AXIS Medical Education

Improved Outcomes in mCRPC with PSMA-Directed Diagnostics and Therapies

This transcript has been edited for style and clarity and includes all slides from the presentation.

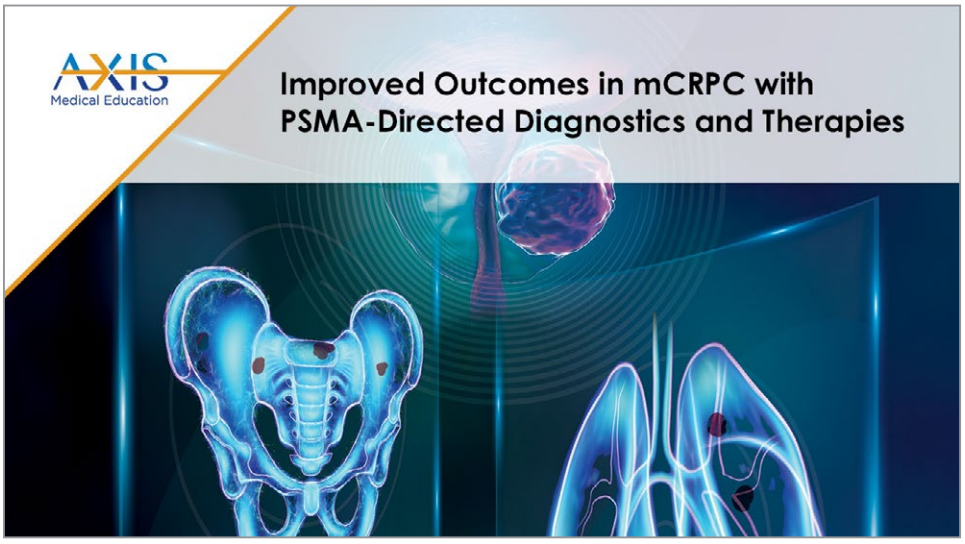
This activity is provided by

AXIS Medical Education

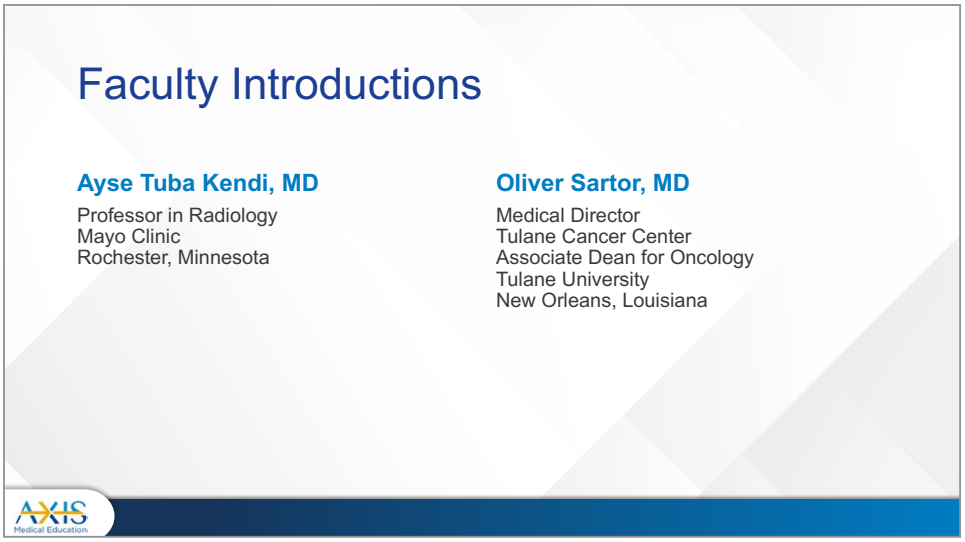
This activity is supported by an educational grant from Novartis Pharmaceuticals Corporation.

Improved Outcomes in mCRPC with PSMA-Directed Diagnostics and Therapies

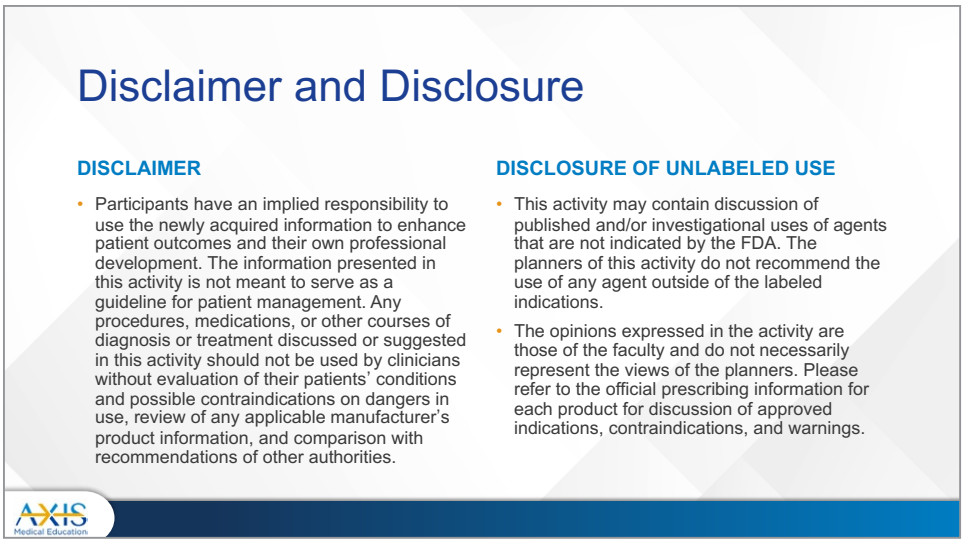
Ayse Tuba Kendi, MD and Oliver Sartor, MD



Ayse Tuba Kendi, MD: Hello, and welcome to this educational activity, entitled "*Improved Outcomes in Metastatic Castration-Resistant Prostate Cancer With PSMA-Directed Diagnostics and Therapies.*"

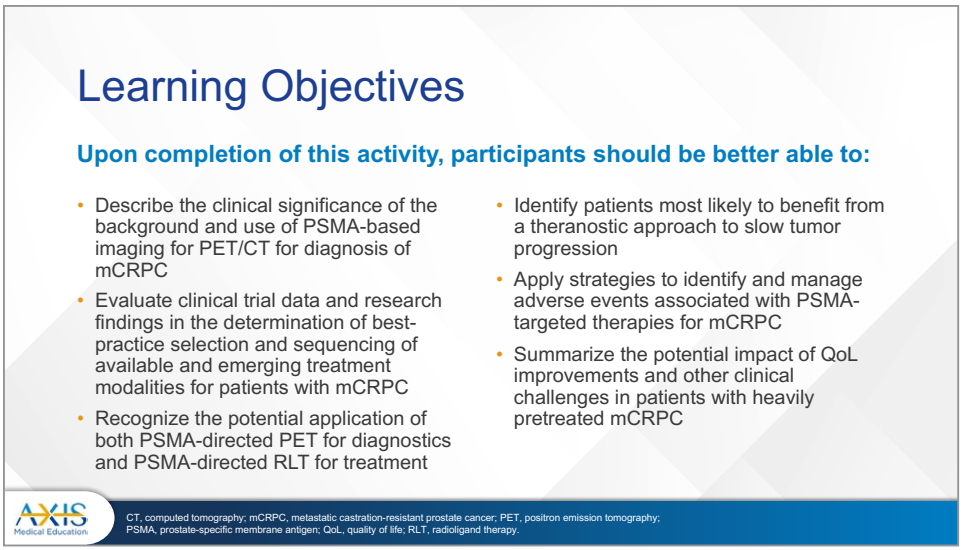


I am Dr. Ayse Tuba Kendi, Professor in Radiology at Mayo Clinic in Rochester, Minnesota. I'm joined today by Dr. Oliver Sartor, Medical Director at Tulane Cancer Center and Associate Dean for Oncology at Tulane University in New Orleans, Louisiana.

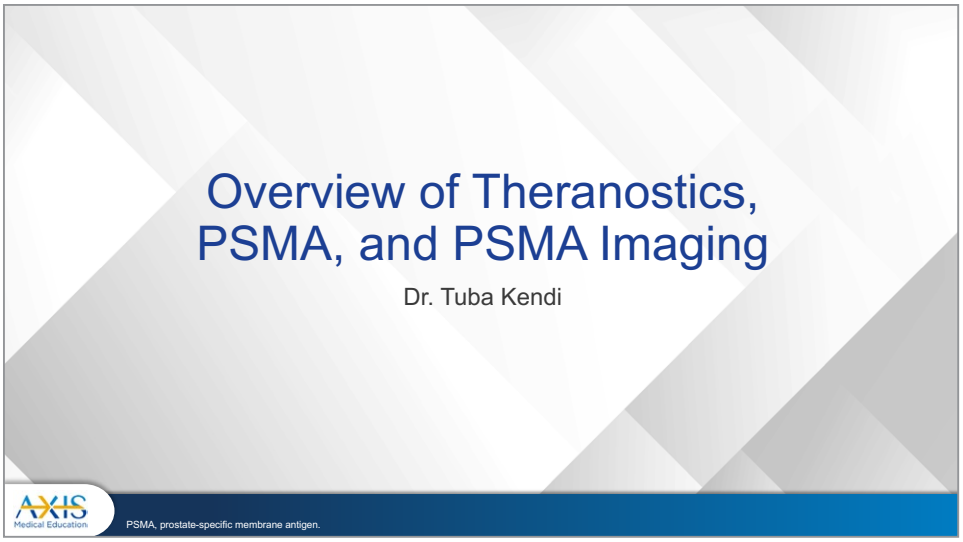


- First, disclaimer and disclosure, indicating that we may be discussing off-label use of approved agents or agents that are in development.

