“The Current and Future Landscape of Metastatic Castrate Resistant Prostate Cancer” (Oliver Sartor) [#62]

Jonathan Starr and Brad Power
June 19, 2023

Meeting Summary

Prostate cancer is not curable for most patients once it becomes metastatic. Advanced prostate cancer patients find themselves trying treatments that work for a while until they fail, then moving on to another therapy. They are continuously worrying about the effects of their cancer and treatments on their quality of life, especially bone metastases and the side effects of hormone deprivation therapy, which leads to bone density issues and muscle loss, among others. Prostate cancer, like all cancers, is unique to each patient, with some patients receiving molecularly targeted therapy, and some patients responding to immunotherapy. New drugs, such as those which use a radiopharmaceutical are now coming to market. Patients might also consider experimental combination therapies, for example combining a radiopharmaceutical with a PARP inhibitor or immunotherapy. Alpha and beta particles can also be combined experimentally, as well as alpha or beta particles with radiation sensitizers, modulating the way the drugs alter DNA. The importance of lifestyle and prevention of complications in advanced prostate cancer is another concern.

A. Oliver Sartor, MD, recently moved to Mayo Clinic, is uniquely qualified to review this complicated landscape and discuss research on immunotherapies, radiopharmaceuticals, and combinations in prostate cancer. His research has mainly focused on translational science and clinical research trials of advanced prostate cancer since 1990, and he is recognized as an expert in that field through his contributions to the practice and the publishing of over 500 peer-reviewed articles and numerous book chapters and reviews. He has been PI or co-PI on pivotal trails that have helped to change the landscape of advanced disease including radium-223, cabazitaxel, and Pluvicto (PSMA-617 Lu-177).

Bullets from Russ Hollyer:

· PSMA targeted alpha therapy delivers highly potent, selective, and local alpha radiation to cancer cells and the tumor microenvironment. The side effects are being worked on.
· BAT provides an interesting way to control PCa. Dr. Sartor has used it approximately 90 times.
· It might not be necessary to swing testosterone high and then low. Constant high testosterone is an intriguing possibility.
· Prior therapies, future order, patient preference, and side effects should be considered prior to choosing a therapy.
· Darolutamide should be preferrable to Xtandi based on side effects.

From Ben Nathanson:

He was frank about how slim the survival benefits have been in trials and how few men can currently benefit from precision medicine, issues that we as patients are painfully aware of but many doctors seem to evade. I appreciated the mindshare he's giving to inadequately

understood areas like chromosomal disorder and noncoding DNA. Even his quick description of when PARPi shows benefit, including cases like DNA methylation that don't show up in genomic studies, was invaluable.

From Arthur Bruno:

1. I was surprised by his suggestion of continuous Hi T.
2. I noted that his strongest endorsement for the next major advancement in PCa care was the alpha particle radioligand therapy. Makes sense to me.

From Jeff Dwyer:

Sartor presented as such an open and giving man and he impressed me with his candor. He was quick to point out the reality of the Pharma industry control on the development of new drug protocols along with the expense of RCTs and explained that he doesn’t spend a lot of his thinking time on treatment programs for his patients that will not be reimbursed by insurers. I had considered a trip to Tulane - dipping into NO can usually be a lot of fun - to consult personally with him. But, the pandemic nicked that. He offered his email address and appears open to remote consultations. If this turns out to be possible, we’d all be very fortunate.

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Meeting Notes

The information and opinions expressed on this website or platform, or during discussions and presentations (both verbal and written) are not intended as health care recommendations or medical advice by Prostate Cancer Lab, its principals, presenters, participants, or representatives for any medical treatment, product, or course of action. You should always consult a doctor about your specific situation before pursuing any health care program, treatment, product or other course of action that might affect your health.

Discussion Outline

1. Introduction to Dr. Oliver Sartor.
2. Prevention and treatment of adenocarcinoma. (5:34)
3. Tissue biopsy vs. circulating tumor DNA tests. (10:44)
4. What is the status of the sabizabulin treatment for prostate cancer? (18:45)
5. The RGCC Greek test. (28:52)
6. High T vs. BAT (34:11)
7. How do you look at PSA and disease-specific survival? (39:57)
8. How does proteomics fit into precision medicine? (45:58)
9. What are your questions about prostate cancer? (51:19)
10. Novartis and the Lutetium trial. (59:18)
11. The durability of testosterone. (1:05:11)
12. Next steps for patients with high-risk prostate cancer. (1:13:07)
13. How do you know when to start treatment? (1:17:19)
14. Radium vs. Taxane for treatment of prostate cancer. (1:21:55)
15. A quick table of RNA expression in prostate cancer. (1:29:25)
16. High mutational burden and mismatch repair deficiencies. (1:34:40)
17. Pelvic lymph nodes and genomics. (1:40:19)
18. Dr. Sartor’s recommendation for patients with mismatch repair deficient and genomic. (1:47:57)
19. What is the tolerability of a PARP inhibitor? (1:52:54)
20. PSMA PET vs. Choline scans. (1:57:43)

SUMMARY KEYWORDS

patients, trial, psa, good, talk, positive, bit, biomarkers, docetaxel, mutation, radiation, work, high, pretty, data, hormones, tumor, people, therapy, hormonal therapy

SPEAKERS

Oliver Sartor (69%), Brad Power (5%), Allen Morris (5%), Jonathan Starr (4%), Rick Stanton (4%), Eric Hall (3%), Russ Hollyer (3%), Noel Resch (3%), Robert Gurmankin (1%), Rick Davis (1%), Brian McCloskey (1%)

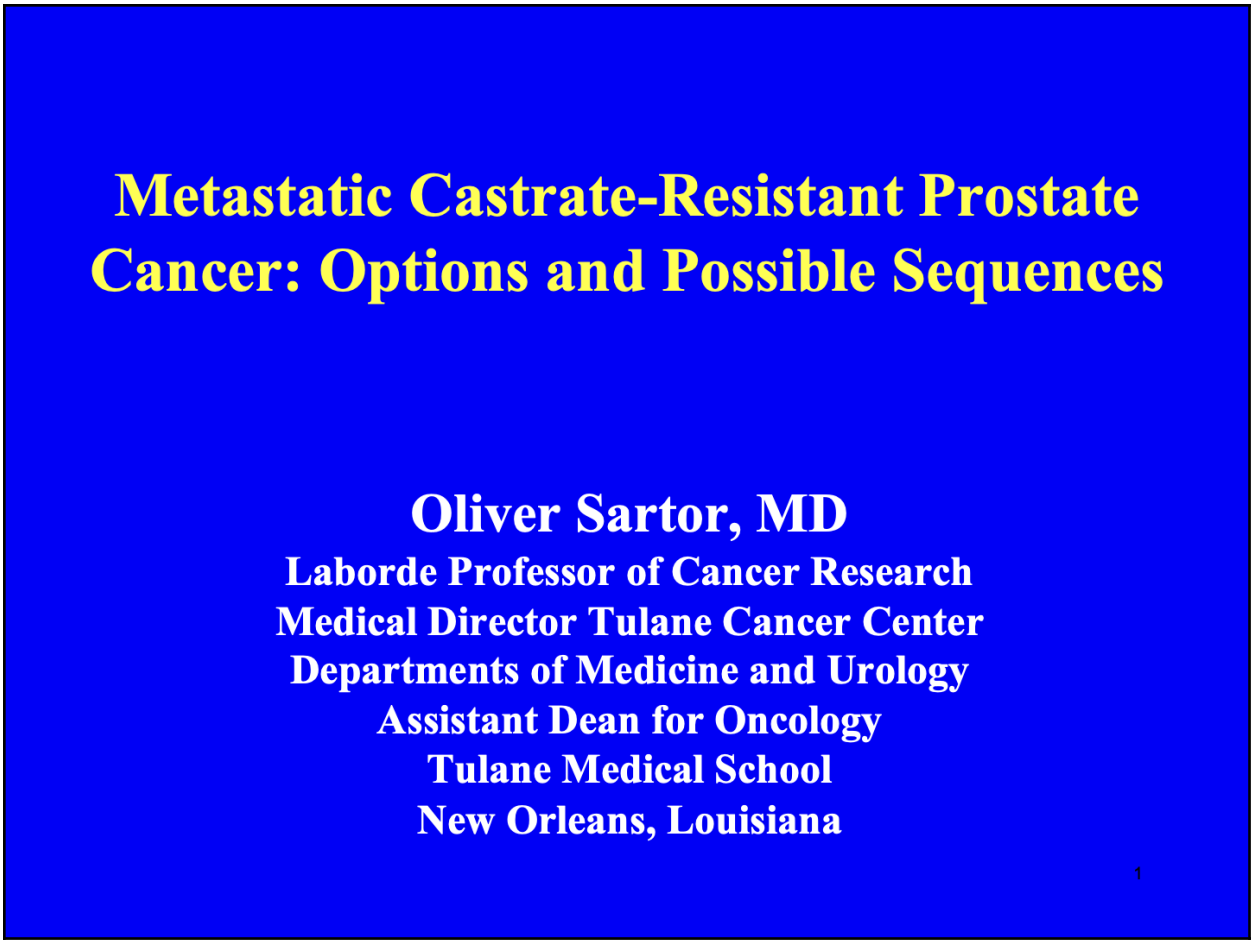
Meeting Transcript (lightly edited)

Brad Power 0:02

“The Current and Future Landscape of Metastatic Castrate Resistant Prostate Cancer” (Oliver Sartor) [#62]

We're very honored to have Dr. Oliver Sartor with us today.

Dr. Sartor, you'll remember that part of our connection is through Jeff Hoffman, who was a classmate of yours at Tulane back in medical school, and Jeff is my cousin. Jeff pointed me to Dr. Sartor, and Dr. Sartor has been very helpful in providing advice to a number of the patients we've had, especially, Bryce Olson, on some of the choices that he faced. A number of patients in our community have requested to have a conversation with Dr. Sartor. He's moving from Tulane to Mayo Clinic. Does that mean a physical move for you?



Oliver Sartor 2:03
Yes. I realize as I pull up the slides, that it shows me still at Tulane. I'm at Mayo now. I'm happy to give you my email and stuff like that. Let me let me put that in the chat. But yes, I'm physically at Mayo.

Brad Power 2:21
So you're beaming to us now from Minnesota?

Oliver Sartor 2:24
Beaming to you from Minnesota. I'm in Rochester, Minnesota, right at this particular moment.

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Brad Power 2:30
Dr. Sartori is going to run through a few slides really quickly, five or 10 minutes, and then we will mostly have Q&A. We had some email conversations about questions that patients had in advance. There's a request that you focus on castrate resistant prostate cancer patients who are beyond hormone sensitive prostate cancer so that we get kind of skinnier branches of people that are more advanced, as much as you can.

Oliver Sartor 3:09
I’m at Mayo Clinic right now. I’ve been involved with advanced prostate cancer for a long time. And I think first of all, you have to have some feeling for where the field is before you can understand the rest.

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TRIAL	FRONT LINE mCRPC	HR	Survival (months)
TAX 327	Docetaxel/prednisone vs mitoxantrone/prednisone	0.79	19.2 vs 16.3* (2.9 months)
IMPACT	Sipuleucel-T vs Control	0.78	25.8 vs 21.7 (4.1 months
COU-AA-302	Abiraterone/prednisone vs Placebo/prednisone	0.79	35.3 vs. 31.1* (4.2 months)
PREVAIL	Enzalutamide vs Placebo	0.71	35.3 vs. 31.3* (4.0 months)
	POST-DOCETAXEL mCRPC		
TROPIC	Cabazitaxel/prednisone vs mitoxantrone/prednisone	0.70	15.1 vs 12.7 (2.4 months)
COU-AA- 301	Abiraterone/prednisone vs Placebo/prednisone	0.74	15.8 vs 11.2* (4.6 months)
AFFIRM	Enzalutamide vs Placebo	0.63	18.4 vs 13.6 (4.8 months)
	FRONT LINE and POST-DOCETAXEL mCRPC		
ALSYMPCA	Standard of care +/- radium-223	0.70	14.9 vs 11.3* (3.6 months)
	POST-ABI OR -ENZA OR POST-ABI OR -ENZA AND -DOCETAXEL (HRR SUBSET)		
PROfound	Olaparib vs abi/enza second line	0.69	19.1 vs 14.7** (4.4 months)
	Third Line (POST-ABI or -ENZA and POST-DOCETAXEL		
CARD	Cabazitaxel vs abi/enza second line	0.64	13.6 vs 11.0 (2.6 months)
VISION	Standard of care +/- PSMA-617 Lu-177	0.62	15.3 vs 11.3 (4.0 months)

* Mature analysis **BRCA1/BRCA2/ATM subset

This particular slide encapsulates all the phase three trials that have been shown to have an overall survival advantage. All of these are in the New England Journal, except for one. That's the TROPIC trial. And we have a variety of things that I think are sort of noteworthy. So first, I'll make a comment that when you look at the overall survival benefit, I think the first thing that you would conclude as a patient is that this is pretty unimpressive. And I think it is not as impressive as we would like. But that's just the reality. And there are a variety of reasons for this, some there may be crossover and but nevertheless, these are factual data that I think is important for people to know.

A couple of other things. The field has really been changing since the early trials showed a benefit for things like Sipuleucel-T, that's Provenge. I don't know how relevant it is today. The same is probably true for radium. Sipuleucel-T was FDA approved in 2010, radium FDA approved in 2013. And there's really been a wholesale change since then, if we want to look at clinical decision making, and I can spend an hour on this, but I won't. You have to kind of think about, first of all, what is available and what is affordable. And that's not always so clear, a lot of these things are very expensive now. So that's really a problem.

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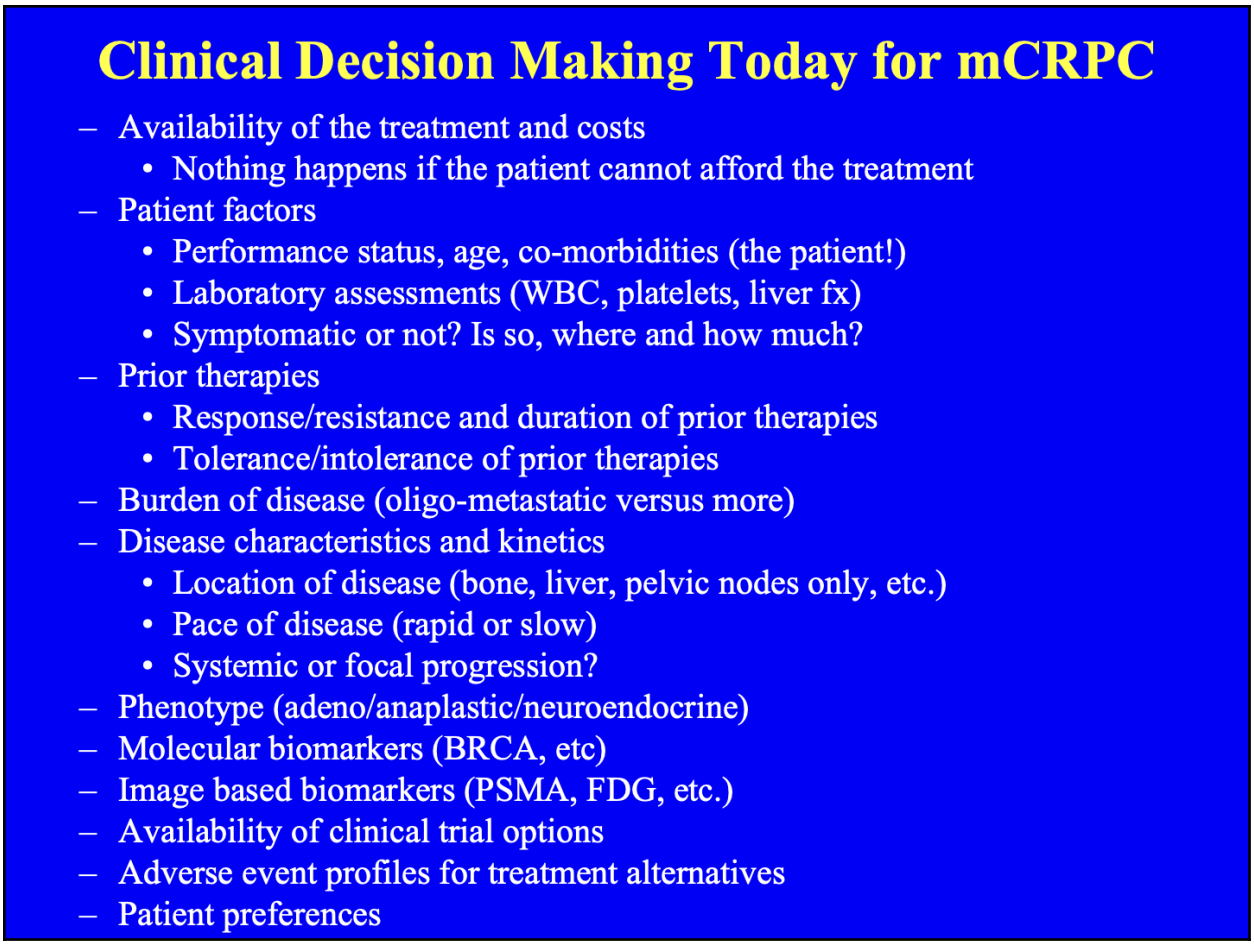

There are a lot of therapies that may not be suitable for everybody, you know, performance status, age, comorbidities, laboratory assessment symptoms all sort of dictate how we think prior therapies, response and resistance and duration of prior therapies. I just spoke to a patient today. He underwent chemotherapy with no response. I’m probably not going to give him another chemotherapy. Oh, it's an intolerance of prior therapies burden of disease, I'll go mass not only go BAT. Where's the disease located? Bone only, liver, pelvic lymph nodes only – makes a big difference, particularly liver. The liver is a bit of a challenge. What about the pace of the disease, is it rapid or slow? And it's very different for different people, that this progression is a systemic progression or focal progression for the phenotypes. You know, we talk about adenocarcinoma, like it's the only thing that there is, but it's not true there. anaplastic Sydnor integrins. Their molecular biomarkers rock up being a clear one image based biomarkers like Pitts May and FTG, clinical trials, options, you know, what's out there, what's not out there, advertisement profiles and patient preference. So all of these fit in imaging is important. genetics are important. Histology is important prior treatments. All of these are really critical.

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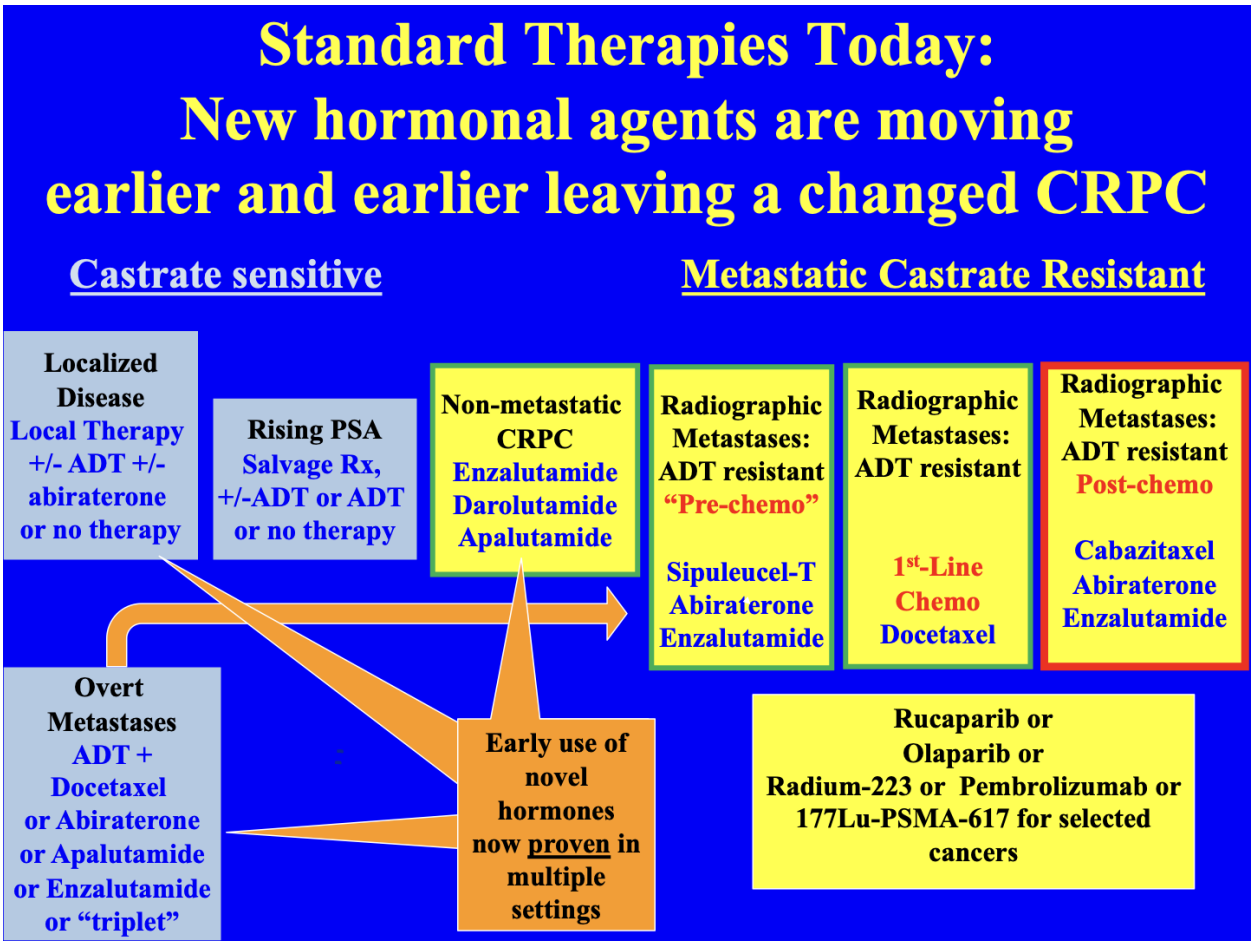

When we begin to look at the current landscape, the novel hormones are all going up front so everybody gets a novel hormone. And that could be Abiraterone, Enzalutamide, darolutamide apalutamide. Everybody gets a novel hormone and it typically is even before you get to be metastatic CRPC What's your mistake CRPC. There's our conventional things, and then there's PARP inhibitors, and pembrolizumab fits man with tissue and radium that are specific for certain populations.

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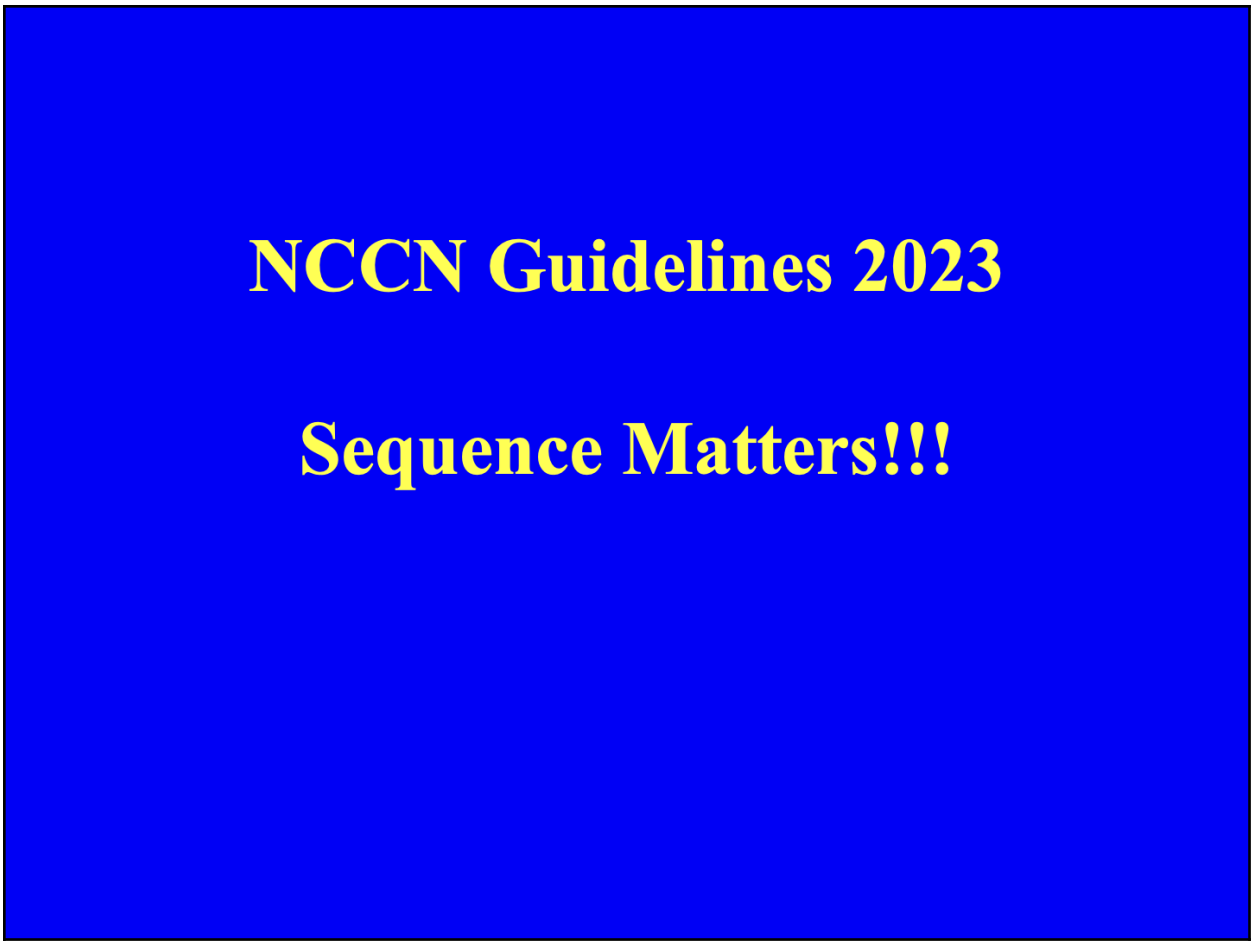

This is from the NCCN guidelines 2023 You can sign up and get them. The sequence matters.

