4.43: VKPrasad Lab Update Part 2 With Timothee Olivier

Season	4
Type	Plenary Session
Status	Complete

We Discuss:

- Introduction [0:00]
- Twitter [0:45]
- BOLERO [5:29]
- CHECKMATE-067 [10:51]
- Critics [30:00]
- Elacestrant [42:00]
- Iceberg [50:00]
- Closing thoughts [57:00]

Plenary Session 4.43

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

- **Twitter [0:45]**

> "Twitter was really important for me in my career and my development of thinking, but in another way for further reasons, I find it a place really difficult to navigate" - Dr. Olivier

    - On Twitter, there is a large presence of congratulatory culture without enough constructive criticism
        - If trial design is substandard and no improvements are made, patients will gradually lose faith as they are exposed to a sub par level of treatment
    - Timothee observes that, despite the many limits of oncology twitter, there are a few accounts that provide valuable knowledge.

- **BOLERO [5:29]**
    - **Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer**
        - Baselga et al., NEJM
    - The role of censoring on progression free survival: oncologist discretion advised.
        - Prasad & Bilal; *Eur J Cancer*

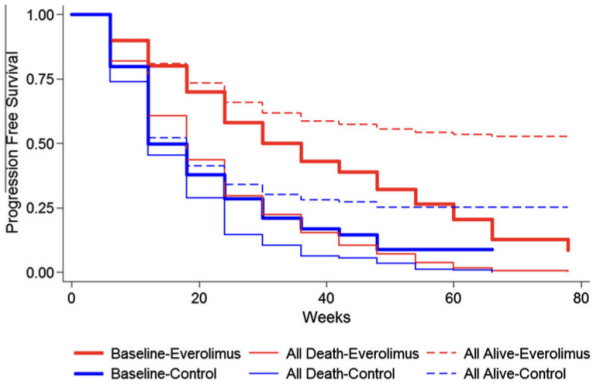


Fig. 1. The role of censoring in BOLERO-2. The graph shows a reconstruction of the progression free survival curves in the BOLERO-2 study, testing the addition of everolimus or placebo to exemestane in metastatic hormone receptor positive breast cancer. The upper dotted curves show a best case scenario—if every censored patient would not undergo the event of interest, and the lower solid line shows the worst case scenario—if every censored patient immediately experiences progression.

Prasad & Bilal

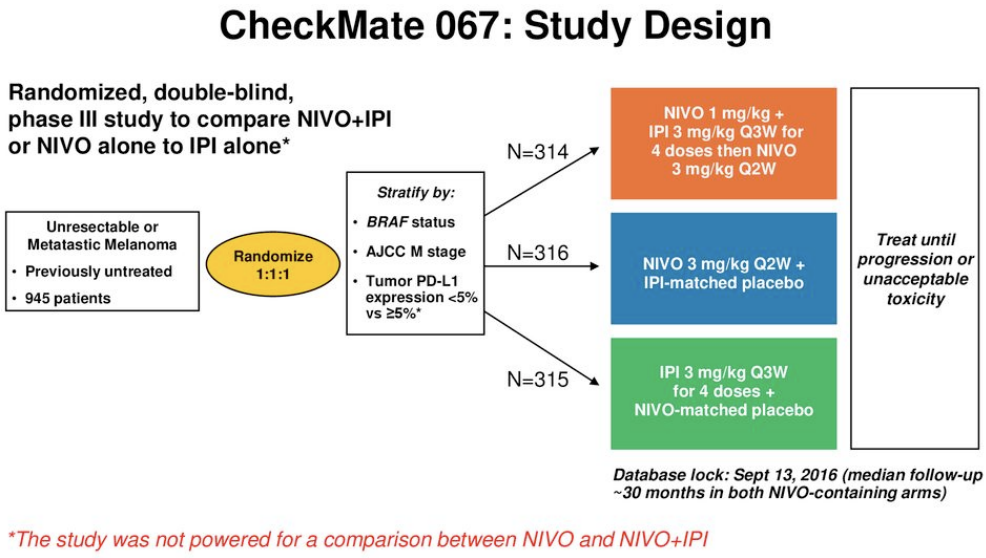
- When you no longer have follow up for some people → that is censoring
    - In the context of the BOLERO trial, the toxicity of everolimus led to many patients dropping out
        - This creates a problem
            - That is, the persons whose survival you are averaging are not all of the patients that should be measured.
                - I.e., Only people who are healthy enough to avoid being filtered out by the everolimus challenge are being measured
- The Kaplan Meier method assumes that the people who are dropping out have the same rate of the event as the people who stayed in

