4.42: Timothee Olivier, Geneva in the first Installment of VKPrasad Lab updates

Season	4
Type	Plenary Session
Status	Complete

We Discuss:

- Introduction [0:00]
- Physician’s Choice [2:20]
- Sacituzumab govitecan [5:57]
- Melflufen [24:32]
- Parachutes [37:32]
- Mechanism of action [45:00]
- A little about Timothee Olivier [53:00]

Plenary Session 4.42 Show Notes

Overview

Conversation with Dr. Timothee Olivier

- **Introduction [0:00]**
    - Dr. Olivier is a practicing oncologist at the **Hôpitaux Universitaires de Genève**
        - He is a visiting scholar at University of California San Francisco

        - His research interests span medicine, oncology, and public health policy
    - He is a member of the **VK Prasad Laboratory**
        - This lab focuses on drug policy, medical evidence, study design, and governmental regulation
- **Physician's Choice [2:20]**
    - Reporting of Physicians' or Investigators' Choice of Treatment in Oncology Randomized Clinical Trials
        - Timothée Olivier, MD; Alyson Haslam, PhD; Vinay Prasad, MD, MPH; *JAMA Network Open*

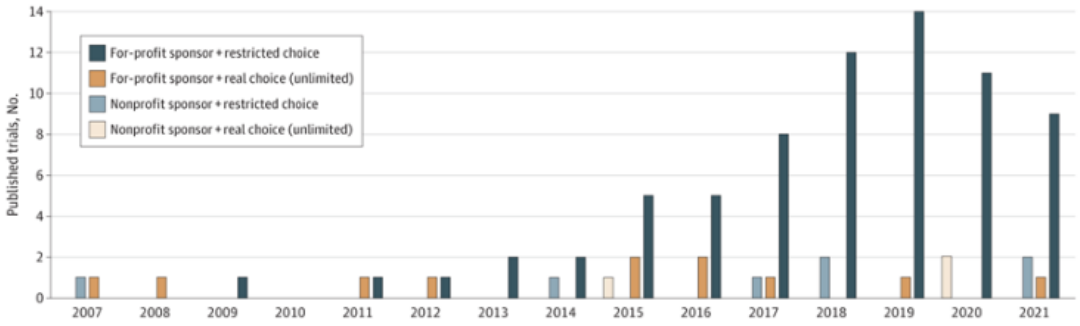
> ⚕ *"Randomized clinical trials (RCTs) aim to rigorously evaluate the benefits and risks of any intervention. However, RCTs may be limited if the control group does not reflect the ongoing standard of care, and especially if the control group is inferior to standard care. A cross-sectional analysis of 95 consecutive Food and Drug Administration approvals of anticancer agents between 2013 and 2018 showed that 16 (17%) were based on RCTs with suboptimal control groups.*
> *1" - Olivier et al.*

    - Among the 82 industry-sponsored trials, there were 71 RCTs (77.2%) with a **restricted choice** and 11 (12%) offering an unrestricted choice
        - The industry loves to run this agenda

> "It wasn't a physician choice, it was a restricted choice." - VP

            - This is a marketing approach known as the illusion of choice; you believe you have a wide range of options, but your options are somewhat skewed.

