# “Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]

Brad Power
September 27, 2023

*“Many men in the community are not getting any genetic testing, especially in rural oncology or urology practices, and especially disproportionately-impacted patients such as Black men or men of lower socio-economic status. This creates a disparity in testing but also in treatment. One message that we try to convey in discussions with patients and patient advocate societies is to ask your doctor about getting tested for both germline and tumor testing, where that can only help you.’* – Andrew Armstrong

*“The standard of care until the last couple years has been sequential single agent therapy. When you do that, you see very incremental improvements in survival, but it doesn't work as well as hitting the cancer hard up front with combinations when men are hormone-sensitive. In men who start their journey with metastatic hormone-sensitive prostate cancer, it's no longer standard of care to give single agent therapy such as androgen deprivation therapy (ADT) alone.”* – Andrew Armstrong

*“It has really radically changed in the last few years. It's no longer standard of care to offer Lupron, for example, alone, or ADT alone, but rather, treatment intensification is the standard of care for men with newly diagnosed metastatic prostate cancer.”* - Andrew Armstrong

**Meeting Summary**

Advanced prostate cancer patients want to know what their next treatment option should be if their existing treatment regimen fails. But that’s a moving target as new treatments are approved, clinical trials of new treatments start, and experience is gained in old and new treatments. It is important to occasionally scan the range of newly approved treatments and research on treatments currently in clinical trials. For example, a number of new drug combinations and sequencing of systemic therapies in metastatic castrate-resistant prostate cancer can hit the cancer harder and earlier.

Dr. Andrew (Andy) Armstrong is uniquely qualified to talk about the latest personalized approaches to treating men with prostate cancer. (This is a follow-up to Dr. Armstrong's presentation of his research on predictive biomarkers and liquid biopsies. Please see the summary and details of meeting #64.) Dr. Armstrong seeks to develop and provide treatments that prolong and improve the quality of the lives of patients with aggressive prostate, kidney, bladder, and testicular cancer. His work involves the direct care of patients in the clinic and clinical research involving the development of new therapies in clinical trials. He devotes over half of his time to understanding how prostate cancer spreads and resists therapies, as well as methods of measuring this biology in patients, which may lead to improved therapies designed to block this process. His research includes prognostic and predictive biomarkers, circulating tumor cell biology, and how cancer spreads (metastasis). He oversees multiple clinical trials of new therapies for patients ranging from new hormonal and chemotherapies to new immunotherapies, and molecularly targeted agents.

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***What are the trends in (prostate) cancer treatment strategies?***

- **Increase in treatment intensity**: Treatment intensification is now standard of care for prostate cancer, involving therapy combinations of a systemic therapy, potent androgen receptor blockers, and perhaps radiating the primary site so that eventually we might be able to stop hormonal therapies. As Bob Gatenby has shared, hitting the cancer hard and early can be more effective due to the reduced heterogeneity of your cancer population at an early stage. In addition to combinations, potent androgen receptor inhibitors are moving into earlier and earlier settings, and earlier use will have implications for subsequent therapies.
- **Increase in treatment combinations:** For example, combining systemic therapy and radiation can improve prostate cancer outcomes. Another example: “PARP inhibitors,” which regulate DNA repair, are being used in combination with androgen receptor inhibitors.
- **Better cancer treatment outcomes for black men**: Black men have better outcomes with immunotherapy and with other drugs than white men. In a study with a double androgen receptor drug combination, black men had better outcomes with delayed progression, and better survival. The chance of making it to two years was 86% for black men and 67% for white men.
- **Whole health emphasis**: Men with prostate cancer are living a lot longer. Patients are enjoying remissions, but they're also suffering from the side effects of the treatments. Lifestyle factors contribute to aggressive disease, survival, and cardiovascular risk and are reversible. There's a movement towards emphasizing the whole patient, mental health, cardiovascular health, reducing obesity, eating healthy diets, vaccinations to prevent other infectious diseases, and long term attention on bone and heart.

***What are the new tests that have recently become available for prostate cancer?***

- **New predictive biomarkers**: predictive biomarkers to guide hormonal therapy in localized prostate cancer were developed using digital pathology and artificial intelligence.
- **More testing for targeted treatments**: Most men in the community are not getting any testing, especially in rural and urology practices. You should ask your doctor about getting both germline (normal tissue) and tumor testing, which can identify potential treatment options for you. For example, finding a BRCA mutation through a liquid biopsy indicates likely responsiveness to PARP inhibitors.

***What are the treatments that have recently become available for prostate cancer?***

- **New drug combinations**: For example, combining androgen receptor inhibitors (like abiraterone) and PARP inhibitors (such as olaparib) for patients with metastatic castrate-resistant prostate cancer, especially for patients with a BRCA mutation, can block DNA repair and kill the cancer cells with overwhelming DNA mutations. Cancer cells often

have faulty DNA repair, which can be encouraged by inhibiting the androgen receptor and the PARP enzyme.

***What are the treatments that are in the research phase for prostate cancer?***

- **Immunotherapy and other treatment combinations**: Therapies leveraging the immune system have demonstrated huge successes in non-small cell lung, small cell lung, kidney, and bladder cancers. Researchers are trying to find similar results from combining immunotherapies with other treatment options in other cancers and developing ways to draw T-cells into tumors to overcome cancer recognition by the immune system.
- **New treatments for neuroendocrine cancer**: Neuroendocrine prostate cancer, a rare and aggressive form of prostate cancer, needs more research and advocacy to improve treatment options. Research on immunotherapy and platinum-based chemotherapy for neuroendocrine prostate cancer is showing mixed results. Researchers are targeting neuroendocrine prostate cancer with unique cell surface receptors (like bombesin). It's the first time it's ever been done.

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**Meeting Notes**

## KEYWORDS

patients, parp inhibitor, study, prostate cancer, combinations, therapy, ar, cancer, survival, inhibitors, men, metastatic, mutations, trial, years, questions, metastases, delay, african ancestry, progression

## SPEAKERS

Andy Armstrong (87%), Brad Power (9%), Allen Morris (2%), John Sandiford (1%), David Plunkett (<1%).

## OUTLINE

1. Prostate cancer research and treatment. (0:03)
2. Prostate cancer treatment advancements and clinical trials. (1:12)
3. Prostate cancer treatment strategies and survivorship. (7:08)
4. Prostate cancer therapies and DNA repair. (11:58)
5. PARP inhibitors for prostate cancer treatment. (17:17)
6. Prostate cancer treatment options and research. (22:41)
7. Prostate cancer therapies and clinical trials. (26:58)
8. Prostate cancer treatment strategies and nomograms. (33:27)
9. Developing prostate cancer survival models. (38:52)
10. Prostate cancer treatment options and darolutamide efficacy. (43:57)
11. Personalized cancer treatment strategies. (48:28)

## SUMMARY

- Prostate cancer research and treatment. 0:03
    - Andy Armstrong shares more research and ideas on prostate cancer in a follow-up session.
- Prostate cancer treatment advancements and clinical trials. 1:12
    - Andy Armstrong discusses prostate cancer research at Duke University, highlighting the use of potent AR inhibitors and multidisciplinary care for advanced disease.
    - Armstrong presents findings on disparities in black men with aggressive prostate cancer, including unique outcomes from trials at Duke.
    - Andy Armstrong discusses the latest advancements in prostate cancer treatment, including new combination therapies and the importance of early detection.
    - He highlights the need for improved screening and early detection programs in emerging economies to reduce the prevalence of metastatic disease.
- Prostate cancer treatment strategies and survivorship. 7:08

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    - Treatment intensification is now standard of care for prostate cancer, often involving potent AR blockers or triple therapy.
    - Dr. Armstrong highlights the need for combined systemic therapy and radiation to improve prostate cancer outcomes.
- Prostate cancer therapies and DNA repair. 11:58
    - Andy Armstrong highlights the limited survival improvement of FDA-approved life-prolonging therapies for prostate cancer, with an average of 4-5 months of extra life.
    - He advocates for comprehensive germline and tumor testing to identify potential treatment options for patients, including PARP inhibitors and liquid biopsy.
    - He explains how combining AR and PARP inhibitors can lead to cancer cell death by overwhelming DNA repair errors.
- PARP inhibitors for prostate cancer treatment. 17:17
    - Andy Armstrong discusses a global study on metastatic castrate resistant prostate cancer patients, with a focus on the impact of PARP inhibitors on overall survival.
    - The FDA approved the combination of abiraterone plus olaparib for patients with a BRCA mutation, as it showed a significant improvement in overall survival for this group.
    - He discusses the benefits and risks of using PARP inhibitors in prostate cancer treatment, including delayed progression and anemia.
    - Talazoparib, a new PARP inhibitor combination, shows promise in delaying progression, but has more anemia than other options.
- Prostate cancer treatment options and research. 22:41
    - An expert oncologist is needed for careful dose reduction and monitoring to maximize benefit from radioligand therapy.
    - Andy Armstrong discusses neuroendocrine prostate cancer, a rare and aggressive form of the disease, and the need for more research and advocacy to improve treatment options.
    - Armstrong's institution is conducting research on immunotherapy and platinum-based chemotherapy for neuroendocrine prostate cancer, with mixed results.
- Prostate cancer therapies and clinical trials. 26:58
    - Andy Armstrong discusses prostate cancer research at the Alliance cooperative group, including new therapies and combinations of treatments.
    - Armstrong highlights ongoing and upcoming trials, including a small molecule inhibitor of CXCR2 and a new AR degrader in conjunction with Celgene and BMS.
    - Andy Armstrong discusses PARP inhibitors and their interactions with other drugs, highlighting the importance of dose reduction and drug combinations in cancer treatment.
    - Drug combinations need randomized clinical trials to provide evidence for off-label prescriptions.
- Prostate cancer treatment strategies and nomograms. 33:27

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    - Brad Power: Exploring more combinations to improve cancer treatment outcomes.
    - Andy Armstrong: Combining immunotherapies with other treatments shows huge successes in non-small cell lung cancer, small cell lung cancer, kidney, and bladder cancer.
    - He discusses developing ways to draw T cells into tumors to overcome cancer recognition by the immune system.
    - Allen Morris asks how patients determine their prognosis in a metastatic castrate resistant state, with many permutations of patient pathways.
- Developing prostate cancer survival models. 38:52
    - Andy Armstrong discusses developing a nomogram for metastatic hormone-sensitive prostate cancer patients.
    - He discusses the development of clinical genetic models for prostate cancer, which use a combination of clinical features and tumor genetics to predict survival rates.
    - He explains that these models are intended to be communication tools between doctors and patients, providing estimates of survival rates that can inform treatment decisions.
- Prostate cancer treatment options and darolutamide efficacy. 43:57
    - Andy Armstrong discusses targeting neuroendocrine prostate cancer with cell surface receptors like Bombesin, GPC3, somatostatin, and other targets.
    - He highlights darolutamide as an equally active AR inhibitor to Enzalutamide, with advantages of less brain penetration and fewer side effects.
    - Patient John Sandiford reports positive experience with darolutamide after 6.5 years of Lupron and docetaxel, with tolerability being a key factor in its selection.
- Personalized cancer treatment strategies. 48:28
    - Andy Armstrong presents data on disparities in cancer treatment outcomes for black men, showing that they have better outcomes with immunotherapy than white men.
    - A study at Duke found that intentionally including African American patients in a clinical trial (PANTHER) of apalutamide plus abiraterone in men with mCRPC which led to better outcomes for black men, with an 86% chance of making it to 5 years compared to 67% for white men.
    - Andy Armstrong discusses the importance of inclusivity in cancer trials, with Brad Power acknowledging our weakness in including African American men in our community.
    - Bob Gatenby is mentioned as a proponent of an adaptive intermittent approach to cancer treatment, which involves hitting the cancer hard and early, due to the heterogeneity of the population.

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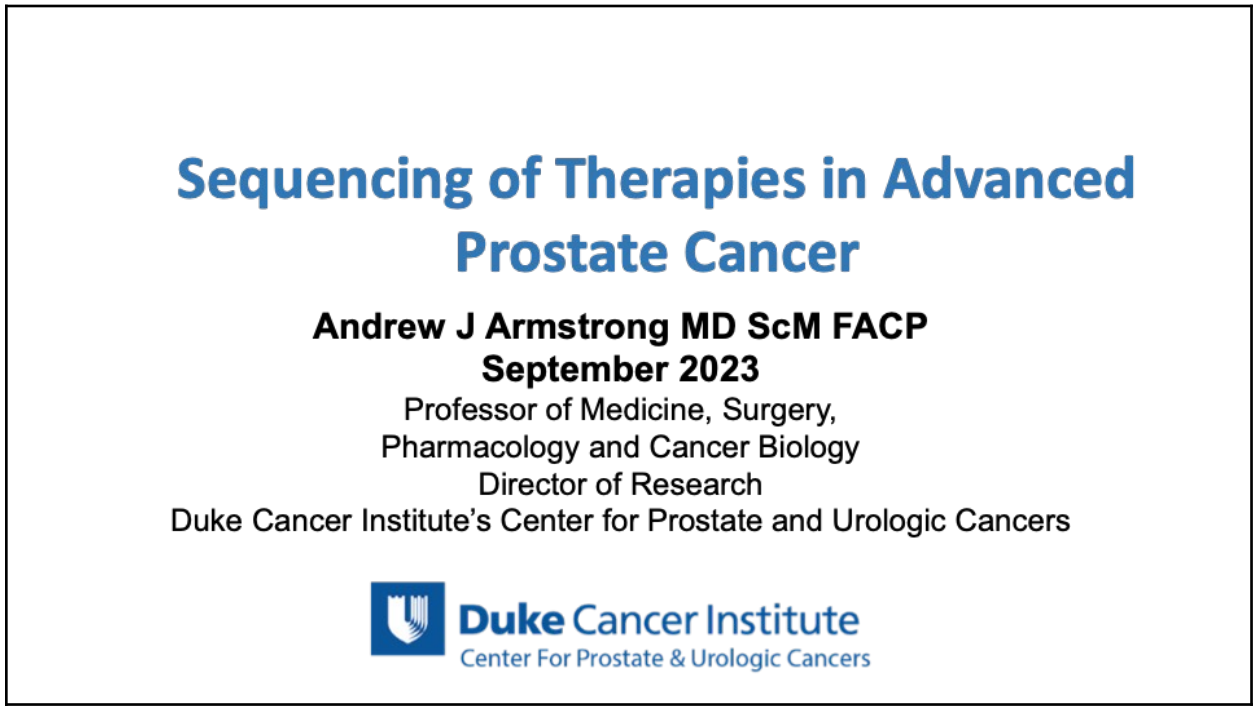
**Meeting Transcript**

Brad Power
This is the Cancer Patient Lab and Prostate Cancer Lab.

We're pleased to have Andy Armstrong with us today. This is round two. He previously had a session with us, where we went through some of his research, and he answered some questions, but he didn't get through everything. He has more research and ideas to share with us, and he's generously offered more time to answer more questions.




Andy Armstrong 1:25
Last time I talked much more about precision biomarkers, artificial intelligence, pathology, liquid biopsies, and how that can guide treatment. But as a medical oncologist, I'm much more invested in new treatments – phase one, phase two, phase three clinical trials. I thought I'd spend a little bit of time just talking about how we think about prostate cancer right now in 2023, and some of the trials that are available at Duke, and how we're thinking of sequencing various therapies as men go through their journey.

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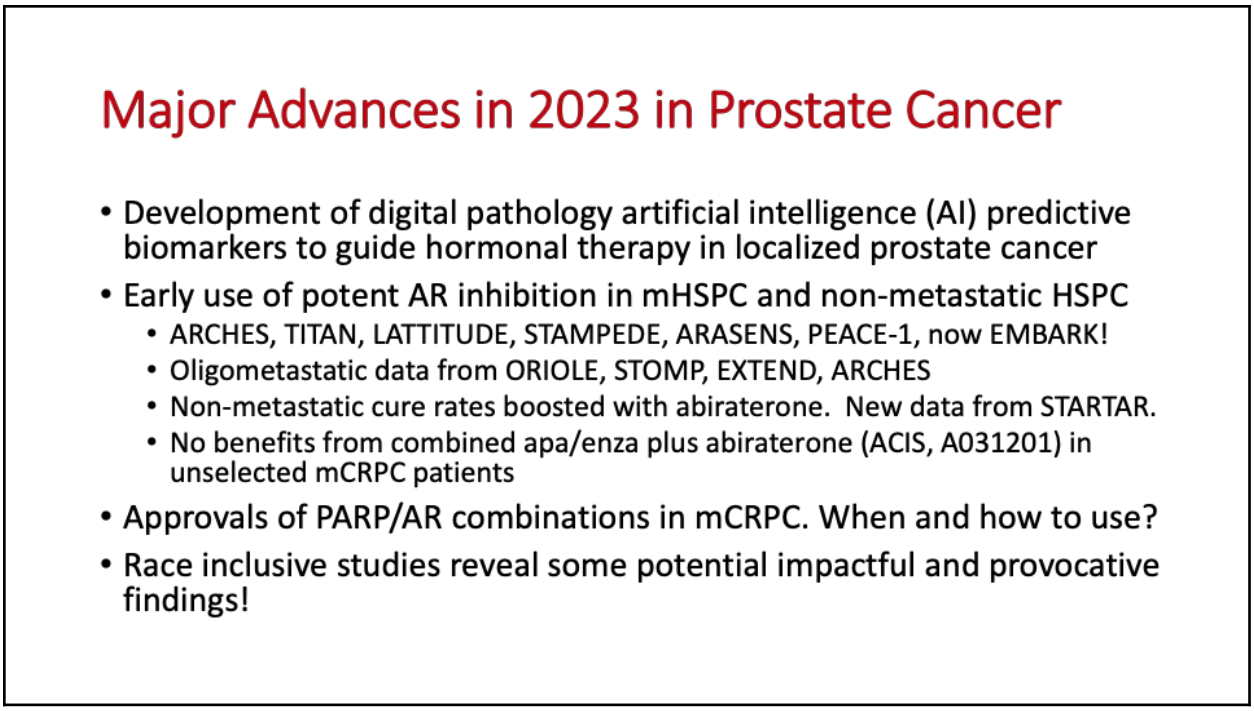


I'll start with the big highlights.

- For this coming year digital pathology is a big highlight. I talked about that last time.
- More impactful to patients who are trying to fight advanced or stage four prostate cancer is the earlier use of potent androgen receptor (AR) inhibitors. Some men are actually experiencing more cures because of that. They never experience metastatic disease.
- The integration of multidisciplinary care with radiation and metastasis-directed therapy from some of these other trials.
- We're seeing these AR inhibitors move earlier and earlier.
- We presented at ASCO, this past summer, on some disparities biology and some interesting findings in black men who are dealing with aggressive prostate cancer. Black men are quite disproportionately affected by this lethal disease. Here at Duke about a quarter of our patients are of African ancestry. We've developed some trials where we found some pretty amazing outcomes that are unique to black men or men of African ancestry.
- There's a lot of interesting research that we're doing. We can talk about PARP/AR combinations in 2023. We have three drug approvals from that. So you guys might be interested in hearing about that.

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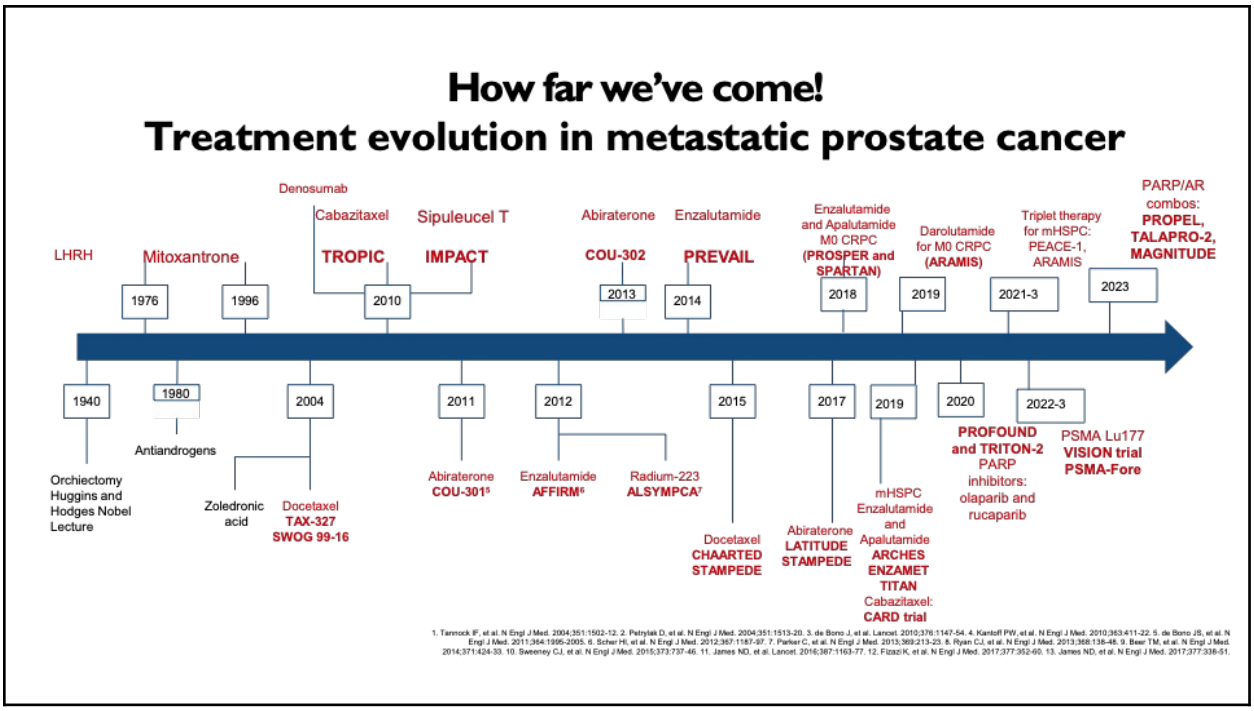


I put together this little timeline for you just to see the long history of prostate cancer since the first Nobel Prize-winning lecture in 1941 for the discovery of Orchiectomy (the surgical removal of the testes, historically a means of hormonal manipulation in the management of patients with locally advanced prostate cancer) all the way to 2023 and maybe next month with the PSMA-Fore study (comparing Pluvicto/177Lu-PSMA-617 treatment with a change in androgen receptor pathway inhibitor in taxane-naïve patients with metastatic castration-resistant prostate cancer). We've gone through hormonal therapies, androgen deprivation therapies, docetaxel, other taxanes, various negative studies not shown here, but these are largely the positive studies and those acronyms that translated into positive life-prolonging studies, both for castration-resistant and hormone-sensitive prostate cancer.

I'm happy to provide these slides so people can have this as a benchmark as we grow this going into the next year.

The biggest impact, as you can see on the far side, has been these newer combination studies. The movement of AR inhibitors into earlier and earlier settings as men are living longer now even with advanced disease.

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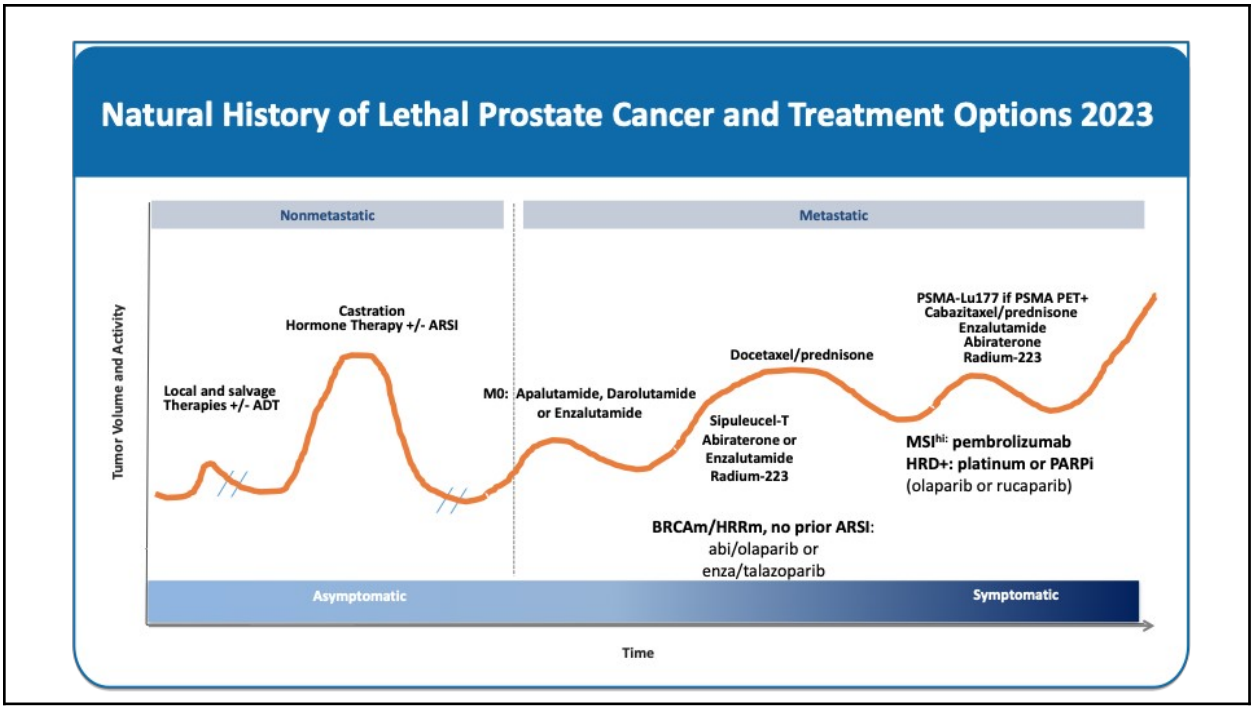


It's a journey for every patient and every patient is different. Their biology is different, and their outcomes and responses differ. Some of those differences are based on the patient, and some are based on the tumor. For some men who start their journey with localized disease, we have remissions and relapses. For those men who are not cured with the range of treatment options that are shown here, according to a standard algorithm of using these AR inhibitors (apalutamide, darolutamide, or enzalutamide) early, Sipuleucel-T (Provenge), radium, taxanes, and then precision medicines, such as Pluvicto, or certain PARP inhibitors, or pembrolizumab, in very certain circumstances.

