceptable representative is unable to read, an impartial witness shall be present and sign consent

Common Misconceptions in Clinical Trials

1. I don’t want to be a “guinea pig”
2. Clinical trials are only for the “last resort”
3. Cost of treatment is not covered by insurance
4. Clinical trials never work – so there is no point participating
5. Clinical trials are not safe

Why and When to Consider Participation in Clinical Trials, How to Prepare Yourself

- We are in a new age of medicine
  - Scientific understanding of disease and disease targets has dramatically increased
  - Availability of I/Os and molecular targeted therapies has widely increased
  - Immuno-oncology, Molecular targeted therapies offer the potential for higher efficacy and therapeutic index
- Clinical trials should be considered at all time points in care
  - Match the trial risk with your disease risk
  - Strong data is ahead of insurance / guideline approvals (though we are getting better at this)
    - Trials with “Me too” drugs allow for potential earlier access to somewhat known therapeutics
- Prepare yourself by understanding your disease
  - All advanced cancers should have molecular testing (i.e. NGS)
- Some examples to follow

Example 1: 56 year old with NCCN low risk clinically localized prostate cancer

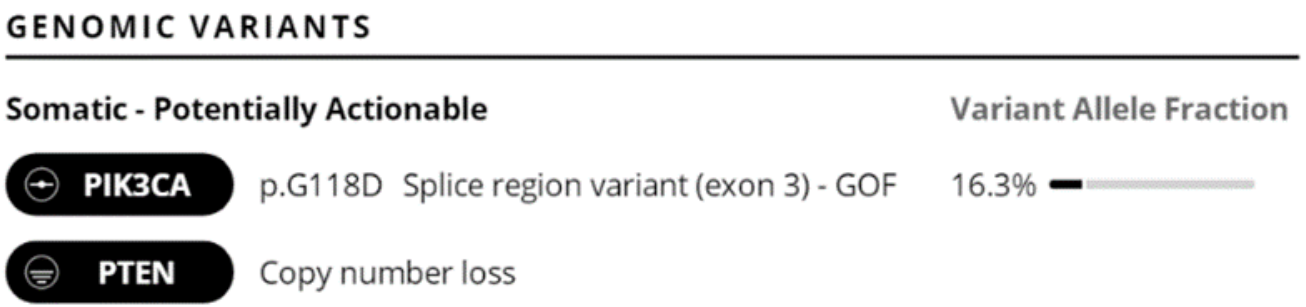
- Standard of Care Options –
  - Active Surveillance
  - Radical Prostatectomy
  - Radiation based therapy

- Discussed and joined Provent trial
  - Randomized 2:1, multi-center phase III trial recently closed to enrollment
  - Provenge Plus Active Surveillance vs Active Surveillance
    - Provenge is a life prolonging cellular immunotherapy approved with mCRPC with favorable toxicity profile
  - Patient risk is low, trial risk should be low

Example 2: 74 year old with locally advanced,radio-recurrent unresectable Gleason Grade Group 5 prostate cancer

- Status post radiation, 2 attempts at HIFU, palliative TURP
- Biopsy shows GG5 disease in multiple cores
- Rising PSA, M0 on PET imaging
- ADT intolerant (hospitalized from psychological issues on last attempt)

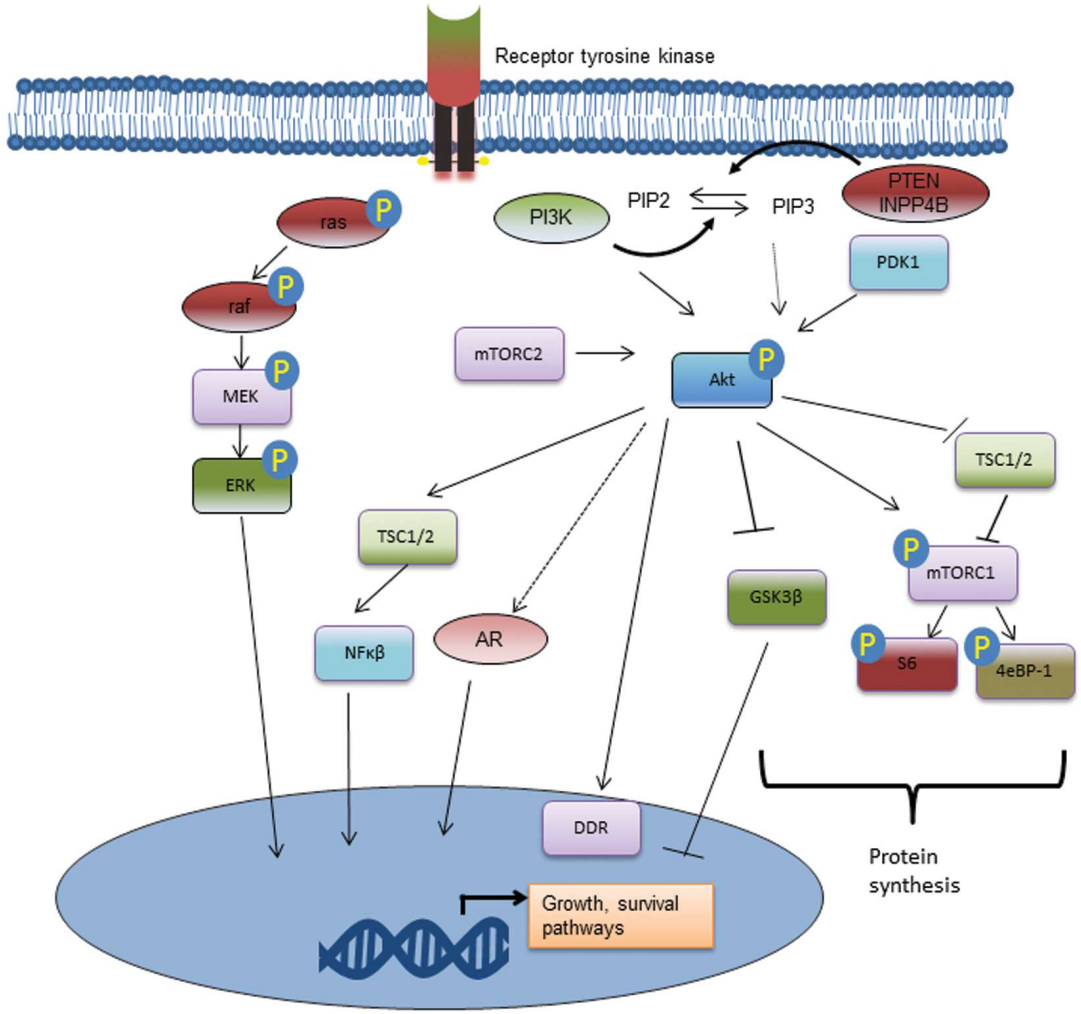
- Locally advanced or Metastatic Disease → Tumor / Germline Genetics