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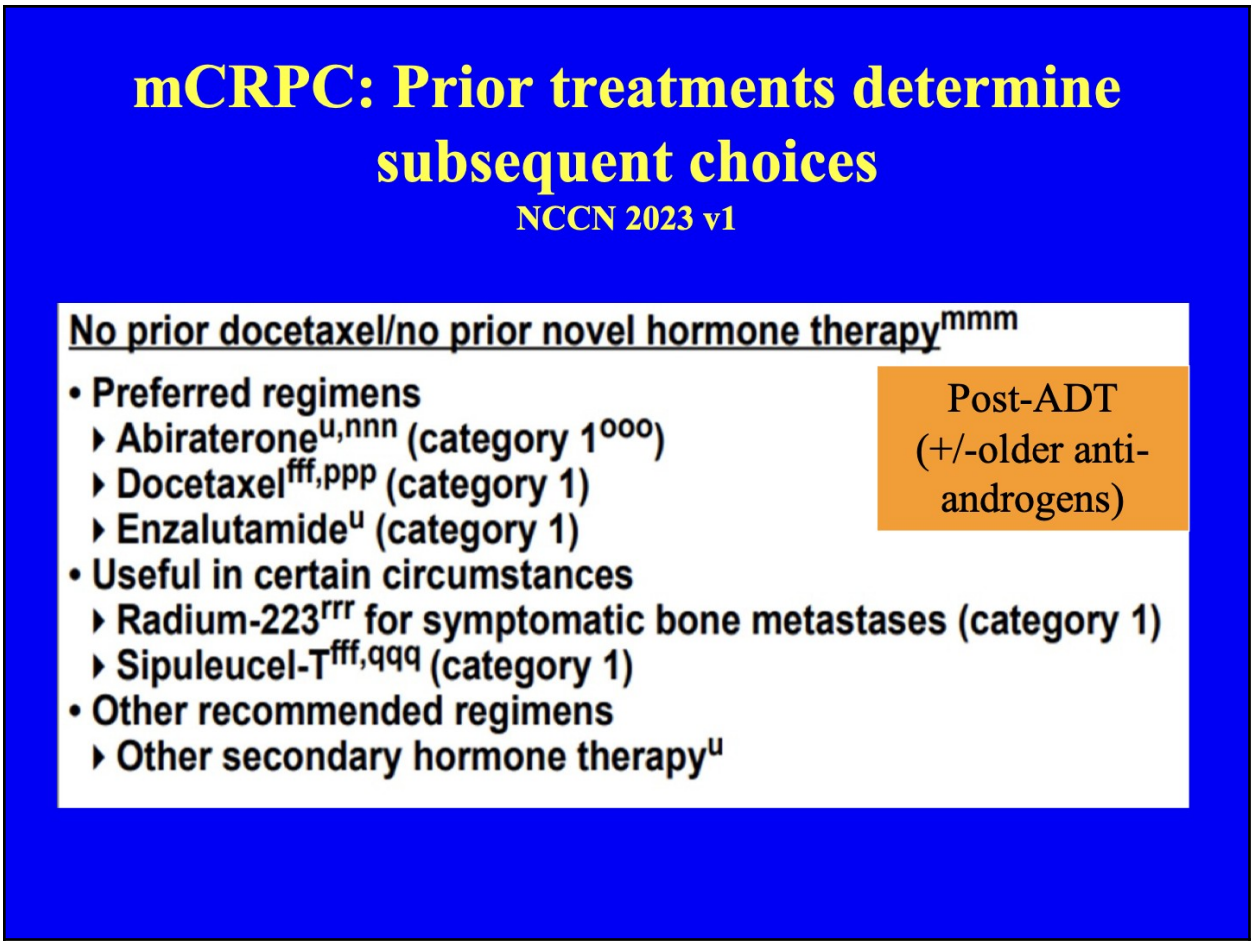

If you have not had any of the novel hormones and all you've had maybe as an omen, androgen something like Byculla mine, then I will use Abiraterone or Enzalutamide typically, in that setting.

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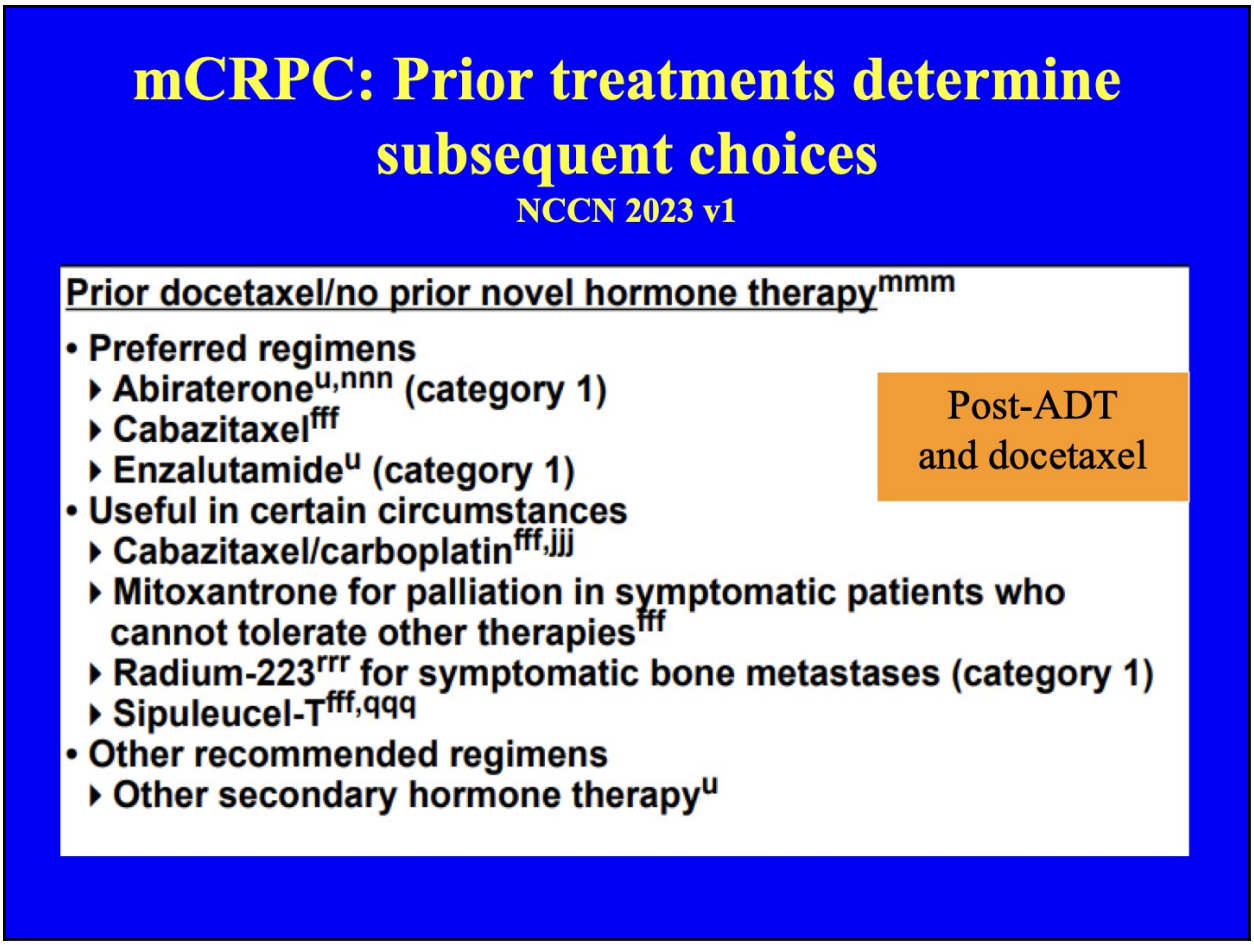

If we're going to be looking at the host into deprivation and docetaxel, a little bit of an older patient, I'm still looking for the hormone. So I'm looking at Abiraterone Enzalutamide typically as my number one and number two options.

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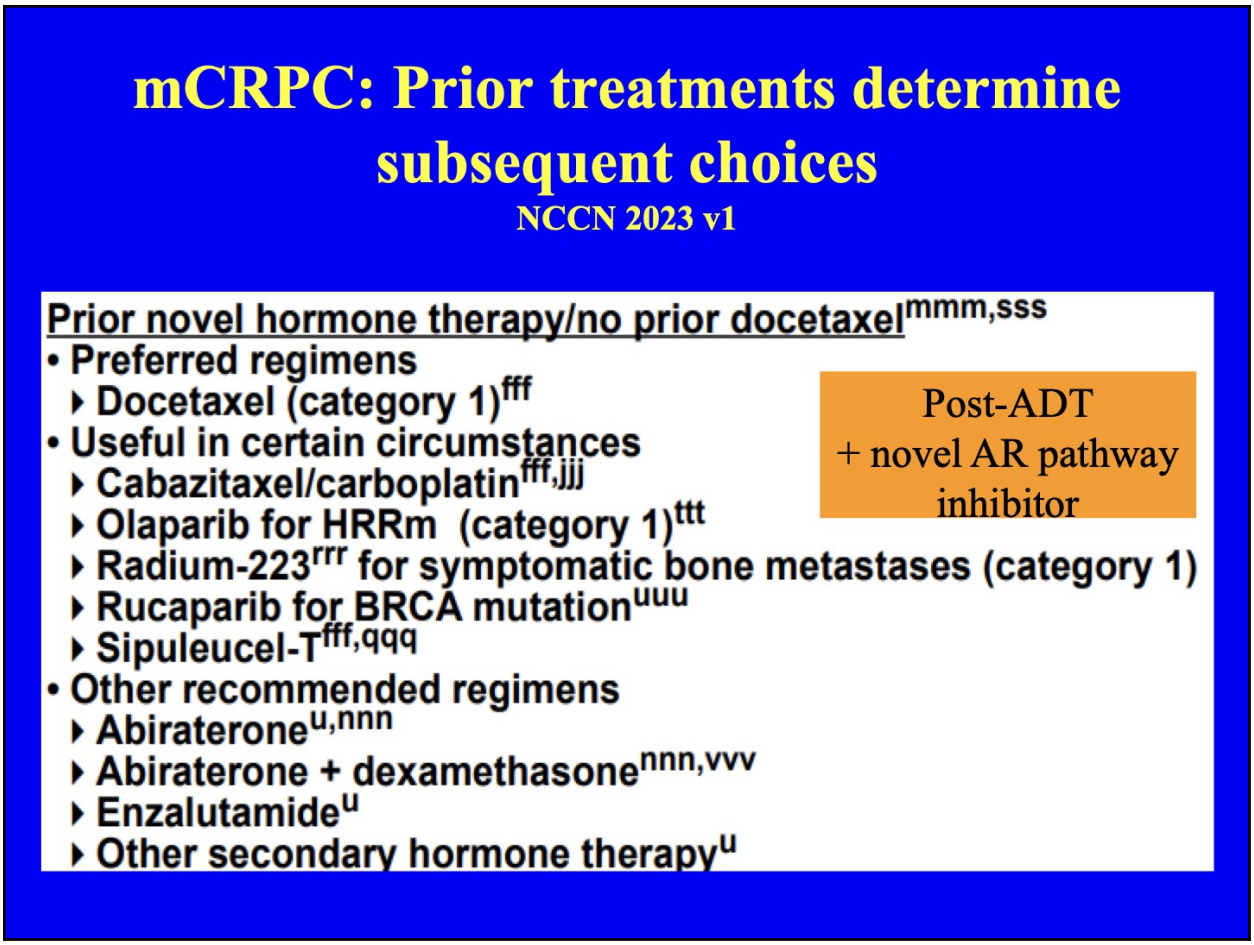

If you've had an androgen deprivation therapy and a novel AR pathway inhibitor, that's the patients who have Abiraterone, Enzalutamide apalutamide darolutamide then, you know, docetaxel is currently category one that may change, but docetaxel is sort of category one. And

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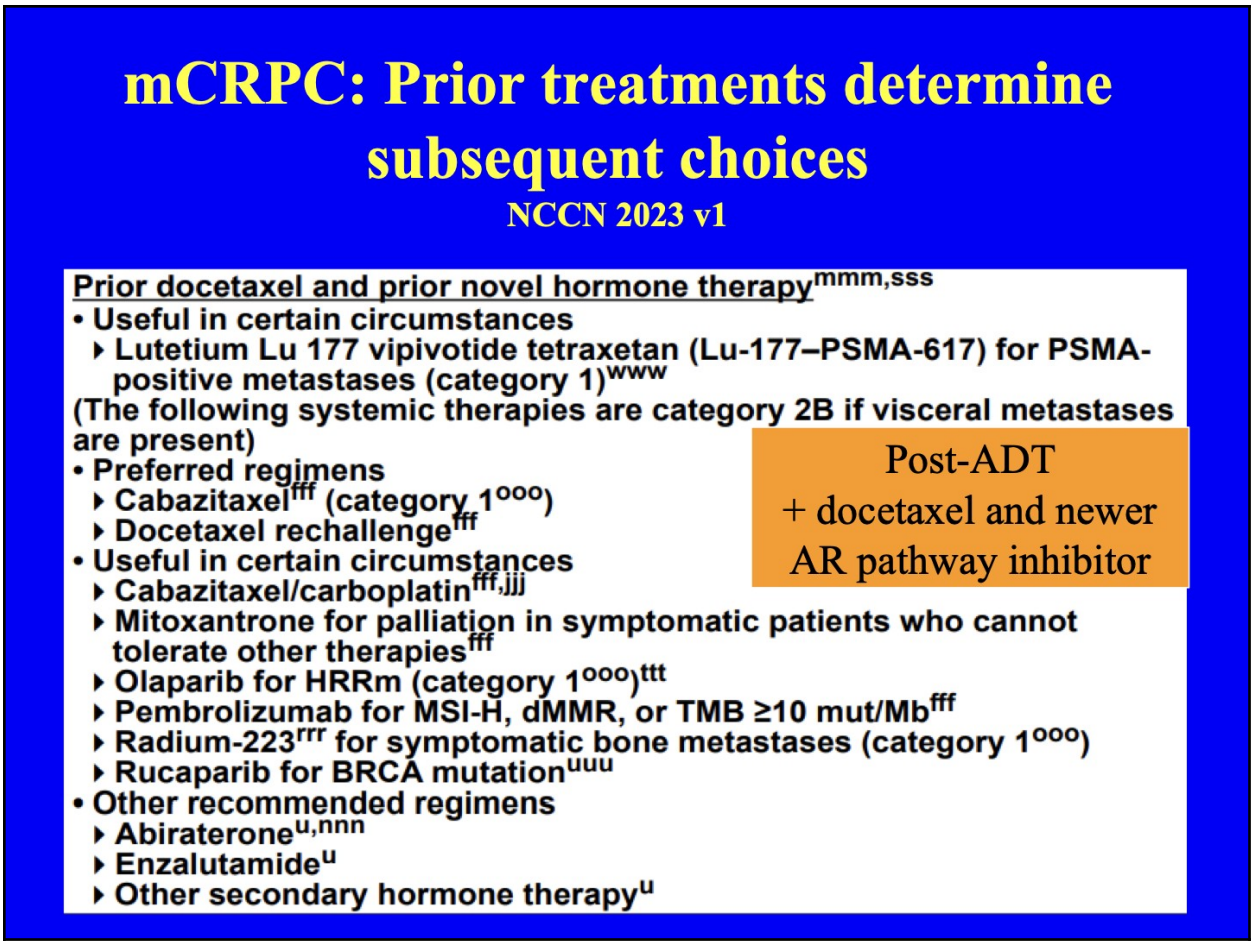

if you've had both, then probably say both I mean docetaxel and a novel AR plus ADT, of course, then we're probably looking at Pluvicto or Lutetium 177 PSMA 617 as being the path forward, but you also have to understand that genetics are real.

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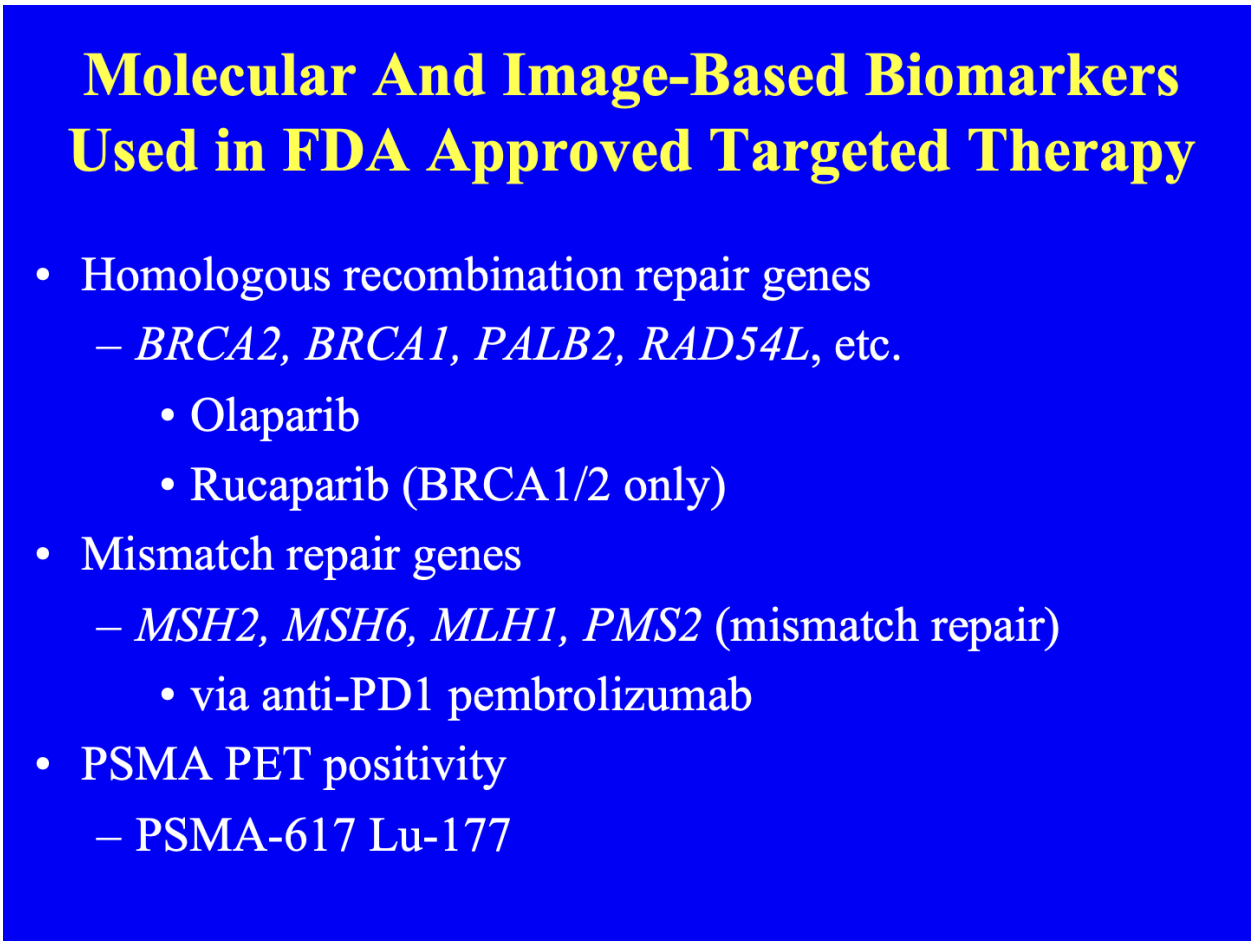

There are a variety of things. These are our molecular image based markers. We have amongst recombination repair genes like BRCA2, BRCA1, PALB2, RAD54L, etc. PARP inhibitors can be effective, particularly for those who have BRCA2 mutations. BRCA2 PARP inhibitors can really be quite important, probably block one Ib two by three pour out a lot of the other ones not so much. Mismatch repair genes and there are 4 of them, but there are two that we understand a little more than the others: MSH2 & MSH6. and here we have pembrolizumab as an FDA approved options are important and then Pluvicto for patients who may PSMA positive.