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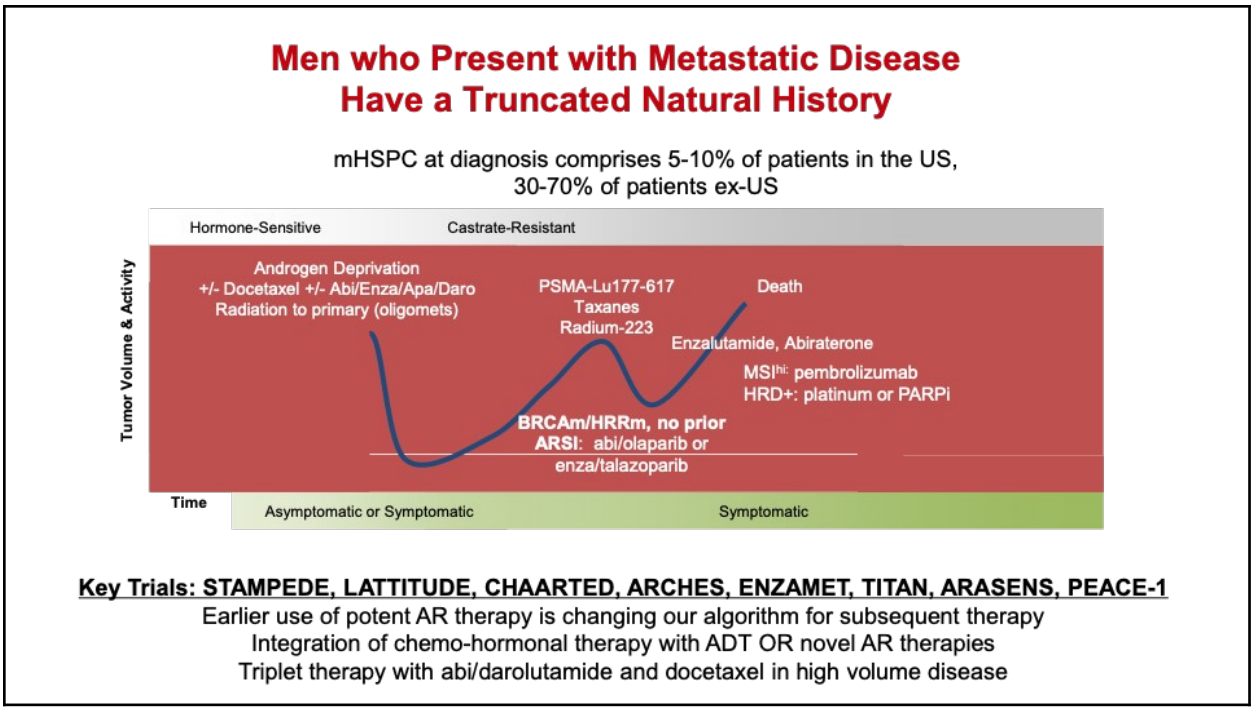


However, there's a group of patients that skip over this. They present with metastatic disease. In the US, that's about 10%. With COVID that's probably gone up a bit as men have often not gone to their doctors to get appropriate screening. We worry about an uptick in the presentation with metastatic disease.

I just got back from India about two weeks ago. There the prevalence of metastatic disease is 70%. It’s 70% of all men with prostate cancer in many emerging economies. Where there's no screening in place, most men with prostate cancer have metastatic disease. That's just an unfortunate reality of what happens when you don't screen and don’t have an Early Detection Program. The journey for these men who start with metastatic disease is often a bit shorter, but we still have the same available standards of care in terms of systemic therapies.

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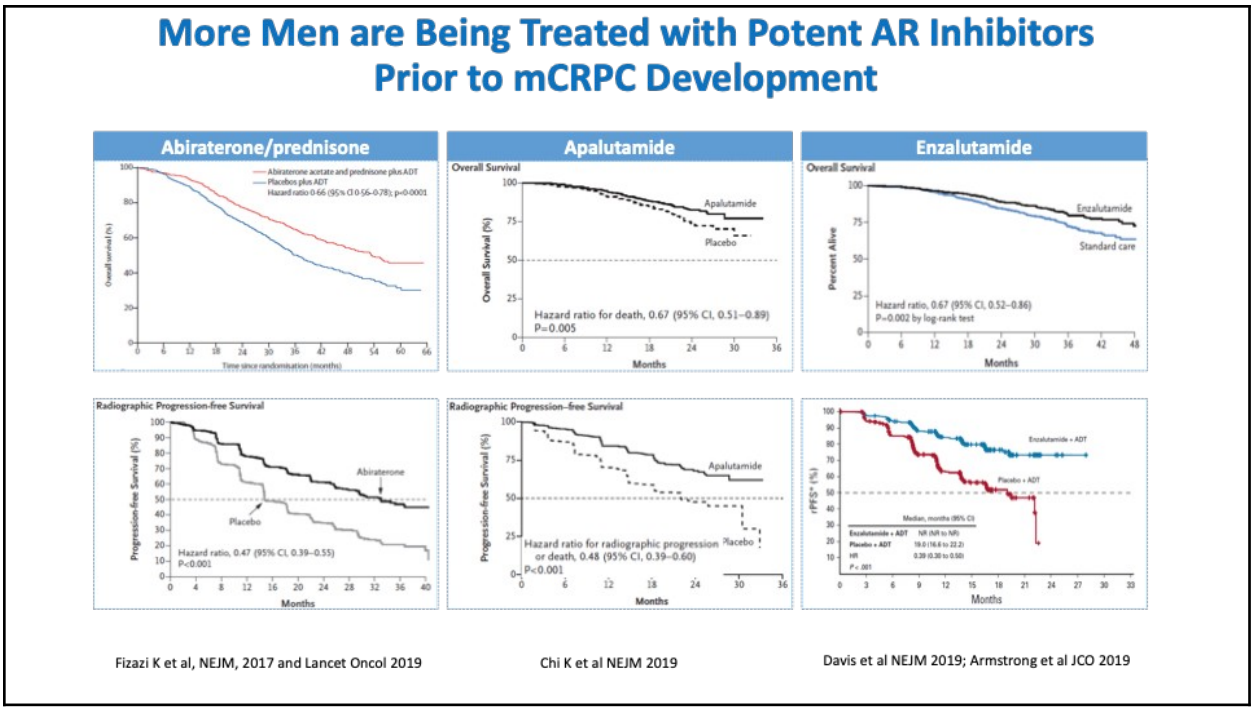


These are just some examples of some of the major phase three studies I was honored to lead. One of these studies, called the ARCHES study, led to the approval of enzalutamide or Xtandi in the hormone sensitive setting, but there are similar survival benefits with abiraterone and the androgen synthesis inhibitor. Apalutamide and enzalutamide are our two main AR blockers that have similarly extended life and delayed progression in this earlier setting.

## mHSPC Therapies with Proven Survival Benefit

| Therapy | Prior Docetaxel | Comparator | FFS/PFS benefit, HR, p-value | OS benefit, HR; p-value |
|---|---|---|---|---|
| **Radiation to the Primary** | No | No radiation, ADT alone +/- docetaxel | Yes: low volume HR 0.59 p<0.0001 | Yes: low volume HR 0.68 p=0.007 |
| **Enzalutamide**<br>ARCHES<br>ENZAMET | 18%<br>44-45% | Placebo/ADT<br>ADT/Bicalutamide | Yes HR 0.39 p<0.0001<br>Yes HR 0.39 p<0.0001 | Yes HR 0.66 p<0.0001 all volumes<br>Yes HR 0.67 p=0.002 all volumes |
| **Docetaxel/prednisone: STAMPEDE** | No | ADT | Yes HR 0.61 p<0.0001 | Yes HR 0.76 p=0.005 all volumes<br>Yes HR 0.63 p<0.001 high volume<br>HR 1.04 low volume |
| **Docetaxel: CHAARTED** | No | ADT | Yes HR 0.61 p<0.0001 | |
| **Docetaxel/Abiraterone** | Yes | Docetaxel/ADT | Yes HR 0.47-0.58 p=0.006, <0.0001 | Yes HR 0.72 p=0.019 high volume de novo |
| **Apalutamide** | 11% | Placebo/ADT | Yes HR 0.48 p<0.001 | Yes HR 0.67 p=0.0053 all volumes |
| **Abiraterone/Prednisone LATTITUDE** | No | Prednisone | Yes HR 0.47 p<0.0001 | Yes HR 0.66 p<0.001 high risk |
| **Abiraterone/Prednisone STAMPEDE** | No | Prednisone | Yes HR 0.31 p<0.0001 | Yes HR 0.61 p<0.001 all risk/volumes |
| **Abiraterone/prednisone (PEACE-1)** | 100% (concurrent) | **ADT/Docetaxel** | Yes HR 0.50 p<0.0001 | Yes HR 0.75 p=0.017; HV: HR 0.72 p=0.019 |
| **Darolutamide** | 100% (concurrent) | Placebo/ADT/ Docetaxel | Yes CRPC HR 0.35 p<0.0001 | Yes HR 0.675 p<0.0001 de novo 86% |

Parker et al Lancet 2018; Armstrong et al JCO 2019 and ESMO/JCO 2021; Davis et al NEJM 2019; James N et al Lancet 2015; Sweeney et al NEJM 2015; Chi KN et al NEJM 2019; Fizazi K et al NEJM 2017; James et al NEJM 2017; Smith MR et al NEJM 2022; Fizazi K et al Lancet 2022

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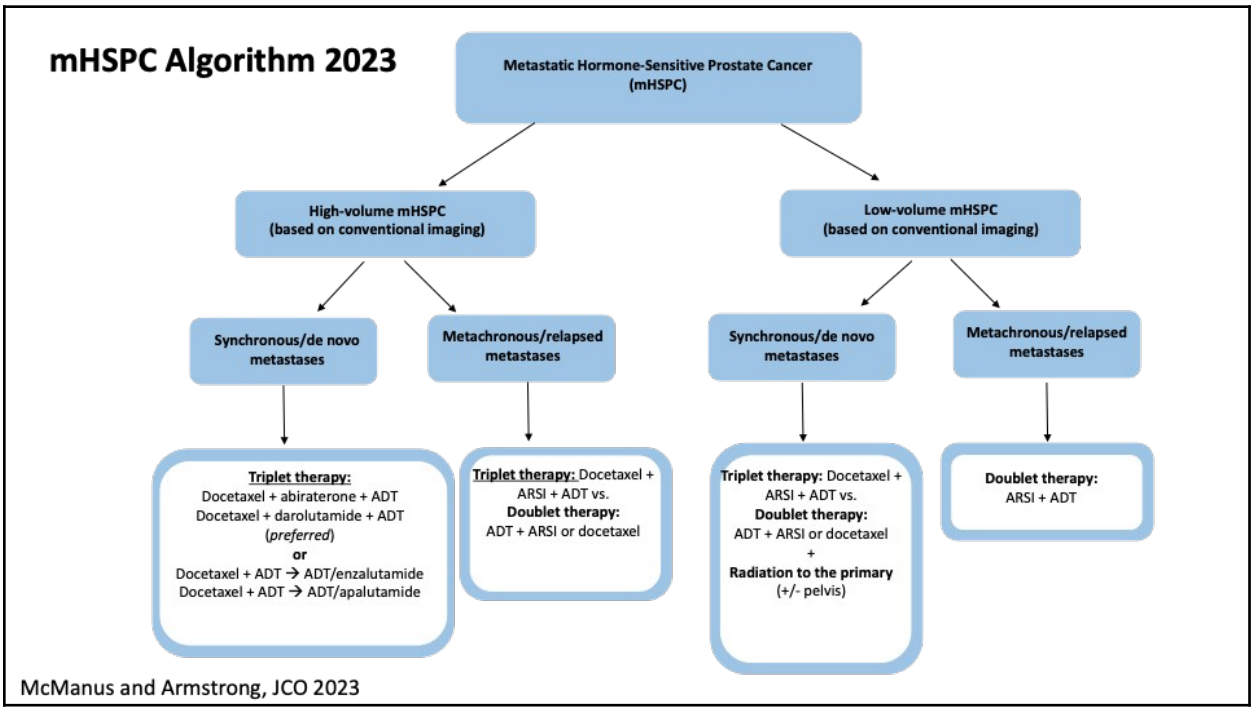
I put a little table together of all the life-prolonging studies in men with metastatic hormone-sensitive prostate cancer, which means they're not yet resistant to hormonal therapy, and that includes radiation, all these hormonal therapies, as well as now triplet therapy where some men are getting combination approaches.




We just published along with a fellow at Duke a nice algorithm that's referenced here. It can be useful as you are counseling patients who are just starting their journey. This journey is the guidelines of evidence supporting what to start with first. It has really radically changed in the last few years. It's no longer standard of care to offer Lupron to a man with newly diagnosed metastatic prostate cancer, for example, alone or ADT alone, but rather, treatment intensification is the standard of care. That treatment intensification often involves a potent AR blocker, sometimes triplet therapy for patients with a large amount of prostate cancer that's metastatic; treatment of the primary, the prostate itself, for men who have a lower amount of cancer outside the prostate. The algorithm really branches depending on how much of a burden the cancer is; whether it's started with metastatic disease or develops metastatic disease later, which we call “metachronous”.

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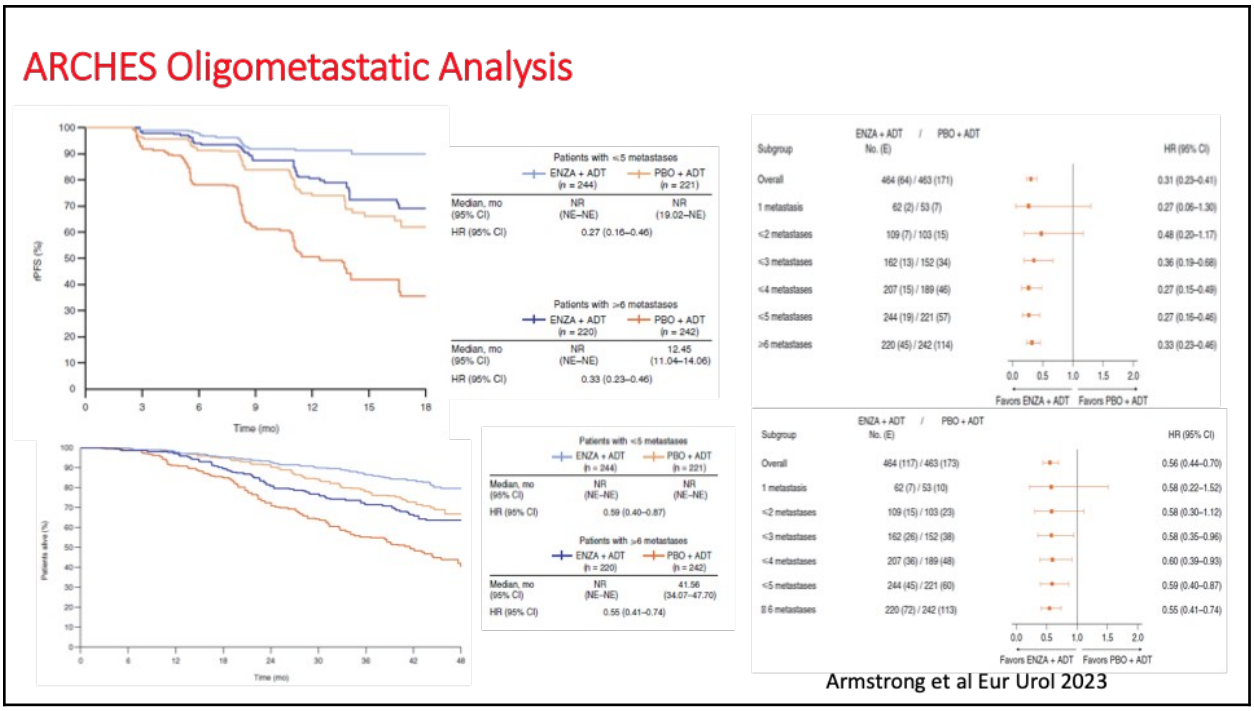
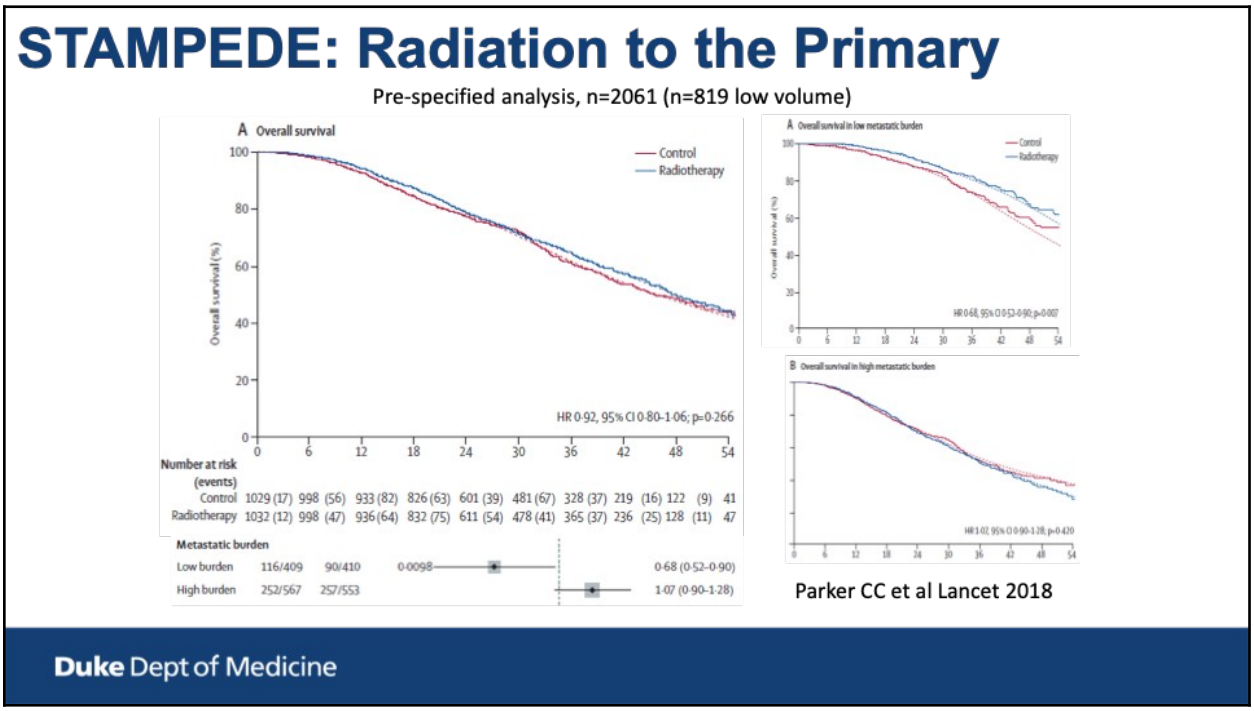



We also just published about a month ago that even with just a single metastasis, there's an improvement in survival with systemic therapy because metastatic prostate cancer is often a systemic disease, and treating it as such improves outcomes, rather than necessarily treating a single spot like it's truly a solitary spot.



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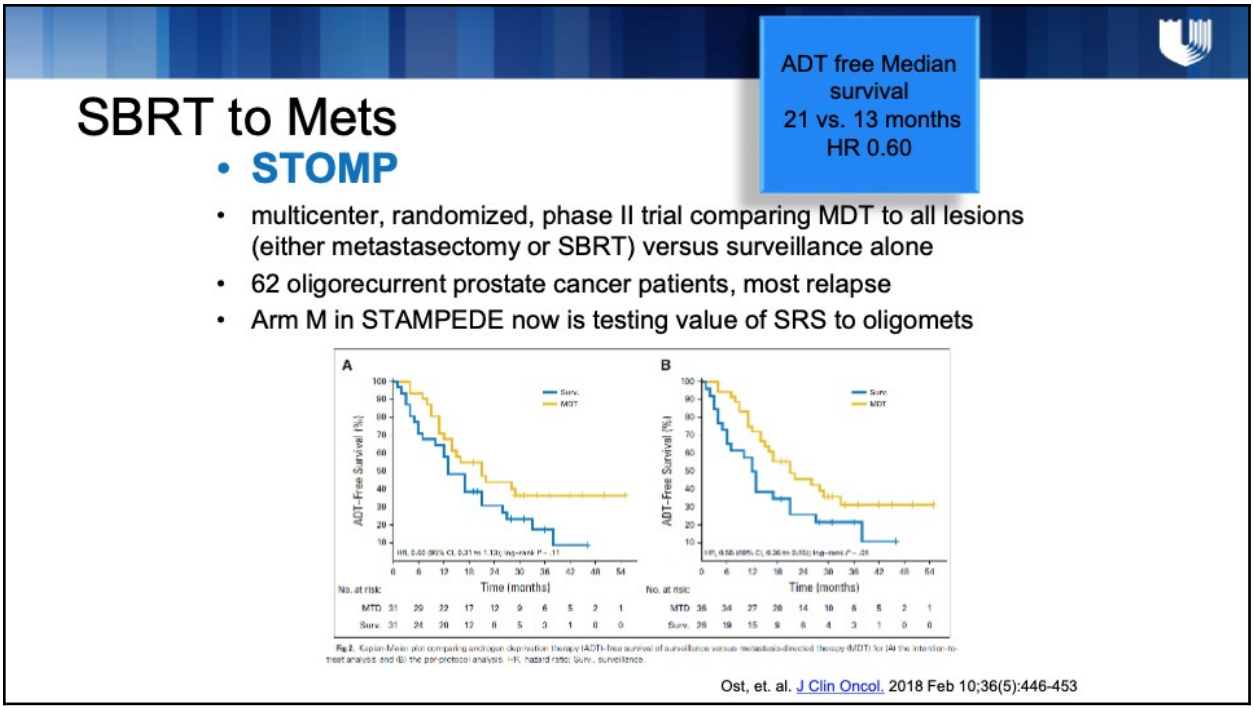
We know that radiation to the primary improves survival, and that sometimes radiating these metastatic spots can improve outcomes.




This is data from STOMP, which was published a few years ago now, where unfortunately, most patients do not benefit from metastasis-directed radiotherapy. But some do. About a third have a prolonged period of time where they get to avoid hormonal therapy. So these men are very happy, and these men relapsed, suggesting that in most patients it is a systemic disease where they should be treated as such, but in some men, they can have a successful delay in systemic therapy.

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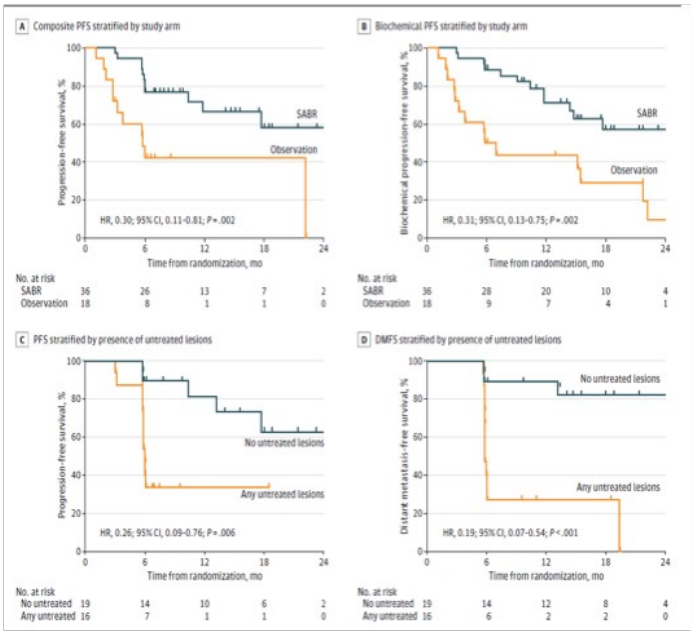
## Oriole Study

- 80 men with mHSPC randomized to SABR vs observation, primary endpoint is % with disease progression at 6 mo (PSA or imaging, symptoms or start of ADT)
- SABR guided by standard imaging, not PSMA PET, no ADT given
- Primary endpoint met by 19% of SABR group vs. 61% observation (p=0.005)
- Many failures at 2 years despite SABR
- Better outcomes noted if PSMA PET+ areas were treated vs untreated




Phillips R et al JAMA Oncol 2020

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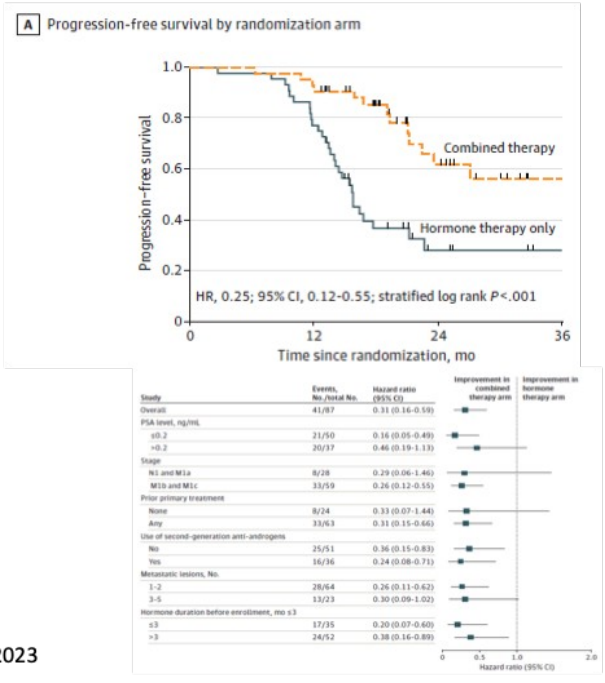
This was also seen in the Oriole study, named after the Baltimore oriole from Hopkins, where radiation, or SABR, stereotactic body radiation, was able to delay hormones in some men, but still most men relapsed over this short period of time. But if you treated all the lesions on PSMA PET, you got better outcomes, but still, almost half the patients are relapsing at about two years.