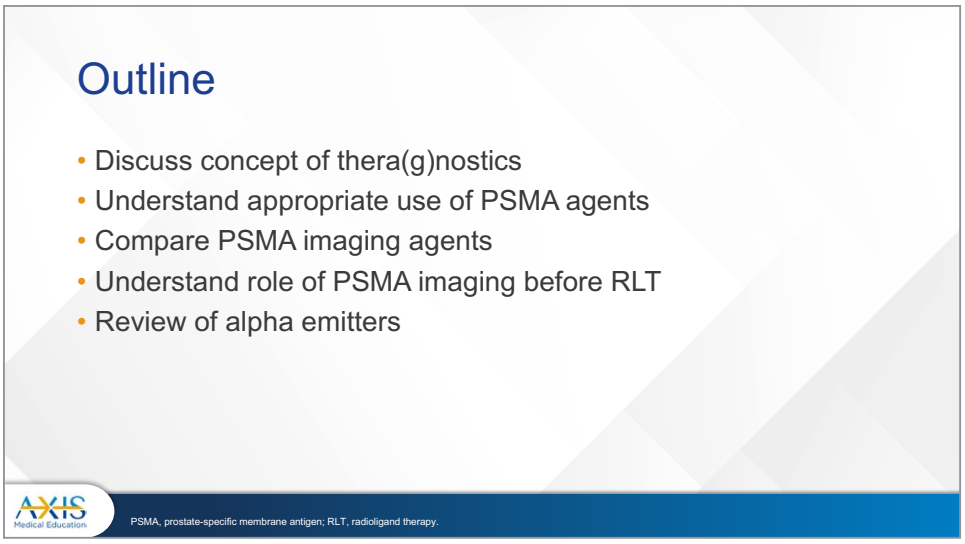
- And our financial disclosure information.



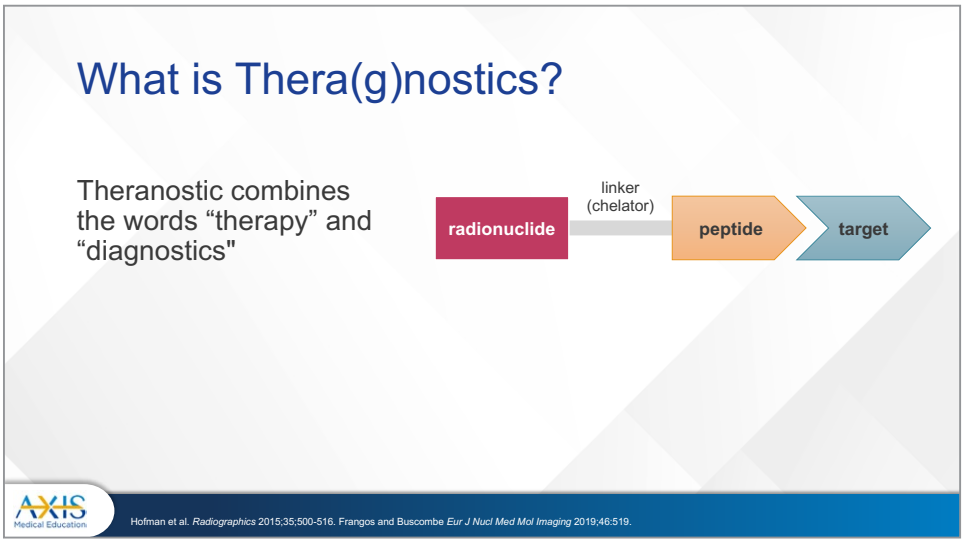
- Here are learning objectives for this activity.



- I'll start today by reviewing theranostics, prostate-specific membrane antigen or PSMA, and PSMA imaging in prostate cancer.

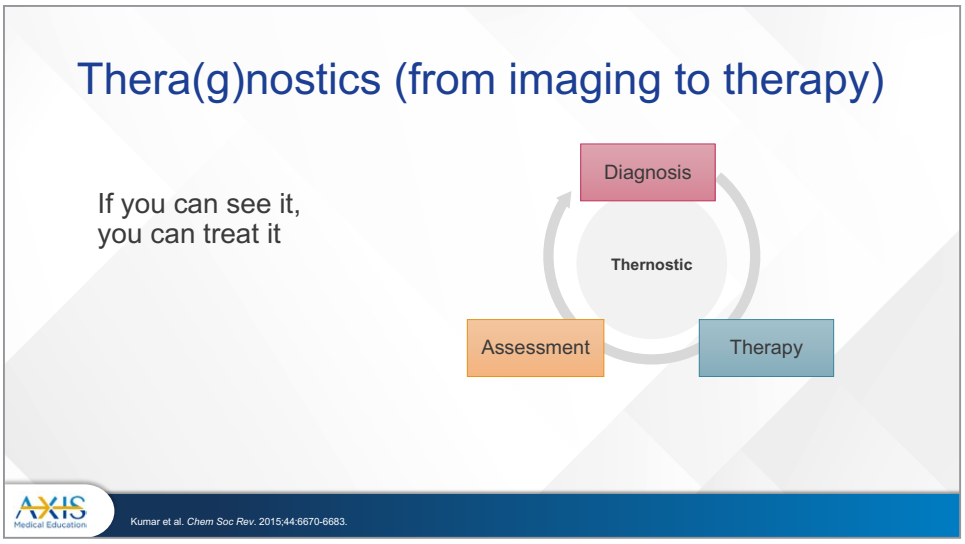


The outline of my talk will be discussion of concept of theranostics, or theragnostics. We will talk about appropriate use of PSMA agents. We will compare PSMA imaging agents and understand role of PSMA imaging before radioligand therapy. And I will also do a brief review about alpha emitters.

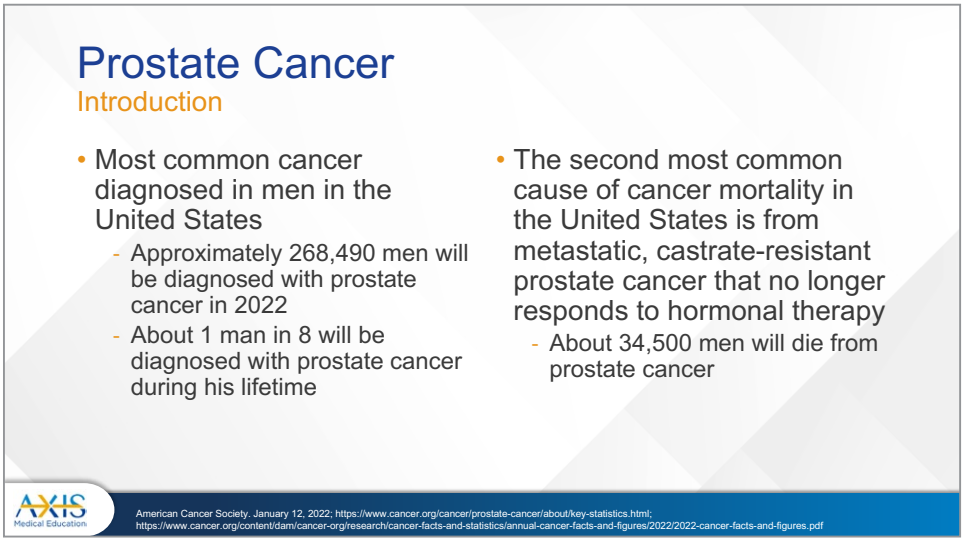


First, what is theranostics or theragnostics? It is actually combination of two words—therapy and diagnostics. Which term is better? In a recent article, the authors asked the same question to a great linguistics professor, Dr. Babiniotis. According to Dr. Babiniotis, theragnostics is the better word to use, as linguistically it is the actual combination of therapy and diagnostics. In word theranostics, thera means hunting, not therapy. I also asked this question to one of my colleagues from medical oncology, Dr. Leventakos. He is originally from Greece. He mentioned that thera is the name of an island, also known as Santorini Island. And theranostics may mean a disease of Santorini Island, as well.

We continue to use both terms, and actually theranostics more than theragnostics. Maybe it is easier to say, or we get used to that term more. How it works. First, you need a vector that could identify the tumor. This is mostly done by having a small peptide or a ligand that can identify targets, receptors, over-populated, or more specific to the tumor. By attaching this peptide to an imaging radionuclide, you form the imaging vector. If patient has abundance of tumor cells that could be identified by this imaging vector, you can consider treating patients with a therapy vector. This time, you have a radionuclide attached to the peptide or ligand, with high energy that will destroy the tumor cell.



- Overall, you can define this concept simply as, "you treat what you see."



- Let's briefly talk about prostate cancer. Prostate cancer is the most common cancer diagnosed in men, and second leading cause of cancer mortality in U.S.