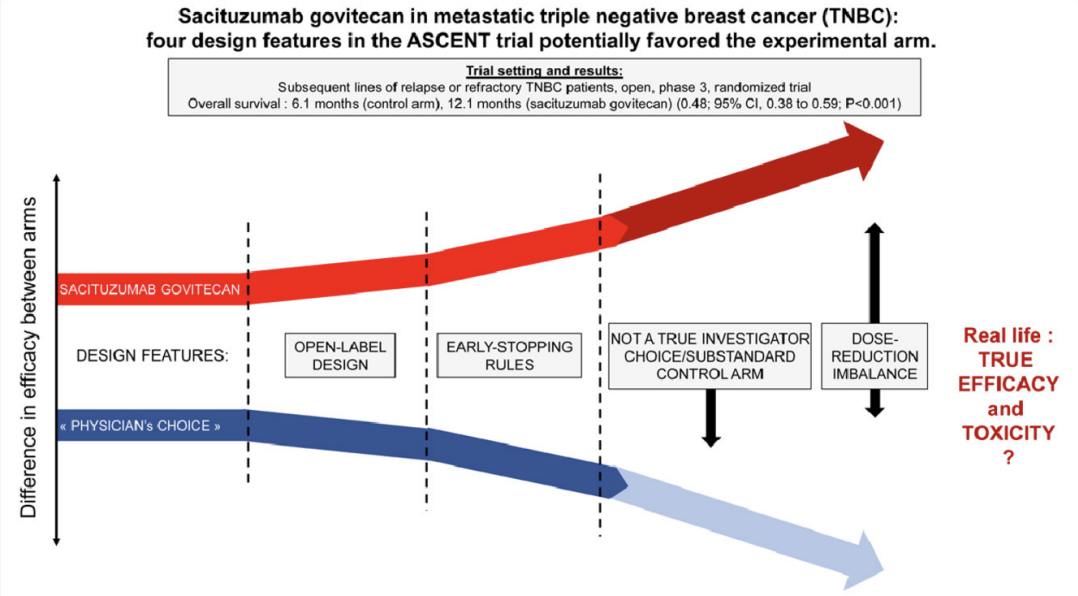
Figure. Cumulative Yearly Number of Published Oncology Randomized Clinical Trials Mentioning Physician's Choice or Investigator's Choice in the Control Group (N = 92)



Olivier et al.

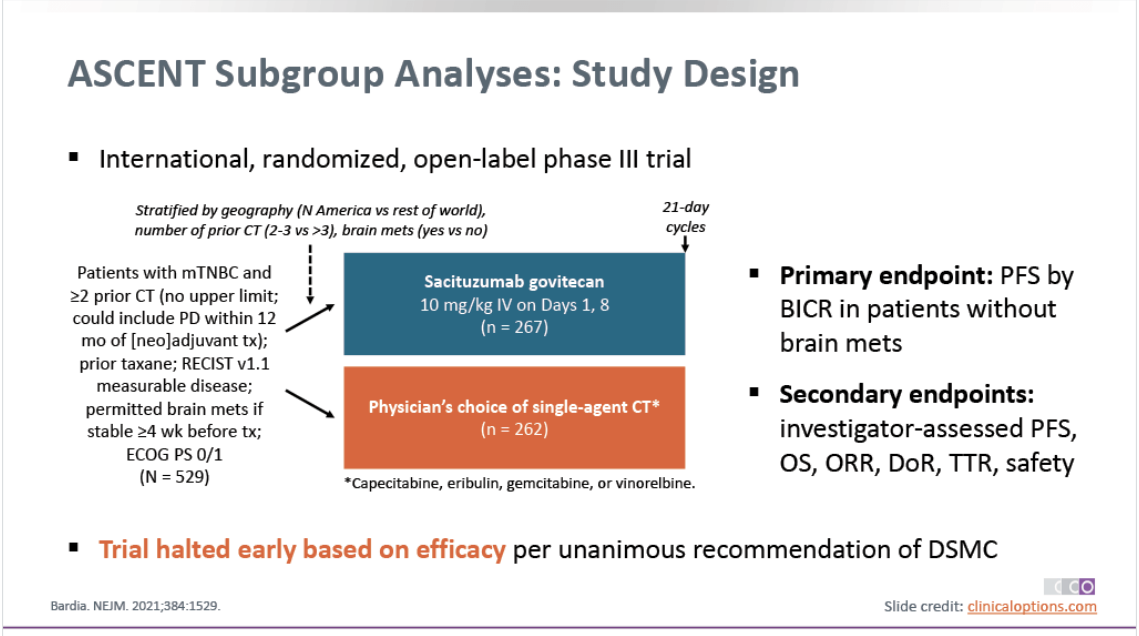
> *"Through imprecise wording, potentially masking substandard control group, treating physicians may inaccurately think that the reported results can be generalized to their patients, whereas this may not be true. Our findings suggest that editors and regulators should demand clarification in the use of these terms within RCTs protocols and reports." - Olivier et al.*

