4.45: Malignant Book Club w/ Dr. Olivier Part 1 of 9

Season	4
Type	Plenary Session
Status	Complete

We Discuss:

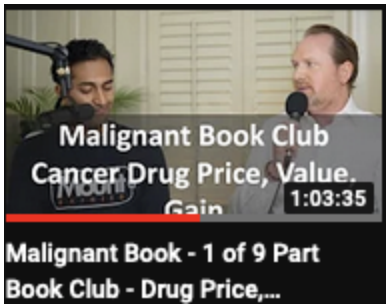
- Introduction [0:00]
- Biology [3:31]
- Breast cancer [6:30]
- History [14:36]
- The Basics of Cancer Drugs [23:23]
- Average benefit [30:00]
- Sorafenib [33:30]
- Cost [39:00]
- R&D [48:00]
- Outcomes [54:54]
- Closing thoughts [59:00]

Plenary Session 4.45 Show Notes

Overview

Malignant Book Club - Pt. 1

- **YouTube**
  - Watch this book club on YouTube



- **Malignant: How Bad Policy and Bad Evidence Harm People with Cancer**
  - Each week, people read about new and exciting cancer drugs. Some of these drugs are truly transformative, offering major improvements in how long patients live or how they feel—but what is often missing from the popular narrative is that, far too often, these new drugs have marginal or minimal benefits. Some are even harmful. In *Malignant*, hematologist-oncologist Dr. Vinayak K. Prasad writes about the many sobering examples of how patients are too often failed by cancer policy and by how oncology is practiced. Throughout this work, Prasad illuminates deceptive practices which promote novel cancer therapies long before credible data are available to support such treatment; and exaggerate the potential benefits of new therapies, many of which cost thousands and in some cases hundreds of thousands of dollars.
  - Prasad then critiques the financial conflicts of interest that pervade the oncology field, the pharmaceutical industry, and the US Food and Drug administration.
  - This is a book about how the actions of human beings—our policies, our standards of evidence, and our drug regulation—incentivize the pursuit of marginal or unproven therapies at lofty and unsustainable prices. Prasad takes us through how cancer trials are conducted, how drugs come to market, and how pricing decisions are made, asking how we can ensure that more cancer drugs deliver both greater benefit and a lower price. Ultimately, Prasad says:

        - More cancer clinical trials should measure outcomes that actually matter to people with cancer
        - Patients on those trials should look more like actual global citizens
        - We need drug regulators to raise, not perpetually lower, the bar for approval
        - We need unbiased patient advocates and experts.

- **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
- **Personal question [1:38]**

> ❓ This book is a continuation of many of VP's work, but is there anything in particular that pulled him in and encouraged VP to begin writing this book?

    - Ending Medical Reversal: Improving Outcomes, Saving Lives
        - Vinay Prasad & Adam Cifu
    - VP's road to writing his second book started with converting the short statements he made on Twitter into a unified argument
        - This allowed people to see the breadth of his thinking
- **Biology [3:31]**

> ❓ How can you claim you'll assist individuals with cancer better their outcomes if you don't speak about biology?

> “Empiricism is sort of the core philosophy that I believe in biomedicine...This isn't a biology book. It's about what works and what doesn't work” - VP

    - People forget that better clinical trials, clinical trials that provide us with better knowledge, better healthcare policy, better healthcare finance, more inexpensive therapies, and more accessible drugs may all save lives.
        - Everything in this book is completely within our control
            - And the majority of the issues are the result of man-made incentives.

- **Breast cancer [6:30]**
    - The introductory story is the story of autologous stem cell transplant for solid tumors, specifically breast cancer

