4.48: The Truth About RCTs In Cancer Medicine

Season	4
Type	Plenary Session
Status	Complete

We Discuss:

- Cost [0:30]
- Do you have to run a randomized control trial to criticize it? [2:15]
- Funding Source [3:30]
- Purpose [7:00]
- COVID [14:00]
- POLO Trial [14:02]
- BOSTON Trial [16:44]
- Speed of approval [18:59]
- Impracticality [22:00]
- Solutions [26:00]

Plenary Session 4.48 Show Notes

Overview

Monologue with Dr. Vinay Prasad

- **YouTube**

- Watch this video on YouTube

- **Cost [0:30]**
  - Is it hard to do a RCT?
    - We have to start by acknowledging it's very difficult
      - It's often costly, it's very tedious, and there are a lot of hoops to jump through
  - Are RCTs expensive?
    - Sometimes it's costly, which is typically due to the overwhelming bureaucracy around conducting trials

> "Just as the seat distance is not a property of the airplane – the cost of the randomized trial is not a cost of randomization. It's a cost of the bureaucracy we've inserted around it – and we can do away with a lot of that" - VP

    - The TASTE trial is an example of a well-executed and low-cost RCT
      - The researchers constructed a registry-based randomized trial costing ~ $50 per participant
- **Do you have to run a randomized control trial to criticize it? [2:15]**
  - Folks who created bad movies found it difficult, expensive, and time-consuming to make them.
    - But the expense should not be a justification for making a dreadful film that no one wanted to see
      - Similarly, cost should be no justification for an unethical, faulty randomized control trial
- **Funding Source [3:30]**
  - Evidence in oncology suggests that the majority of RCTs, almost 90%, are supported by the industry

        - The industry supports these studies with the purpose of increasing market share for their products. As a result, the industry makes more money.
            - A secondary purpose is to help individuals live longer and better lives
                - The purpose of drug regulation is to align those two goals

> “The places where it [two goals above] deviates are the places where randomized trials become unethical, unjust, corrupt, flawed, problematic, and those are the places that warrant harsh criticism. And if we don't give it harsh criticism, then the industry will perpetuate these flawed studies for another decade, and another generation of cancer patients will suffer.” - VP

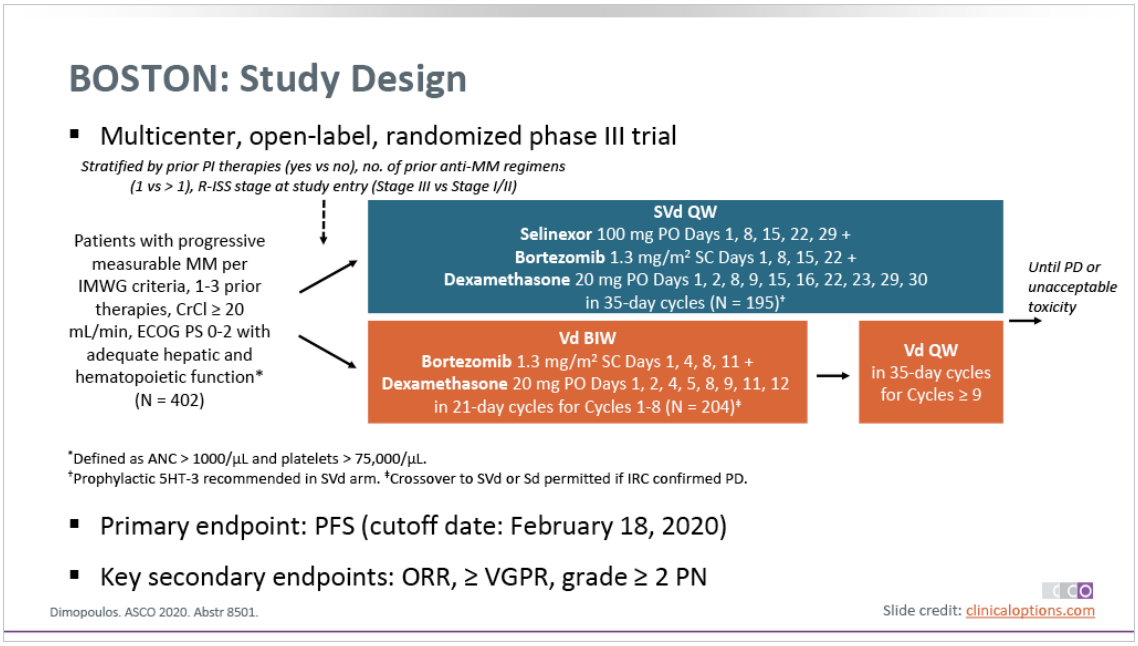
    - Trials can also be run by impartial groups
        - But at the same time, they too can be corrupt and perverted by different interests, including the major goal which is to always claim progress
            - Also in this modern world – if you want to run a cooperative group study, you often need the industry to support the research agenda

