“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]

Brad Power
November 25, 2024

“CRPC is incredibly active. The post-lutetium space is big. There are lots of new, interesting things in development.” – Oliver Sartor, MD

“I love radiopharmaceuticals, because I can see it and I can treat it, and that gives me a power that I can't otherwise have.” - Oliver Sartor, MD

“I mentioned cell surface targets, and there are a bunch of ways to bind to that target. This is where we have a lot of innovation. Here we have small molecules, peptides, antibodies, different ways of approaching this. A lot of what you're going to see over the next five to 10 years is people taking these isotopes, bringing them onto the cell surface with a diversity of targeting molecules. We're not going to be stuck with PSMA-617.” – Oliver Sartor, MD

“Hopefully I was able to provide a little bit of an insight for people here and there, but you've got a well educated group, and keep at it, because that education gives you power, and when you're empowered, you can make better decisions, and that's what it's all about: trying to get to the best decision.” – Oliver Sartor, MD

Meeting Summary

Advanced cancer patients often find themselves trying treatments that work for a while until they fail, then moving on to another therapy. There are many treatment options for some cancers, like prostate cancer, and new ones are becoming available continuously. New drugs which take a radioactive payload and tie it to a cancer cell (a radiopharmaceutical) are now coming to market in new combinations. Different kinds of radioactive particles can be used. These particles can be combined with radiation sensitizers, modulating the way the drugs alter DNA. As a patient or physician, what you thought was the state of the art can change in six months. You need to keep a constant outlook to know what is newly available and what might be available in the coming year.

A. Oliver Sartor, MD, of the Mayo Clinic, is uniquely qualified to review this complicated landscape and discuss research on radiopharmaceuticals, other treatments, 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 principal investigator or co-principal investigator on pivotal trials that have helped to change the landscape of advanced disease including radium-223, cabazitaxel, and Pluvicto (PSMA-617 Lu-177).

What are the standard tests for prostate cancer today?

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Most men monitor their risk of prostate cancer through a blood test, the “PSA” (prostate specific antigen) test and a “digital rectal exam” (your doctor puts a finger up your rectum and feels for lumps or other abnormalities). If your PSA is rising, you can get a “needle biopsy” from the prostate - tissue samples are taken, stained, and examined. You can also get “MRI” (magnetic resonance imaging) and ultrasound for non-invasive images.

To determine if your cancer has spread – to check for “metastases” (progression of the cancer away from the primary site of the prostate), you can get a “PSMA PET” scan (prostate specific membrane antigen, positron emission tomography; a radioactive tracer is injected which lights up where sugar is taken up – which indicates cancer – creating a 3D picture of the inside of your body.) You can also get other imaging tests like a CT scan, MRI, bone scan, or ultrasound. And a biopsy of your metastatic lesion can provide useful information.

What are other tests that you should consider?

- **Genetic testing**: DNA and RNA sequencing of your tissue biopsy to look for genetic mutations, which can point to drugs targeted at those mutations, e.g., BRCA1 or BRCA2. Genetic testing identifies actionable treatments targeted at identified mutations for about 20% of patients.
- **Liquid biopsies**: A blood draw can be analyzed to enable DNA and RNA sequencing to look for mutations and monitor disease response and progression. ctDNA (circulating tumor DNA) can provide useful information, and because it is not invasive, can be taken periodically to monitor your disease. Circulating tumor DNA is not necessarily helpful for identifying sensitive mutations, but you can follow your disease and see what's responding and what's not responding.
- **Functional testing**: If you have fresh tumor tissue, you can apply drugs (chemotherapy or targeted drugs) to test their efficacy and predict whether you will likely respond.
- **Blood test for testosterone**: Monitoring your testosterone levels can be important to measure, especially if you are cycling on and off hormone deprivation therapy.
- **Spatial or single cell analysis**: This advanced test looks at the tumor microenvironment and can help determine if you will be a likely responder to an immunotherapy.
- **Microsatellite instability**: Microsatellite instability (MSI) is an analysis of your “microsatellites” (short, repeated DNA sequences) in your normal and tumor cells. If your cancer cells have a high number of mutations in microsatellites, you have a better prognosis and response to immunotherapy.
- **Mismatch repair deficiency**: You can have your tumor tissue stained to look for mutations in genes that are responsible for correcting DNA errors. When mismatch repair is deficient, DNA errors go unrepaired, which can lead to cancer. If you have mismatch repair deficiency, you are a candidate for immunotherapy, specifically using immune checkpoint inhibitors (a type of cancer immunotherapy drug that helps the immune system identify and attack cancer cells), like pembrolizumab (Keytruda).
- **FDG PET**: An alternative to the standard PET scan (which measures sugar uptake), which can identify neuroendocrine cancer.

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What are the standard treatments for prostate cancer today?

Prostate cancer is typically categorized along two dimensions: “castrate sensitive” (responsive to hormone deprivation therapy) or “castrate resistant” (your cancer continues to grow even when your testosterone levels are low, as if you were castrated), and “metastatic” (the cancer has spread beyond the prostate) or “local” (limited to the prostate).

- If you have “localized” disease (only at your prostate), you can get local therapy (surgery or radiation) with or without androgen deprivation therapy (drugs which lower your testosterone) and with or without abiraterone (or other drugs which block your androgen receptor) or no therapy (watchful waiting).
- If you have progression to one to four additional sites (“oligo-progression”), they can be treated with radiation (stereotactic body radiotherapy).
- If you then have rising PSA (prostate specific antigen, a blood test which measures your prostate cancer), you can then get “salvage” radiation, with or without androgen deprivation therapy, or androgen deprivation therapy, or no therapy.
- If you have metastatic prostate cancer which is responding to androgen deprivation therapy, you can get a combination of androgen deprivation therapy plus chemotherapy (docetaxel) or androgen blocking therapies (abiraterone, apalutamide, or enzalutamide), or all three together (a “triplet”).
- If you have non-metastatic (your cancer has not spread from the original site in your prostate) castrate-resistant (your cancer continues to grow even when your testosterone levels are low, as if you were castrated) prostate cancer, you can get androgen receptor drugs (enzalutamide, darolutamide, apalutamide).
- If you have metastatic castrate-resistant prostate cancer, and you haven’t had chemotherapy, you can get immunotherapy (sipuleucel-T, also known as Provenge) or androgen receptor blocker drugs (abiraterone, enzalutamide).
- If you have metastatic castrate-resistant prostate cancer, you can get chemotherapy (docetaxel).
- If you have metastatic castrate-resistant prostate cancer, and you have had chemotherapy, you can get chemotherapy (cabazitaxel) or androgen receptor blocker (abiraterone, enzalutamide).
- If you have metastatic castrate-resistant prostate cancer, and you have BRCA1 or BRCA2 mutations (BRCA1 and BRCA2 are genes that produce proteins that help repair DNA), you can get “PARP inhibitors”, like olaparib and talazoparib, drugs that treat cancer by blocking the activity of PARP – poly ADP-ribose polymerase – an enzyme that helps repair damaged DNA. PARP inhibitors trap PARP at DNA damage sites, preventing the repair of single-strand breaks, which leads to double-strand breaks that cannot be repaired in cancer cells that are deficient in homologous recombination, causing the cancer cells to die.
- If you are metastatic castrate-resistant, you can get radionuclides (a radioactive particle which attaches to the surface of prostate cancer cells, such as the Prostate Specific Membrane Antigen), like lutetium-177 (Pluvicto), or you can get a checkpoint inhibitor

(drugs that block proteins that stop the immune system from attacking cancer cells) immunotherapy, like pembrolizumab (Keytruda). About a third of the patients who get Pluvicto have really beautiful responses, about a third do not respond very well, and about a third are in the middle.

How is the standard approach to treating prostate cancer changing?

All the novel hormone treatments (enzalutamide, darolutamide, apalutamide, or abiraterone) are being applied as earlier lines of therapy.

What are the new therapies being researched in prostate cancer?

- **Targeted therapies**: There are many cancer cell surface targets in prostate cancer that are being researched: the androgen receptor, PSMA, DNA repair, AKT, B7H3, WNT, DLL3, STEAP1, STEAP2, … And there are many ways to bind to cell surface targets on the prostate cancer cells. This is where we have a lot of innovation. The approaches include: (a) block cancer receptors and enzymes; (b) degrade proteins; attach different payloads to molecules that grab onto the surface of the cancer cells: (c) antibody drug conjugates - a chemotherapy, (d) radiopharmaceuticals - a radioactive particle, (e) bispecifics - an immune cell; and immunotherapies, e.g., (f) CAR-T and (g) immunologic stimulators and inhibitors. Over the next five to ten years people will be taking isotopes and other payloads, such as alpha particles, and bringing them onto the cancer cell surface with a diversity of targeting molecules.
- **Combinations**: There will be combinations of isotopes, alphas with betas, combinations with immunotherapy, and radiation sensitizers. For example, if you're going to damage your tumor DNA with radiopharmaceuticals, you have the potential to be able to inhibit DNA repair by combining it with drugs which do that, like PARP inhibitors.

How should you make tradeoff decisions among these new options and the standard treatments?

- Find a doctor who specializes in your specific situation and who will have the relationship you want, e.g., consultative
- Get a second opinion
- Don't be afraid of a clinical trial if you don't have good options that are available as part of the standard of care
- Personalize to your situation: your very specific scenario demands a very specific set of options
- Stay informed about your testing and treatment options; for example, you have to be aware of what's available and what's not
- Ask questions of your medical team and stay engaged in your testing and treatment decisions

How can you learn more?

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- See the meeting summary, transcript, and video from our discussion with Dr. Sartor in July 2023 “The Current and Future Landscape of Prostate Cancer Treatment”.
- Research the use of non-standard tests, e.g., circulating tumor DNA as a biomarker for monitoring your disease progression, and discuss the new testing and therapy options with your medical team

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Meeting Notes

KEYWORDS

prostate cancer, new pathways, novel targets, castrate sensitive, castrate resistant, precision medicine, circulating tumor DNA, oligo progression, stereotactic body radiotherapy, AR targeted drugs, PSMA targeted drugs, DNA repair targeted drugs, cell surface targets, alpha particles, antibody drug conjugates

SPEAKERS

Oliver Sartor (73%), Brad Power (15%), Nathanael Jackson (8%), Vic Paglisotti (1%), Paul Van Camp (1%), David Plunkett (1%), Arthur Bruno (0%)

CHAT CONTRIBUTORS

Allen Morris, Vic Paglisotti, Nathanael Jackson, Alane Watkins, Arthur Bruno, Eric Hall, Noel Resch, Alexander Lalov, Deepak, Rick Davis, James Ward

SUMMARY

Dr. Oliver Sartor discussed the latest advancements in prostate cancer treatment, emphasizing the importance of understanding the disease's stages (castrate-sensitive and castrate-resistant) and the role of novel therapies. He highlighted the use of radioligands like Pluvicto and J-591 lutetium, and the potential of alpha particles for targeted therapy. Dr. Sartor also addressed the challenges of neuroendocrine prostate cancer, suggesting platinum-based therapies and DLL3-targeted treatments. He stressed the importance of bone health management. There is a need for clinical trials to evaluate new combinations. Dr. Sartor concluded by encouraging patients to stay informed and engaged in their treatment decisions.

OUTLINE

Overview of Prostate Cancer Treatments

- Dr. Oliver Sartor is an expert on new pathways and novel targets in prostate cancer.
- Prostate cancer is divided into castrate-sensitive and castrate-resistant stages, and each has standard therapies.
- He discusses the use of novel hormones like enzalutamide, apalutamide, and abiraterone, and the role of PARP inhibitors and genetic testing in precision medicine.
- Therapies which target a genetic mutation are only useful in about 20% of cases.

Circulating Tumor DNA and Oligo Progression

- Circulating tumor DNA (ctDNA) is a biomarker which can be used to monitor disease response and progression.
- For patients with oligo progression (a few metastatic sites), this limited disease progression can be treated with stereotactic body radiotherapy (SBRT).
- A patient who achieved durable remission with J-591 lutetium and SBRT alone.

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Targeted Therapies and Protein Degraders

- There are a variety of targeted therapies, including AR-targeted, PSMA-targeted, and DNA repair-targeted.
- The AR degrader ProTac has potential for treating castrate-resistant prostate cancer.
- Other degraders are in development, including RV-766 and an interesting degrader from Bristol Myers Squibb.

Cell Surface Targets and Theranostics

- Cell surface targets provide a hook that drugs can latch onto, such as PSMA-targeted (Prostate Specific Membrane Antigen) therapies, including antibody drug conjugates (which grab an antigen on the cancer cell one side and deliver a chemotherapy payload on the other) and bispecific antibodies (which grab an antigen on the cancer cell on one side and deliver a T-cell on the other).
- Theranostics is the use of radioactive tags which latch onto cancer cell antigens to diagnose and treat cancer.
- Different isotopes, such as gallium-68, actinium-225, and terbium-149, are being explored in theranostic (radionuclide) applications.

Challenges and Future Directions in Prostate Cancer Treatment

- The challenges of treating prostate cancer include the need for better targeting and understanding of tumor biology.
- Alpha particles have a potential role in targeted therapy.
- There are many ongoing clinical trials.
- More attention needs to be paid to combining different therapies to achieve better outcomes.

New Treatment Options

- Vic Paglisotti asked about the use of radium-223 and enzalutamide post-Pluvicto, and Dr. Sartor explained the benefits and precautions.
- Nathanael Jackson inquired about the best combination therapies, and Dr. Sartor suggested considering hormonal agents and bone-targeted agents.
- Paul Van Camp asked about identifying neuroendocrine prostate cancer, and Dr. Sartor outlined the use of circulating tumor DNA, LDH, and specific markers.

Deepak asked about the use of calcium supplements and PARP inhibitors, and Dr. Sartor provided practical advice and insights.

Final Thoughts and Closing Remarks

- Dr. Sartor emphasized the importance of finding a good doctor and staying informed about treatment options.
- Continued research is needed, such as in new therapies like targeted alpha therapy.
- Patients should ask questions and stay engaged in their treatment decisions.

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TRANSCRIPT

Brad Power
This is the Cancer Patient Lab.

We're honored to have Dr. Oliver Sartor with us today. He have had one of these discussions with us before, where he gave an update on new pathways and novel targets in prostate cancer, so that all the patients and caregivers can be kept up-to-date on what's possible today, what's new, and what might be coming onstream in the next six months, because the world changes every six months or so.

This is not medical advice. This is for information purposes only. We try to arm patients and caregivers with information that can help them and their medical team manage their care.

We are a patient-led non-profit, all volunteers, and we would welcome any donations that you might want to make, which you can do through our website, cancerpatientlab.org.

We've been connected for some time. My cousin Jeff Hoffman went to medical school with Dr. Sartor at Tulane. We've known each other for quite some time. Dr. Sartor has been very helpful to this community.

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Oliver Sartor 1:41
I'm going to try to go through this relatively quickly. You can think of it as a conceptual overview. I want to leave some time for questions at the end.

It was kind of interesting that there was a little bit of an entree with oligometastatic disease (when cancer has spread to a limited number of distant sites in the body, a subclass of stage IV cancer, an intermediate stage between localized and widely spread disease.), SBRT (Stereotactic Body Radiotherapy, a type of radiation therapy that uses many beams of energy, carefully targeted to focus on growths of tumors), followed by the J591 lutetium (a radiation-based treatment that utilizes a molecule to attach itself to the Prostate Specific Membrane Antigen receptors located on the cancer cells). I'll be mentioning both of those concepts.

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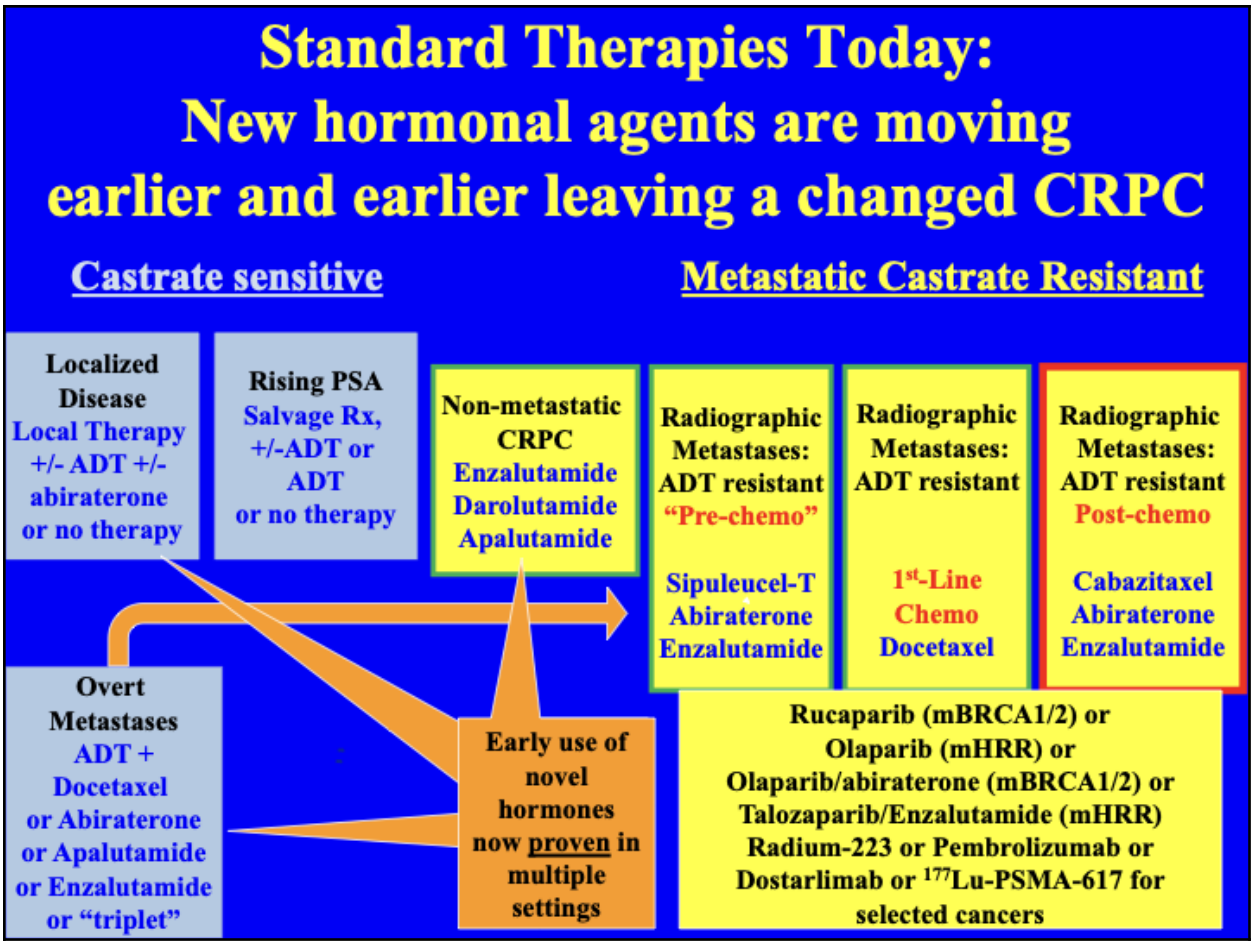

This is where we are today and the standard therapies. We divide the world into castrate sensitive and castrate resistant. We divide the world into metastatic and non-metastatic.

All the novel hormone treatments, whether enzalutamide, darolutamide, apalutamide, or Abiraterone, are all going up front right now.

We have a different type of castrate-resistant disease. We have a number of new agents for BRCA1, BRCA2 – all the PARP inhibitors with olaparib, talazoparib, etc.

We have lutetium for selected cancers, Pembrolizumab for selected cancers.

I'm not going to be going down that pathway today. We could talk more about the MSI-high, deficient in MMR-type things at another time.

I do a lot of genetic testing, and I always want to look for those PARP-sensitive mutations, and I also want to be able to look for the rare possibilities of pembrolizumab or just sensitive mutations.

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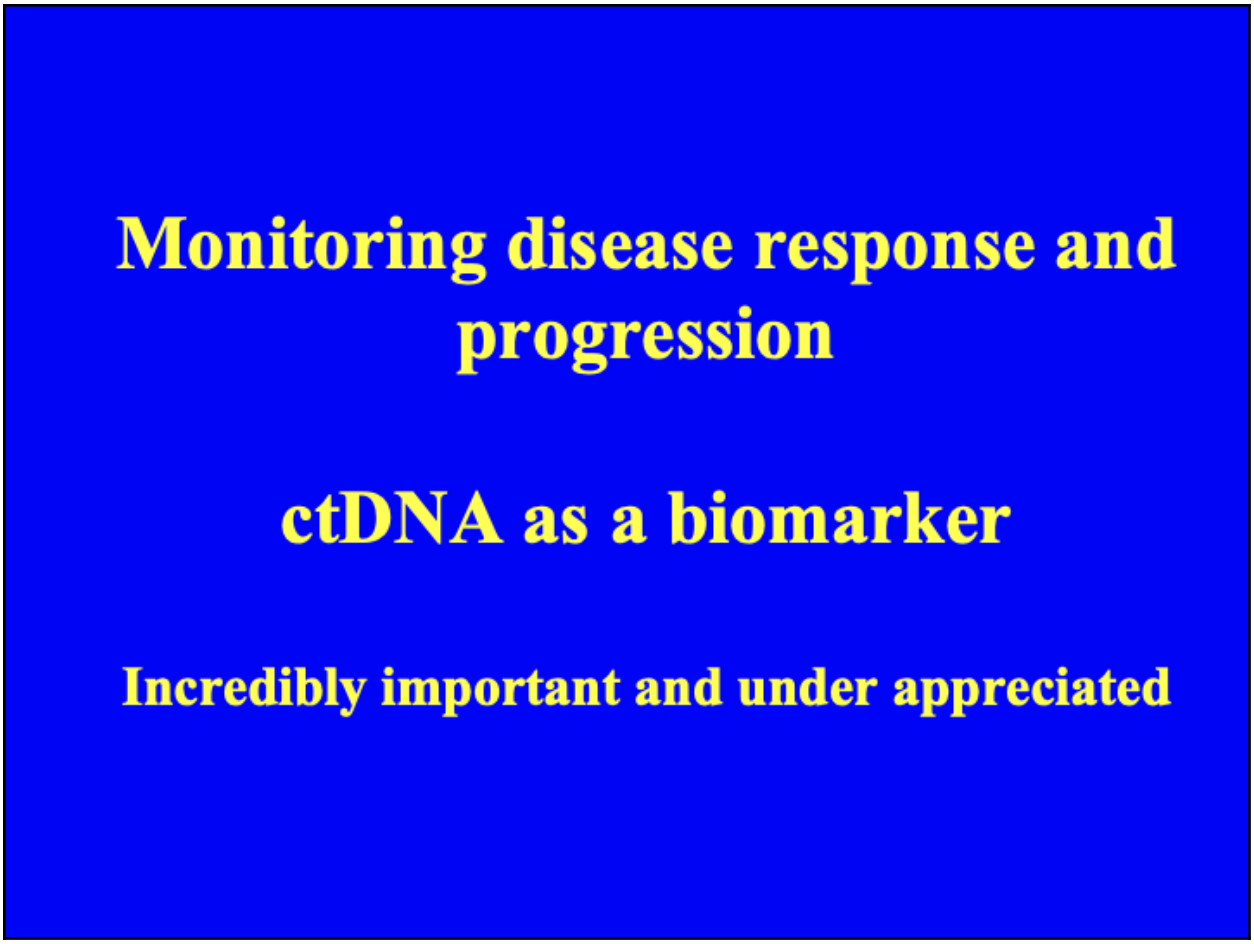
But one thing about precision medicine (drugs targeted at genetic mutations) you have to understand is: it's only useful at most about 20% of the time. 80% of our patients are not going to be treated differently because we find something in their genetics, and that's very important. A lot of people believe that if we just do the genetics enough, we'll find actionable mutations. Unfortunately, it's not true. 80% of the time, you don't find anything.



This is a bit of an ad lib here for patients, particularly with those that have a lower PSA, I like circulating tumor DNA as a biomarker.

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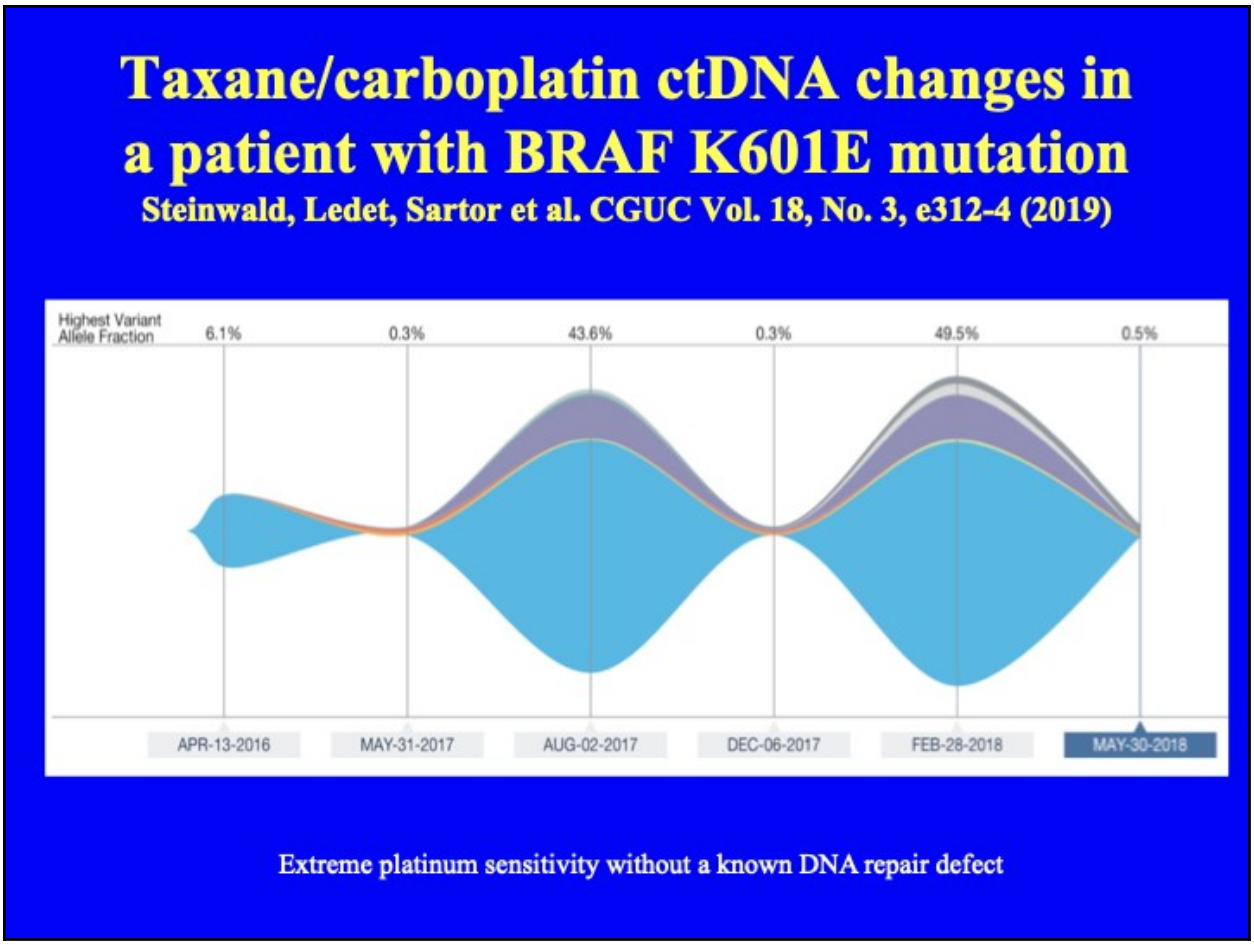

This is an example of a patient that I have with the BRAF K601E mutation, by the way, not thought to be actionable, but we did quite well here with a taxane/carboplatin (a chemotherapy combination) regimen. The allelic fractions (Allele frequency, or gene frequency, is the relative frequency of an allele – variant of a gene. It is a measurement of the proportion of reads in a sample that support a variant allele, often used as a proxy for disease burden.) will either expand or diminish in accordance with expansion or diminishing of the disease with treatment. This is just one thing we published a while back. This was five years ago, but occasionally the circulating tumor DNA is not necessarily helpful for identifying sensitive mutations, but you can follow the disease and see what's responding and what's not responding. That can be helpful.