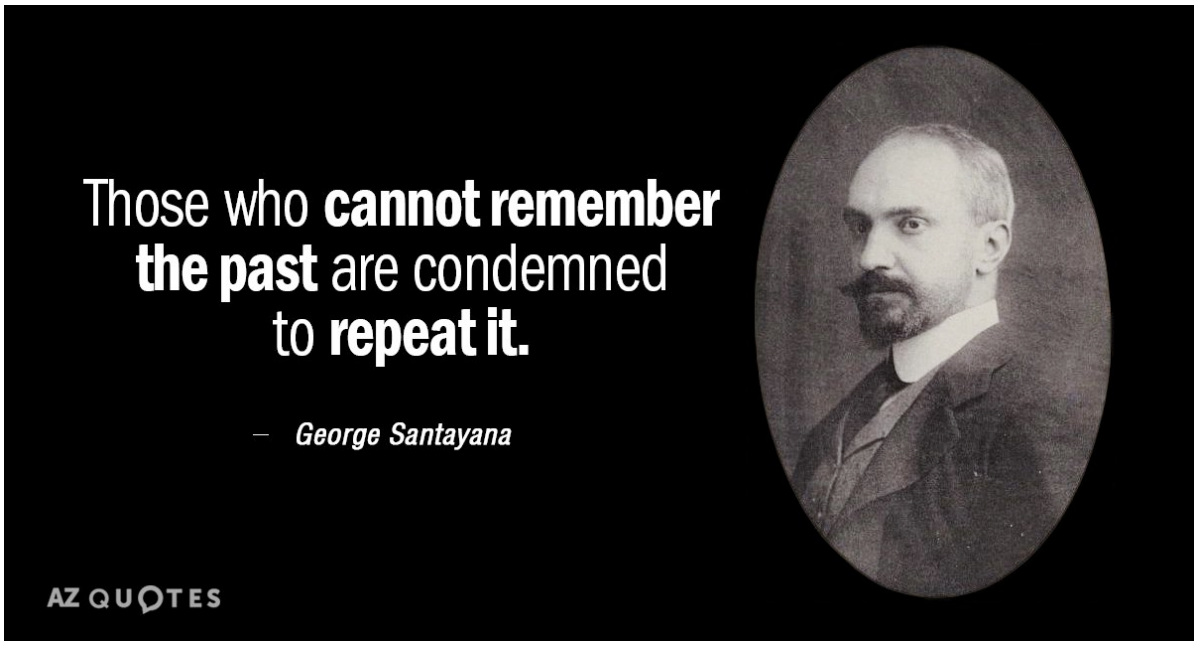
> ❓ Can you talk about this therapy?

        - This story touches on many of the subjects that the book as a whole discusses in detail
            - Take away points:
                1. *Many cancer therapies have astonishing and unsustainable costs*
                2. *Surrogate endpoints often fail to predict which therapies improve survival*
                3. *Randomized trials are needed in cancer medicine, and historically controlled studies often exaggerate benefit*
                4. *Enthusiasts of novel therapies often hype them long before credible data are generated*
                5. *Cost-effectiveness studies can be deeply problematic*

> *"All together, more than 30,000 women received autologous stem cell transplants in the United States between 1989 and 1995, and over 40,000 by the end of that decade. This cost billions of dollars. Three to 15 percent of women died during the treatment, while survivors faced massive toxicity. Patients were not helped." - Malignant*

- **History [14:36]**

> ❓ What do you think history is so important in your scientific approach?



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  - Major points:
    1. History is important to know
       a. We learn not just from trial and error, but we learn from what our ancestors knew
    2. It's also important to know the history that doesn't get told too often

> "What we tried to do in medical reversal is to provide a more balanced, truthful, honest, representative history" - VP

- **Audience [20:00]**
  - The core audiences that were targeted in this book were:
    1. The layman

> "The first goal is that if you're somebody reads the newspaper, they should be able to pick this up and read it" - VP