- **Purpose [7:00]**
    - **Cancer Lectures**
        - Video series at VK Prasad Laboratory
            - **Lecture 2 - Surrogate Endpoints in Oncology - Reading and Interpreting Cancer Trials**
    - Papers mentioned
        - Haslam A, **Prasad V.** When is crossover desirable in cancer drug trials and when is it problematic? *Annals of Oncology*
        - Hilal T, Gonzales-Velez M, **Prasad V.** Limitations in Clinical Trials Leading to Anticancer Drug Approvals by the US Food and Drug Administration. *JAMA Internal Medicine*

        - **Prasad V**, Massey PR, Fojo T. Oral anticancer drugs: how limited dosing options and dose reductions may affect outcomes in comparative trials and efficacy in patients. *J Clinical Oncology*
        - Olivier T, Haslam A, Prasad V. Reporting of Physicians' or Investigators' Choice of Treatment in Oncology Randomized Clinical Trials. **JAMA Network Open**
        - **Prasad V**, Kumar H, Mailankody S. Ethics of Clinical Trials in Low-Resource Settings: Lessons From Recent Trials in Cancer Medicine. *Journal of Global Oncology.*
    - Ethics
        - The key point here is no matter what your goal – all your trials have to be ethical
            - What does it mean to be ethical?
                - The control arm must always be standard of care or placebo (if the standard of care *is* placebo i.e., no other therapy works)
                    - e.g., Effect of VIA Screening by Primary Health Workers: Randomized Controlled Study in Mumbai, India
                        - Because the standard of care in that area was no effective therapy, and because the thing they were testing was something that were it to be successful, it could be deployed *in the country it was tested in*
                            - Those two things conferred the ethical prerequisites to do such a study

- **COVID [14:00]**
    - At the beginning of the pandemic, RCTs of vaccines were ran against placebo because there was no standard of care established (i.e., there was equipoise)
        - Since then, a placebo control is unethical, even in the global setting because of the numerous types of vaccines/makers available
- **POLO Trial [14:02]**
    - Published in the NEJM

        - This was a randomized controlled trial of patients with germline mutation BRCA positive metastatic pancreas cancer
            - Patients were randomly assigned, in a 3:2 ratio, to receive maintenance olaparib tablets or placebo
        - The primary end point was PFS
    - At the time of trial design, 6-month treatment with FOLFIRINOX was a standard of care
        - However, patients did not receive an average of 6 months of therapy before enrolling on the trial
            - Is placebo control acceptable control arm in that situation?
                - The answer is no
    - 9.7% of patients who get on sugar pill have a radiographic response to sugar pill
        - <u>Placebo effects in oncology</u>
            - Ian Tannock found 2-3% of people on placebo containing arms have a response
        - The heightened placebo response in the POLO trial is likely due to patients continuing to response to Platinum based chemotherapy
- **BOSTON Trial [16:44]**
    - Trial overview



Source

> "The control arm is a form of pushing someone and harming them because it's beneath what you would otherwise do, which would be a triplet [therapy] at the time of this study" - VP

- Some people say well, "the FDA compelled us to use this control arm"
  - Counterpoints:
    1. Worst case scenario, if they wanted that comparison, you could have had a third arm of actually being the prevailing standard of care
    2. Second of all, no one has ever stopped anyone from running the ethical and correct study and then submitting it and pushing on FDA

- **Speed of approval [18:59]**
  - Chen EY, Joshi SK, Tran A, **Prasad V.** Estimation of Study Time Reduction Using Surrogate End Points Rather Than Overall Survival in Oncology Clinical Trials. *JAMA Internal Medicine*
    - In a randomized trial, as you start randomizing, you're constantly assessing for the signal as time goes on at any moment in time

        - In an uncontrolled study, you have to first enroll a certain amount of people on it → then you get a robust estimate of the response rate
            - Once you figure out your fraction of responders, you have to keep watching these people until you see the median duration of response
                - So you have to wait both for the response and then for the median DOR
    - The individual patient experience is not the same thing as an aggregate trial experience
        - To get an aggregate response rate, an aggregate trial may take longer than an OS readout versus the current standard of care

- **Impracticality [22:00]**
    - The vast majority of decisions are not based on randomized controlled trials, but they serve a vital role, one of which is to illustrate the underlying effectiveness of therapies
        - That's the thing that separates real medicine from witchcraft
- **Solutions [26:00]**
    1. We need a federal randomized trial budget run by non conflicted investigators based on roughly 5% of CMS Medicare spending
        - We have to have it run by truly non-conflicted people, people with methodologic expertise
    2. Every RCT must be ethical
    3. We need to be in the superiority business until we're in the cure business

> “We don't need to be in the more options business, we need to be in the good options business” - VP

- **Literature mentioned:**
    - The Cardiac Arrhythmia Suppression *Trial* (*CAST)*
    - Cancer disruptors: When Bernie Fisher refused to grovel

- Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women
- ORBITA
- Mohyuddin G, Koehn K, Sborov D, McClune B, Abdullah A, Goodman A, **Prasad V** Quality of control groups in randomised trials of multiple myeloma enrolling in the USA: a systematic review. *Lancet Haematology*
- Olivier, Prasad, Marini. Hard-wired biases in trials: maintenance azacitidine in patients with acute myeloid leukemia and framework for future trials. *Blood Advances*

Plenary Session is a podcast on medicine, oncology, & health policy.

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