Prostate Cancer

Current treatment landscape

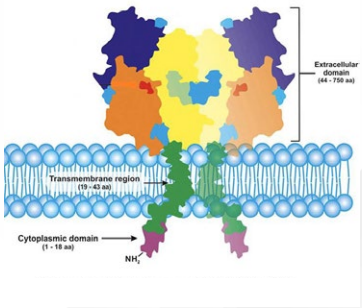
- Radical prostatectomy or radiotherapy (local disease)
- Hormonal therapy (androgen deprivation)
- Enzalutamide and abiraterone (androgen receptor inhibitors)
- Chemotherapy (docetaxel/cabazitaxel) + prednisone
- Sipuleucel-T (cell-based immunotherapy)
- Radium-223 (alpha particle-emitting radioactive therapeutic agent)

Schaeffer et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Prostate cancer. V.4.2022. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

- Currently available treatment landscape includes radical prostatectomy and radiation therapy when disease is local, hormonal therapy with androgen deprivation during hormone-sensitive periods. Chemotherapy, androgen receptor pathway inhibitors, immunotherapy, radium-223, PARP inhibitors, are other forms of therapies, mainly used at castration-resistant, advanced stages. Unfortunately, these therapies, including chemotherapy, have survival benefit less than 5 months in advanced metastatic castration-resistant prostate cancer stage. In addition, chemotherapy comes with significant side effects, and it is not a walk in the park for patients. There is an urgent need for more effective therapies, especially at metastatic castration-resistant stage.

Prostate-Specific Membrane Antigen

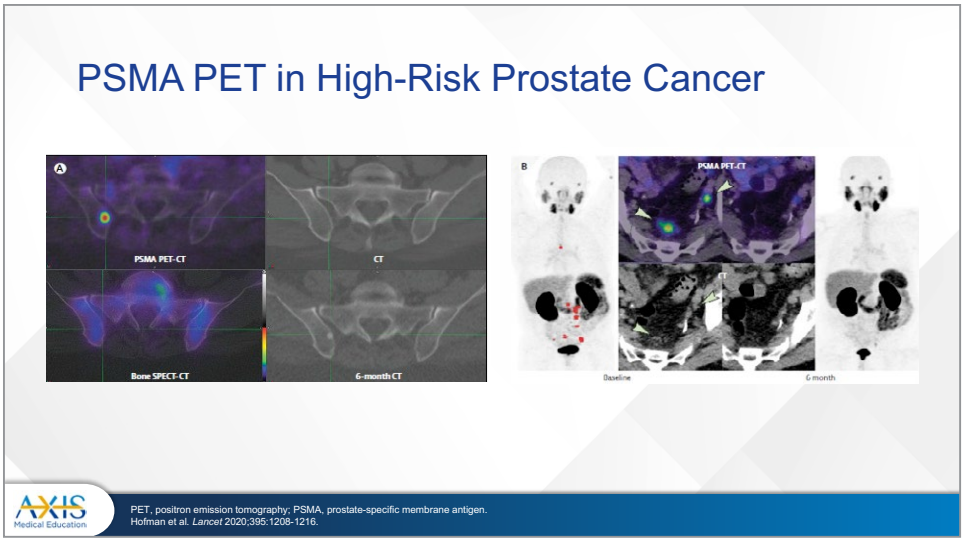
- A glutamate carboxy peptidase/folate hydrolase cell surface enzyme
- Overexpressed on the surface of prostate cancer cells (up to 100-1000 fold)
- Highly attractive target for imaging and therapy



Evans et al. *Br J Pharmacol*. 2016;173:3041-3079.

- Concept of theranostics works best when there is a specific target, and PSMA is a great example for that. PSMA is a cell surface enzyme, also called glutamate carboxypeptidase, or folate hydrolase and it is overexpressed at most of prostate cancer cells. PSMA mostly has no expression at normal tissues, which is a great advantage. That is why PSMA is a highly attractive target for both imaging and therapy. PSMA imaging and therapy work with lock and key system. PSMA ligand can identify PSMA receptor on the cell surface like a key. For imaging, you form a vector with an imaging agent like gallium-68 or F18. If there are cancer cells with PSMA expression, then you can use therapy vector, by using lutetium, a beta emitter with favorable characteristics for radionuclide therapy.

- Let's now talk about why do we need PSMA imaging? What is the advantage over currently available conventional imaging, like CT?



- According to a multi-center Australian-based study, called proPSMA, PSMA imaging performs with 27% more accuracy compared to conventional imaging. There is also less exposure to radiation, higher reported agreement, with greater treatment impact. As you can see from this example, PSMA imaging can identify sites of metastasis that are not identifiable at CT.

CONDOR Study: ^{18}F-DCFPYL-PET

^{18}F-DCFPYL, F-DCFPyL=fluorine, 2-(3-{1-carboxy-5-[(6-[(18)F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid; PET, positron emission tomography; PSA, prostate-specific antigen.
Morris et al. *Clin Cancer Res*. 2021;27(13):3674-3682.

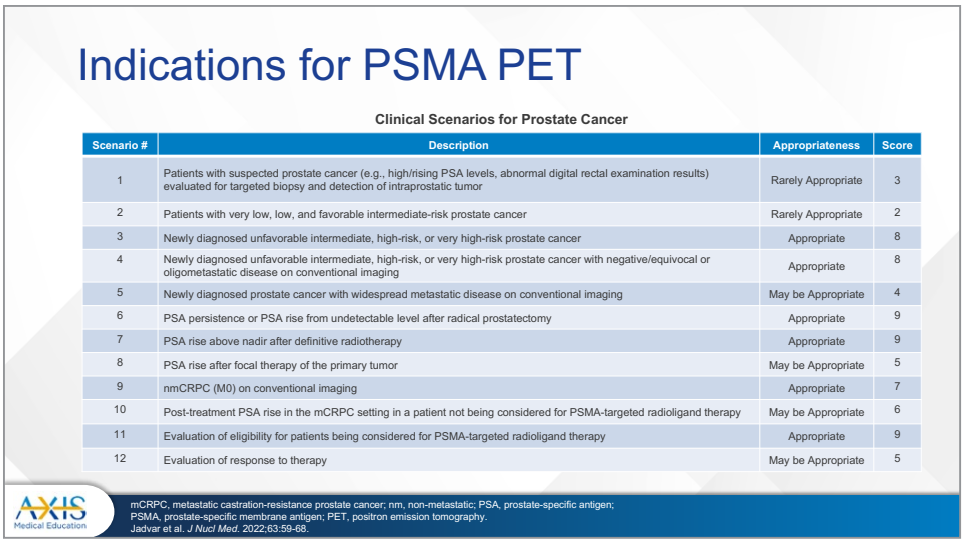
- Another recently published study, CONDOR, is a phase 3, single arm study assessing diagnostic performance and safety of PyL/PSMA/PET in patients with suspected biochemical recurrence, who were negative or equivocal at conventional imaging, including fluciclovine PET CT, C11 choline PET CT, MRI, CT and bone scan. Study population was 208 men. Correct localization rate, or CLR, was 85-87%. A change in management after PSMA PET CT was 63.9%. This image, from CONDOR study, shows correct localization rate, or CLR, and detection rate by baseline PSA levels for each group of three readers provided.

Benefit of PSMA Imaging

- High detection rate and diagnostic accuracy
- Results frequently result in changing management plans
- Assesses patients for eligibility for PSMA RLT

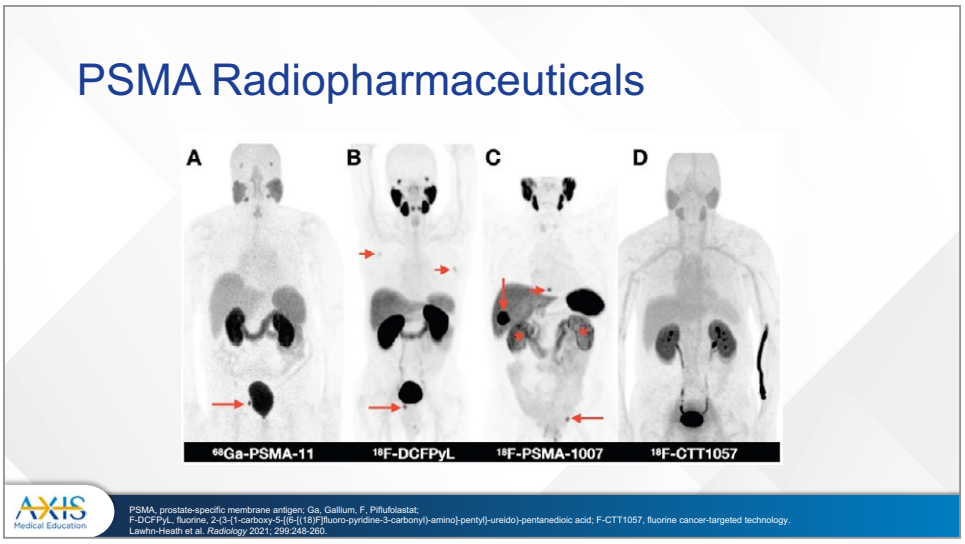
PSMA, prostate-specific membrane antigen; RLT, radioligand therapy.

- Overall, we can come to conclusion that PSMA imaging has high detection rate and diagnostic accuracy, compared to conventional imaging. In addition, it results in more frequent change in management plan, and it is the imaging tool for assisting patients for eligibility for PSMA radioligand therapy.