    2. Oncology aficionados
    3. Policy makers
    4. Trainees
- **The Basics of Cancer Drugs [23:23]**

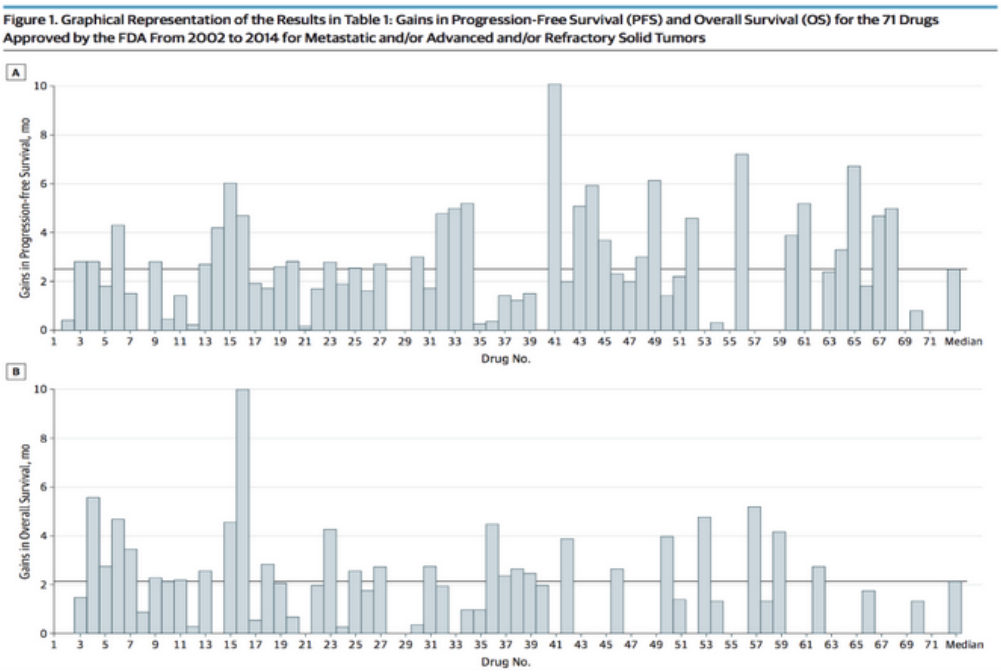
> Let's start with one example. Imatinib (Gleevec, Novartis) is used in the treatment of chronic myeloid leukemia (CML), a cancer of the white blood cell. Full disclosure: imatinib was developed by my boss, Dr. Brian Druker, at my place of work, Oregon Health and Science University. But, ask anyone: it is a wonderfully effective drug.

  - Nowadays, the life expectancy of a patient with CML is about the same as that of a patient without CML
    - Despite gleevec's enormous benefit and effect, this medicine initiated a precision oncology initiative that lasted over a decade and yielded several essential treatments (EGFR inhibitors), but was otherwise highly taxing in the oncology space

> "One of the themes of this book is that science – basic science funding – should be always a diversified portfolio" - VP

- **Average benefit [30:00]**
  - The average cancer drug

- Fojo T, Mailankody S, Lo A. Unintended Consequences of Expensive Cancer Therapeutics—The Pursuit of Marginal Indications and a Me-Too Mentality That Stifles Innovation and Creativity: The John Conley Lecture
  JAMA Otolaryngol Head Neck Surg



  - Salas-Vega S, Iliopoulos O, Mossialos E. Assessment of Overall Survival, Quality of Life, and Safety Benefits Associated With New Cancer Medicines
    . *JAMA Oncol*
    - This paper was addressed in Malignant:
      - *In this case, whether it is 2.1 or 3.4 months, the point remains the same*
        - *Most cancer drugs are marginal, and the oncology profession owes it to people with cancer to do better*

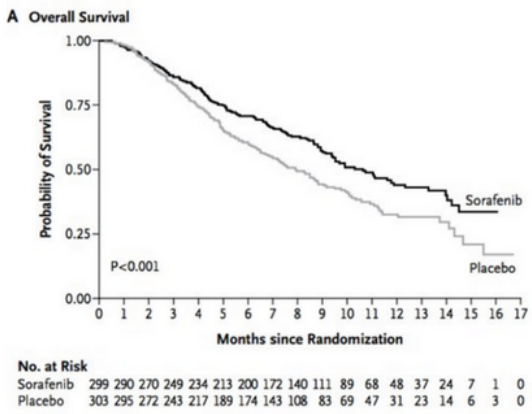
- **Sorafenib [33:30]**

> Not only did sorafenib's marginal benefit evaporate in the real world setting, but the study also showed how exemplary clinical trial patients can be. The ones in the clinical trial who took placebo (sugar pills) lived an additional 7.9 months, while real world patients who took sorafenib lived less than half this time (3 months). When patients in a trial taking sugar pills live twice as long as patients taking an active cancer drug, you have an unrepresentative trial population.