## EXTEND Study

- Phase 2 trial of men with mHSPC, randomized 1:1 to MDT or ADT alone, with a planned break after 6 mo of therapy (intermittent ADT) n=87 2-18-2020
- Up to 5 sites (typically 1-2) including prostate identified by CT, BS, or fluciclovine PET (25%)
- All sites targeted
- No potent AR inhibition given in about 60% of patients
- Primary endpoint PFS improvement includes imaging, PSA, clinical progression or death
- No survival data available, most data is based on PSA endpoints
- No QOL differences noted




Tang C et al JAMA Oncol 2023

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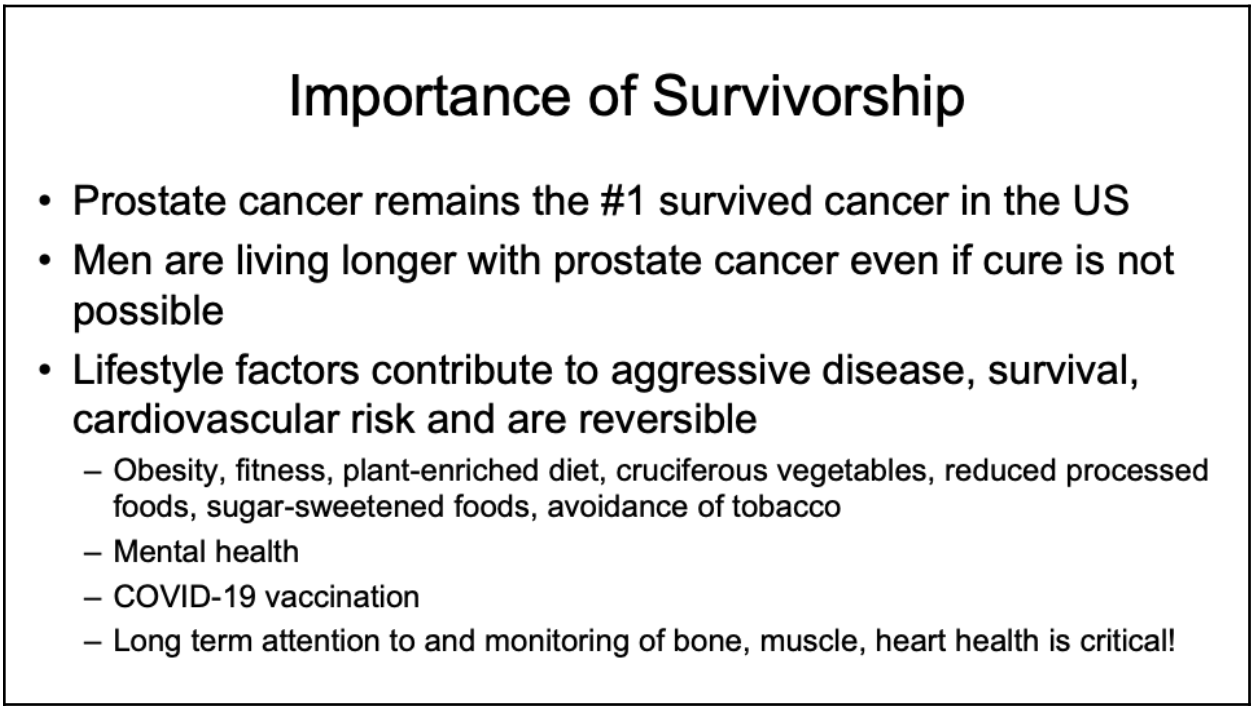
What about in combination? Using hormones and radiation to these spots together does suggest a better approach than just Lupron alone. But as I think I showed you in the ARCHES study, you'd rather be on the curve way up at the top, than on this curve at the bottom, and this is the data with enzalutamide and Lupron. If you look at Lupron alone in the EXTEND study, even with radiation, you're way down here. The field is in general moving towards a combined approach of best systemic therapy, whether that's Lupron or drugs like it, potent AR blockade, and perhaps radiating the primary and metastatic sites so that eventually we might be able to stop these hormonal therapies, and allow patients to enjoy remission without all these hormonal therapies.




I highlight survivorship because these men are living a lot longer. Patients like you are enjoying remissions, but they're suffering from the side effects of these treatments. So there's a lot of movement towards emphasizing the whole patient, mental health, cardiovascular health, reducing obesity, eating healthy diets, vaccinations to prevent other infectious diseases, and long term attention on bone and heart.

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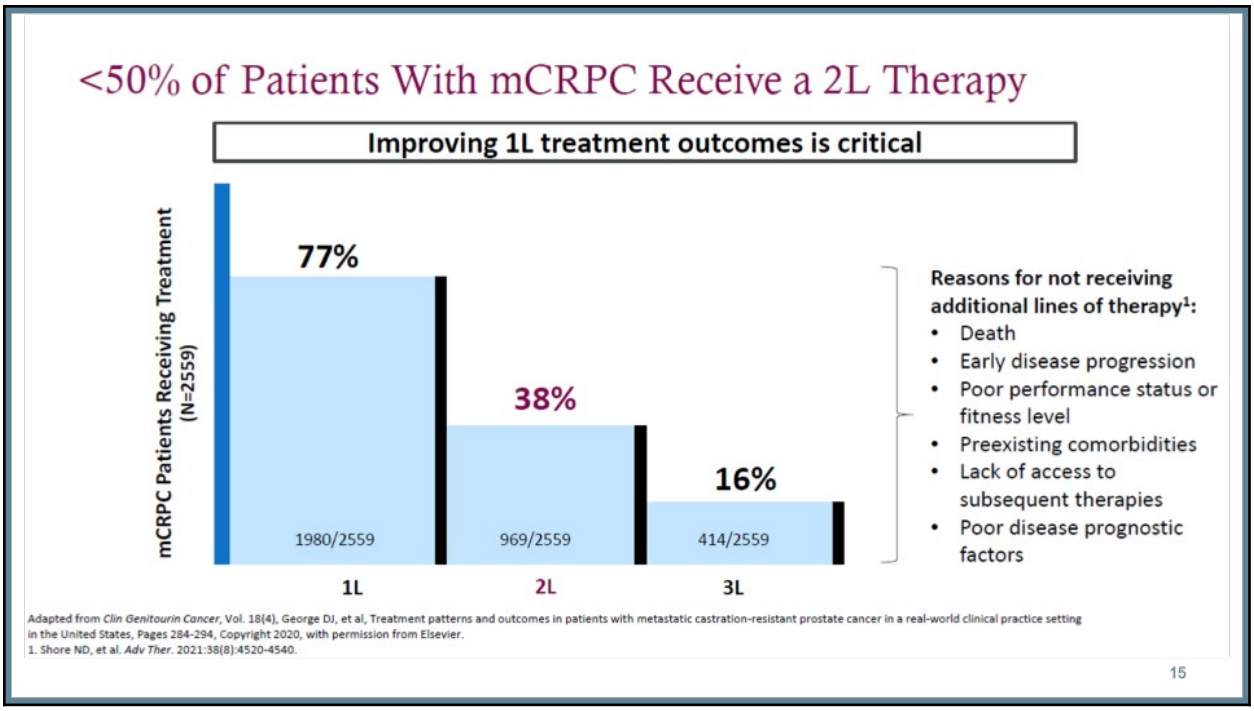



Andy Armstrong 11:13
When we talk about what you do next after your disease has become resistant to an AR inhibitor, the unfortunate reality is that most men in the US are not getting many therapies. They're definitely getting first line therapy, but there's a steep drop off where less than half of patients even make it and get second line, and another half drop off before third line. The reason is because a progression event is often very morbid. It can cause a lot of problems for the patient, who may already be dealing with a lot of other health problems. It's really important to hit the cancer upfront with your best weapon and see if that can prolong survival, and delay progression the longest.

**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**

## Positive Life-Prolonging Phase 3 Trials in Men with mCRPC

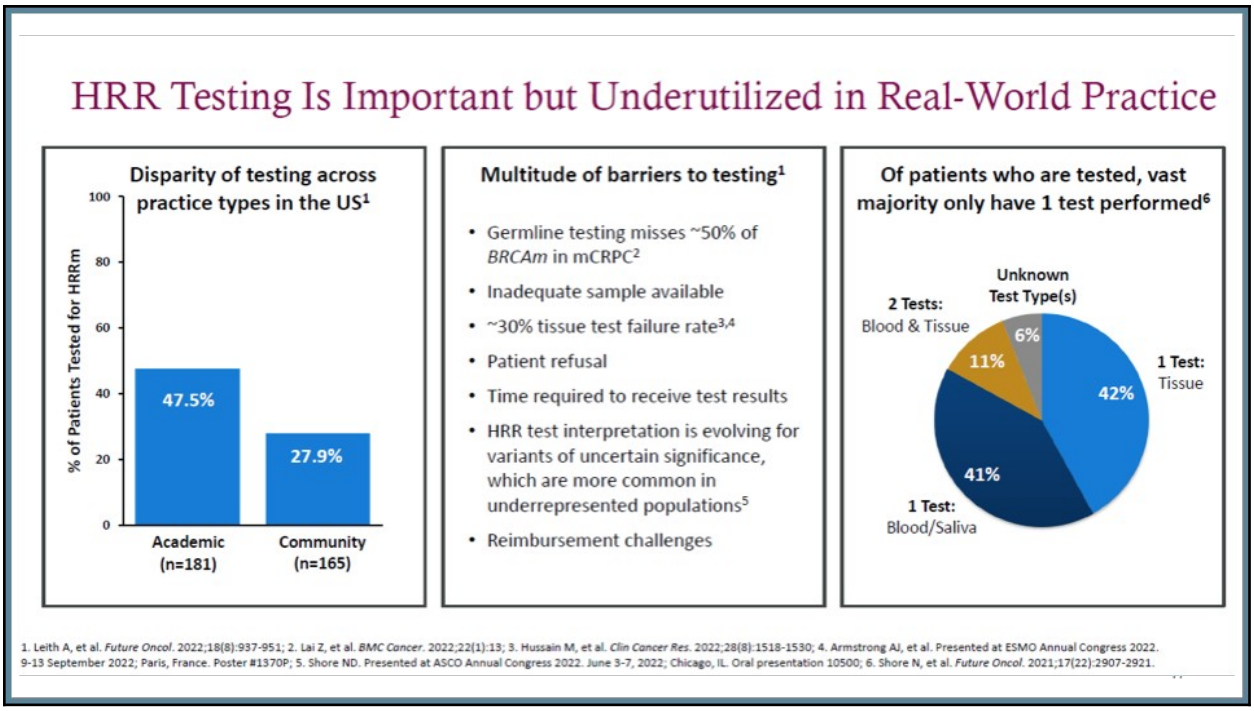
| Study | Agents | N | Indication | HR | ΔOS (mo) |
|---|---|---|---|---|---|
| **TAX-327**[1] | DOC / P vs mito / P | 1006 | mCRPC, symptomatic or not | 0.76 | +2.9 |
| **COU-AA-302**[2] | ABI / P vs P | 1088 | mCRPC (pre-DOC), mild / no symptoms<br>No visceral metastases | 0.81 | +4.4 |
| **COU-AA-301**[3] | ABI / P vs P | 1195 | mCRPC (post-DOC) | 0.74 | +4.6 |
| **PREVAIL**[4] | ENZ vs PBO | 1717 | mCRPC (pre-DOC), mild / no symptoms | 0.77 | +4.0 |
| **AFFIRM**[5] | ENZ vs PBO (or P) | 1199 | mCRPC (post-DOC) | 0.63 | +4.8 |
| **TROPIC**[6] | CABA / P vs mito / P | 755 | mCRPC (post-DOC) | 0.70 | +2.4 |
| **ALSYMPCA**[7] | Radium-223 vs PBO | 921 | mCRPC (post-DOC or unfit for DOC) | 0.70 | +3.6 |
| **PROfound**[8] | Olaparib vs NHT | 245 | mCRPC post-NHT (with HRRm) | 0.69 | +4.4 |
| **VISION**[9] | Lu-PSMA vs NHT | 831 | mCRPC post-NHT (with PSMA+) and chemo | 0.62 | +4.0 |

ABI, abiraterone; CABA, cabazitaxel; chemo, chemotherapy; DOC, docetaxel; ENZ, enzalutamide; HR, hazard ratio; HRRm, homologous recombination repair gene mutation; Lu-PSMA, Lutetium-177 prostate-specific membrane antigen; mCRPC, metastatic castration-resistant prostate cancer; mito, mitoxantrone; mo, months; NHT, neoadjuvant hormonal therapy; OS, overall survival; P, prednisone; PBO, placebo

1. Tannock IF, et al. *N Engl J Med* 2004;351:1502–1512; 2. Ryan CJ, et al. *Lancet Oncol* 2015;16:152–160; 3. Rathkopf DE, et al. *Eur Urol* 2014;66:815–825; 4. Beer TM, et al. *Eur Urol* 2017;71:151–154; 5. Armstrong AJ, et al. *Cancer* 2017;123:2303–2311; 6. de Bono JS, et al. *Lancet* 2010;376:1147–1154; 7. Hoskin P, et al. *Lancet Oncol* 2014;15:1397–1406; 8. Hussain M, et al. *N Engl J Med* 2020;383:2345–2357; 9. Sartor O, et al. *N Engl J Med* 2021 Jun 23. doi: 10.1056/NEJMoa2107322. Online ahead of print.

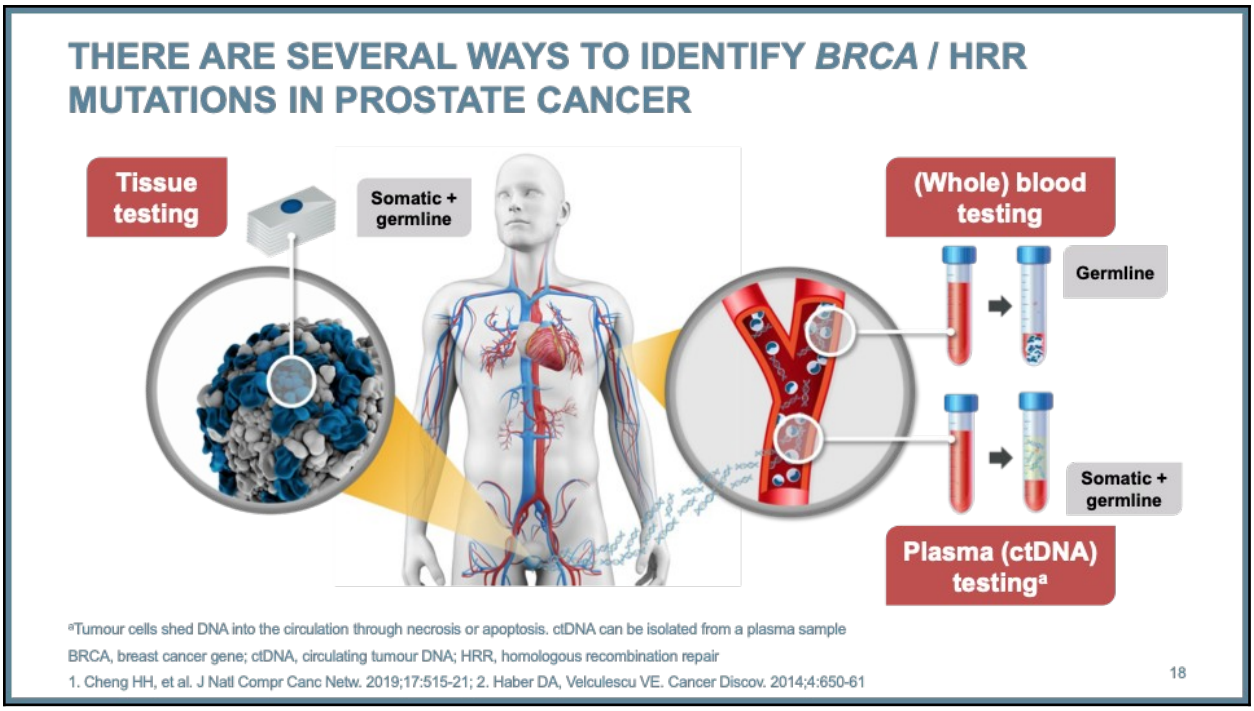
This is a table of all of the life-prolonging therapies. I can't cover all of them. This would literally take many hours and hopefully your group is going through some of these. These are the conventional FDA-approved therapies that are all life-prolonging, all with hazard ratios below one, but you can see that we still have a long way to go. The average survival improvement for all of our approved therapies is generally four to five months or less. So that's not great. That's a median. There's generally a bell curve distribution of these improvements. Some men get extra years of life, but some men don't respond at all. This ranges from docetaxel to our potent AR inhibitors, to some newer precision therapies like Pluvicto and PARP inhibitors.

**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**

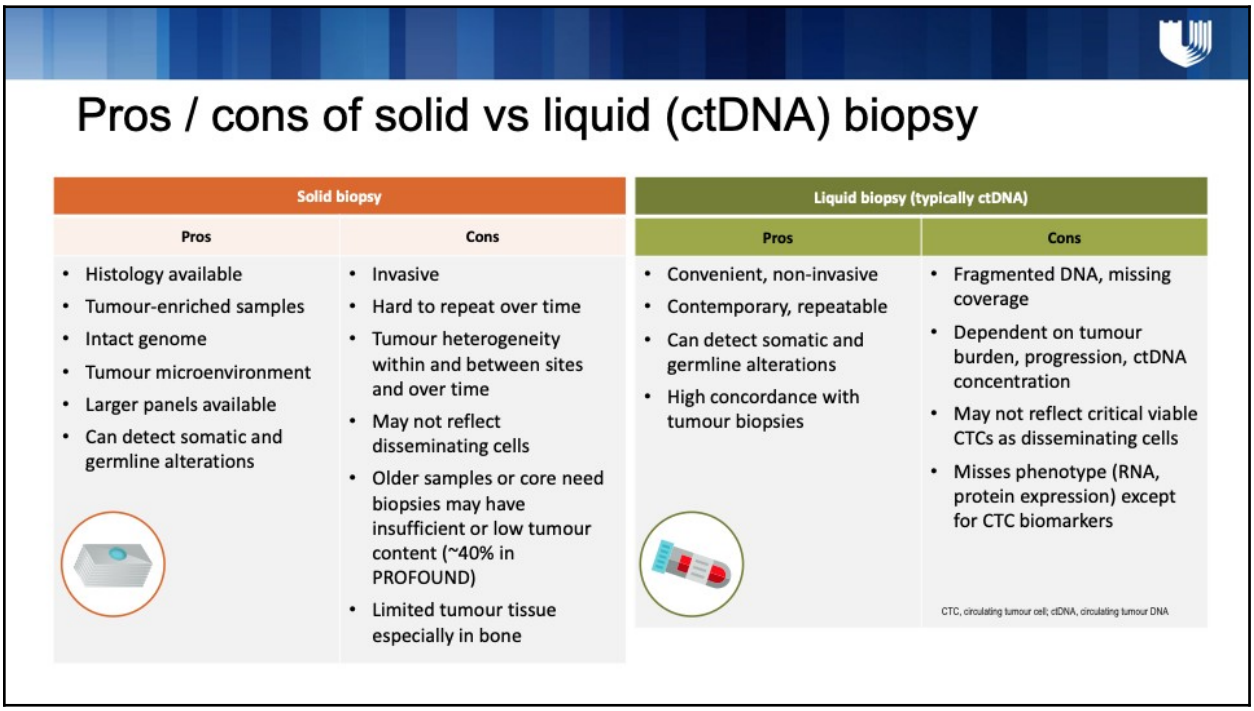



Like I talked about in my last lecture, DNA testing, either from your tumor or by a liquid biopsy, is very helpful to help guide these therapies that you wouldn't otherwise know about. Most men in the community are not getting any testing, especially in urology practices. One message that we try to convey in discussions with patients and patient advocate societies is to ask your doctor about getting tested for both germline and tumor testing, where that can only help you. This lack of testing disproportionately and negatively impacts Black men, rural patients, and patients of a lower socioeconomic status, leading to major disparities in care and treatment. It can help save the lives of your daughters or sons who might have a BRCA syndrome or BRCA mutation, where cancer can be intercepted in the next generation, but it might help the patient directly open the door for a PARP inhibitor or a PD-1 inhibitor that may extend or improve their survival.

**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**

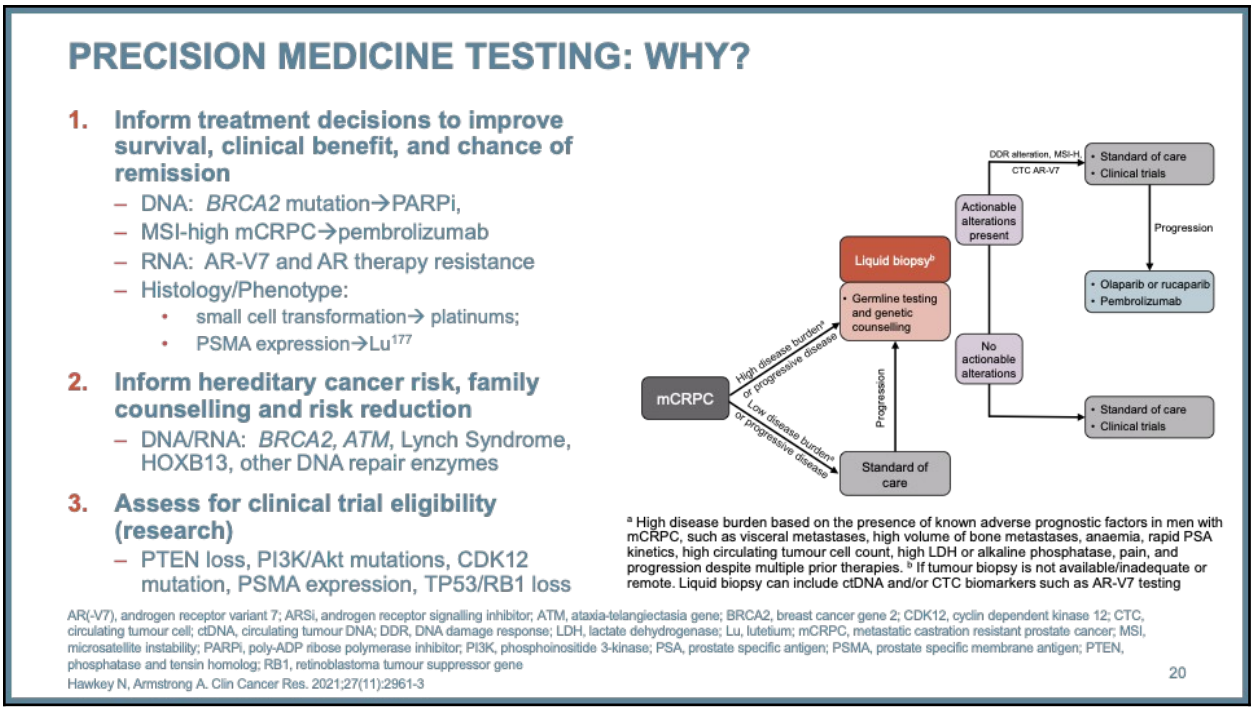



There are lots of different ways to do the testing, both solid and liquid.