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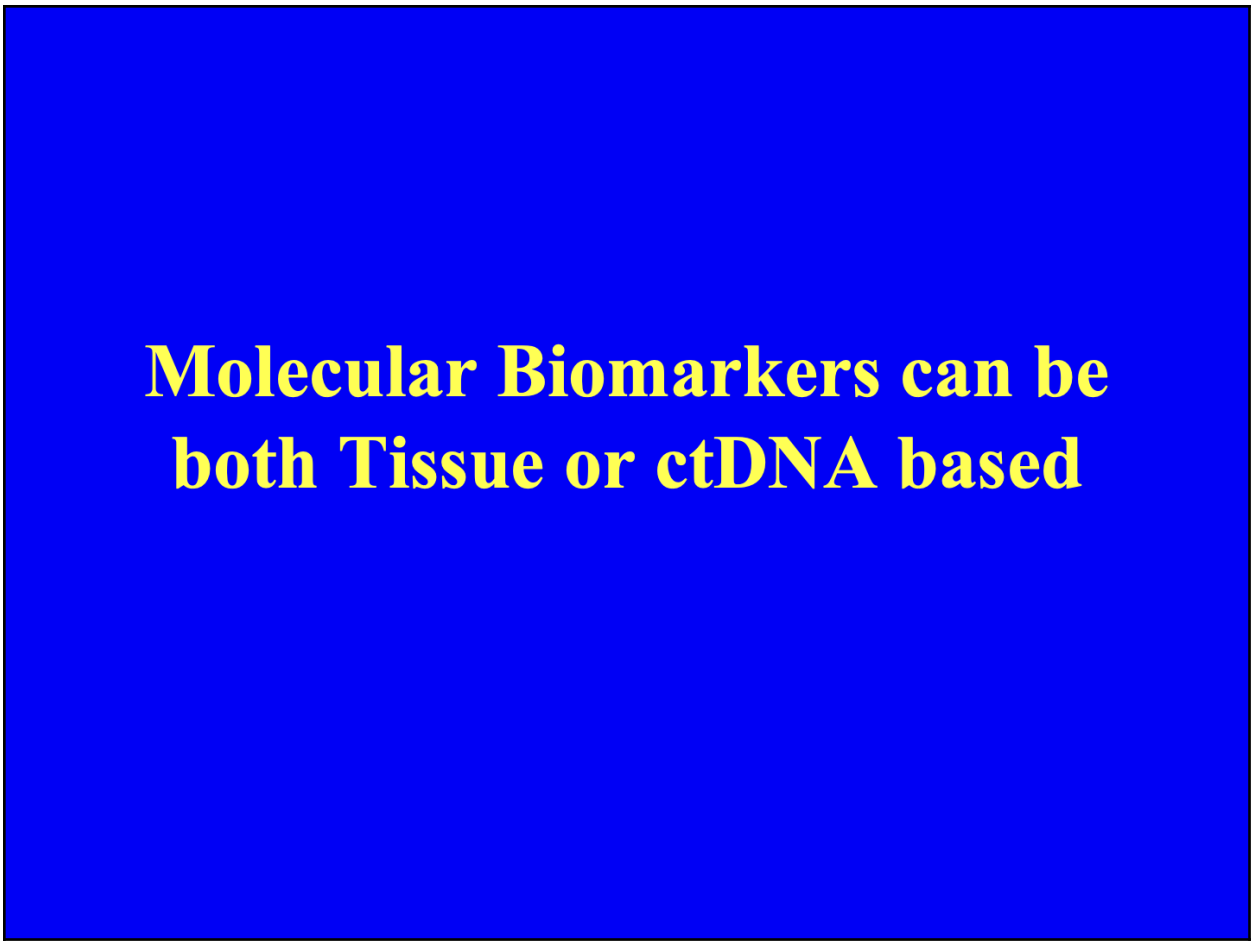

When we look at these biomarkers that can be either tissue or circulating tumor DNA base,

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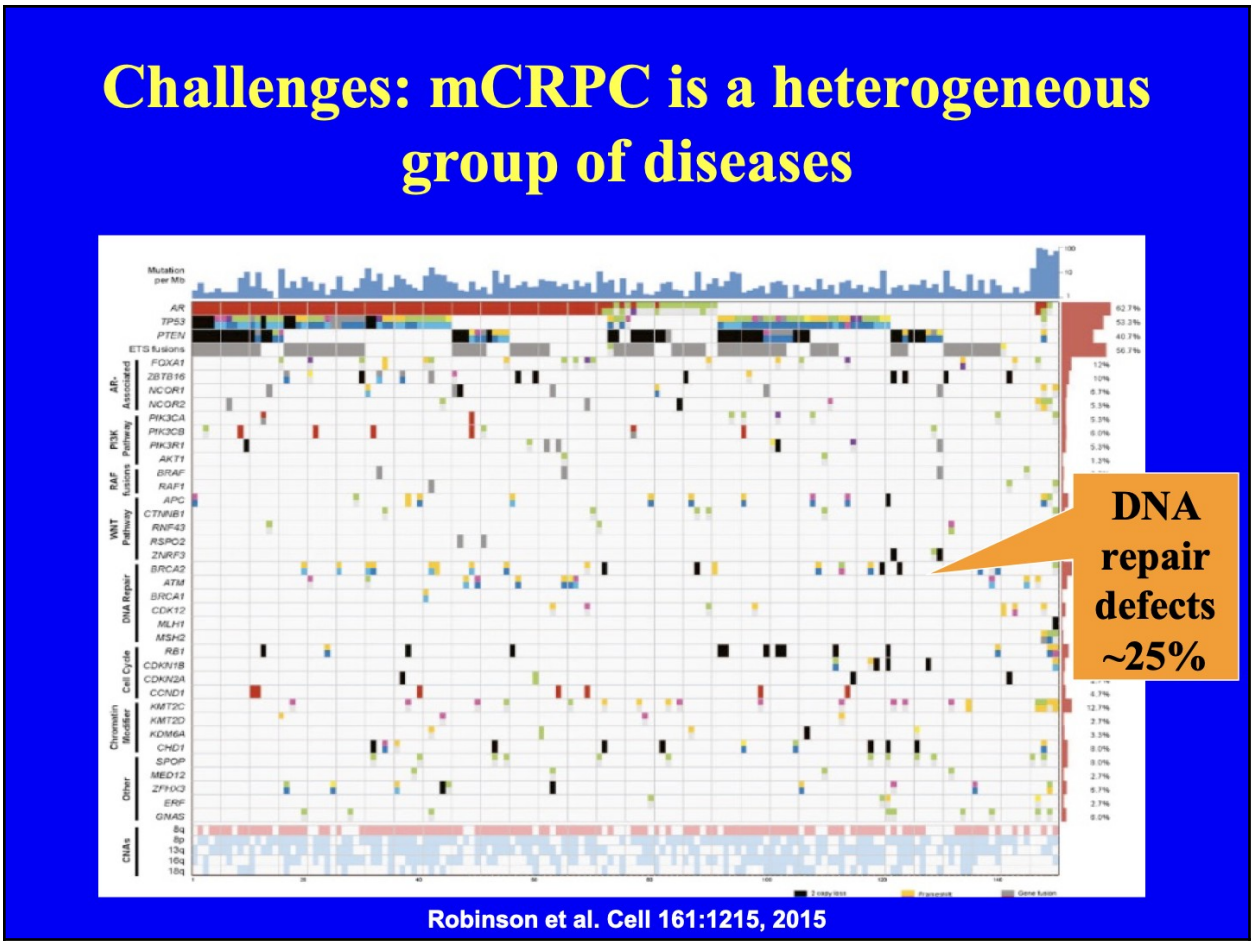

there are a variety of DNA repair defects that are noted if you look at the tissue base genetics,

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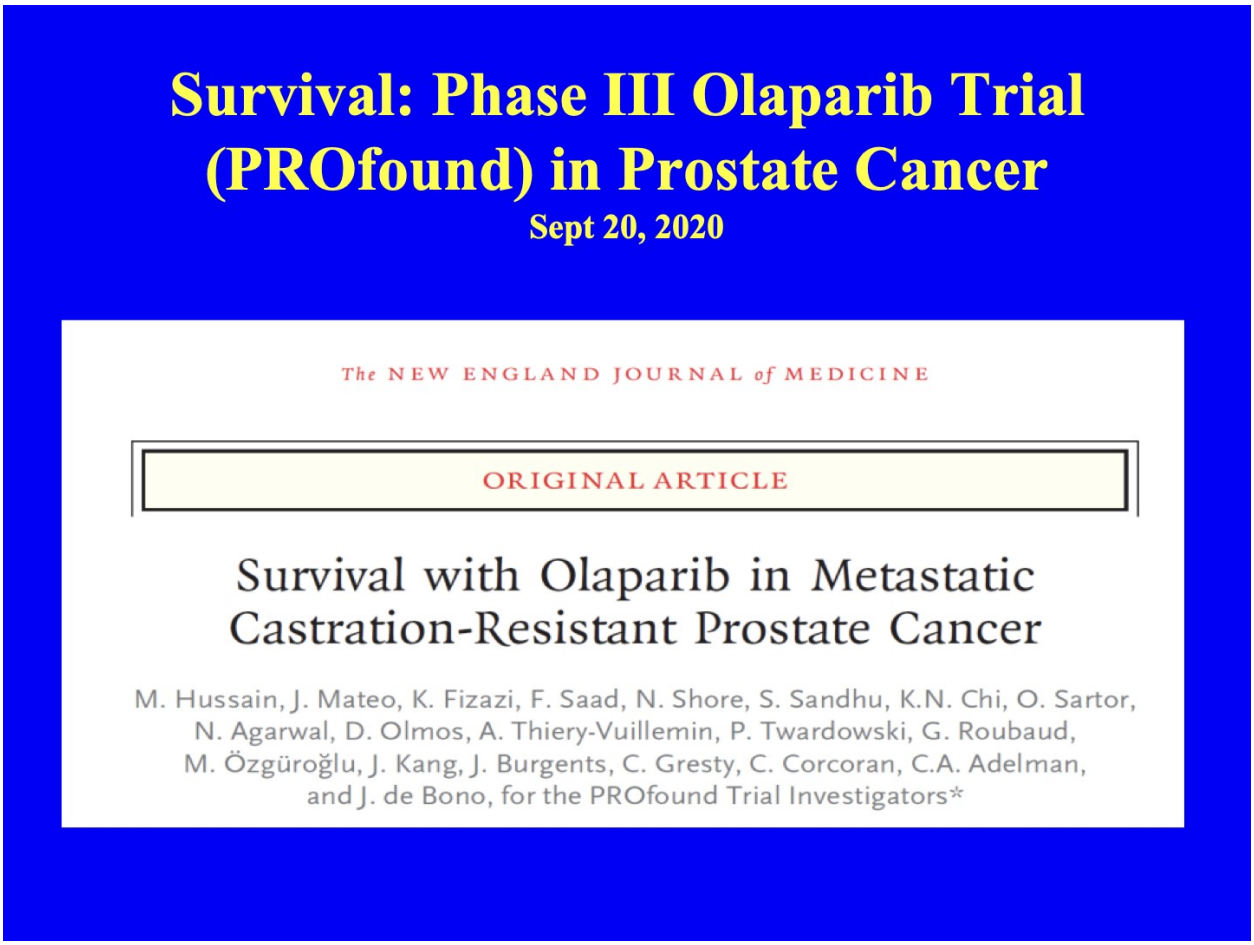

but we have things like olaparib that have prolonged survival in individuals with metastatic castrate resistant prostate cancer.

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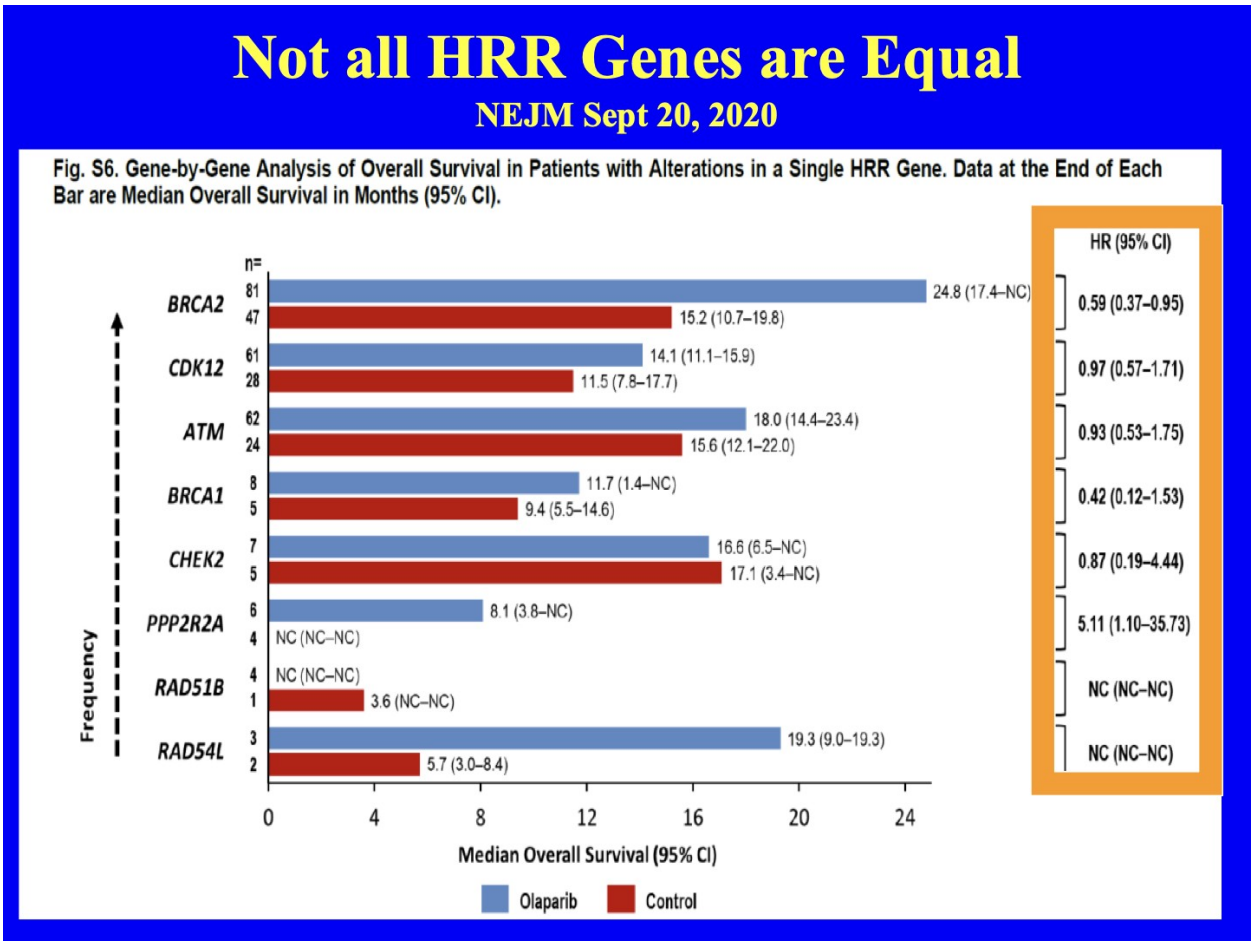

But not all the genes are created equal. It's very, very important that genes that seem to be particularly sensitive BRCA2, probably BRCA1, RAD51B, maybe RAD54L.

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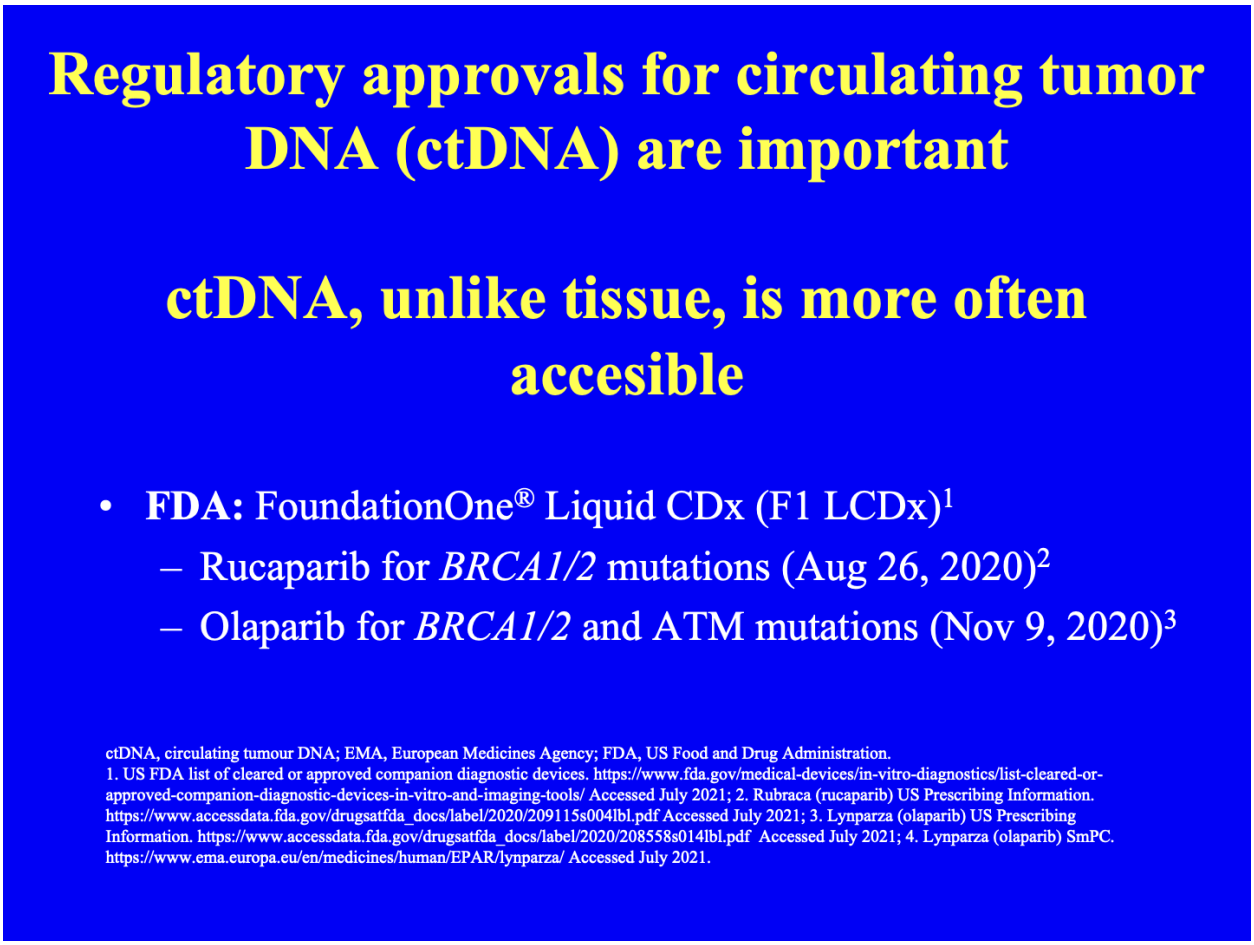

It turns out that you don't need to have tissue, you can get tissue, but you can also use circulating tumor DNA, and that's pretty accessible.

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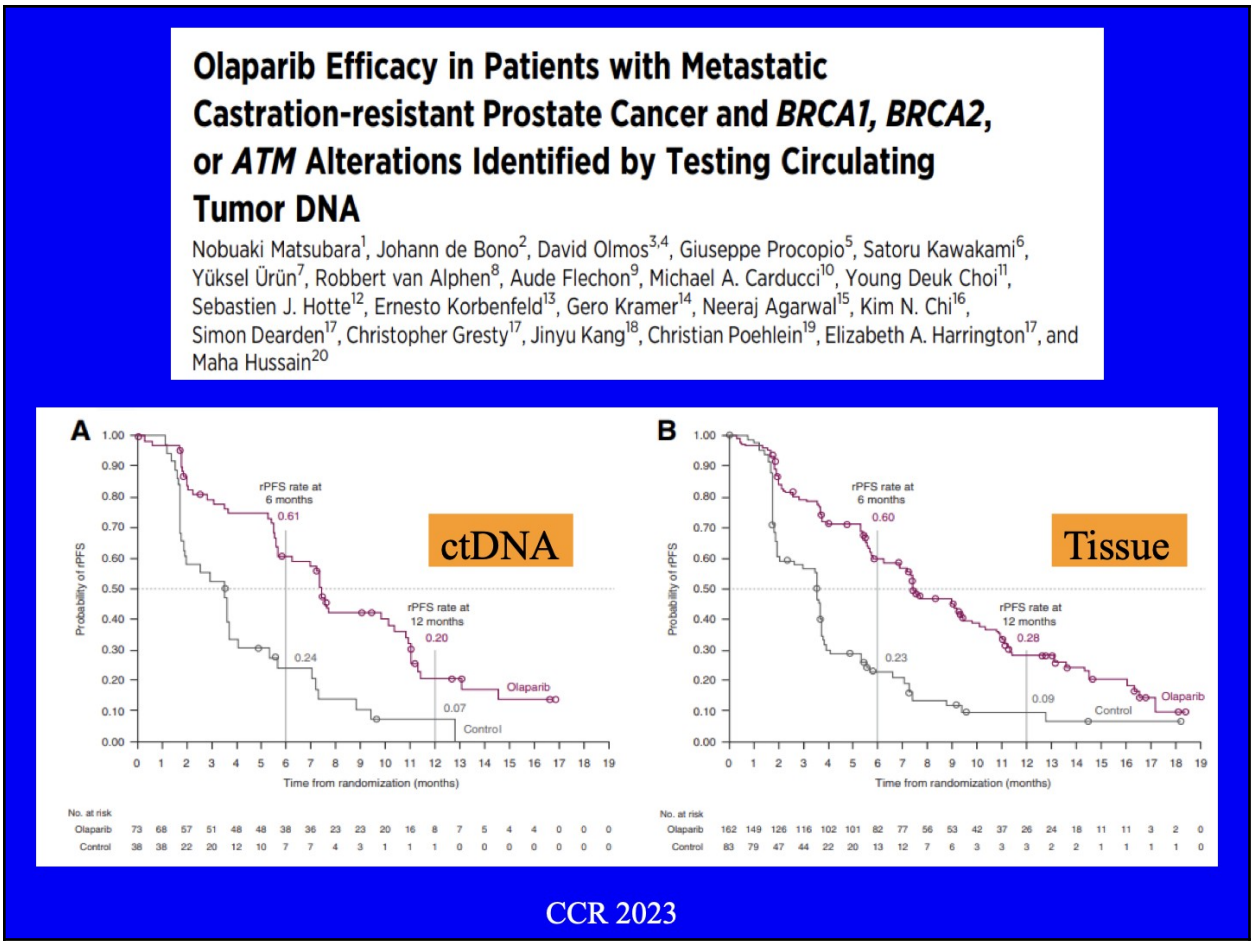

Here's the efficacy, comparing tissue tissue and circulating tumor DNA per olaparib. And basically, you can see there's no difference. So circulating tumor DNA is a good way to go.

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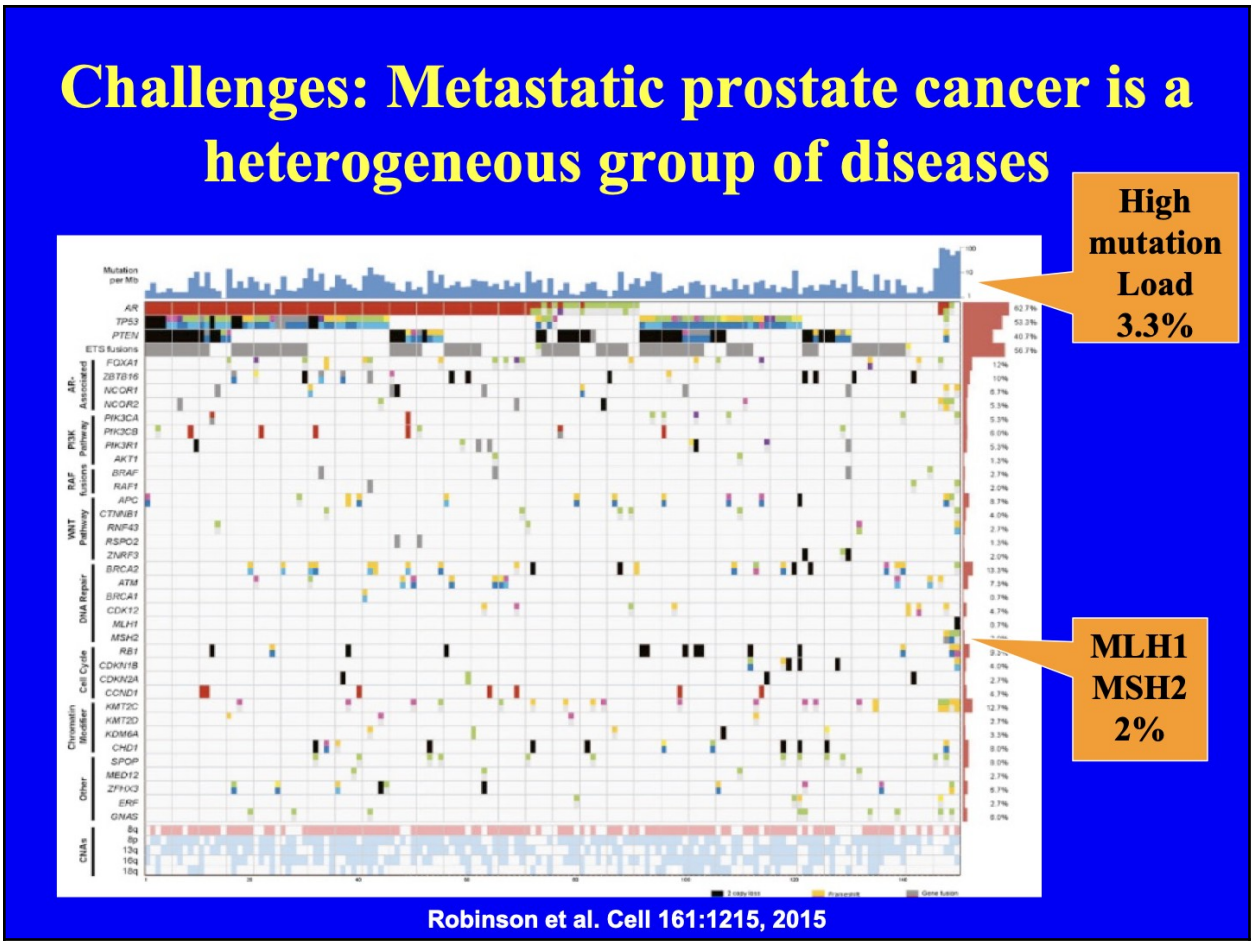

When you get your genetics do not generally favor getting genetics, they're small subsets with a high tumor mutational burden, and a mismatch repair deficiency, particularly MLH1 in the states to Msh six.