- Sorafenib in advanced or metastatic HCC

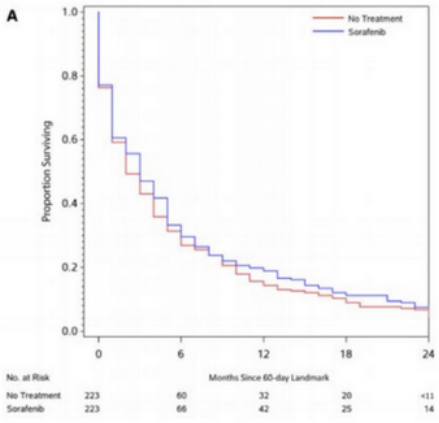
Sorafenib in advanced or metastatic HCC

Pivotal Trial for FDA Approval



Marginal Benefit under IDEAL circumstances

Real world outcomes



No Benefit under REAL WORLD circumstances

Vinay Prasad @VinayPrasad82 · May 22

Y we need PRAGMATIC trials 4 drug approval; MARGINAL CA drugs DON'T WORK in the REAL WORLD: theoncologist.alphamedpress.org/content/early/…

Stacie Dusetzina, Daniel Goldstein MD, Michael Joyner and 7 others

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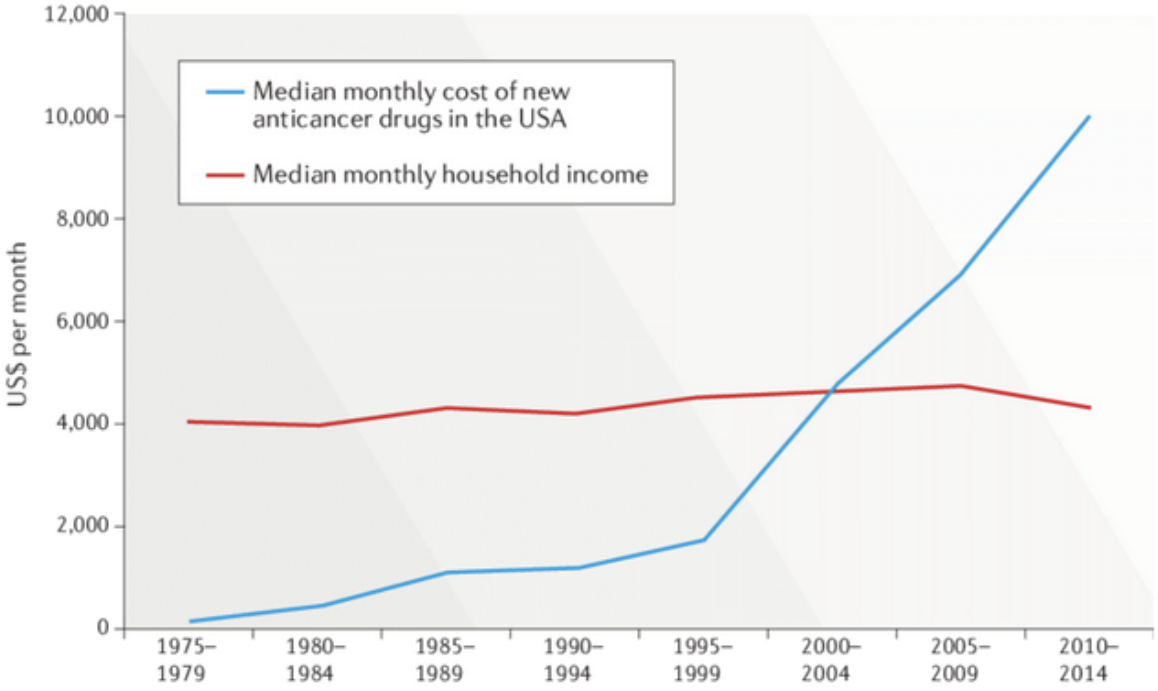
- **Lung cancer [37:00]**

> those organs are not affected by the treatments.[11] Researchers from Kaiser Permanente put this all together. They asked what percentage of Kaiser patients with lung cancer—who are broadly representative of all Americans with lung cancer—would be eligible for two randomized trials that shape treatment decisions. The answer was just 21%,[12] suggesting that trials do not enroll typical patients.