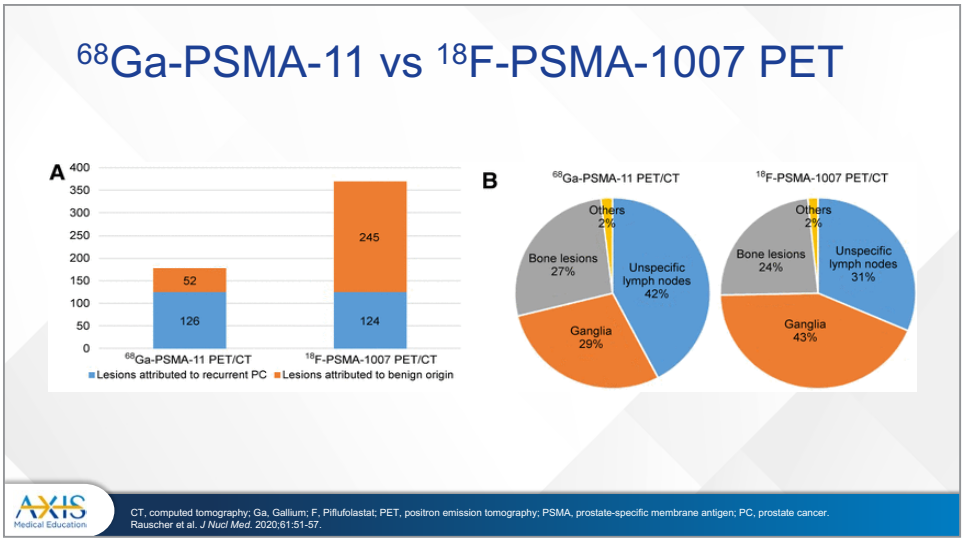


- Certain indications for PSMA PET CT is nicely summarized at Society of Nuclear Medicine Molecular Imaging, Appropriate Use Criteria, updated in March 2022. Main appropriate use areas are newly diagnosed unfavorable intermediate, high-risk patients, patients with biochemical recurrence after radical prostatectomy or radiation therapy, and for review of patients for eligibility for PSMA-targeted therapy. Now, we have support and guidelines to use PSMA imaging.

- We need to decide which PSMA imaging agent to choose, or do we need to choose.

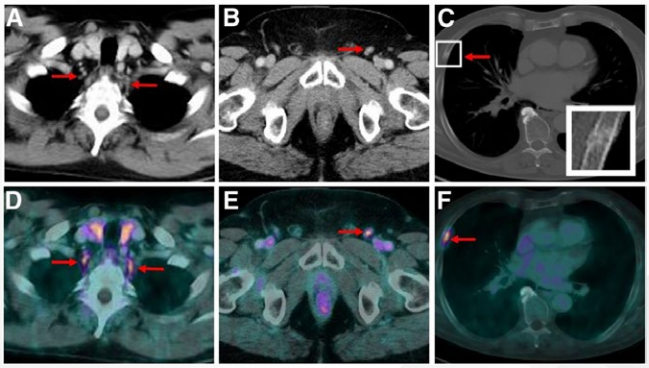


- There are PSMA imaging agents at clinical use, and at clinical trials or at development. Currently, gallium-68 PSMA-11, and F18 DCFPyL, PSMA PET are FDA-approved. Here, you see physiologic radiotracer distribution with different PSMA radionuclides. From these agents, PSMA-1007 shows minimal urinary bladder excretion, which could be a potential advantage to other PSMA agents.



- However, F18 PSMA-1007 reported to have higher false positive rates compared to gallium-68 PSMA-11. There are more benign conditions with uptake at PSMA-1007, including bones, lymph nodes, and ganglia.

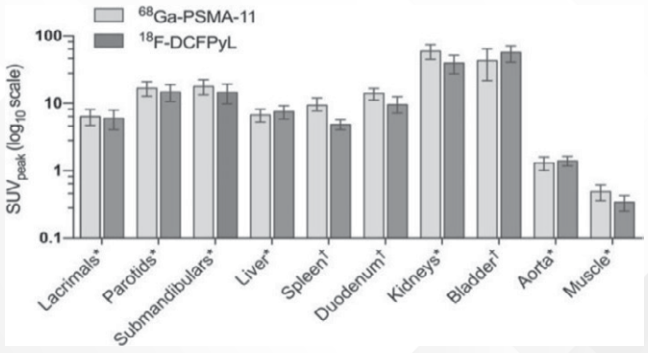
CT vs ^{18}F-PSMA-1007 PET



CT, computed tomography; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.
Rauscher et al. *J Nucl Med*. 2020;61:51-57.

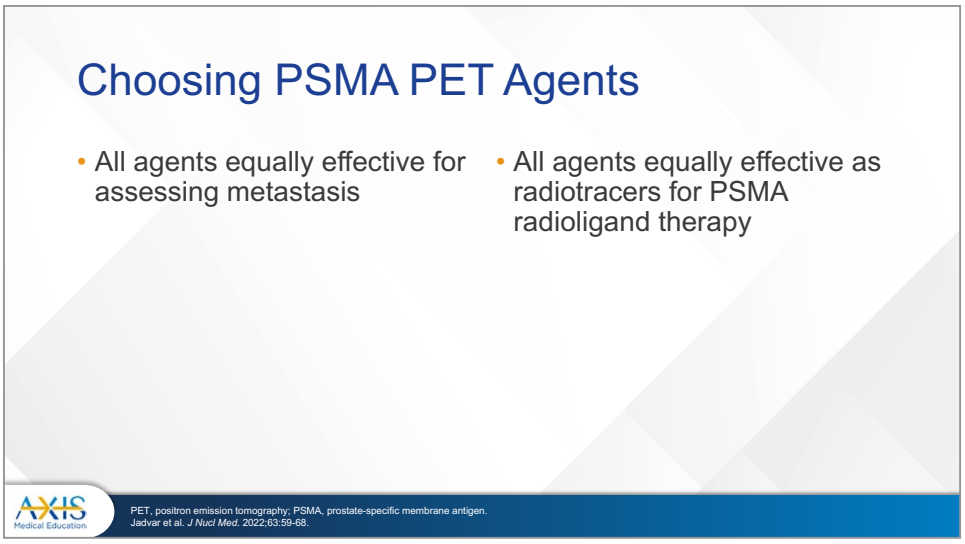
- In these images of PSMA-1007, you can see uptake at ganglia, inguinal lymph nodes, and ribs that are more pronounced or avid, that may cause false-positive results.

^{68}Ga-PSMA-11 vs ^{18}F-DCFPyL

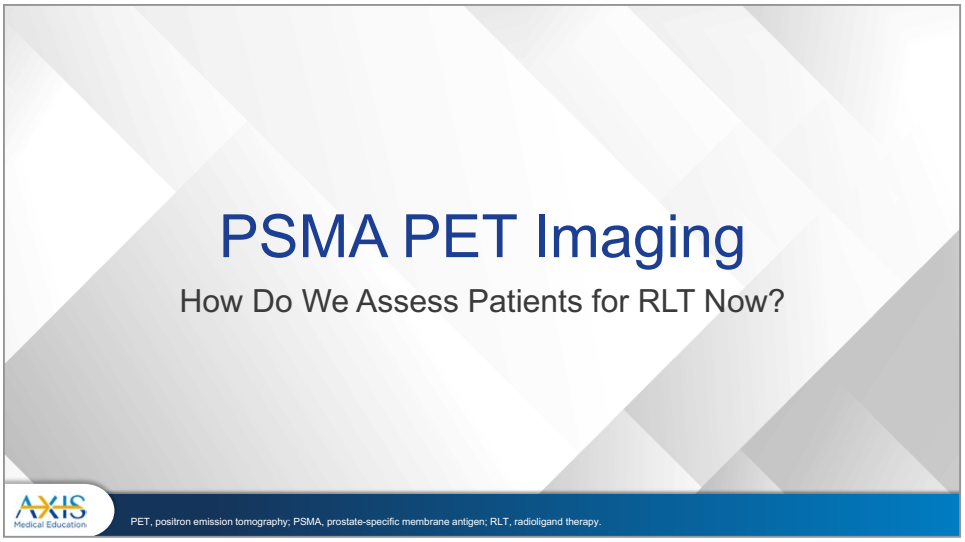


Ga, Gallium; PSMA, prostate-specific membrane antigen; SUV, standardized uptake value.
Ferreira et al. *Cancer Imaging* 2019;19(1):23.