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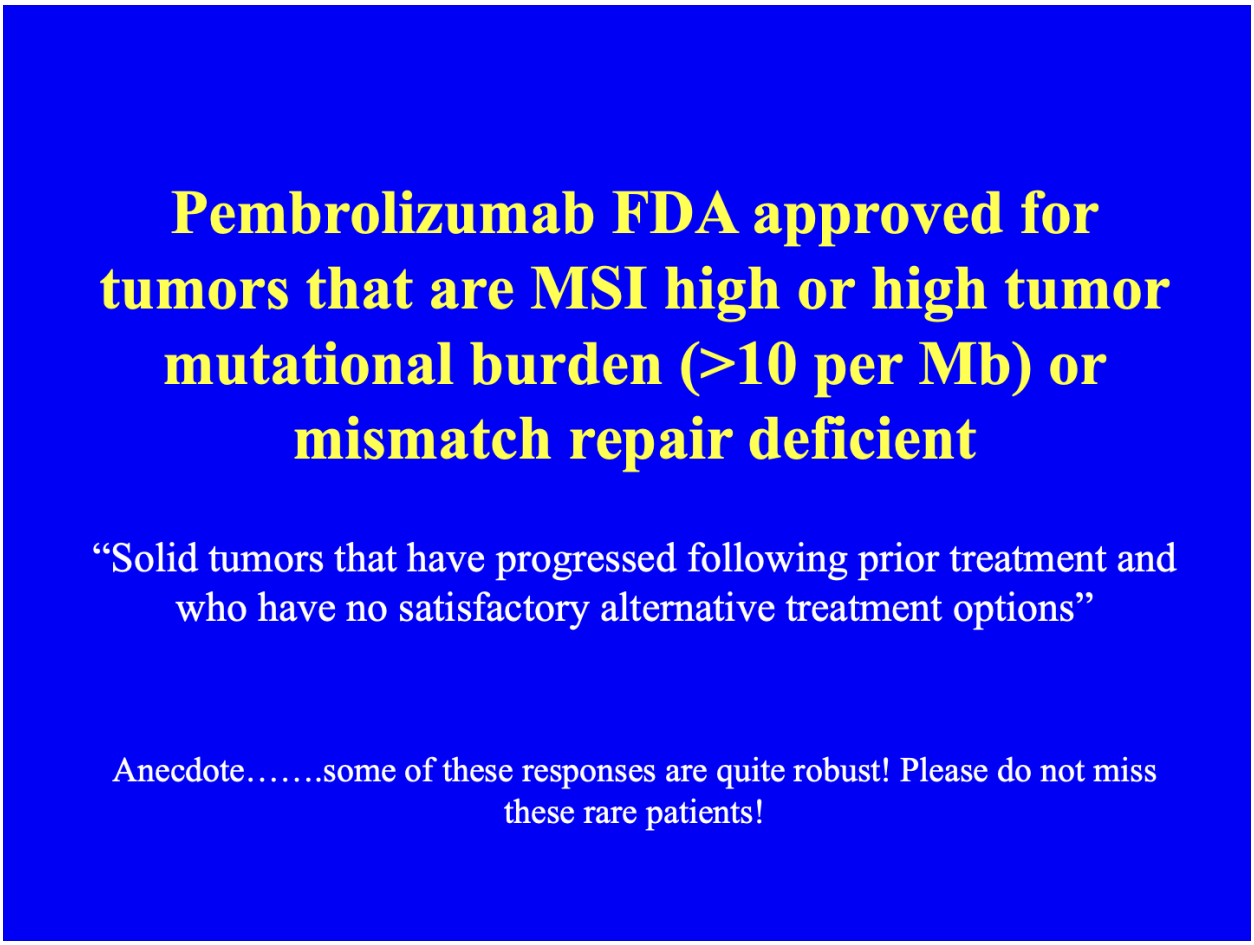

And it turns out that pembrolizumab is going to be FDA approved here, that one of the things that's a little bit problematic is looking at circulating tumor DNA. You don't necessarily have this high TMB greater than 10. That's a tissue based marker. But if you're using circulating tumor DNA to get your high tumor mutational burden, you probably ought to be 20 or above. We don't have good lessons.

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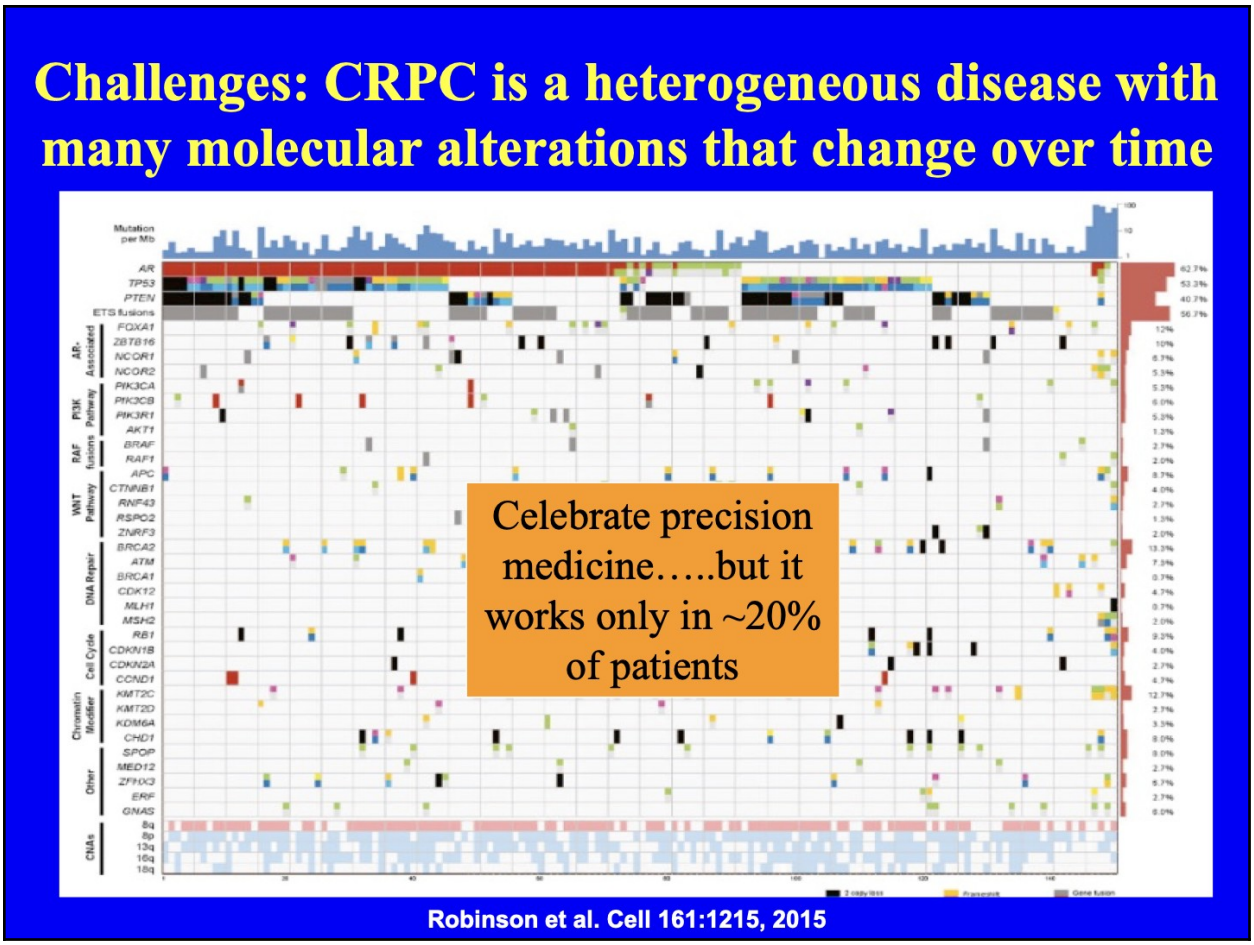

We don't have good data there. We can celebrate precision medicine. But it only works in 20% of the cases. This, you know, people working long hours, but the vast majority of men will not benefit from traditional precision medicine by genomics. So that's our knowledge that they should see phased in and move on. You just have to move on.

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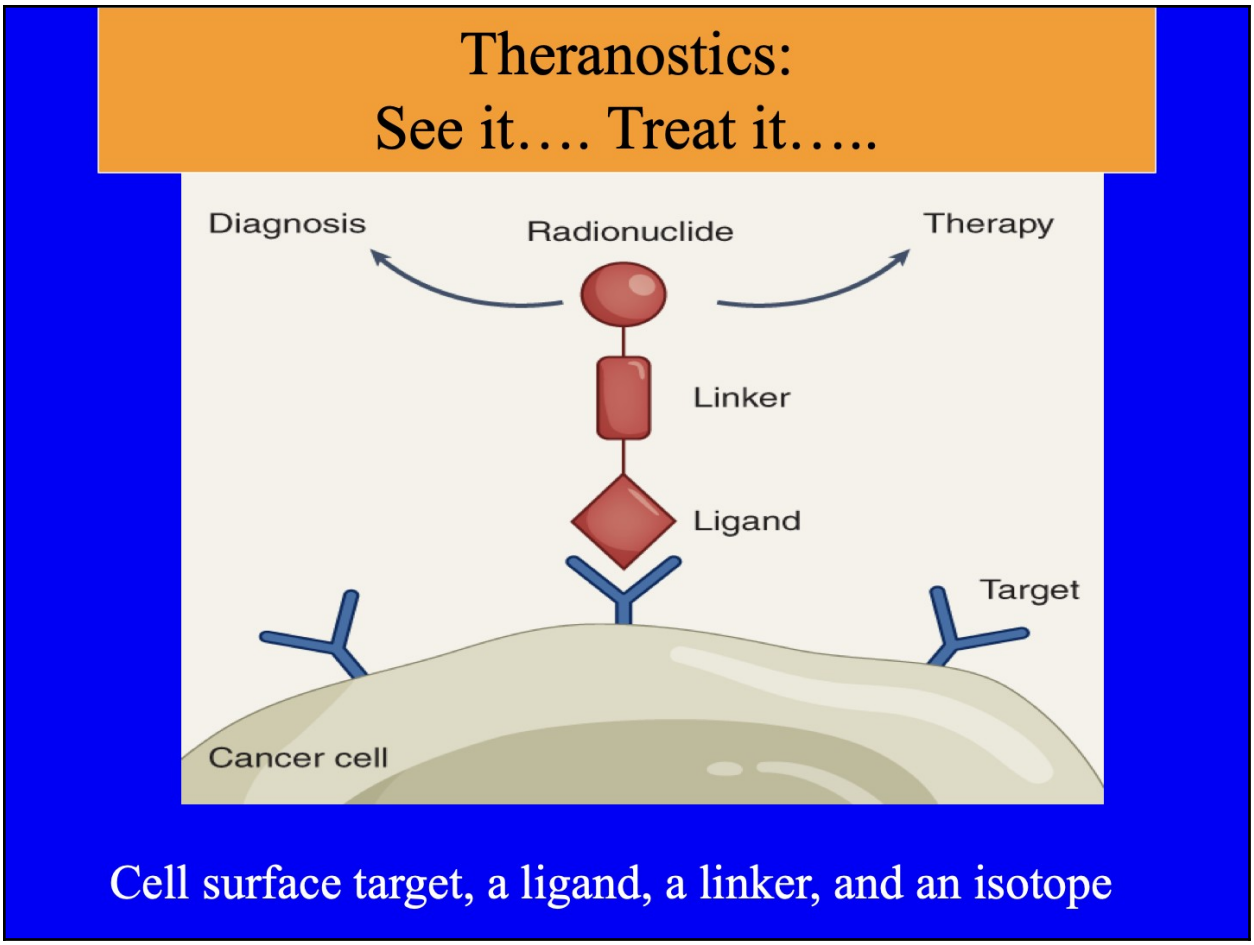

I like theranostics. I spend a lot of my time thinking about theranostic CSA is my title and Mayo Clinic is director of radio pharmaceutical trials, very simple concept. Something on the cancer cell can serve as a target, you devise a molecule that has a ligand, linker, and radionuclide. If you have a particular radionuclide, like gallium 68, or F 18, you can diagnose if you have another radionuclide, such as lutetium, or actinium.

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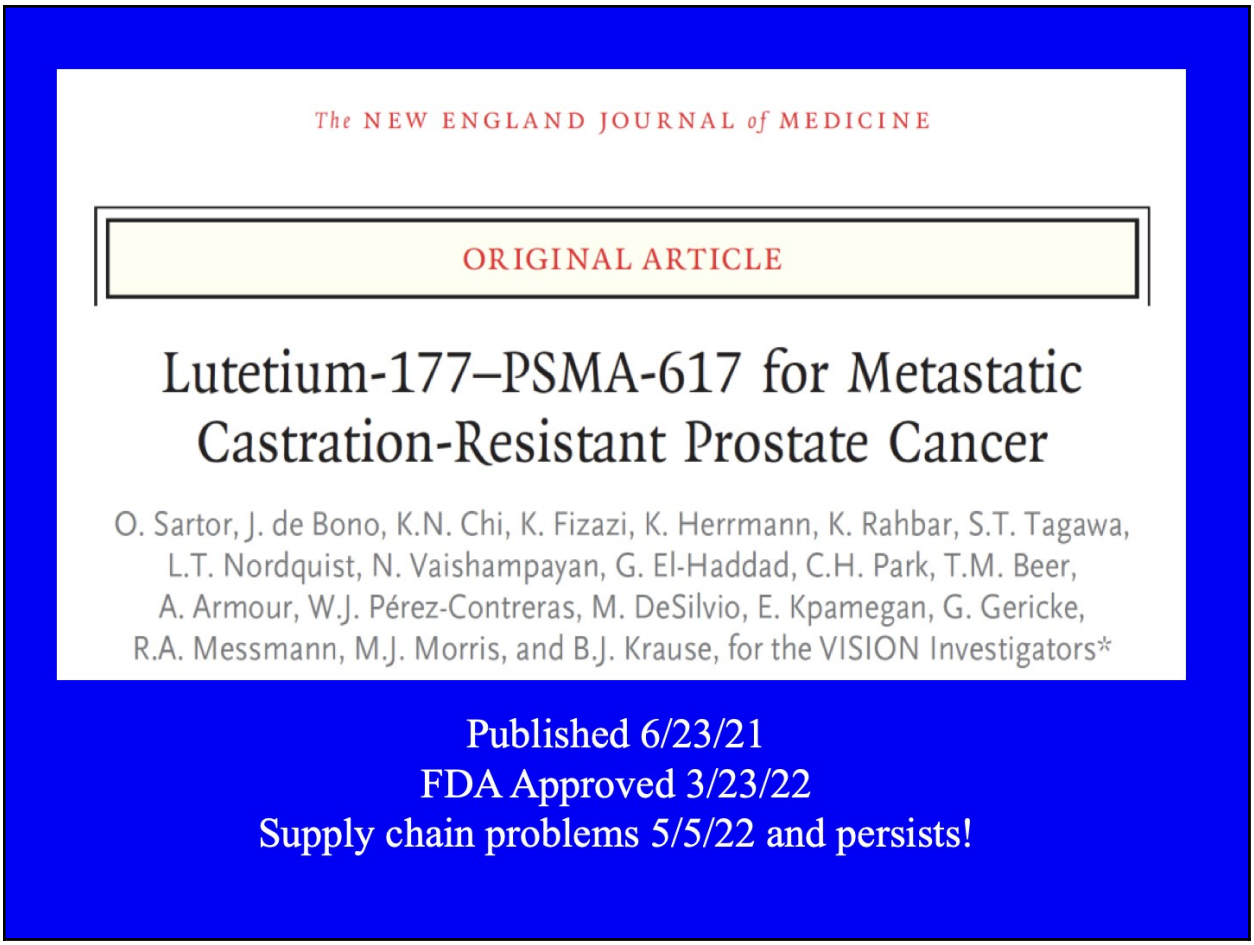

You can treat and the one that of course got a big publicity is the Lutetium - 177 - PSMA - 617 or Pluvicto. Supply chains are getting better. But they've been a nightmare. They've really been a nightmare.

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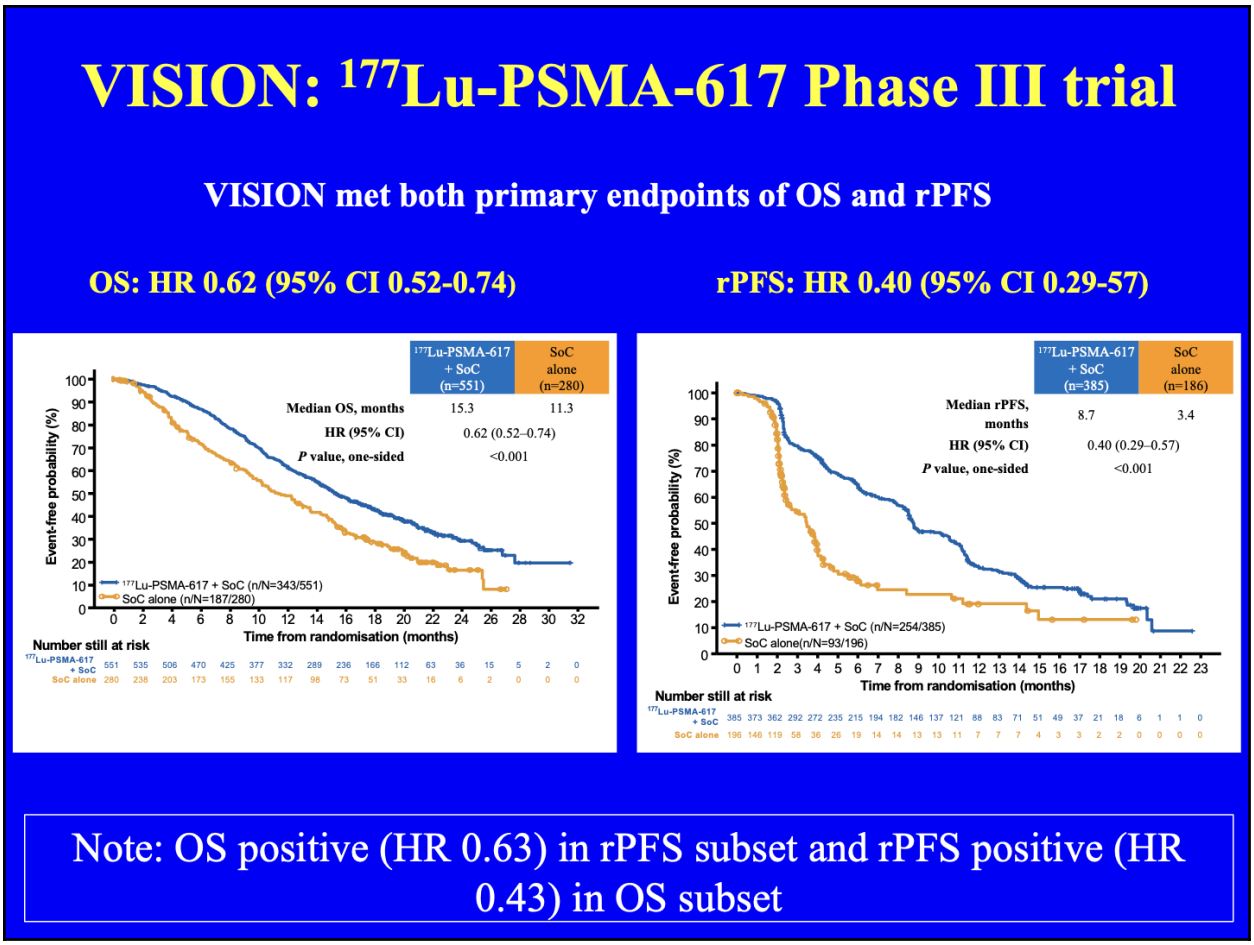

With regard to survival, I think many people were disappointed in the survival curves. We were all hoping for better. Here's the RPFs curve. But it turns out that a lot of these patients went on to receive other therapies and it could be that, you know, I think Pluvicto is a good therapy. It's just we want to do more. And I'm certainly in the “want to do more” category.

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Are there therapeutic combinations that deserve to be used as standard of care? The only one I think is really clear is adding olaparib to abiraterone from first line metastatic CRPC BRCA mutated patients, and has been FDA approved.

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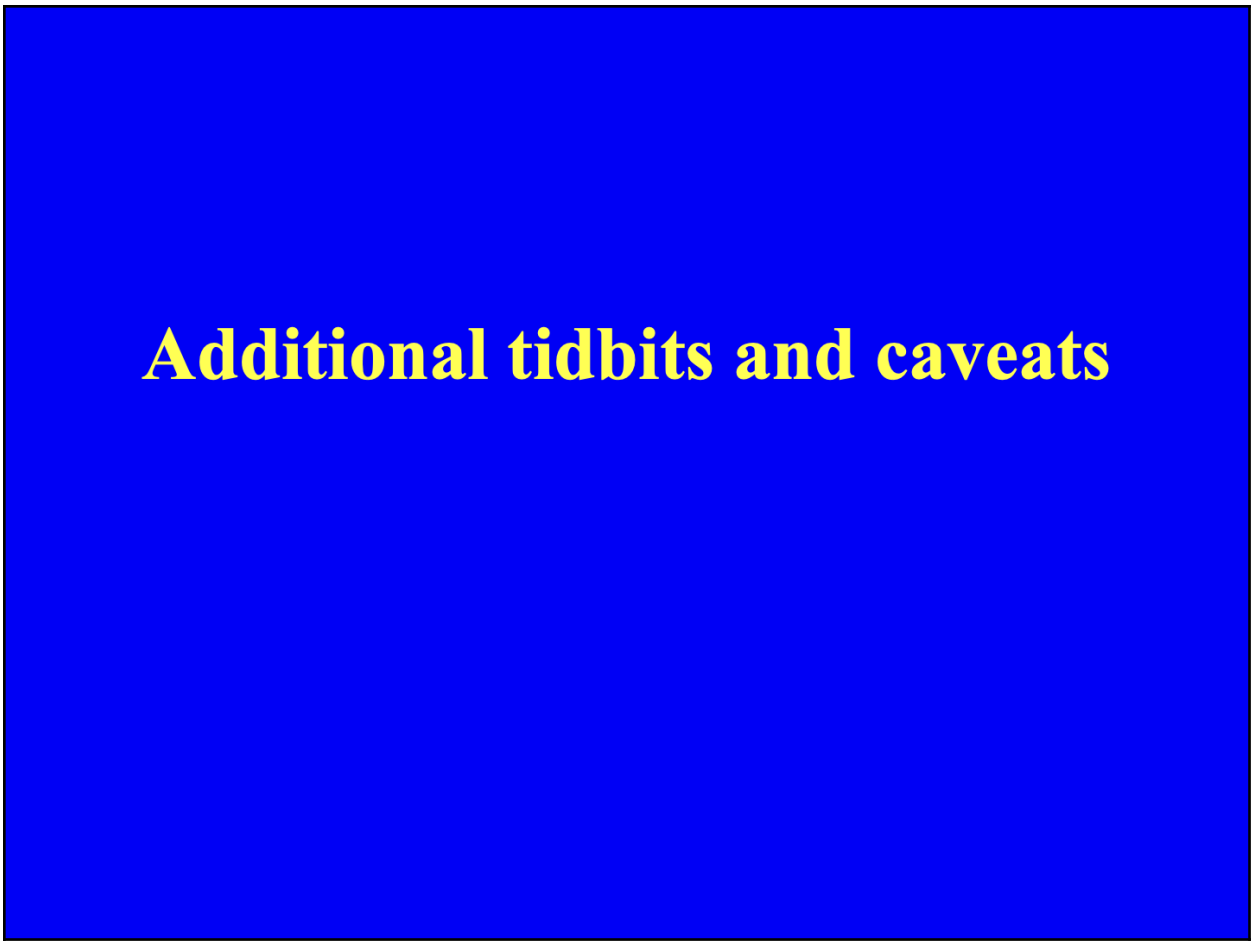

Additional tidbits and caveats.