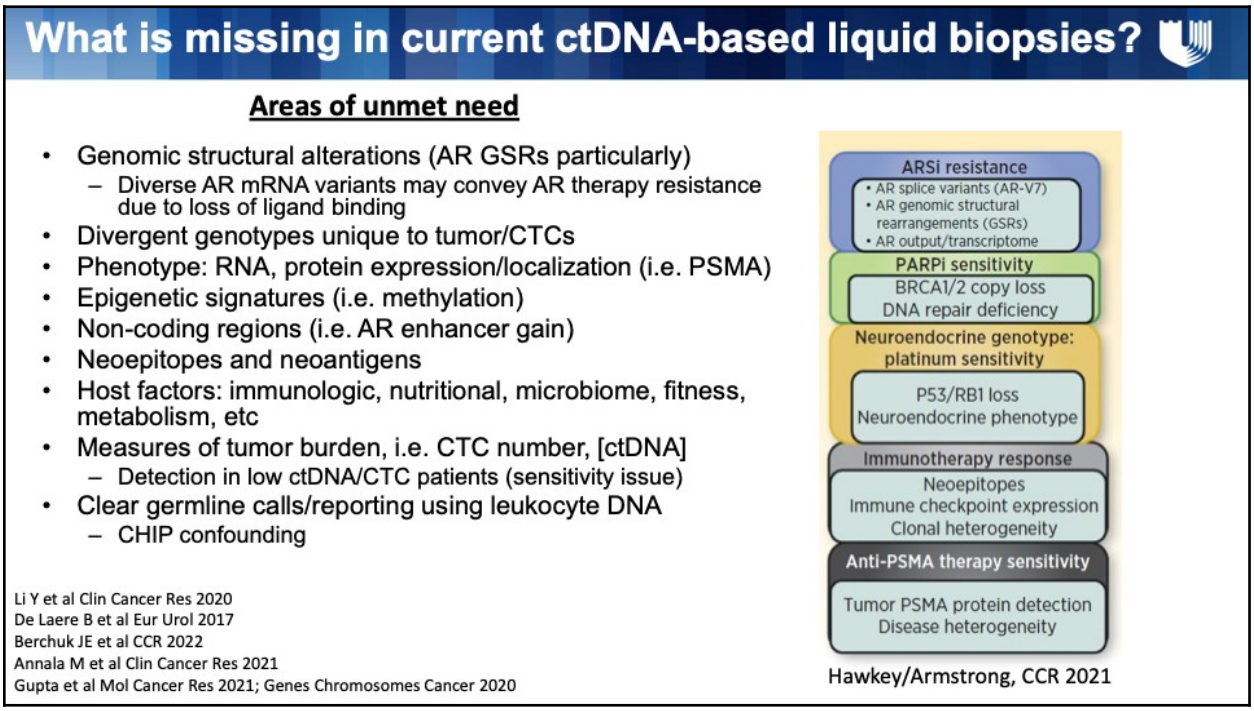



I covered this last time. Part of my research is trying to improve the liquid biopsy.

**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**

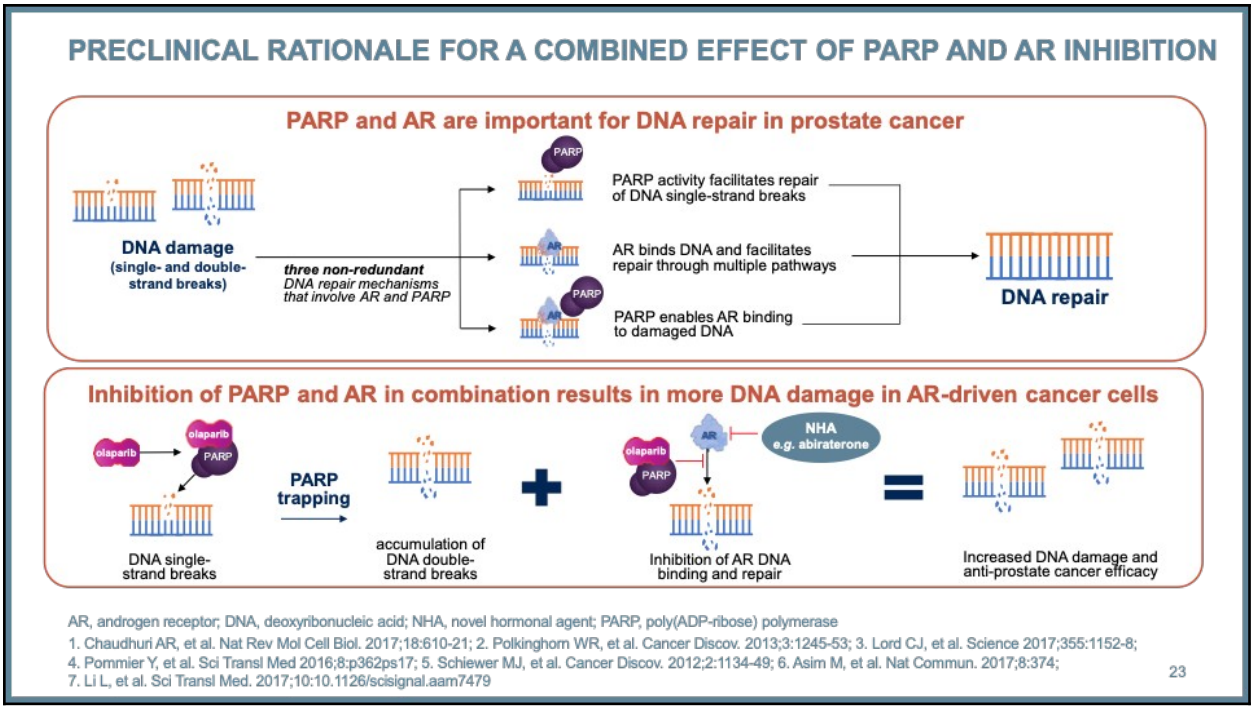



There are a lot of things that for commercial assays are missing in the way we do our testing.




I'm one of those types of doctors that was mentioned earlier that sees patients, but I also run a lab. A lot of what I do in the lab is to try to develop precision medicine tests and understand the cancer's biology so that we can bring new treatments into the clinic. There's a lot of work being done on circulating DNA, circulating RNA, and circulating epigenetics, to understand cancer

biology, how it evolves and adapts and develops resistance to our therapy. We could not just objectively measure that, but ideally target some of those features to improve patient outcomes.




Have you guys had a talk on the PARP inhibitor combos? This was the biggest breakthrough of this year for these FDA approvals in 2023, so I could spend five minutes on it.

Brad Power 14:59
Please do.

Andy Armstrong 15:02
The idea behind this whole concept is that in prostate cancer, DNA repair is really important. The lack of DNA repair is what causes cancer mutagenesis (mutations). In our normal cells, we have these enzymes that are proofreaders. They correct DNA mutations that occur during cell division. But cancer often has faulty DNA repair, and the mutations pile up. Some of that's caused by just breathing oxygen and having free radicals. But some of this is because of inherited mutations in DNA repair enzymes, like a patient with a BRCA2 mutation. DNA damage can get repaired. One novel finding is that the androgen receptor inside prostate cancer actually regulates DNA repair. Another enzyme called PARP – think of that as a backup proofreader. You've got genes like BRCA1 and BRCA2 that are your primary proofreaders. Then PARP is a backup proofreader. The idea behind combining AR and PARP inhibitors is that you can block the proofreaders inside the cancer cell directly, so that the cancer basically falls apart from overwhelming errors. The cancer really needs to protect itself from all those errors, so that it survives. But if you push the cancer over the cliff with a huge number of mutations, the cancer cell can die. That's where olaparib or Lynparza, or talazoparib, and AR blockade comes in.

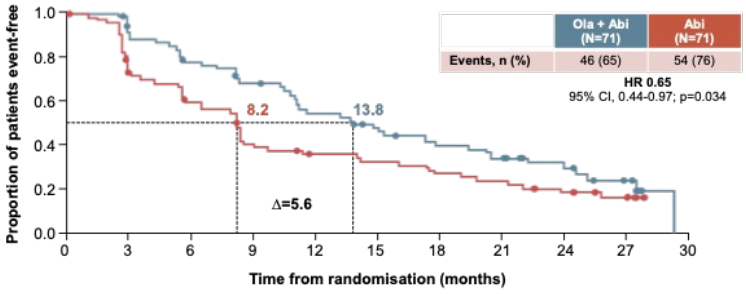
**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**

You're enhancing DNA repair breaks. You're blocking DNA repair enzymes. That's leading to more anti-cancer efficacy. I hope that little biological primer helps.

## PROpel: CLINICAL RATIONALE FOR COMBINATION OF OLAPARIB WITH ABIRATERONE

- In a phase 2 trial (NCT01972217), **abiraterone + olaparib prolonged rPFS vs abiraterone + placebo in biomarker-unselected patients with mCRPC**, who had received docetaxel[1,2]

**INVESTIGATOR-ASSESSED rPFS**




Abi, abiraterone; CI, confidence interval; HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; Ola, olaparib; rPFS, radiographic progression-free survival

1. Clarke N, et al. Lancet Oncol. 2018;19:975-86; 2. Carr TH, et al. Cancers. 2021;13:5830

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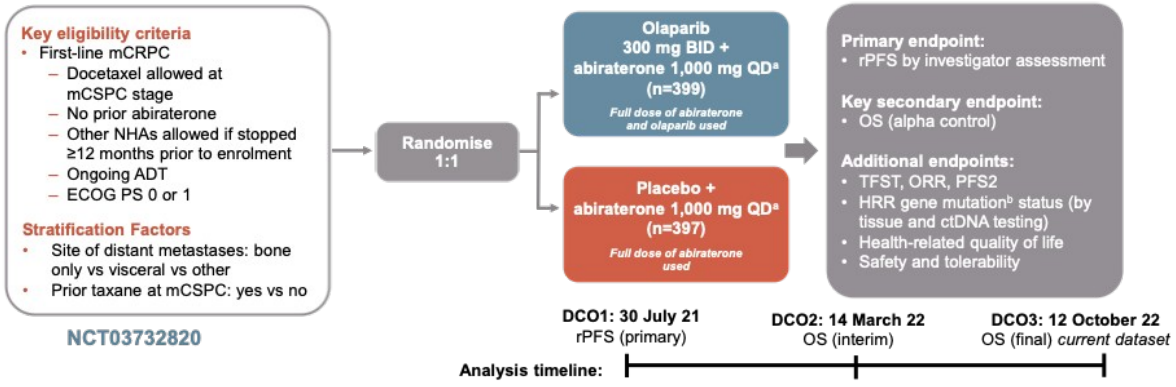
There is some data to support this from early on where we conducted a trial with abiraterone and a PARP inhibitor that delayed progression or death in unselected patients, even in patients that did not have inherited mutations.

## PROpel: STUDY DESIGN

### A GLOBAL, RANDOMISED, DOUBLE-BLIND PHASE 3 TRIAL




First patient randomized: Nov 2018; last patient randomised: Mar 2020

Multiple testing procedure is used in this study: 1-sided alpha of 0.025 fully allocated to rPFS; if the rPFS result is statistically significant, OS to be tested in a hierarchical fashion with alpha passed on to OS

[a] abiraterone used in combination with prednisone or prednisolone 5 mg BID; [b] HRR mutation, including 14-gene panel, using the FoundationOne®CDx test and FoundationOne®Liquid CDx test

ADT, androgen-deprivation therapy; BID, twice daily; ctDNA, circulating tumour DNA; DCO, data cut-off; ECOG PS, Eastern Cooperative Oncology Group performance status; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; NHA, novel hormonal agent; ORR, objective response rate; OS, overall survival; PFS2, time to second progression; QD, per day; rPFS, radiographic progression-free survival; TFST, time to first subsequent therapy or death

1. Clarke NW, et al. J Clin Oncol. 2019;37 Suppl: TPS340; 2. https://clinicaltrials.gov/ct2/show/NCT03732820; 3. Clarke N, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA16) (ASCO GU 2023 oral presentation)

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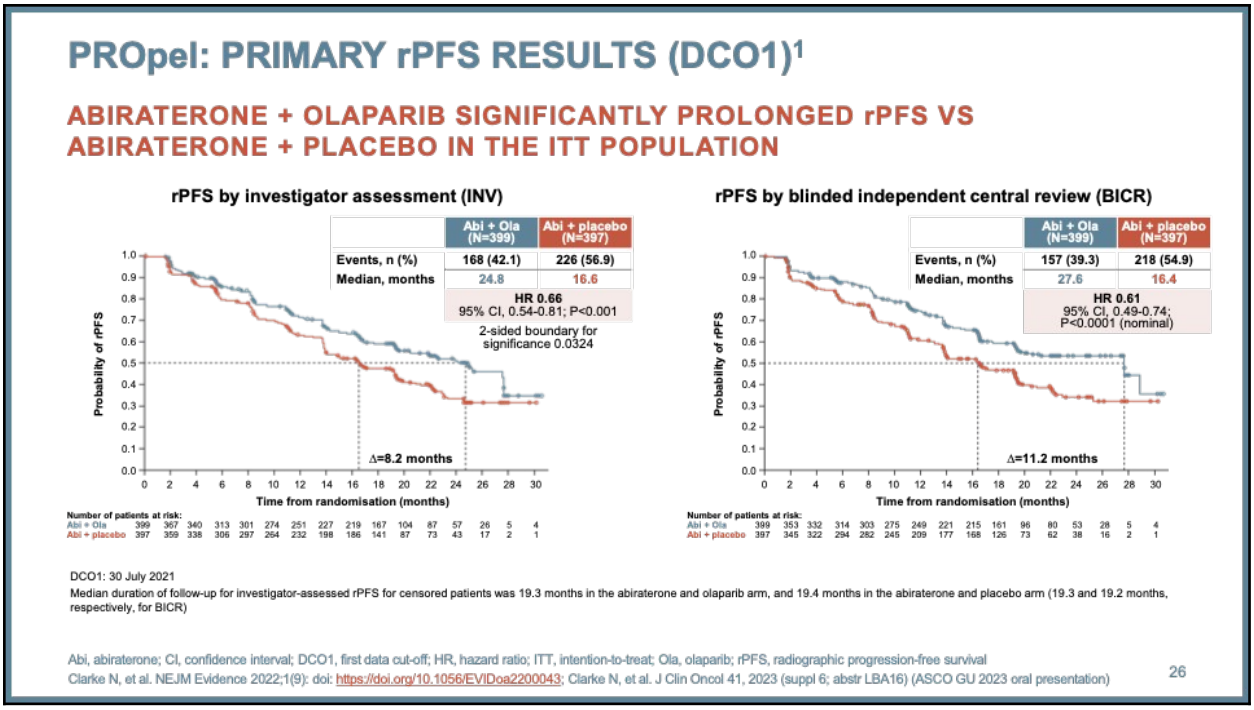
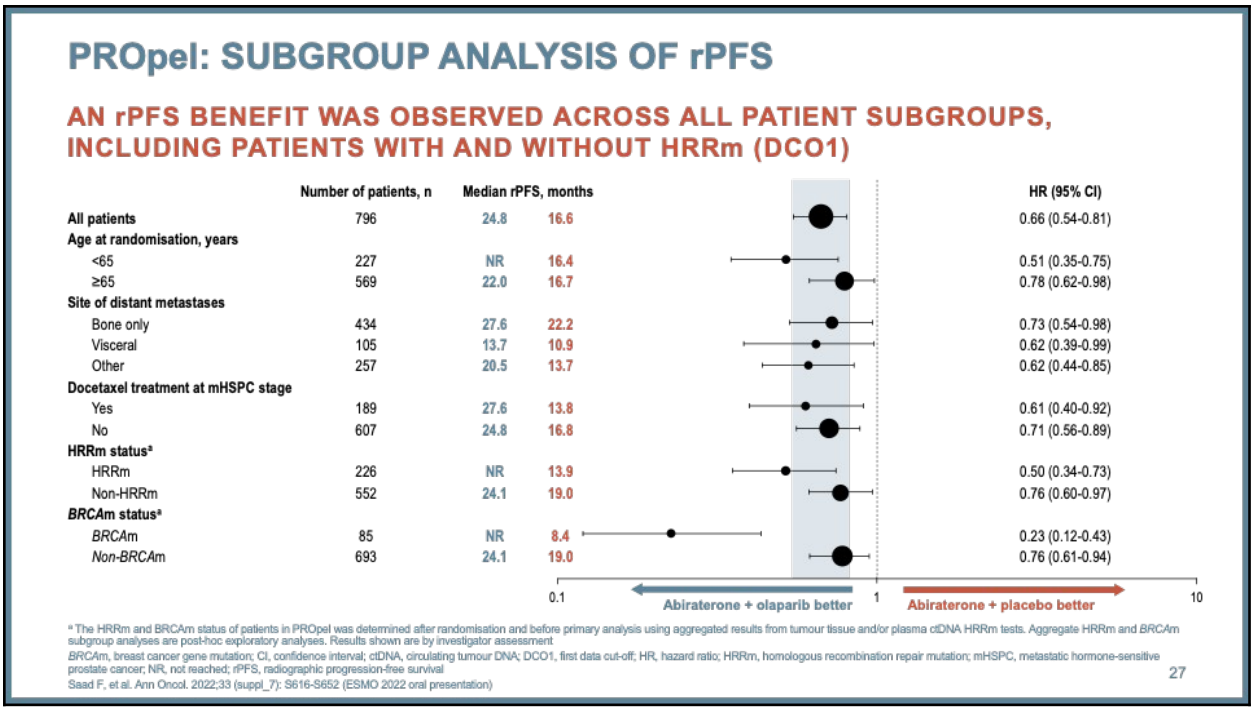
**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**

This led to the PROpel study, which has now been published twice, and just a couple of months ago led to an FDA approval. It's important to look at the patients in this study. This is a global, big study, with 800 patients. These are all metastatic castrate resistant prostate cancer patients. They had good functional status. They had not had a prior novel hormonal therapy, but they could have had prior chemo, and they either got the standard of care, which is abiraterone, which many of you are familiar with, or abiraterone plus olaparib (a PARP inhibitor). Everybody got the standard of care.

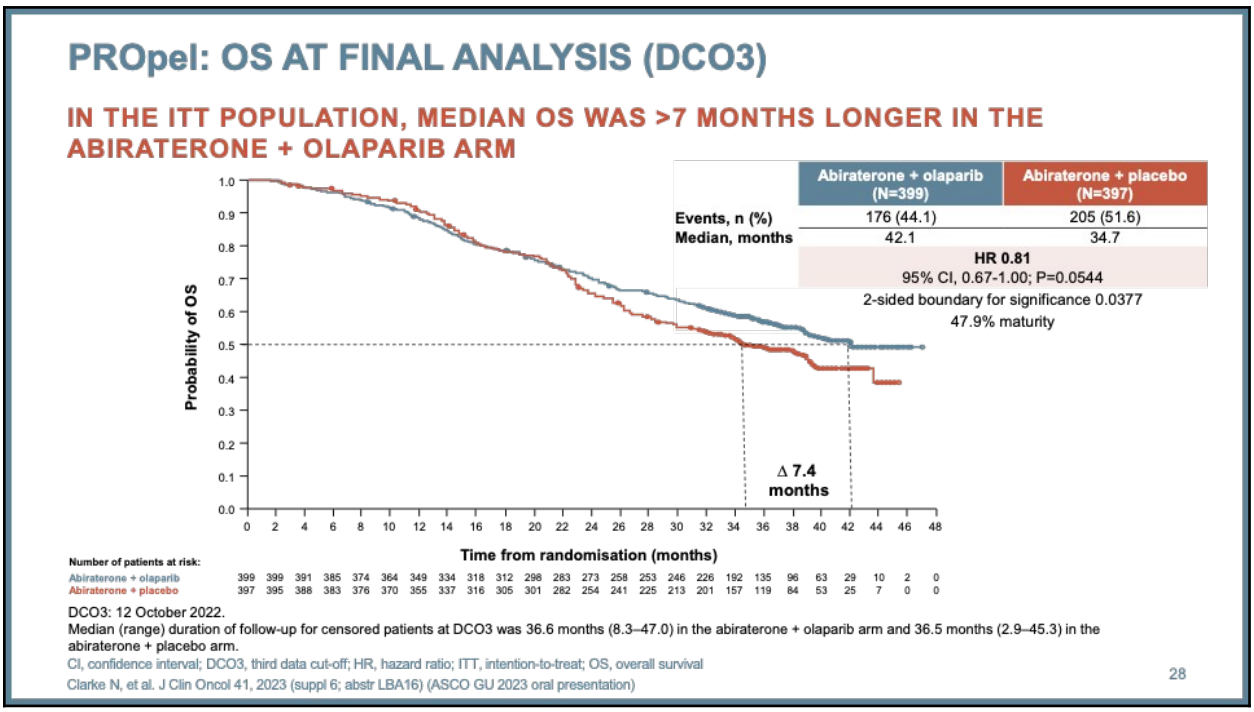



The experiment was to see if the PARP inhibitor could improve outcomes. It did. In an all comer patient population, fewer men experienced progression. This is a significant result of about an eight-month delay by the investigator assessment. Then by a blinded radiologic review, it was about an 11-month delay. That is substantial. The European Union looked at these data and approved it for all comers. This is the primary endpoint.

**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**

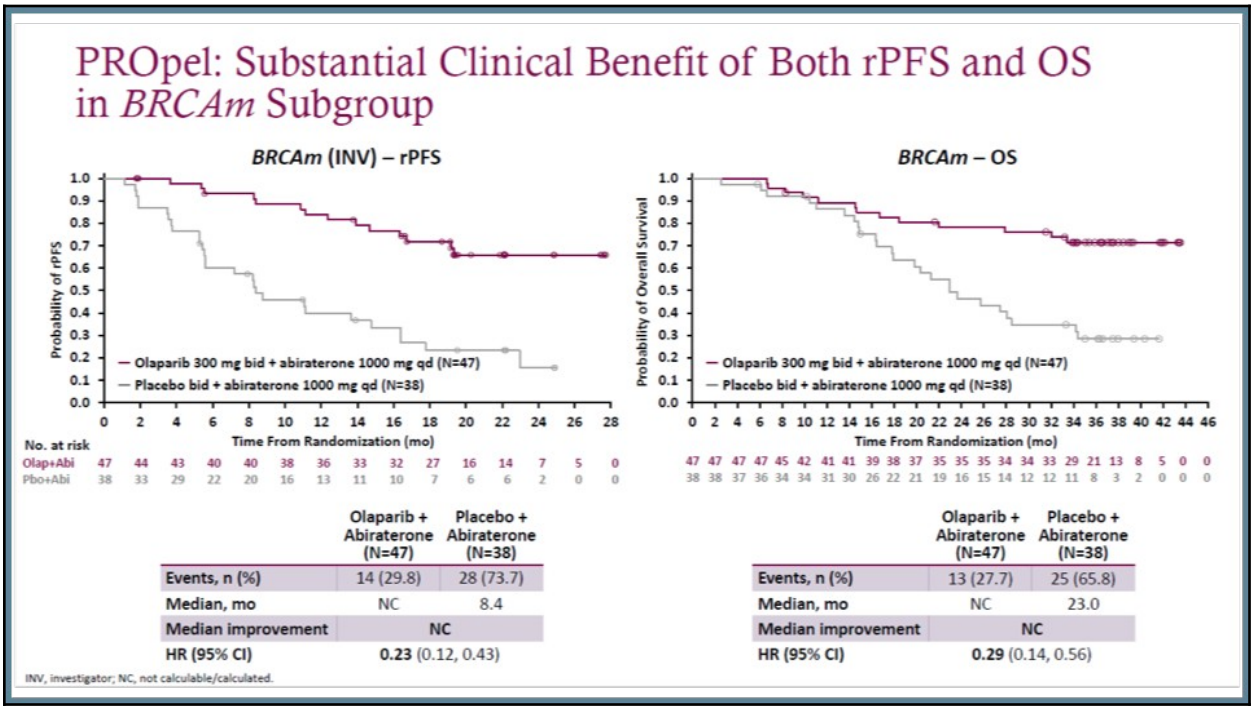



The FDA, however, did not look at it in the exact same way. They looked at the all comers, but they saw that the patients who are deriving the greatest benefit are those that had a BRCA mutation. The hazard ratio here is 0.2. That's a phenomenal impact on patients with BRCA mutations. But patients without BRCA mutations still benefited. But this is the group that the FDA approved for this combination.



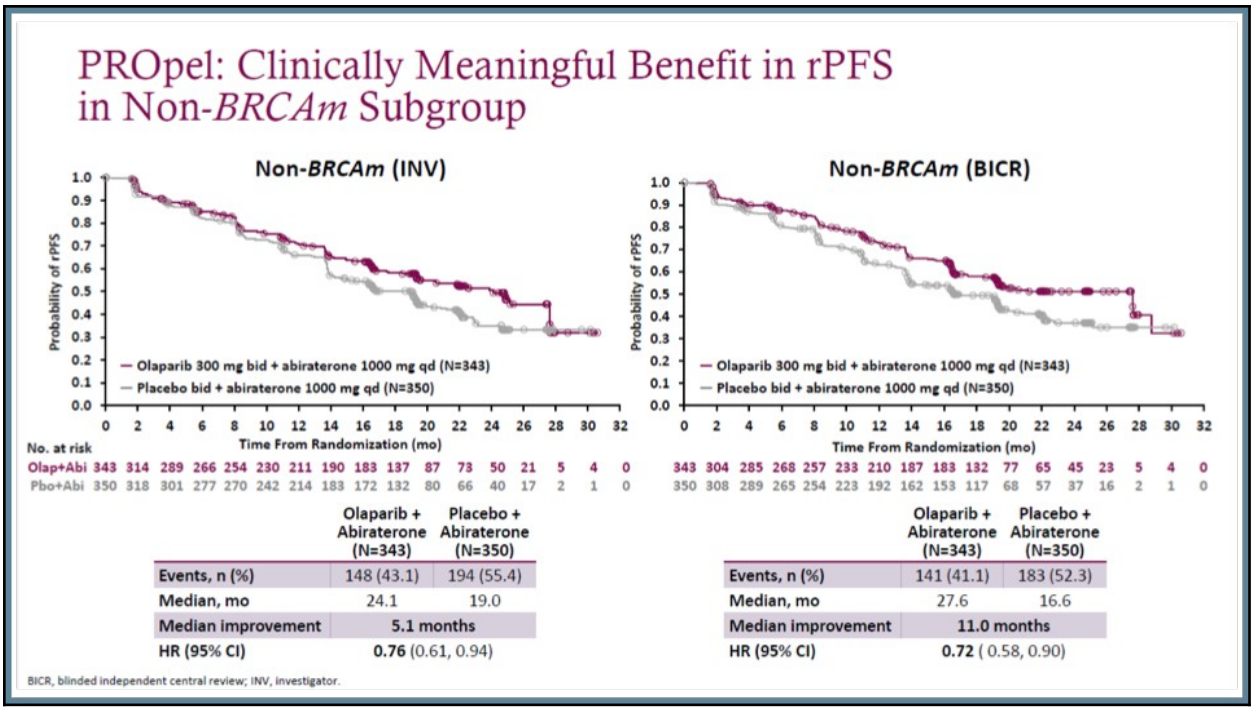
**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**

Another reason for that is the overall survival. While it technically was numerically greater, it did not yet meet the statistical significance that was pre-specified. It was very close, .05 versus .0377. Numerically, it is about a seven-month improvement.