Example 2: 74 year old with Locally Advanced, PIK3CA Mutated, PTEN loss PCA who is ADT Intolerant

- Placed on a Phase Ib Study of ARQ 751 for tumors with PIK3CA/AKT/PTEN Alterations
  - Oral available, potent pan-AKT inhibitor
  - No grade ≥ 3 AEs in phase I dose finding trial

PTEN/PI3K/AKT Pathway



Example 3: 58 year old with Hormone Sensitive Metastatic Prostate Cancer

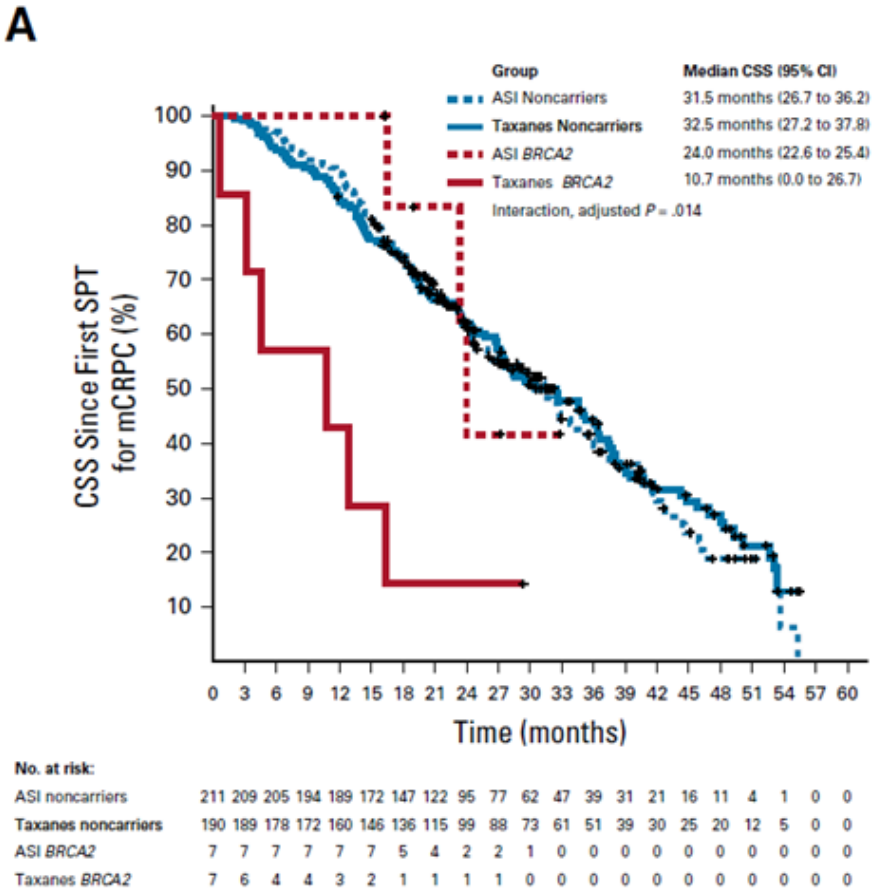
- Newly diagnosed with NCCN very high risk localized prostate cancer
- Genomic testing showed deleterious germline BRCA2 mutation
- Prostatectomy showed pT2N0MxR0 Gleason Grade Group 5 disease
- First PSA at 1.5 mo, 1.04 and repeated at 2mo at 1.58
- Restaging shows M1b disease with 7 mets
- Systemic therapy should be intensified, but with what…

Example 3: 58 year old with Hormone Sensitive Metastatic Prostate Cancer

- Treatment Considerations –

- mHSPC PROREPAIR-B (Castro et al JCO 2019) Chemo vs Androgen Axis
  - BRCA2 mutated patients treated with androgen signaling inhibitors (ASI -- i.e. Abi or Enza) had significantly greater PFS and CSS when compared to those receiving docetaxel
- PROfound trial demonstrates PARP superiority to ASI in mCRPC (ESMO 2019)

- Patient placed on a clinical trial to study the relative bioavailablity and bioequivalence of Niraparib tablet versus capsule formulations in patients with advanced tumors (allows mHSPC, allows ADT)



Thank you

Patients

A special thanks to all patients who patriciate in clinical trials. It is because of them that other will live.

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