3.08: Racial Concordance in Birthing Mortality & HERO for Journal Club with Fellow Dr. Michael Burns

↗ Type	Plenary Session
Category	

We Discuss:

- Racial Concordance in Birthing Mortality [2:10]
- Social Science Research [20:00]
- Final Points [29:09]
- Conversation with Dr. Michael Burns [40:06]
- HERO [40:36]
- Results [1:06:17]

Plenary Session 3.08 Show Notes

Overview

Racial Concordance in Birthing Mortality [2:10]

- **Twitter Thread**
  - Here is the link
- **Black newborns more likely to die when looked after by White doctors**
  - News article from CNN

"Black newborn babies in the United States are more likely to survive childbirth if they are cared for by Black doctors, but three times more likely than White Babies to die when looked after by White doctors, a study has found...Our study provides the first evidence that the Black-White newborn mortality gap is smaller when Black MDs provide care for Black newborns than when White MDs do, lending support to research examining the importance of racial concordance in addressing health care inequities," co-author Rachel Hardeman said on Twitter." - Picheta

- **Background**
  - Dr. Prasad believes there is a huge imbalance and injustice in the people who are matriculating, graduating and becoming doctors
    - Particularly those who are holding key positions of power in the medical infrastructure
      - This exists across several dimensions:
        1. Racial
        2. Gender bias
        3. Gender identity
        4. Sexual orientation
        5. SES

> "I want to say that having a medical workforce that looks like America, that is a virtue in and of itself. that is a goal in and of itself, it would be wrong to have a workforce that doesn't look like America, that is preferentially loaded with people from high SES backgrounds, who are more likely to be from majority groups." - Dr. Prasad

  - That said, it is very important that beliefs and arguments have very strong evidence to support it

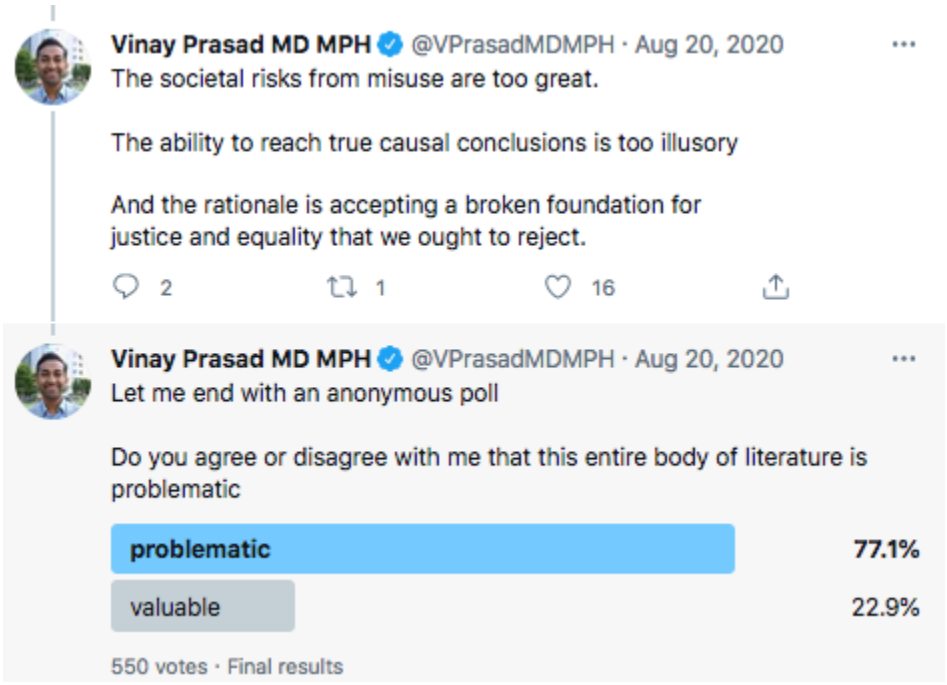
- **<u>Physician–patient racial concordance and disparities in birthing mortality for newborns</u>**
    - Published. by Greenwood et al.
- **Delivery**
    - When when a mother comes into the hospital to give birth to a baby, there are a couple different paths that that could happen:
        1. Scheduled delivery
            - This allows preference in selecting an outpatient doctor and pediatrician
        2. Variable delivery
            - Some birth is unpredictable and does not allow this choice
- **Infant mortality rates are low**
    - Black babies do have worse infant mortality outcomes, but that is not the claim of the paper
        - The claim of the paper is that the gap in mortality outcomes in part is attributable to the race of the doctor who's providing care
            - This is a claim that speaks to either one of two things:
                1. Black doctors are providing superior care for black babies
                2. White doctors are providing inferior care, simply by virtue of the fact that the baby is black
                    - This is a very strong claim to make
                        - The only way to show this is to show that white doctors are making different decisions → and these decisions have large effect size differences in outcomes