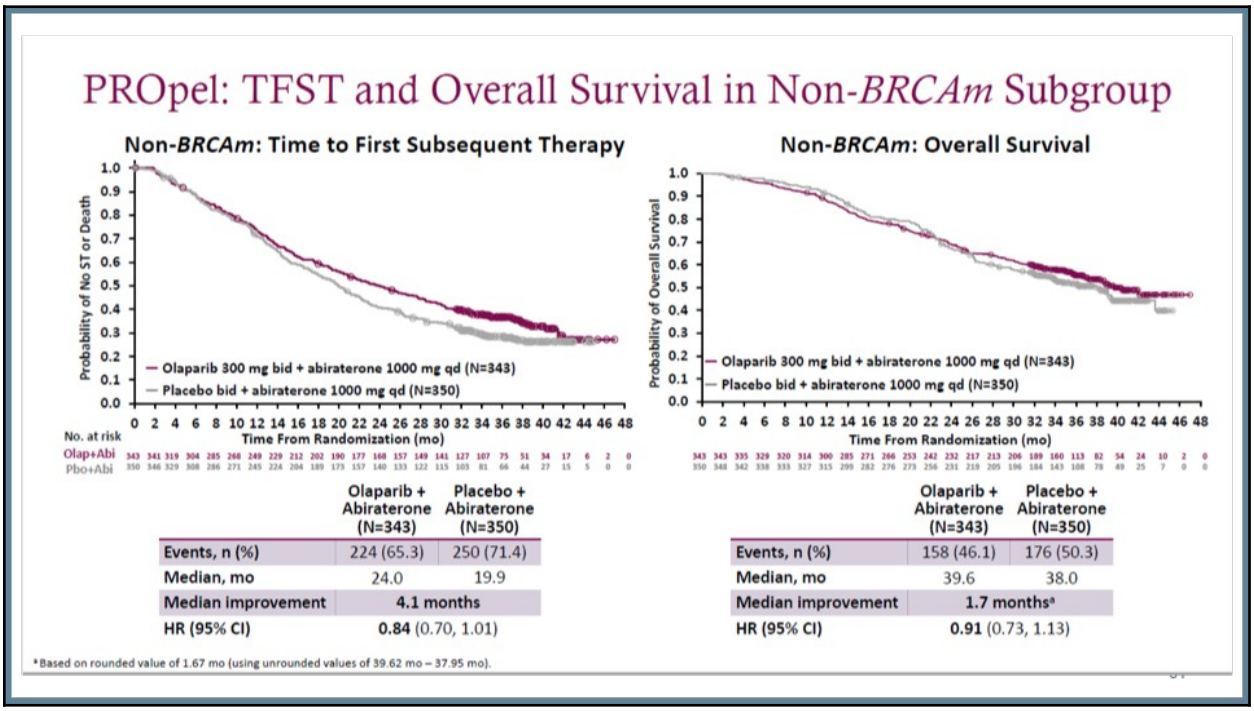



But if you look at the BRCA carriers, this is survival, not progression free survival. That's a huge difference in overall survival. Again, this is what the FDA approved the combination for: if you have a BRCA mutation either inherited or in your tumor – half of patients are either way – there's a massive improvement in survival. This is now a standard of care for these patients.

**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**

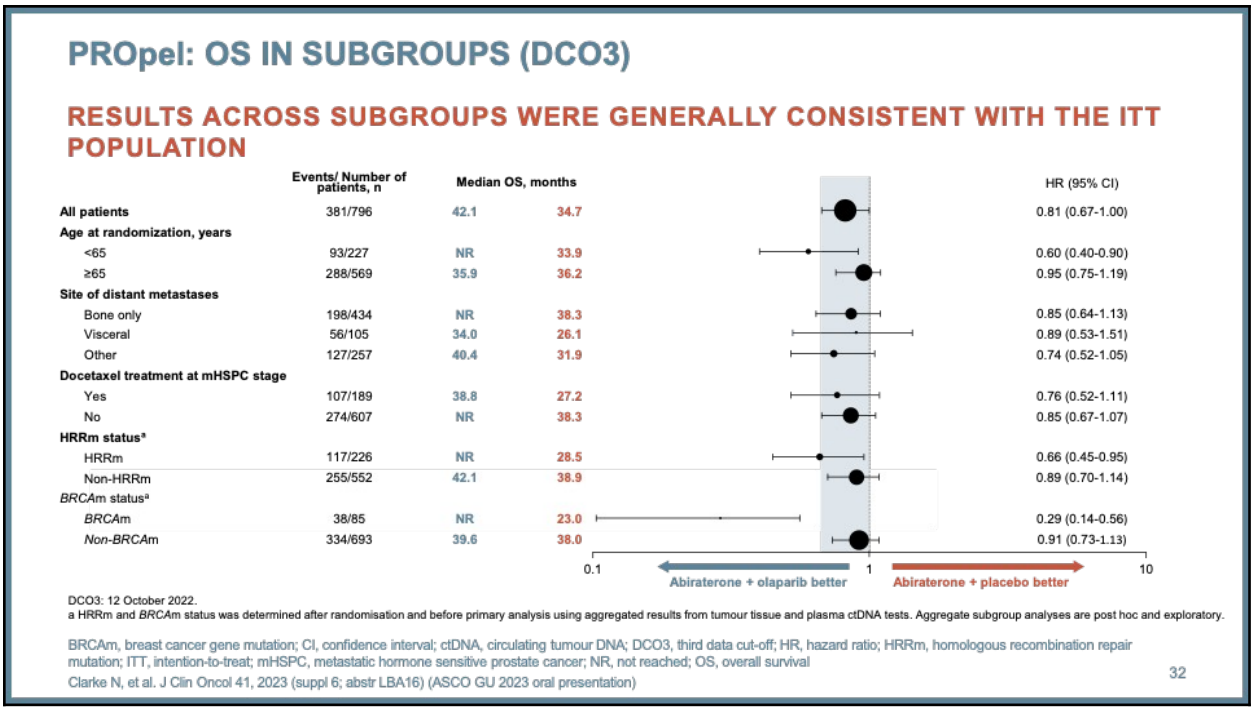



But if you don't have a BRCA mutation, while there's a delay in progression, …

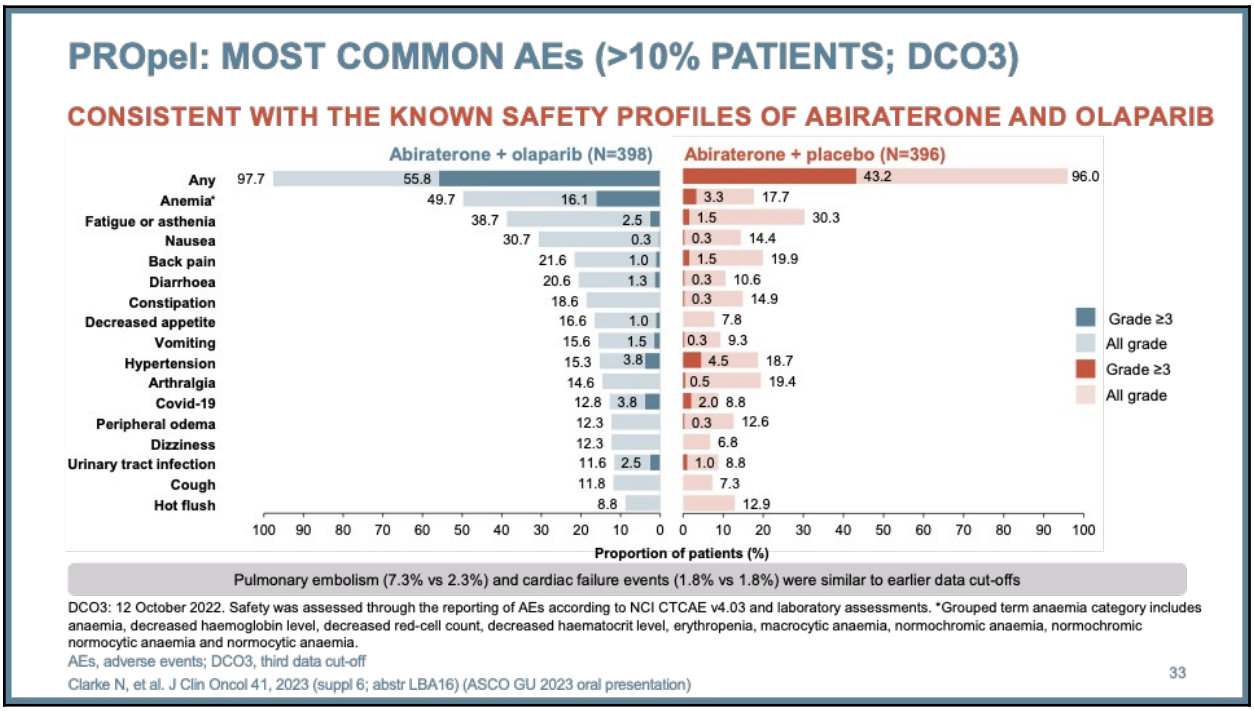



… the survival benefits are not very clear, and these data are pretty immature. There's only a one- or two-month improvement in survival. That's why this combination is not as exciting as for a BRCA carrier. There's a minor impact on survival.

**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**




There's a more major impact on delaying progression, which is important,

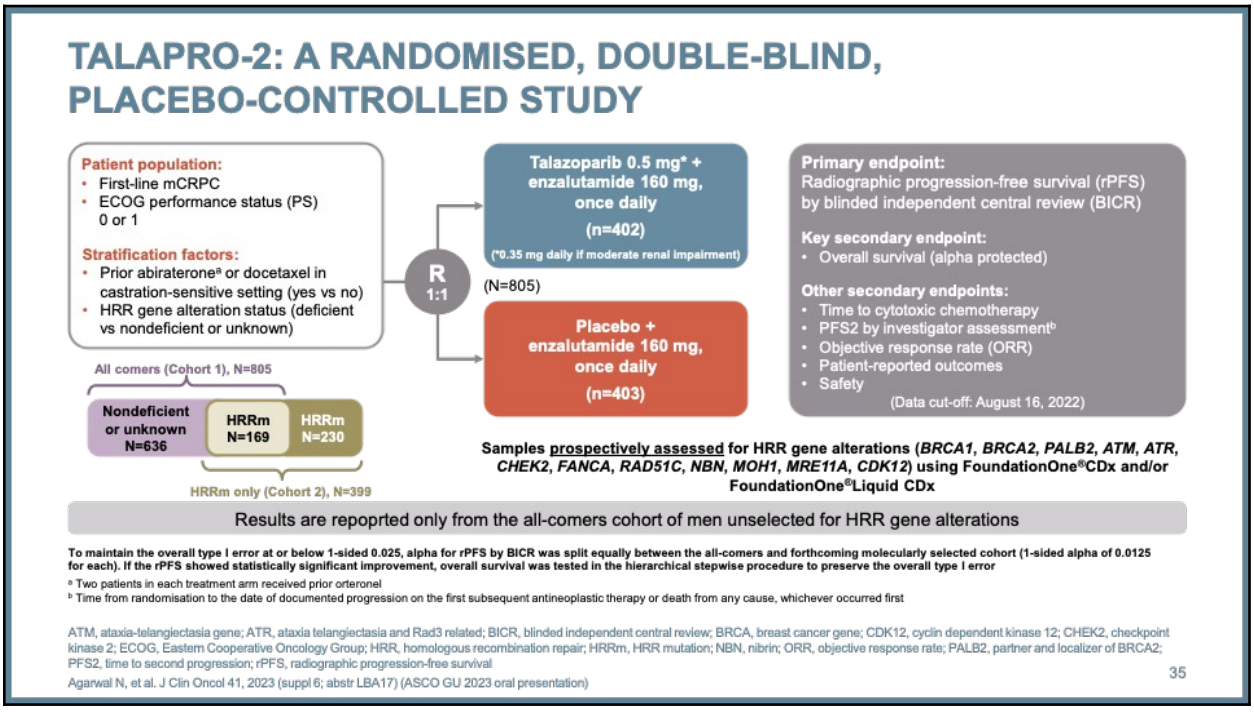



but there are risks for this combination. Those risks are things like anemia. About one out of six patients will require a blood transfusion because of the PARP inhibitor. Most of these patients do experience some fatigue. You can see with abiraterone, there are side effects as well. There are no treatment combinations that have generally fewer side effects. More pills, more costs.

**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**

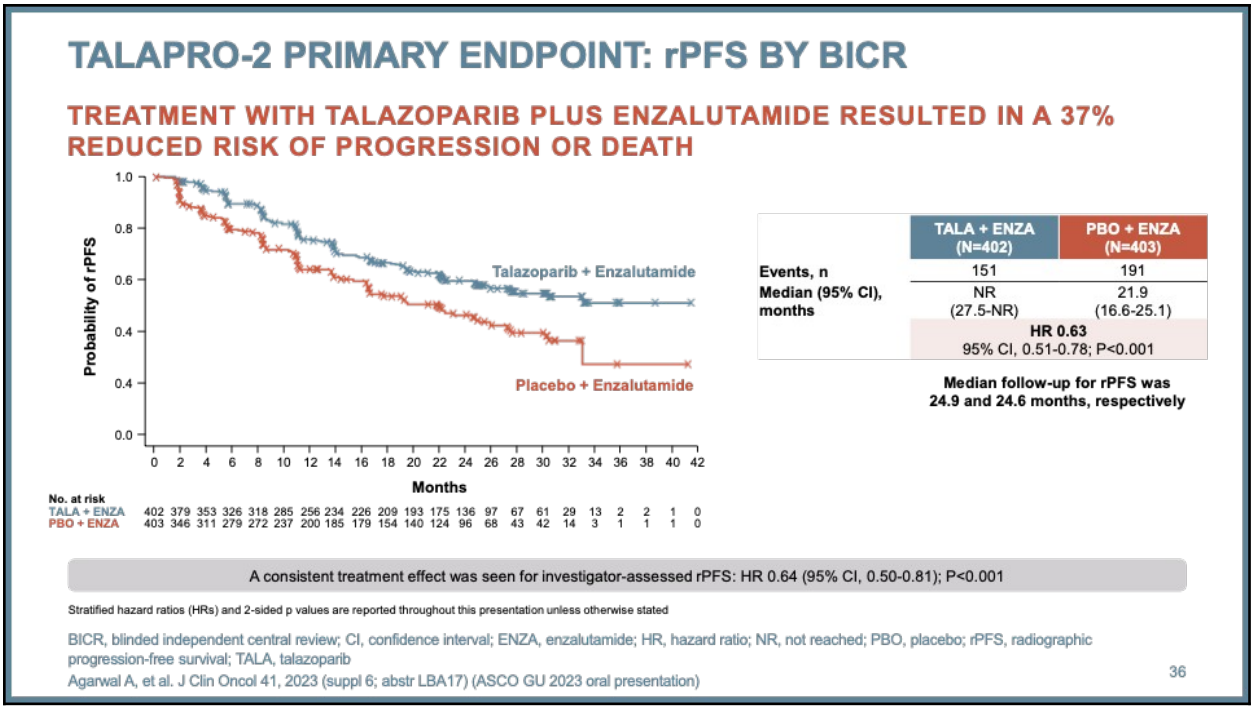
Each patient obviously should weigh the risks and benefits of this approach. The advantage of delaying progression versus the side effects and added costs. It's not for everybody. Certainly patients who are more frail, who don't have a BRCA mutation are going to have much less benefit.


These are the FDA labels now. The European labels are different, a little more broad.



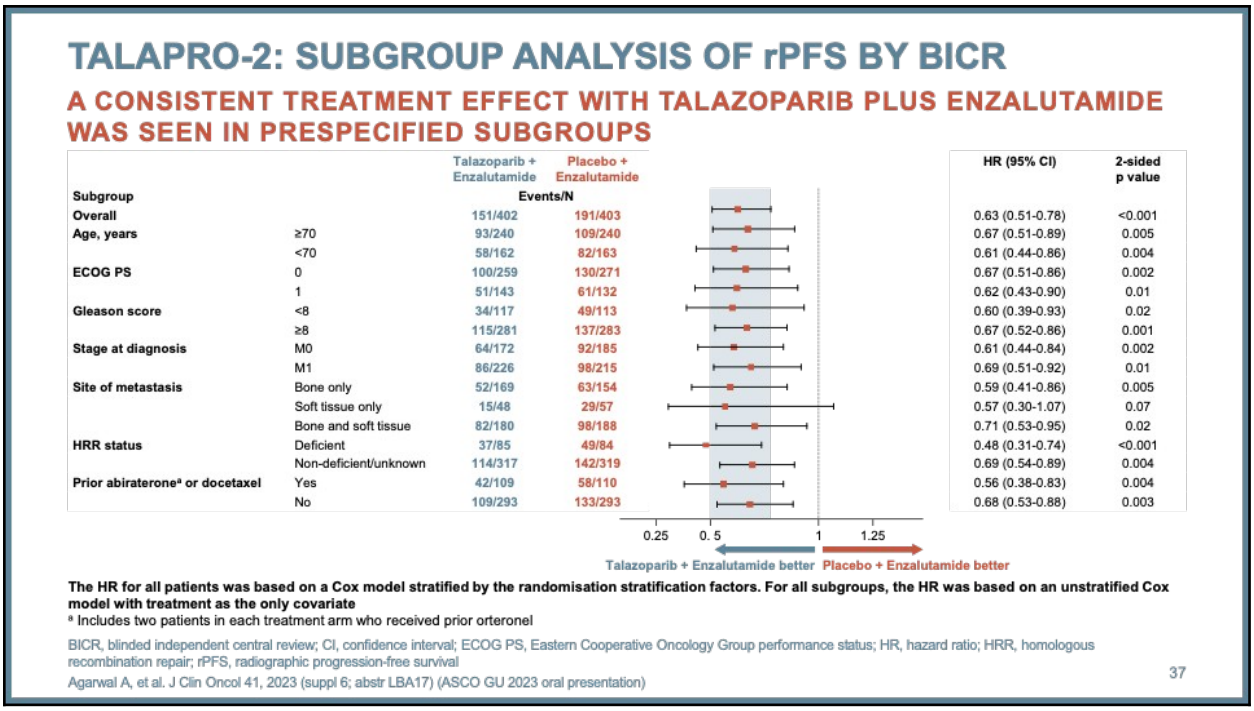
**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**

There's another combination that just got approved a few weeks ago. The TALAPRO-2 phase three trial is based on talazoparib, another PARP inhibitor, this time in combination with Xtandi or enzalutamide. It’s a similar design to PROpel, where the control group got enzalutamide. The goal was to delay progression, and ultimately hope that it would lead to improved survival.

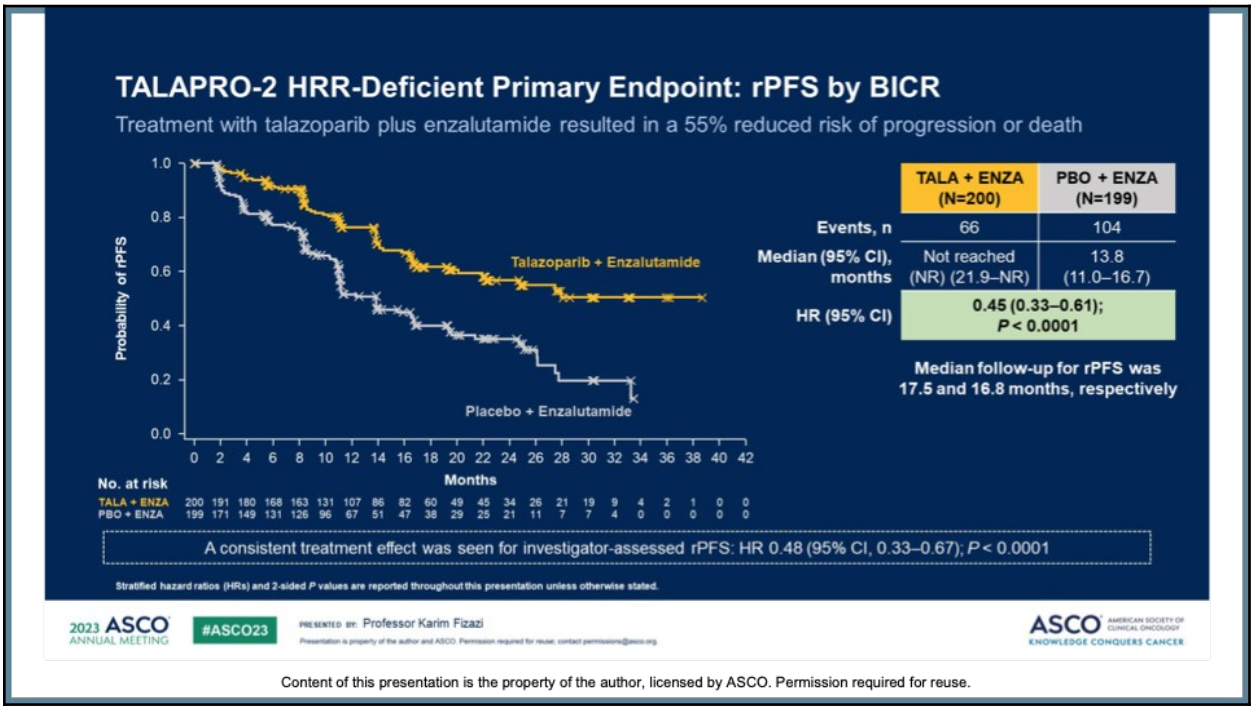



Just like PROpel, the study was positive for all comers, with a significant delay in progression, somewhere by 8 to 10 months again.

**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**

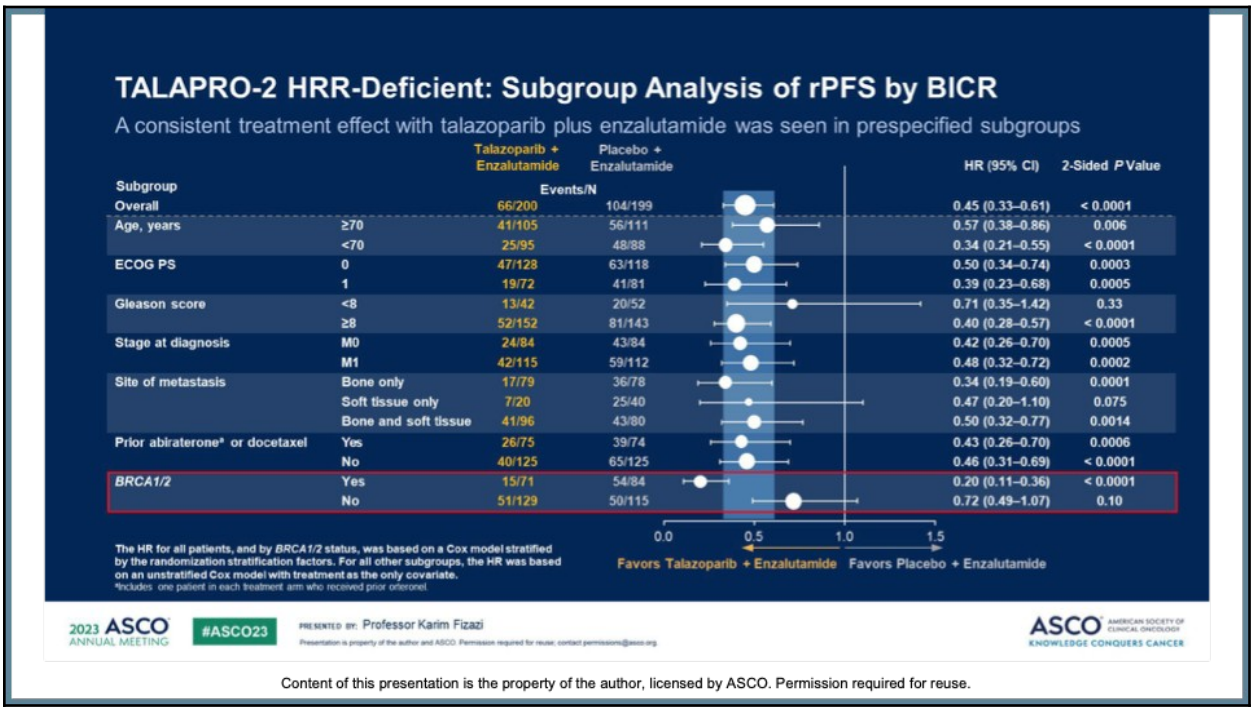



The FDA approved this for patients with what's called “DNA repair defects” or “homologous repair deficiency”, where there is a greater benefit in delaying progression, a hazard ratio 0.48. They did not approve it for a broad population.