- **Sacituzumab govitecan [5:57]**
  - Sacituzumab govitecan in metastatic triple negative breast cancer (TNBC): Four design features in the ASCENT trial potentially favored the experimental arm
    - Olivier T, Prasad V, *Translational Oncology*



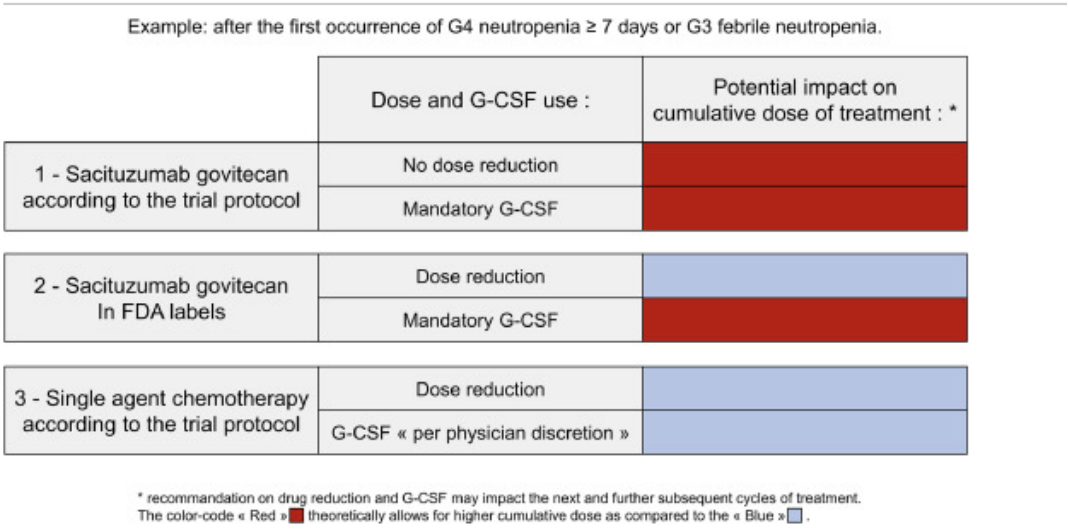
- Trial overview

> *"The ASCENT trial reports a progression-free survival and overall survival (OS) advantage with sacituzumab govitecan over single-agent chemotherapy, in metastatic triple negative breast cancer (TNBC) patients in second and subsequent line of therapy. Specifically, the authors found that the median OS increased from 6.7 months to 12.1 months (hazard ratio = 0.48; 95% CI, 0.38 to 0.59; P < 0.001) [1]. However, despite these impressive results, several concerns remain."*



Source

- Main concerns
  - A major concern with this trial was that physicians could not choose platinum nor anthracyclines
    - A significant proportion of patients were not allowed to receive these highly active drugs in this setting
      - There was also a high rate of patients initially dropping from the control arm
- Other concerns:
  1. First, the study used an open-label design, which meant that patients and their physicians were aware of both the trial sponsor and the drug they received
  2. A disparity in dose-reduction recommendations across arms further penalized the control arm



Olivier et al.

3. Early stopping
    a. When trials stop early–on average–the effect sizes exaggerated
4. PFS
    a. What is the justification to choose PFS in this setting?
        i. Overall survival would have been suitable in this setting because it is tim
    b. Background
        i. Progression free survival is composite time endpoint in which four things can happen:
            1. The patient dies
            2. There's new lesions on imaging
            3. The tumors get 20% bigger
            4. The tumors grow 20 percent larger than the smallest size they ever were if they shrank, whichever occurs first.
                a. But, of course, that 20% figure is arbitrary.