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Oligo-progression.

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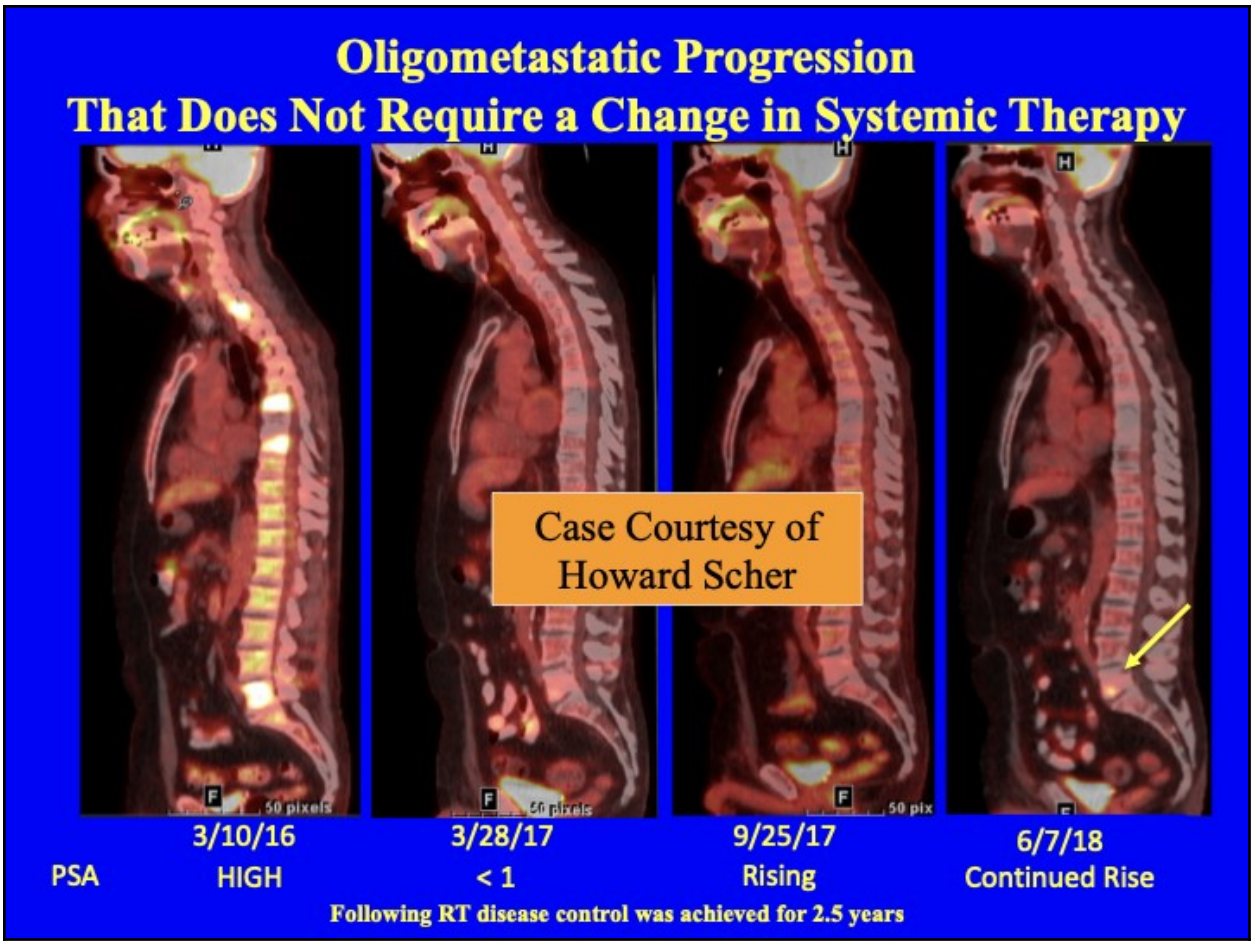

This case is courtesy of Howard Scher. A while back, a patient that was responding to therapy then ended up with progression. But what they had was oligo-progression. You need to be able to look and find which patients have oligo-progression, because this can be treated with SBRT (stereotactic body radiotherapy, a precise, high-dose form of radiation therapy), and that can be sufficient in many cases. That's not necessarily a bad thing if you find progression to one, two, three, or four spots, because we can achieve remissions at times with SBRT. Now the patient mentioned had been in remission for two years after getting J-591 lutetium. This particular patient had SBRT alone, nothing else. It was controlled for 2.5 years. Sometimes you can get these durable responses with radiation/ We definitely look for oligo-progression.

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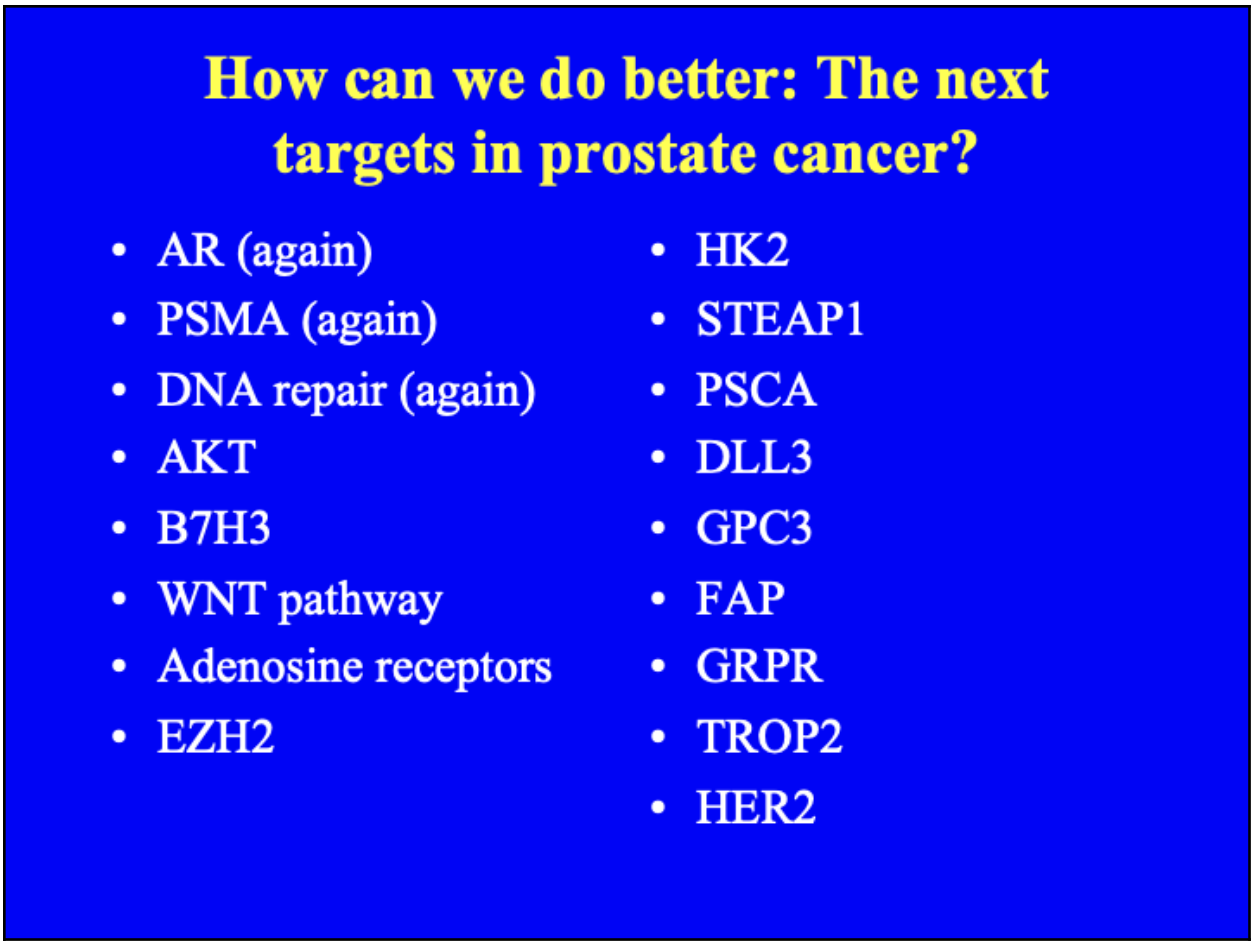

As we move forward, I'm going to again speak conceptually about how we're going to be targeting this disease.

- We still have AR-targeted drugs.
- We have PSMA-targeted drugs.
- We have DNA-repair-targeted drugs.
- AKT
- B7H3
- WNT pathway
- Adenosine receptors
- EZH2
- Then we have cell surface targets like HK2
- STEAP1 and STEAP2
- PSCA
- DLL3
- GPC3
- FAP is a stromal-targeted, that's fibroblast activated protein
- GRPR
- TROP2

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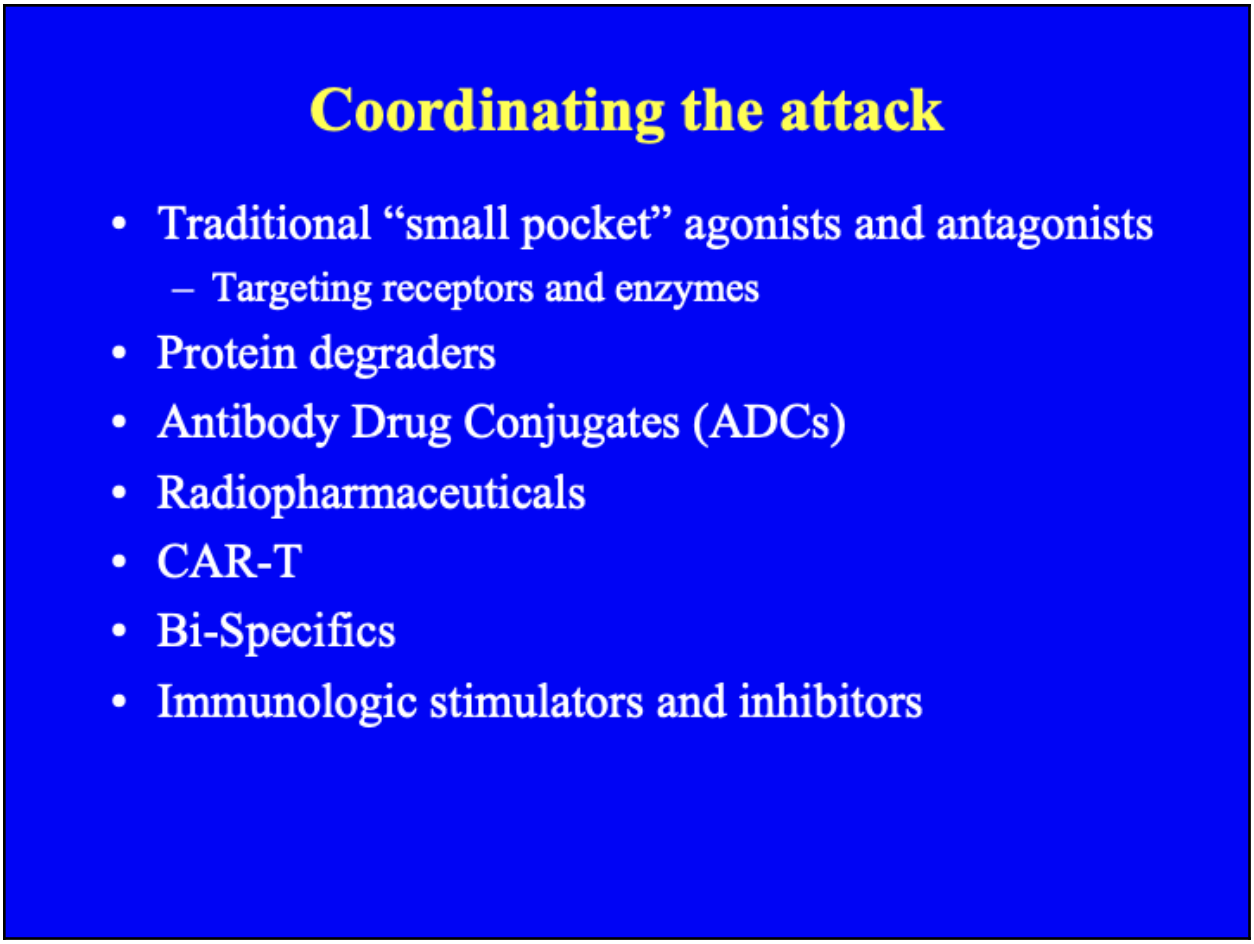
- HER2.

There's more. I can't name them all here, but I'm going to give you a tour of what's going on in the field right now. It's not perfect, by the way. There's always new stuff popping up. My slides aren't perfect, but they'll conceptually be a way to lead you to the right spot.



If we're going to be attacking this disease, we have to figure out how to do it. It's not so easy to identify a target and then bring that target into submission. What we've traditionally done in medicine is used what we call “small pocket” agonists and antagonists. Things like darolutamide all bind to the antigen receptor. They've blocked the binding of the testosterone and other androgens to that receptor. That's a traditional small pocket agonist or antagonist. That's the way we have traditionally developed drugs. And it works. We can target a bunch of receptors, a bunch of enzymes. Abiraterone works this way. All the antigen-receptor-targeted drugs work this way, etc.

We're getting into a new era with protein degraders. Protein degraders are getting interesting. We still have more work to do, but I think we're starting to see clinically significant things.

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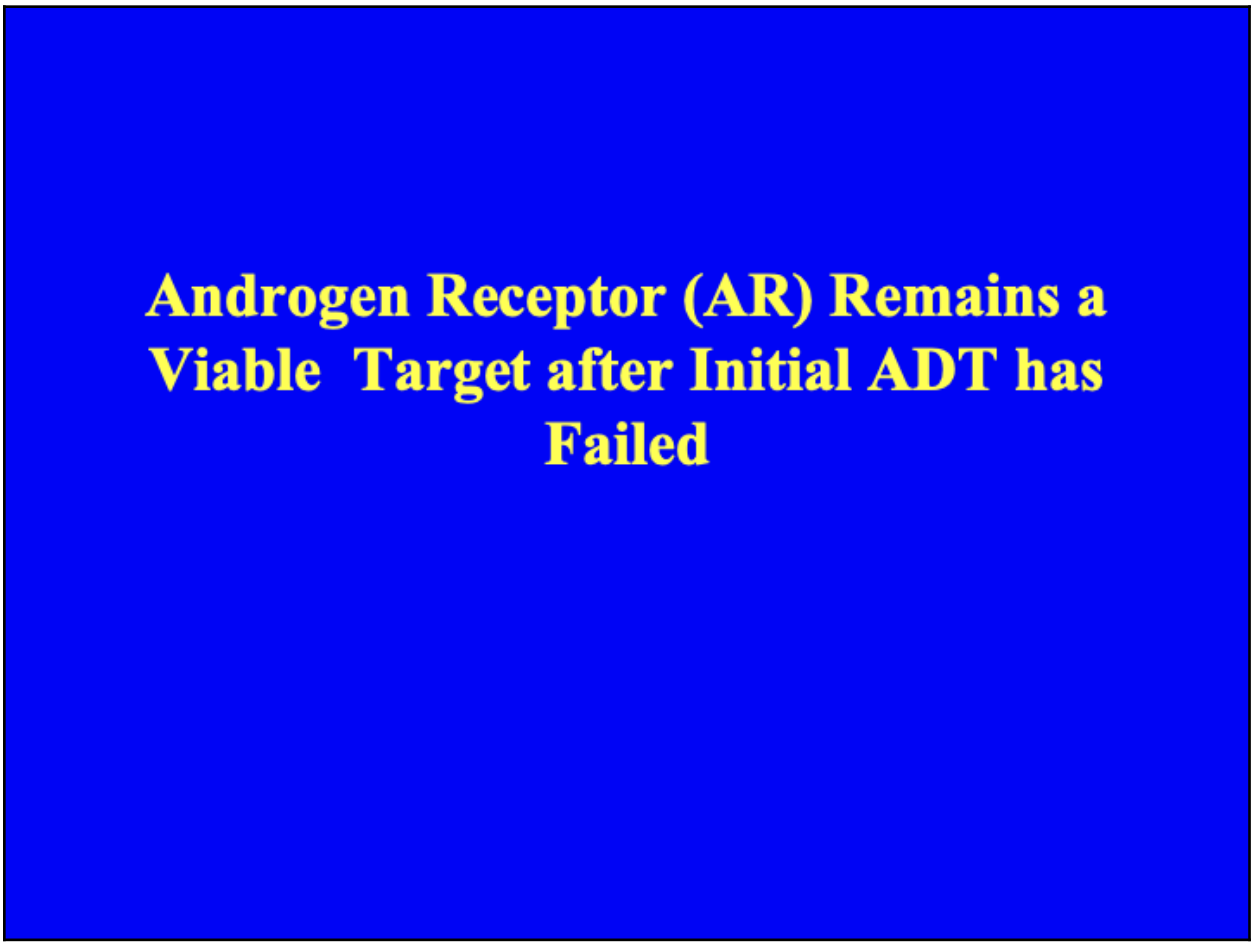
Antibody drug conjugates, radiopharmaceuticals, CAR-Ts, bispecifics, immunologic stimulators, inhibitors.

All of these are different ways to think about treating the disease.



The androgen receptor remains viable even after initial ADT (androgen deprivation therapy) has failed.

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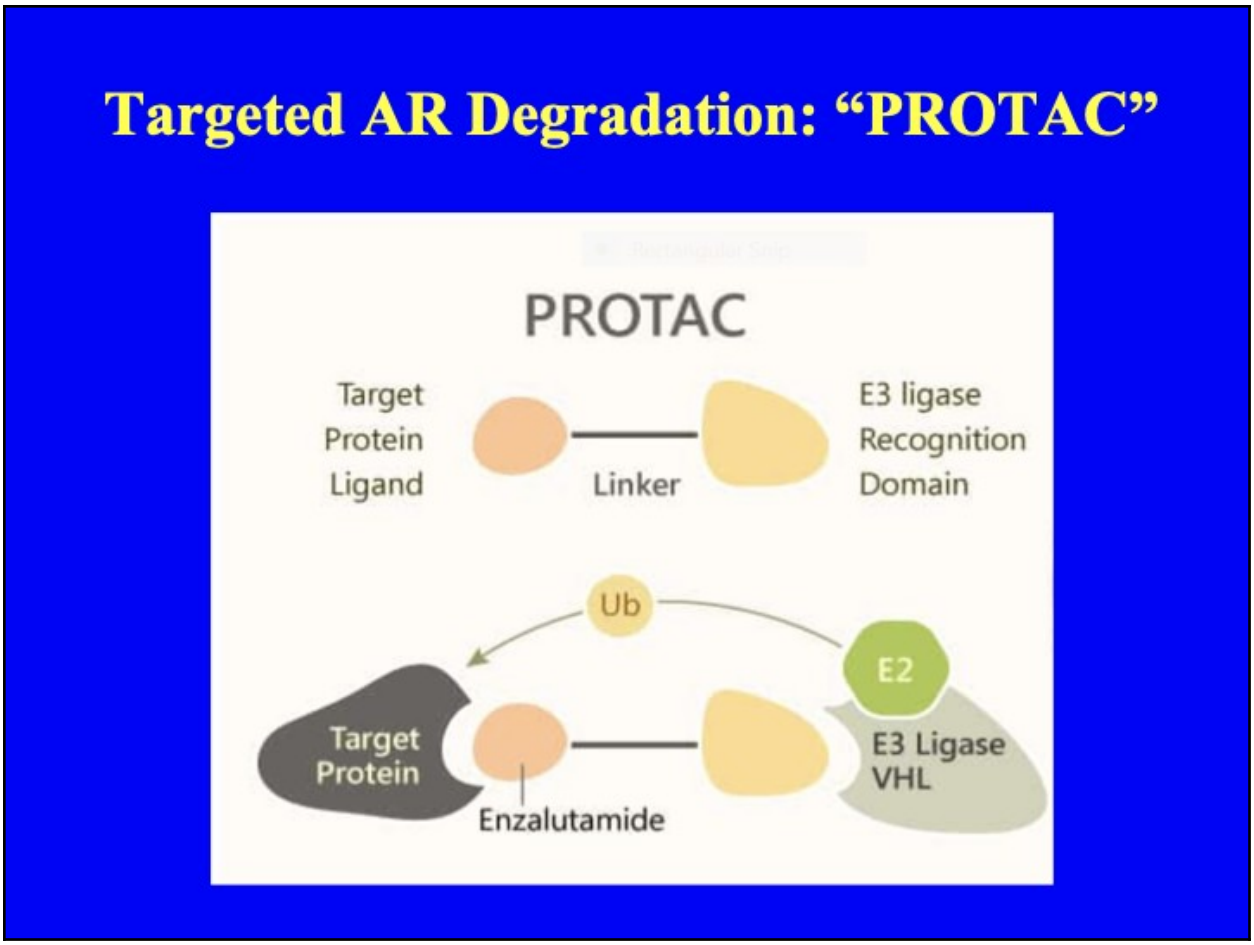

I'm going to draw attention to an AR degrader called “PROTAC” (Proteolysis TArgeting Chimeras, are small molecules that can selectively degrade harmful proteins in cells). This is a proprietary thing that has now been sold to Novartis from a little company called Arvinas. You take your target protein, and over here is the androgen receptor, and you're going to put on an enzalutamide compound, bind it to AR, but link this molecule to an E3 ligase, which is a degrader, and now you can target your protein for degradation. Your protein begins to go away. The problem is, it doesn't all go away. People have the overexpressed receptor, and it may not work as well.

Interestingly, this approach seems to work best for some of the mutations.

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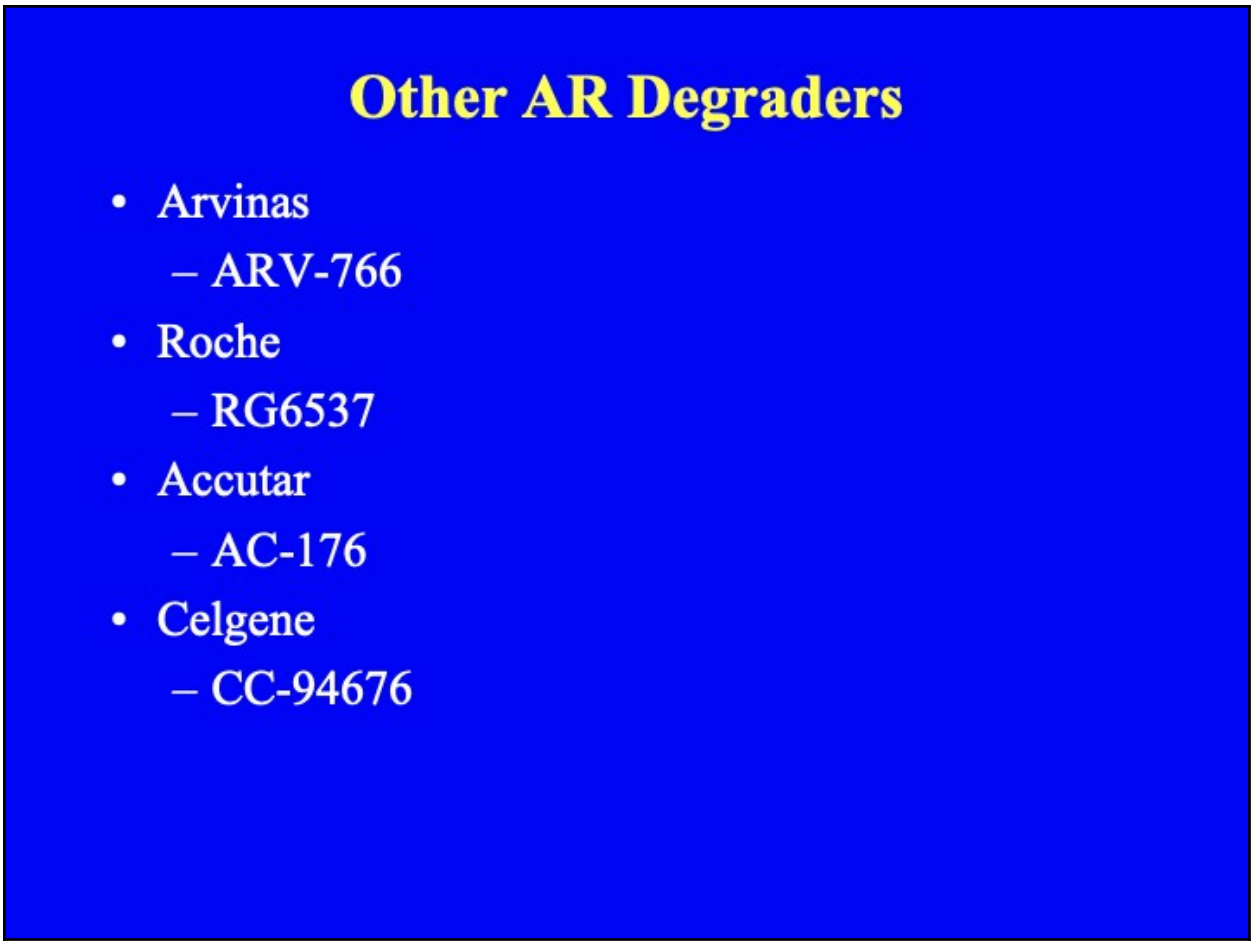

Here are some of the degraders out there. ARV-766, is now in Novartis, and that's come a pretty good way. There's also an interesting degrader that's coming out of BMS (Bristol Myers Squibb). I don't have it on the slide right now, but BMS has an interesting degrader presented for the first time in ESMO (European Society for Medical Oncology, the European cancer organization and conferences). This is not a complete list of all the degraders, I’m trying to be conceptual.