- The studies are just not representative of average cancer patients

- **Cost [39:00]**
  - The rise in costs – a representative depiction
    - These prices are rising much faster than inflation
      - It's also worth noting that this statistic is out of date and that the situation has almost certainly become worse



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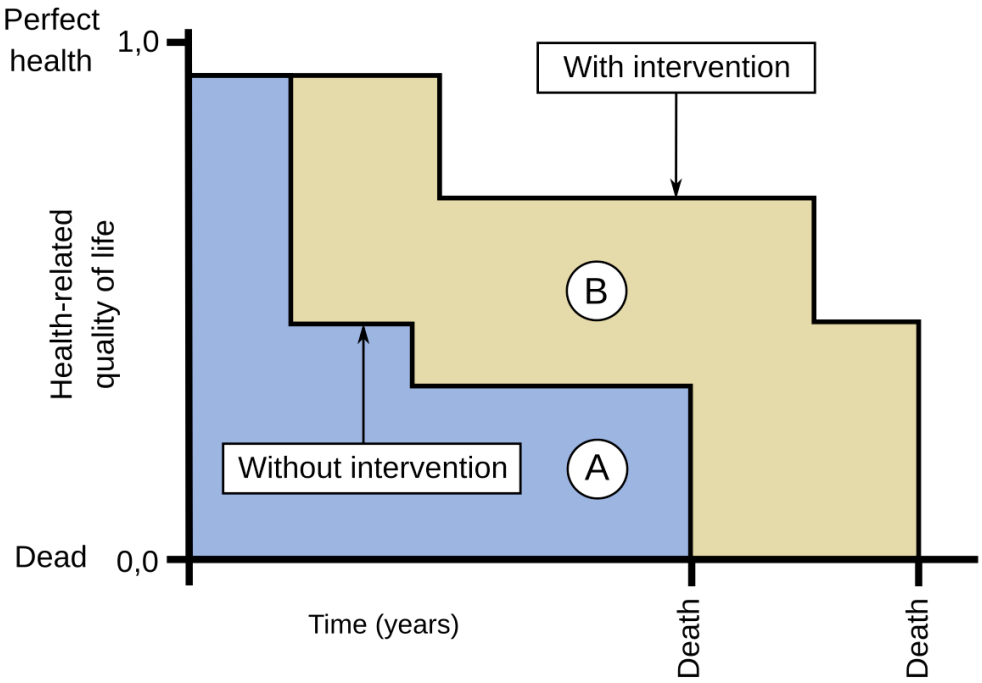
- Price is what you pay → value is what you get
  - The value of a drug is linked between the nice things it offers and the terrible things it causes
    - Value has something to do with the drug's effectiveness, which is offset by its high cost and toxicity (financial, physical, etc.)



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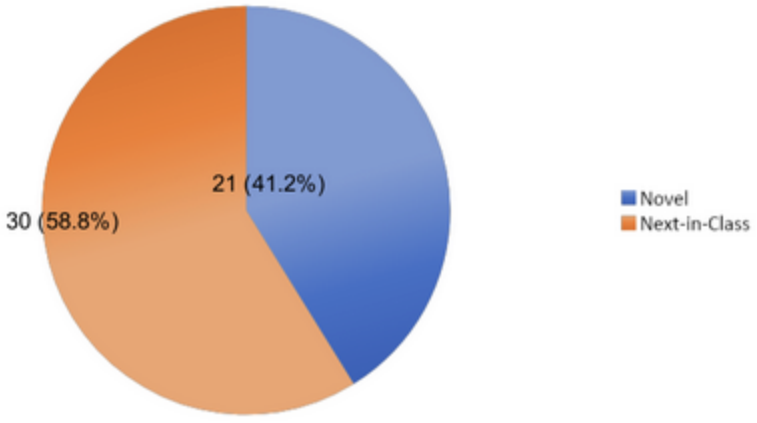
- How can you limit some benefit to a price?
  - Every society is rationing
    - There's no society that pays for every single thing for every single person in every single way possible
      - The objective should be to ration in the most effective manner possible, and to eliminate these financial products in order to enact true policies that will result in long-term, high-value change