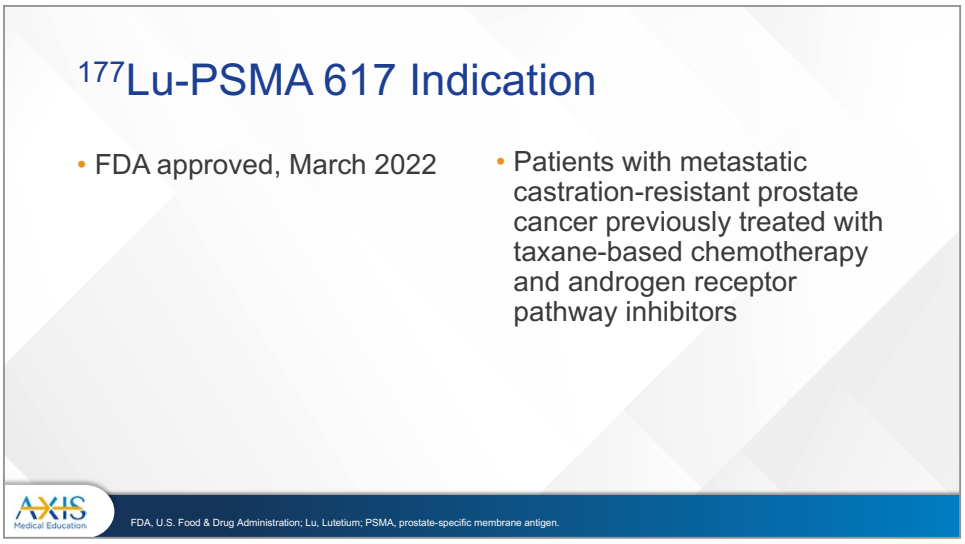
- Here is a figure from a study comparing gallium PSMA-11 to F18 DCFPyL. This study showed similar normal tissue distribution, with subtle differences between these two imaging agents.



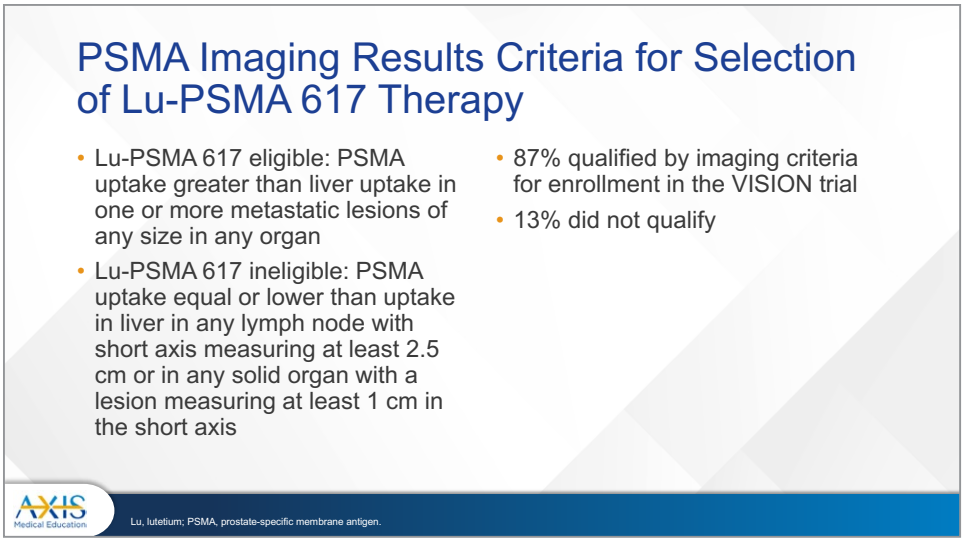
- Overall, where you look at the literature currently available, PSMA PET agents are equivalent to each other for metastasis assessment as well as for selection of patients for radioligand therapy.



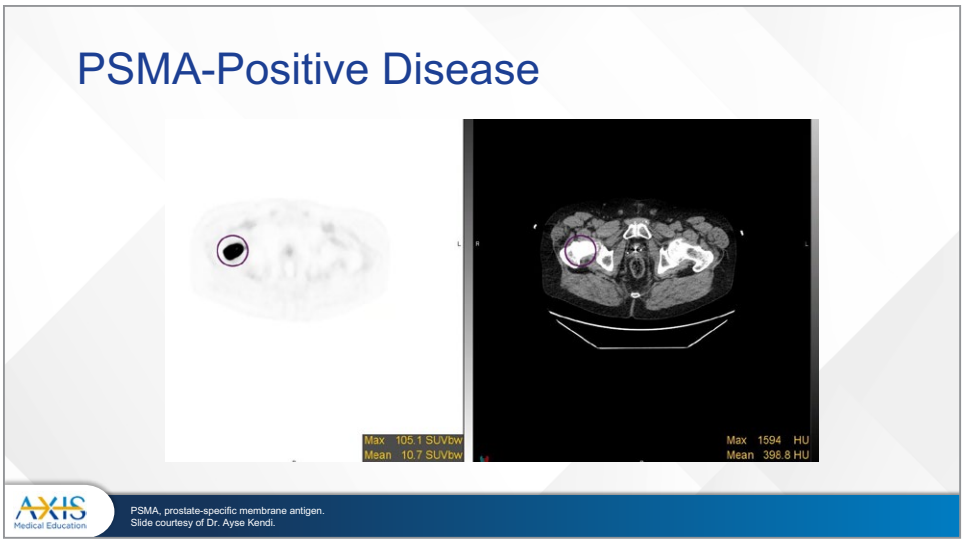
- PSMA PET imaging – how do we assess patients for radioligand therapy now?



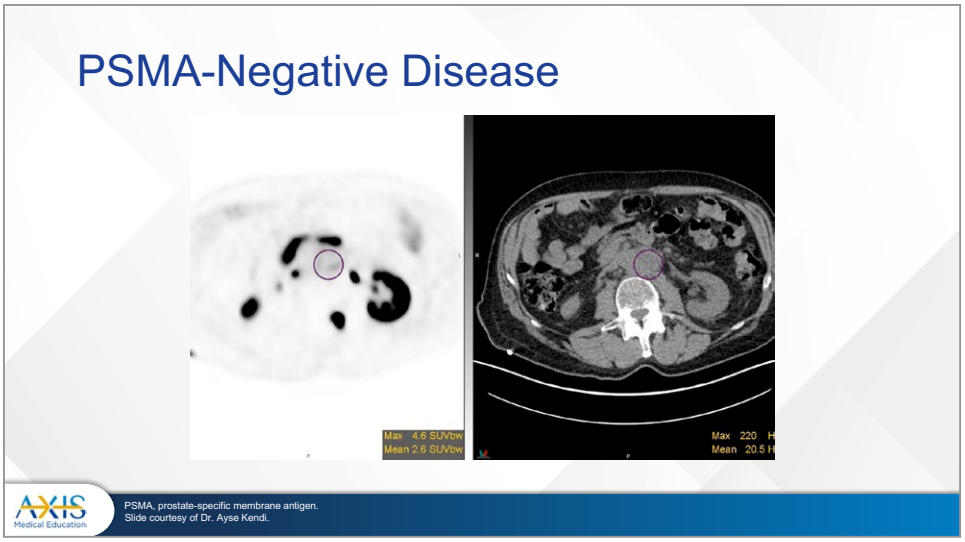
- Lutetium PSMA-617 has recently been approved by FDA for the treatment of metastatic castration-resistant prostate cancer patients, who have been previously treated with taxane-based chemotherapy and androgen receptor pathway inhibitors.



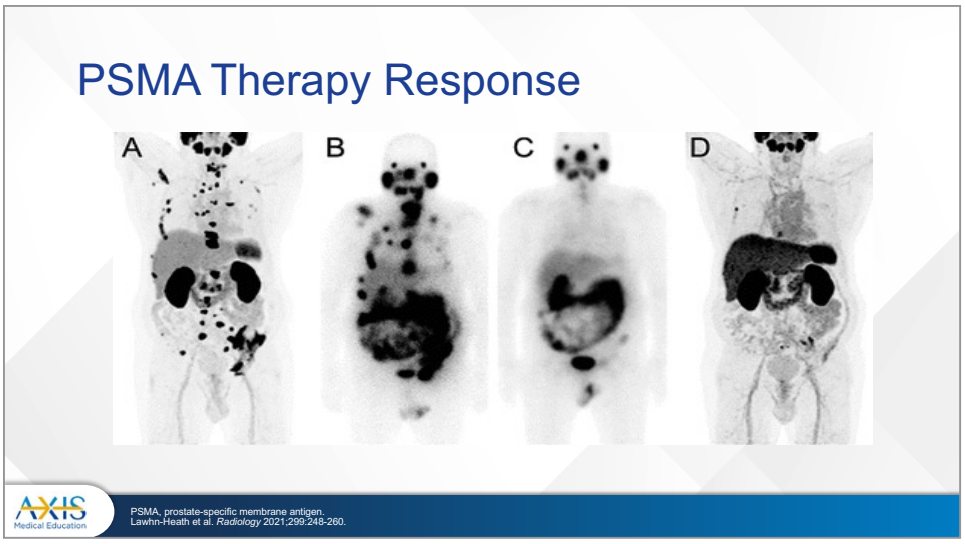
- PSMA imaging selection criteria, used in phase 3 recent trial, has been accepted as imaging review criteria. The recent criteria define PSMA-positive disease as uptake greater than liver uptake in 1 or more metastatic sites. PSMA-negative is defined as PSMA uptake equal or lower than liver in any lymph node, with short axis of at least 2.5 centimeters, or solid organ lesion which showed excess of at least 1 centimeter.