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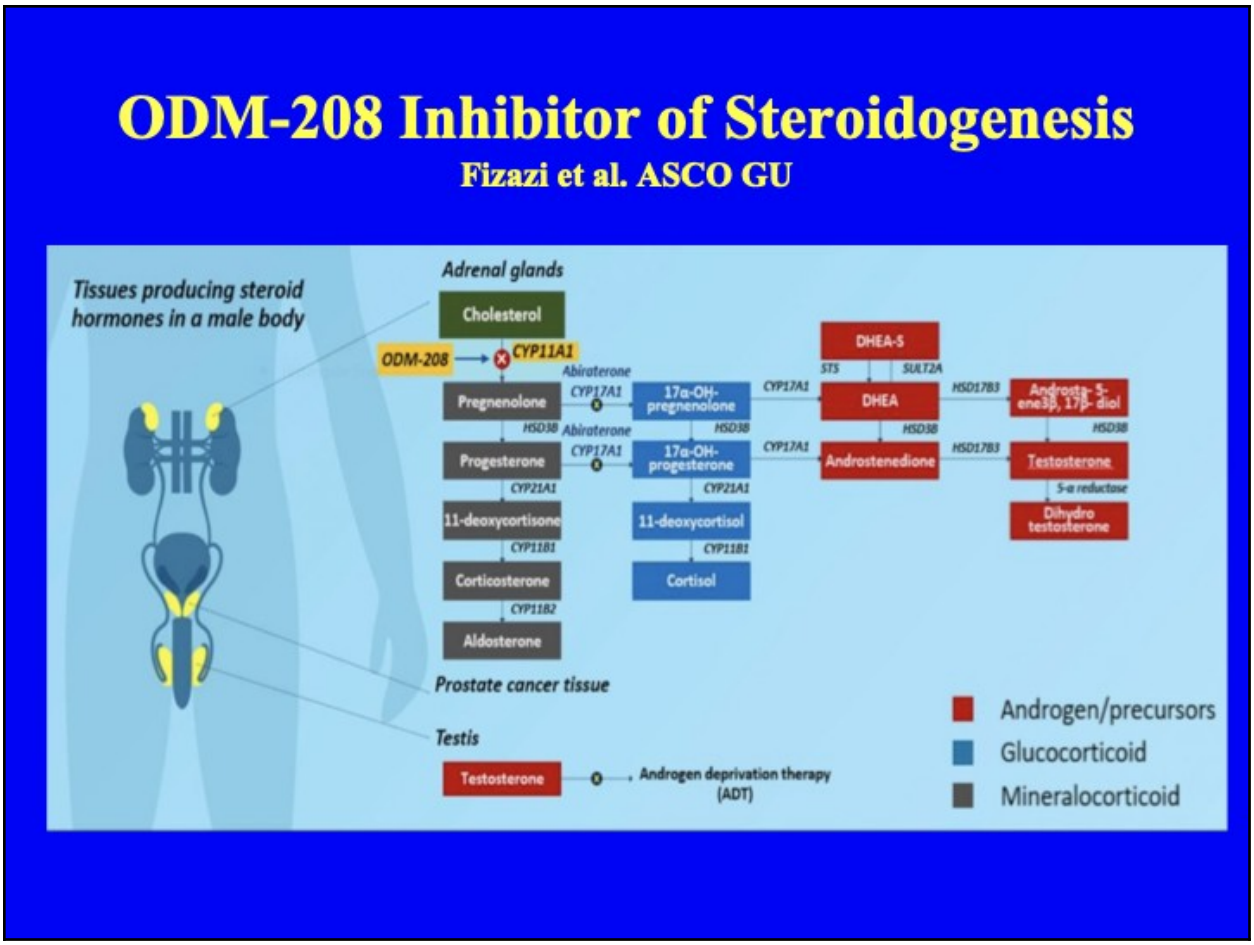

Another way to try to approach the ARs is to get rid of the ligand in even more ways than what you might be able to get with something like Abiraterone, because Abiraterone is going to bind 17 Alpha hydroxylase and 17 keto ilase. You can see the inhibition that occurs with Abiraterone. This is a compound called ODM-208. This has gone to phase 3. It blocks the cholesterol conversion to pregnenolone, which is the first step for all of the steroids. The problem is you're going to be depleting not only the steroids that you don't want, but also the steroids you do want. But if you take this by itself, you will die, because it will cause an Addisonian crisis (an acute adrenal insufficiency, a life-threatening condition that occurs when the body's cortisol levels drop too low) due to glucocorticoid depletion. You must take it with glucocorticoids. I'm really scared of how this is going to play out, because I'm worried that people are going to take the drug and forget the steroids, and then they're going to go into addisonian crisis, hypertension, and have a real disaster on their hands. But anyway, it is an interesting drug. It's active, particularly for those with AR mutations, a little bit like the Arvinus compound. But safety-wise, you just need to be very, very careful. You have to take it with steroids. This is going to go into phase 3 with Merck.

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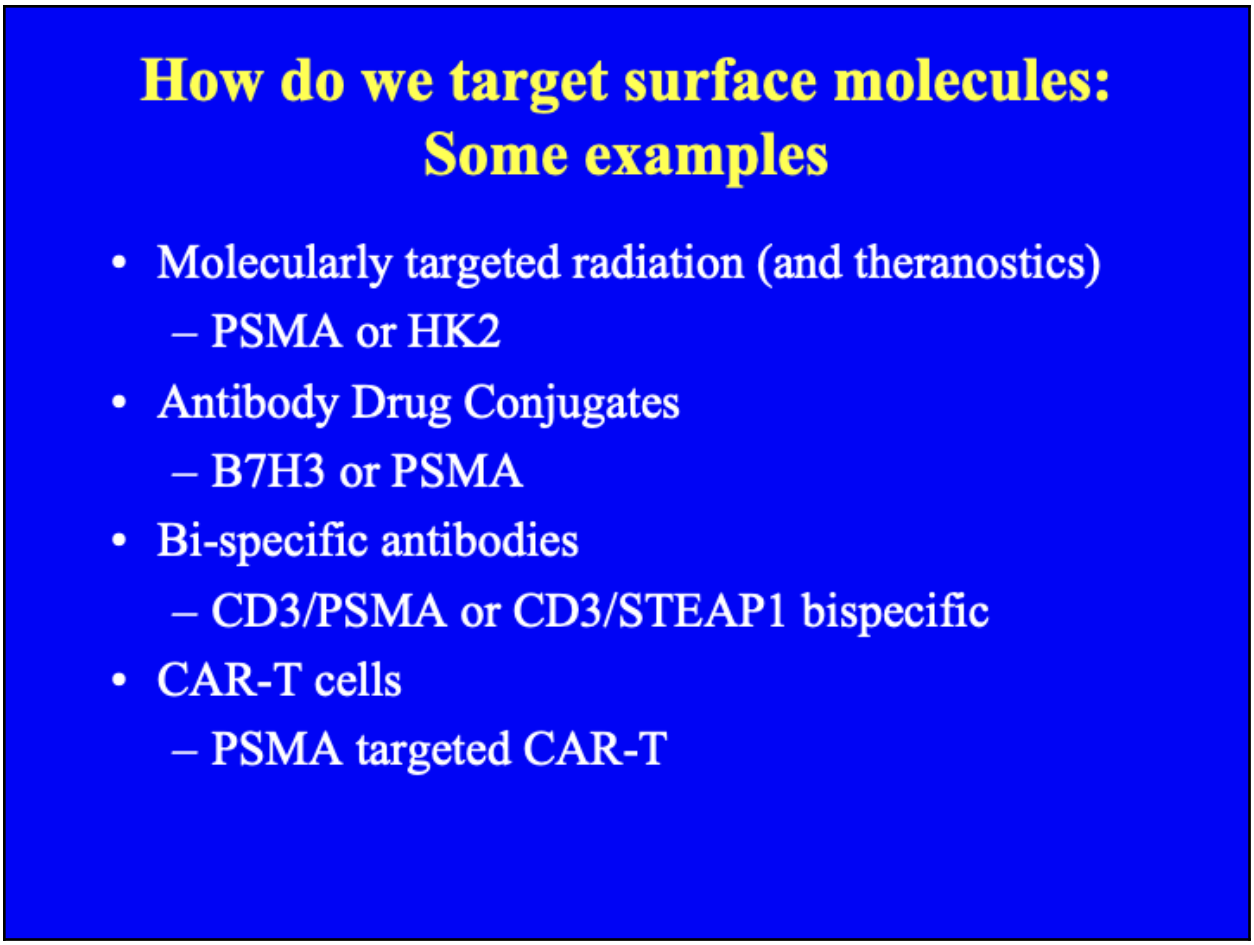
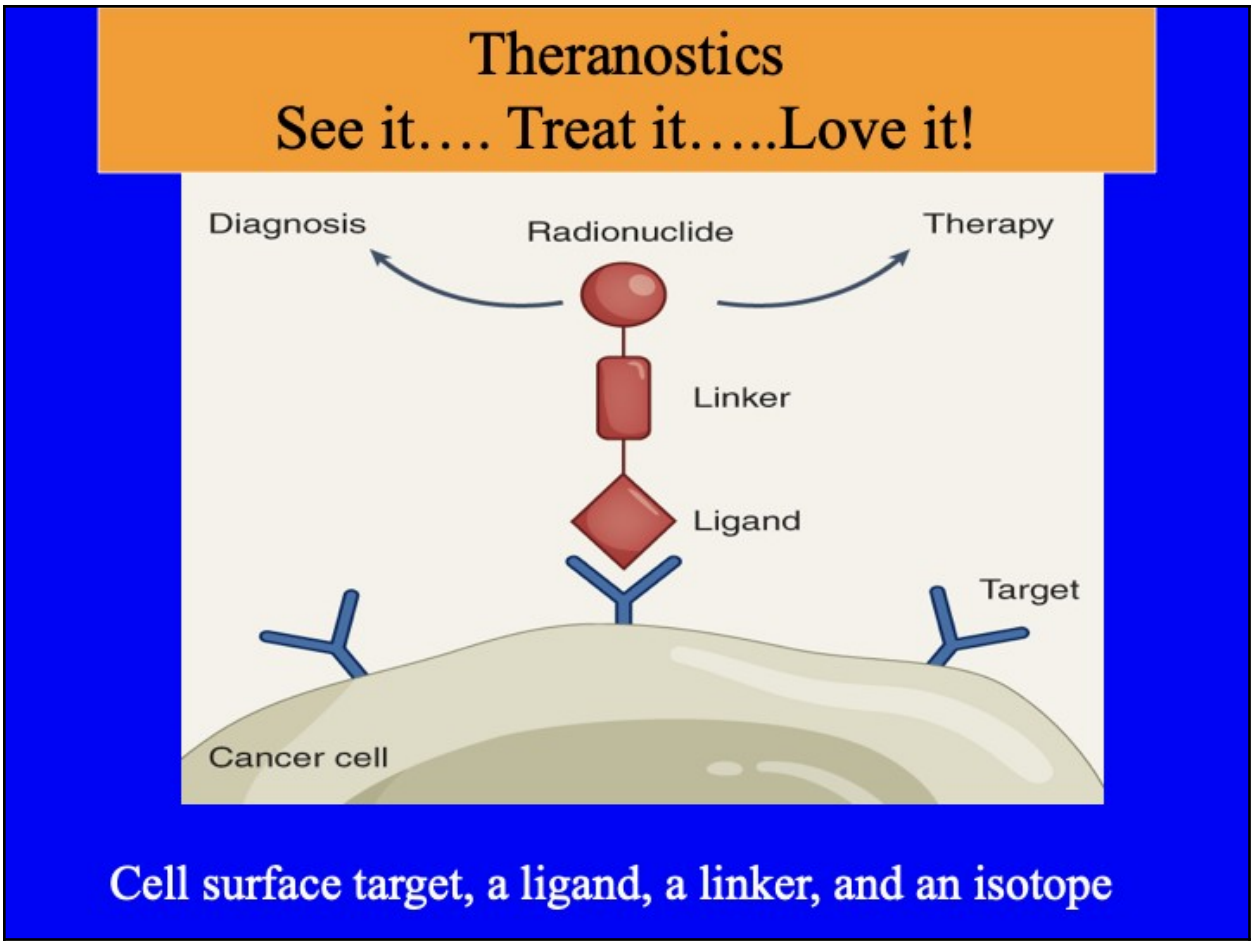


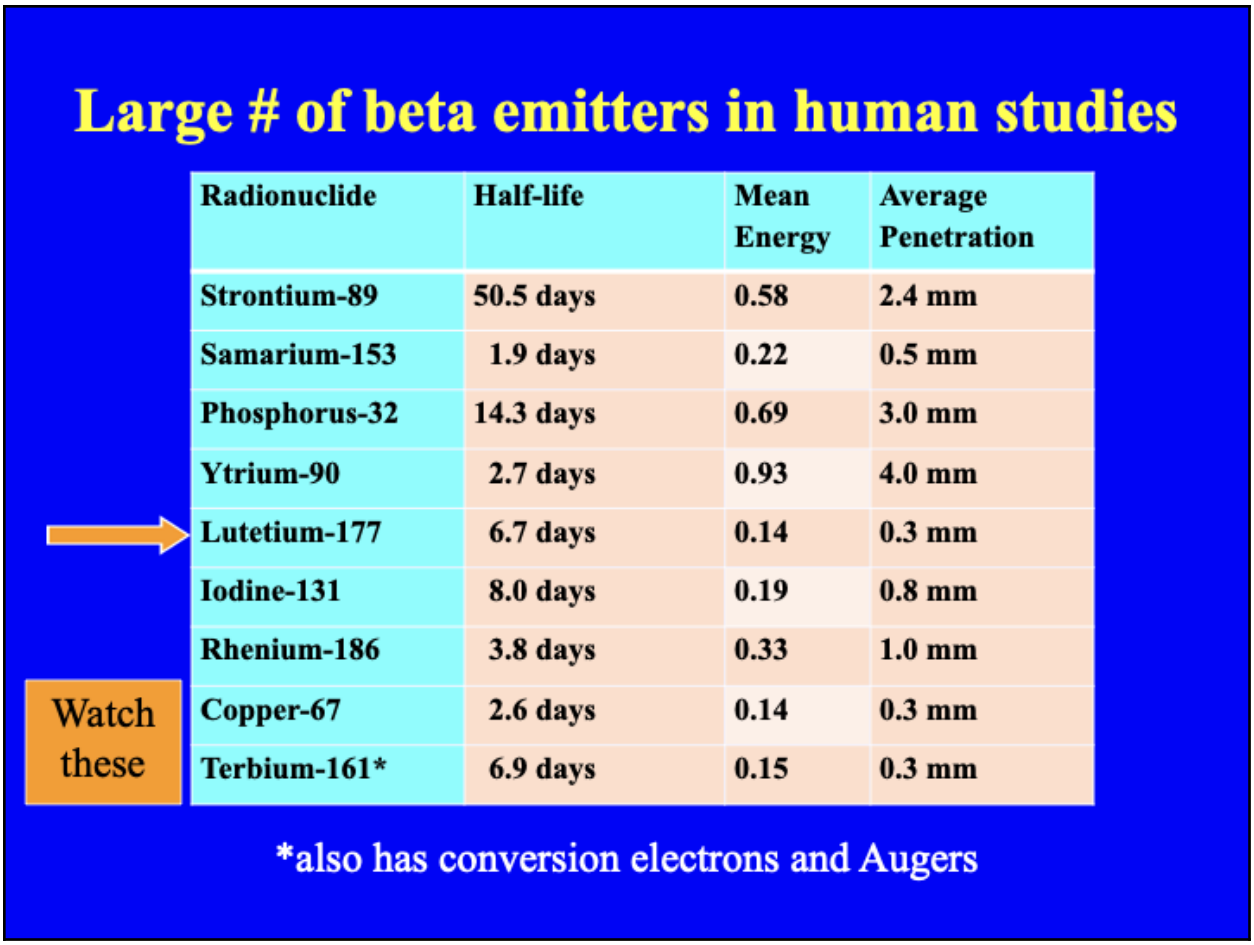
We talk about cell surface molecules, and that's an important thing. We can talk about molecularly-targeted radiation. We have PSMA and HK2 right now. HK2 is the same thing as KLK2. We have antibody drug conjugates, also to PSMA, and B7H3 is another target. We have bispecific antibodies to PSMA, STEAP1, and these are ongoing right now, and then CAR-T cells. We also have some PSMA-targeted CAR-Ts and more. If we have a cell surface molecule, there are a couple of things you want. You want a lot of expression. We want to be able to make the cell surface target exploitable. You've got a lot of expression on the cancer cell, and you don't have much expression elsewhere. Otherwise you're going to be attacking wherever you have the expression. That's important as you go forward. You have to think about not only expression of the prostate, but expression elsewhere.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



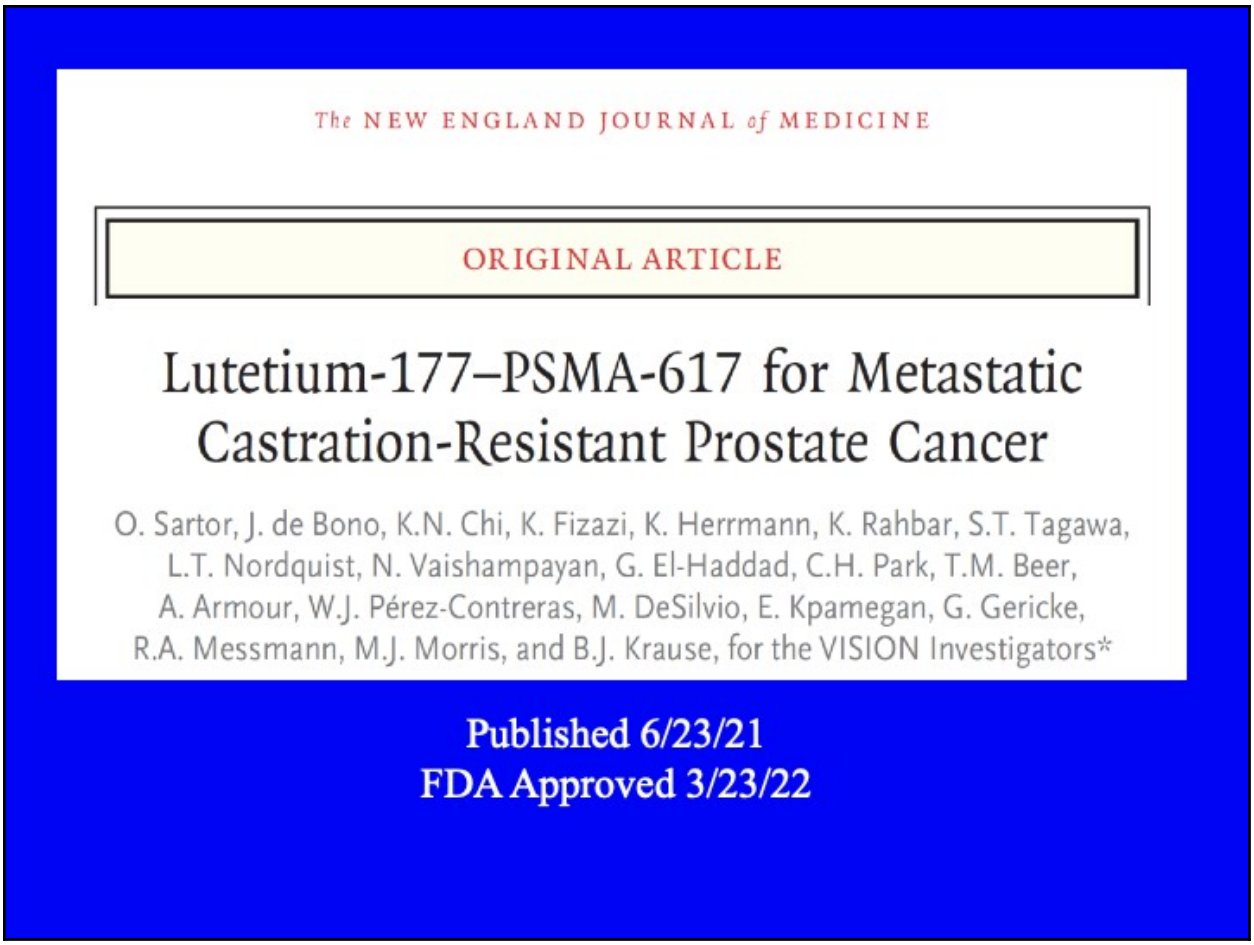
This is what I call “theranostics”. We see it. We treat it. We love it. You take a cell service target – PSMA is the prototypical target. You take a ligand there – the one where we have the most advanced therapy is PSMA-617. We also have PSMA I&T, and other ways of doing it. You have a little linker and then bind it to the radionuclide. You can use that for things like Gallium-68 (a radioisotope) and have a PSMA PET. Or you can use something like leutetium-177, and you can have a therapy, or actinium 225. This concept is very simple. We're just going to put a radioactive tag on something that binds to the cell, particularly the cancer cell. We're either going to diagnose it, or we're going to treat it. We're going to do either, depending on the isotope we use.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



We have a variety of isotopes here. We have the beta emitters, which are present in human study. I’m focusing on lutetium-177, that's where most of the data is. But there's some interesting data coming out with copper-67 and some very preliminary data with terbium-161. Watch these. Terbium has also got some conversion electrons and Augers (Auger electrons are very low-energy electrons emitted by certain radioactive isotopes when they decay, which are being investigated as a potential targeted therapy for cancer due to their ability to deliver a concentrated radiation dose directly within cancer cells, causing significant DNA damage and cell death with minimal damage to surrounding healthy tissue due to their short range.), which may make it a little more interesting.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



Nevertheless, lutetium is what is brought to this point. We're going to be focusing on lutetium here.

[Dr. Sartor had to restart his computer here and dropped out for a few minutes.]

Brad Power 14:35
I hope everybody's following. He's using a lot of jargon. He's talking about oligo-metastatic, I assume everybody knows that's just a few mets. He's assuming this is a very educated audience. He's referring to radioligands. Because I write up the notes, I'm thinking I will be translating a lot of terms that he's using. So I hope everybody's following along.

Nathanael Jackson 15:10
I'm a retired level one trauma center emergency room registered nurse. He's talking way over those of us that have the disease. He's using acronyms and stuff. If I took him to my block, he'd be totally lost, because he's talking like he's talking to other colleagues. I thought this was going to be an educational forum for simple guys like me.

Brad Power 15:38

Thanks, Doc. I'll mention that to him when he comes back, because I was very aware of that. We'll see if we can get him to simplify. When we get these doctors on, they think that they're talking to a set of peer experts at an ASCO conference. I've gone to an ASCO conference where they do this, and it's like, “Here's the update.” And they're talking peer-to-peer with other MD PhD researchers, and there's a lot of translation required.

David Plunkett 16:20
The good news is that the slide decks are usually posted so that you can review them later and look up terms, things like that. It's helpful that way. I don't bother trying to take scribbled notes. I just wait for the recording later.

Nathanael Jackson 16:49
I'm a simple man. Having all that knowledge, looking it up and everything, ain't going to do a thing with this cancer that's inside of me today. I want to hear how we're going to deal with it in a way that I can understand it, and when I understand it, it's much easier in my mind and spirit to take this treatment, because I'm trusting you guys. I'm trusting Novartis. I'm putting my life in my oncologist’s hands and everything like this. I'm trusting God first. I like to understand what is going on. They stuck that needle in my arm and gave me that Pluvicto. I came home. I thought I was going to light up and have a Peter Parker Spider Man experience. Explain things to me that I can understand. I'm not trying to be difficult. I'm just a simple man.

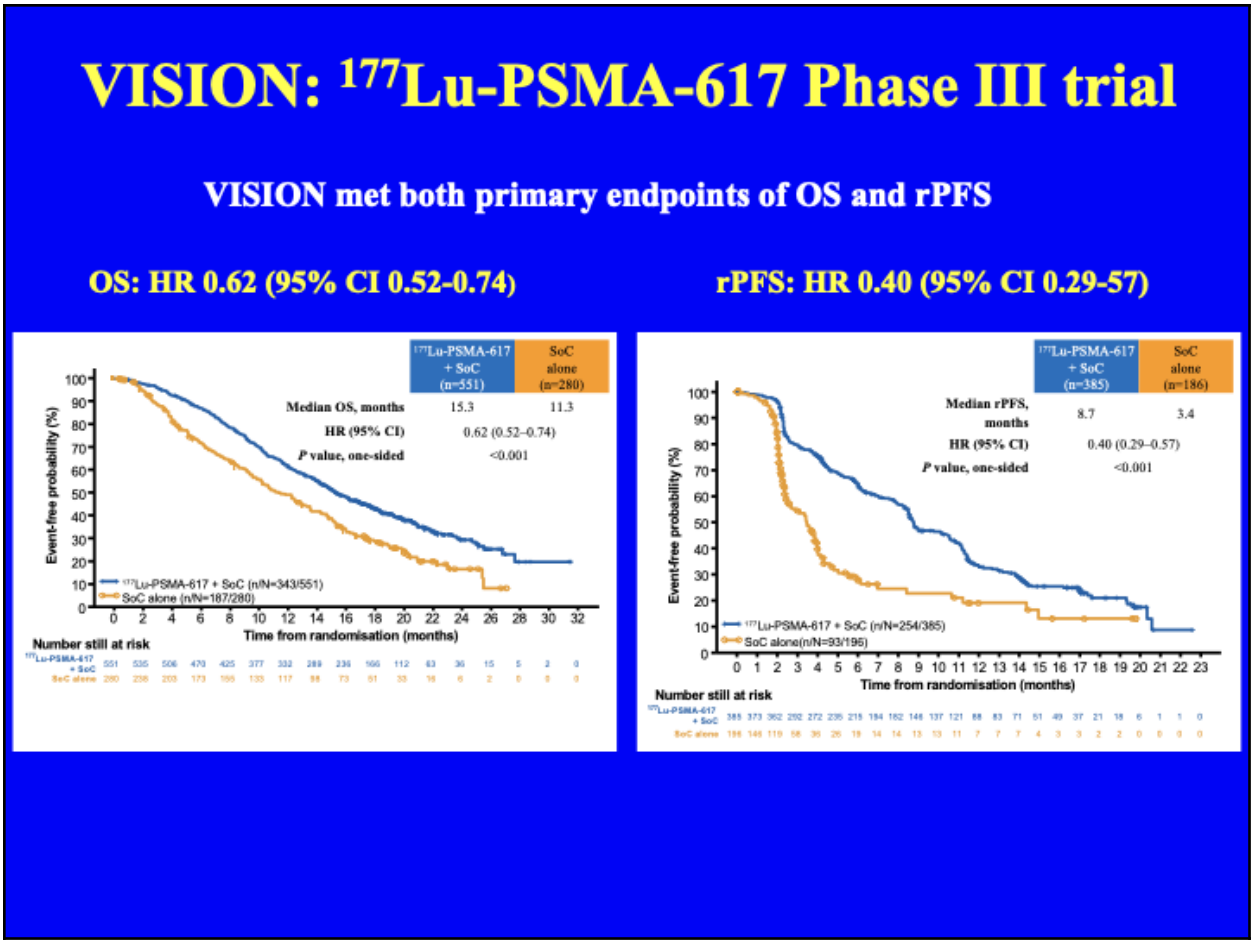
Brad Power 18:05
Let me just give you my layman's version of what he's talking about. He was doing it in the last part there. You have on the surface of a cancer cell unique antigens, which are like the Coronavirus. For COVID, they've got these antigens, which are sticking out on the surface of the cancer. PSMA is Prostate Specific Membrane Antigen. It's an antigen that's unique to prostate cancer. Or you can have other antigens, like he talked about AR, which is androgen receptors. You have these antigens sticking out on the surface, and then you can have things that grab that antigen. Then you can have things attached to that thing that grabs the antigen. They could be radioactive particles. Hence all the radiopharmaceuticals, like Pluvicto. It can be chemotherapy. It can be an anti-drug conjugate, so it can grab onto that antigen and then have as a payload of some chemotherapy that's delivered directly to the cancer cell. You can have an immunotherapy. It can be a bispecific which can grab onto that and on the other end is an immunotherapy, like a T-cell, like a white blood cell, that's going to kill the cancer. All of these are working at a molecular level to latch onto the cancer cell on one side and then give some kind of drug delivered at a cellular molecular level.

[Dr. Sartor returned here.]

Brad Power 20:08
Dr. Sartor, while we were talking offline, waiting for you to come back, one of the things that Doc pointed out is a lot of what you've been saying is as if you're talking at an ASCO or an ESMO conference to peers, and a lot of this has been going over the head of a lot of the people in this audience. You're using a lot of terminology that you're assuming, because we have an educated

audience, that they're getting this. But if I could make a request that you simplify some of the concepts you're presenting as if you're presenting to a lay audience and not a set of peers at an ASCO conference.