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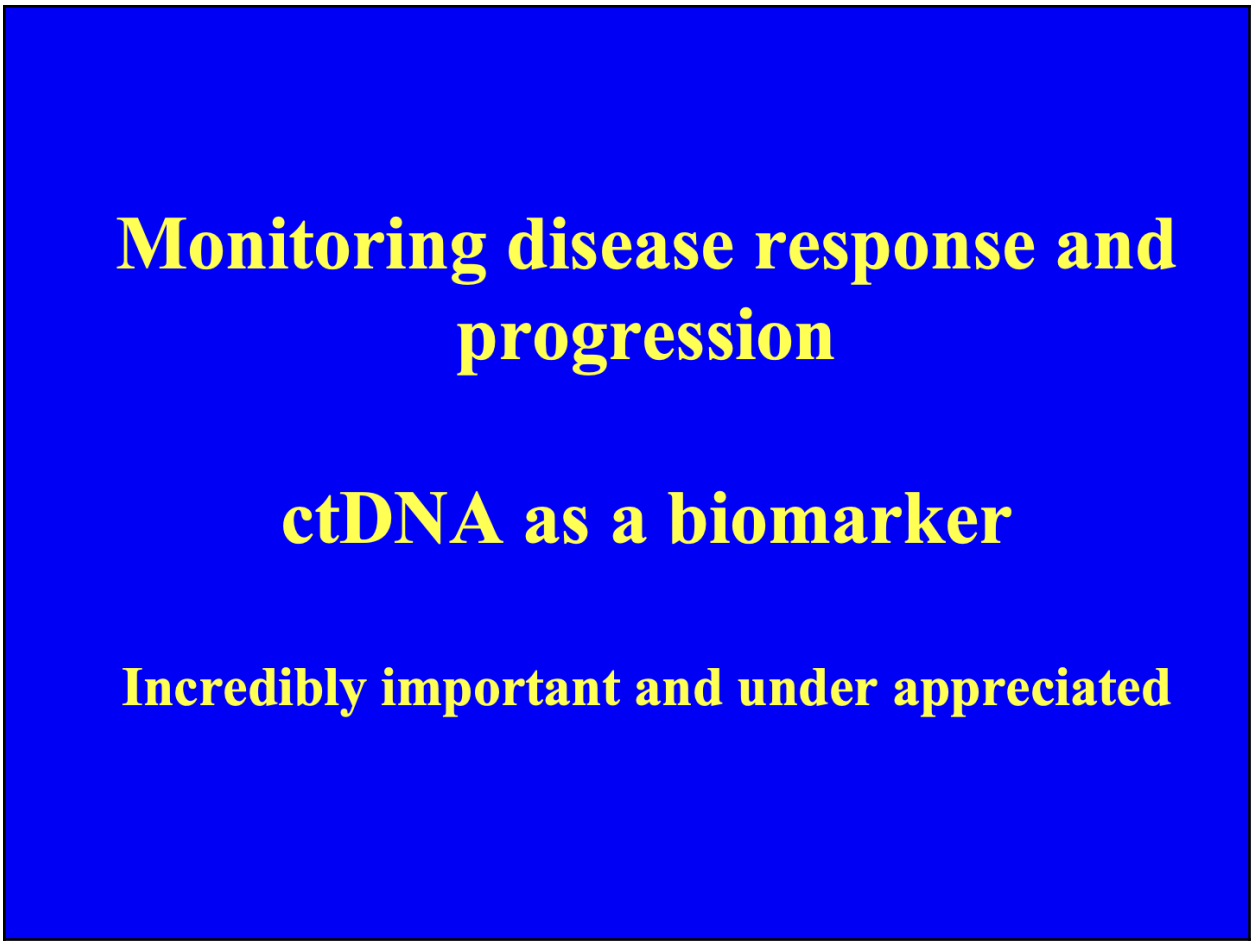
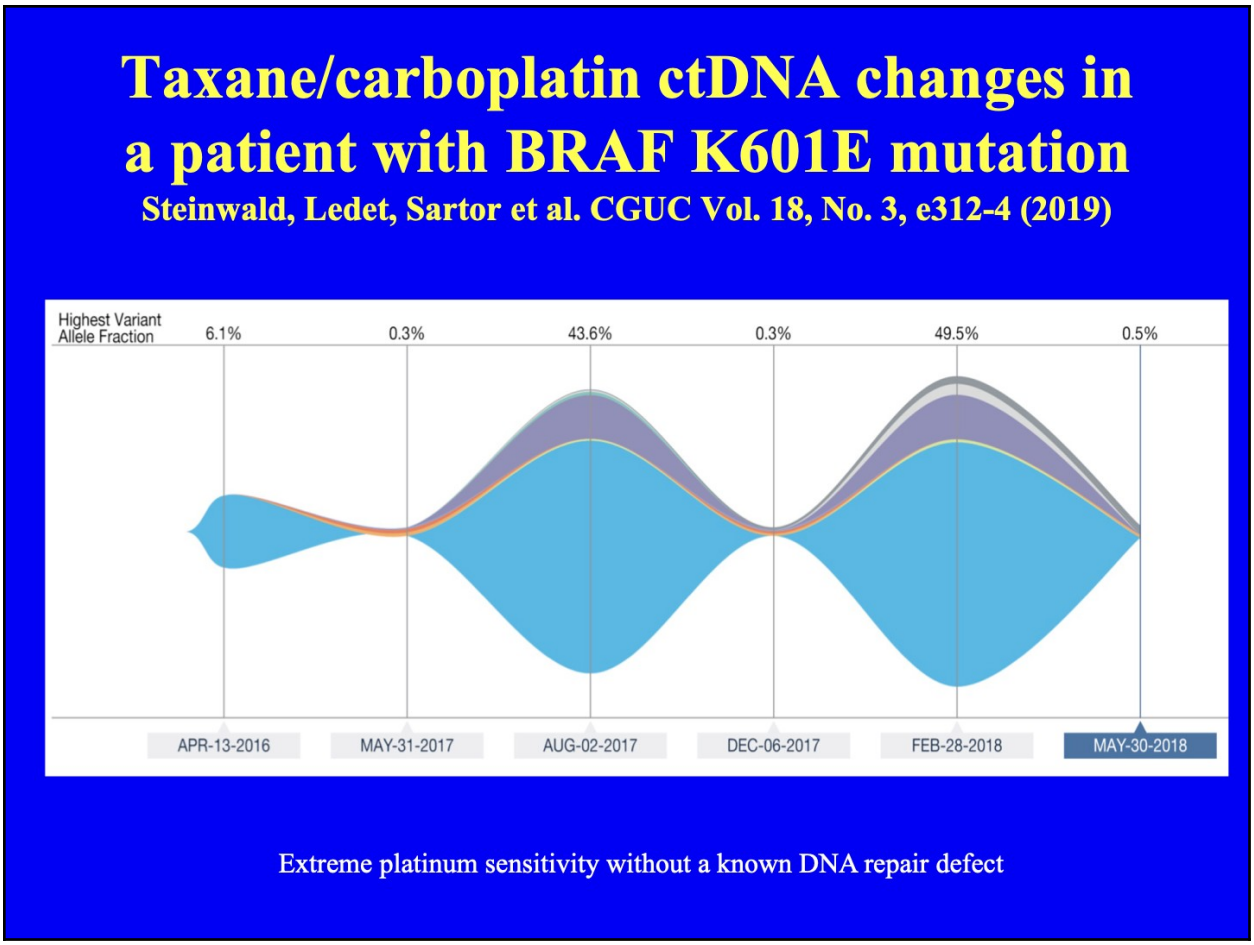


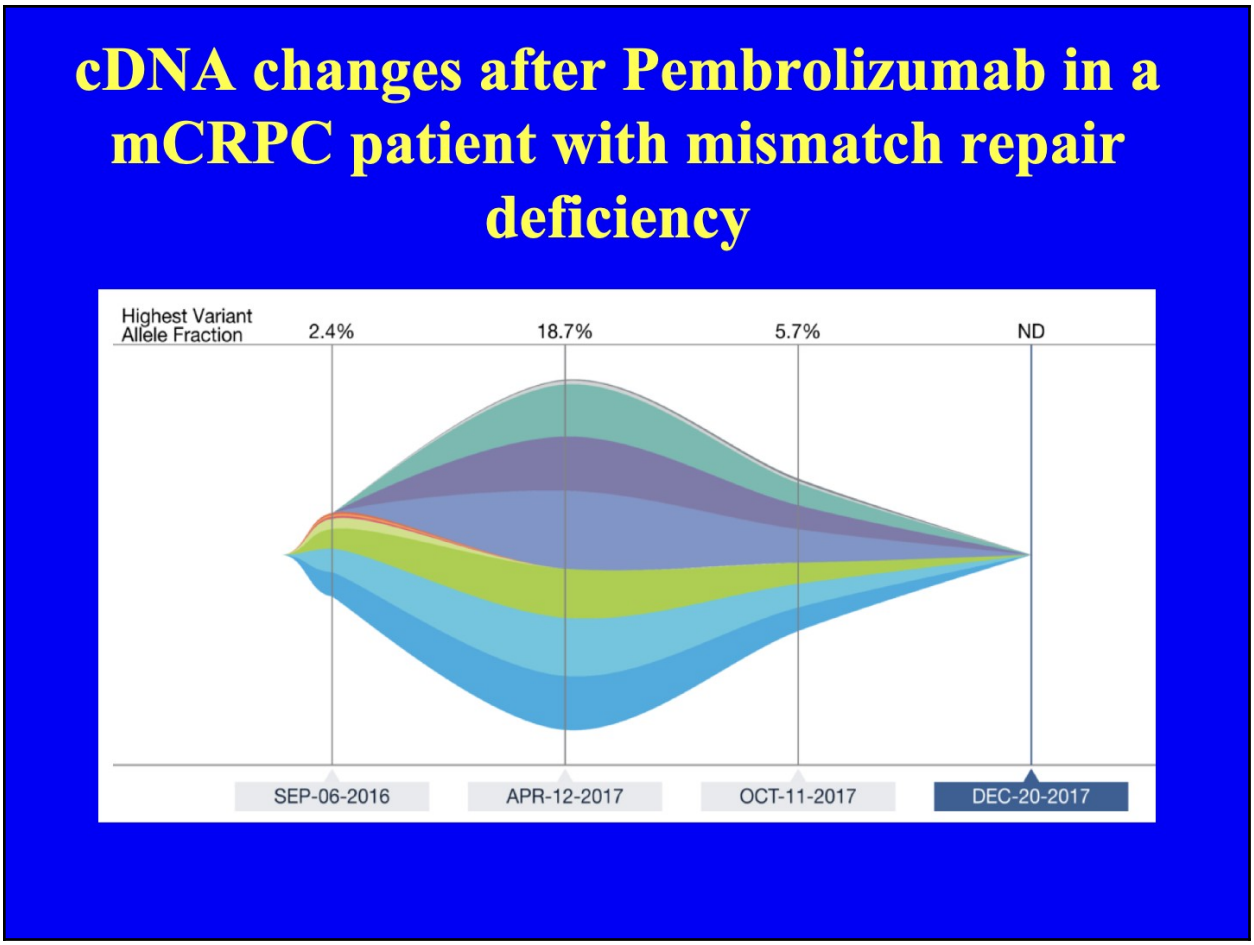
ctDNA as a biomarker I think is important.

“The Current and Future Landscape of Metastatic Castrate Resistant Prostate Cancer” (Oliver Sartor) [#62]



Here's a case at my clinic where we look at the BRAF K601E mutation treated with platinum with using it a bit in therapy, we would shrink down the circulating tumor DNA findings. And then it would expand back up and we retreat and it would work.

“The Current and Future Landscape of Metastatic Castrate Resistant Prostate Cancer” (Oliver Sartor) [#62]

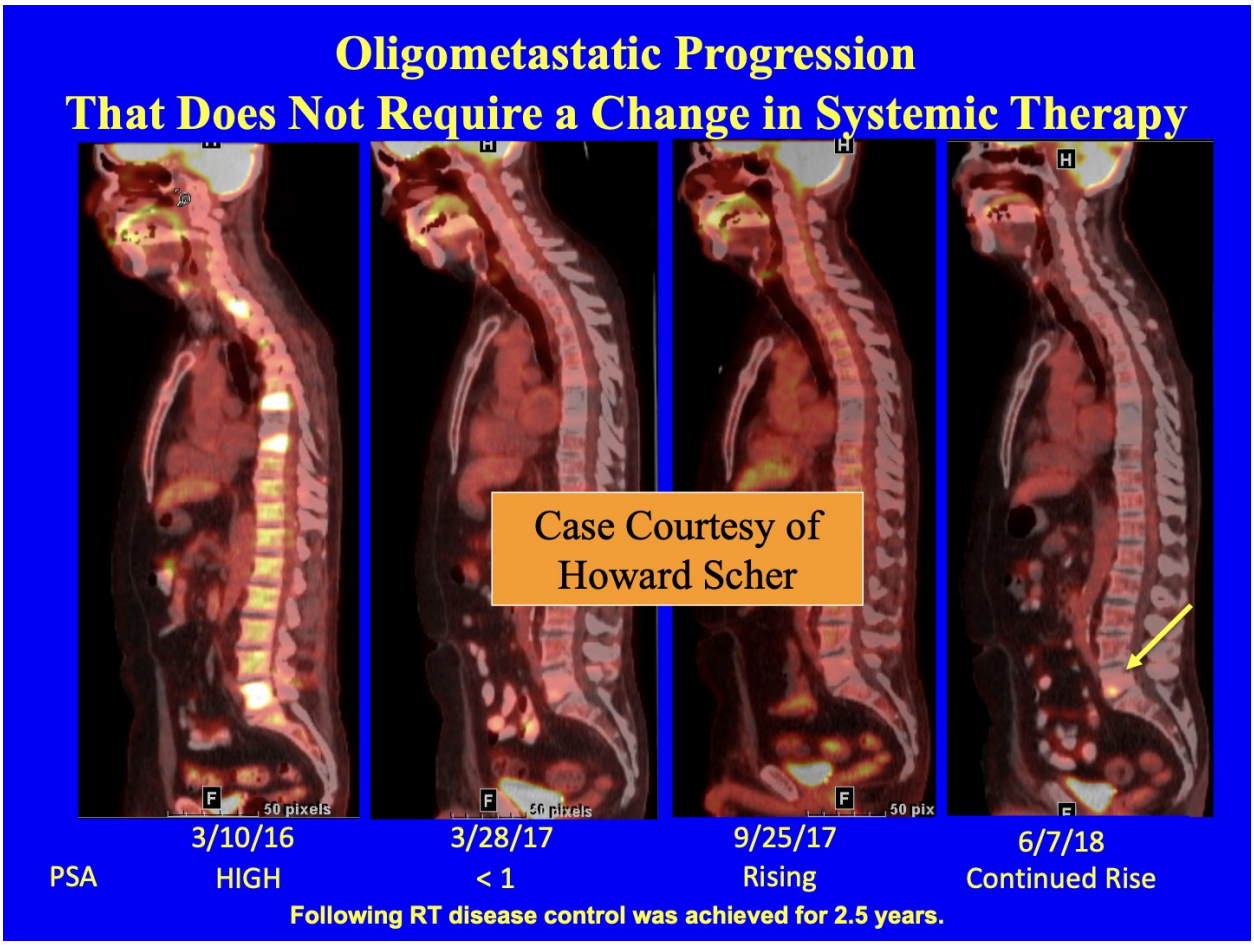


So this isn't a case of an extreme quantum sensitivity without or no DNA repair Deepak were the oddball but nevertheless, I've seen it more than once. And I think it's likely true. With regard to this is people, that's a map you're looking at a patient with a lot of circulating tumor DNA. And those abnormalities go away. That's what you want to see in D is non detected.

“The Current and Future Landscape of Metastatic Castrate Resistant Prostate Cancer” (Oliver Sartor) [#62]

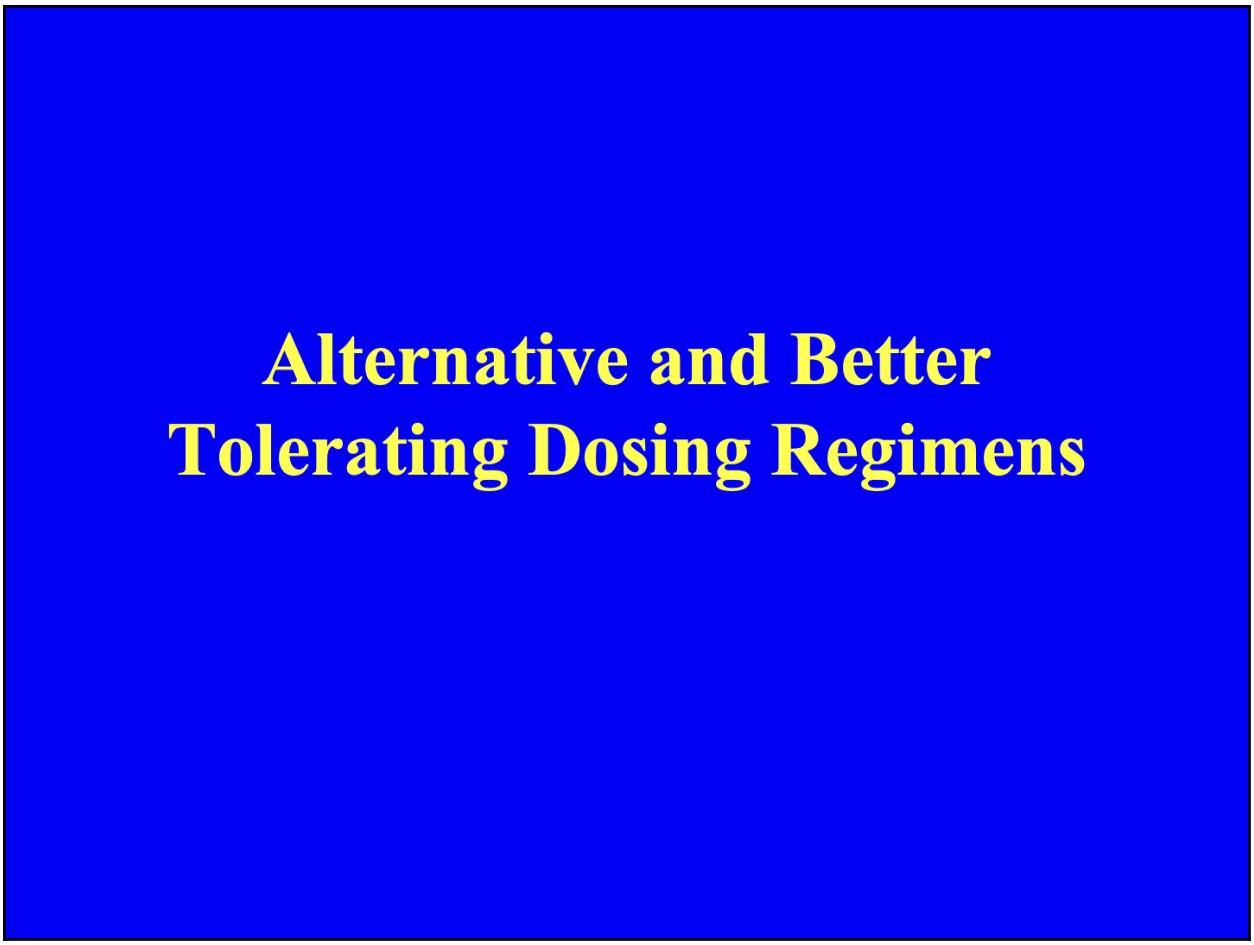
Oligo-progression is important.

“The Current and Future Landscape of Metastatic Castrate Resistant Prostate Cancer” (Oliver Sartor) [#62]



This is a case where what we have is a let me see can I make an advance Yeah, make it make it in advance. The patient starts out with a multiplicity of lesions on the PSMA. The PSA gets to be undetectable, the PSA starts to rise, and you have one spot that's called oligo progression and hear you radiate that one spot. And this patient continued the same therapy for two and a half years. So that's pretty good. That's a case from Howard Scher. He gave me the slides so I gave him credit.

“The Current and Future Landscape of Metastatic Castrate Resistant Prostate Cancer” (Oliver Sartor) [#62]



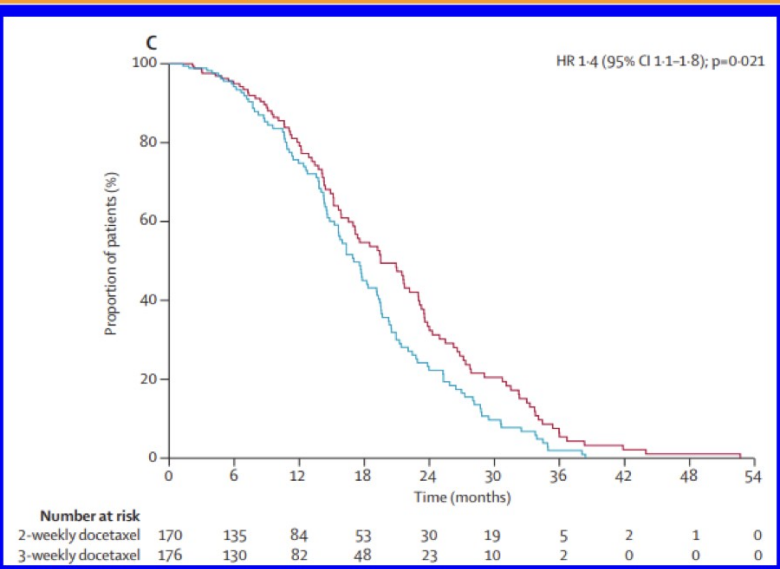
There are alternative and better dosing regimens.

“The Current and Future Landscape of Metastatic Castrate Resistant Prostate Cancer” (Oliver Sartor) [#62]

2-weekly versus 3-weekly docetaxel to treat castration-resistant advanced prostate cancer: a randomised, phase 3 trial

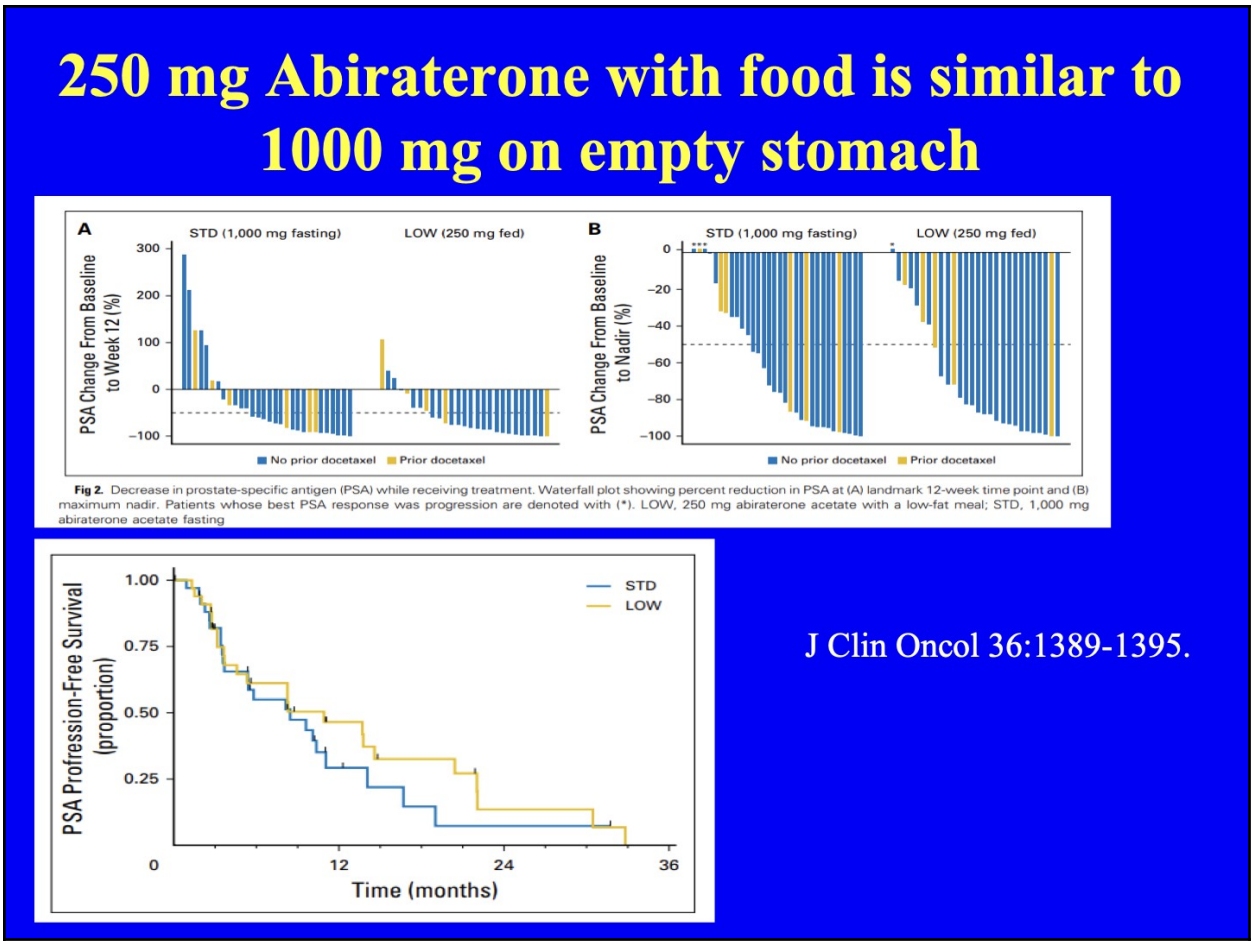
Pirkko-Liisa Kellokumpu-Lehtinen, Ulrika Harmenberg, Timo Joensuu, Ray McDermott, Petteri Hervonen, Claes Ginman, Marjaana Luukkaa, Paul Nyandoto, Akseli Hemminki, Sten Nilsson, John McCaffrey, Raija Asola, Taina Turpeenniemi-Hujanen, Fredrik Laestadius, Tiina Tasmuth, Katinka Sandberg, Maccon Keane, Ilari Lehtinen, Tiina Luukkaala, Heikki Joensuu, for the PROSTY study group

Better survival with 50 mg/M2 q 2 weeks vs to 75 mg/M2 q 3 weeks



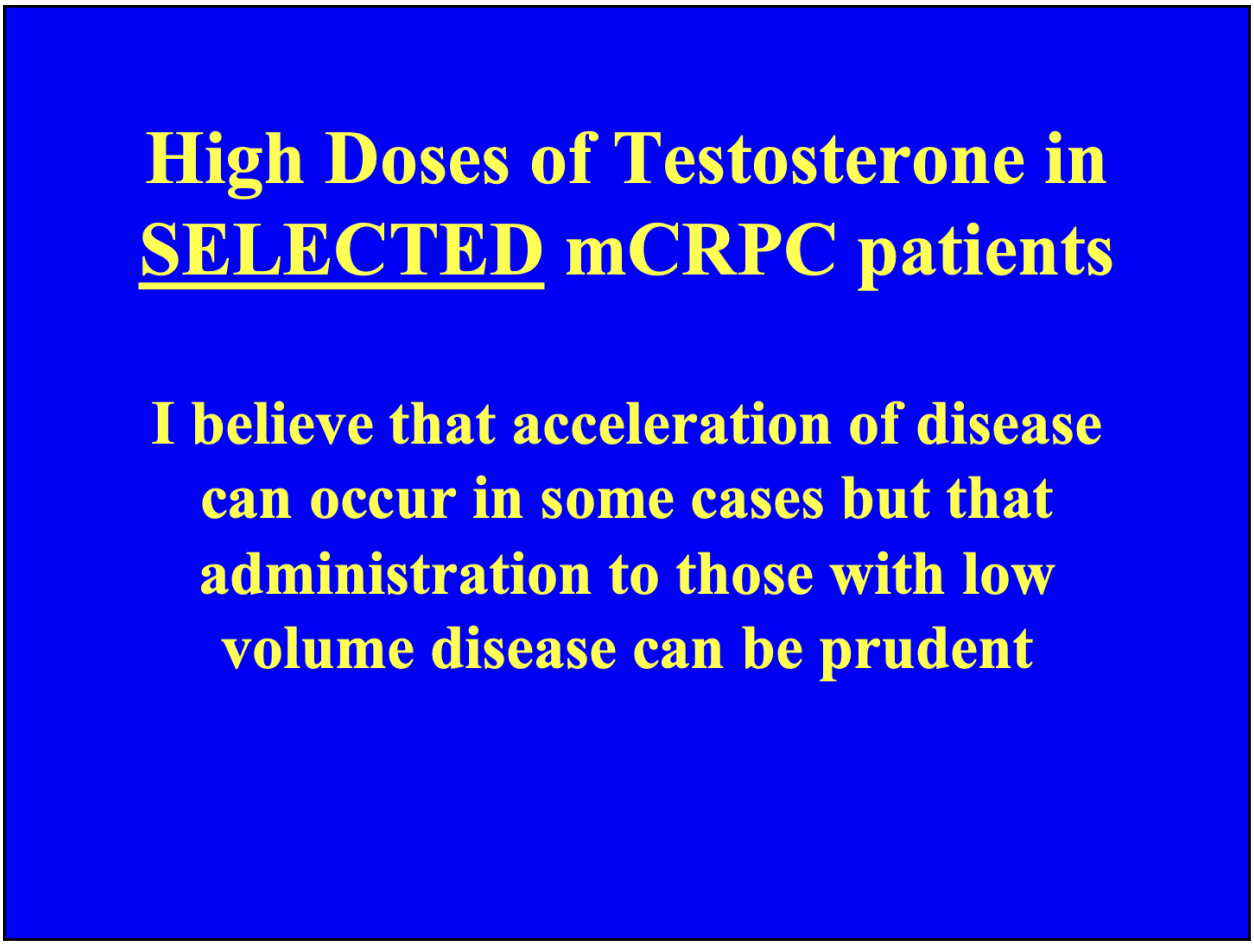
Docetaxel does a little better with the 50 milligrams Q two weeks, as opposed to 75 Q 3 weeks.