- Censored patients in Kaplan–Meier plots of cancer drugs: An empirical analysis of data sharing
    - Rosen et al., *EJC*

> "In randomized controlled trials of anti cancer drugs early on, there is an imbalance in censoring more people. But this turns out to be that more people drop out of control arms, likely

> because they have – what do they call it – *patient disappointment*" - VP

- **CHECKMATE-067 [10:51]**
  - **<u>Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma</u>**
    - Wolchok et al., *NEJM*

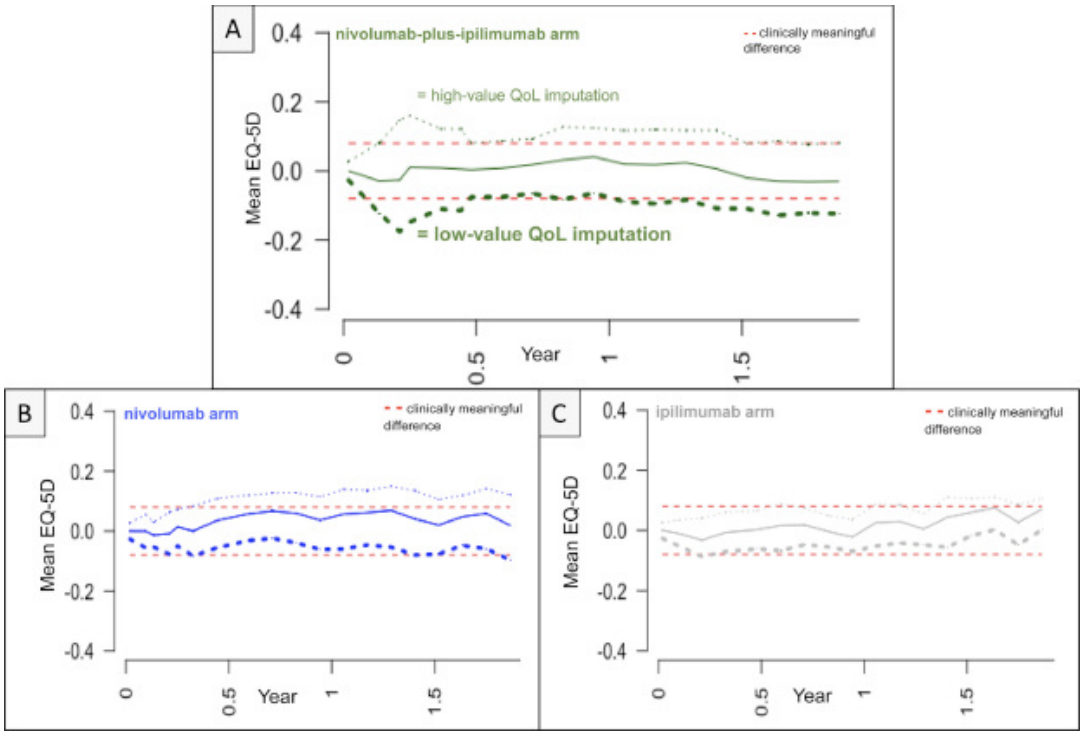


Source

  - **<u>Informative censoring due to missing data in quality of life was inadequately assessed in most oncology randomized controlled trials</u>**
    - Olivier et al., *JCE*

> *“In observing the imputed QoL curves, based on either low-value or high-value for missing data, we find a clinically meaningful decrease in QoL in the nivolumab-plus-ipilimumab when missing data were imputed*
> *with low values (*
> *Fig. 1). In other arms (nivolumab and ipilimumab), such difference was not seen. With high-value imputation, results showed a clinically meaningful improvement in nivolumab-plus-ipilimumab arm and the nivolumab arm.”* - Olivier et al.