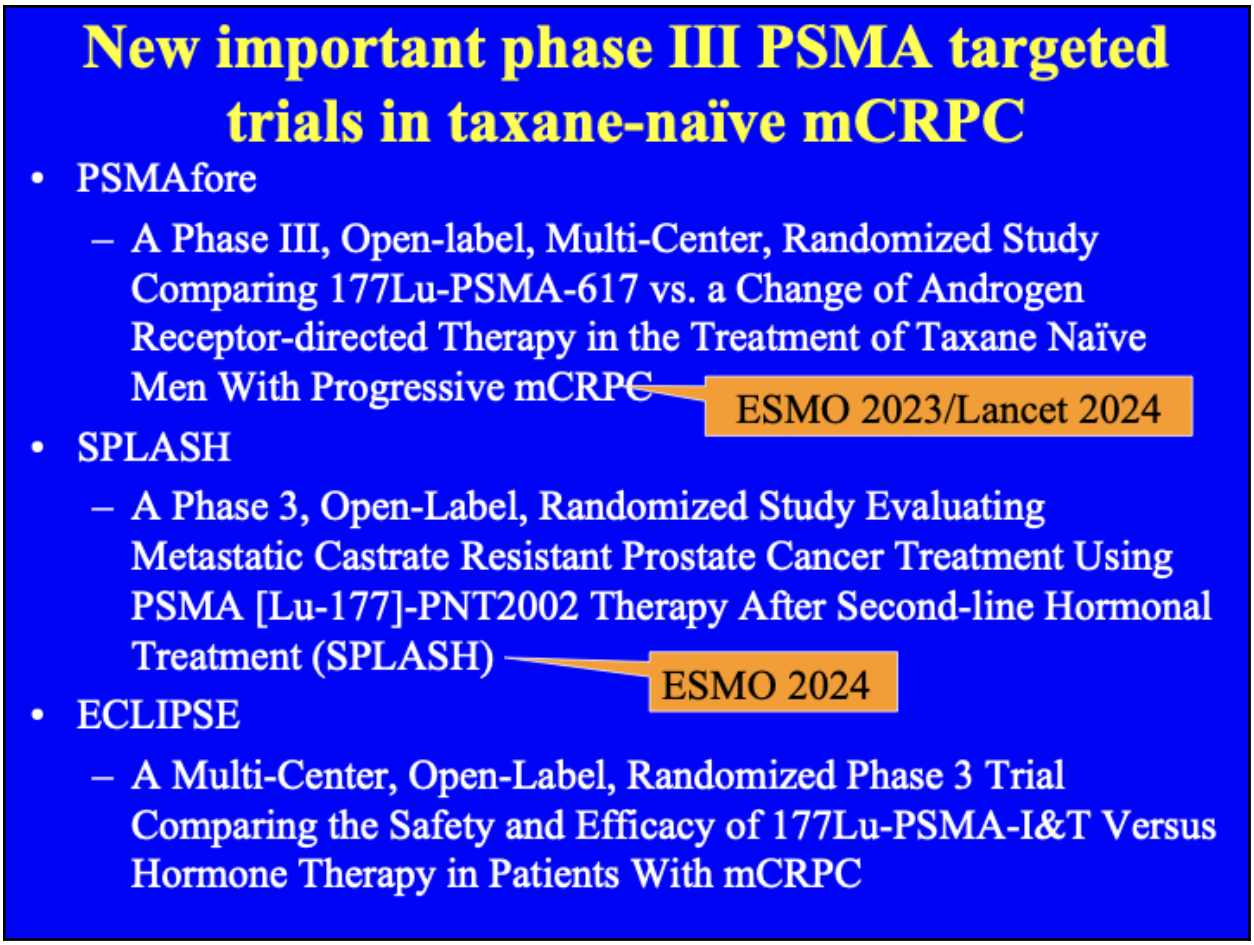
Oliver Sartor 20:45
Good point. In speaking with you guys before I found you to be a very sophisticated audience, so I didn't want to dumb it down too much. Let me be a little more plain, and then we'll go from there.



Beta emitters are one form of radiation, and it turns out they're a bunch of different beta emitters out there, and the one that we count the most is lutetium. That's because we have the VISION trial, which led to the FDA approval, and we have survival.

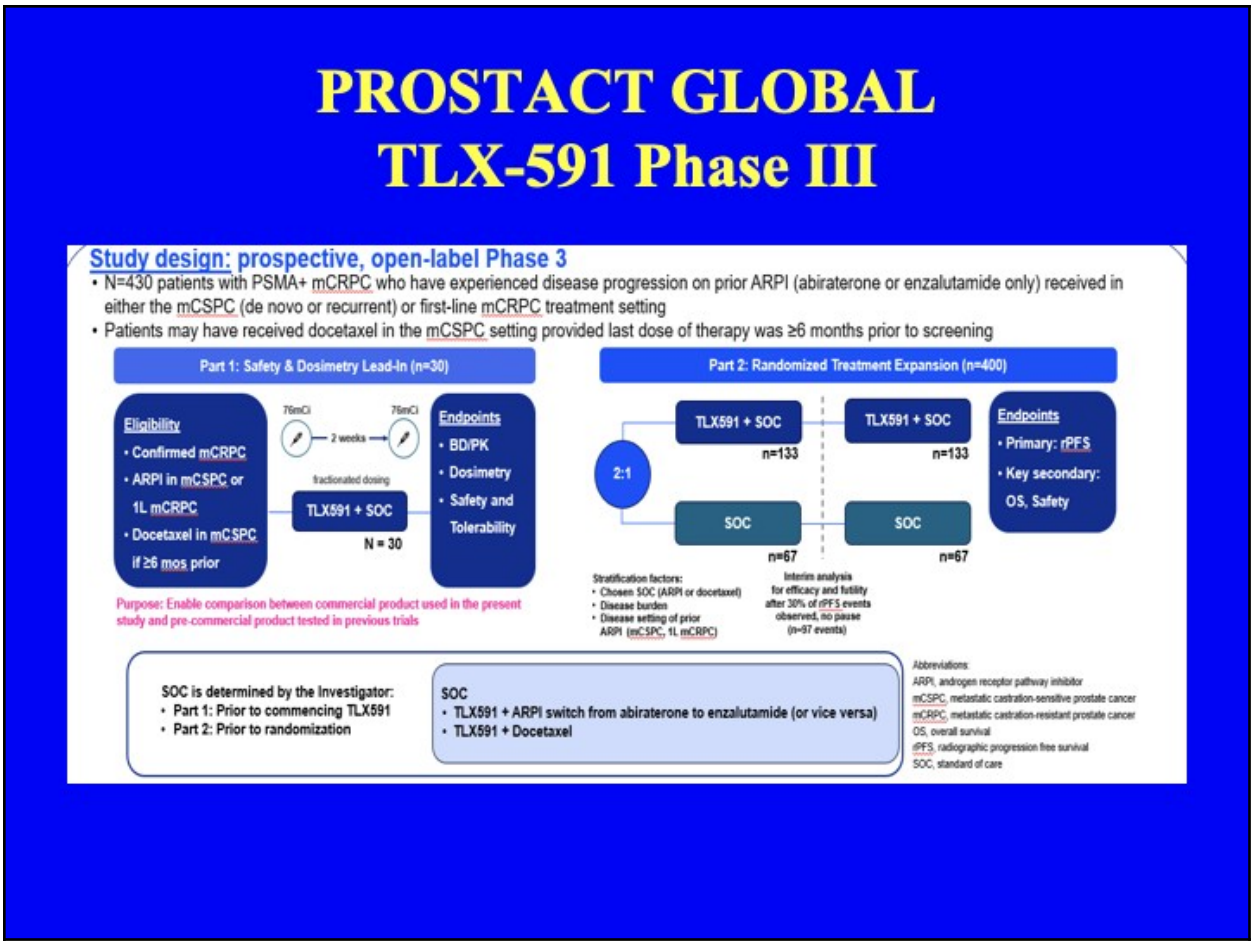
I could go into a lot of detail here. This is Pluvicto. About a third of the patients have really beautiful responses. About a third of the patients do not respond very well, and about a third are in the middle. So it is effective, but we need even more effectiveness. And that's the zone with lutetium.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



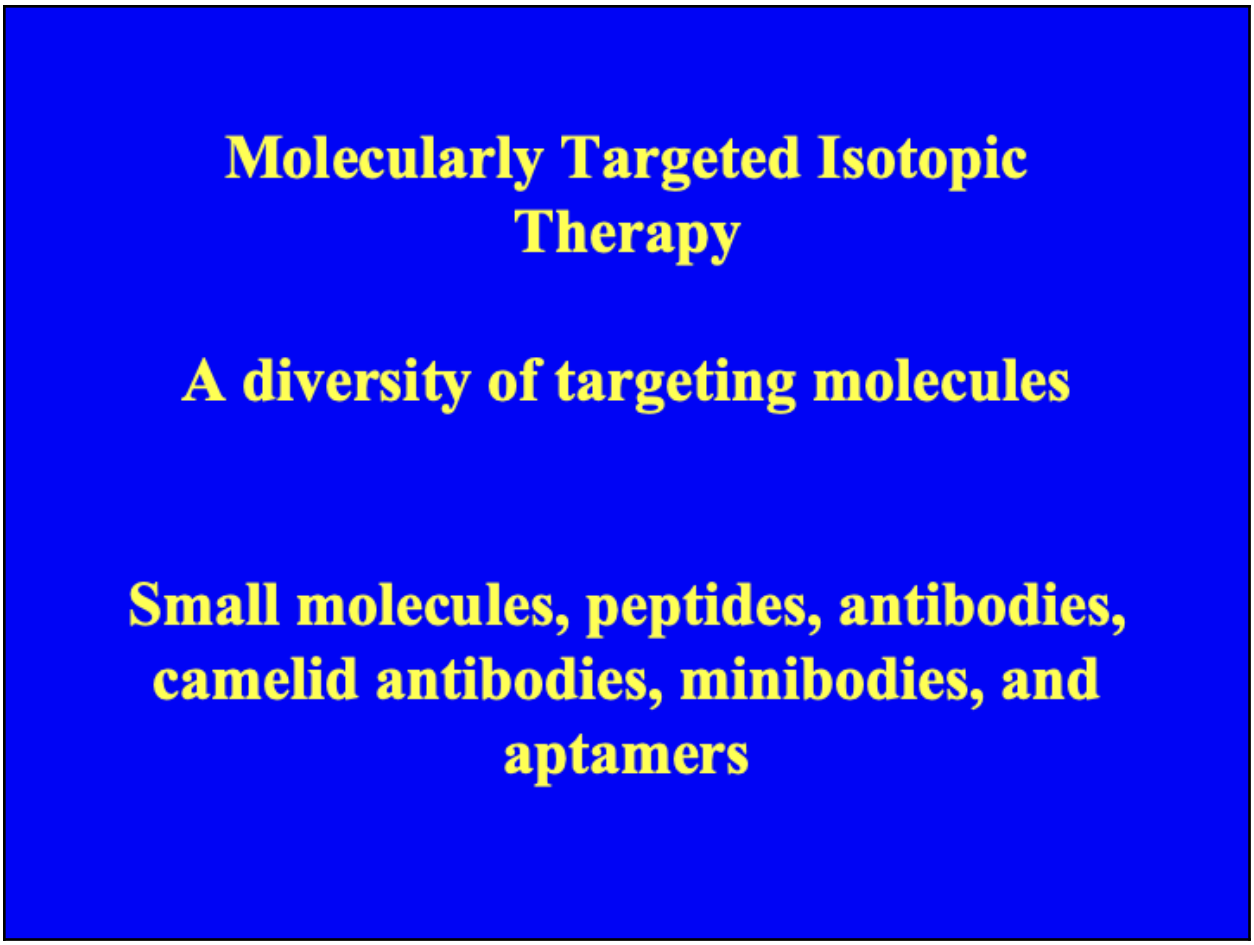
We have new trials. They're going to move it earlier without the chemo, but we're not there yet. The FDA has to approve it, and that's really critical.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



There was a mention of the J591 lutetium a little bit earlier, received in Perth by Nat Lenzo. I happen to know Nat quite well. I happen to know this compound quite well. It's called TLX591 because it got sold over to Telix. I'm co-PI (principal investigator) on the trial, so I probably know a little bit about it. This came out of the Scott Tagawa and Neil Bander group at Weill Cornell. This initial phase is the part one lead in. But the TLX591, which is J591 lutetium, is moving forward into phase 3.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]

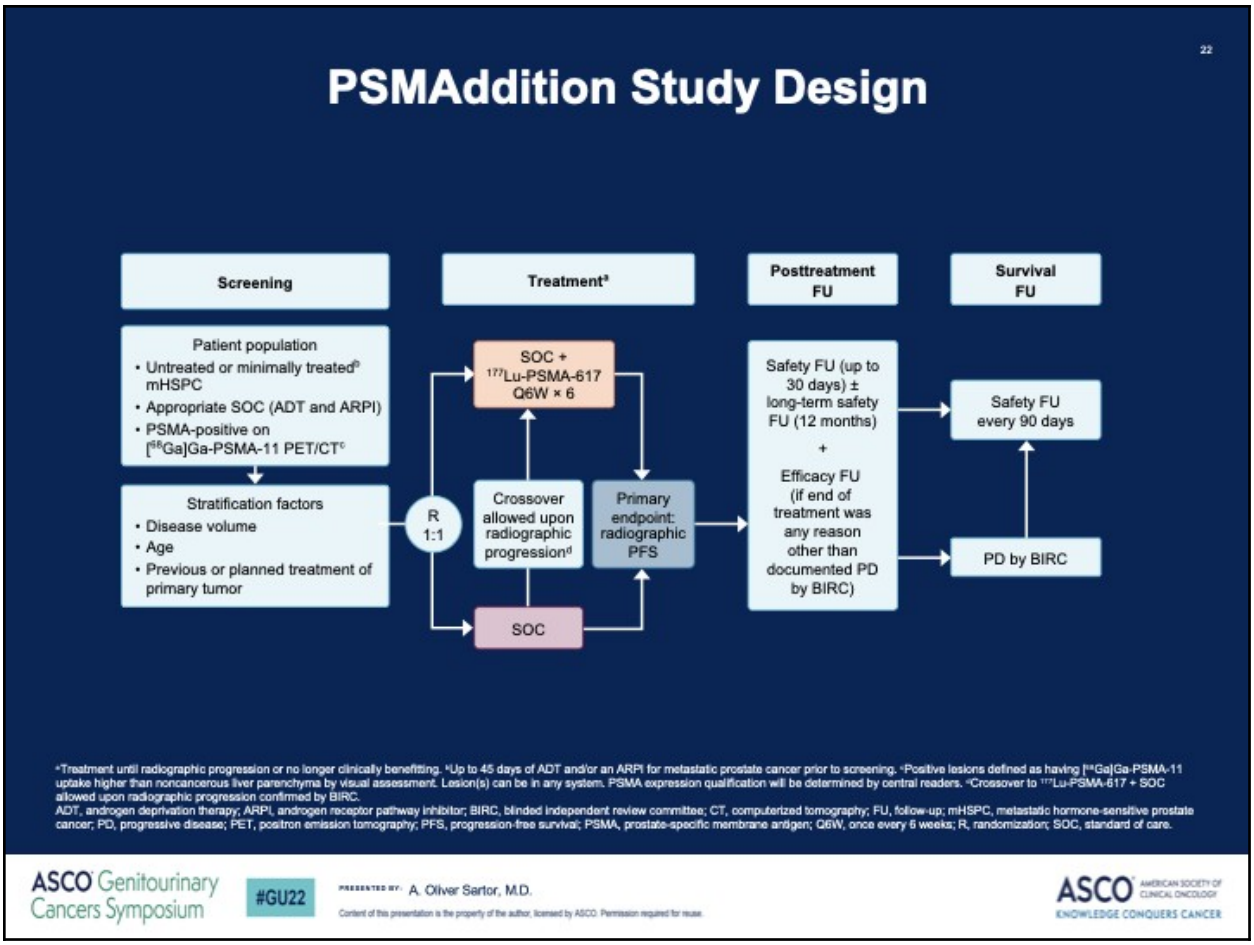


I mentioned cell surface targets, and there are a bunch of ways to bind to that target. This is where we have a lot of innovation. Here we have small molecules, peptides, antibodies, different ways of approaching this. A lot of what you're going to see over the next five to 10 years is people taking these isotopes, bringing them onto the cell surface with a diversity of targeting molecules. We're not going to be stuck with PSMA-617.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]

Castrate-sensitive disease is not really the topic, but I do want to keep in mind that we have castrate-sensitive protocols.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]

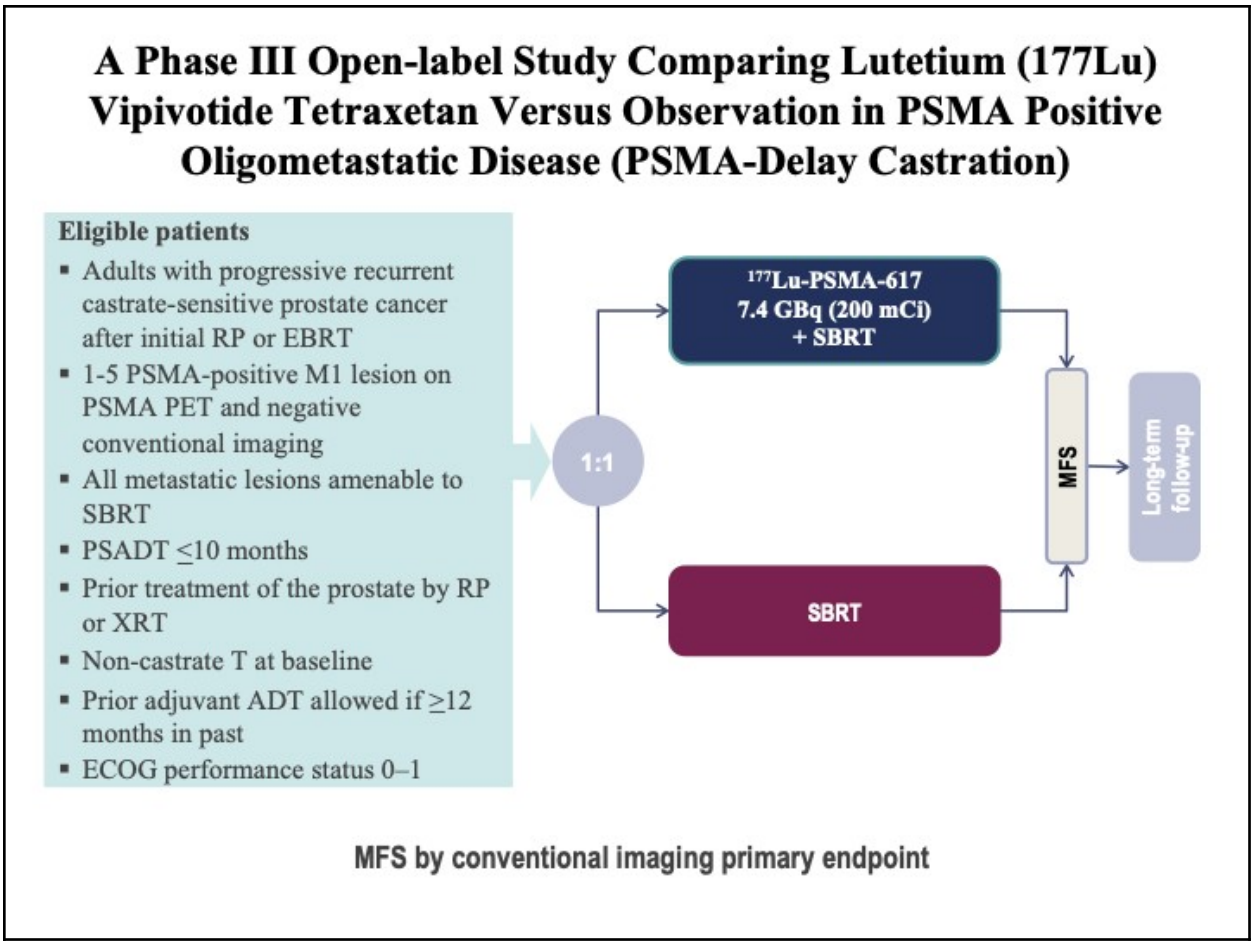


One is called PSMAddition. It is for hormone-sensitive metastatic disease, and that one is already in the bag. We've fully accrued it. We're going to be looking at this in hormone-sensitive metastatic disease, and we'll have some output maybe next year.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]

Very early disease. This is a trial that we're going to be accruing to now. It's a trial that's open called PSMA DC. PSMA PET positive disease, conventional imaging negative. So you have to have a PSMA PET that shows metastatic disease, conventional imaging negative, have to recur after either radical prostatectomy or radiation, and then everybody is going to be getting SBRT radiation to the spots.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



But now the randomization is going to be to Pluvicto or no Pluvicto. The idea here is no hormones. It's called the PSMA DC trial for “delay castration” trial, oligo-metastatic PSMA PET positive disease. Patients must have SBRT to all the lesions. Then the randomization is here. And of course, like every trial does, the inclusion criteria are here.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]

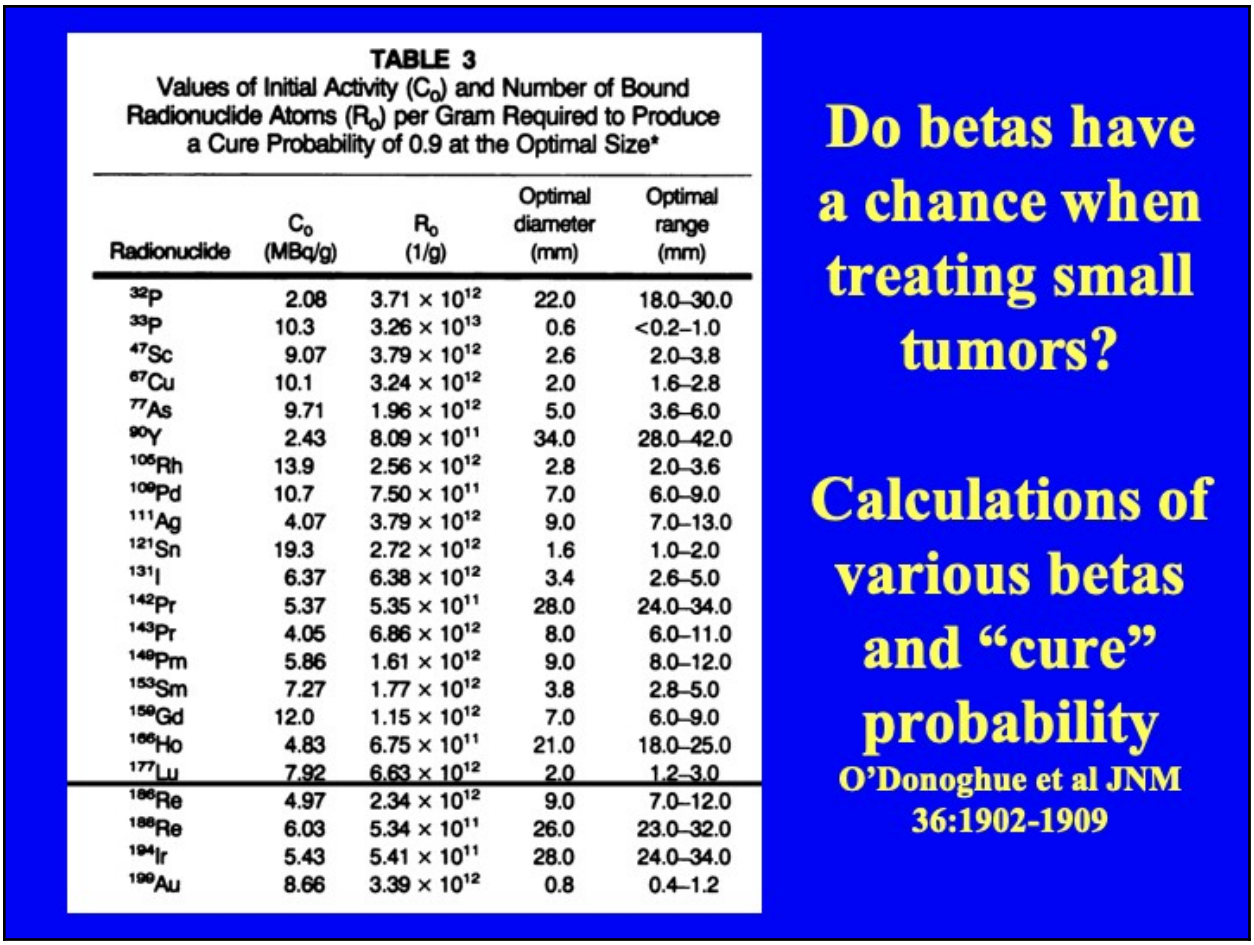


TABLE 3
Values of Initial Activity (C_0) and Number of Bound Radionuclide Atoms (R_0) per Gram Required to Produce a Cure Probability of 0.9 at the Optimal Size*