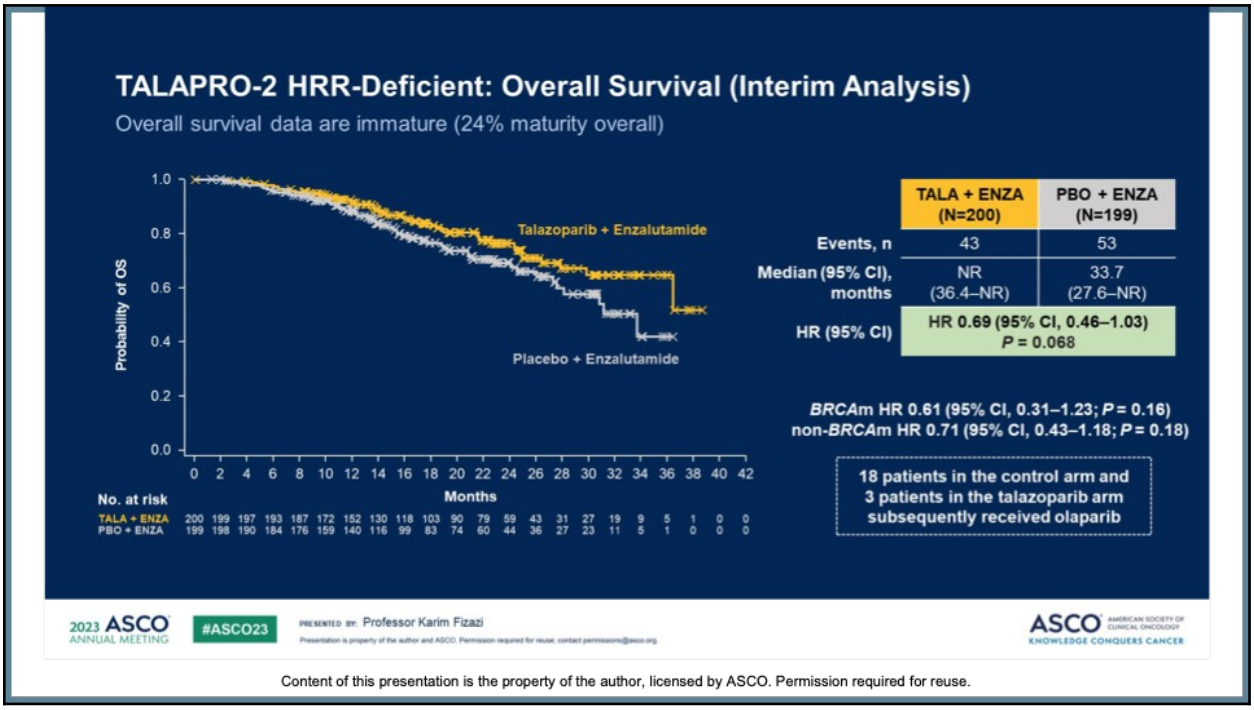

The data for that population where it's approved is where you see a substantial delay in progression.

**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**



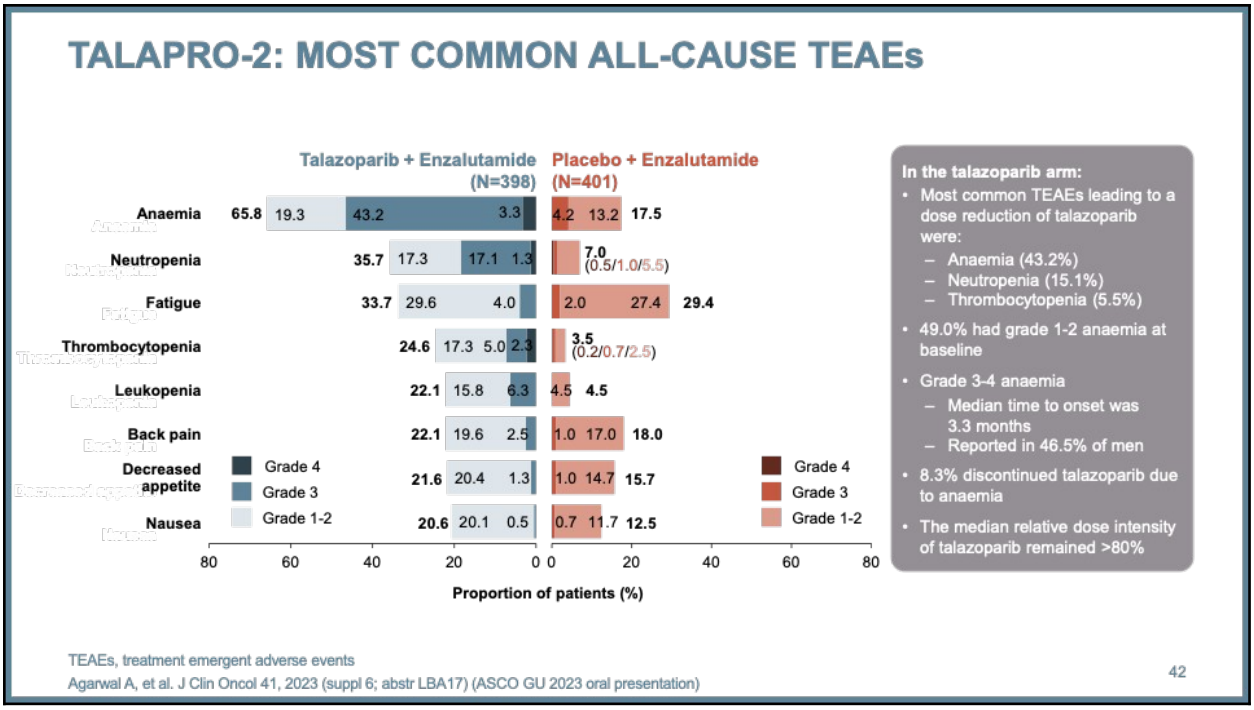



The data for overall survival is not mature yet, so I can't really comment on it. But again, just like in PROpel, the patients with BRCA2 mutations are largely the ones getting a humongous benefit. So if you have a patient with BRCA2, you've got now two choices, both of which should be strongly considered above and beyond using a potent AR inhibitor.



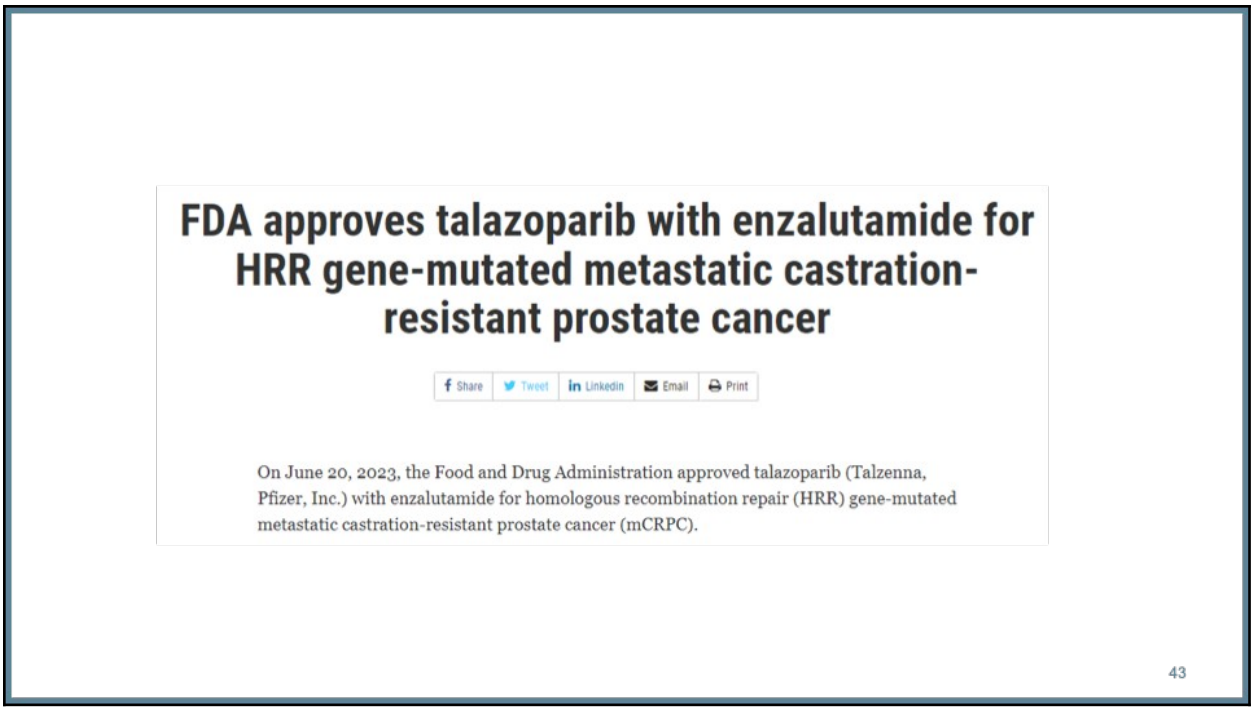
**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**

This is the overall survival. There's a strong suggestion that it will be positive with more time. Stay tuned for next year for this.



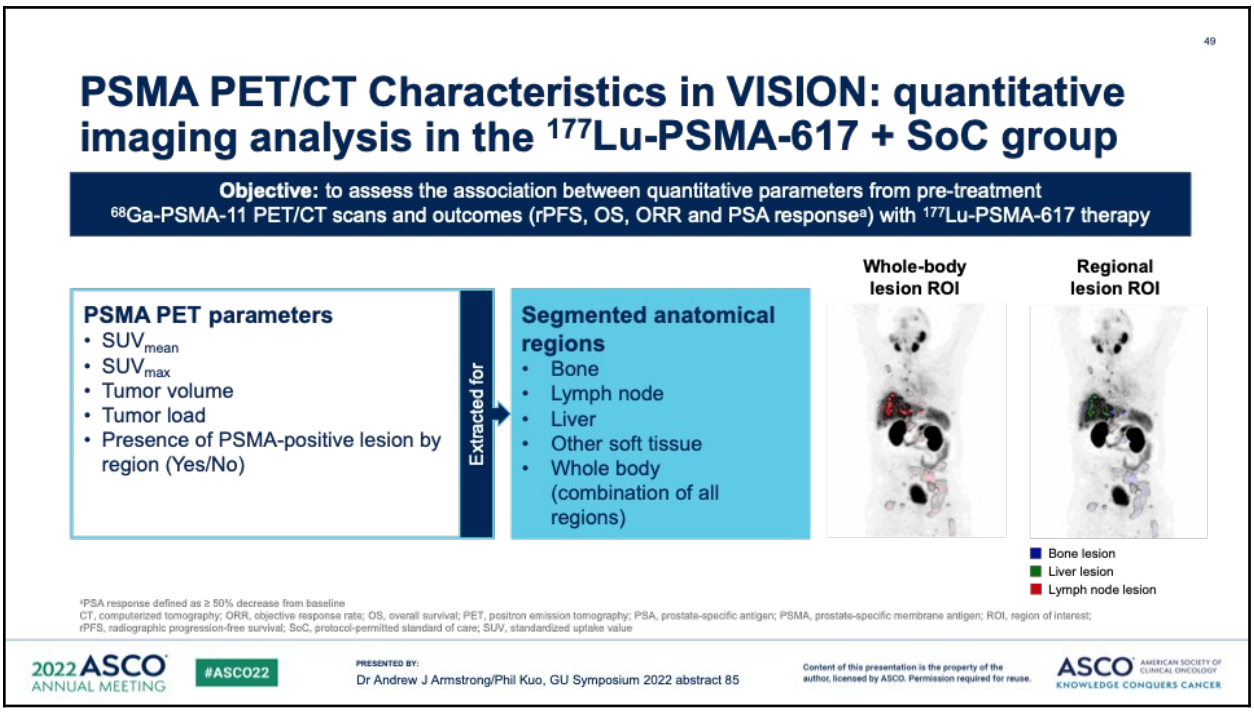

Again, the downside of using PARP inhibitors is anemia. Talazoparib has a bit more anemia – 43% instead of 16% – which required blood transfusions. That's a much bigger number. There are risks with using PARP inhibitors. These are like chemo pills. It can cause drops in your blood counts. Patients have to be followed very carefully. You really need an expert oncologist to follow you carefully and dose reduce and dose hold when that's needed, or to give blood if that's needed, and to continue with perhaps a dose reduction so that you can still see those benefits.

**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**



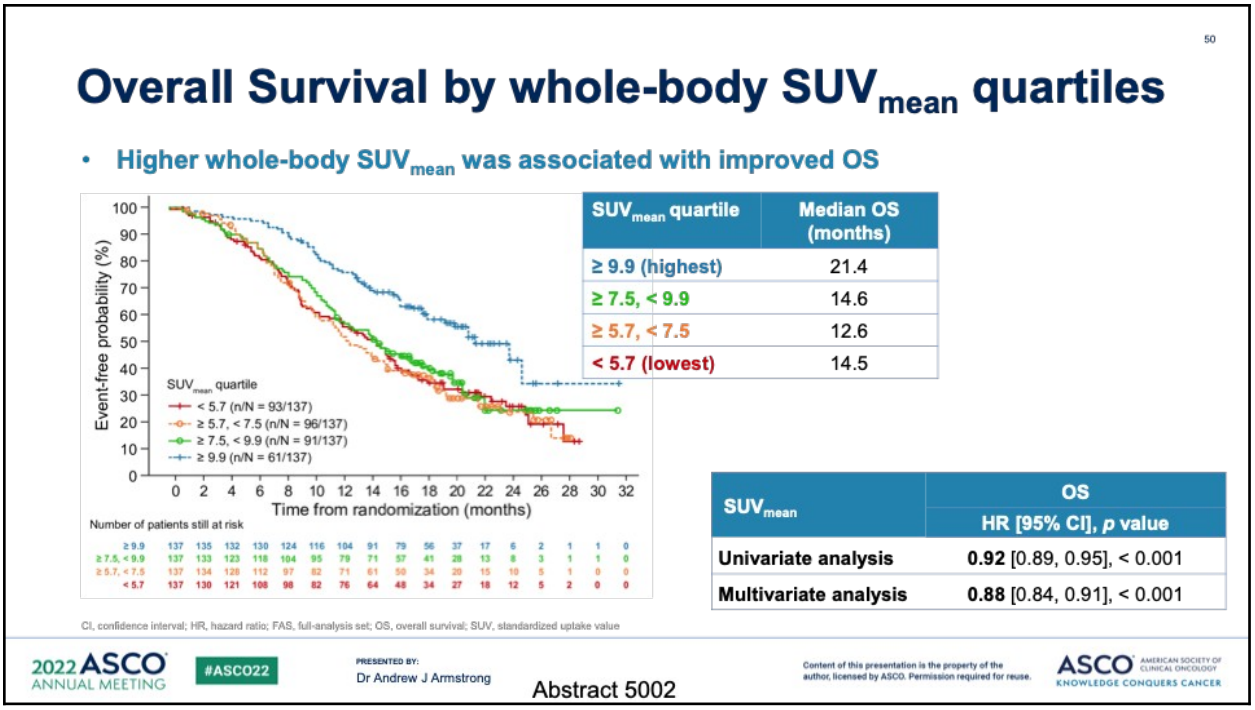

This is the new FDA label in June. I'm going to skip through this because I know we wanted to have you guys talk about Pluvicto (PSMA Lutetium).

Brad Power  23:12
Yes. Dr. Sartor covered it.



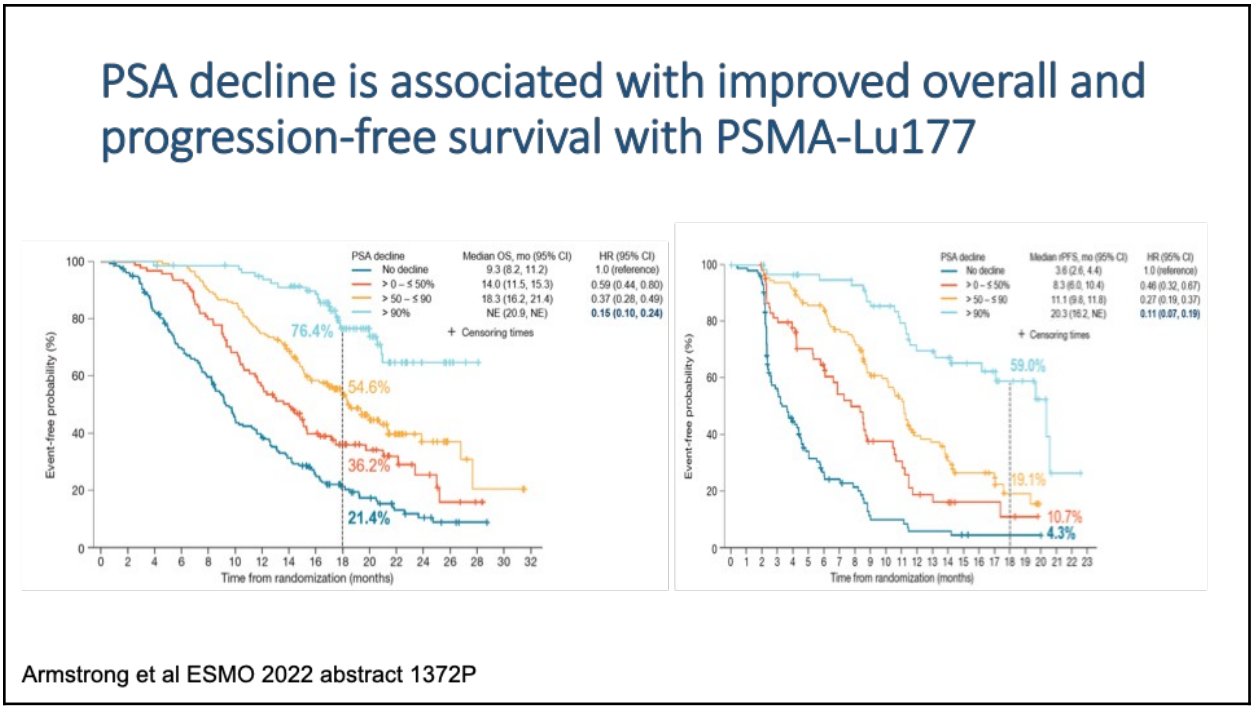
**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**

Andy Armstrong 23:15
Great. You should be very familiar with the VISION study. So I'm going to skip over this. Dr. Sartor and I are working on additional analyses on the VISION study and Pluvicto, using these fancy PET scans and 3D to look at who benefits the most from radioligand therapy targeting PSMA.

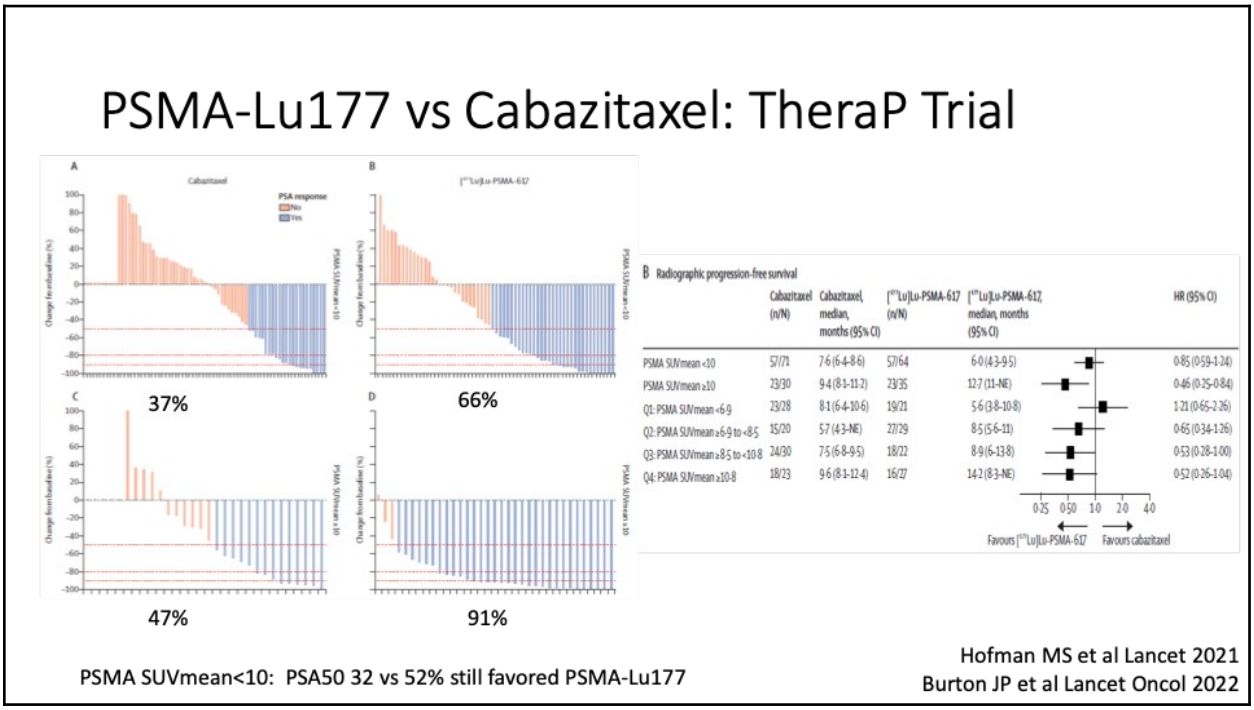



This is a paper we just submitted a week ago, based on a presentation we had last year that shows the patients with the brightest tumors have the best survival.

**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**

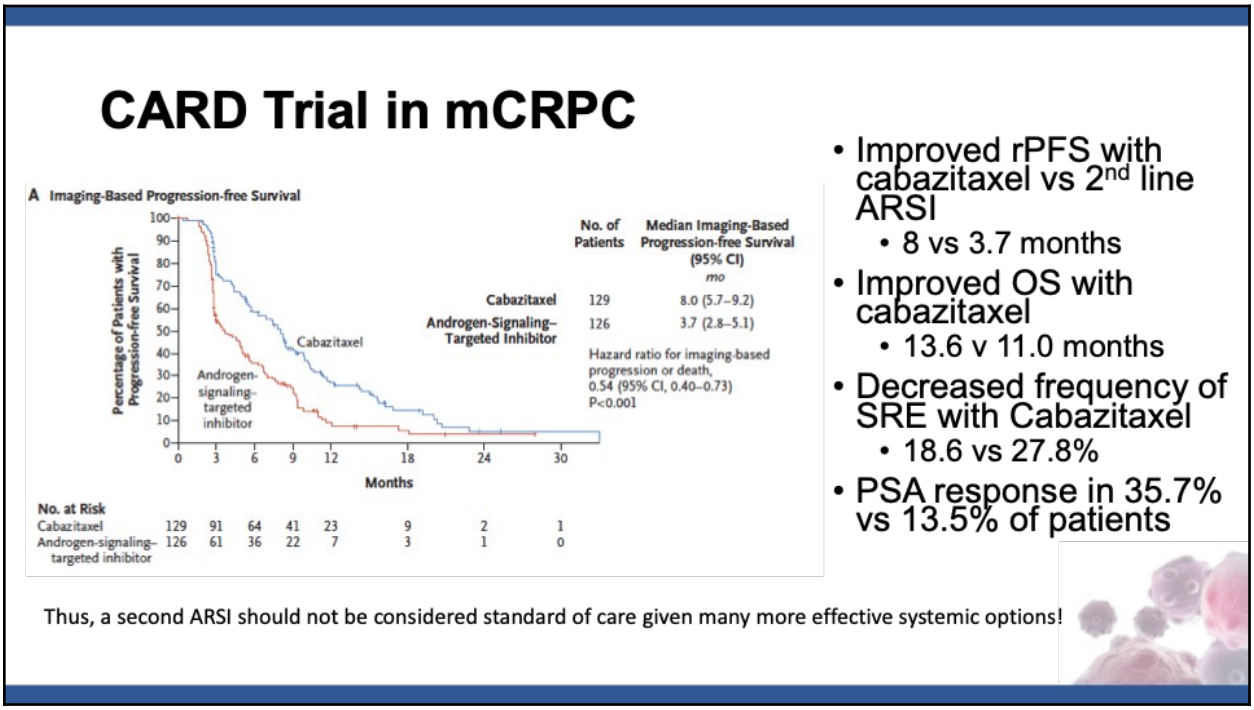



Patients that have their PSAs go down the most also have the best survival. There are ways when you get drugs like Pluvicto to know if it's working. Usually the PSA in the first 12 to 24 weeks will capture a lot of that benefit.