> "This paper doesn't do that–it's an administrative data set. Large datasets looking at this problem from 30,000 feet in the sky, and the problem with looking at it from so high is you so easily can

> mislead yourself and find signals that don't tell the story. You think you're finding they're telling a different story, and you are not teasing that out." - Dr. Prasad

    - Once the baby is born
        - The baby may be seen by a pediatrician who may put in a billing code
            - The physician who deliver the baby may visit but it also may be another doctor
                - Many hospitals now running on constantly changing teams
        - If a baby gets sick they are transferred to NICU
            - If this baby dies, potential doctors of record would be the NICU attending, who is responsible for the discharge or death summary
                - This adds complication to the dataset–because this paper never tells you how the pairing is made
- **The entire paper rests on the idea that physician-patient pairing is quasi-randomized**
    - However, it is likely the case that some subset of these interactions are not quasi-randomized
        - They are in fact chosen, that the patient and their family selected their provider
    - The pairing may also be based on socioeconomics, where wealthier black families may be more likely to seek out practices with Black physicians than poorer Black families
        - The racial-pairing may then account for the differences seen
    - Finally, the order of pairing it of utmost importance
        - If it was the last doctor who saw the baby, then you're baking in all the problems of where the baby is passing away versus the babies who are alive
- **Ascribing the outcome of the child to one of many doctors who plays a role in the care of that child**
    - This paper does not address who is the admitting doctor of record nor do they address the specialties of the doctor

        - The care of a baby being born in a hospital does not have one doctor, there is a massive team at play with many roles
            - Why is the race of the nurse, the race of the resident, the race of the intern, the race of the anesthesiologist all being accounted for?
- **We should not have prove that having this diverse workforce lowers mortality**
    - We need a diverse workforce for reasons of justice and equality
        - Whether or not Black doctors have the same outcome is not germane to the discussion
- **Social Science Research [20:00]**
    - Administrative datasets fail to identify the driving force or doctor that made the decisions
        - There's a gap between who is being labeled as making decisions and who's making decisions in administrative data
    - Physician characteritistics
        - There are different ratios of gender, racial makeup, ethnic groups in different specialties
            - Separating the doctor and the patient from the circumstances surrounding the place timing and details and communities of their employment is a tall task
    - Many Analysts, One Data Set: Making Transparent How Variations in Analytic Choices Affect Results
        - This paper shows that massive analytical flexibility allows for range of possible outcomes
    - Racial justice should be based on a workforce representative of the population not outcomes data



- **Final Points [29:09]**
  - Many of the people who are speaking in this space about this paper are in fact allies with the cause of justice and equality
    - However, many more allies are afraid to engage in the conversation due to the fear of being ridiculed over misinterpretation
      - This is dangerous because we might push them out and exile them and we won't have the coalition we need to actually get substantive change

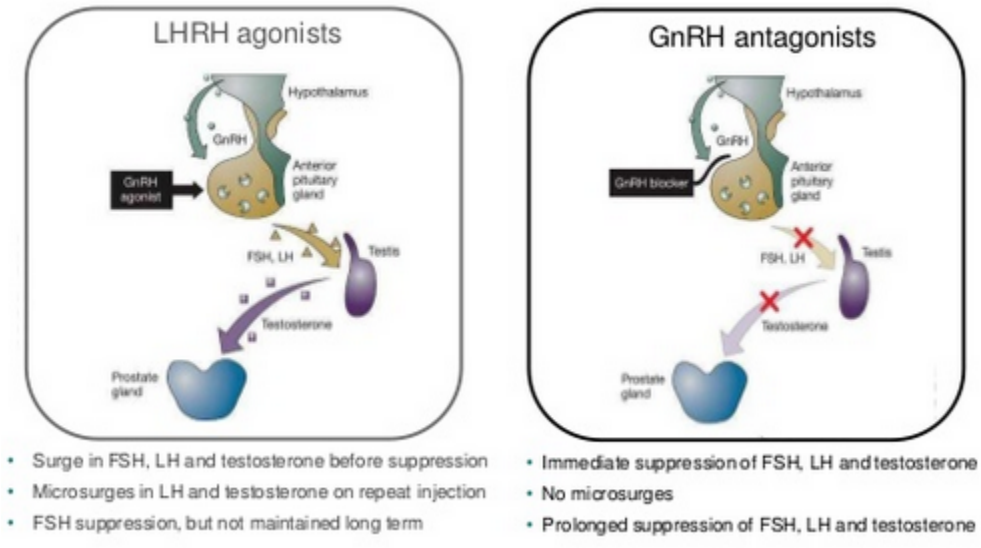
Conversation with Dr. Michael Burns [40:06]