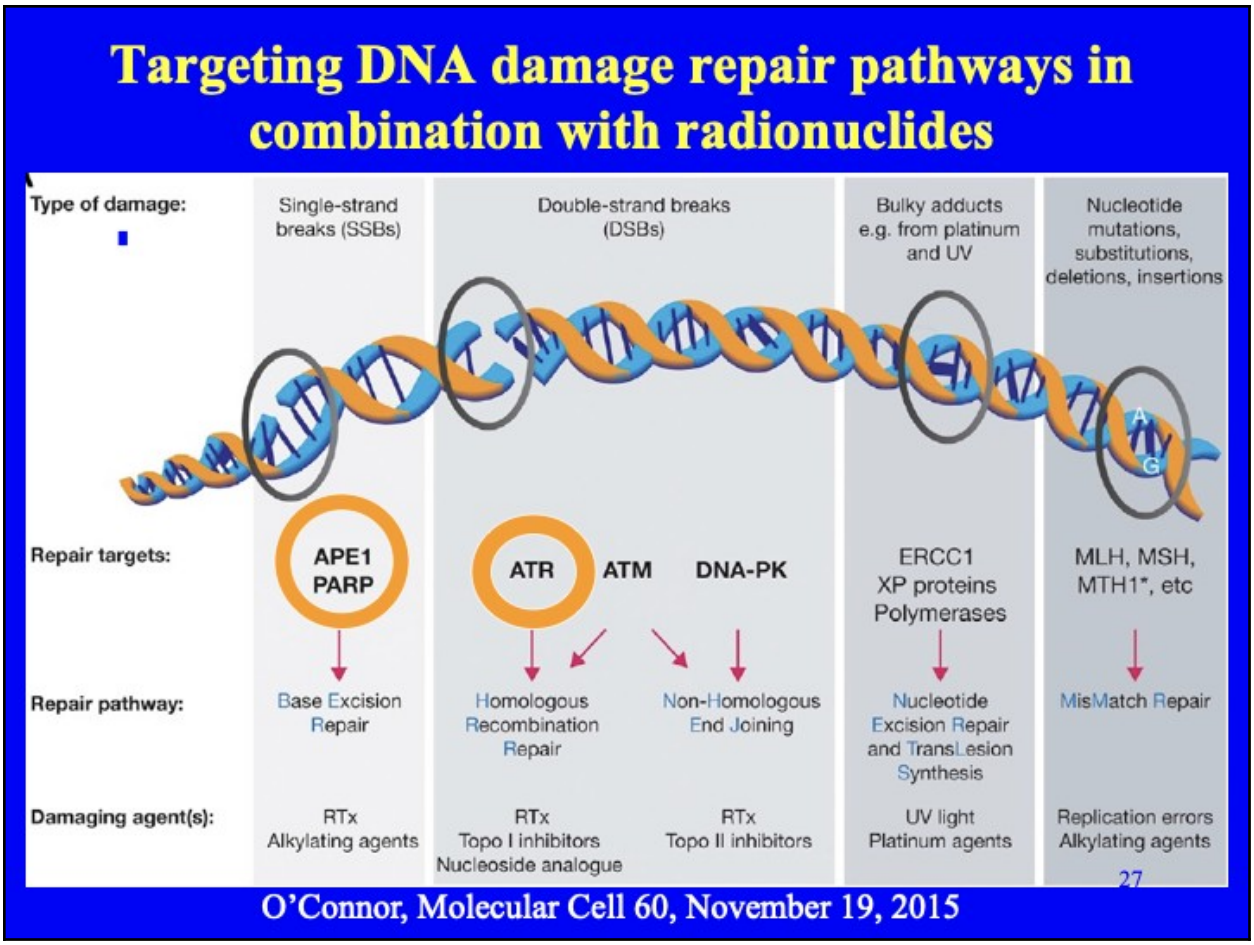
Radionuclide	C_0 (MBq/g)	R_0 (1/g)	Optimal diameter (mm)	Optimal range (mm)
^{32}P	2.08	3.71×10^{12}	22.0	18.0–30.0
^{33}P	10.3	3.26×10^{13}	0.6	<0.2–1.0
^{47}Sc	9.07	3.79×10^{12}	2.6	2.0–3.8
^{67}Cu	10.1	3.24×10^{12}	2.0	1.6–2.8
^{77}As	9.71	1.96×10^{12}	5.0	3.6–6.0
^{90}Y	2.43	8.09×10^{11}	34.0	28.0–42.0
^{105}Rh	13.9	2.56×10^{12}	2.8	2.0–3.6
^{109}Pd	10.7	7.50×10^{11}	7.0	6.0–9.0
^{111}Ag	4.07	3.79×10^{12}	9.0	7.0–13.0
^{121}Sn	19.3	2.72×10^{12}	1.6	1.0–2.0
^{131}I	6.37	6.38×10^{12}	3.4	2.6–5.0
^{142}Pr	5.37	5.35×10^{11}	28.0	24.0–34.0
^{143}Pr	4.05	6.86×10^{12}	8.0	6.0–11.0
^{149}Pm	5.86	1.61×10^{12}	9.0	8.0–12.0
^{153}Sm	7.27	1.77×10^{12}	3.8	2.8–5.0
^{159}Gd	12.0	1.15×10^{12}	7.0	6.0–9.0
^{166}Ho	4.83	6.75×10^{11}	21.0	18.0–25.0
^{177}Lu	7.92	6.63×10^{12}	2.0	1.2–3.0
^{186}Re	4.97	2.34×10^{12}	9.0	7.0–12.0
^{188}Re	6.03	5.34×10^{11}	26.0	23.0–32.0
^{194}Ir	5.43	5.41×10^{11}	28.0	24.0–34.0
^{199}Au	8.66	3.39×10^{12}	0.8	0.4–1.2

One of the things that's interesting – and this is a big controversy – is how small a tumor can you treat with a beta emitter? I'll simply say that if you look at lutetium, we're probably going to be good down to about two millimeters or so. It’s a theoretical issue, but we're moving ahead.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]

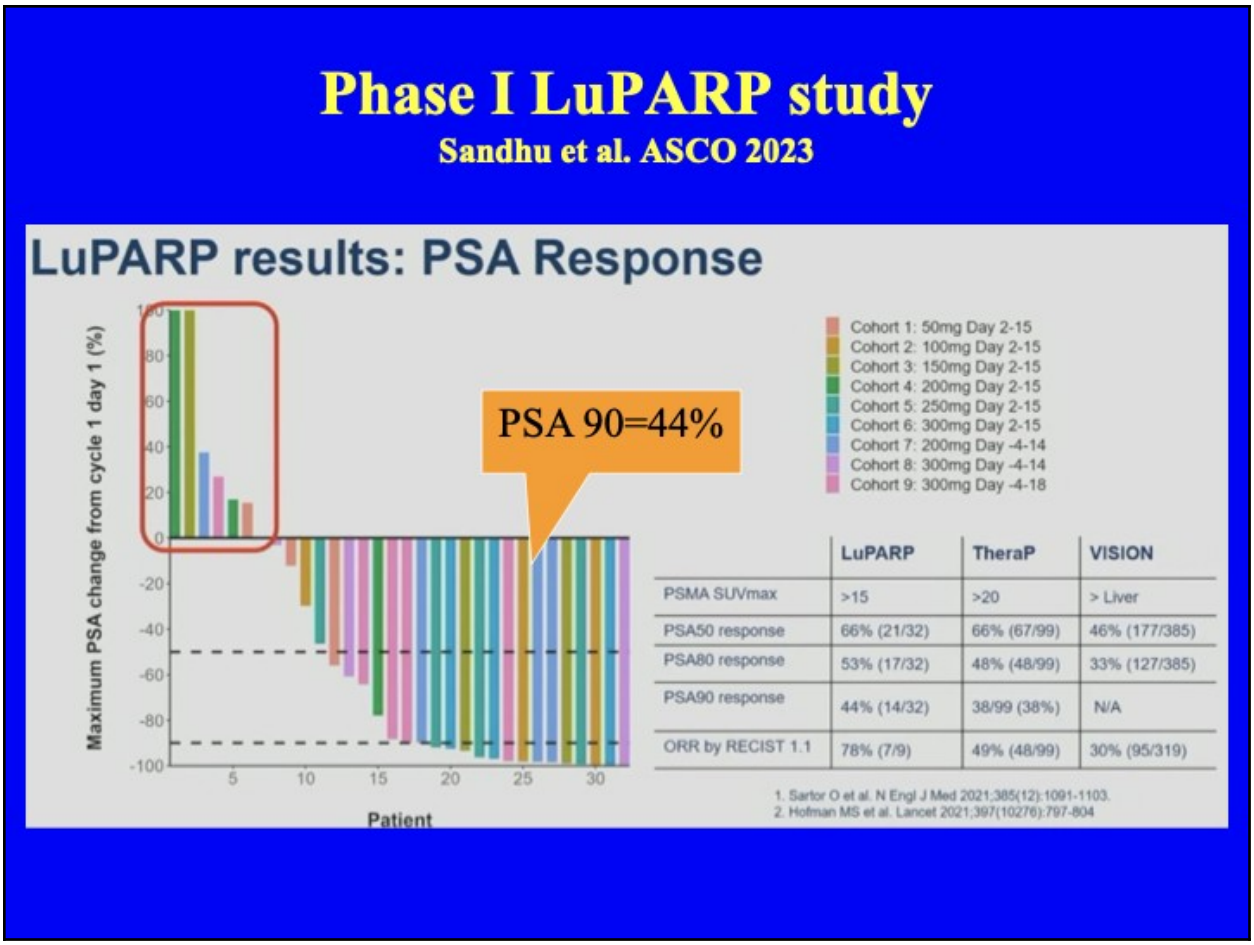
Synergy. If we're going to damage the DNA with radiopharmaceuticals, we have the potential to be able to inhibit that DNA repair.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



The DNA repair is going to be mediated by enzymes such as PARP inhibitors, ATR inhibitors, and ATM inhibitors. We have a built in way of inhibiting the DNA repair from the damage that has been caused.

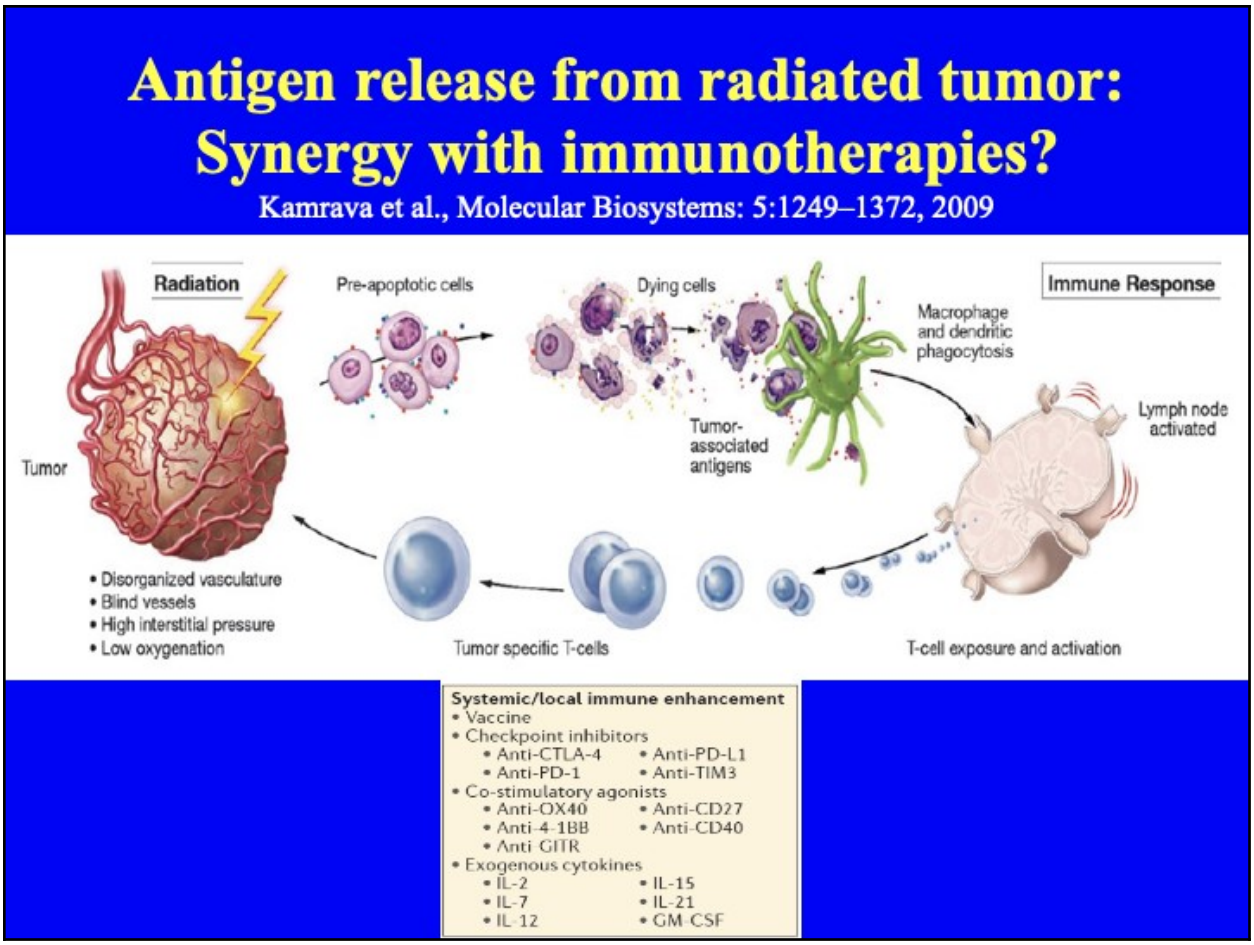
“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



	LuPARP	TheraP	VISION
PSMA SUVmax	>15	>20	> Liver
PSA50 response	66% (21/32)	66% (67/99)	46% (177/385)
PSA80 response	53% (17/32)	48% (48/99)	33% (127/385)
PSA90 response	44% (14/32)	38/99 (38%)	N/A
ORR by RECIST 1.1	78% (7/9)	49% (48/99)	30% (95/319)

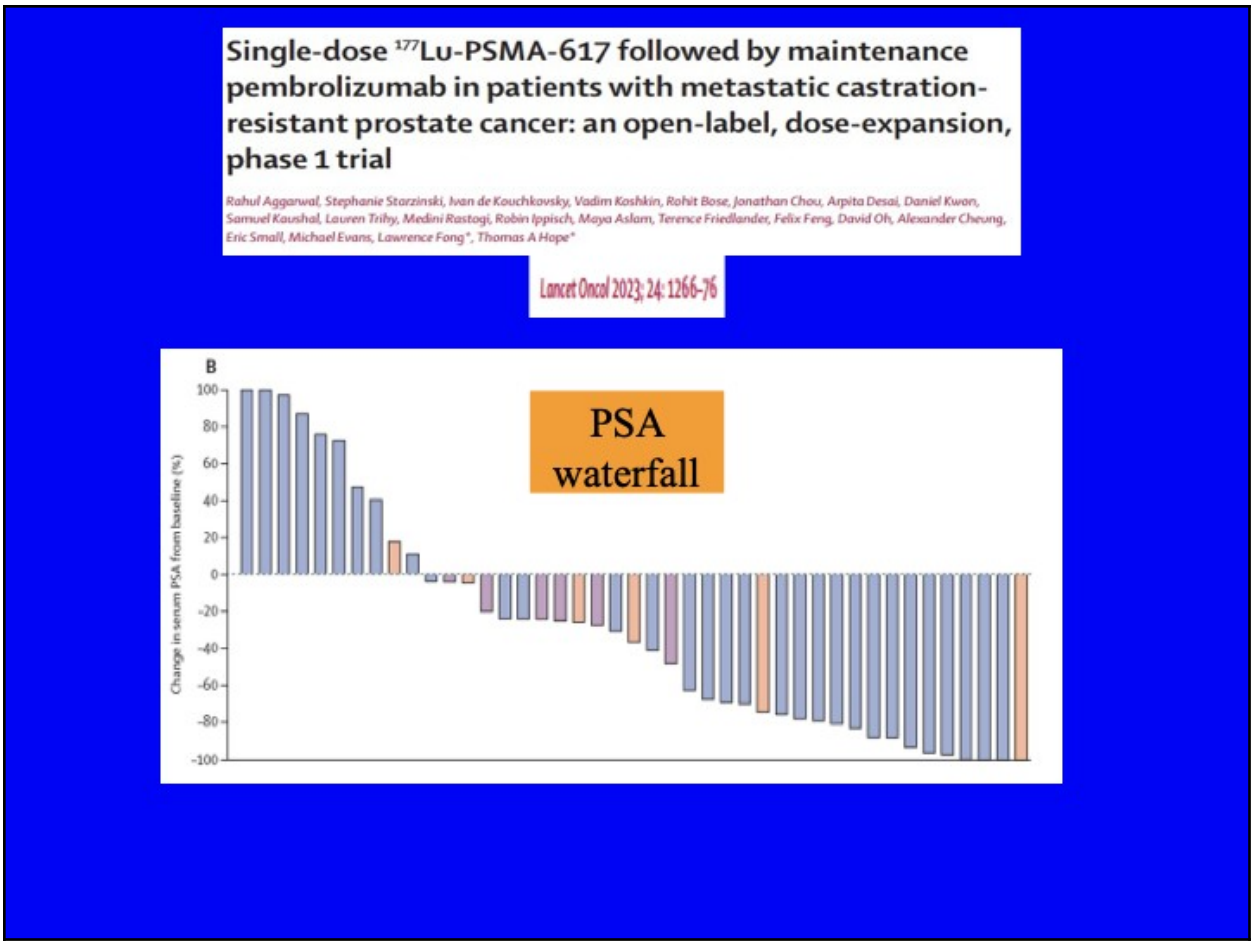
Here is an example called the LuPARP study, where we're combining olaparib, which is a PARP inhibitor, with the PSMA lutetium, and trying to find some synergy. This actually looks pretty good, and we're going to get more data here pretty soon. There's a lot more data emerging from this space.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



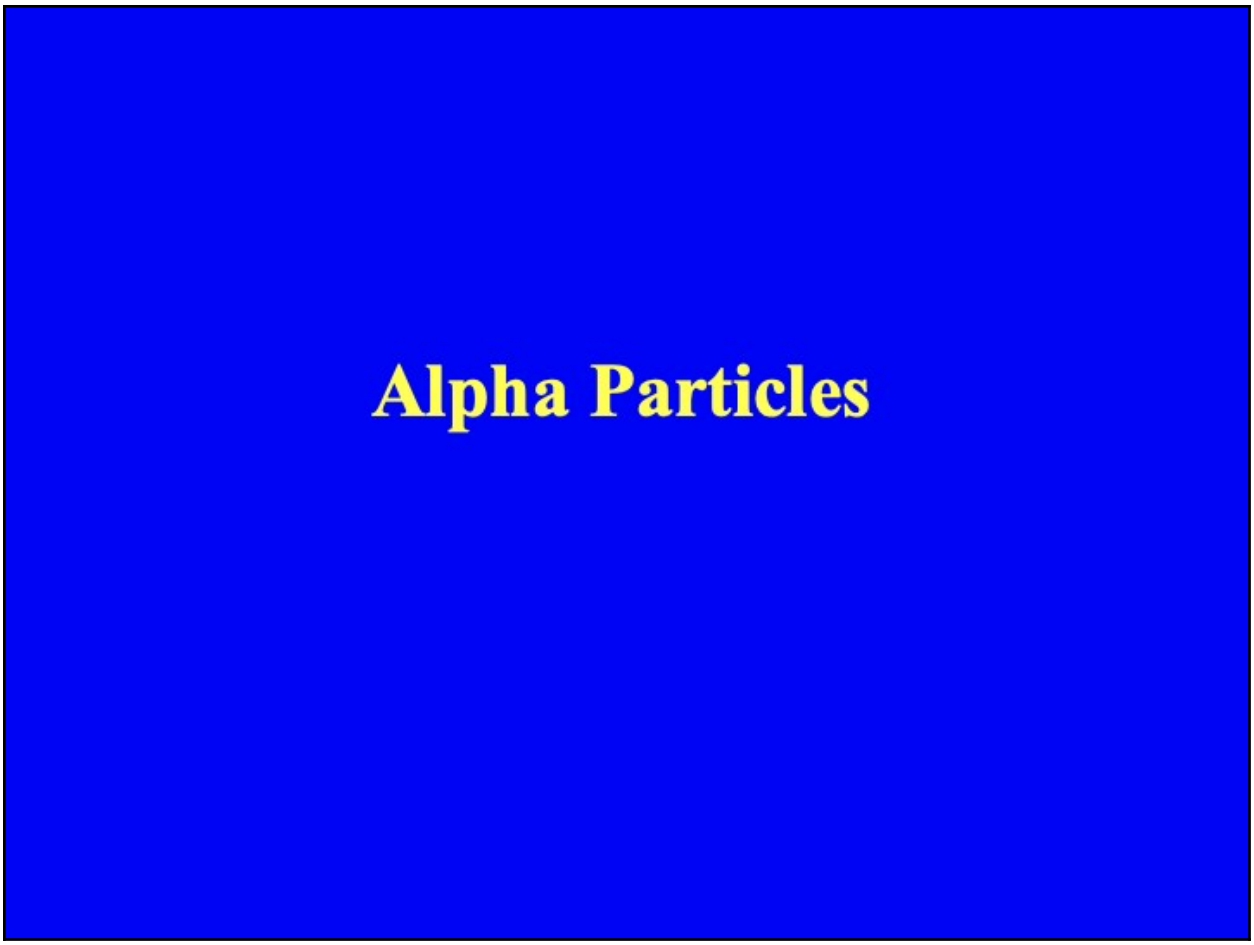
Immunotherapy. Everybody loves immunotherapy. I love immunotherapy too, but it doesn't work in 95% of cases if you're using a PDL-1. If you want an active response with a PD-1 inhibitor, what you have to do is have the right mismatch repair gene alteration with a high “TMB”, tumor mutational burden, or you need to be able to have a deficiency in the proteins the MSH-6, MSH-2, which are two of the proteins involved with mismatch repair. So immunotherapy is great, but it doesn't work for 95% of patients. Don't get it in your head that it's going to work, because we need help.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



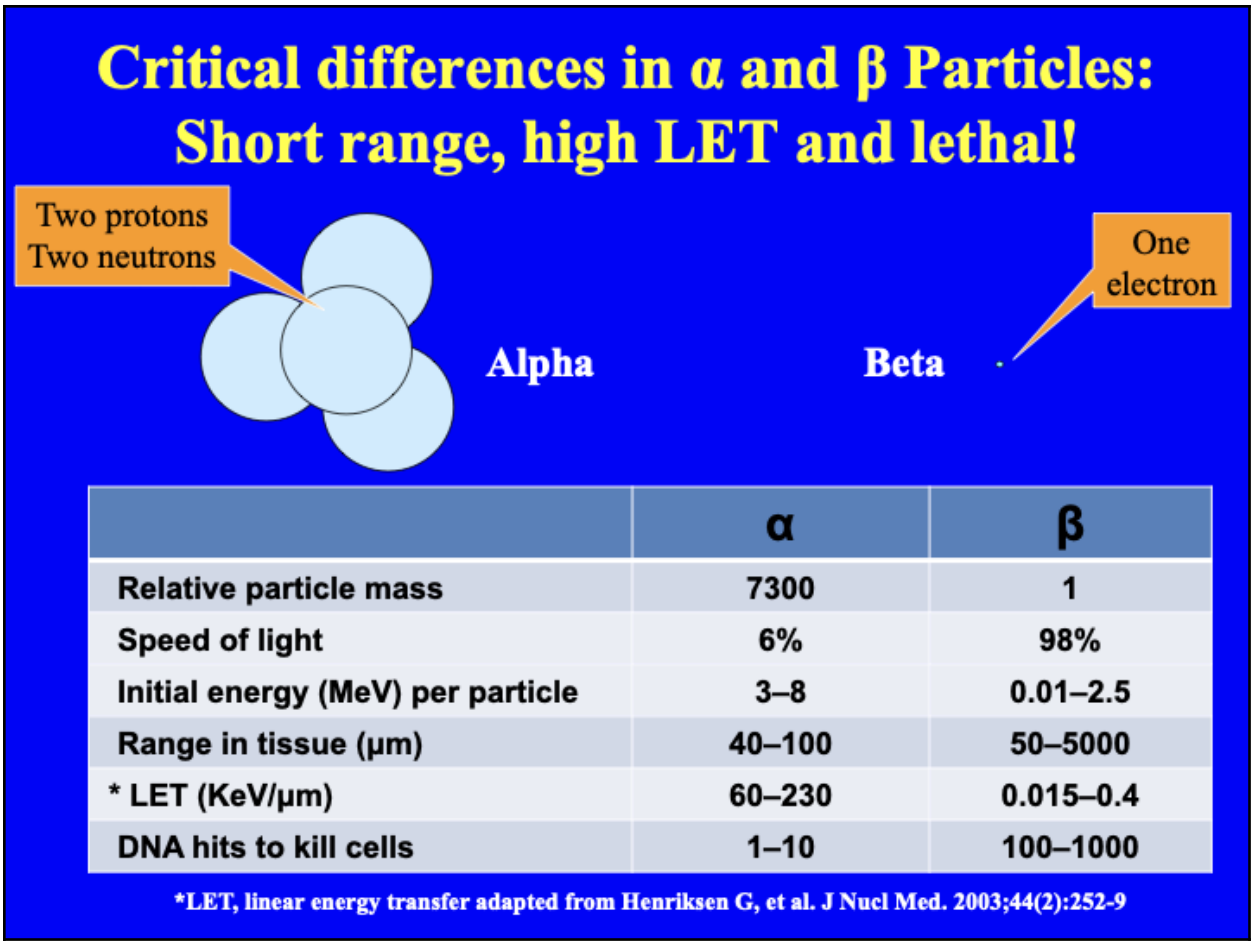
Now, there could be synergy here. This is a PSA waterfall chart. Down is good. Up is bad. This is a single dose of PSMA lutetium Pluvicto in combination with pembrolizumab, which is a PD-1 inhibitor. It's pretty good, but we need more follow up.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



Alpha particles.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



	α	β
Relative particle mass	7300	1
Speed of light	6%	98%
Initial energy (MeV) per particle	3–8	0.01–2.5
Range in tissue (μm)	40–100	50–5000
* LET (KeV/μm)	60–230	0.015–0.4
DNA hits to kill cells	1–10	100–1000

*LET, linear energy transfer adapted from Henriksen G, et al. J Nucl Med. 2003;44(2):252-9

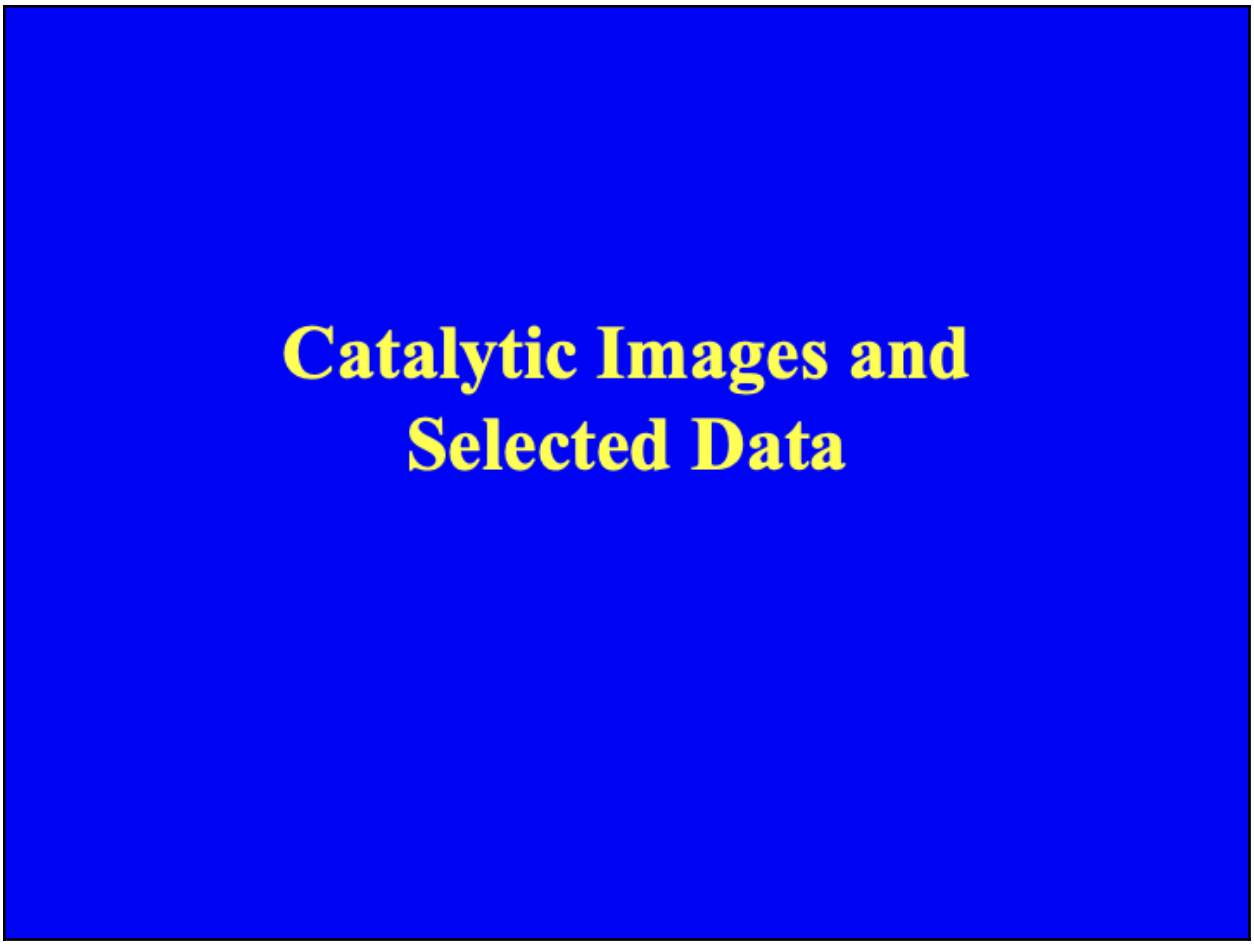
Alpha particles are big as compared to the betas. The beta is a little tiny thing – one electron. Alphas are big, two protons, two neutrons. We have an FDA-approved alpha particle therapy and radium-223. New data with radium, by the way, in combination with enzalutamide. These are big particles that cause a lot of damage, but they don't cause damage in a very distant way. They're very confined to the area of deposition.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]