- **Melflufen [24:32]**
    - The approval and withdrawal of melphalan flufenamide (melflufen): Implications for the state of the FDA

- Olivier, Prasad; *Translational Oncology*

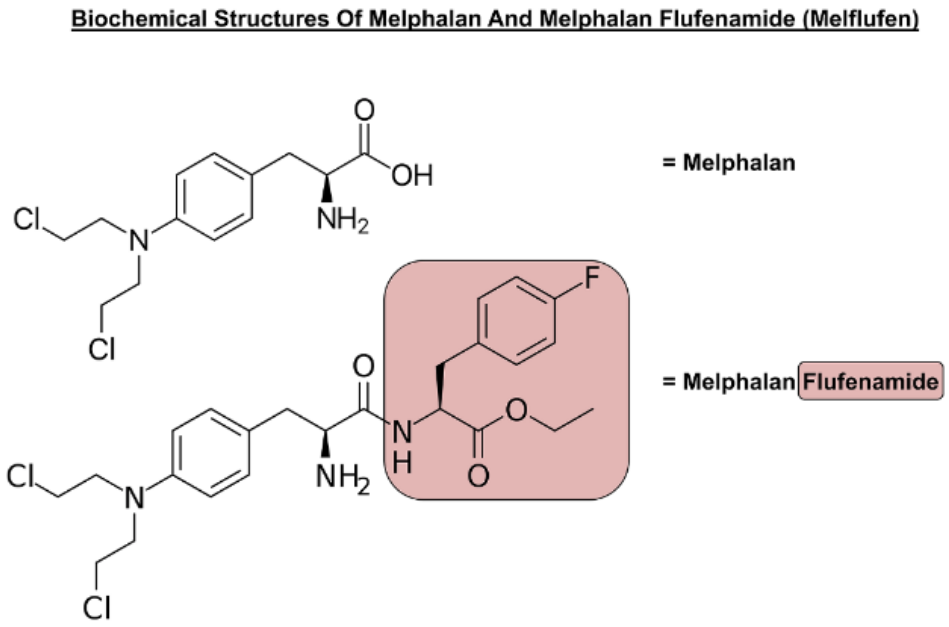
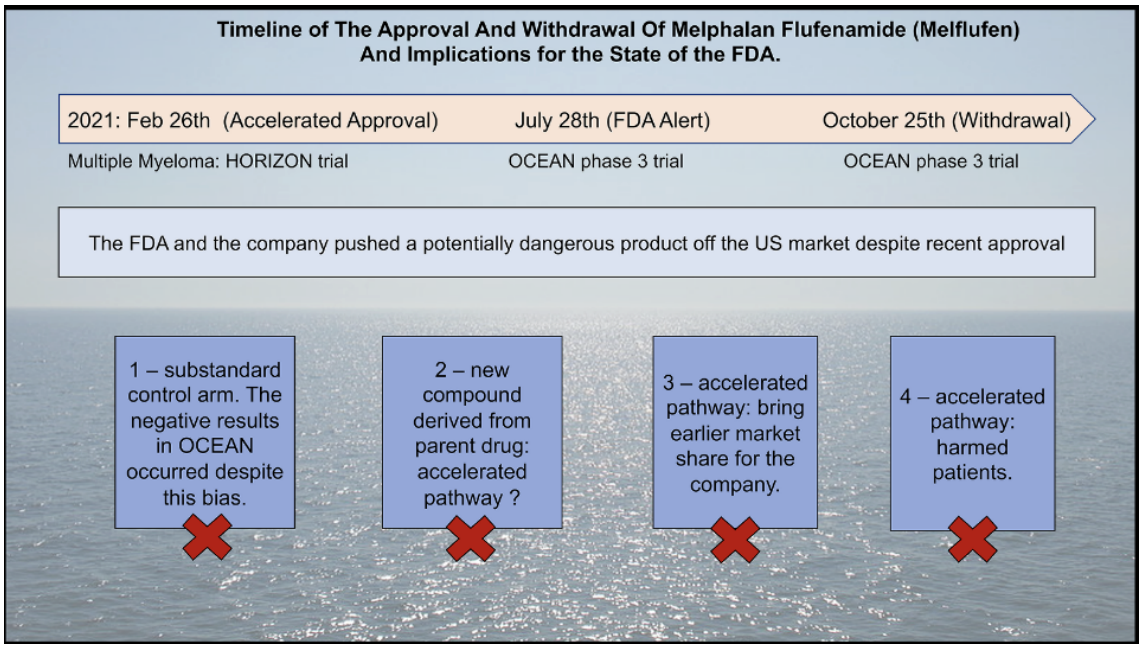


Figure 2. Biochemical Structures Of Melphalan And Melphalan Flufenamide (Melflufen).