- **Introduction**
  - Dr. Burns earned his M.D. from Vanderbilt University
    - He completed his internal medicine residency at Northwestern
      - He is currently a Hematology and Medical Oncology Fellow at Northwestern
- **HERO [40:36]**
  - Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer
    - Published in the NEJM

- **Background**
  - Prostate Cancer

> *"In 1941 the beneficial effect of androgen ablation on metastatic prostate cancer was realised when Huggins and Clarence Hodges treated patients by either castration or estrogen therapy."* - Source

  - Luteinizing hormone-releasing hormone (LHRH) agonists are a cornerstone of our treatment for prostate cancer
    - They are used as an injection, they have a slow onset, and eventually result in suppression of the testosterone levels
      - Prostate cancer is a disease that is driven by male hormones and androgens and reducing that slows the progression of disease
  - This study compares an LHRH agonist to a new oral GnRH antagonist that will rapidly reduced testosterone levels
    - Relugolix (GnRH antagonist) has the advantage of being in pill form
  - Mechanism of action



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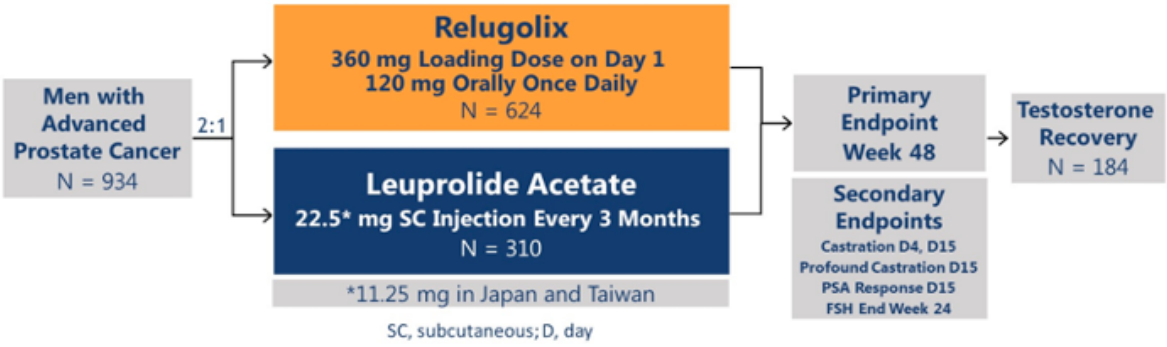
- Concerns
    - Both testosterone and the medications that you use to inhibit this pathway are cardiovascular events (strokes, myocardial infarctions, and death)
        - ~30% of patients with prostate cancer actually end up dying from a cardiac event, not just their disease

> "This is becoming a more important thing that we consider with all of these medications because part of their adverse event profile can put you at increased risk for cardiovascular." - Dr. Burns

- **Methodology**



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- Concerns
    - An immediate concern is that this trial does not include other agents that hit the androgen axis pathway
        - e.g., degarelix (once a month injection) was not included in the study
            - This should have been a control arm because this study tested a oral GnRH antagonist while degarelix is an injectable GnRH antagonist
- Primary Endpoints
    - Maintenance of maintain serum testosterone suppression to castrate levels (< 50 ng/dL)