Radionuclide	Chelate	Half life	Total alpha	“Long lived” Intermediate	Final
Terbium-149	DOTA	4.1 hours	1 alpha		Nd-145
Astatine-211	Various	7.2 hours	1 alpha		Pb-207
Bismuth-212	C-DEPA/ DTPA/DO TA	61 minutes	1 alpha 1 beta		Pb-208
Lead-212	TCMC, DOTAM, and more	10.6 hours	1 alpha 2 beta		Pb-208
Bismuth-213	C-DEPA/ DTPA/DO TA	46 minutes	1 alpha 2 beta		Bi-209
Radium-223	None yet	11.4 days	4 alpha 2 beta		Pb-207
Radium-224	None yet	3.6 days	4 alpha	Lead-212	Pb-208
Actinium-225	DOTA Macropa	10.0 days	4 alpha 2 beta	Bismuth-213	Bi-209
Thorium-227	HOPO	18.7 days	5 alpha	Radium-223	Pb-207

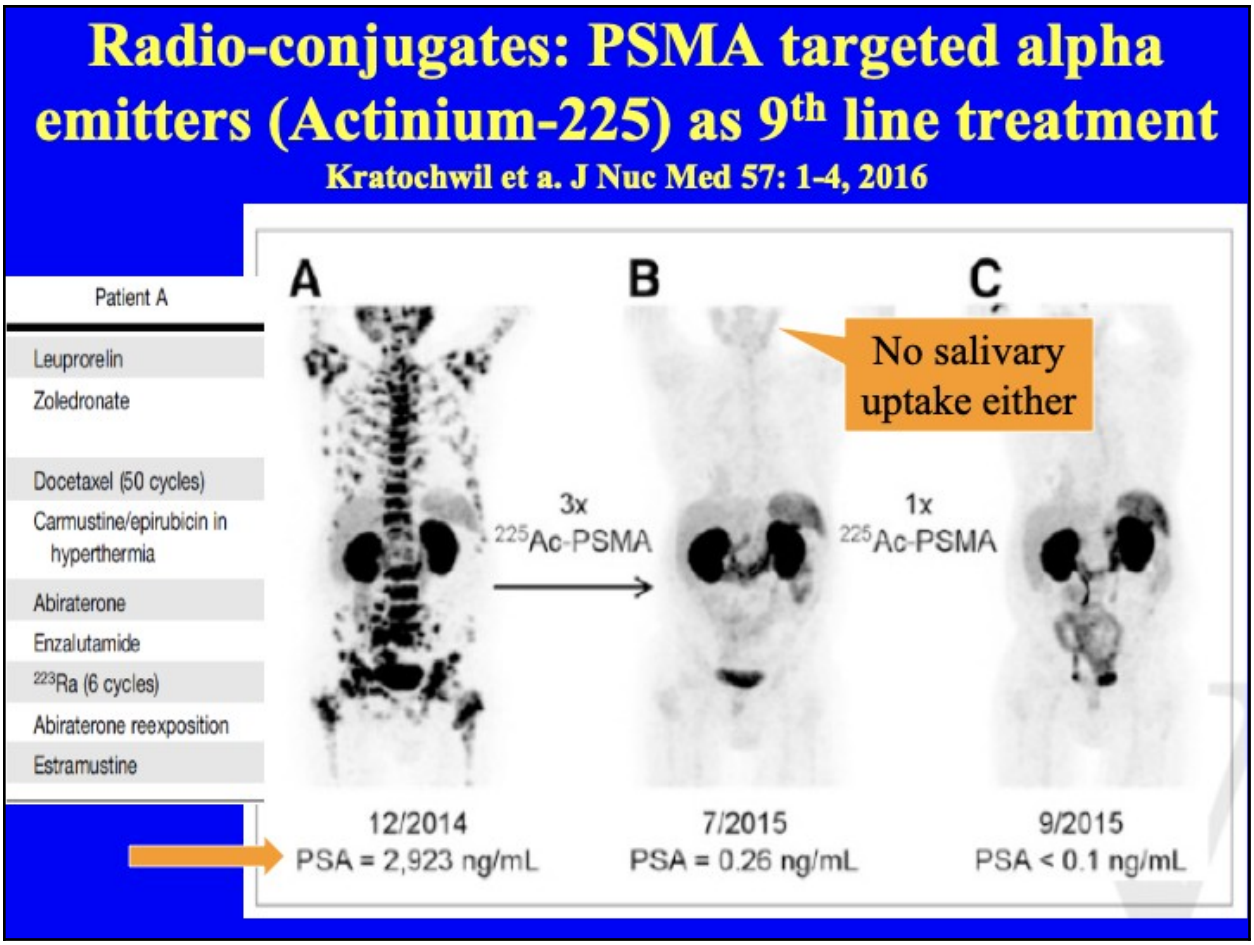
We have three different alphas we're looking at now, in addition to radium-223: Astatine-211, Lead-212, Actinium-225 are some of the new particles that are coming.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



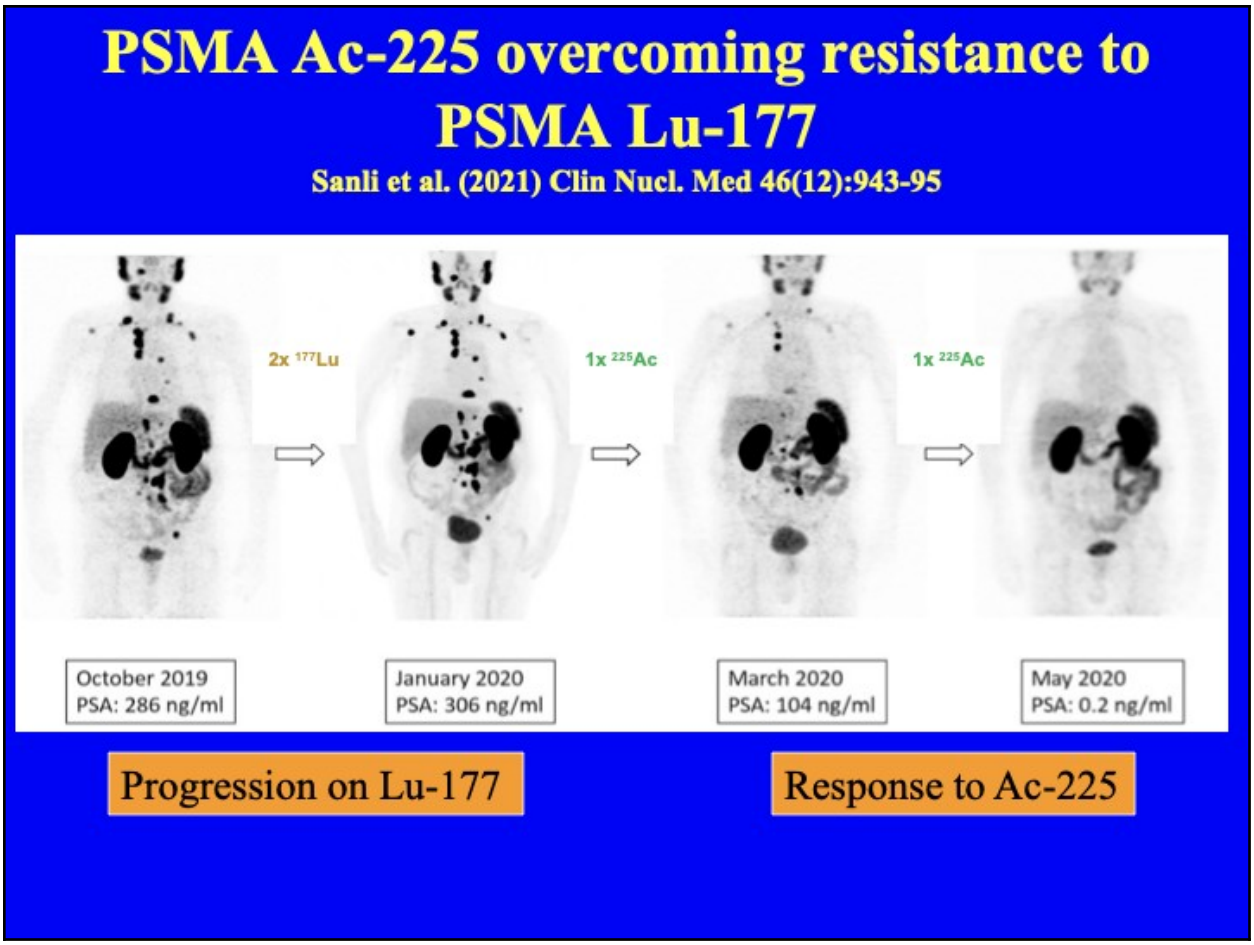
We have some catalytic images here.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



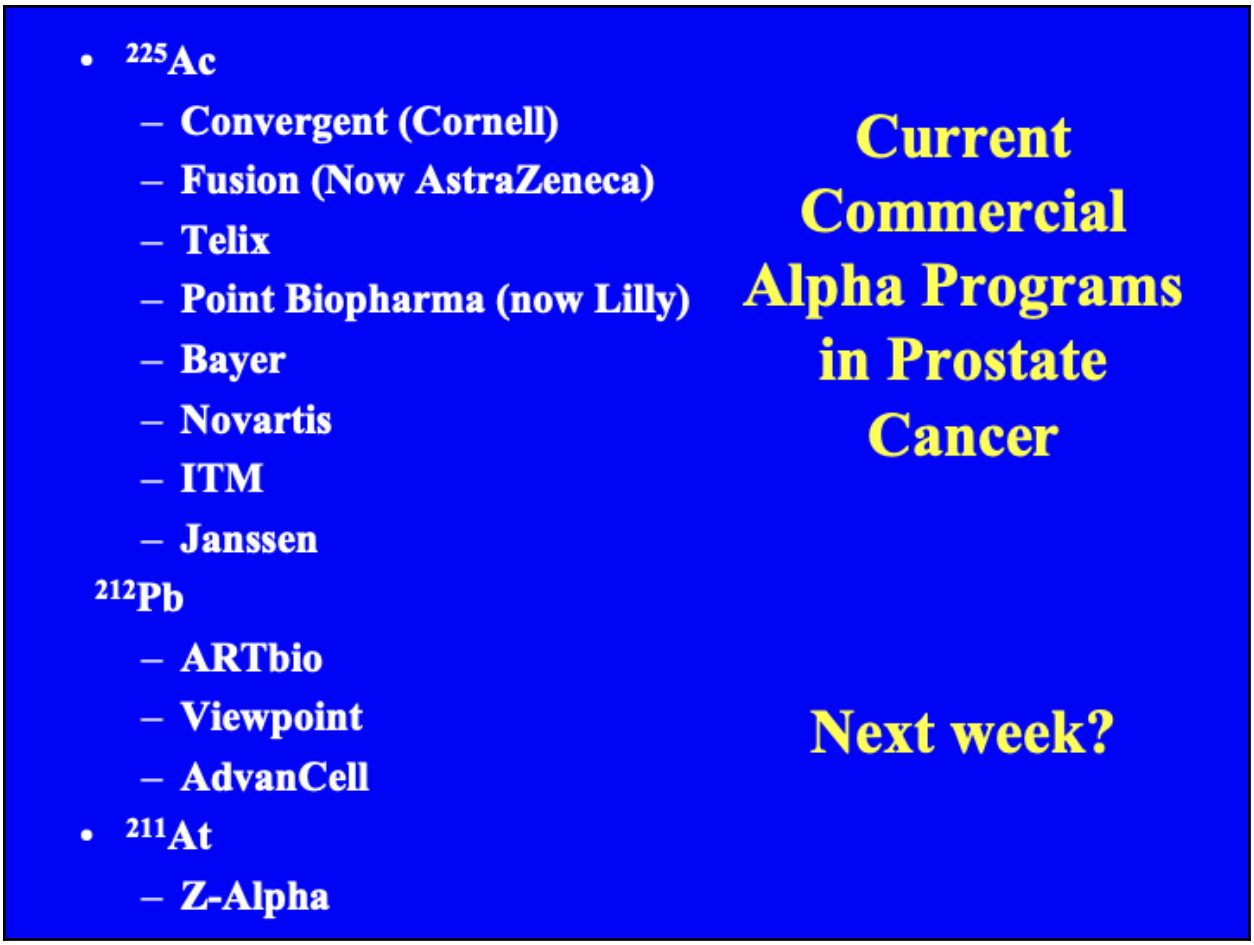
Here's some very powerful data that came out of Heidelberg with the alpha emitters. This is drug and alpha therapy at its best. But please note that the salivary glands have been ablated. This individual doesn't have any salivary glands left because we have blown them apart with the actinium-225. That's one of the things that you have to be careful of here. You go into new areas. You want to kill cancers, but you might kill part of yourself as well. So that's something to be careful about.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



There is some pretty good data about actinium being able to overcome lutetium resistance. There's a lot of work ongoing now in this area, lots and lots and lots of work.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]

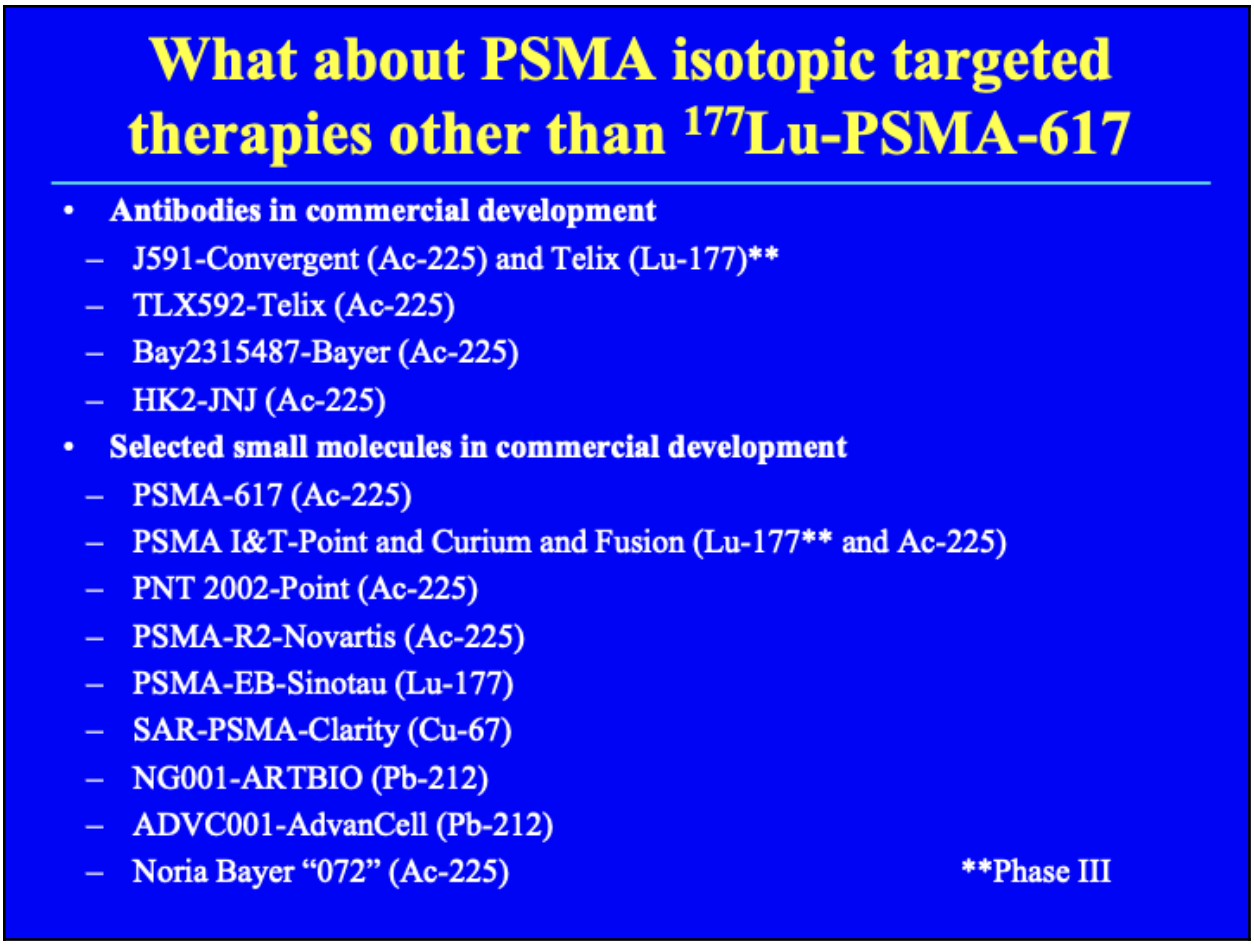


There are a bunch of current Alpha programs available:

- Convergent that came out of Cornell with J591.
- Fusion, which is taking PSMA I&T, a small molecule, was bought by AstraZeneca.
- Telix, I've already mentioned, with their J591. They also have one called 592.
- Point Biopharma has got a compound now developed by Lilly, that compound Is about to get underway.
- Bayer has two PSMA actinium-targeted protocols.
- Novartis is moving forward with 617, and a new protocol called R2.
- ITM has got one.
- Janssen got one called HK2, an interesting molecule.
- ARTBio.
- Viewpoint.
- AdvanCell is moving forward with lead-212.
- Z-Alpha is looking at astatine-211.

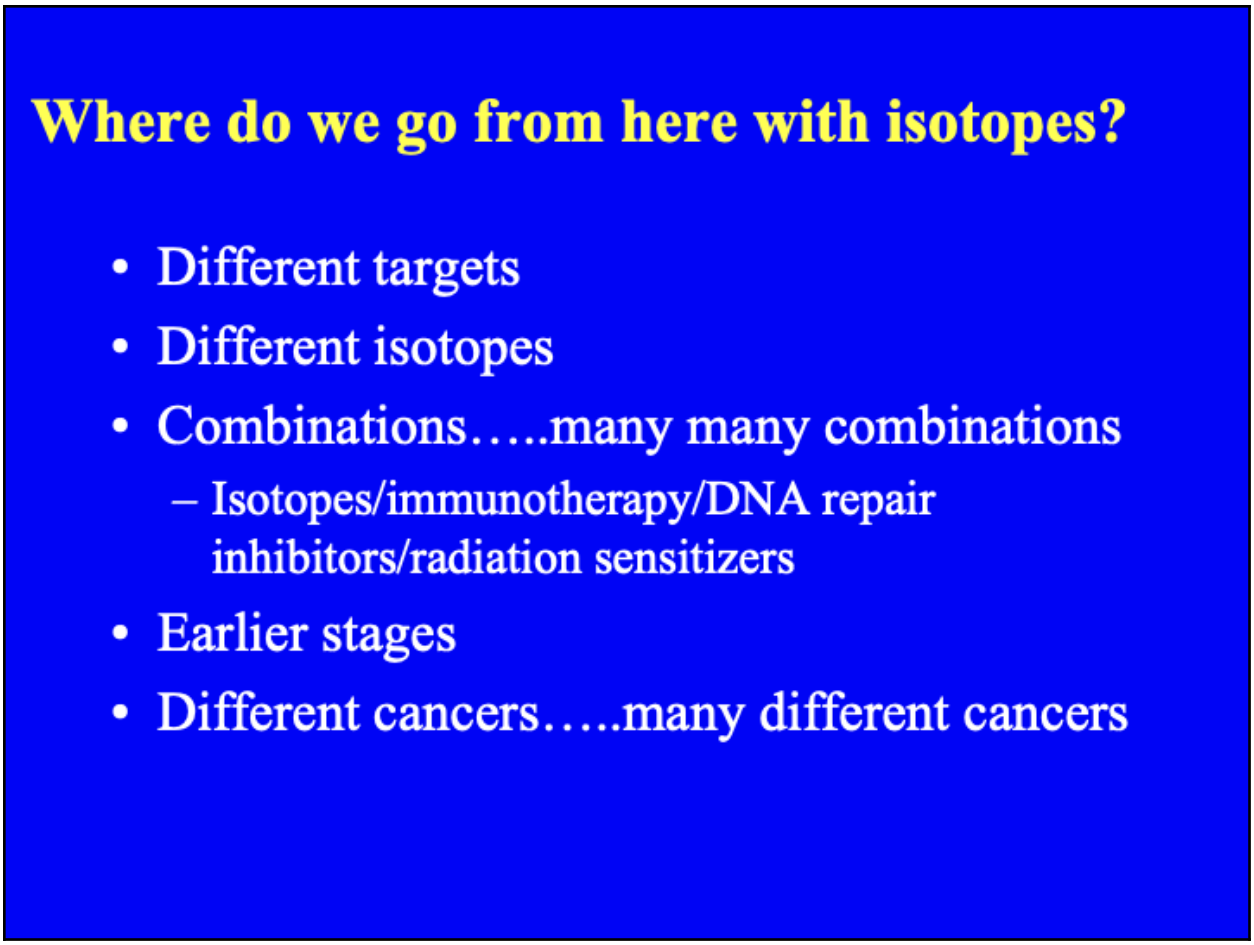
I know this is complicated. It just has to be complicated. I can't simplify it because I don't know how you talk about actinium-225 in a simple way, but it is an alpha emitter.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



This is sort of a quick look at antibodies in commercial development, with selected small molecules in commercial development. As you can see, there are a bunch of them. By the way, it's not just actinium. It's not just lead. I mentioned copper-67. Clarity has got an interesting copper-67 compound. This is moving forward in a whole bunch of different ways. We're going to come up with active therapies here. We just don't know which one is going to win the race.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]

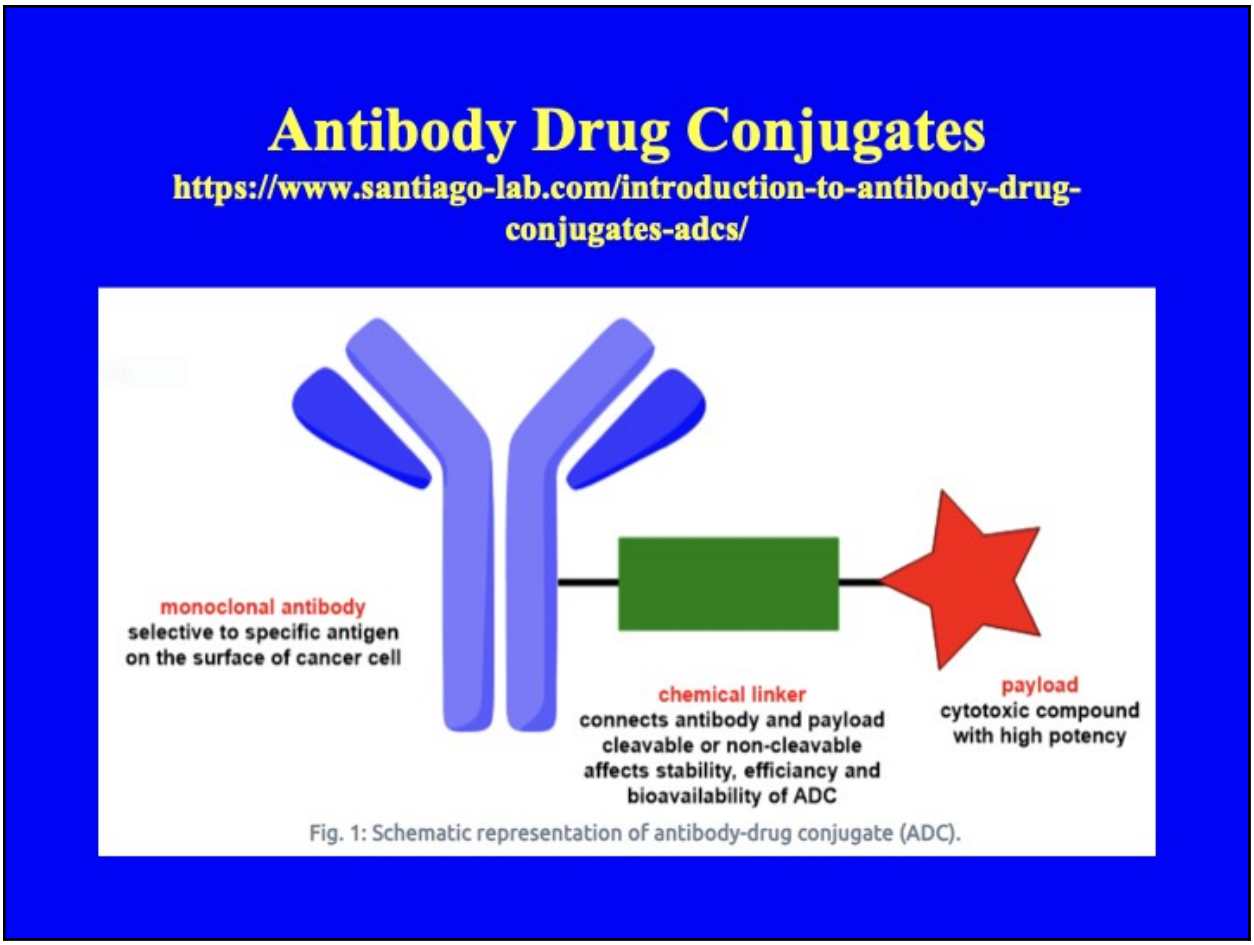


Where do you go from here with isotopes? We're going to go to different targets. We've been talking about PSMA, PSMA, PSMA, but we're going to be talking about different targets, potentially things like STEAP1, STEAP2, HK2, different isotopes. I've already covered that.

Many, many, many different combinations: combinations of isotopes, alpha betas, combinations with immunotherapy, combination of DNA repair inhibitors, radiation sensitizers, earlier stages, different cancers.