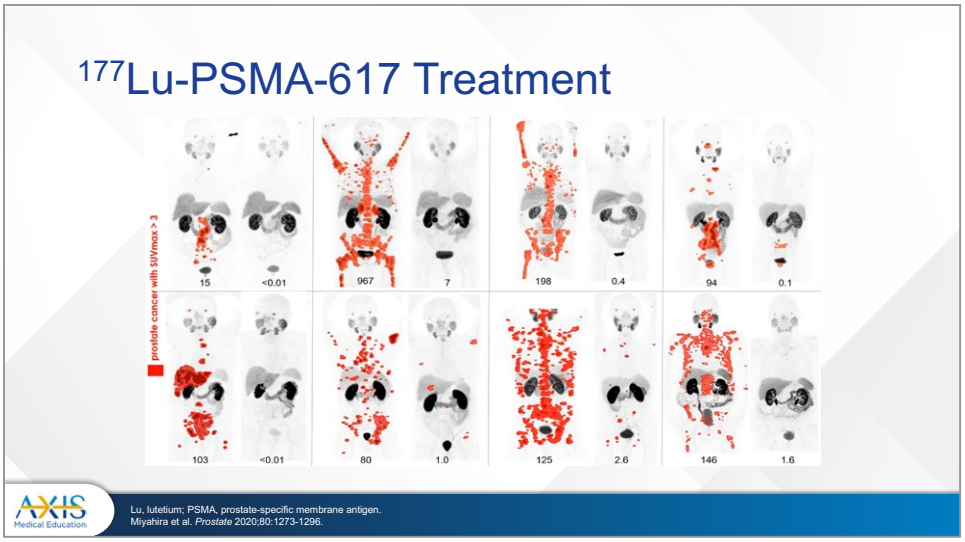
- Let's look at a couple examples. As you see, this patient has marked uptake and right femoral metastasis. The patient did not have any PSMA-negative metastasis; thus, he was eligible for therapy according to imaging criteria.



- However, this patient, who has a large PSMA-negative nodal metastasis, is not eligible according to imaging criteria.



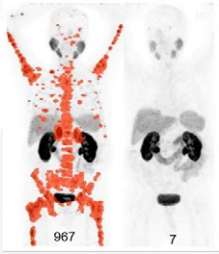
- Here is an example for a patient with excellent response to therapy. This is a 75-year-old, metastatic castration-resistant prostate cancer patient, treated with 6 cycles of lutetium PSMA therapy. Initial PSMA imaging, post-therapy imaging after first and sixth cycles, as well as follow-up PSMA imaging 4 weeks after completion of therapy show excellent response to therapy.



- This is the image from our Australian colleagues from Peter Mac, of patients before and after lutetium PSMA therapy. You see remarkable response in these patients after 3 months. This image was selected as image of the year at Society of Nuclear Medicine and Molecular Imaging annual meeting in 2018.

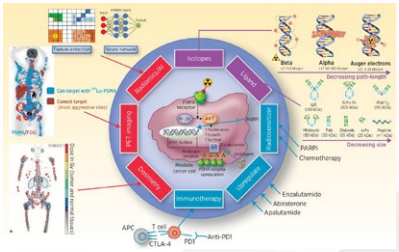
PSMA Theranostics

Current State



- High response rate
- Low toxicity
- Significant improvement of clinical symptoms
- Well-tolerated

Potential Mechanisms to Optimize



- Given the large number of patients with metastatic prostate cancer, it is projected that 160,000 cycles of Lu-PSMA will be administered annually
- Discovery → Research → Education → Application

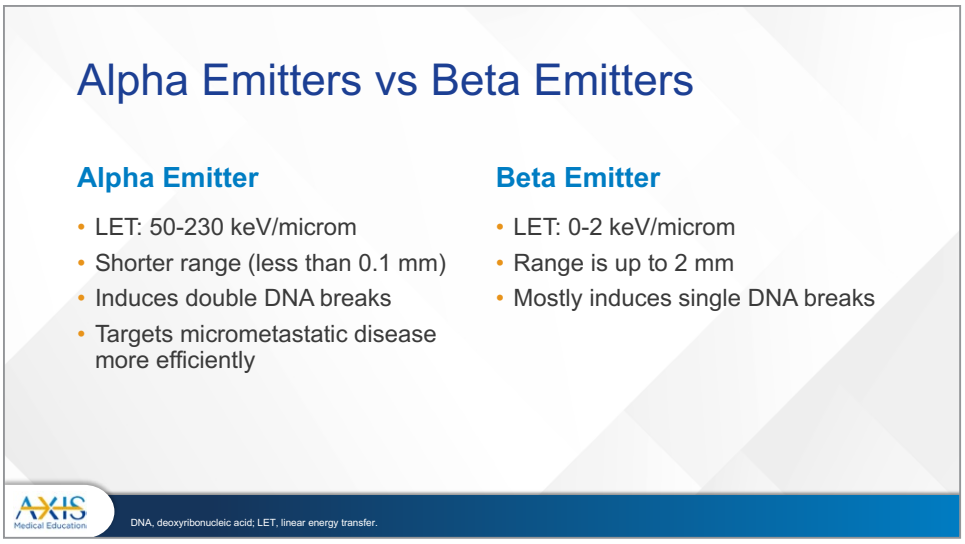
Lu, lutetium; PSMA, prostate-specific membrane antigen.
Miyahira et al. *Prostate* 2020;80:1273-1296; Kumar and Hofman. *Clin Cancer Res.* 2020;26:2774-2776.

- If we summarize, PSMA therapy has a high response rate with low toxicity, and significant improvement of clinical symptoms, with excellent tolerability by patients. Given high number of metastatic prostate cancer patients, expect that lutetium PSMA cycles per year at U.S. may reach to 150 to 160,000. To meet these demands in U.S., we need multiple, fully functioning theranostic centers.

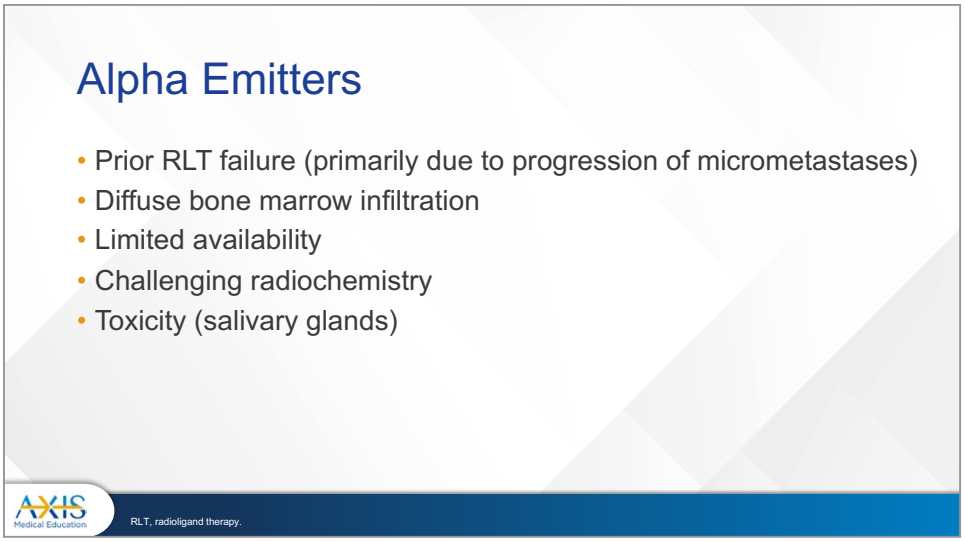
  What is the near future for lutetium PSMA therapy? Combination of radioligand therapy with other agents, like radio-sensitizers or immunotherapy. Another area is starting therapy at earlier stages, like before chemotherapy, and developing other therapy agents. These are a few items that I would like to mention that are in development.

If Patients Don't Respond or Stop Responding to Beta Emitters, What's Next?

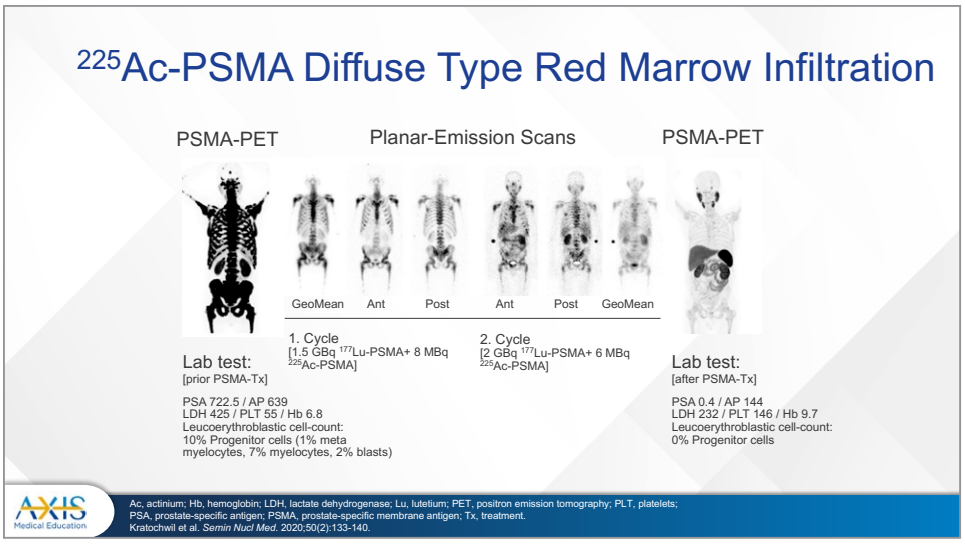
- What if patients don't respond or stop responding to beta emitters? What do we do now?