“The Current and Future Landscape of Metastatic Castrate Resistant Prostate Cancer” (Oliver Sartor) [#62]



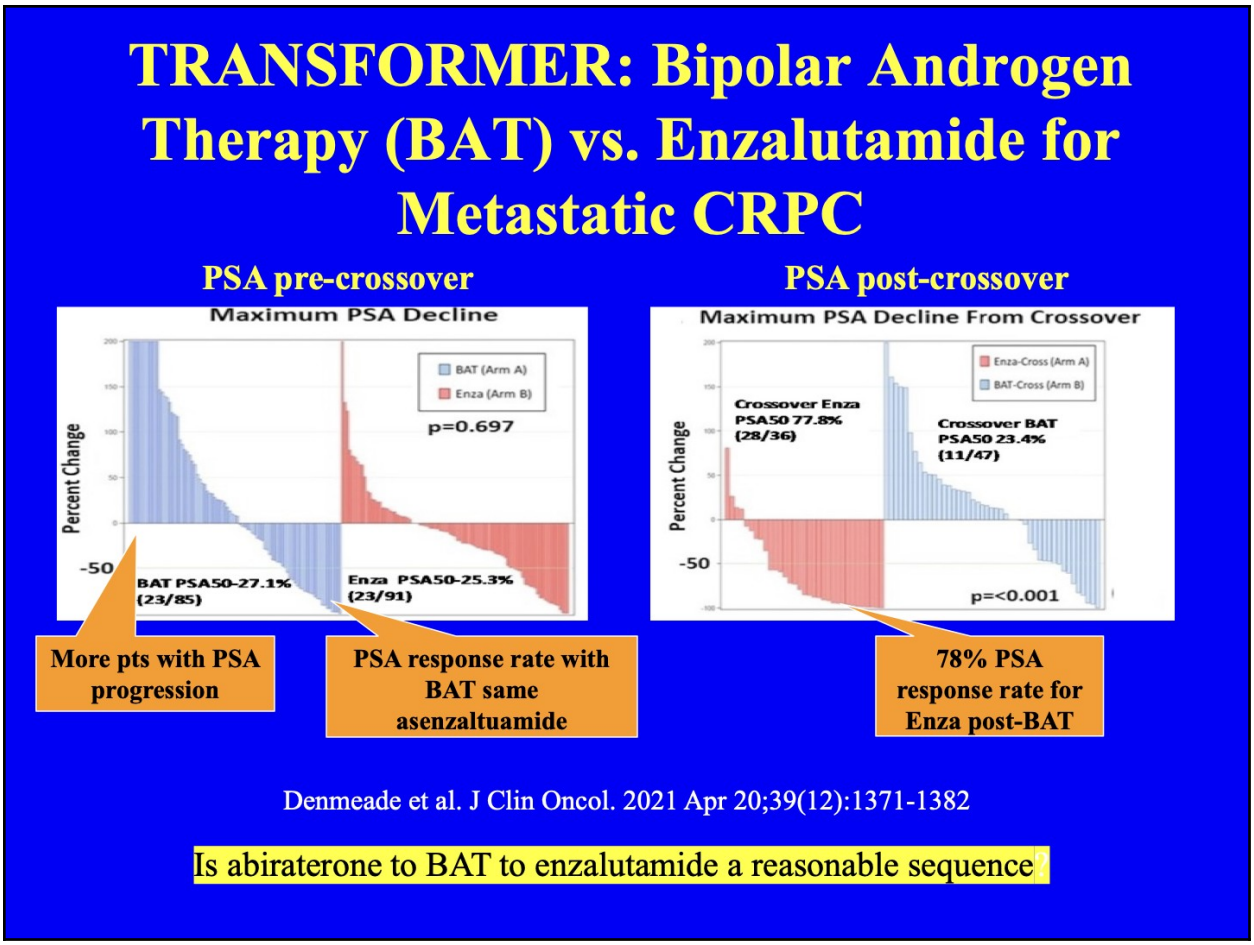
Abiraterone on empty stomach is probably just as good as abi with food, 250 milligrams with food, probably pretty similar to 1000 milligrams on an empty stomach. Not absolutely proven, but certainly good data to support that.

“The Current and Future Landscape of Metastatic Castrate Resistant Prostate Cancer” (Oliver Sartor) [#62]



High dose testosterone, you gotta be careful with it. I'll simply say some people have disease acceleration, we typically use it post to Abi.

“The Current and Future Landscape of Metastatic Castrate Resistant Prostate Cancer” (Oliver Sartor) [#62]



We published on their system from the TRANSFORMER trial in JCO. Sam Denmeade. And basically, on the left hand side, what you can see is the PSA response rate is pretty much the same as Enzalutamide. But more of these patients have PSA Progression. And I've only used it in patients that I think it's safe to have progression and still not hurt the patient. But one of the really interesting things is, after you give testosterone in a high dose, you can resensitize to the hormonal axis. Here, you're looking at a crossover, for Enzalutamide post BAT and have a 78% response rate. So going from Abiraterone to BAT to Enzalutamide is a reasonable option for some patients. And I think that's something that the field has not picked up on very well.

“The Current and Future Landscape of Metastatic Castrate Resistant Prostate Cancer” (Oliver Sartor) [#62]

Brief summary then will go to q&a. Multiple agents have been shown to prolong survival. Newer hormones are going earlier that changes your downstream options. Chemotherapy continues to play a role and I didn't really talk about cabazitaxel. And it continues to play a role and you cannot dismiss it. Biomarker selection is here to stay and precision medicine by genomics is only about a 20% hit, I think that we already have from Saito Sitacles early going to shape the landscape. I could go on a lot about the newer radiopharmaceuticals. I think a lot about that. But I think we might cover it in q&a. But I could put up some slides we already have, by the way, the victors that announced positive in the pre chemo space metastatic CRPC piece PSMA PET positive.

Brad Power 18:20
That was a great summary. And thank you for keeping it short, so we can have time to chat. Jonathan, I know you wanted to ask some questions.

Jonathan Starr 18:45
Thank you very much for giving this talk and also responding in advance to some of my questions. I'm interested in the things that are in development that might become available soon, that might have some special advantages. And one that I've been following for a while that I've mentioned to you is Sarasabulin, also called Veru 111. It's in a phase three clinical trial

or was, and it was close to completion. But according to what I heard from someone at veru, sort of late in the game. The FDA informed veru that this was not going to be enough to get FDA approval that they would have to do yet another phase three clinical trial, comparing them to chemotherapy, and veru is sort of short on cash and this would take a long time. and all of a sudden, something that seems promising. Looks like it's not gonna be available.

Oliver Sartor 20:06
Yeah. Jonathan, let me just stop you there because it's not very promising. Okay. And the thing is that it is not a particularly active agent. It's probably an oral taxane in so many ways, you know, they cast it as Ivanka. The the way, the the the sort of ran the trial that I think they wanted to run was not going to pass FTA muster. So they dropped it, it is not being pursued. I don't think if you go to the very website, and I did check it out, they made note that they have dropped prostate from the development. So I just don't think it's going to go forward. And to be honest with you, I didn't think it was very promising in the first place.

Jonathan Starr 20:55
Well, it seemed to have maybe not better efficacy than Taxanes, but a lot less toxicity. And that seemed to be a positive thing.

Oliver Sartor 21:06
You know, if you want to do a non inferiority trial, you got a big task ahead. I'll simply saying that they chose not to do it. So it's not going to be developed. I think we can probably move on to other topics because that topic is not going to go forward.

Jonathan Starr 21:24
Okay, disappointing..

Russ Hollyer 21:34
What is your opinion of the Step-Up trial? A bipolar androgen therapy trial.

Oliver Sartor 21:47
I don't even know Step-Up. But I know that bipolar androgen very, very well. Remind me what Step- Up is.

Russ Hollyer 21:55
Step-Up is testing two different arms. One is doing BAT for three months, and then enzalutamide for three months and then repeating. The other one is doing BAT until progression, and then doing enzalutamide until repeating. And then they have a control arm.

Oliver Sartor 22:19
You know, I like that. Unfortunately, I don't think that'll change practice. The way you've described the trial, it's not going to be a true phase three. But what I'll say is that both are probably reasonable. The data that we have now confirms that you could use BAT until you begin to have a failure, then you switch over to the enza. I think that's a good way to proceed.

And I do it. Whether or not you know, a 3 month cycle is better than 1. It sounds like a Hopkins trial. Is that a Hopkins trial?

Russ Hollyer 22:58
Yes, it is. It is a clinical trial registered with the government.

Oliver Sartor 23:07
It’s an NIH funded trial. I think that is interesting. I really do. And I've used BAT in probably about 90 patients. And in particular the post enza. And by the way, you can sometimes just go back and forth. So I like the concept. I'm not sure about just comparing two different ways of doing it. But I, you know, I don't have any data on the second way. We know the first one, but I think it's a good concept.

Russ Hollyer 23:52
What do you think of Abiraterone with BAT?

Oliver Sartor 23:53
You know, it works. I think the rationale is a little bit better on darolutamide, enzalutamide and apalutamide. Because of the blocking. If you're going to be using Abiraterone and BAT you're kind of dependent to what's called the d4 metabolite to block the AR. And that's a little less proven. I mean, even though it'll work and I published on it, nevertheless, I think that darolutamide and enzalutamide are more proven. And by the way, they're basically the same. They bind to the same receptor and bind in a very similar way. The side effect profiles are a little different. But the bottom line is that they're all in the same domain.

Russ Hollyer 25:16
I find that darolutamide is very easy to take. And Xtandi was extremely difficult for me.

Oliver Sartor 25:23
I would concur. If I had a choice, I would use darolutamide. I don't always have a choice because we don't have a metastatic CRPC indication for darolutamide.

Brad Power 25:40
Rick Stanton is a co founder of the Prostate Cancer Lab, just to introduce him, and he's a bioinformatician, was at Amgen and Human Longevity. So he's very technically knowledgeable.

Rick Stanton 25:59
I've got CDK12 mutations. Is olaparib promising for that or was that a coattail thing?

Oliver Sartor 26:08
It was a coattail. If you go to the gene by gene analysis, which I actually showed very quickly in the slide deck, the CDK12 is not much now. Rick, we have published and I had more experience of using a carbo platinum based regimen in CDK 12. And I've actually done pretty damn well. I mean, I could look up the reference. But if you look up starter Carbo, Platinum CDK

12, you'll see a case report where it just really worked very, very well. There could be a little bit more activity. If you look at the talents app or in the total separate data in tempo Pro two turned out to be a little bit better with city cage, as well. But you don't have access to tell that brand. And I still think that the olaparib is pretty, pretty borderline at best. Okay. Yeah. I mean, I mean, look at the data, go to the appendix, go to the appendix of the New England Journal paper, and look carefully at the gene by Gene analysis. And you'll see the data. Okay. Yeah. Thank you. Just wanting craps.

Rick Stanton 27:37
I love your target slide. And we've heard promising things about B7H3. What do you think about that as a target and a clinical trial that's going on?

Oliver Sartor 27:57
I think it's reasonable. And what else say is, it's more toxic than what you would prefer? So I will talk to one of my Johns Hopkins colleagues who's given it. And I'll simply say that the toxicity is not so easy. Um, I think it's a reasonable target. I think, you know, there are two B7H3s out there. There's some Macrogenics, and there's also Daichi Sanyo. I think that the Daichi might be a better way to approach it. But at the same time, I don't know, I don't have personal experience with it. But I think it is a reasonable target and needs to be explored further..

Rick Stanton 28:52
We've heard about the Greek test, which is from RGCC, and it's based off of basically a blood draw, and CT DNA and they grow your tumor cells from the blood draw, and then submit a battery of tests. It's out of pocket. So I think it's like $2,300. I wondered if you had any comments on that test? Was it worth it? When your backs against the wall or math or,

Oliver Sartor 29:34
I'm not familiar with that particular test, but I'm very familiar with the concept of like we would in bacteria, we do a culture and sensitivity, right? You know, we culture the cell and then the bacteria and then we treat it with x different things and come up with a treatment plan. It turns out that you can get biomarkers of resistance pretty well, but finding sensitive Yeah, but he has been a little bit tough. I haven't seen anything that I find totally convincing yet. Um, and and so I'd have to learn more about it. But there's smart people working on it, it might be worth a try. I'm not familiar with the Greek tests per se. Okay.

Rick Stanton 30:26
I'm on BAT. I'm about to find out whether I have significant progression. I think it's mixed. I had a met in my spine disappear. And yet I've had progression and other parts of my body evidently. So with sippy and eight, it's a pretty long half life, relative to the duration of the cycle four weeks are great. And so I thought, well, you know, I can get sippy and eight from my doctor, rather than pro pronate, which is, I don't know, I'd have to figure out how to self administer. And Russ has been great with, you know, incident and advice.

Russ Hollyer 31:15

if I can interject. Rick, you can get propionate from Empower pharmacy.

Rick Stanton 31:26
Okay, but I went with cypionate. And I thought, hey, you know, who cares that much? If about the half life? If why don't I put darolutamide in at the half cycle. And then I would kind of get, you know, some type of bipolar activity. But my doctors were like, whoa, whoa, whoa, whoa, whoa, you know, if, if we wanted to do that, we do that. So, what do you think?

Oliver Sartor 32:02
Rick, I have a different opinion than the Hopkins folks. And I, I go, I'm gonna go back briefly, to the first case report that I use for the high dose testosterone. And I am not at all convinced that BATt is necessary, I don't think you need to go up and then down, I think you need to go up. Now. Let me give you the example. And let me give you a way to turn it on, turn it off a little bit better. I think. If you use transdermal, the halflife is very short. If you're using cypionate, you have it lingering around for a long period of time. So the very first time that I was using this, I was scared. And the reason I was scared as I was using it on a very, very advanced patient, PSA was 400 and rising rapidly and a guy who had been through umpteen lines of therapy, and we were just running out of options. So I put on the patch and titrated it to 1000. That's nanograms per deciliter. And he responded, there was no back there was no there was no, there was no up and down there was just now that gets you a little bit closer to testosterone control. Now, what you want to do is reset the androgen receptor and you reset it with the high not the low. So if I had a little more time on my hands, I might explore something. We're just looking at high T, not BAT. And I think I would come out ahead, personally, or at least I would come out equal. But nevertheless, I'm basing that on a very minimal number of patients. And I guess the bottom line is I'm not totally convinced that BAT is necessary, but the high T is necessary.

Brad Power 34:17
Robert Gurmankin is a dentist. He comes to us with a bit of medical knowledge. If we have any jawbone, salivary, or teeth issues that come up in discussion, he's our expert.

Robert Gurmankin 34:35
I know that PARP inhibitors can be used with BRCA when it's found in genomic analysis from the tumor. What kind of percent of cells do you need for that to be effective?

Oliver Sartor 34:50
Yeah, great question. Um, you know, in the germline, you'd have a pretty fair amount of BRCA absence in cells, okay, what you need and a lot of people forget this, we assay for, a monoallelic deletion, and then use the PARP. But the truth is, in order to get the synthetic lethality, you have to be missing the PARP protein. If you have one part allele that is normal, then you're not going to respond to the PARPr inhibitors. But it turns out, particularly for BRCA2, that you end up with biallelic-like deletion, although at times, it's a little confusing, because it's not always a double mutation. Sometimes it's deletion and a mutation. Sometimes it's a double deletion, sometimes it's an alteration, perhaps even in the methylated portion of the promoter,

so you don't get expression. So I'll simply say that our science behind BRCA choice is not perfect. But the germline and the somatic, you both are going to do pretty well. If you have BRCA2, but on the other hand, it's not perfect. And we need deeper genomics, but we're not quite there yet.

Robert Gurmankin 36:16
Where are we with CAR-T?

Oliver Sartor 36:19
Yeah, disappointing, you know, every CAR-T seems to stop. So there were two that have been looked at. Number one, with the PSMA, as a target and another looking at PSCA as a target. One was done by Bellicum. And the other was done by, I forget. But it's disappointing. And if you want to look globally, at disappointment with the solid tumors in CAR-T. I think there's just a lot of heterogeneity. And we need something more than the CAR in order to hit it off the way. And we know the biospecifics you can get it. One of the reasons I like isotopes is what I call the Umbra and penumbra. When you bind to an isotope and you have something like lutetium, you not only radiate the cell that it binds to, you radiate the microenvironment. That microenvironment can include blood vessels and stromal supportive cells. And you're basically treating the tumor as a whole, even when there's heterogeneity in the expression of whatever your target might be on the tumor cell. I'm worried with CAR-T, you need to have a little more homogeneity. And where you see the beautiful CAR-T responses is the hematologic malignancies that have much more simplicity, they don't have the same degree of aneuploidy. You know, this is an aneuploid tumor. And we don't talk about that enough. There is huge heterogeneity in the chromosoma;l we're looking at CT DNA, we're not assessing diploid status, their whole genome duplications, whole chromosome arm duplications, I'm telling you it's complicated as hell. Okay, thank you. I hope that helps, Robert.
Jonathan Starr 38:21
Thanks for the answer about Sabazabulin. On other drugs that have been in development that seemed to hold some promise, let me select out the sorts of other AR-oriented drugs like the N terminal domain inhibitors and the AR degraders. Yep.

Oliver Sartor 38:53
Yeah, so just like ARV Yeah. So ARV 110 is probably going to go into a phase three. There, there is a second or Venus compound. I'm sorry, I forget the number. They just had an announcement on it, which may be even better because the ARV 110 doesn't hit the 7027 66. That's it air 767 or below 7666. Thank you. Who said that? Right? Yep. Anyway, thank you.

Rick Stanton 39:29
Yep, it was Rick.

Oliver Sartor 39:31
Yeah, no, no, thank you. Um, you know, there's clear activity within the 870 587 Da, which is the more common mutations. And it looks like the bit newer compound may hit the 702 is well, they're trying to catch to this overall login binding domains which will take in things like 716 and

a 77. But the day It's not very strong there. But the error degraders are potentially interesting, particularly if you have a mutation, whether or not this new set of 66 is going to hold up. I don't know, I need to look at the data more carefully. But I'm very familiar in an author on on the 110. The in terminals have been disappointing to date, you know, the first in terminal turned out to be a real failure. The second in terminal did have a response. And I haven't gotten an update on that. It could be interesting, but part of the problem is, after you inhibit the AR with Abiraterone and Enzalutamide nail, you're beginning to have tumors that are driven by non AR components, the error components are getting smaller. And when you're starting to run into things, you know, more p 10. Loss, more RB loss, and the air driven tumors are present in a minority, but they just you're not going to you're not going to kill them all. And you also have to deal with the problem of heterogeneity. So after you going through Abbey and ends, or apalutamide, darolutamide, whichever one you want to use, you're ending up with only a minority of the patients being AR driven in my opinion.

Jonathan Starr 41:27
Okay, and my final question, if I can have it, is about Sipuleucel-T. You know, I've read about this, you proceed study, when we look back at, you know, huge 2000 patients, you know, scaled by initial PSA, and it appeared that or baseline PSA. And it appeared that, that there was a pretty strong correlation in disease specific survival between baseline PSA, and disease. Well, PSA and disease specific survival. I mean, on the order of years, you know, several years of difference. So, like in the lowest quartile PSA, survival was

Oliver Sartor 42:17
Jonathan, I'm an author. I'm an author on all those papers. I know the day. Okay.

Jonathan Starr 42:22
All right. Well, you sort of dismissed it earlier in your talk today again. Yeah. Why?

Oliver Sartor 42:29
Well, you know, because it was developed in an era where there was no ABI, enza, there was only taxanes. And we really have entered into a different realm today. And I am a little skeptical about the one positive randomized trial published in 2010. And nothing that has followed that in a randomized way. But what you don't know is they had another randomized trial that failed, and they never published it. And there's no RPFs there's no PSA. And the biomarkers are inconsistent. I am not very strong and simple cell T based on 13 year old phase three data, show me something new, and then I'll be more enthusiastic, but you better use it in the current landscape. Don't go back and crank up the ADT and docetaxel has been your only treatment alternatives.

Jonathan Starr 43:33
Well, isn't that Proceed study, something new? No,

Oliver Sartor 43:38

The Proceed study was first of all, non randomized. Second of all, it's real world data. And third of all, if you look and see when most of the data were published, in order to get that long term follow up, you have to start a long time ago. So that real world data is pretty good, but it's not controlled. I'm an author. I published it. I think if you're going to use Sipuleucel-T, you use it early. That's where you get your biggest benefit. But on the other hand, I just think we have better drugs today. And I don't use it. I really haven't used it in my practice in a while.

Russ Hollyer 44:27
You mentioned constant testosterone. I just want to make a quick comment. I did RP and then I did four and a half months of ADT and then two years of constant high testosterone. My PSA went from <0.01 to 0.17 over two years. And then I started BAT. My PSA dropped to <0.01 and now it's slowly risen. However my CTCs have gone from a moderately high value to undetectable and I don’t have any mutations. PSMA-PET scans are clean.

Oliver Sartor 44:59
I think It's very interesting. And if I had a little more time on my hands, I would pursue it more. Because I think there's some interesting elements there that we just haven't fully figured out yet. I have many friends at Johns Hopkins. They're my friends and are my collaborators. But it doesn't mean I agree with everything they say. And I think that BAT has gotten a little bit fixed. I think there are different ways of doing it, perhaps. And that it's going to take a little while to get it unraveled. But I applaud the investigation into testosterone. I think it's very interesting. It gives a great quality of life, too. Yeah. Absolutely.

Brad Power 45:47
Brian McCloskey is a co founder of the Prostate Cancer Lab.