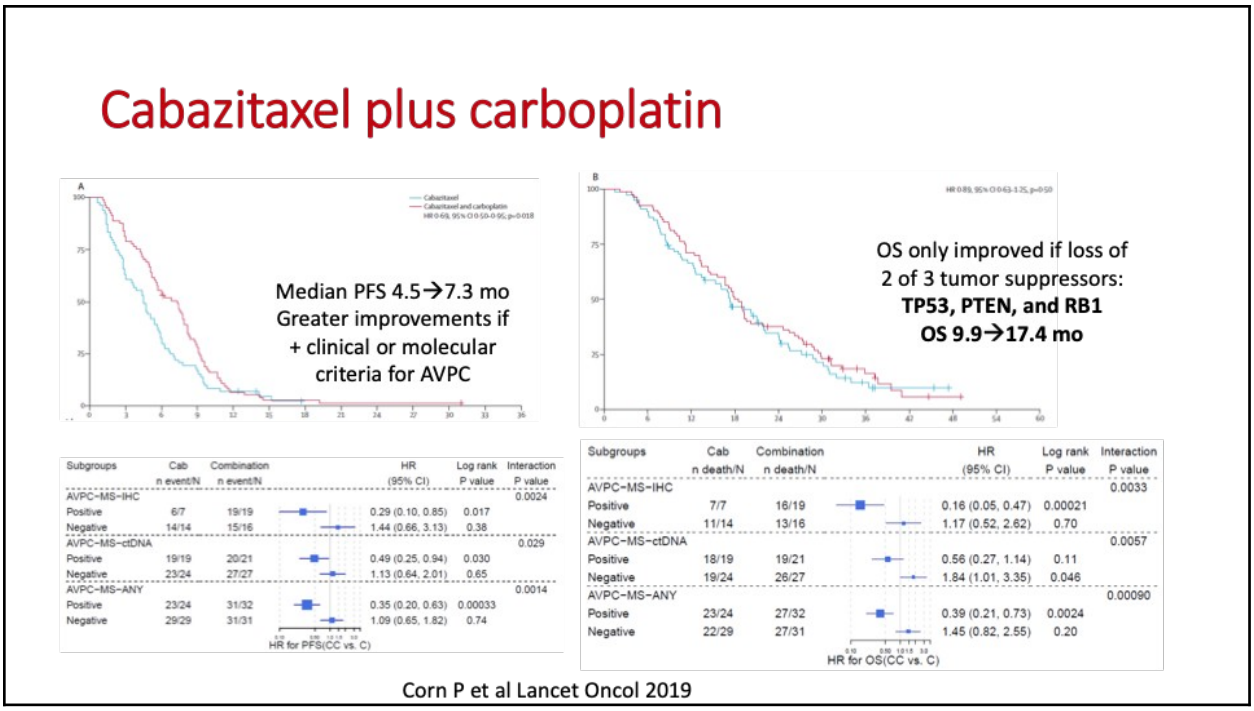

Making decisions for the subsequent therapy: should you get Pluvicto, or should you get more chemo, e.g., Cabazitaxel, in patients with very bright PET scans – SUVs of 10 or higher – it's

very clear that Pluvicto tends to be better. If the target is there, it makes sense to target it, but if the target is not there, it's a more dim tumor, then Cabazitaxel. It's pretty much a tie. It's a good option for some patients.




Cabazitaxel has been around for 10 plus years. It’s still a very good weapon. You should not abandon it. We're still learning about how it works, but it does work. You can see that using another AR inhibitor generally doesn't work. That should not be a common standard of care. Most patients tend to progress at their first scans when they do that – from one AR inhibitor to another. But chemotherapy, with Cabazitaxel here, delayed progression significantly.

**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**



Corn P et al Lancet Oncol 2019

Sometimes we will tack on a second chemo drug if I have a patient with liver metastases, or neuroendocrine features, or if they have loss of two of these three tumor suppressors in their tumor DNA sequence. There's a survival benefit from the addition of a platinum drug, which is like a PARP inhibitor. It causes more DNA damage. Tumors of the prostate can still be platinum-sensitive, but typically only if they have what are called aggressive variant phenotype features or genotypes.

**NEPC: Current Evidence for Available Therapies**

| Author/year | Study design | Patient n | Patient population | Regiment | Treatment result |
|---|---|---|---|---|---|
| Papandreou et al. 2002 | prospective | 36 | 67% NEPC<br>33% mixed | Cis/ Eto/ Dox | RR 61%; TTP 5,8m<br>OS 10,5m |
| Steineck et al. 2002 | retrospective | 30 | 30% NEPC, 43% anaplastic, 13% mixed | Cis *oder* Carbo/ Eto/ Est | RR 50%; OS 8-941 d |
| Culine et al. 2007 | Prospective Single arm | 41 | CRPC and sNE marker | Cis/ Doc | RR 41%; OS 12m |
| Flechon et al. 2011 | Prospektive Single arm | 55 | CRPC + M (visz)<br>*And/or* sNE Marker | Carbo/ Eto | RR 8,9%; PFS 2,9m, OS 9,6m |
| Aparicio et al. 2013 | Prospective, single arm | 113; 74 | mCRPC , stratified for AVPC | 1st line: Carbo/ Doc<br>2nd line: Cis/ Eto | TTP1: 5,1m, TTP2: 3,0m<br>OS 16m |
| Beltran et al. 2018 | Prospective, Single arm | 60 | NEPC, AdenoCa + NE markers, liver Mx without PSA, sNE | Aurorakinase A Inhibitor Alisertib | 13,4% without progression at 6 months; PFS 2,2m, OS 9,5m |
| Corn et al. 2019 | prospective randomised | 160 | CRPC, stratified for AVPC | Carbo/ Caba vs. Caba | AVPC: PFS: 6,0 m vs. 2,2 m<br>OS: 17,4m vs. 9,9m |
| Apostolidis et al. 2019 | retrospektive | 46 | 45,7% NEPC<br>43,5% mixed | Carbo/Cis + Eto | RR 48,1%; OS 15,5m |
| Brown et al. 2022 | Prospective Single arm | 15 | AVPC/ NEPC | Avelumab | RR 6.7%; rPFS 1.8m; OS 7.4 m |

Modified according to Tsaur et al. Cancer Treatment Reviews 2019: 20-26

**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**

We have a dedicated research program at our institution and many others on neuroendocrine prostate cancer.

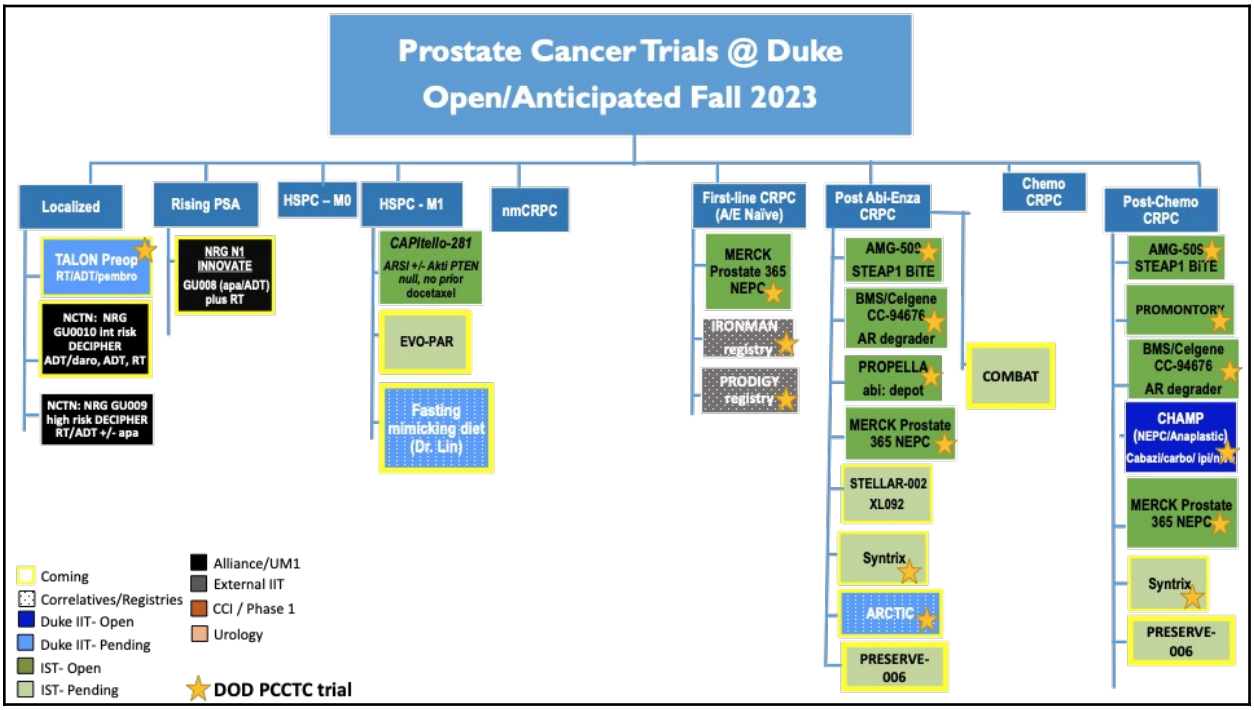
Have you guys had much in the way of lectures on neuroendocrine prostate cancer?

Brad Power  25:50
One of our patients, Amit Gattani, has neuroendocrine.

Andy Armstrong  25:54
He has emailed me many times and we have discussed his care and options.

Brad Power  25:57
He's kept us thinking about that, and treatment options for it.

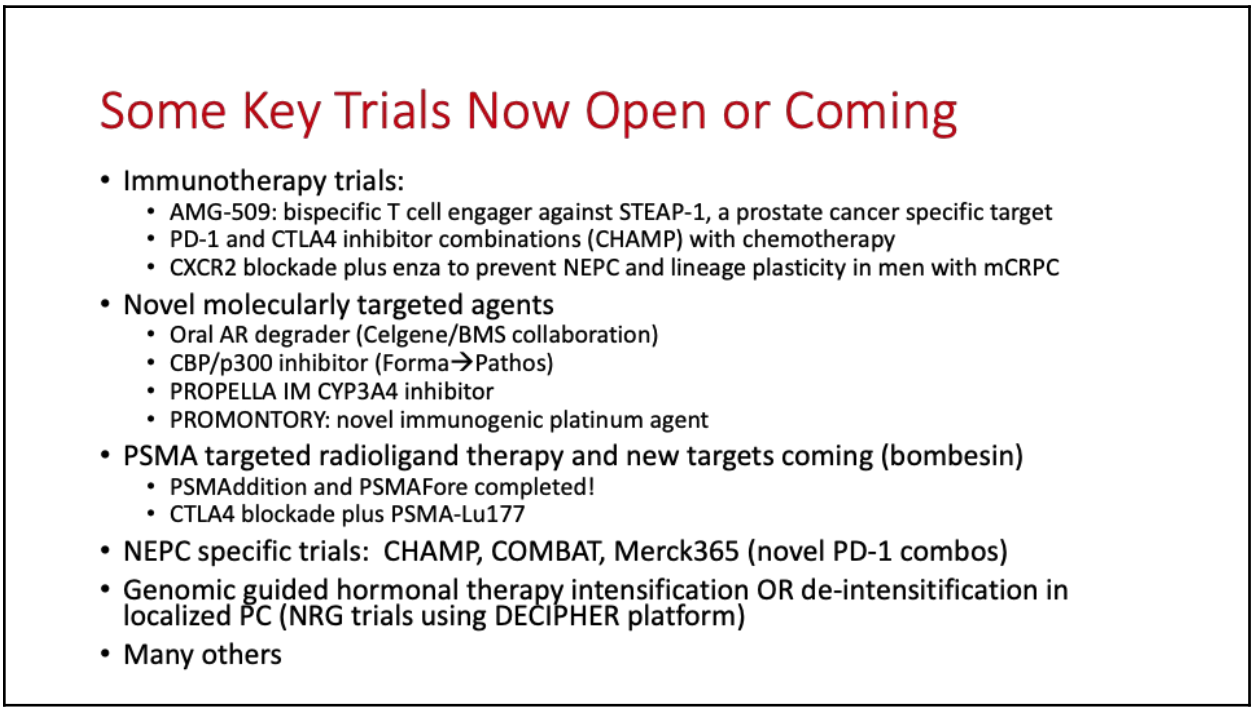
Andy Armstrong  26:02
This is an area that needs a lot of help and advocacy from you, and from the whole field, for funding for new drugs. You can see that the standard of care has been platinum-based chemotherapy. But the response rate, while it seems pretty high, it doesn't last very long. Patients tend to blow through chemotherapy within a year. There have been many attempts to try other therapies. We published on immunotherapy. Again, by itself immunotherapy – like with a PD-1 blocker – is not very effective. We only had one patient who had a complete response, but most patients tend not to respond.



**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**

Here's some of the research we're doing at our institution. We are part of several consortia at Duke. We have the Alliance cooperative group, which is a national cooperative group. We're part of the Department of Defense Prostate Cancer Consortium, which are all the studies that are marked with a star.

We try to organize our studies so that we have something for everybody, whether it's localized prostate cancer, PSA recurrence, or metastatic hormone-sensitive. We're missing studies in non-metastatic castrate-resistant prostate cancer right now because it's a very crowded space with a lot of recently approved drugs. We have trials for the first line, second line, and beyond, that are attacking different ways that prostate cancer adapts and develops resistance.




I put a few of these in context. Some of these are focused on immunotherapies. AMG-509 is a bispecific T-cell engager against a prostate cancer cell surface membrane called STEAP-1. It's a protein that's commonly expressed in prostate cancer. It's AR regulated. If you attend ESMO next month or hear the press releases, this data will be presented for the first time.

We're also looking at combinations. One checkpoint inhibitor does not help most patients with prostate cancer. So we're doing this trial called the CHAMP study. This is for patients with neuroendocrine prostate cancer, or aggressive variant prostate cancer where we're giving both chemotherapy and two checkpoint inhibitors. That's why we call it the CHAMP study. It's really a kitchen sink approach, which these patients really need because one therapy generally doesn't work very well.

We published in Science Translational Medicine a couple years ago that one of the ways to get neuroendocrine prostate cancer is that cells hijack chemokine receptors, CXCR2, and that

promotes that lineage plasticity. Fortunately there are drugs that block that. We're about to start next month, a trial where we use a small molecule inhibitor of CXCR2, which is a chemokine receptor. That also works to augment immunity, but also blocks cell signaling within the cancer. We do that in combination with enzalutamide to see if we can delay or prevent the emergence of that resistance.

We also have a number of other really interesting trials, a new AR degrader that's being done in conjunction with Celgene and BMS. You'll have to wait to see the adult data in January of 2024 for that one. There's also some co-activators that work with the AR to turn the AR androgen receptor on, and we have drugs that can block that. We're testing those in phase one. A number of other novel agents that are either immunogenic or DNA-damaging.

A lot is happening on these PSMA therapies. You've heard about the VISION study from Dr. Sartor. But next month the PSMAFore study, which is pre-chemotherapy, will be presented in a year or two the PSMAddition study, which is even before hormone resistance takes hold the value of Pluvicto.

We're studying new targets. We have a new multicenter study targeting something other than PSMA with radioligands, called bombesin. We have some neuroendocrine prostate cancer-specific studies testing that.

David Plunkett 30:40
Given the different PARP inhibitors, what recommends one over another?

Andy Armstrong 30:58
They're not all interchangeable. As I showed you, talazoparib has more anemia. There are also drug-drug interactions. For example, enzalutamide will induce the metabolism of certain PARP inhibitors, but not with olaparib. The olaparib-abiraterone combo is very safe. You can give both drugs at full dose. But if you were to just swap out abiraterone for enzalutamide, then the enzalutamide would induce the metabolism of olaparib, making it much less effective. So that would not be recommended by anybody. It shouldn't be. Of course, some people can recommend things without any data or evidence.

Talazoparib has to be dose-reduced when you give it with Enzalutamide because of drug-drug interactions. So instead of the monotherapy dose of a milligram, you have to give a half a milligram, otherwise it would not be safe.

Niraparib is a different PARP inhibitor. It also got FDA approved a couple of weeks ago, but it seems to be less effective, and more toxic, so it wouldn't be something I'd recommend to patients.

David Plunkett 32:10
Niraparib was the one that I saw a mention of this past weekend. So that's good information.

## “Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]

Brad Power 32:21
A recurring theme that I saw – with many of the trials and with the last one as well – is therapy combinations, including drug, radiation, or immunotherapy combinations. Early in our journey as a community we worked with CureMatch. They recommend drug combinations. A recurring problem was that they would see that a patient has certain biomarkers, and therefore looks like they would respond to a combination. They could have three monotherapies, but the pregnant question always was, “Should they combine those and maybe worry about toxicity, reduce the dosages, and thereby maybe have a more sustained response?” But then there was always the challenge that there were no randomized clinical trials that had been done on those specific combinations. There was no evidence. You're now off label, and doctors don't want to prescribe it. Is there a trend to exploring more combinations?

Andy Armstrong 33:32
The standard of care until the last couple years has been sequential single agent therapy. When you do that, you see very incremental improvements in survival, but it doesn't work as well as hitting the cancer hard up front with combos. In men who start their journey with metastatic hormone-sensitive prostate cancer, it's no longer standard of care to give single therapies.

The AR inhibitors, like I showed you, even docetaxel, may extend life. We're looking at quadruplet therapy now with PSMA lutetium, in that setting, or PARP inhibitors, have moved now even earlier too, as part of a research study. Those trials are ongoing looking at new triplet combinations.

The idea is that cancer is like a species in your body. It's got lots of different subpopulations and heterogeneity, much like tuberculosis or lymphoma, where multi-drug regimens have actually cured people. When we had HIV infection, using AZT alone did not do much, but once you had highly active antiretroviral therapy with four drugs, you had patients like Magic Johnson, living 20 plus years with excellent disease control.

The idea is to hit many non-redundant mechanisms in the cancer, but do it safely. Just because somebody in the lab found that a pathway is active, doesn't mean you can just safely throw that at the patient. There's a lot of normal tissue cells in your body that have these targets also. That's why it's very important to pay attention to safety and how you dose it, if there are drug interactions, what the normal organ toxicity and tolerability for patients is. It is important to study combinations and most of the field is moving towards these sorts of combinations, particularly immune therapies, where you're seeing huge successes like in non-small-cell lung cancer, small-cell lung cancer, kidney cancer, and bladder cancer, which I also treat. These are huge combination successes.

Immunotherapy is one of those things that has mostly failed men with prostate cancer. That is a reason that we're focused a lot on developing ways to draw those T-cells into the tumor, to have the cancer be recognized by your immune system, to overcome those shields, the checkpoints, whether they're myeloid checkpoints or T-cell checkpoints, those combinations, in my opinion, will be the most successful going forward.

**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**

Assays that predict combinations are not yet valid in the clinic. That might work in a mouse model or a cell line. Humans are not mice, and humans are not cell lines, and you have Oregon's and you have important drug interactions to consider. If you have that finding, that should be validated in clinical trials, through phase one, careful dose finding and drug development. But those cocktails, if they're found to be common, should spur more research, not just using those things off label.

Allen Morris 37:16
Because there are all these new advances in the last five years and with combinations, the permutations of how a patient gets into the metastatic castrate-resistant state is incredibly variable.

How do patients determine their prognosis?

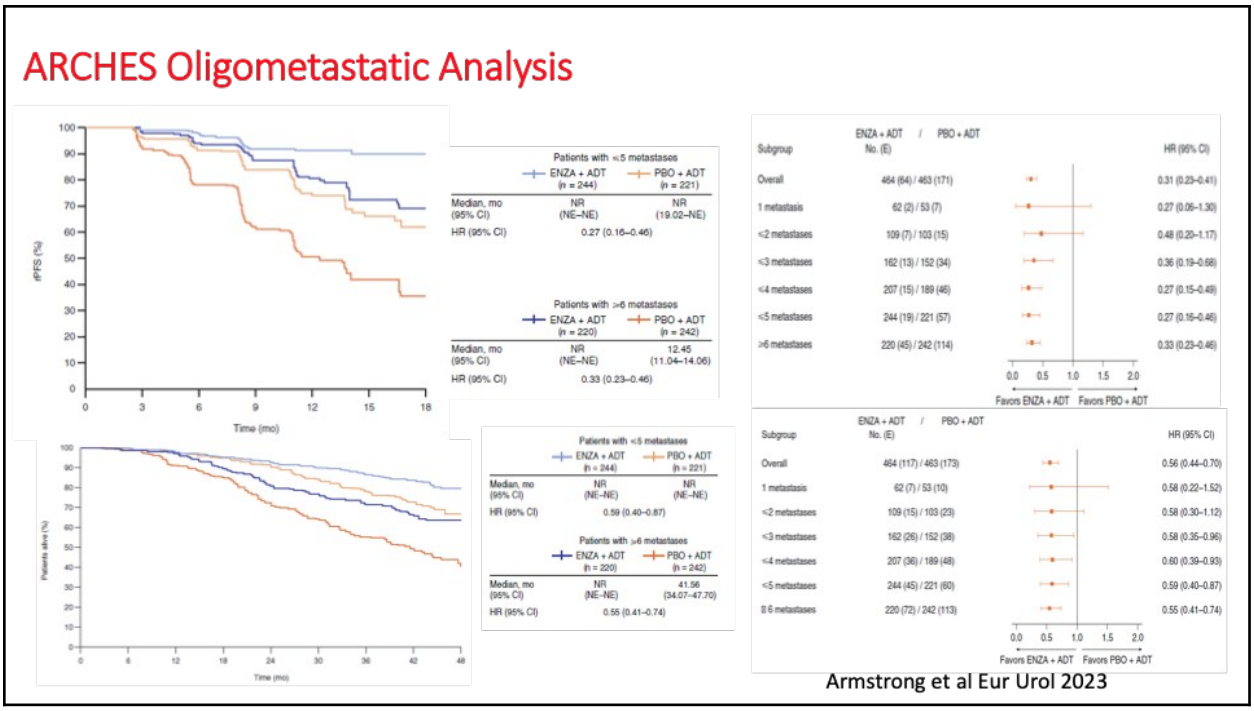
In earlier stages, like localized disease, there are MSK (Memorial Sloan Kettering) nomograms (mathematical models), where you can, for example, post prostatectomy, estimate your likelihood of BCR (biochemical recurrence).

Is their development of nomograms for all the many permutations of longitudinal treatment that happen in later stages, such as the castrate resistant state?

Andy Armstrong 38:29
I've published at least five nomograms over my career. All of these are in hormone-resistant patient populations, based on thousands of patients. If you just look up my publications in PubMed, you'll find them, but by the time you publish these nomograms, often the field has moved on. For example, just this year, we validated a nomogram that was developed by a colleague of mine here at Duke, Susan Halabi. She's probably got the most famous nomogram. We call it “the Halabi model”. She validated it with 8000 patients. That's an amazingly validated model for men with castrate-resistant prostate cancer who are getting treated with an AR inhibitor or chemotherapy. That was published in JCO 2023. However, that model, even though it was just published this year, as I've just shown you, and all the slides, we are now using these AR inhibitors earlier in the hormone-sensitive setting. So now we need models that are valid in the metastatic hormone-sensitive setting when a patient is treated with appropriate intensification.

For example, as the principal investigator of the ARCHES study – that's a project we're working on right now – our purpose is to develop and validate a model along with other docs like Chris Sweeney, who's the PI (principal investigator) of ENZAMET, or Kim Chi or others for TITAN, combining datasets that allow a lot of power and sample size. We know already that prognosis is related to disease volume, whether patients started with stage four disease or relapsed. The amount of prostate cancer you have determines prognosis.

**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**




At the beginning of my talk, I showed you some survival curves in the hormone-sensitive setting where survival widely differs based on the number of metastases that you have. This is overall survival. All men got conventional intensified therapy with ADT and Enzalutamide. The men in the orange group had a large number of metastases, and the men in the blue group had a small number of metastases. With treatment intensification, they live longer. The blue curves are Enza. You live longer with Enza. The orange curves are ADT alone. Then they're color coded by how many metastases you have – less than five or more than five. Disease volume matters, but that's just one variable. There are other features like pain, hemoglobin, functional status, alkaline phosphatase. Your genomics matter.

We have an NIH grant right now where we're putting together what's called a “clinical genetic model”, where we fuse all the clinical features. There are about 10 that are important. When we fuse those with the tumor genetics, P53, RB, AR, BRCA2. We make a model that combines that and thousands of patients that can then predict the future. It's always an area of active development, an area that I work on very closely with statisticians and molecular biologists to always make the models as pertinent and contemporary as possible. But the datasets have to be mature. In order to be a good prognosticator, you need years of follow up. A lot of these trials just got FDA approved in the past two or three years. Patients are still alive, fortunately, and in follow up. You really need more mature data to develop something that you can actually speak to a patient about in terms of their prognosis.

Brad Power  42:33
What is a “nomogram”?

Andy Armstrong  42:39

## “Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]

It's a mathematical model. You can put it in an app. We have little app models in prostate cancer in an online tool. Statistically, it's just a multivariable model. These variables are your clinical terms, like, “Where is your cancer spread?” “Are you having pain?” “Are you anemic?” “What's your functional status?” You put those little things into your variable, and the nomogram, or model spits out: “What's your five year survival?” They're not always correct. We give you the most accurate up-to-date information that we have. But there's some error to it. We always phrase this very gently when we're talking to patients. “This is what the model says. Obviously, our treatments have gotten a lot better. Your survival could be a lot better. Your survival could be updated and even better if you respond to the next therapy that we're giving you. These are just estimates.” They're intended to be more doctor-patient communication tools. If you knew that you had a six-month survival, you might do things differently than if you had an expectation of living five years or more.