        - This is a conventional way in which we define testosterone suppression–but what really matters to patients?
            - Prostate cancer patients typically care about:
                1. Living longer
                2. Skeletal metastases
                3. Pain/discomfort
    - Secondary endpoints
        - Refer to diagram
    - Statistical analysis plan
        - This study is not designed primarily to show the superiority of testosterone suppression. It's a non inferiority study
            - Non-inferiority (margin -10%) design

> "They power this study with tons of power for a huge margin in for an endpoint that makes no sense" - Dr. Prasad

        - This study is interesting because it's looking at day 29 to 48 weeks
            - This might be the tail of the flare up from Leuprolide Acetate, a GnRH agonist, of which the researchers are comparing relugolix to with huge margins
    - Eligibility criteria
        - Definitive management (i.e. surgery or radiation therapy) followed by biochemical relapse
        - Metastatic disease
        - Advanced localized disease
        - Candidates must have received at least 1 year of continuous androgen-deprivation therapy
        - Patients had to have a measurable serum testosterone (> 150 ng/dL) and PSA
    - Exclusion criteria

- Chemotherapy or surgical therapy expected within two months of initiating androgen deprivation therapy
    - i.e. We're excluding people with high volume disease per Stampede guidelines
- Major adverse cardiovascular event within the past six months

- Population

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Relugolix (N=622)	Leuprolide (N=308)	Total (N=930)
Median age (range) — yr	72 (48–91)	71 (47–97)	71 (47–97)
Age category — no. (%)			
≤75 yr	444 (71.4)	220 (71.4)	664 (71.4)
>75 yr	178 (28.6)	88 (28.6)	266 (28.6)
Geographic region — no. (%)			
North and South America	216 (34.7)	106 (34.4)	322 (34.6)
North America	182 (29.3)	87 (28.2)	269 (28.9)
Europe	247 (39.7)	122 (39.6)	369 (39.7)
Asia–Pacific region	159 (25.6)	80 (26.0)	239 (25.7)
Presence of metastatic disease — no. (%)	198 (31.8)	97 (31.5)	295 (31.7)
Clinical disease presentation — no. (%)			
Evidence of biochemical or clinical relapse after local primary intervention with curative intent†	309 (49.7)	158 (51.3)	467 (50.2)
Newly diagnosed androgen-sensitive metastatic disease	141 (22.7)	70 (22.7)	211 (22.7)
Advanced localized disease not suitable for primary surgical intervention with curative intent	172 (27.7)	80 (26.0)	252 (27.1)

Shore et al.

- Medications prohibited

Table 5-2 Prohibited Medications and Washout Periods

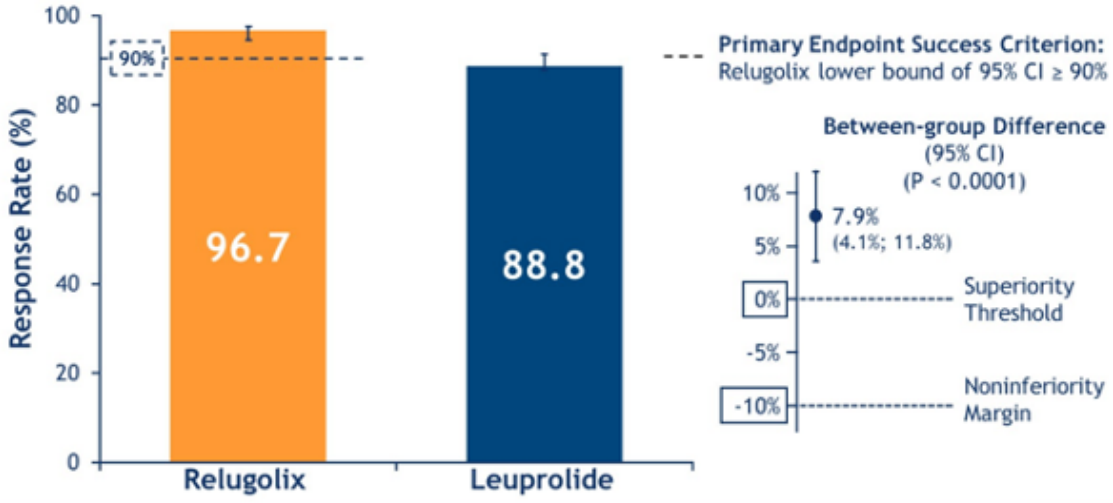
Drug Class	Examples		Minimum Washout Period
GnRH analogues	Leuprolide acetate injection[a] Goserelin acetate injection		12 months
GnRH antagonists	Degarelix		12 months
Antiandrogens[a]	Bicalutamide Flutamide	Nilutamide Enzalutamide[b]	12 months
CYP17 inhibitors	Abiraterone acetate + prednisone		12 months
Other androgen suppressing agents	Estrogens Ketoconazole	Megestrol acetate Progestogens	12 months
Class IA an III antiarrhythmics	Amiodarone Procainamide	Quinidine Sotalol	2 weeks (3 months for amiodarone)
Moderate and strong CYP3A and P-glycoprotein inducers	Bosentan Carbamazepine Efavirenz Etravirine Mitotane Modafinil Nafcillin	Phenobarbital Phenytoin Rifampin St John's Wort Primidone Rifabutin Rifapentine	2 weeks
Moderate/strong P-glycoprotein inhibitors	Amiodarone Azithromycin Captopril Carvedilol Clarithromycin Conivaptan Cyclosporin Diltiazem Dronedarone Eliglustat Erythromycin	Felodipine Itraconazole Ketoconazole Lapatinib Lopinavir/Ritonavir Quercetin Quinidine Ranolazine Ticagrelor Verapamil	2 weeks (3 months for amiodarone)