Olivier et al.

- Timeline of The Approval And Withdrawal Of Melphalan Flufenamide (Melflufen)



Olivier et al.

- Issues
    1. *The confirmatory study showed a trend towards excess death despite multiple trial design features that were biased in favor of the melflufen arm.*
    2. *The flexible regulatory pathways are being made available to unremarkable, next in class drugs*
    3. *Melflufen raises the question of who benefits from profits generated during the period of approval*
    4. *How much acceleration is needed to tolerate increased uncertainty? - Oliver et al.*

- **Parachutes [37:32]**
    - The use and meaning of the parachute metaphor in biomedicine: a citation analysis of a systematic review and a randomized trial of the parachute for freefall
        - Xu & Prasad, *Journal of Comparative Effectiveness Research*

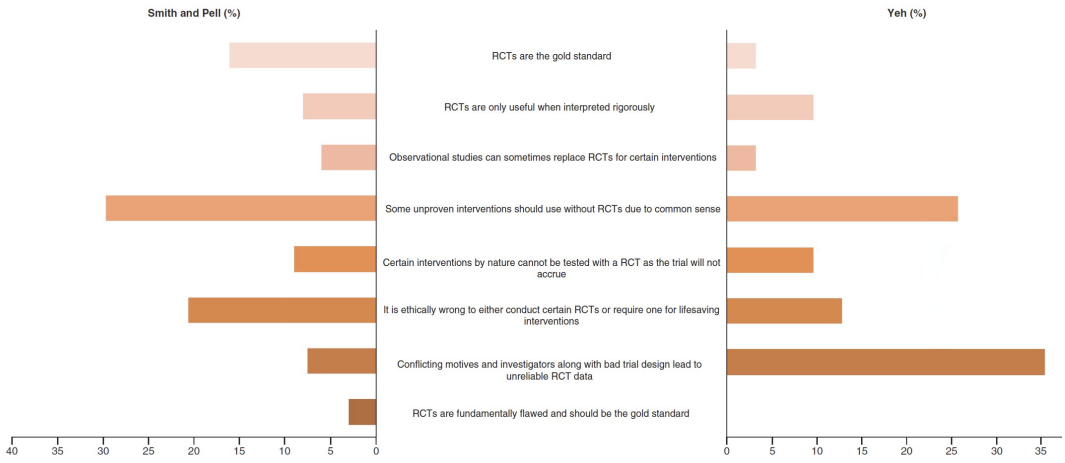
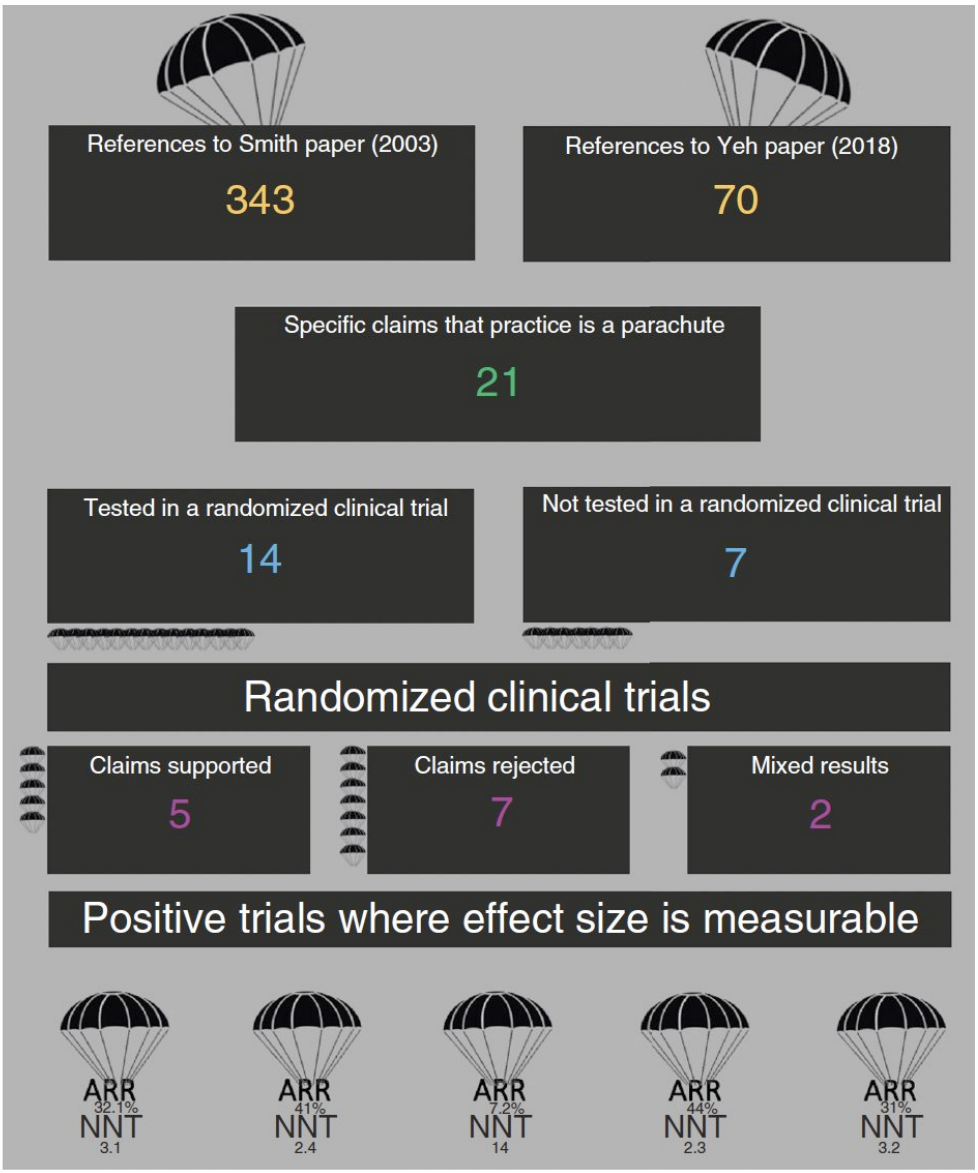
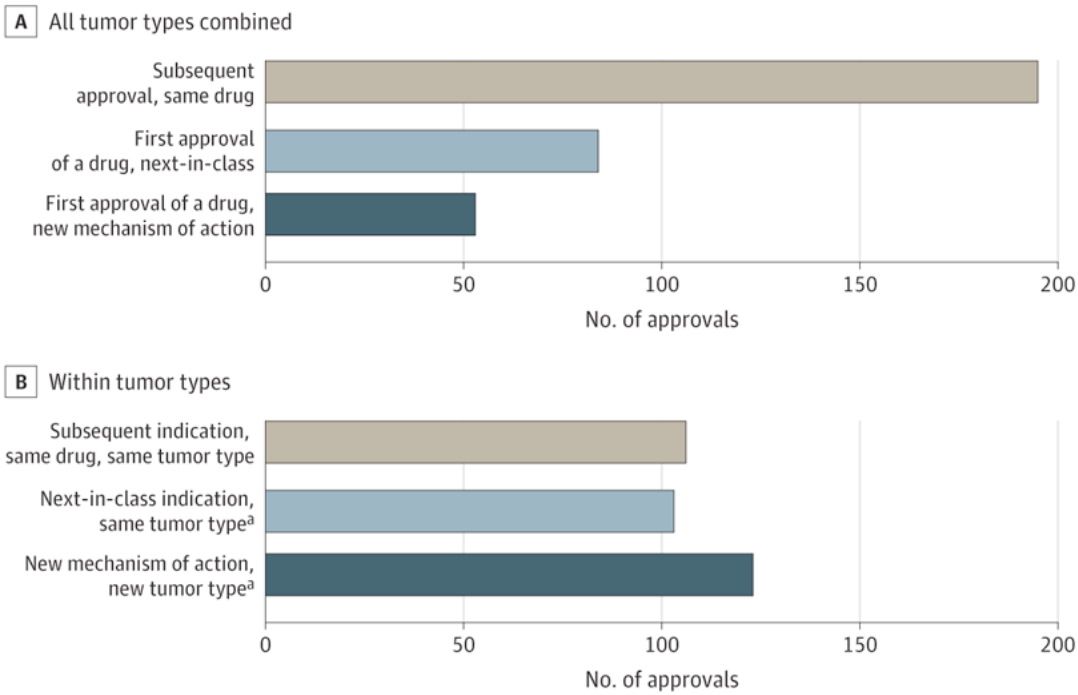