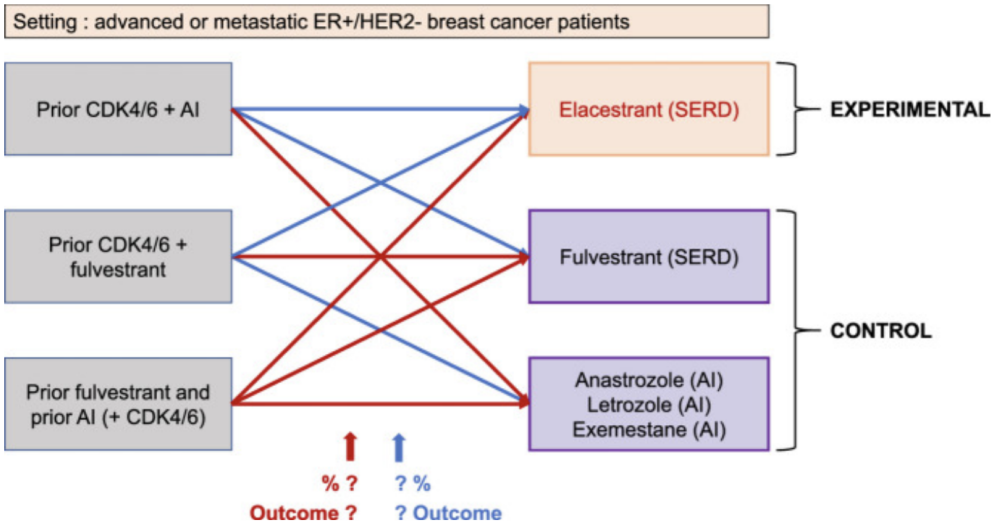
- Why are the individuals that were on the Nivo-ipi arm not filling out the compliance table as often as the ipilimumab arm?
    - If the individuals who do not fill out the form are disproportionately the ones suffering, then the people who **do** fill out the forms are not suffering
        - → Then the quality of life of the people who fill out the forms is not the same as the quality of life of everyone in the study
            - Unfortunately, in biomedicine, data is often not absent at random, introducing bias into the research.
- Imputation analysis



Olivier et al.

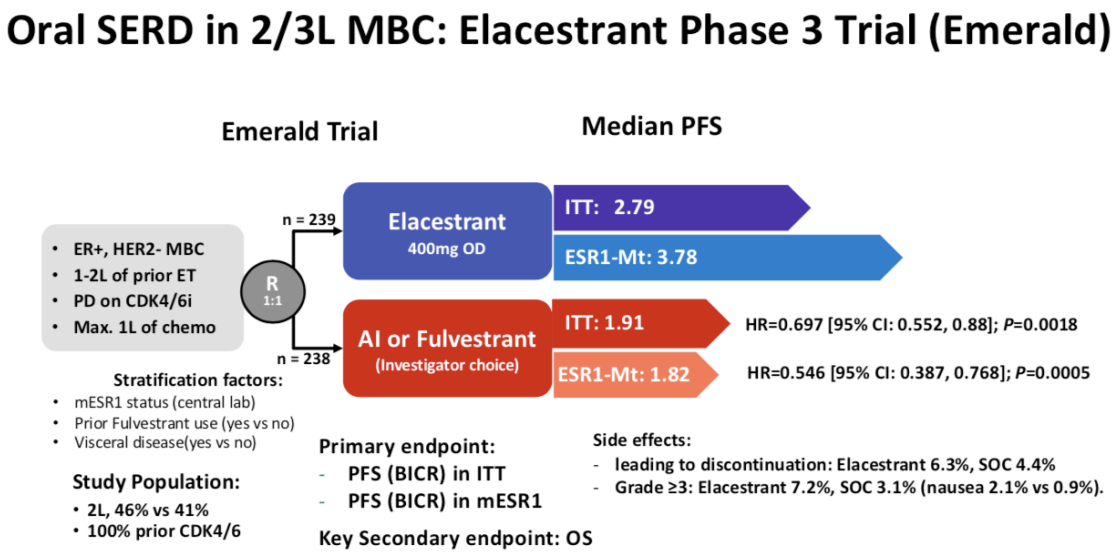
- Quality of life reports
  - *Missing data in quality of life are adequately reported in 7.4% of oncology trials*
    - i.e., 93% of the time you don't know what you don't know

- **Critics [30:00]**
  - Refer to the audio for VP's commentary.
- **Elacestrant [42:00]**
  - **<u>Elacestrant in metastatic breast cancer: Is the "standard of care" meeting standard requirements?</u>**
    - Olivier & Prasad; *Translational Oncology*