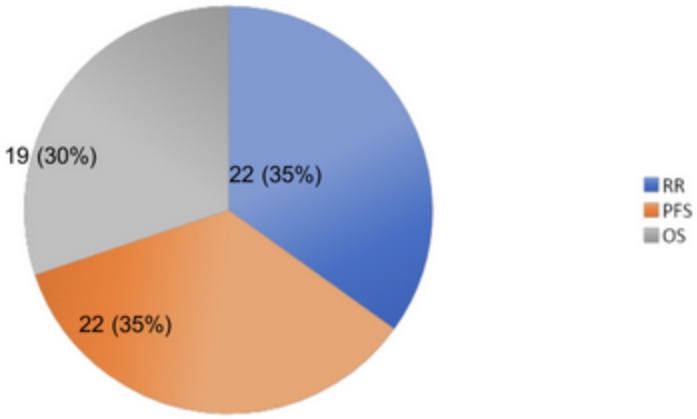
- **R&D [48:00]**
  - **Prasad V,** Mailankody S. Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval. *JAMA Intern Med*

Cancer drugs cost an enormous amount of money and are manufactured for just a fraction of that price. Surely, the research and development (R&D) costs explain this discrepancy. In other words, while making an additional iPhone may be cheap, the research that went into designing the first iPhone might be quite high. For years, prevailing wisdom had been that the research and development cost for one new drug was $2.6 billion.[30] This estimate came from an analysis by the Tufts Center for the Study of Drug Development.

There are some concerns with this estimate. First, the center that conducted the research received funding from the biopharmaceutical industry. Obviously, the industry has every incentive to exaggerate the R&D cost of its products (more to come on the role of financial conflict of interest in chapters 6 and 7). Second, the analysis was nontransparent. We don't know what companies and drugs were examined and, as such, no one can externally audit the data. Third, it appears about half of the $2.6 billion figure came, not from money that companies spent, but from theoretical lost earnings on capital. What does that mean? Every time you spend $10 to develop a drug, that is $10 you didn't put in your interest-bearing savings account. A year later, the cost of that $10 is $10 plus the lost interest, which may be a few percent and the cost of inflation. In the Tufts analysis, the group used a 10.5% interest rate for the lost interest. This is a large number and a return on investment that few of us actually achieve. In this analysis, 1.2 of 2.6 billion dollars is lost interest.

- **Outcomes [54:54]**
  - Mailankody S, Prasad V. Five Years of Cancer Drug Approvals: Innovation, Efficacy, and Costs. *JAMA Oncol*





        - We would anticipate that medications proved to extend life expectancy would be the most expensive, while the other two groups will be the least expensive
            - However, we discovered that medications that shrink tumor size are the most expensive, while the other two groups are the same price
                - The weakest evidence shouldn't have the highest drug price
- **Closing thoughts [59:00]**
    - VP entered oncology with the goal of understanding the fundamentals and has grown from there
        - He asked himself questions similar to the following:
            - What about my patient doesn't look like my *trial* patient? What about my patient who has a high copay that's crushing them? What about the price of the drug that's just so high?
                - He started looking for answers as a result of these issues, which are addressed in the following chapters of the book
- **Other people mentioned:**
    - Sham Mailankody, MBBS
    - George W. Sledge Jr., M.D.
    - Louis Fehrenbacher
- **Other studies or literature mentioned**

- Fehrenbacher, L., L. Ackerson, and C. Somkin. "Randomized clinical trial eligibility rates for chemotherapy (CT) and antiangiogenic therapy (AAT) in a population-based cohort of newly diagnosed non-small cell lung cancer (NSCLC) patients." *Journal of Clinical Oncology*
- The Emperor of All Maladies
- A Commotion in the Blood: Life, Death, and the Immune System

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

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