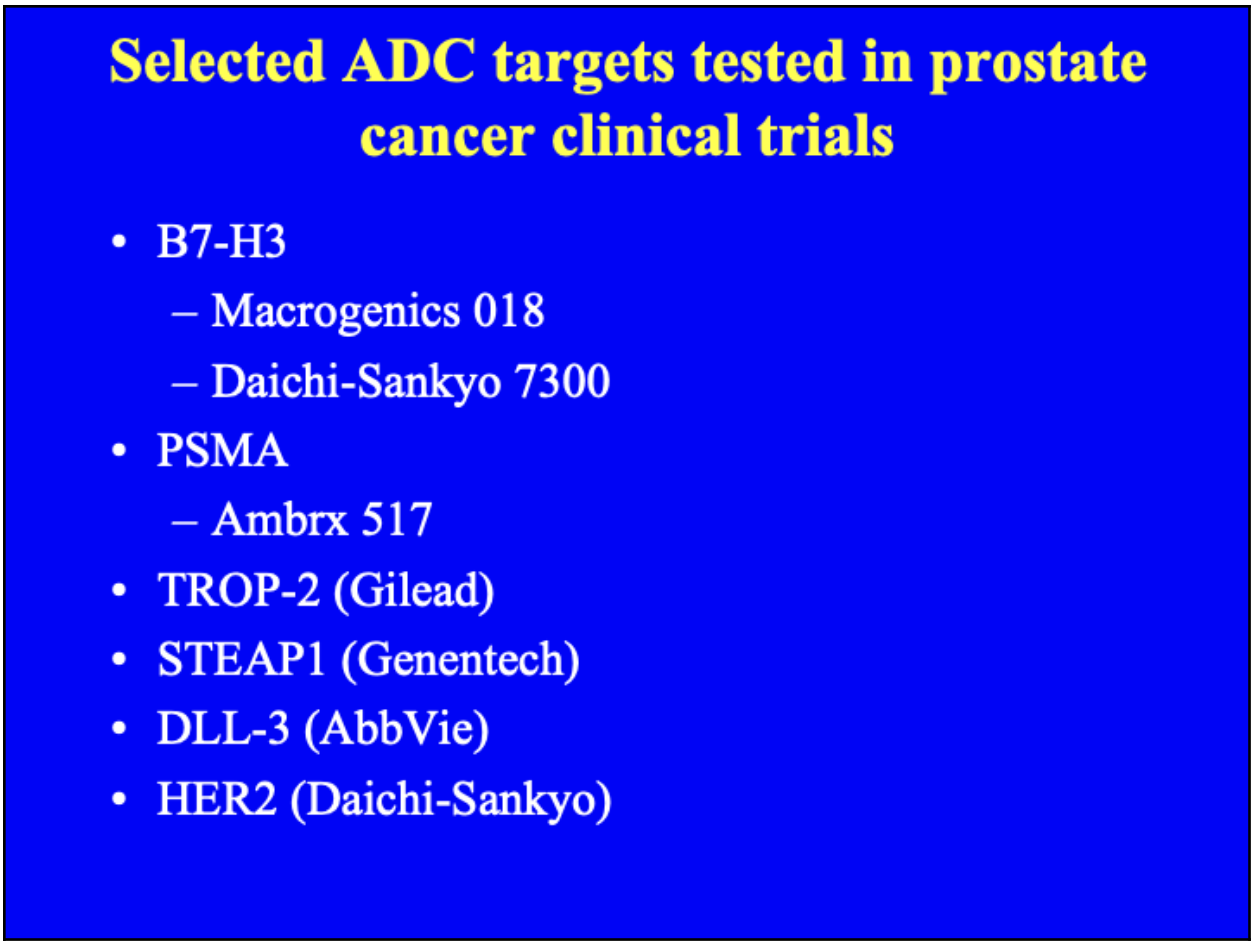
This thing has gone absolutely wild.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



Antibody drug conjugates. Here, we're taking an antibody, and we're putting a payload on it, we're putting in a linker on it, and now we're going to target that monoclonal to something it can bind to and bring a toxin onto the cell.

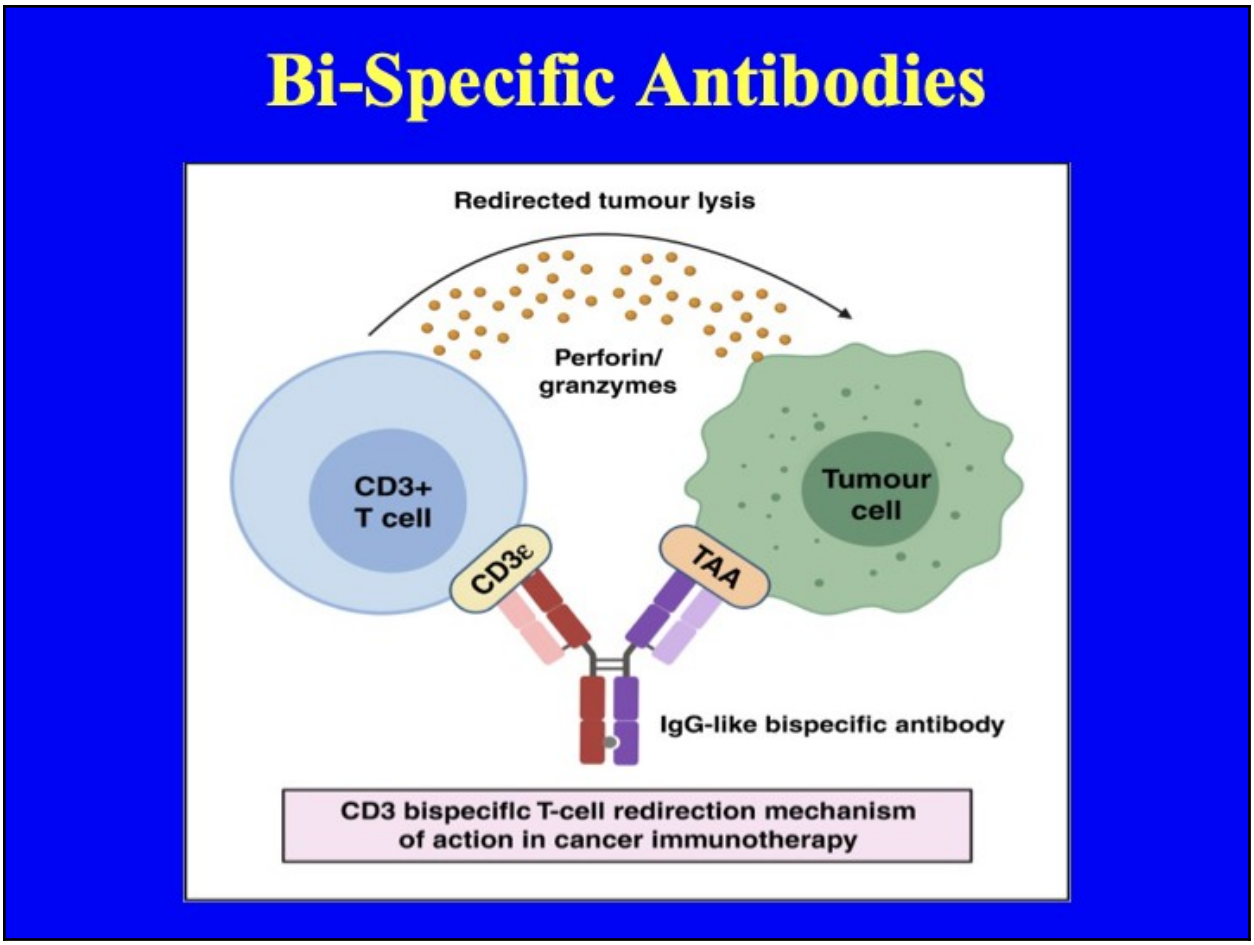
“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



These are some of the ones that are ongoing. One is a cell surface target called B7-H3, PSMA again, TROP-2, STEAP1, DLL-3, HER2. These are different cell surface molecules. Bottom line is Ambrx 517 is very interesting. The Daiichi-Sankyo molecule is interesting. B7-H3, these are going into clinical trials. We need more data.

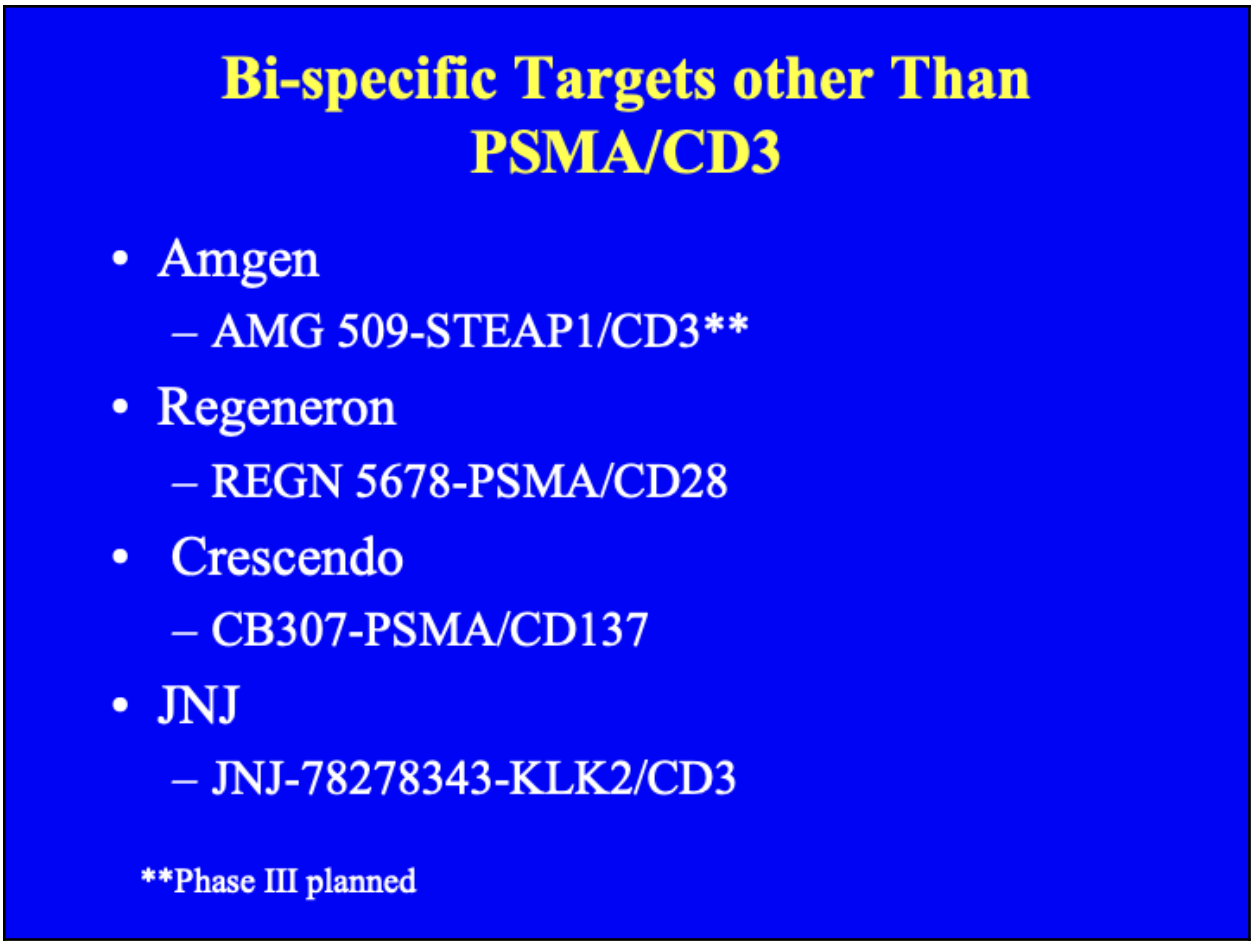
ADCs, antibody drug conjugates, take an antibody, take a drug, conjugate them together, deliver the chemotherapy to the target. We'll see what happens.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



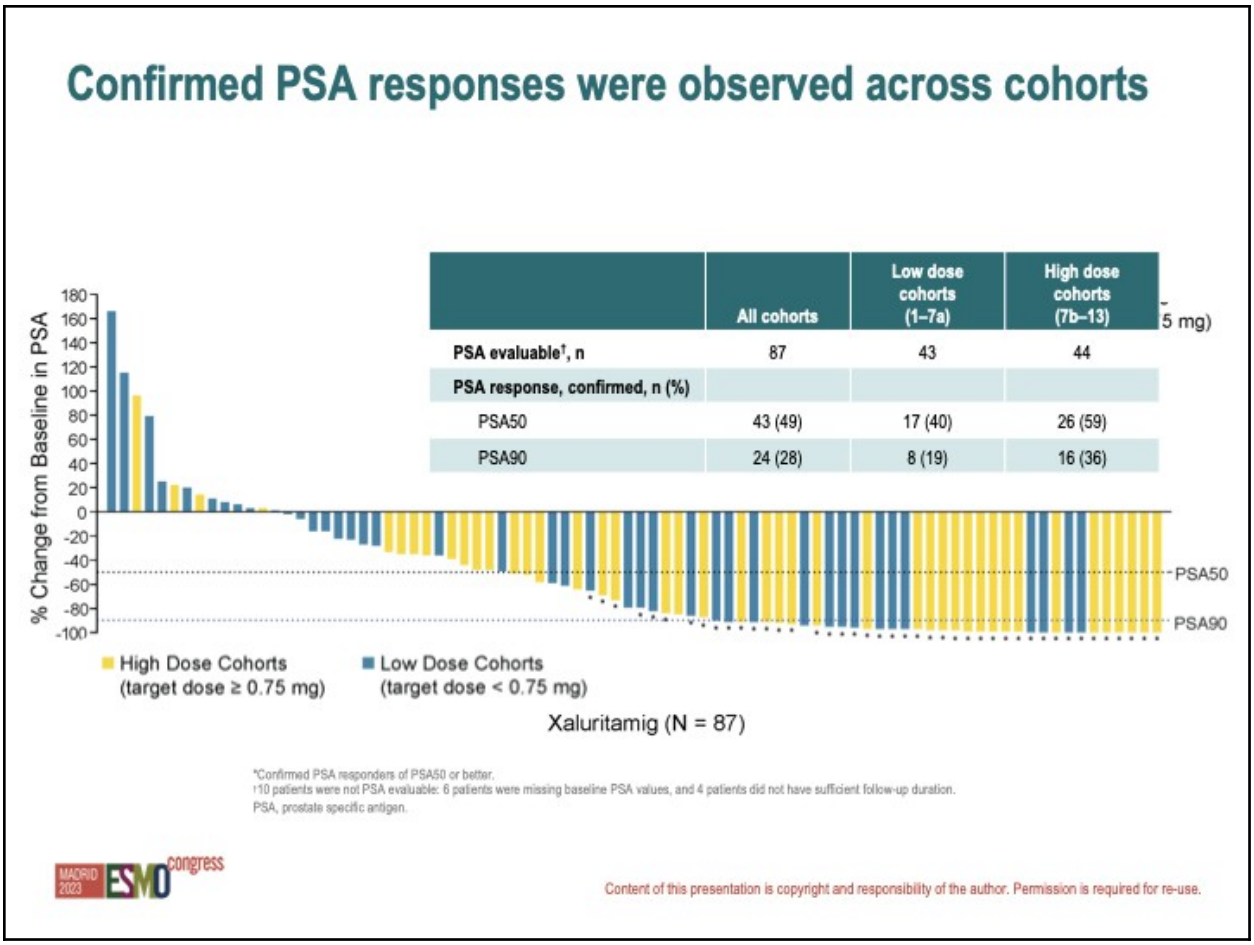
Bispecific antibodies. These are interesting concepts, and we have a couple that are FDA approved. You bind to the tumor target – “TAA” is the tumor-associated antigen. You bind to the immune cell, in this case, a CD3+ T cell, and you redirect tumor lysis onto the tumor cell from the immune system. It's very interesting. This is not a typical immune therapy. This is a targeted immunotherapy to a cell surface binding molecule.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



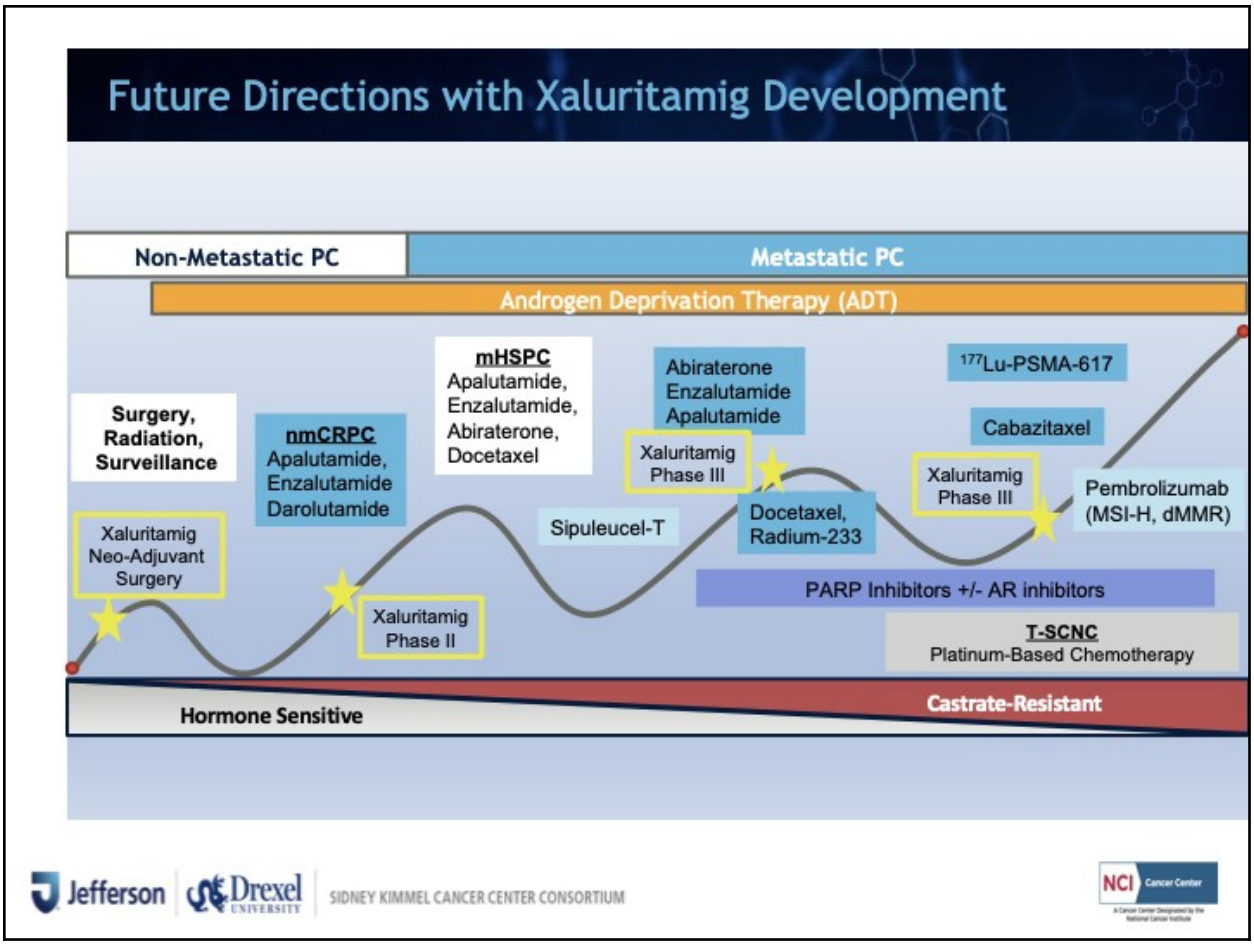
The one that's taken the lead here is AMG 509, (xaluritamig). STEAP1, CD3, going into Phase 3, and there are a bunch of others here. This KLK2 to CD3 molecule is a very good one.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



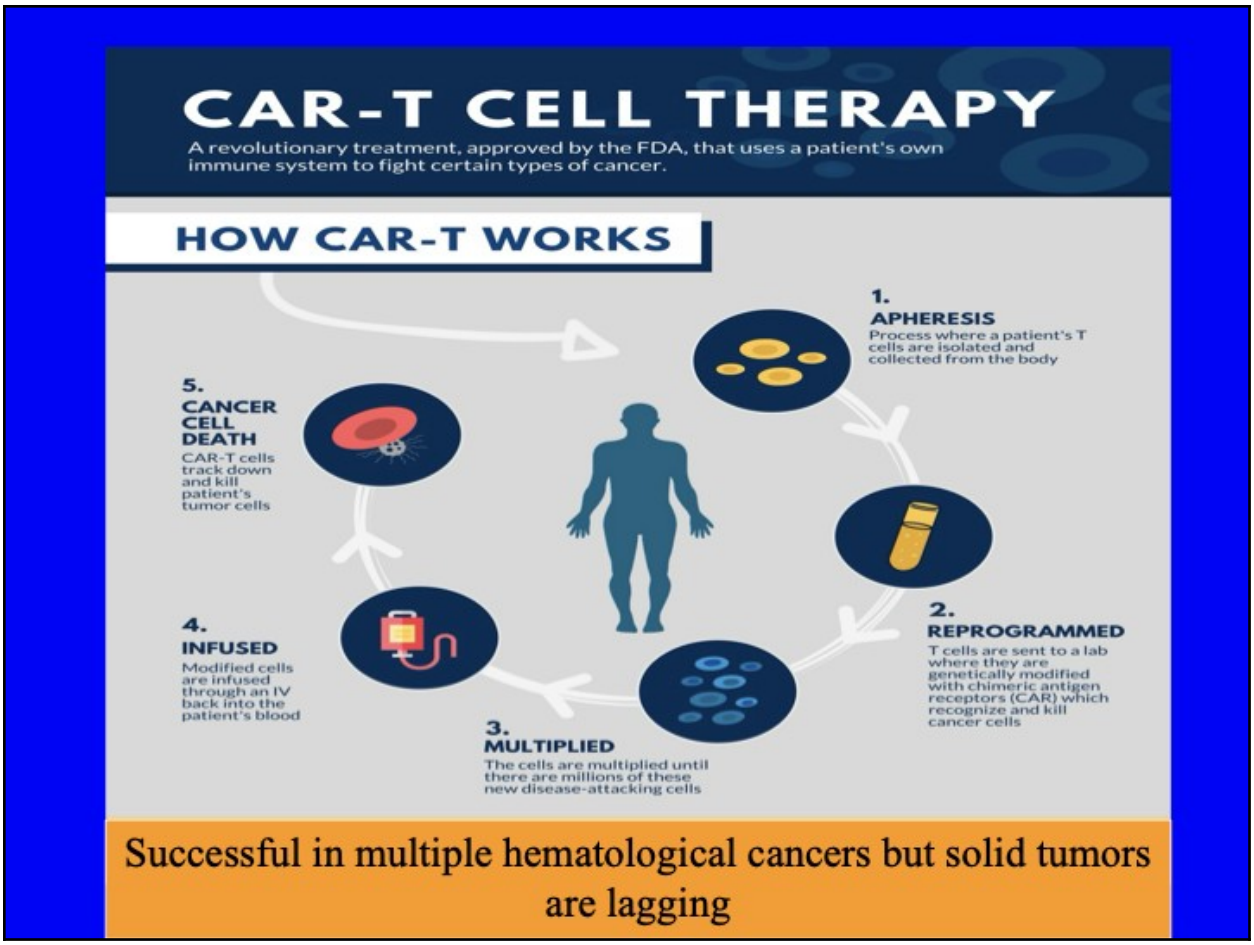
Here are the waterfall plots with the STEAP1 Xaluritamig. This was presented at ESMO. You've got a lot of downs and not many ups. This is going into phase 3.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



There are two phase 3s, one of them in the post-chemotherapy space, another in the pre-chemotherapy space. Everybody must have failed ADT and AR inhibitors. They're also going to be looking at some earlier studies here. But the bottom line is, this is an active molecule, but there's some significant toxicity associated with it, and you have to be really careful, because there's some muscle aches and pains, and they're still working that out. I haven't gone into the side effects with all these things, but everything we talk about has side effects.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



CAR-T cells. You basically take a T cell, put on a target that'll be binding into the cancer cell. This has been beautiful, beautiful, beautiful for the hematologic malignancies, things like multiple myeloma.

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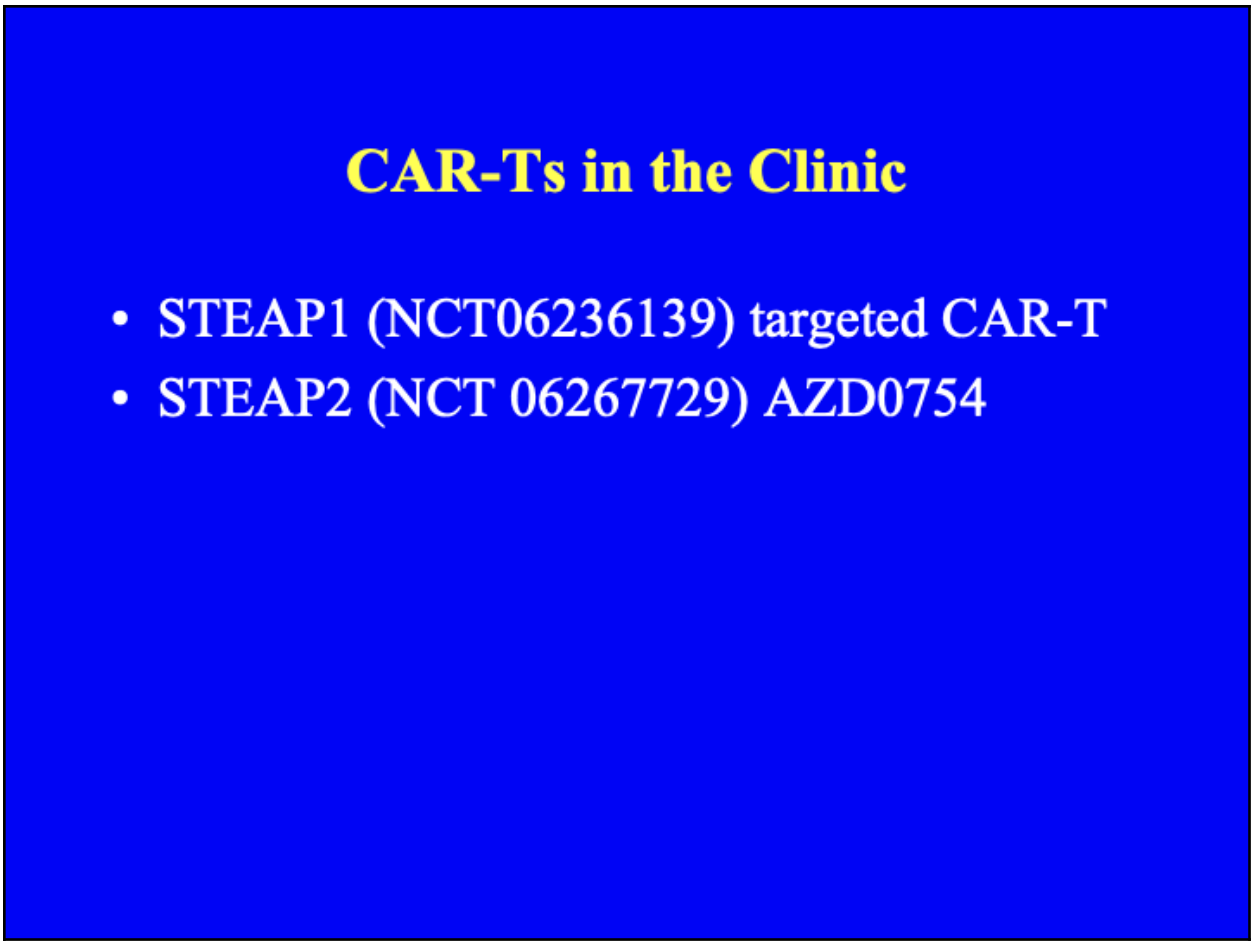
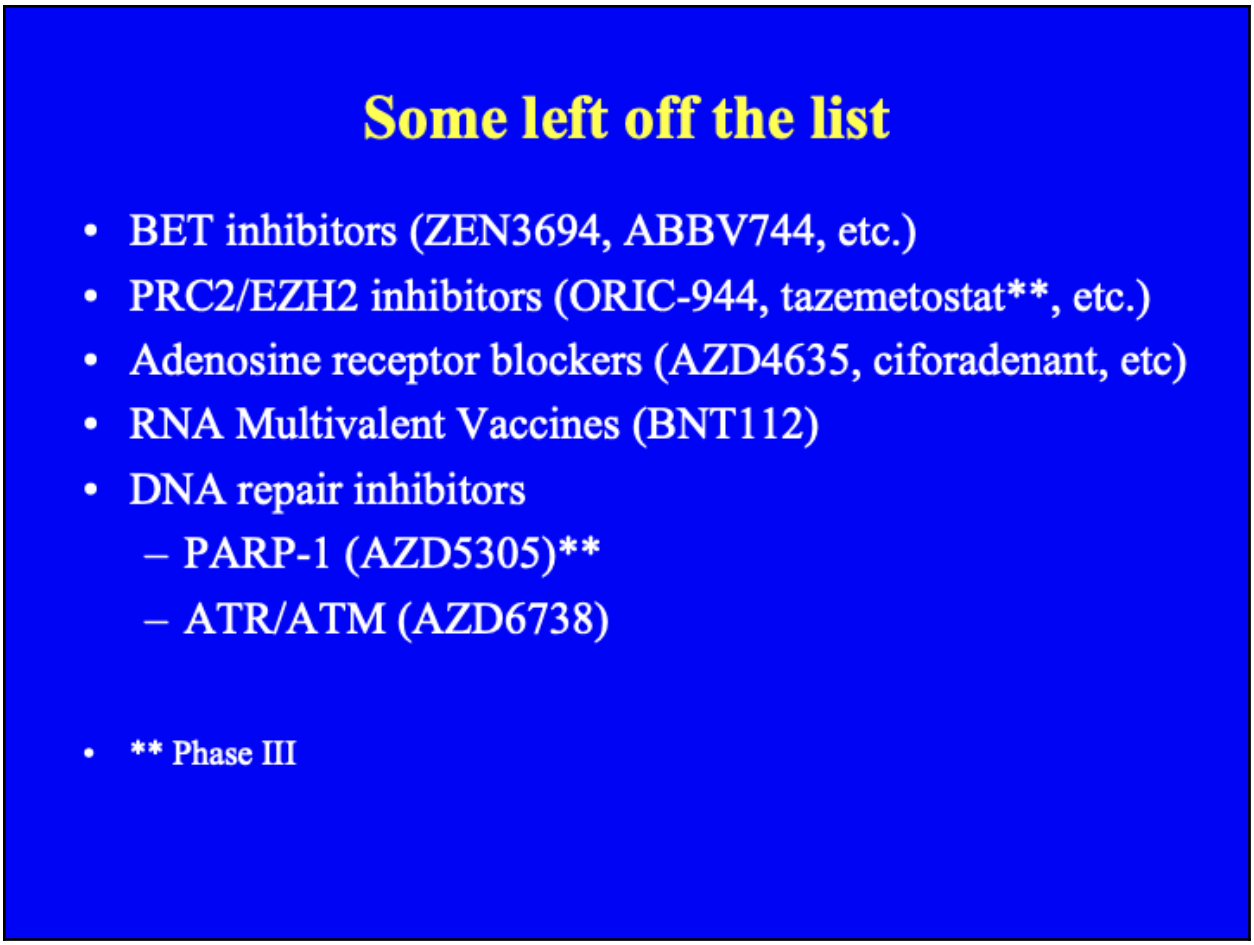


Up

But now we're starting to get into prostate, and we have a STEAP1- and STEAP2-targeted and PSMA-targeted out there. PSMA has been a little bit disappointing so far with significant toxicity, but STEAP1 and STEAP2 are cell surface targets, and we're going to be targeting these with these particular clinical trials.