Olivier & Prasad

- **EMERALD Trial design**

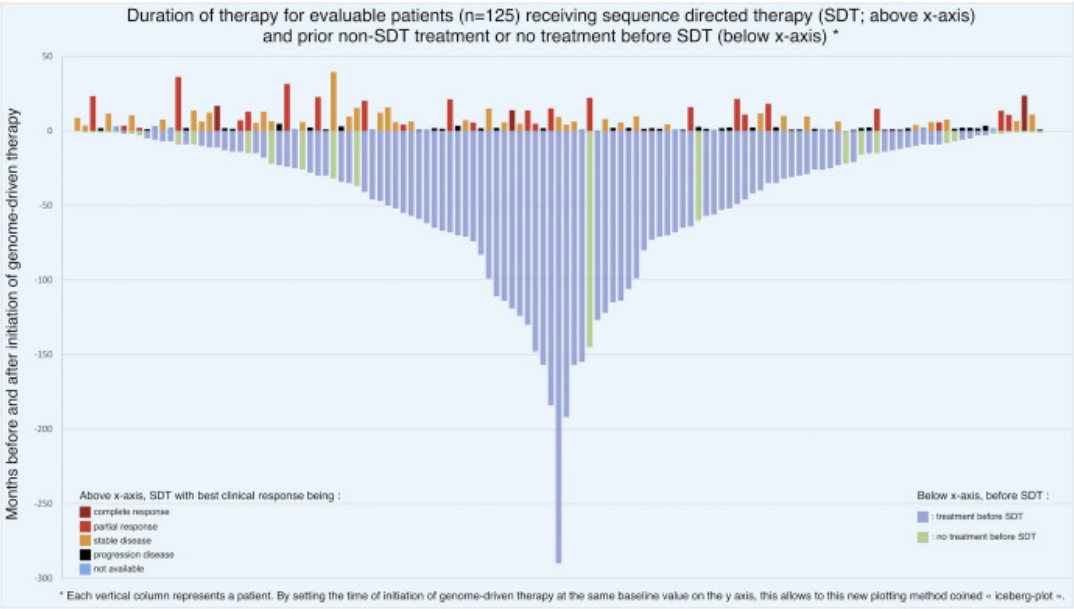


Source

- Pan-line trials

> "There may be settings where you can make some lines, but at least you have to provide a control arm that is [reflective]" - Dr. Olivier

- **Iceberg [50:00]**
  - **<u>The iceberg plot, improving the visualisation of therapy response in oncology in the era of sequence-directed therapy</u>**
    - Lythgoe et al., *EJC*



Lythgoe et al.

  - Iceberg plot
    - Ideally you would want a Mt. Fuji plot → where a majority of the plot is above the x axis indicating that the drug is effective

> “If 1/5 of the iceberg is underwater, and 4/5’s is above water, that tells you the precision drug is something remarkable, because it did what other drugs couldn't do.” - VP

    - However, the alternative (the iceberg plot) shows the contrary
  - Put in another way, there are two possibilities that happen when you treat somebody with a drug and they live a long time or take that drug for a long period of time
    1. The drug extended survival (Mt. Fuji)

2. The other possibility is that through your implicit and explicit inclusion criteria, you found a way to weed out people so that you're only left with people with indolent biology (Iceberg)

- **Closing thoughts [57:00]**
  - ~
- **Other people mentioned:**
  - Antonio Tito Fojo, MD
  - Dr. David Collingridge
  - Ian F. Tannock
- **Other literature mentioned:**
  - When is crossover desirable in cancer drug trials and when is it problematic?
    - Haslam & Prasad; *Annals of Oncology*
  - Patient Experience Captured by Quality-of-Life Measurement in Oncology Clinical Trials.
    - Haslam et al., *JAMA Network Open*
  - EMERALD: Phase III trial of elacestrant (RAD1901) vs endocrine therapy for previously treated ER+ advanced breast cancer
    - Bardia et al., *Future Oncology*
  - The FDA's latest move to expand eligibility for oncology trials — a double-edged sword?
    - Lythgoe & Prasad., *Nature Reviews Clinical Oncology*
  - Assessment of Accuracy of Waterfall Plot Representations of Response Rates in Cancer Treatment Published in Medical Journals
    - Kim & Prasad., *JAMA Network Open.*

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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Written By: Kerrington L. Powell, BS | MD Candidate 2025