Oliver Sartor 46:00
I did want to make one quick, quick comment on Provenge, I used it. I actually have no benefit from it, either through PSA or through radiographic view. So, no one but take it for what it is. My question really is about understanding precision medicine. And digging into that a little bit deeper. One of the challenges that I've seen as a patient going through this process is that there really is not quite an emphasis on advanced diagnostics. So a lot of it is focused on selecting panels. And so I've really pushed on that lever in my treatments. I've been, I've had three different lesions over six, seven years and have been sequenced. I've had DNA sequencing I've had RNA seek, I've also had proteomics, and one of the things I found working with campus, in comparing my RNA seek curl 20,000 gene is my expression relative to 1000, advanced prostate cancer patients. And I use that information to identify targets I think would work versus those that wouldn't. So for example, if we look at p SMA, my expression relative to 1000 patients is only in the 38th percentile. So I'm really not too excited to go after, for example, for victo, when I'm looking at my AR expression to be in the 98th percentile, so I use that plus got AR copy number gain, I have a high AR expression through proteomics, and I've gone after bat. So I just started back. But I wanted to dig a little bit in terms of get your thoughts in terms of is how does RNA how does how to proteomics fit into the landscape of precision? Medicine? I

just don't think that we're really leveraging a lot of the advanced diagnostics that are sitting in life sciences companies.

Yeah, Brian, I agree with you, you know, the you said a couple of things that that are interesting. You talk about our RNA seek clip and kind of explain what that is. So as we get everybody on the same page, first of all, when we're looking at typical genomics, we're only looking at the DNA. And we're talking strictly today are we talking about the typical genomics are two major types, there's the germ line of what you're born with as a tumor, which is in your tumor. And we're looking things like rocketed mutation or deletion or something like that. Gene expression is a completely different approach. And I think it has the potential to be very powerful. The problem, in general, has been getting pure populations of cells, number one, number two, it turns out that DNA sequencing is really powerful. And RNA is really unstable. So you can do RNA analysis. And by the way, there's some really interesting things that have come out of decipher, which is a way for prognostication, that's an RNA based approach. But RNA stability is a real issue. And when you use the formalin fixed issue, you often end up with very degraded RNA and it's hard to get really good signals. Proteomics could potentially help to overcome that. I think we need to leverage proteomics, I think we need to leverage exosomal cargoes I think we need to leverage circulating tumor cells, I think we need to we need to leverage RNA expression, all of them in more detail. One of the things and this is a little bit unrelated, but it gets to what I think is your very important point is how do we classify these tumors anyway? You know, you talked about individual expression patterns, it turns out is a beautiful man New scriptures in science last year from Cornell, and it broke down CRPC into four components. Number one was the typical ad. No, that was about 50%. But in addition, there was a stem cell that nobody is really talking about. Nobody talks about AD no and neuro endocrine. But the stem cell is probably more important to neuro endocrine. It's characterized by certain transcription factors, AP One, we don't know a lot about what's on the cell surface, we don't know a lot about that we don't necessarily know how to treat it very well. And then there's a wind driven, and when windpipe pathway is one of the oncogenes, is quite important in a number of tumors. And it's probably going to be important in prostate for probably somewhere around eight to 10%. But nevertheless, classification with novel methodologies are in a better DNA, including whole exome or whole genome, running RNA seek wanting proteomes. All of those are going to be I think, part of our future. We're just not quite there commercially, yet. Okay, thank you. Yeah. But you raise a good point.

Brad Power 51:13
That's a good segue to Allen Morris, who's a pathologist, who is there in his lab.

Allen Morris 51:22
My question, so this biomarker stuff, this genomic stuff, concerning prostate cancer is new stuff. It turns out that some of the prostate cancer patients in our lab have overexpression of HER2. And the reason I bring that up is this is not new. We can stand on the shoulders of breast cancer, HER2 has been investigated, and as well vetted concerning breast cancer. And there has been a recent sea change in breast cancer where let me give you guys a backgrounds, pathologist semi quantitatively graded her to new overexpression on a zero to three scale. And

forever. Her two new positive was only considered three plus, well, there's a currency change in breast cancer, where even one plus and two plus are now instead of being considered negative are considered low expresses. And that's visa vie, this new class of drugs, the antibody conjugates with her two new and they have this isn't something novel like B BH seven, three. And whether it's superduper, toxic or not. This thing has been vetted in breast cancer, and has shown incredibly positive results so that it is revolutionary in breast cancer. And the reason I say this is because one of the oncologic principles that you are relaying to us is that earlier is better that all these things that have been vetted in the metastatic castrate resistant space have now been a lot of them migrated all the way back to hormone sensitive state. And the idea is that you want to start these things earlier. Well, my I guess my opinion and I want your advice on it is anybody that's uh her to new overexpressed or should run and get this this treatment that's already been vetted in breast cancer, they shouldn't wait around for trying to figure out what the seat rights sequence is, which is never going to be found out in this short period of time of two or three years right now, which is the window that these that we have,

Oliver Sartor 53:46
gosh, you know, the only problem is something called pair approval, and they won't do it. And so what you're gonna do is if you can afford $20,000 In infusion, you can get it but the insurance companies won't do it until they have an appropriate trial run and prostate. I agree with you. The drug is called Enhertu. I made a reference to be 783. And the date she's Sanyo a little bit earlier, that using the same warhead in her two and the B 783. From date she sent you, but the problem is the drugs not available unless you can afford to pay. And I think you'll I think it'll be $20,000 An infusion. So I that's the problem. You have to do the trials. And then you have to do the trials and get the FDA approval.

Allen Morris 54:46
Let me just comment that the standard of care in the United States is one year of treatment, but in Europe, they get equivalent results with six months. So I think there's a lot of people with means here. It would be six times 20,000, which is actually in the same ballpark, as Sipuleucel-T at 100,000, unless the price tag has changed.

Yeah, the only problem is one is paid for by insurance and the other is not. That's that's the distinction.

Jonathan Starr 56:01
What is this drug ENHERTU?

Oliver Sartor 56:05
It's a toplus pomerase one put on the HER2 antibody. It's an antibody drug conjugate. It's the best antibody drug conjugate I've ever seen. There's it is the best antibody drug conjugate I've ever seen, period, it really has been a game changer in the hurt to positive breast cancer field.

Can I just jump in here for just a second, I want to dovetail a little bit of the information I have on my proteomics, my proteomics, and my RNA seq. actually so that I have heard to using any

limited gene panel diagnostics, it never identified her for me. So I know, for example, with RNA seek my expressions in the 75/75 percentile for for advanced prostate cancer patients and my proteomic confirmed that a little bit. So just as a map was actually put on my list of potential drugs. And I think this is an example of how you can use more advanced diagnostics to identify patients who might actually benefit from this, this drug, how many advanced prostate cancer patients even know that they have or do?

Brian McCloskey 57:22
Yeah, Brian, it's, it's interesting, you know, we don't know a lot about the expression. And I think it's going to be modulated in part by the prior treatments. And so I think it could be an evolutionary acquisition, I actually think that when you when you look at the herd, to, it's a good target, but here's here's the problem, Brian, you can't go from an unvalidated biomarker to a treatment, you really have to put the two together, you have to walk in you biomarker walk in your treatment, and do the trial in order to show that it's going to work because otherwise the expression patterns, you know, it may not even be on the cell surface. And the way it hurts you binds. It has to be on the cell surface in order to be active. Yep. Okay.

Jonathan Starr 58:20
I was hoping to get some sense of what we could hope for going forward. That seems to be or at least high testosterone and Enzalutamide Resensitization seems to be a possibility to be excited about. But what else? It seems like that?

Oliver Sartor 58:46
Nobody asked me till now, what I'm excited about.

Jonathan Starr 58:50
What are you excited about?

Oliver Sartor 58:52
I am really, really excited about the targeted Alpha therapies, you know, so first of all, I mean, let me let me let me give a little bit more data on the nutrition so Titian is going to be FDA approved, in my opinion in the pre chemo metastatic CRPC pits may pet positive space, that's going to be a huge sea change for the vision trial. I think we'll open it up to probably triple the number of patients. There's a press release on December 5 from Novartis saying that that trial is positive, but it's yet to be presented in a public forum, that public forum may come up in the fall and somebody you know, might be presenting it. The data that is more conjectural is in the upfront metastatic hormone senescence space with Lutetium. And that trial is accruing very, very well, with ADT choice of hormonal therapy. For biospecimen rotation, right, that fits my location. I could also bring up the slash trial, also pre chemo preliminary data at ESMO. Last year, but you know what looks good enough. I think it's gonna be a positive phase three. All right, the other phase three, which is worth mentioning, I don't have a lot of enthusiasm for it. But the intentionalism plus cap is at NAMM trial, the contact was a contact to or contact rate, whatever it is. Some people think that that could be a pretty reasonable winner. But the data for

the actinium games is really the best data that I've seen. And some of the data is absolutely outstanding. Have you seen any of that data?

Jonathan Starr 1:00:54
I have not. I thought it was very toxic, though.

Oliver Sartor 1:00:58
Well, the most toxic thing I can think of is advanced prostate cancer. That's pretty. That's pretty damn toxic stuff. I mean, I may put up a slide right here. Let's just see if I can pull one up real quick.

I think this is worth talking about. Because I think it's, I think it's something that is potentially important. So hang on a second. I'm gonna display my screen one more time. And we'll go, we'll go here. Can you see that? Yes, yes. Okay. So this is from a lecture I gave in word I think I gave this in South Africa are no no, this was posted up half copy of where I gave a lecture I gave it on someone come. So first of all, the alpha particles are two protons, two neutrons, they're really big. Compared to the beta, they're about 7000 times bigger. And something we call the linear energy transfer is monstrously bigger. And that's the damage that it causes, that the range of tissues is extremely small, it's only about 40 to 100 microns. And that's, that's important to know, there, there are a whole variety of alphas that are being looked at as 13 to 11 led to 12 actinium. Up actinium is probably in the lead here's kind of the basic landscape right here. convergeone t lakes there have anybody's pitch me it is now with Fusion points, developing the artists developing Bayers develop, developing advanced sell it and more. And, you know, the the this is, so this is what without prior Abby ends up using actinium 2258617. maestro's fk out of out of Pretoria, South Africa. And that's his waterfall plot in the 617. Now, what's the problem here? The problem is the salary toxicity. That's the issue. This is a fascinating article from Mike am very recent. This is hormone sensitive prostate cancer without the hormones. There's no hormones being used here. And this is the activity of 617. Now, the toxicity, I think, still needs to be further explored. And you know, one of the things that we know, and this is from Mike, you know, you, you end up without a lot of salivary glands. But I think we're going to work on that. I think we're going to get better on the salad berries. And one of the things about the alphas is they work post beta failure. And, you know, here's here's an alpha post beta failure, people are looking at it. This is also from Mike right here looking at siltronic acid with actinium. So the bottom line is, I think that we're going to have solutions here. I think it does have toxicity. But I think there are ways to get around it. I think the J 591. is interesting. That's out of Cornell. But we're gonna get more exploration, this instead of fusion plus relationships with them in therapy, possibly, and more. There are a lot of commercial Alpha programs that are ongoing, and you got to be aware. So that's just, you know, I'm pretty excited about this stuff. And I'm trying to get more. Get my hands on more and moving forward.

Jonathan Starr 1:05:11
Alright, so we can hope for that.

Russ Hollyer 1:05:25

“The Current and Future Landscape of Metastatic Castrate Resistant Prostate Cancer” (Oliver Sartor) [#62]

What is your opinion using cypionate vs. propionate for BAT?

Oliver Sartor 1:05:37
I don't really know. I've used cypionate .

Russ Hollyer 1:05:41
Have you ever used proprionate?

No, cypionate. I've only used proprionate a little bit. I've had, you know, a little bit of luck with it. I had a patient over at the VA, that got it. But I just don't have a lot of experience, I think it'd be great to look at comparative trials. One of the problems is that clinical trials are really expensive. So something like the PSMA addition is probably a 250 to $300 million trial. I put that together with Scott Tagawa. You want to do big trials, you better spend big money. And the problem is on a non commercial product. You can't get anybody to put up that kind of money. You just can't do it. And you can write little trials so you can play around. But if you want to do practice changing trials, you're going to have to have some real money behind it. And that almost means Pharma. And Pharma is going to use IP protected compounds. And that's how you're gonna get the 100 million dollar trials. That's just that's just the way it is.

Oliver Sartor 1:07:00
Russ, I like what you're doing. It's just hard. It's hard to get it done in the proper way.

Rick Davis 1:07:33
Hello, Dr. Sartor. So last time I saw you was over the coffee table at the GU ESCO. Durability. We've talked a lot about some good stuff like radionuclides and testosterone. But I'm really interested to hear your opinion on durability, especially with testosterone and radionuclides not early in the game like with Ross, but where people are using BAT late in the game because they don't know what else to turn to. How durable is it? And the same thing with the radionuclides? How durable are they and how often can they be used?

Oliver Sartor 1:08:25
The radionuclides we know a pretty fair amount. And, you know, one of the things that's a little bit interesting is the degree to which … I might throw up a couple of slides here. Again, real quick to help answer your question. And so let me come up to the share screen real quick, and I think we can do that. But the bottom line is that we, we know, you know, so on the vision trial, the median trend, radiographic progression free survival was about 8.7 months and very, very, very, very advanced patients. That is not good, but a lot it. If you want to look at the PSA decline as a predictor of survival, it's surprisingly good for those people who get a good PSA decline, because the PIs may look rotation, the survival is really, really, really good. And I'll simply say that we're needing to get more data on this for the bat. It's a bit disappointing. The bat as a whole is median is probably going to be put us in around around four to five months. But of course, some patients do extreme ordinarily, well, we have patients that have done extraordinarily well. But a lot of patients don't respond at all. Or they even have acceleration.

Rick Davis 1:10:08
How about repeating the BAT or repeating the radionuclide? Have you had experience with that?

Oliver Sartor 1:10:16
Yes, we definitely repeat that in the, you know, if we go back to say, Enzo, and then back to bat, and then potentially back to n. So we've done that, Rick, in some patients that seems to help. I've got a guy down in Alabama right now who's kind of migrating back and forth between bat and Enza. And he's done pretty well. And by the way, I put darolutamide in there. And, and apalutamide, probably in the same category. And I do prefer darolutamide. But it's hard to get unless you have the indication.

Rick Davis 1:10:54
How about repeating radionuclides? Because that's an issue we see more and more the guys want to repeat it. Eight, nine months out when they

Oliver Sartor 1:11:04
Yeah, you know, the problem. The problem is that the data that we have, is predominantly out of Australia and a little bit out of Germany, and it's non reimbursed. So I think if you had a good response, and then relapse, going back to the radionuclide would be a reasonable option. But the problem is, insurance is not going to pay. And now we're talking, you know, if you go to Germany, if you go to South Africa, you can get about 10,000 a dose. I don't know where it is, and in Germany right now, but I would guess it's probably somewhere between 10 and 20,000.

Rick Davis 1:11:44
Yeah, Turkey too. And what and how are you treating men? Because we have at least one man on this call right now in this category. How are you treating men who are hybrids who only partially respond to the radionuclides? Because they have both cells that express PSMA and cells that don't express PSMA?

Brad Power 1:12:13
Yeah, that's really a conundrum. You know, phase one trials. We use our you know, capacitor tactful carbo is a real is a really nice drug combination. Some people do quite well, with capacitor facts or Harboe. And even capacitor facts soul is remember, FX was a real drug. It's in the Australian trial. It was head to head compared to victo. And there was no difference in survival even in their FDG selected patients. So, you know, don't forget about capacity tax. So it's chemotherapy and nobody likes. But it's actually a legitimate drug. Thank you. Hope that's helpful.

Eric Hall 1:13:06
I guess I'm a little bit different place than a lot of these patients, I'm still kind of new to the prostate cancer journey. I was diagnosed last July with oligometastatic. I've been on Abiraterone and Orgovix this whole time and I had surgery, radical prostatectomy and pelvic lymph node dissection in February, but I had positive margin. So I'm kind of looking at what are

my next steps there? So yeah, I mean, it's high risk because I was Gleason 10. So I guess my question is, you've talked a lot about, you know, promising promising future things. Does that, would that change how you might treat someone like me, given that that's coming in the future? Like, I know, you mentioned some of those things are kind of like pre pre chemo chips with a lot of promise for example, right?

Oliver Sartor 1:14:08
Eric, are you on hormones now?

Eric Hall 1:14:12
Yes, I am still on that. The ABI and the Orgovyx.

Oliver Sartor 1:14:15
I would anticipate your PSA is probably undetectable.

Eric Hall 1:14:18
It's undetectable right now.

Oliver Sartor 1:14:20
Did you get a PSMA PET scan prior to surgery?

Eric Hall 1:14:25
Not prior to surgery, I had one at my original diagnosis.

Oliver Sartor 1:14:31
And you said oligometastatic,

Eric Hall 1:14:33
I had one lymph node show up. I had one llmph that would show up on the PSMA PET as well as I had extracapsular extension.

Oliver Sartor 1:14:44
Was that a pelvic lymph node or an extra pelvic pelvic lymph node? Yeah. Okay. So, you know what, what I might be tempted to do in this is we're entering into an unknown area here. So first of all, let's acknowledge that the beneficial effects of hormonal therapy and your setting were. There's one study, it was published in 1999, by Dr. Messing, and he uses lifelong hormonal therapy for node positive disease, and said people did better. Nobody does that today, nobody. So what I might be interested in doing is stopping hormonal therapy after X amount of time, and we can talk about what x is because nobody really knows and waiting for the PSA to rise. If it does, then doing your PSMA PET scan and trying to find out where the disease is. Now, we don't know if your surgery removed that lymph node. And even if it did, the standard of care for our pelvic lymph node positive disease is not surgery. They've done it in Mayo Clinic. And what they found out was if you wouldn't walk the lymph nodes, you didn't do very well. I heard your Gleason ten, I don't like that. On the other hand, treating the pelvic lymph nodes with radiation

in combination with hormonal therapy is a pretty good way. But on the other hand, we have pitched a pet I would use it. I wouldn't keep going hormones forever. And one could use a two year hormonal therapy. But that's sort of out of the blue. I'm making it up. I mean, we don't really no stampede trial use radiation in two years, and had very good results, but they use combined radiation and hormonal therapy for two years. So you're kind of out there. We don't have data for people IQ.

Eric Hall 1:16:48
Yes. I'm considering adjuvant radiation right now.

Oliver Sartor 1:16:54
It's not necessarily unreasonable. Um, but um, I keep you on the hormones for X amount of time. Then let the PSA rise up and try if it will rise up. It may not rise up and then repeat the PSA pet. So you could give a boost to exactly where the radiation is needed. But we're getting pretty conjectural. Now. You know, I mean, nobody can promise you the right path forward.

Eric Hall 1:17:24
Yeah. I have two unique genetic mutations. I have a CHK2 mutation. And I have an AlK fusion. Oh, wow. Yeah. Which is not really rare. Exactly. I was on the call earlier. She could attest to that the rareness of that.

Oliver Sartor 1:17:41
What's ALK fused with?

Eric Hall 1:17:46
dt m B.

Oliver Sartor 1:17:50
Dtmb. That's a transcription factor. I don't know much about I don't know much about that. Um, gosh, I would have to go looking at it to check to I would say is not actionable right now. That ALC is really weird. And I'd have to go look at it. Yeah, I wouldn't be able to give any any opinion off the top of my head.

Eric Hall 1:18:16
Can I email you with a couple other questions about that?

Oliver Sartor 1:18:20
My email is Sartor.Oliver@mayo.edu

Rick Stanton 1:18:38
I used to be a bioinformatics scientist back in the day, and we had hopes for personalized vaccines and offs, and we would sequence the whole exome. It seems like it's really hard to do or get anyone to do it, it seems outside of the mainstream. And I don't know whether an interesting question came up. Do you know anyone who had actually helped? And my answer

was no. Even though we would match, you know, try to do it, whether it was a driver mutation or not. So any comments on personalized vaccines?

Oliver Sartor 1:19:20
Yeah, you know, it's interesting that the only data that I can recall off the top of my head was in melanoma. And I actually think that it worked. And I'd have to go back and I'd have to go back and read about it a little bit more. But it actually may be feasible to do. I'm doing a quick search for Derma and Merck on December 13, of 2022. Did a reduction in disease recurrence with a personalized cancer vaccine. And this is not one that I have a lot of familiarity with. But I think it's encouraging, it's going to take a lot of effort. So first of all, as you know, prostate is a pretty cold tumor. But there probably are some epitopes that could be exploited. It'll take genuine science in order to get that done. It's going to be incredibly expensive, but I think it ought to be done but I have not worked with Maderna and I think they're likely going to go with lower hanging fruit and try things like melanoma first because there you have such a wide variety of epitopes these are hot tumors. I think they're gonna go hot tumor before they go cold tumor.

Rick Stanton 1:21:10
Okay, thanks. The other question was, since I'm getting spread in my bones, what do you think of Xofigo? I think he mentioned it, but I shied away from it. Because I just felt like it was swirling down the toilet bowl of death and not you know, just could wipe out my bone marrow and scared me. But you know, now I'm about to see whether that worked. And I don't maybe have too many other options.

Oliver Sartor 1:21:44
Well, how many? How many mets do you have?

Rick Stanton 1:21:46
I don't know. I'd say 10.

Oliver Sartor 1:21:49
10. That's a lot. You know, it's kind of interesting. You may or may not know the senior author on the radium 223 paper. I did not do well, and you might also be interested. I was also senior author on the Cabazataxol paper, phase three. So you know, I've been around these agents for a long time. I know them intimately from running the trial to take it into commercialization. That said, the radium data to me has been a little bit like the Sipuleucel-T. It was performed in an era when there were no abiraterone or Enzalutamide. We have a phase 3 trial to be coming out with NS radium. But the apparaten Roan in combination with radium was a debacle was era two to three trial. So I am not that keen on radium as a whole. If you repeat some a PSMA positive, then I would think about the Pluvicto and I just think we have a little better angle with the pelvic toe armpits made pet positives. Alright. You've not had any chemo.

Rick Stanton 1:23:09
I have had the taxane docetaxel, and I've also had Pluvicto. Oh, yeah, I had four rounds of Pluvicto, at which point my PSA was rising. Pluvicto failed. That's when I started BAT. Got it. I

had a washout period of six weeks where my PSA went from, like eight to 24 in that wash out period. And then I started BAT and went to 112. And so now I'm about to see if I take my third BAT?

Oliver Sartor 1:24:01
If you had to, but if you had to bear to win from 24 to 112. I would probably say no. But now you're in a conundrum. I would, I would want to know your genomics. what you know we see have CDK 12 Yeah, well, I would treat you as combat sackful carbo. Okay. Yeah. Well, I'm gonna look up real quick. I'll give you the reference

Yeah, but you're, uh, you're, you're facing a tough situation. Um All right. We published this long term disease control using taxane platinum based chemo and CDK 12, mutated, advanced prostate cancer. We published it in the oncologist, I'll put the citation in the in the in the chat

Rick Stanton 1:25:19
I was hoping to go back to darolutamide.

Oliver Sartor 1:25:27
Oh, I'm sorry. I'm sorry. No, you should go back to darolutamide. Or you should go back first. I'm sorry, I apologize. You've already had it. But now you're in the post. Bad period. I apologize, Rick, you should go to darolutamide or Enzalutamide as the next step, but this would be your next step after that. I apologize for not getting that. See if I can get it. Yeah. Okay. Now, because you're right now you're that post BAT period, you're probably progressing. And I would go to an AR antagonists. And I would probably not choose Abi; I think darolutamide would be fine and solidify to be fine. Right? Yeah, I apologize. But this is your plan B.

Look, these are real questions. People know they're there. You know, I mean, obviously, this is tough stuff. And, you know, to the extent that I can be helpful, I enjoy being helpful if I can be.

Just as you talked about the treatments that you're excited about, I'm gonna go back to my inclination, what? What are the diagnostics that you're excited about? If you could wave one? And you could have every patient go through certain diagnostics that they're not getting today? What would they be?

Yeah, great question. You know, I'm, I'm really starting to have greater interest in the whole genome sequencing, which you couldn't do remarkably cheap now. And admittedly, that's another look at the DNA. But there's a lot going on in DNA that we don't fully appreciate it from the targeted exomes that we're getting today, I think we're just going to have a lot more, a lot more information, I really would enjoy the transcriptomics in more detail. But I don't quite know how to do it. Because if we look at the beginning, like a radical prostatectomy specimen, that's not what you want to get it these tumors are plastic, they, they they, you know, people have used different terms for lineage. plasticity is one of the common terms that is used. And I'll simply say this very, very well, when you induce a selective pressure called treatment on a tumor cell, it evolves and then comes out in a new way, we need to understand more about that.

I love the transcriptomics. But I don't quite know how to do it. But I don't want you to get whole genome. And by the way, even low pass whole genome, the context of circulating tumor DNA can be very valuable. One of the things I mentioned earlier that we're missing is the degree of what I'm going to call aneuploidy, our whole chromosome. Generations and duplications is a beautiful manuscript out that shows that the pointy status, the overall aneuploidy and pointy and the chromosomal arms are more important than the individual mutations. And we have no handle for that. I'm trying to press for that. Working a little bit with Tempus, and maybe they're listening, maybe they're not, they act like they're listening, but they're not there yet. It just takes

if you're gonna if you are interested, I can send you just a quick table, the Tempest. And I worked on Rick was part of this as well, where they looked at my RNA expression from my prostatectomy and 2016 met lesion and 2020 and met lesion in 2022 for all 20,000 genes and looked at my expression for each of those genes relative to 1000 advanced prostate cancer patients. So you can start to see you know, is it is it morphing over time or new things popping up so you get a little bit of a sense of that I The complexity is very huge. If you're not familiar with that, and you're interested, I'd be happy to send you a little snippet.