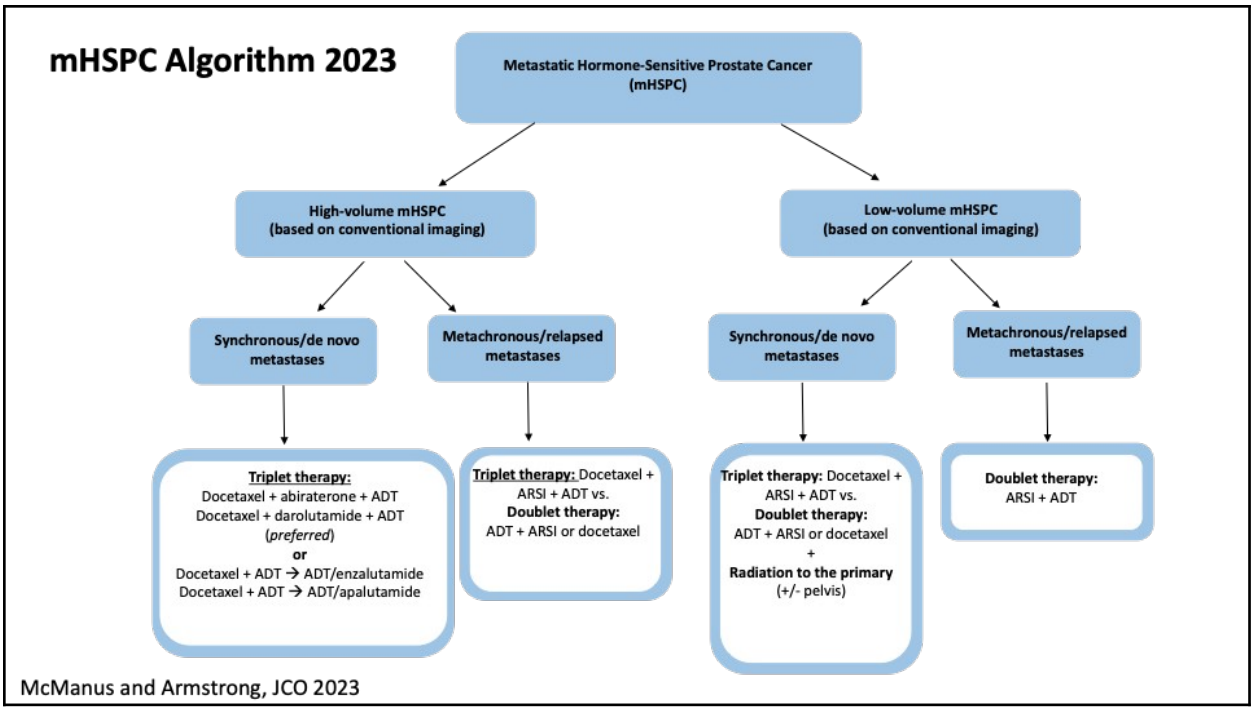
Chad Magnussen 43:57
Could you please expand on the Bombesin Radiotherapy?

Andy Armstrong 44:06
I just touched on that briefly. Bombesin is a great name. It is a cell surface receptor that is on neuroendocrine prostate cancer. Neuroendocrine prostate cancer is a very different beast than typical prostate cancer. It lacks PSMA. In two thirds of cases there's no PSMA, so you can't use Pluvicto. You can't use PSMA targeting at all because it's not there. Neuroendocrine cells up regulate other cell surface receptors – maybe a talk for a different day – DLL3 and CCAM and CXCR2 and bombesin are just four examples of cell surface receptors that you can leverage to both image neuroendocrine prostate cancer with positrons or target neuroendocrine prostate cancer with radioligands. A trial that we're about to open targets bombesin. We will see if that works. It's the first time it's ever been done.

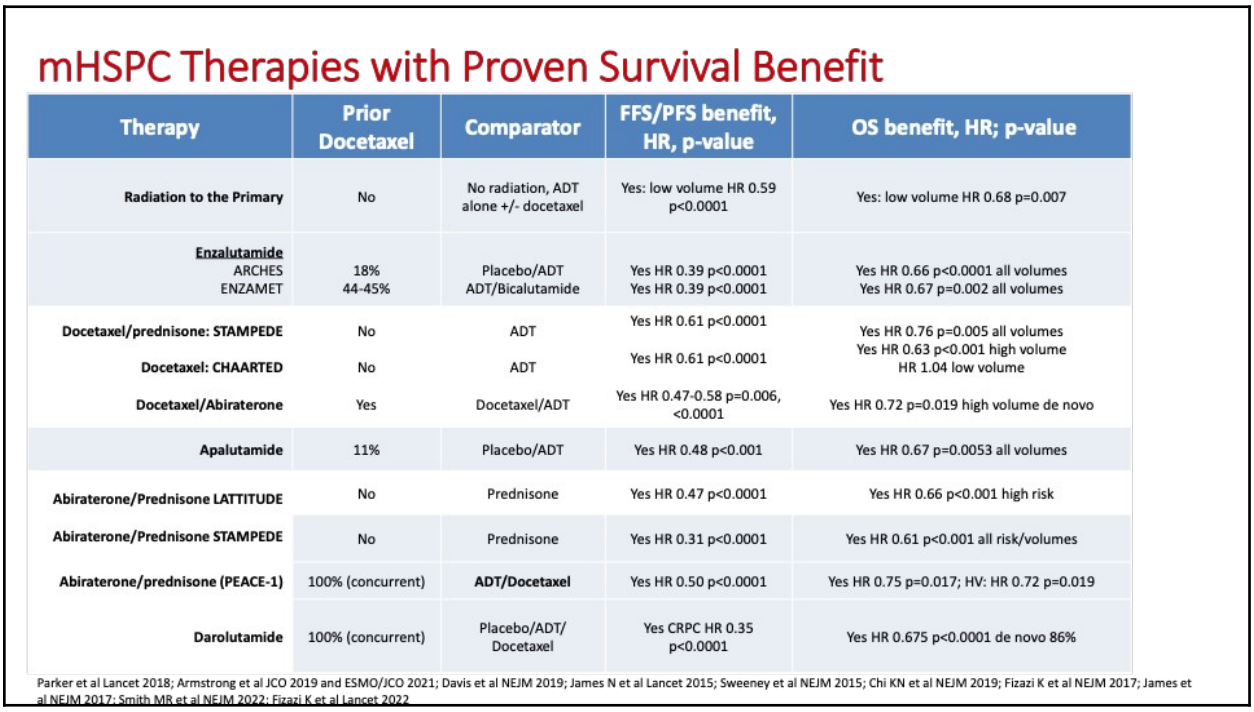
John Lancaster 45:10
I see Enzalutamide mentioned all over the place with ADT (androgen deprivation therapy) in your slides. What about Darolutamide? How does it compare to Enzalutamide?

Andy Armstrong 45:19
Darolutamide is a great drug. It did show up in my slides when I was talking about triplet therapy.

**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**




Darolutamide is here as part of a recommended triplet therapy.



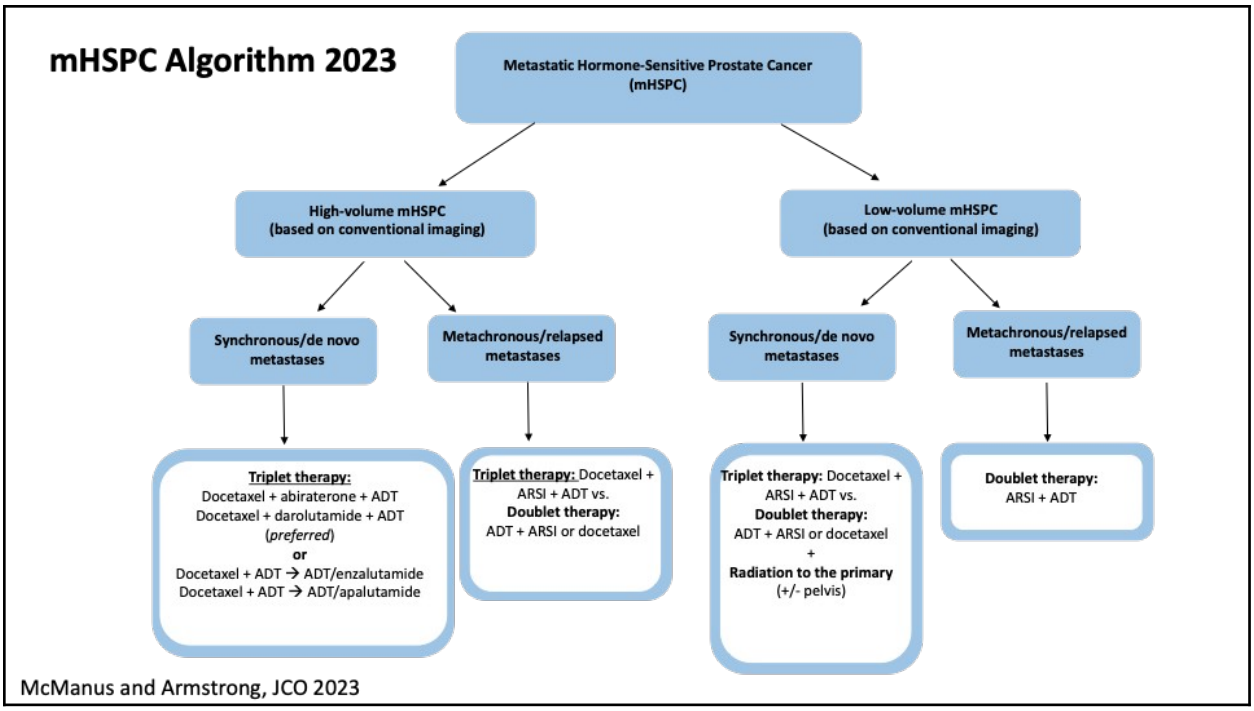
## mHSPC Therapies with Proven Survival Benefit

| Therapy | Prior Docetaxel | Comparator | FFS/PFS benefit, HR, p-value | OS benefit, HR; p-value |
|---|---|---|---|---|
| **Radiation to the Primary** | No | No radiation, ADT alone +/- docetaxel | Yes: low volume HR 0.59 p<0.0001 | Yes: low volume HR 0.68 p=0.007 |
| **Enzalutamide** ARCHES ENZAMET | 18% 44-45% | Placebo/ADT ADT/Bicalutamide | Yes HR 0.39 p<0.0001 Yes HR 0.39 p<0.0001 | Yes HR 0.66 p<0.0001 all volumes Yes HR 0.67 p=0.002 all volumes |
| **Docetaxel/prednisone: STAMPEDE** | No | ADT | Yes HR 0.61 p<0.0001 | Yes HR 0.76 p=0.005 all volumes Yes HR 0.63 p<0.001 high volume HR 1.04 low volume |
| **Docetaxel: CHAARTED** | No | ADT | Yes HR 0.61 p<0.0001 | |
| **Docetaxel/Abiraterone** | Yes | Docetaxel/ADT | Yes HR 0.47-0.58 p=0.006, <0.0001 | Yes HR 0.72 p=0.019 high volume de novo |
| **Apalutamide** | 11% | Placebo/ADT | Yes HR 0.48 p<0.001 | Yes HR 0.67 p=0.0053 all volumes |
| **Abiraterone/Prednisone LATTITUDE** | No | Prednisone | Yes HR 0.47 p<0.0001 | Yes HR 0.66 p<0.001 high risk |
| **Abiraterone/Prednisone STAMPEDE** | No | Prednisone | Yes HR 0.31 p<0.0001 | Yes HR 0.61 p<0.001 all risk/volumes |
| **Abiraterone/prednisone (PEACE-1)** | 100% (concurrent) | **ADT/Docetaxel** | Yes HR 0.50 p<0.0001 | Yes HR 0.75 p=0.017; HV: HR 0.72 p=0.019 |
| **Darolutamide** | 100% (concurrent) | Placebo/ADT/ Docetaxel | Yes CRPC HR 0.35 p<0.0001 | Yes HR 0.675 p<0.0001 de novo 86% |

Parker et al Lancet 2018; Armstrong et al JCO 2019 and ESMO/JCO 2021; Davis et al NEJM 2019; James N et al Lancet 2015; Sweeney et al NEJM 2015; Chi KN et al NEJM 2019; Fizazi K et al NEJM 2017; James et al NEJM 2017; Smith MR et al NEJM 2022; Fizazi K et al Lancet 2022

Because we have this trial called the ARASENS trial, where darolutamide, when studied in combination with both ADT and docetaxel, delayed progression and improved survival. Darolutamide is another AR inhibitor that is active.

**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**




It has not been studied as a doublet therapy. It only has data in conjunction with docetaxel. That's why it doesn't show up as an option in any of these other boxes. Enza (enzalutamide), Abi (abiraterone), and Apa (apalutamide) have the data to support doublet therapy. Darolutamide doesn't yet have it, not saying it won't, it probably will, if you just wait for the ARANOTE trial, which is an ongoing study being done globally. I would expect darolutamide to have very similar data. I think of it as an equally active agent. Largely these AR inhibitors are very similar to each other. They do have differences in side effects, but their efficacy potencies are very similar. Darolutamide has some advantages of not going into your brain, causing cognitive problems, which can affect some men with the other AR inhibitors like Enzalutamide, about 3% of the time. Darolutamide has less fatigue and fractures, less of a fall risk. It is a good therapy. It's approved in non-metastatic CRPC. It's approved in hormone-sensitive metastatic disease. It's in many, many trials right now. You'll see data roll out over the coming years where it will become probably a very much more popular therapy.

It is a good choice. I'm glad you asked about it. I prescribe it all the time.

John Lancaster 47:20
I'm interested because I've just started on darolutamide, on top of the past six-and-a-half years on Lupron, for which I received a course of docetaxel right at the beginning of the Leuprolide treatment. My oncologist at Dana Farber said that that combination, in other words, docetaxel briefly at the beginning of the Lupron therapy, could have significant benefits.

I had a reaction to the docetaxel, so they stopped it fairly quickly.

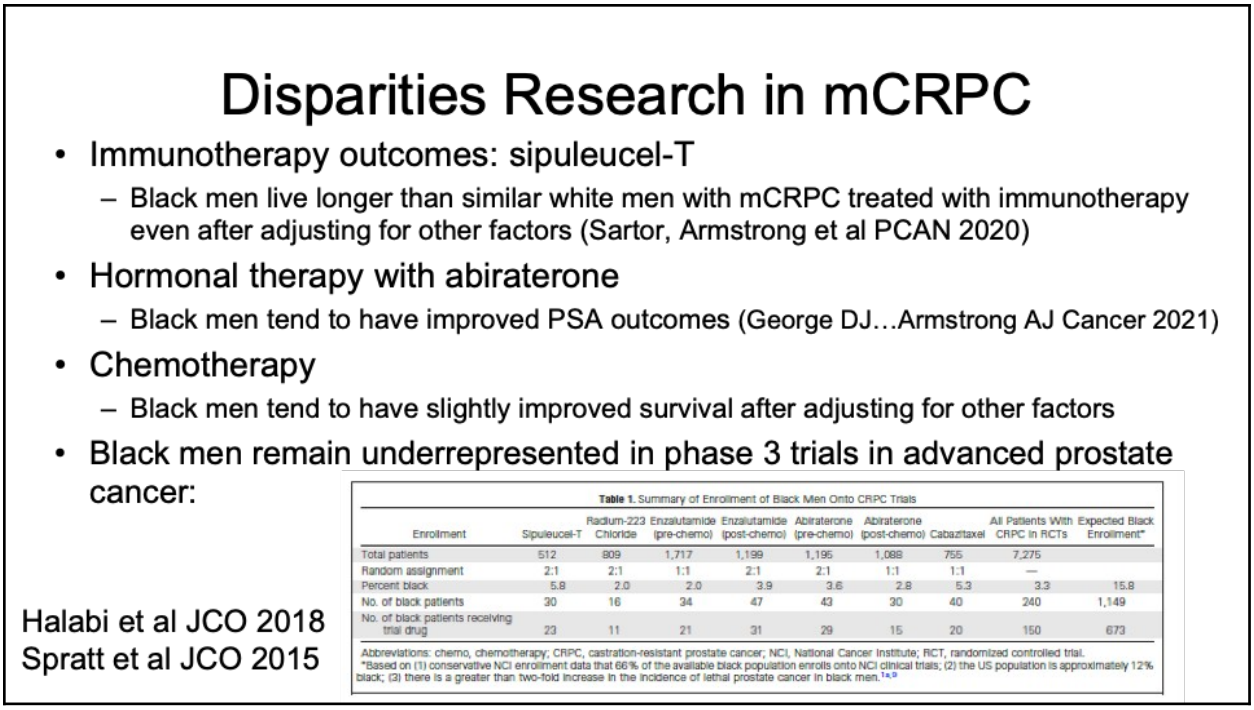
Andy Armstrong 48:10

**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**

Darolutamide is very well tolerated. Not everybody tolerates it, but of the AR inhibitors, it is probably the best tolerated. So that may be one of the reasons they picked it.

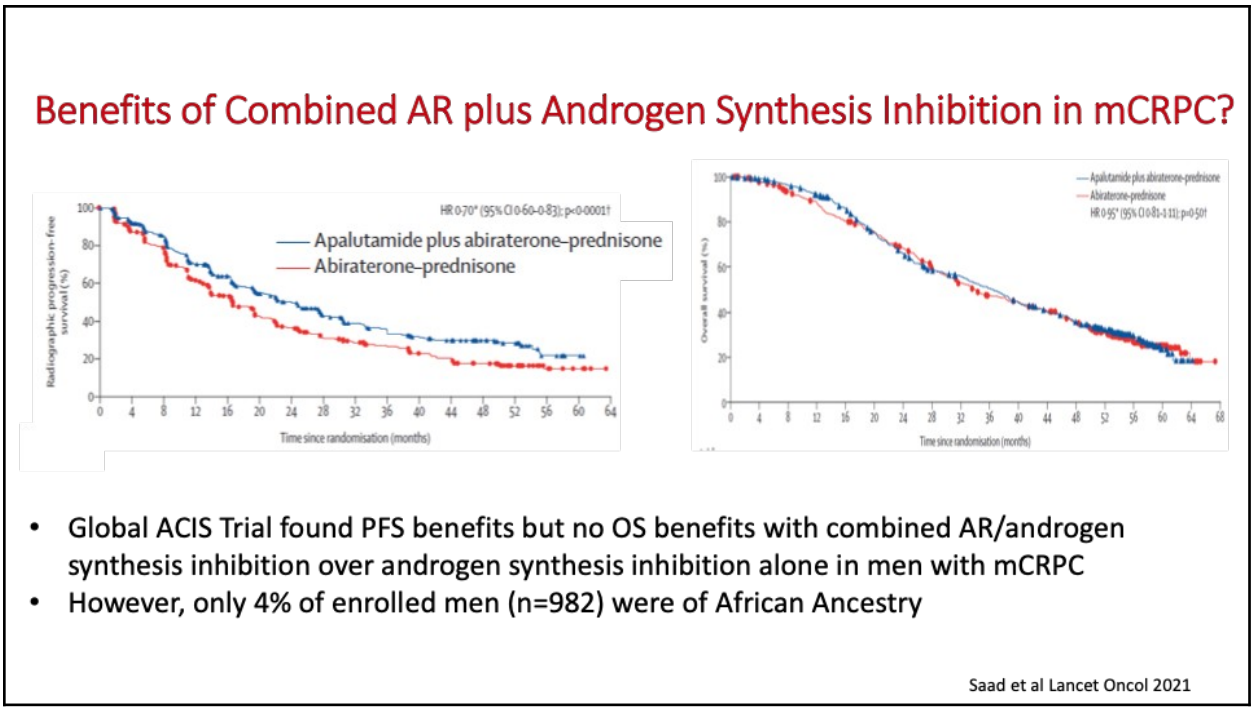
John Lancaster 48:21
So far, so good.

Andy Armstrong 48:31
I skipped over one little section that I think is important, and it's the disparity issue. I don't know in your group what the diversity of the group is like, but if you look at it nationally, black men are dying at about two-and-a-half times the rate of white men. I just wanted to show one little slide here of the data we're doing here to overcome that disparity.

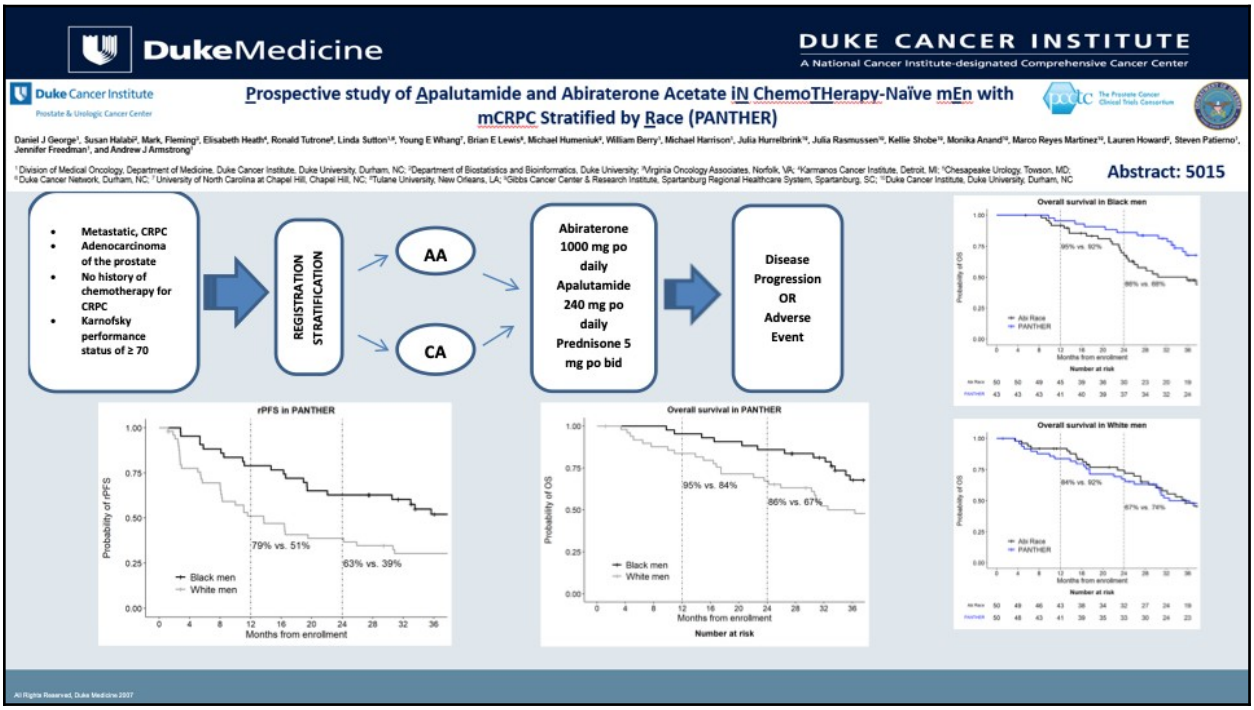



We know that black men are dying at a higher rate. But when black men are included in clinical trials, they're often doing equal to, if not better than, white men, which is pretty cool to think about. We've published this with sipuleucel-T (Provenge), an immunotherapy that black men, when matched to white men, have a better outcome with immunotherapy. We've published with Abiraterone that there's better PSA outcomes in men of African ancestry. Susan Halabi has published that with docetaxel, black men tend to do a little bit better, but yet, they still are majorly underrepresented in our clinical trials. The percent of our trials that are black men is somewhere around 3%. It's awful.

**“Guiding Personalized Treatment for Advanced Prostate Cancer (Round Two)” (Andrew Armstrong) [#70]**




This is a negative study you'll probably never read about because it did not get FDA approved. This Is a trial called “ACIS”, where two AR (androgen receptor) inhibitors were given as compared to one AR inhibitor, so abi (abiraterone), standard of care, or apa (apalutamide) plus abi. This trial did delay progression, but did not improve survival. That's probably why you haven't heard about this study. This was largely a white study. This patient population was global, and 96% were not of African ancestry.



We did a study at Duke, and we just presented this data at ASCO. We gave this regimen, apa (apalutamide) and abi (abiraterone), but now we were intentionally inclusive of race. We had a European- or Caucasian-American group 50/50 with African Americans. We were amazed to see at the end of this study that black men did amazingly well with this double AR combo. Not only did they have better outcomes with delayed progression, but better survival. The chance of making it to two years was 86% in black men and 67% for white men. This suggests that while we're typically taught that race is a cultural, non-biological construct, which is true, ancestry can have biological effects. African ancestry may have an association with sensitivity to AR blockade, and perhaps two AR inhibitors in men of African ancestry might be advantageous. We're looking at this data and thinking maybe we should advance this further in an appropriately inclusive trial.

That was just a plug for being more inclusive in our trials. You can certainly advocate for that as a patient organization.

Brad Power 51:57
To be honest, it's one of our weaknesses. We've made efforts to include more African-American men in our community, but they're very under-represented at present.

Andy Armstrong 52:09
There's a great group called PHEN (Prostate Health Education Network), that I'm sure would love to work with you.

Brad Power 52:14
Thank you. If you could make a connection, we would appreciate it.

David Plunkett 52:29
This all just reinforces my opinion that it pays off to hit it hard and hit it early.

Andy Armstrong 52:35
Exactly. Or cure it right up front, if that's possible. If a cure is not possible, then there's so many mutations in the cancer that it's not surprising that a multi-drug regimen is the way to go.

Brad Power 52:52
Are you acquainted with Bob Gatenby at Moffitt?

Andy Armstrong 52:54
Yes. He is the proponent of the adaptive intermittent approach.

Brad Power 52:59
Correct. He is viewing it from an evolutionary biology perspective, and therefore “hitting it hard and early” is also part of the strategy because it's a heterogeneous population. For us, it was quite enlightening to hear his strategic approach, which seems, as we've discussed today, more

combinations, more adaptive, more personalized. All these things that we don't typically hear, which is more like, “Try a monotherapy until it fails. Go on to your next monotherapy, and try it until it fails.”

Andy Armstrong 53:36
The difference between what Bob is doing is he's got a small number of patients where he's done this, and there's not really a control group, and it hasn't taken off in the real world because it doesn't have that medical evidence you need. It's not to say that it's not true, but it just hasn't been developed further so that we can recommend that to patients. That's what has to happen.