Figure 2. Bar graphs of the various attitudes of authors citing Smith and Pell/Yeh papers (%).
RCT: Randomized controlled trials.



Xu & Prasad

- **Mechanism of action [45:00]**
    - Anticancer Drugs Approved by the US Food and Drug Administration From 2009 to 2020 According to Their Mechanism of Action
        - Olivier T, Haslam A, Prasad V; *JAMA Network Open*



Olivier et al.

- Me-too drug's
  - Are these drugs better than their predecessors? Are they cheaper? What is the advantage to the patient?
    - Benefits:
      1. There is a tiny fraction of people who are idiosyncratically intolerant to one drug, and it benefits them to have other options
      2. For somebody who progresses on one drug, there may be incomplete cross resistance to a different drug of that class
         - However, for both of these cases, they must be validated in RCT's

- **A little about Timothee Olivier [53:00]**
  - Timothee's thoughts about his research focus

> "This is one one thing I really like in this research. So it's not – you know – *far from the patient*."

1. This research is analytical thinking focused on clinical questions

2. In its purest form, the majority of this work is patient-centered.
3. This research relates to the other topics we raised, as well as your role as a physician

- **Other literature mentioned:**
  - Censored patients in Kaplan–Meier plots of cancer drugs: An empirical analysis of data sharing
    - Rosen et al., *EJC*
  - Lutetium 177 PSMA - Problems with the Vision Trial
    - YouTube commentary by VP
  - Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer
    - Sartor et al., *NEJM*
  - Analysis of Control Arm Quality in Randomized Clinical Trials Leading to Anticancer Drug Approval by the US Food and Drug Administration.
    - Hilal T, Sonbol MB, Prasad V**,** *JAMA oncology*
  - Quality of control groups in randomised trials of multiple myeloma enrolling in the USA: a systematic review
    - Mohyuddin et al., *Lancet Haematology*
  - Oral anticancer drugs: how limited dosing options and dose reductions may affect outcomes in comparative trials and efficacy in patients.
    - Prasad V, Massey PR, Fojo T; *JCO*
  - Randomized trials stopped early for benefit: a systematic review
    - Montori et al., *JAMA*
  - Overestimation of the effect size in group sequential trials
    - J.J. Zhang et la., *Clinical Cancer Research*
  - Estimation of Study Time Reduction Using Surrogate End Points Rather Than Overall Survival in Oncology Clinical Trials
    - Chen EY, Joshi SK, Tran A, **Prasad V,** *JAMA Intern Med.*

- Melflufen or pomalidomide plus dexamethasone for patients with multiple myeloma refractory to lenalidomide (OCEAN): a randomised, head-to-head, open-label, phase 3 study
  - Schjesvold et al., *The Lancet Haematology*
- Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials
  - Smith & Pell., *BMJ*
- Parachute use to prevent death and major trauma when jumping from aircraft: randomized controlled trial
  - Yeh et al., *BMJ*
- The Wild West of Checkpoint Inhibitor Development
  - Beaver & Pazdur, *NEJM*

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

Host: Vinay Prasad, MD MPH from University of California, San Francisco.

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