Shore et al.

- An important thing is to consider what medications are not allowed that are important for our cardiovascular outcomes
    - e.g., captopril, amiodarone, diltiazem, etc.
        - The researchers claim that participants can't take those because of P glycoprotein interactions, but the reality is the prohibitions will further deplete the population of people with age typical CV comorbidities
            - This may be one reason the people on this study may be of lower CV risk that what is seen in the clinic

- Flare implications
    - Before starting lupron, many providers consider if a patient (particulary those who have metastases near the spinal cord or visceral organs) should receive 1 or two months of bicalutamide
        - That said, some patients with high volume players may be ineligible because they are scheduled to receive chemo
    - Antiandrogens are permitted unless randomized to leuprolide acetate control arm of this study
        - The interesting thing about their design is even though they don't prohibit bicalutamide, they're basically getting a group of people in whom the doctors will probably not be giving by bicalutamide
            - This essentially is going to compare a drug without a flare to a drug with a flare and then the primary endpoint is going to capture the tail of the flare because it starts at 29 days

- **Results [1:06:17]**



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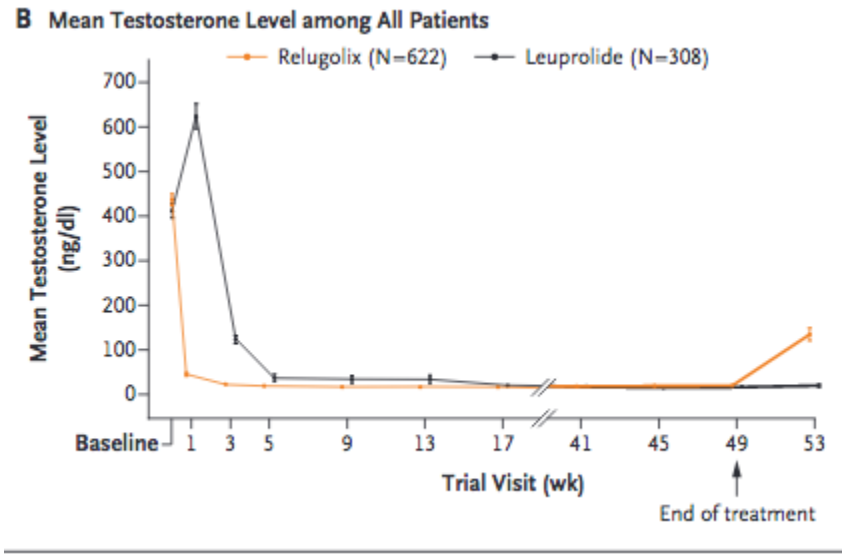


Shore et al.