Yeah, no, it is huge complexity. And this is where we have to do a lot of exploratory work. You know, I don't even think we begin to know about the potential interactions. You know, people talk about the dark matter of the non coding RNA. It's really important for things like Schweppe, one, that that are out there. These Well, you know, these non coding RNAs are a whole new world and we don't even know what to think about them. And it's important. So we've got a lot of work to do in order to really optimally personalized therapy. We're at the beginning right now. Not the end. Yep. Okay. Awesome. Thank you. Yeah. Thank you.

Jonathan Starr 1:31:01
I've read about these D E P, capacitor taxall. And d p, docetaxel. These are products of a I think it's a Dutch company called Star pharma, that has gone through clinical been going through clinical trials in Europe, not here. But the essence of them is that they are sort of different formulations of dusts. taxall and composite tassel, you know, the, I think it's like the nominally non active ingredients are different. And because of that, they have far less toxicity than just regular dusts. taxall and composite taxall. At least that's what was, that's what I read to my guess is you have some familiar familiarity with those

Oliver Sartor 1:31:55
just just just a little bit. And, you know, I have really, in my own mind, tried to emphasize novel agents. I mean, you know, going, going back and doing another version of docetaxel, or Cabazitaxel was not very entertaining to me, it may diminish some toxicity a little bit. But I'm really more after new targets personally. And by the way, I haven't mentioned other interesting targets like HK two or steep one. But yeah, I would rather not recycle the old, I'd rather go look for the new because I know the best you're going to do is to come out with something that is probably maybe a little bit better than just facts, or maybe a little better tolerated, but it's not going to be a game changer.

Jonathan Starr 1:32:46
Well, what about those two? You said steep two and H K? are easy. H two or?

Oliver Sartor 1:32:52
Yeah, easy. eight students bit disappointing so far. You know, there have been a couple of them. It's a great target, but it just didn't turn out that it's as druggable as we thought it was either that or there's more to the story. Steep one looks a little bit interesting. I'm not able to fully comment on on that simply because it's unpublished data and it's proprietary. But I'm lucky keeping a workout on steep one, HK two I'm keeping a while keeping a lookout on SK two as well. Okay, yeah.

Jonathan Starr 1:33:29
All right. And and I sort of missed what you said about the ARV 766 and 110. What your final word was on that?

Oliver Sartor 1:33:40
Yeah, no, I think the ARV 110 is going to be good for the 875/ 878 mutations in AR, but it's not going to hit a 702. The 766 looks more interesting, but I haven't had I haven't had a chance to deep dive in the data yet. I know ARB 10 backwards and forwards. It's an active drug in selected mutations, particularly the 875/ 878. But beyond that, it gets a little more conjectural.

Robert Gurmankin 1:34:19
You've earlier talked about prostate cancer, being cold, immunologically; so I have the markers and am starting pembro soon. Is there anything that I can do to kind of make a better situation?

Oliver Sartor 1:34:41
Well, you said you had the markers, which markers do you have?

Robert Gurmankin 1:34:46
I have high tumor mutational burden, MSI high, and I have two of the mismatch repair mutations.

Oliver Sartor 1:34:55
You might be lucky, Robert. The most spectacular results that I've ever seen, maybe in my entire life, has come from pembro and the high MSI, mismatch repair deficient. What's your mismatch repair deficient gene?

Robert Gurmankin 1:35:22
Yeah. Give me a second. I can find it. Okay, I shouldn't do this off the top of my head. But I guess my question is, what, if anything, can I do to, you know, amp things up? Even more so, if possible?

Oliver Sartor 1:35:36

Yeah, I don't know. But certainly gotta give the pembro or another PD-1 or PDL-1 inhibitor a try. And how high is your TMB? And what was the assay?

Robert Gurmankin 1:35:51
It was 23.

Oliver Sartor 1:35:55
Yeah, not super high. Yeah.

Robert Gurmankin 1:35:59
As far as, so here it is. immunohistochemistry. So um, MLH1 positive & PMS2 positive
Oliver Sartor 1:36:09
Okay, positive there is not positive. That means you don't have the mutation.

Robert Gurmankin 1:36:15
Okay, then it's MSH2 and MSH6.

Oliver Sartor 1:36:19
Okay, if they were missing, they said negative. Yeah. All right. So that's good. MSH2 & MSH6 are more likely to respond, so give it a shot. I don't know how to ramp it up. But give it a shot. It might serve you. I've had spectacular responses in your situation.

Robert Gurmankin 1:36:45
Is going through six rounds of docetaxel likely to improve the situation? In terms of the microenvironment?

Oliver Sartor 1:36:55
I don't know. Let us know how you do on the pembro. That's important.

Eric Hall 1:37:11
I'm gonna go back to my adjuvant radiation questions. So if I decided to do adjuvant radiation, would that maybe potentially limit or impact any choices for me down down the road?

Oliver Sartor 1:37:26
Probably not. You know, it's it's an interesting question. That that if you were known to be what, what I wish I had in your case, is the postdoc piece of a PET scan to see what it worked, why? We know your margin positive and you had a single lymph node, right? Yes. Well, the pathology single lymph node comm for the pets made pet was positive on the pelvic lymph node at the beginning of your diagnosis. Was it someplace else? No, yet?

Eric Hall 1:38:06
I'm not sure I understand your question. Sorry.

Oliver Sartor 1:38:09

Did the surgery get the picture of a pet positive note?

Eric Hall 1:38:16
At the surgeon said, There's no way to guarantee that

Oliver Sartor 1:38:20
Was it in the same vicinity?

Eric Hall 1:38:23
Yes. They took 25 nodes, 13 from one side and 12 from the other and it was in that chain that there was one positive.

Oliver Sartor 1:38:36
Yeah, you know, it's an interesting question. We don't have data from it for men in your situation. What was your What was your postop PSA?

Eric Hall 1:38:47
I was undetectable six weeks post op.

Oliver Sartor 1:38:50
But, but, but you went on the hormones anyway.

Eric Hall 1:38:54
I was on the hormones for about eight months prior to surgery. Ah,

Oliver Sartor 1:38:59
okay. So your post op PSA has no meaning.

Eric Hall 1:39:05
My PSA at diagnosis it was 146. And so they put me on this to start with.

Oliver Sartor 1:39:11
Oh, okay. That's really high.

Eric Hall 1:39:13
That's really wicked Gleason 10.

Oliver Sartor 1:39:17
You had metastatic disease. We just don't quite know where it is. I didn't realize you were that high in the beginning. Yeah. You know, it's a hard call but I'm not completely sure that I would go with the pelvic radiation because you just don't quite know you. It's a it's a reasonable shot on goal because it's where it was. And you can do it but with you kind of operating without a lot of information.

Eric Hall 1:39:59
Even with the positive margins?

Oliver Sartor 1:40:02
The positive margins are likely problematic. If you stayed on the hormones for two years total, you'd be treated like you would be in the Proteus trial, which we don't have a readout on yet. And how long have you been on hormones him?

Eric Hall 1:40:19
Almost 11 months.

Oliver Sartor 1:40:24
You know, Eric, your margin positive is not good. Your lymph node positive is not good. You're all you're being treated in a manner that's a little bit unconventional. And so the the water is really muddy. We don't quite know where you are. You could radiate the pelvis. In which case you would certainly radiate the margin positive. Right. But it's it's not a straight shot on goal, in my opinion. But PSA being as high as it was initially.

Eric Hall 1:41:04
Yeah. Do you know if there's any kind of trials or tests that look at like biomarkers or anything to determine the efficacy of or toxicity of radiation therapy prior to doing it? Because I've gotten a lot of a lot of data, a lot of different tests.

Oliver Sartor 1:41:19
Yeah. There's there's nothing really good, though. Okay. What about your genomics? Do you know anything about your genome at the diagnosis? So while I told you the check to the ALC few, Oh, that's right. Yeah. But I also didn't

Eric Hall 1:41:39
the the liquid biopsy the garden 360. And I had that the Met a three five for a ID h one, and the e g. F. EGFR show up as somatic alterations.

Oliver Sartor 1:41:55
Was that drawn at the beginning? Prior to any therapy? Yes, prior to all therapy? Hmm. So your CT DNA did not match up with your with your other genomics? Because you mentioned the ALC? And the check

Eric Hall 1:42:13
for correct those come from doing whole exome testing?

Oliver Sartor 1:42:17
Yeah, I think that's I think that's more reliable. I'm not sure I would put much credence on the on the CT DNA. I think it's a tough call Eric as to whether or not you radiate the pelvis or not. I personally doubt if all your diseases in the pelvis, I don't know where your disease is. Part of me

would be interested in finding out where the disease is. But you're you're being treated with hormonal therapy that is good. And hormones, you have an undetectable PSA. There could be a rationale for going up to two years, and then stopping and seeing what happens, or you could radiate the pelvis to it's really an IT, you're living in a data free zone, unfortunately. Yeah. And

Eric Hall 1:43:04
you say that, maybe not do the pelvic radiation because you're saying you believe there's probably other spots outside of the pelvis,

Oliver Sartor 1:43:12
or other spots outside of the pelvis? I think the margin positive is real quick, there's no doubt about it. That's real. No, the left note is positive. And that's real. But I wonder about how much more there is to the story and how long since you started on this hormone journey? I wonder about how long you should continue it. And if you could radiate. It's just the the the the the issue here, I'm surprised you only had one piece may pet positive lymph node at the time you're diagnosed with a with a PSA that high

Eric Hall 1:43:52
and has been surprised by that. No bone mets. Nothing..

Oliver Sartor 1:43:58
Did you have conventional imaging?

Eric Hall 1:44:00
Yes. It showed the same lymph node.

Oliver Sartor 1:44:06
Yeah. You are a tough case. Eric. radiate, no, radiate the pelvis, plus or minus problem probably doing what I know now I'd probably say two years on the hormones. And then, you know, you can't target the check to the ALC I'd have to do more work on the

Eric Hall 1:44:30
there's one thing I maybe I didn't share, share as well as I could have is I had what I call extra capsular extensions. So my tumor was extending outside of the prostate and it was touching the rectum. So it was sizable was like five by four centimeters, I think.

Oliver Sartor 1:44:45
Yeah, that's another that's another thing about vocal control. That could be an issue. By the way, the reason the data presented from piece one, did it fax it Yes, that radiation in the pelvis could help with local control later on. And we'll go from there. But yeah, you've got a tough case. And you could kind of go either way, you're in a data free zone.

Rick Stanton 1:45:17
Why wouldn't you radiate? What's the downside?

Oliver Sartor 1:45:25
The downside is that you, you don't really know what you've accomplished with the current therapy. The The upside is maybe you can eradicate, he told me now that he had T for disease with rectum. So that's kind of pushing me more toward the radiation extracapsular extension margin positivity, initial T for disease, plus lymph nodes, clean up the pelvis and then go from there. The downside is that when you deploy the radiation, what you want to do is you want to booths where you can vote, if you're going to use typical pelvic radiation, you're going to go about 45 - 46, gray to the pelvis, and you don't know where to boost and 45 - 46 might be enough, but I'd rather boosted if I knew where it was. The problem is, his case is you're going to deal with a generic radiation and not know exactly where to radiate. If you do a little more detail, you might know how to pull out the radiation a little better. That's my conundrum. But the radiation, Eric, after you told me about the T4 for extra capsular extension, positive margin & lymph nodes, maybe the radiation of the pelvis would would serve you better. I think it can be done with a with a minimal amount of side effects. But it's still not equate and call.

Eric Hall 1:46:53
The positive margin is at the bladder neck.

Oliver Sartor 1:46:59
Get a good radiation oncologist where you're being treated. What's your location?

Eric Hall 1:47:05
I'm in North Carolina, but I have been seeing Mayo actually..

Oliver Sartor 1:47:11
Yeah, with the mayo guys are good. The radiation up here, it's actually exceptionally good. It really is.

Eric Hall 1:47:17
I've been talking with Dr. Ryan Phillips from radiation.

Oliver Sartor 1:47:21
I enjoy Brian very much. He's very thoughtful. He's very good. I know. I know him. Well. I like him a lot.

Yeah, if you want to, I can discuss your case with Ryan.

Eric Hall 1:47:39
I will email you more about it. I'm also with Dr. Phillips.

Oliver Sartor 1:47:45
He's a good man.

“The Current and Future Landscape of Metastatic Castrate Resistant Prostate Cancer” (Oliver Sartor) [#62]

Allen Morris 1:47:59
Dr. Sartor, you were considering and I can't remember the patient's name. You were considering that he would be a good candidate for Keytruda by virtue of him having mismatch repair deficient and genomics. He then asked, what more could I do to help? And what came to mind to me is that in melanoma with double checkpoint inhibitors, they have astonishingly got Kaplan Meier curves to settle down at about 50 to 60%. Admittedly, double checkpoint inhibitors are very toxic. If he were at the end of the road would you not possibly recommend him trying double checkpoint inhibitors to enhance his possible response?

Oliver Sartor 1:48:57
You know, the problem is payment, that stuff is $25,000 to $30,000 a dose for the ICI? You know, that's in you know, there's not a bad rationale for doing it. But I guess the problem is, you know, how many doses do you need and when that's $100,000 out of pocket, if you get four doses, and it would be out of pocket, no insurance company is going to cover it.

Allen Morris 1:49:28
Did you see the July 2022, New England Journal of Medicine article concerning rectal cancer and just one checkpoint inhibitor on mismatch repair deficient patients.

Oliver Sartor 1:49:43
Yeah, yeah. And everybody had a complete remission. I have a major quibble with that paper. Let me tell you what it is. Okay. Everybody quotes rectal cancer. Yes, they do not specify the mismatch repair and it has generated so much discussion because they don't emphasize every single patient was mismatch repair deficient in that trial.

Allen Morris 1:50:08
The person that you're talking to is mismatch repair deficient. So they would fit into that cohort.

Oliver Sartor 1:50:14
No, no, no. And I said, I said, you know, I would say go with pembro. But by the way, the PD-1 inhibitors are all the same. So I would not, I would not draw a distinction. You know, everybody talks about the drug. The mechanism is all the same. I think you could have gotten the same thing with either pembro & devo.

Allen Morris 1:50:40 How can you say that when double checkpoint inhibitors efficacy is superior in melanoma. There are different there are different checkpoints that are being hits.

Oliver Sartor 1:50:53
right now, I'm saying that the reason that the ICI is not really accessible is the cost of the drug, the lack of trials, and the extreme costs and the fact that it's no insurance is going to be covering. Yeah, really, it's really hard to make a recommendation unless the patient's willing to put out a huge amount of money.

Allen Morris 1:51:20

Right. But I mean, we are in the context of some people that are at the end of the road. So admittedly, obviously, the studies haven't been done in prostate cancer. So we you know, it would be the leap of faith, you know, going from rectal as well as melanoma.

Oliver Sartor 1:51:37
But the rectal was only a PD-1 inhibitor. It wasn't a double.

Allen Morris 1:51:42
Yeah, all. Yeah, but I agree with that. But all the more reason that checkpoint inhibitors show unbelievable promise and in melanoma in particular, that promise is improved with double checkpoints. I'm just addressing his one question that's, you know, is there something else I could do? And there is, though, it would be costly. There's no prostate cancer trials concerning it's, you know,

Oliver Sartor 1:52:18
I guess to be honest with you, that is, it's hard to recommend a combinationwhen we just don't have much data. So I don't typically recommend that we go in a space where we have no data at all. Now. The combination has been looked at in prostate but not a mismatch repair. Your point is well taken that maybe adding up could be better. But I don't think in my practice would be a typical recommendation.

Allen Morris 1:52:54
Yes. Because you don't want to stray from what's proven. I understand that.

Oliver Sartor 1:53:01
It's, you know, we have really good responses with pembro monotherapy. And if you look at that rectal cancer series, and the mismatch repair, one of the things that is evident is the melanoma did not have mismatch repair, whereas the rectal did. So the rectal with only PD-1 inhibition led to complete remission in every single patient? So you may not need the 2nd checkpoint inhibitor.

Rick Stanton 1:53:30
What was the second checkpoint? CTLA4?

Oliver Sartor 1:53:33
Yeah, CTLA4, ipilimumab, which is the the checkpoint inhibitor

Allen Morris 1:53:39
In melanoma they're using multiple combos, in as far as trials go to try to reduce the toxicity because the combination is incredibly toxic.

Oliver Sartor 1:53:56

Yeah, they're playing with the dose or going with one milligram per kick and initially, that we're using three and that helps, and they're cutting down the to four cycles and not going further. But, you know, with mismatch repair, hopefully the PD1 we'll get you into a really good spot.

Robert Gurmankin 1:54:16
Not not to jump in, but I'm the one you've been talking about. Yeah. Any place for a PARP inhibitor in conjunction?

Oliver Sartor 1:54:25
No, you know, there was initial enthusiasm for that idea of the studies coming out of the NIH initially looked promising, but they haven't panned out.

Robert, we don't need to talk about you as if you weren't there.

Robert Gurmankin 1:54:43
No, that's perfectly fine.

Oliver Sartor 1:54:45
You have a very interesting case.

Jonathan Starr 1:55:00
You're up at Mayo Clinic and they have C11 choline imaging. I think they still do. Yeah. Are you going to utilize that? Are you going to use it in combination with PSMA, or if PSMA comes out negative?

Oliver Sartor 1:55:17
Probably not. There are a couple of issues with if you look at the trials where they've been done together, they're actually head to head trials. Looking at choline and PSMA. It's just not as good. Now there are a few people who believe that maybe the choline is a metabolic marker may be different. But that I, I don't envision using a lot of choline.

Jonathan Starr 1:55:44
You wouldn't even if someone is PSMA negative?

Oliver Sartor 1:55:48
I would, it depends on how high they were, you know, we've got other trials, things like GRPR. That may be a little more interesting there. I mean, choline could be in the PSMA negative setting. The fellow that had the very high PSA might be a case for choline to be considered. But as a routine that would not use it; it would only be potentially be used in very restricted patients. Okay. Yeah, there's a phase three trial comparing the two. I don't know if you saw that. Um, and let's see - choline vs PSMA. Here, it's a journal of nuclear medicine. Fairly recently published,

Detection rates are higher. And, you know, head to head there's no doubt thatPSMA is better. And again, we come into the reimbursement thing, you know, the insurance will pay for one PET

and not gonna pay for two. So if you want the second PET, you'll have to pay for it. Yeah. I try to be pretty sensitive to patient pocket books, but maybe, you know, patients ought to be aware that you could do more imaging, we just don't always know what we're gonna get.

Jonathan Starr 1:57:43
Yeah, well, I paid out of pocket for C 11 acetate when it was available. And it was much better than anything else available.

Oliver Sartor 1:57:55
it was the best in the world before the PSMA PET came along.

Rick Stanton 1:58:04
Can we hear from Noel because she's had a very interesting chat comment?

Noel Resch 1:58:18
Philip is a patient of Dr. Kwon. And he we just met with them Phil just had his fourth Gleevec dual treatment, his PSA has been steadily declining throughout treatment. But he told us after his six dose, we wait six weeks we go back. He's not giving him a PSA scan. He's giving him a C 11 choline scan. Okay. Do you know why that would be? And I did ask. He just says they like to use it because maybe it'll show something that the PSA didn't. But we've had trouble in the past getting the choline approved where the PSM a has been approved a lot easier.

Oliver Sartor 1:59:02
Yeah, I wouldn't be more likely to use the the PSMA PET as opposed to the choline plant that

Noel Resch 1:59:10
well I guess my you know, the issue I have with it is since we've been monitoring throughout treatment with the PSM A, if we look when treatments completed, and we use the C 11 choline now we're comparing apples to oranges. Like I would prefer to use the same scan throughout so we can you know, effectively compare it.

Oliver Sartor 1:59:29
Well. I would agree with you. I just put in the chat by the way, the direct comparison. Um, they they when they looked at the comparison of the PMA pattern and calling the PMA Pat are the choline pet contributed in only six patients. And that was out of a total of let's see, I think it was 200 And let me double check the number.

100 190 patients, so in six patients that have 190, the coin was better than the BMA. But it's it's it's a low probability event.

Noel Resch 2:00:26
So yeah, I will maybe have to discuss that. And I don't want to hold you up any further. But you had a chart you displayed earlier. And you said typically with patients, Phil has a pretty low disease burden. I mean, he's got just three spots. Oh, he's been doing well. And when we

started, his PSA was point eight, one. It is now point one, one, and he just had his fourth treatment. So we'll we'll find out. But it's been steadily declining throughout. I think when I saw your chart, you said those patients typically do pretty well.

Oliver Sartor 2:01:01
Yeah, they do extremely well. That's a much more PSA than typical in that setting. But what I'll say is, if you're down to three spots, why don't you SPR to?

Noel Resch 2:01:11
Well, we asked. That's funny, because I had actually asked that we were a little worried about play victim and thought maybe save that for later. Because he gave us the option initially of either. And, you know, we were supposed to come back. And then it just, we were put on a waiting list. And we were supposed to come back and have a consultation, but we ended up happening is we're on that waiting list forever. And then when we came back for the consultation, it was more nope, here we go with treatment. So and I even Dr. Stiff, if you're familiar with him? Very well. Yeah. So he did some sbrt on Phil, what two years ago to two spots, put Phil in remission for almost a year. And now he then he was Onyx standy. after that. So are that's what got him into remission was the SPR t plus IC standy. And then just last fall the exam, he started to fail, but he's still on the expanding and doing pelvic toe and more for treatments in.

Oliver Sartor 2:02:15
Well, you know, I mean, I would be interested in taking another look at the PSA pen. If you're positive consider sbrt to those remaining lesions. Um, and, you know, that's a reasonable. I mean, that's probably how I would handle it.

Noel Resch 2:02:33
So are you available? Like we'd be able to arrange to see you when we come for our next visit? Um, you see patients, I mean, something you can do?

Oliver Sartor 2:02:42
Yeah, I see. I see patients, and they have to be a little bit careful about the diplomacy between departments. But yeah, no, I'm no, of course, I'm seeing patients. I've been seeing patients for 33 years.

Noel Resch 2:02:59
Okay. Yeah, it might be worth, you know, we haven't been able to get a lot of answers. We're very grateful for the care there. But we haven't been able to get a lot of answers about his specific mutations and things. So maybe it would pay to sit down with you?

Oliver Sartor 2:03:15
Well, I think you can go through the mail portal and make that request, if you like.

Noel Resch 2:03:21

Yeah, absolutely. Thanks for your time, this has been awesome. Really appreciate your two hours.

Oliver Sartor 2:03:27
Well, I'm, you know, my heart goes out to the prostate cancer community, I know you guys work really hard, in an effort to press boundaries and come up with the right solutions and practicing medicine is very much of an art form in these circumstances. And, you know, good people may or may not necessarily agree with the same approach. I can certainly say that, you know, Dr. Morris is mentioned mention of the, you know, that the map will be an example, you know, if you had, if you had unlimited funds, and were willing to tolerate a lot of toxicity, then maybe you go with a combination of two checkpoints instead of one. Could be probably wouldn't do that myself. But it is, you know, there's a rationale for that. There's, you know, one can construct a reasonable argument for making a case.

Brad Power 2:04:28
I think that was starting to wrap. If you'll allow, it's been two hours. I think this has been a very generous contribution for you, Dr. Sartore. And also your candor. I know that many of the folks we have on shy away from giving what sounds an awful lot like medical advice. I know. We talked about this boundary between medical information and medical advice. And we know that you're you're sensitive to that as well. But it's been very, we very, very much appreciate your candor, and your personalization I I'm sure everybody's walked away with, with information that's very, very useful to their specific cases.

Oliver Sartor 2:05:07
Good. Well, thank you, Brad, and you know, glad to be able to be here. And you know about the medical advice, you know, just as sort of an example. You know, in a real medical consultation, the fellow that had the T for disease with rectal invasion, you know, what it is an initial PSA of 176, or whatever it was, you know, that colored my interpretation of the case was initially presented as March and positive lymph node positive, but I didn't hear about the PSAP in well over 100. I didn't hear about the rectal involvement. So that's one of the things it's a little bit of a danger about trying to get medical advice. I don't really have all the facts. In a real consultation, I sit down before the patients in the room I review all those facts before I ever walk in the room. Yes.

Brad Power 2:05:59
And we're well aware of that. So we really appreciate your going. I don't know if it's, I was gonna say going off half cocked, but at least you know, based on the evidence that you have, which may not be full. So anyway, just see your appreciation and willing to go out on those lambs and make those comments. Thank you. Bye.

Oliver Sartor 2:06:19
All right, guys.