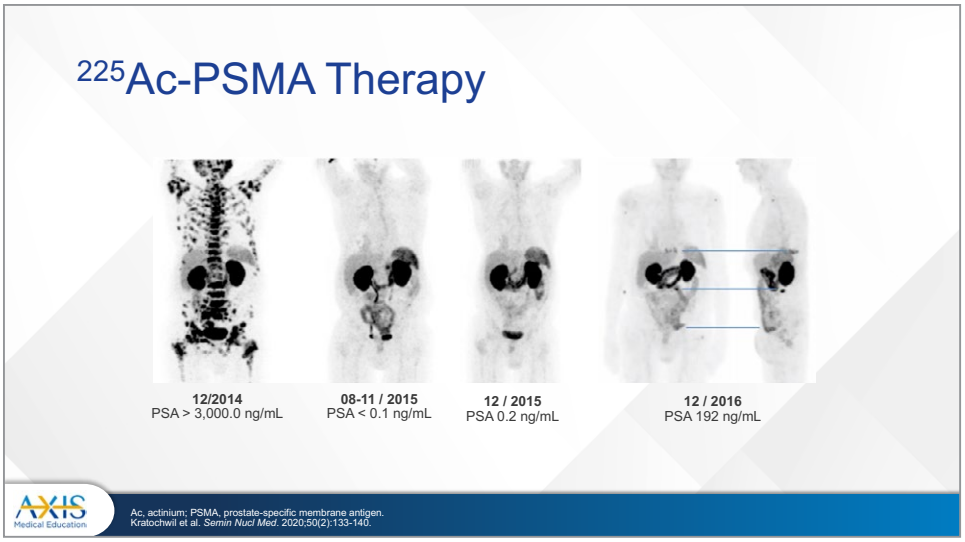
- Although high response rates reported with lutetium PSMA, there are still about 30% of patients not responding, or developing resistance to beta emitter therapy. Could we consider alpha emitters, like actinium-225 for therapy? Yes. When you compare alpha emitters, they have higher energy, shorter range, they induce more double DNA breaks, and they can target micrometastasis more efficiently compared to beta emitters like lutetium.



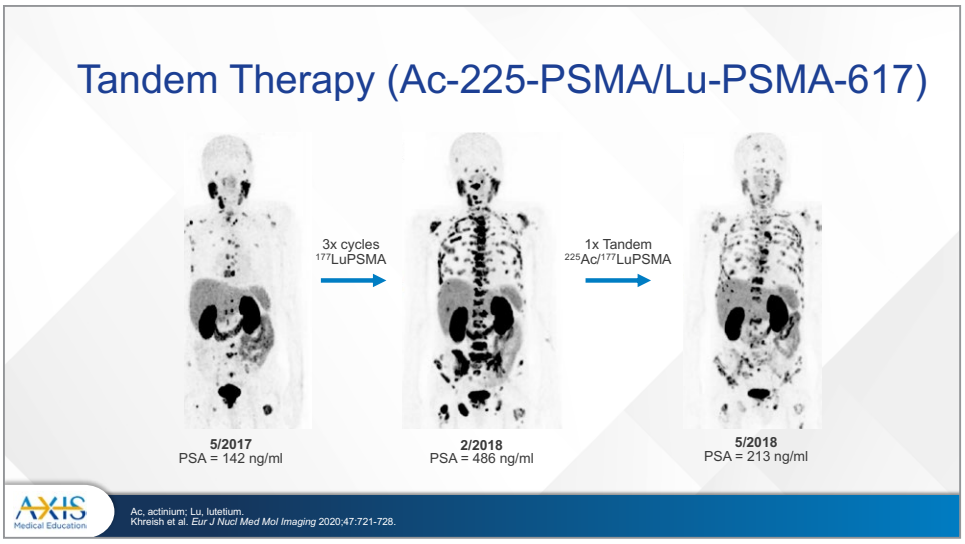
- Alpha emitters can be considered in patients with prior radioligand therapy failures, patients with diffuse bone marrow infiltration. However, limited availability, challenging radiochemistry, and toxicity are currently limiting factors.



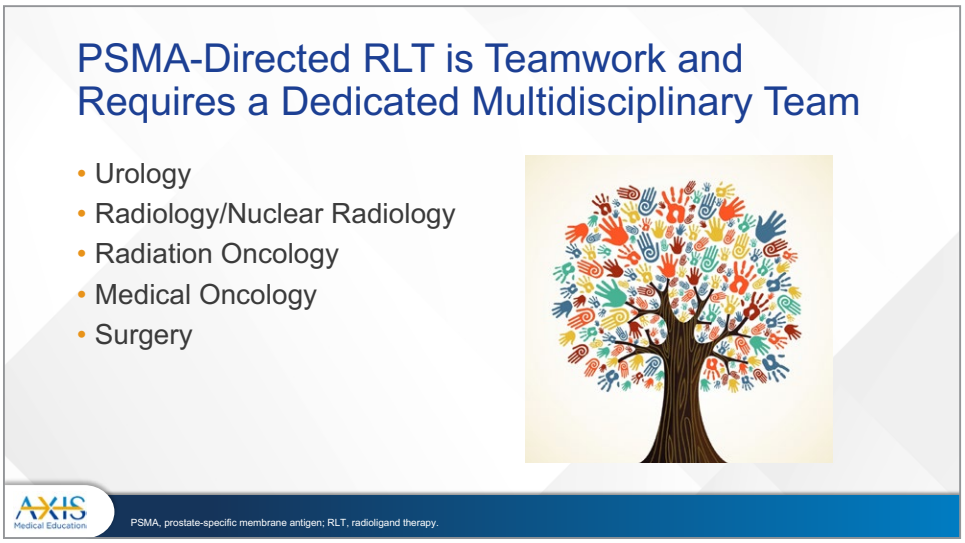
- Here is an example of a patient with response to actinium PSMA, who had refused red marrow infiltration. There is theoretical advantage regarding hematological toxicity compared to lutetium PSMA. However, severe xerostomia could be a major issue in alpha emitter treatment. This is an important limited side effect for alpha therapies.



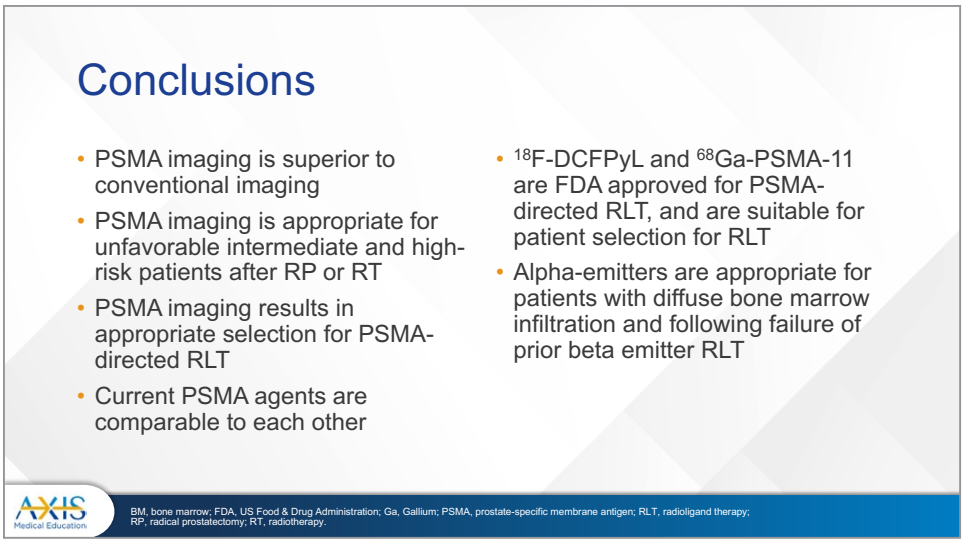
- This image shows a long duration of disease control in a patient with actinium PSMA therapy, suggesting promising result.



- I would like to briefly mention about a retrospective study from Germany. In this study, authors shared a pilot experience from a small group of patients. They used tandem therapy in patients who are not responding to lutetium PSMA monotherapy. This study suggested that when lutetium PSMA is not effective alone, by using tandem therapy with low activity actinium-225 PSMA plus full activity of beta emitters, safely enhanced response to PRLT, while minimizing xerostomia. Here is an example for tandem therapy. Image A shows tumor spread before lutetium PSMA monotherapy. Image B shows progressive disease after three cycles of lutetium PSMA monotherapy. Image C shows partial remission after one cycle of actinium-225 PSMA and lutetium PSMA tandem therapy.