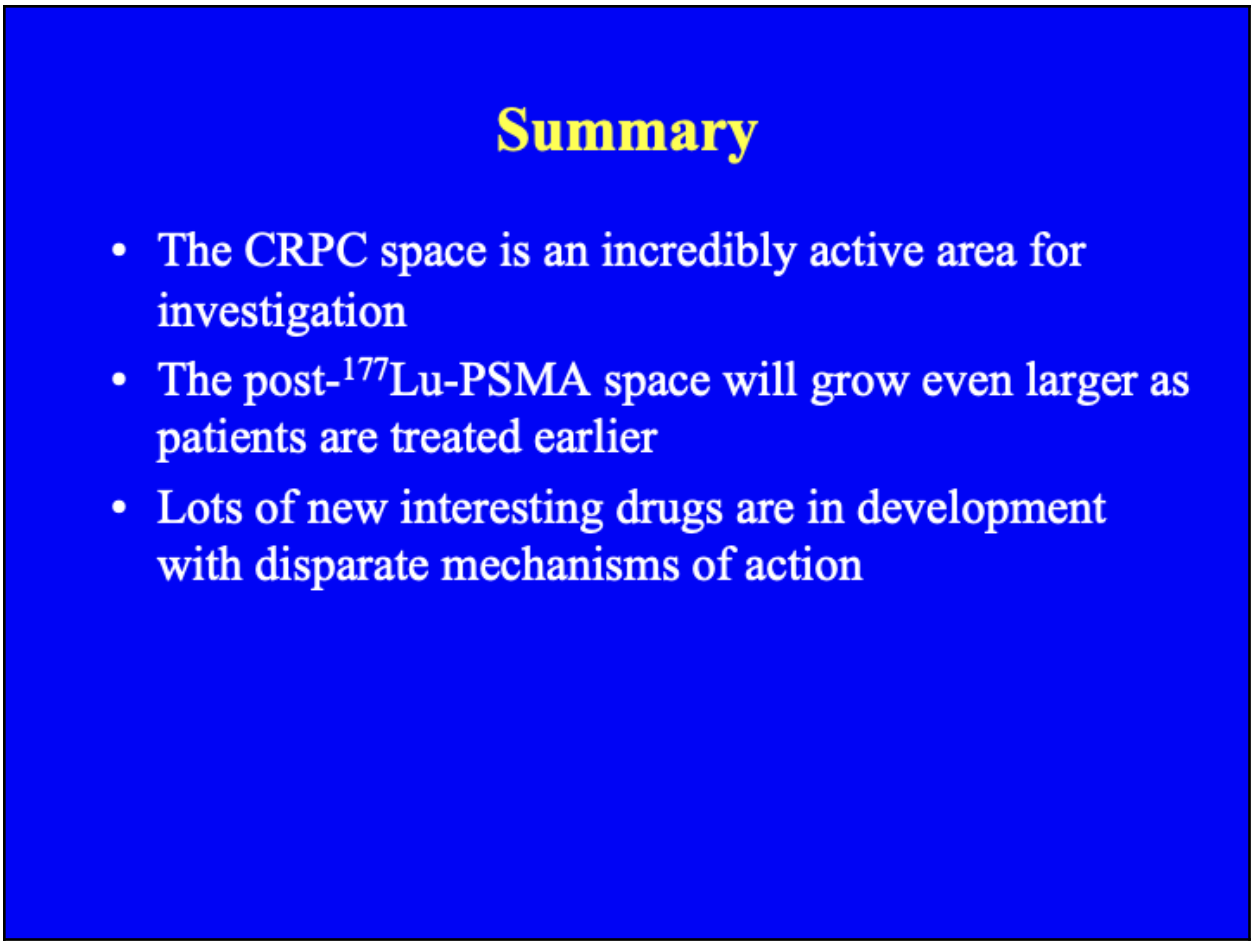
“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



I left a bunch of things off the list: BET inhibitors, EZH2 inhibitors, adenosine receptor blockers, multivalent vaccines. I haven't gone into the PARPs because they've been out for a while, but there are new PARP inhibitors, ATR/ATM inhibitors, DNA repair inhibitors, and these things are moving forward. Tazemetostat is an EZH2 inhibitor that's going into Phase 3 at Pfizer. That EZH2 inhibitor drives things back.

Sorry I can't speak English here, but there's just no other way we have to describe the biology. We can't speak in terms other than the non-English terms.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]



CRPC is incredibly active. The post-lutetium space is big. There are lots of new, interesting things in development.

I've achieved my goal with the terrible interruption to finish early and give people a chance to ask questions. I want to be able to be able to answer questions, because that's probably more helpful than anything else.

Anyway, that's the landscape and new drugs in development.

Vic Paglisotti 34:37
My question is for widespread, metastatic, bone-only disease, and you mentioned there's something new coming out with radium-223 and Enzalutamide.

Why go to Pluvicto first? Or maybe that's not the better thing to do.

Oliver Sartor 34:56
Radium was FDA-approved in 2013, and radium is an active agent. But here's a problem with radium: that trial, which I'm a senior author on, was published in an era where we didn't have the ARPIs (androgen receptor pathway inhibitors), and it's a little bit conjectural to say how well

it's going to work in the post-enzalutamide, post-apalutamide, post-daralutamide, post-Abiraterone space. The new data was in the post-ADT space, so no prior ARPI, combining enzalutamide with radium, and it showed really nice results, as presented at ESMO, not published in the literature yet, but I really liked it. Enzalutamide radium was good.

However – critically important – you have to use your bone health agents, things like zoledronic acid or denosumab with it. If you did not use zoledronic acid or denosumab in combination with enzalutamide and radium, the fracture rate was 50%. So if you are castrate resistant, and you have multiple bone mets, you need to be on bone health protection: zoledronic acid, denosumab, are the two ones that are out there. I think radium could be a good one. We don't have comparative studies with the Pluvicto PSMA lutetium, but I think radium could be reasonable in that setting. And you can give the Pluvicto post-radium. That's the RALU study, which we recently published as well.

Vic Paglisotti 36:24
I'm on my fifth dose of Pluvicto.
So what about this radio enzalutamide post-Pluvicto?

Oliver Sartor 36:30
That's interesting. First of all, I want to know how you're doing. You might not want to go into it individually. If you're feeling good, you are probably responding. I'll simply say, play it out with Pluvicto. Make sure you're on bone health agents, and then afterwards, make an assessment, decide which direction to go. But radium can be reasonable for bone-only mets, as long as you take the bone health agent.

Vic Paglisotti 36:57
I have the bone density of a teenager.

Oliver Sartor 37:03
No. Bone density doesn’t matter. Bone density is not the critical element. It's the bone metastatic disease that's the critical element because it weakens the bone. Bone density is very relevant for the ADT-associated fractures. When you have a bunch of mets, you have to think about, “I have mets”. No matter how strong your normal bone is, you have to worry about how weak the bone is in the area of the metastatic disease.

Nathanael Jackson 37:59
Thank you for spending time and doing this. I appreciate all you guys trying to save my life. On the last screen it said that the TCM, the tumors get larger. On my first six rounds, everything went away. From my head down to my femur, I had tumors, and then it went away. I was good for about nine months, and then they started creeping back. What do you mean by the tumors get larger after the first round?

Oliver Sartor 38:48

You may have misinterpreted what I said. First of all, I'm glad that they've gone away. And you might be a guy – and this is a very interesting topic about whether or not you ought to be getting retreatment or not. I didn't say the tumors got larger. What I said is the space is going to grow. By that, I mean the number of patients eligible for post-Pluvicto treatment. You're a post-Pluvicto guy right now.

Do you know how many clinical trials we have good data on for you? The answer is about zero. We think that a patient with a good response could be retreated with lutetium, if you can do it. The FDA has only approved six doses. You have a problem there. But work with your docs and figure out how to treat this thing. But it sounds like you had a great response with lutetium.

Nathanael Jackson 39:39
I did. I started dancing again. I will talk to him. I am on bone protection, Zometa, and calcium. I'm doing well, thank the Lord.

I found this on the internet. A dude told me to go to the internet. I found you, and I wanted to learn.

You said something that just got me. You said I was able to take it a second time. Now I know this isn't medical advice. What are your thoughts about that?

Oliver Sartor 40:24
First of all, we have to evaluate the patient. We have to make sure the blood counts are good, kidney function is good. I have administered repeated doses in patients who've been good responders and then recur. But you have to check the PSMA PET scan too to make sure you are PSMA avid, and you have to make sure you have a lot of PSMA expression in your tumor.

What's the safety profile on that? And the answer is, we don't really have great long-term data. It could be a problem. However, you need to take a risk, and other people like you need to take a risk, because the problem is we don't really know what to do with you. Anybody who acts like they know all the answers is false. They don't. We don't know all the answers here. You're going to be in an unknown space, and your doc is going to have to take some risk with you and figure it all out. That's not medical advice. I'm just saying I see patients all the time who run out of options, and then you have to do something else.

Nathanael Jackson 41:32
My doc is thinking we're going to do maybe three or four because she doesn't want to weaken my bone marrow and everything else. It's like you said, they don't know. I'm like at the tip of the sword. I don't know, but that's what I was in Vietnam. At the tip of the sword.

Oliver Sartor 41:58
You’re at the tip of the sword. You're going to have to make a calibrated risk assessment, discuss it with your doctor, then decide what's best for you.

Are you at the VA in Nashville?

Nathanael Jackson 42:09
Yes, I am.

Oliver Sartor 42:10
I might know your doctor. I won't bring up any names, but there are some very good doctors there.

Nathanael Jackson 42:15
Awesome. I'm going to tell them about you. As soon as I get out, I'm going to start typing them: “Guess who I spent the morning with?”

Arthur Bruno 42:37
What can you tell us about neuroendocrine prostate cancer and what is coming up behind the scenes on that?

Oliver Sartor 42:51
I've been thinking about that a lot. Along with a lot of folks in the field, we were struggling with neuroendocrine. Here's what we know: that neuroendocrine is probably going to come out to some degree in about a third of patients. These are typically patients that have a low PSA, and they're more prone to visceral metastases (soft tissue lesions that occur in the organs of the chest or abdomen, such as the liver, lungs, adrenal glands, brain, and dura; less common than bone metastases, but can have serious clinical implications.). The standard therapy for that is going to be a platinum-based therapy, cisplatin, carboplatin-type thing, maybe with etoposide. Etoposide VP16 platinum is a pretty standard regimen.

The problem is that there are all kinds of gradations. There's the pure neuroendocrine, like a small cell, and then there's the partial neuroendocrine, and we're going to call that an “anthocrine.” That is a fancy new term, and that's a mixture of the AR and the neuroendocrine. We are targeting that with platinum for a second chemotherapy. But there are new things that we're thinking about, things like DLL3-targeted therapy. DLL3 is a cell surface target, specifically in the neuroendocrine, and that's one of the things we're going to be looking at there.

There is a lot of work going on with neuroendocrine right now. We're trying to get better at it. First of all, you have to recognize it, then you have to treat it. It gets to be a little bit complex because often it's mixed up with other tumors. It's not a pure neuroendocrine; it may be a partial neuroendocrine.

We're working on it. Platinum and DLL3 are the top two right now.

Brad Power 44:38

Doc was getting at this a little bit. You laid out a big menu, like more targets, more payloads, and so the menu of possibilities for a patient who is reaching a certain stage, like they're starting to fail whatever they're on now, becomes pretty extensive.

How do you have principles to help navigate amongst those many menu of options?

Oliver Sartor 45:08
One of the lectures I gave is talking about treatment choices and how you make them. The first thing you have to be aware of is what's available and what's not. I've listed a lot of clinical trials. I wanted to expand the brain here of the possibilities. That was intentional on my part.

Your question is more focused: how the hell does a patient figure out what to do?

First of all, you really do have to find a good doctor that can work with you. I realize, of course, that different people have different levels of access, but getting access to somebody who really specializes in prostate cancer. It doesn't necessarily have to be in a major center, but somebody who really focuses on prostate cancer is the best way to go. Then they can help you navigate.

It depends so much on the landscape. What have you failed? How did you respond to the prior therapy? Like we had Doc talk about how he had been on Pluvicto, had a great response, and now he's relapsing. That's a very specific scenario that demands a very specific set of options. Then we just had a brief discussion about neuroendocrine. If you've got neuroendocrine, you have a separate set of options. It's hard as hell to figure it all out. Find a good doctor, stick with them. Don't be afraid of a second opinion, and don't be afraid of a clinical trial if you don't have good options that are available as part of standard of care.

Those are good principles, but they're tough ones.

Paul Van Camp 46:49
On the neuroendocrine: you have patients with very low PSA, maybe undetectable, but they're not cancer free.

What is the best way to possibly identify the emergence of neuroendocrine?
Is there a scan that's available that would be better than the others at this time, or circulating tumor DNA, or something like that?

Oliver Sartor 47:17
Let's think about this in a couple of different parameters.

First of all, not everybody is pure neuroendocrine. I continue to monitor the PSA because some people have a mixture of different cells. But what are the ways you can do it? I mentioned the circulating tumor DNA. The circulating tumor DNA can find things even when the PSA cannot. Another important thing to measure could be LDH, lactic dehydrogenase, a traditional thing to measure, easy, and LDH often goes up in neuroendocrine even though the PSA may not. Two

specific neuroendocrine markers, one called “chromogranin A”, another called “neuron-specific enolase”, and you can check on those. Neuron-specific enolase and chromogranin A are circulating markers. Occasionally, CEA can be elevated as well. So occasionally we look at CEA. So CEA, LDH, PSA, chromogranin A, neuron-specific enolase are five.

Scans are another way of doing it. The typical neuroendocrine is negative on a PSMA PET. But again, please remember that a lot of times you have mixtures of tumors present, and some of these patients that are classified as neuroendocrine may, in fact, end up with PSMA PET positivity. The best scan to do today is an FDG PET. The FDG PET can pick up the neuroendocrines that are PSMA PET-negative. That's another way to look at it.

In the future, we may have a DLL3 scan, but we don't have that right now.

Taken together, you've raised a very, very important point. Not everybody has PSA as a good marker. Don't forget your conventional imaging, CAT scans, and bone scans. If you see something that's funny, you may need to do a biopsy. Getting a biopsy of a metastatic lesion, particularly for a PSMA low patient, can be very helpful.

I struggle with it every day.

Brad Power 49:59
There are some questions in the chat from Allen Morris – I think you touched on this – asking about the different radioisotopes that might be used.

Will actinium supplant lutetium, or will it be synergistic?

Oliver Sartor 50:17
These are questions that we grapple with, and we're trying to work through. A lot of the actinium data is going to be comparing the individual toxicities. Right now we have a lot of salivary toxicity with our small molecules. We need to learn more. I don't know if actinium will fully supplant lutetium, or whether or not it'll augment it – the so-called “tandem therapy” – where we're using combinations of both. We're learning a lot. I'm not quite sure if we're going to have a replacement. Please remember that there are other Alpha therapies like lead-212, which are in the preliminary stages, and are looking pretty interesting. Let's evolve together. Come back in two or three years. I'll have a better answer.

Brad Power 51:23
That jibes with Chad Magnussen’s question: what are you most excited about for future potential treatments?

Oliver Sartor 51:31
I like the targeted alpha therapy. I am very excited about the ability to use these alpha particles in a targeted way, but I also want to explore very carefully the optimal approaches to targeted alpha therapy, and I don't quite know what it is yet. We know the activity in the small molecules

like PSMA-617, PSMA-IMT, they have known activity, but we also are still sorting through their toxicity, and it could be some variations. I'm not quite sure what the winners are, but I love the radiopharmaceuticals, because I can see it and I can treat it, and that gives me a power that I can't otherwise have. I really like the ability to see what I treat.

Brad Power 52:19
I heard about a company that has a novel idea. They use a cold isotope, and then it gets activated by a neutron beam. Have you heard about that? Is that something on the horizon as well?

Oliver Sartor 52:41
It feels like the past and the future. It's a great concept. What you're going to be doing is activating the isotope preferentially by a neutron beam after a targeted approach. Here's the problem: People have been talking about it for a long time, I mean, like over a decade, and it hasn't come into reality yet. I love the concept. It's a powerful concept. As yet, it's unproven, and there are no trials in prostate at this time.

Nathanael Jackson 53:24
On combinations: I would like your top three combinations that I can discuss with my doctor when I go see her in a week or so. What combinations would you talk to me about?

Oliver Sartor 54:04
We have to be a little bit realistic about what's available in combination therapy. If I list the menu of possibilities, it is broader than what is practical. Again, I was giving a conceptual talk. The combination that I might consider today for somebody who is being treated with lutetium is to combine it with an AR receptor pathway inhibitor, and that would be something like enzalutamide, apalutamide, or abiraterone. We have a little bit of data to suggest that when we give hormonal agents in combination with Pluvicto, we do a little bit better. I don't know what you're on now, but I like the combinations.

When it comes to things like the PARP inhibitors, that's a little too stretchy. That ought to be clinical trial stuff. We can't put together the isotopes yet. We don't have the data. I wouldn't combine it with chemotherapy, because we don't really have the data. That leaves us with the hormonal agents to manipulate the best way possible, and the bone-targeted agents, which is another combination.

That’s an imperfect answer, but we have imperfect data here.

Nathanael Jackson 55:15
I'm still on the 7.5 Lupron, nothing else.

Oliver Sartor 55:23
Consider the possibility of recycling an agent you likely have previously seen, and the two that are approved in the castrate resistance setting could be either enzalutamide or Abiraterone.

Abiraterone is typically given with a steroid, prednisone or dexamethasone. Talk to your doctor about combination therapy, and make note in the VISION trial, the combination therapies were used in more than half the patients. We used either abiraterone or enzalutamide in combination with Pluvicto, and it seemed to come out a little bit better.

Stick with them. Talk to your docs. Keep in touch with your docs and communicate. Ask good questions.

Brad Power 56:50
Vic asked: What is the best somatic test for progression with bone-only metastasis?

Oliver Sartor 57:02
I typically use circulating tumor DNA. There are several out there. There's Tempus. There's Foundation. There’s Guardant. Are all good. I typically use circulating tumor DNA there.

Brad Power 57:23
We like to put a plug in for BostonGene too.

Oliver Sartor 57:29
I don't know them, but I cast no aspersions.

Brad Power 57:31
Deepak had a question: for hormone-sensitive patients with normal serum calcium levels who are on ADT: Is it necessary to take calcium supplements, or is that not needed if calcium levels are normal?

Oliver Sartor 57:45
We're not really driven by the serum calcium there. But let me mention, this is a very controversial point: the ability to inhibit the development of osteopenia and osteoporosis on ADT. It's still imperfectly understood. I'm going to say that calcium is a plus minus to me. I don't insist on it. The serum calcium has nothing to do with it, because virtually nobody's hypocalcemic – too low in calcium.

If I had to say one thing to keep your bones going strong, it is exercise and moving around. The worst thing you could do is be a couch potato. The more you sit, the weaker your bones get. If you really want to do something bad for your bones, go to outer space and circulate around in a zero gravity environment. That's terrible. Don't do that. Move, keep lifting, light weights, walking. That's the way to keep your bones going strong and your muscles too.

Brad Power 58:52
From Allen Morris: how long would you theoretically guess to treat with PARP when trying to synergize with SBRT or radiopharmaceuticals?

Oliver Sartor 59:02

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]

In the study that I showed you very briefly, called the LuPARP study (a clinical trial combining lutetium plus PARP inhibitors), they started out only using five days of PARP, and with the radiopharmaceutical, they then extended it out to about 18 days. But it's not continuous. It's an intermittent use for the radiopharmaceuticals. We're still learning here. We don't really know the right answer. With SBRT, you probably don't need the PARP inhibitor. Let me tell you why: because SBRT is so damn good. You control the disease, literally, 95% of the time. You don't need to augment the effects of radiation, but you already have 95% control rates.

Brad Power 59:48
When do you predict the radiotherapeutics will enter the hormone-sensitive space?

Oliver Sartor 59:59
We'll have the first readout next year on the trial called the PSMAAddition trial. (An International Prospective Open-label, Randomized, Phase III Study comparing 177LU-PSMA-617 in combination with Standard of Care, versus Standard of Care alone, in adult male patients with Metastatic Hormone Sensitive Prostate Cancer). It's a big trial, over 1100 patients. I'm co-PI (principal investigator) on the trial. That initial readout will most likely be negative, because not everybody is going to respond. With further time, maybe it'll be in 2026, but that's conjecture. I don't really know, because these are all what we call event-driven clinical trials. I think in 2026 we might have a pretty good read out there.

Brad Power 1:00:38
This is always a huge eye opener, particularly for men who have gone through many rounds of therapy and figuring out what's next. It's always good to understand the landscape.

Oliver Sartor 1:01:00
I'm sorry I got a little bit technical there, but it's hard to convey these concepts in normal English, because we have to talk about cell surface targets and their names, things like “DLL3” and “PSMA”, and it's just not English. I apologize for that, but it's kind of necessary.

I'd like to thank you for putting this together, Brad, and the group of questions that I received today were absolutely top notch.

Hopefully I was able to provide a little bit of an insight for people here and there, but you've got a well educated group, and keep at it, because that education gives you power, and when you're empowered, you can make better decisions, and that's what it's all about: trying to get to the best decision.

“Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]

CHAT DISCUSSION

00:11:23 Allen Morris: Will Actinium supplant Lutetium or will it be added, synergistic with it?
00:22:32 Allen Morris: Will and if so when do you predict the radiotherapeutics will enter the hormone sensitive space?
00:25:32 Vic Paglisotti (he/him): Why Pluvicto instead of RA-223 for widespread bone only metastatic PCa
00:25:51 Alane Watkins: I like the format of peer to peer
00:26:27 Alane Watkins: Save the educational type for a separate session…ty
00:31:49 Arthur: Please keep this a sophisticated cutting edge seminar. The basics are all over the Internet, there is only one Dr. Sartor.
00:32:30 Nathanael "Doc" Jackson: should I leave to satisfy you
00:35:09 Brad Power: The notes that I will write up will translate the technical terminology and hopefully make it accessible to a lay audience.
00:35:17 Allen Morris: How long would you theoretically guess to treat with PARP when trying to synergize with SBRT or radiopharmaceuticals?
00:36:26 Noel Resch: Replying to "should I leave to s…"
Please don’t leave! If you’d like to talk about Pluvicto on a more personal experience level, please call me. Phil (my husband) had 6 rounds and we’d be happy to talk to you. 920-362-1754
00:38:05 Eric Hall: Reacted to "Please keep this a s..." with 👍
00:40:45 Eric Hall: Reacted to "Please don’t leave! ..." with ❤️
00:41:31 Noel Resch: Reacted to "Please don’t leave! …" with ❤️
00:41:41 Noel Resch: Reacted to "Please don’t leave! …" with ❤️
00:41:42 Noel Resch: Reacted to "Please don’t leave! …" with ❤️
00:42:12 Noel Resch: Reacted to "Please don’t leave! …" with ❤️
00:44:46 Eric Hall: Hi Dr Sartor!!! He is my medical oncologist and is awesome!!
00:44:51 Alexander Lalov: Reacted to Please don’t leave! ... with "❤️"
00:45:59 Noel Resch: He is Phil’s, as well. I agree!
00:47:44 Eric Hall: Reacted to "He is Phil’s, as wel..." with ❤️
00:59:58 Rick Davis, AnCan Foundation: Compare FDG and PSMA - that's what we suggest. If variance, you may have an issue with small cell.
01:00:07 chad magnussen: What is Dr. Sartor most excited about for future potential treatments?
01:00:55 Deepak: My question is for hormone sensitive patients with normal serum calcium levels who are on ADT , is it necessary to take calcium supplements or that’s not needed if serum calcium levels are normal ?
01:02:27 jamesward: Reacted to "Compare FDG and PSMA..." with 👍
01:02:58 Allen Morris: Is there preliminary data from Europe for dual Actinium and Lut (synergistic) therapy?
01:03:01 jamesward: Reacted to "Hi Dr Sartor!!! He i..." with 👍
01:03:51 jamesward: Reacted to "Please keep this a s..." with 👍
01:04:30 Vic Paglisotti (he/him): Best somatic test for progression with bone only metastasis?

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01:10:04 Vic Paglisotti (he/him): Thanks so much for a fantastic presentation and great Q&A!
01:10:14 Alane Watkins: Wonderful…ty!
01:10:48 Rick Davis, AnCan Foundation: Look forward to absorbing the slides...tx, Dr. S