- Figure 1B:
  - The mean testosterone level drops immediately in the relugolix arm
    - Leuprolide goes up immediately
      - Both arms becomes indistinguishable by Week 9
  - Because the primary endpoint captures day 29 (Week 4-5) there's going to be a difference between the two arms due to the T-Flare from people in the leuprolide arm
    - The same goal is achieved in the end–the MOA of each drug is driving the difference in the beginning
      - The "benefit" is in terms of testosterone level, an endpoint that is not a measure of what matters at a time point that penalizes Lupron

- **Concerns**
  - Whether or not the initial testosterone drop will have a long term difference in a clinical outcome is not clear
    - Did patients have clinical flare? What was their time until PSA progression? Is this going to help OS?
      - Since the intervention is a pill, there will not be an injection site reaction, but QoL is also not reported

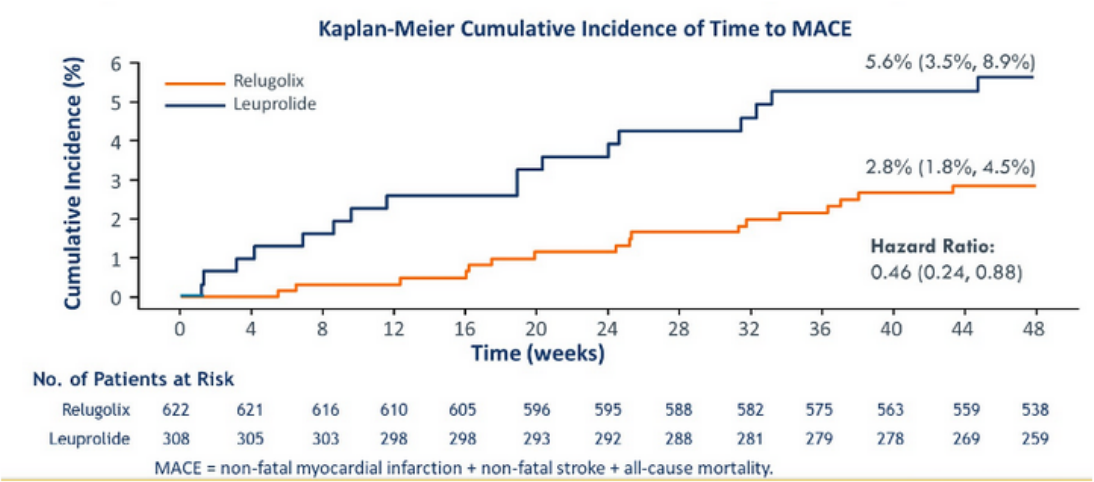
- Dr. Prasad does not believe this drug will make any difference on a clinical endpoint that affects a patient
    - This thought stems from degarelix never demonstrating those benefits over lupron
- Lupron may even be superior to relugolix in the real world because lupron is more convenient with larger time intervals between administration, even though it is a shot
    - Without carefully curated patients, how many people will take a pill everyday to ensure their T doesn't creep back up?
        - It is not an advantage to a take a shot every 3 months and turn it into a daily pill, it is an advantage to take a daily shot and turn it into a pill

> *"Diarrhea was reported in a higher percentage of patients in the relugolix group (12.2%) than in the leuprolide group (6.8%)." - Shore et al.*

- This should have been a randomized trial against degarelix
    - Degarelix would not cause an initial T flare
        - Dr. Prasad also points out that showing non-inferiority against degarelix would be very difficult because degarelix has a 100% suppression rate

> "The reason we don't give degarelix is not because it's a shot, and it's not because of the site reaction, which occurs rarely. It's because it's expensive, and that's what their pill is going to be too expensive. And the reason we give Lupron is it's cheap." - Dr. Prasad

            - Financial toxicity is real
- Cardiovascular events



- It is plausible that most of the separation is from early testosterone mediated CV events
    - There also isn't enough power to find a difference in this endpoint

> ""You either die a hero, or you live long enough to see yourself become the villain." - Dr. Prasad quoting Harvey Dent

- But the question that we have here is, when did these events occur? And is this due to flare or not?
    - it is plausible that most of the separation is from early testosterone mediated CV events
        - It is also possible that the lack of power from the secondary endpoint doesn't provide enough input to find a difference
            - If the researchers want to find out if these MACE events are a problem, then they need to run a trial based on survival
- Potential roles
    - The company should run a continuous versus intermittent trial in the biochemical relapse space to assess QoL
- Final point

- Dr. Burns makes the final point that combination therapy is becoming the new standard of care fro patients with metastatic disease
    - If you're going to say that using a pill for androgen deprivation is important, it also needs to be important for everything we're going to use it with

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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 B.S.