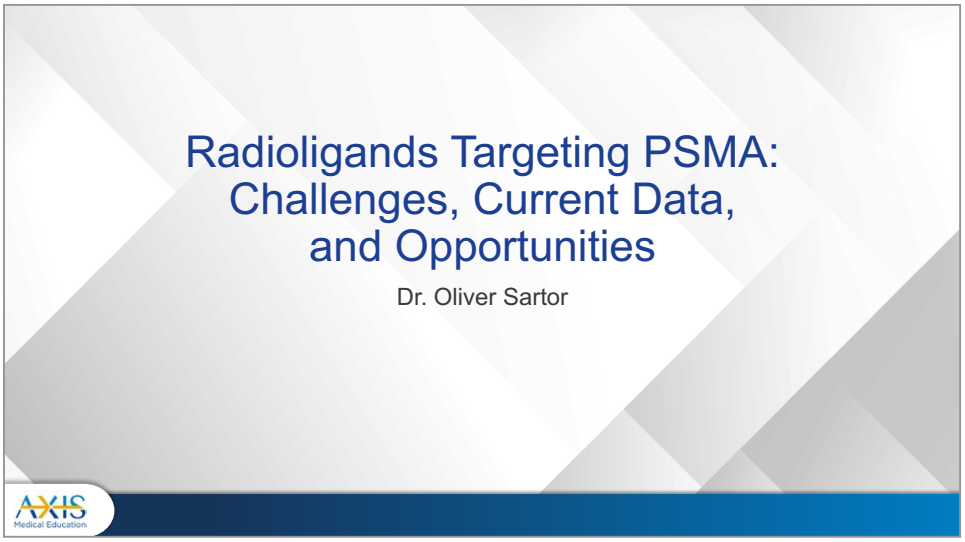


- Before conclusion slide, I would like to emphasize importance of teamwork for success at PRLT. PRLT truly requires multidisciplinary teamwork for success.



- PSMA imaging is superior to conventional imaging. Appropriate in favorable intermediate, high-risk patients, and biochemical recurrent after radical prostatectomy and radiation therapy. PSMA imaging is appropriate in selection for radioligand therapy. Current PSMA agents are comparable to each other for imaging. Currently FDA-approved F18 DCFPyL, and gallium-68 PSMA-11 are suitable for patient selection for radioligand therapy. Alpha emitters can be considered, especially at diffuse bone marrow infiltration and prior beta emitter radioligand therapy failure patients.

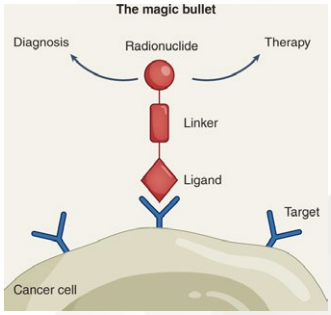
  Now, we will hear from Dr. Sartor about radioligand therapy targeting PSMA.



- **Dr. Sartor:** Thank you, Dr. Kendi, and really a pleasure to be able to be here today. I'll be discussing the radioligands targeting PSMA, and I'm going to talk about some of the current challenges, the current data, and the opportunities.

Theranostics: See it... Treat it

- Cell surface target
- A ligand
- A linker
- An isotope



AXIS Medical Education

I think Dr. Kendi covered very nicely what theranostics represents today. And if I were going to simplify it, I would simply say the ability to use a ligand, a linker, and a radionuclide for either diagnosis or therapy. She covered very nicely about how we can use imaging to predict the presence of a target, and that presence of a target can then be potentially translated into therapy using a radionuclide.

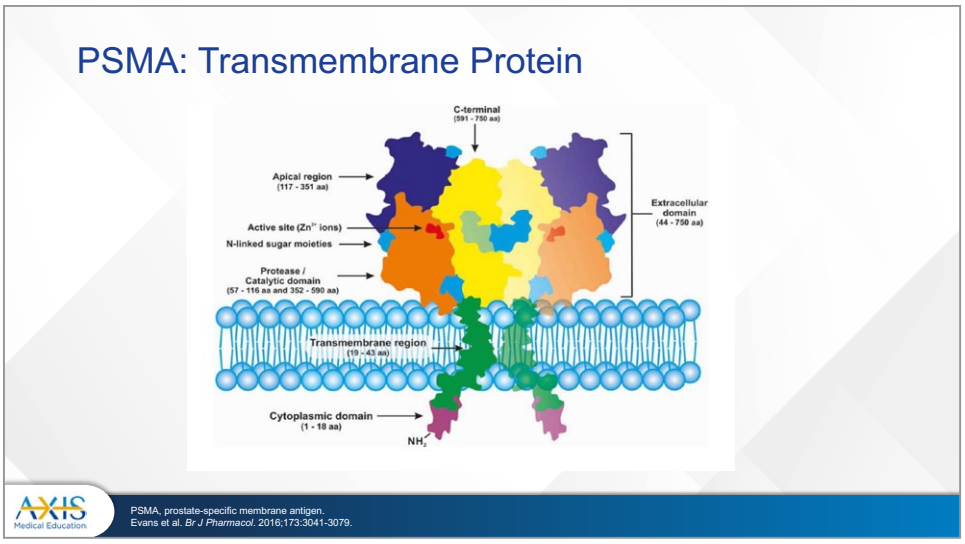
Some Targets of Note

- SST2R (NETs)-proven success with isotopes
- PSMA (prostate)-proven success with isotopes
- CD19 (leukemia/lymphoma)-proven success with CAR-T
- CD37 (lymphoma)
- HER2 (breast)-notable recent success with new ADC
- HK2 (prostate)-interesting new target
- IGFR-1 (multiple)
- FAP (huge number of tumors for a stromal target)
- MC1R (melanoma)
- CA IX (renal)

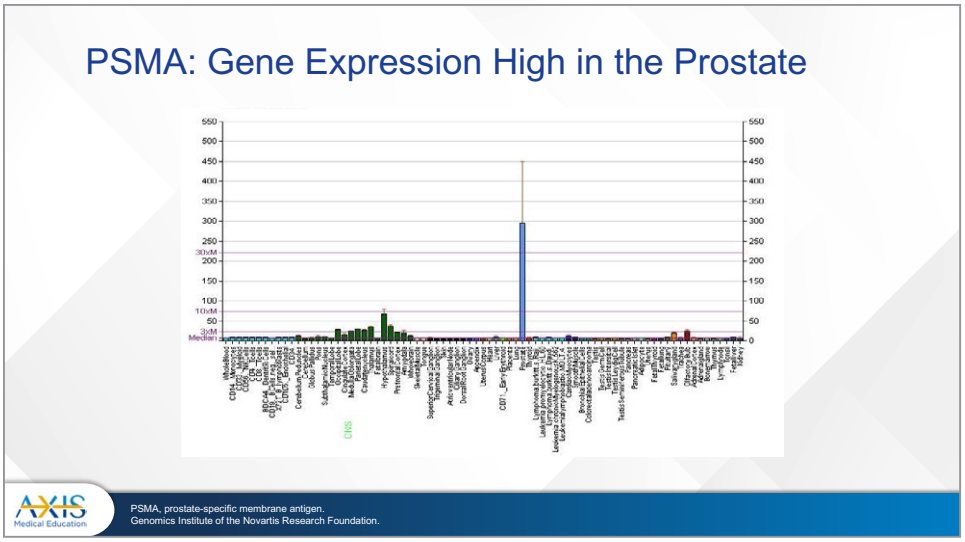
AXIS Medical Education

SST2R, somatostatin receptor 2; PSMA, prostate-specific membrane antigen; CD, cluster of differentiation; HER2, human epidermal growth factor receptor; HK2, hexokinase 2; IGFR, insulin-like growth factor receptor; FAP, fibroblast activation protein; CA IX, carbonic anhydrase IX.; NETs, neuroendocrine tumors; CAR-T, chimeric antigen receptor T-cell therapy; ADC, antibody-drug conjugate; MC1R, melanocortin receptor-1.

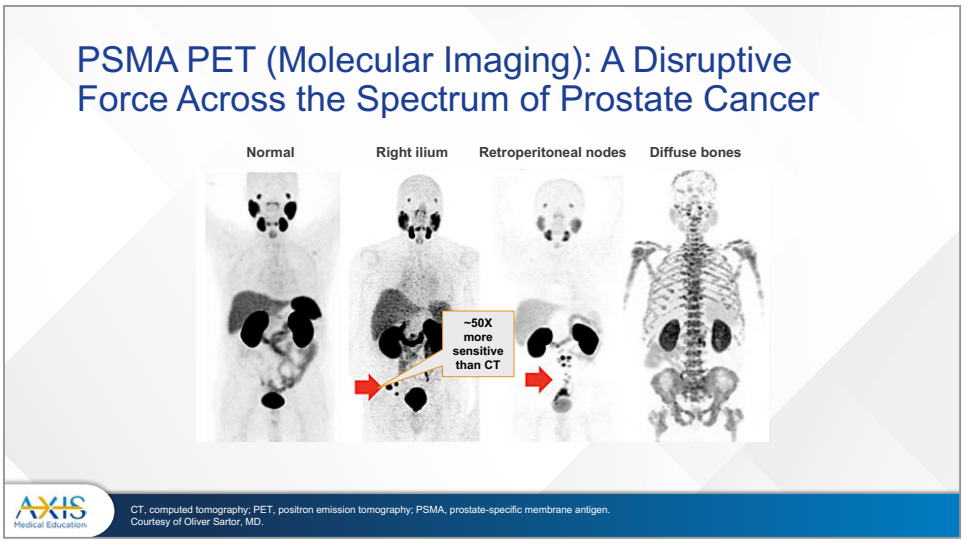
So, this is a really exciting area, right now, and one of the things I wanted to make sure that people were aware of is that PSMA is just one of the many targets that are under discussion in the theranostics field. I think we have lots of experience with neuroendocrine cancers, and in particular, those agents that target somatostatin type 2 receptors. And here we have proven success and FDA approvals. In addition, there are a whole variety of other targets that have been discussed—CD37, HER2/neu, HK2 in prostate insulin-like growth factor 1, fibroblast activated protein, or FAP CA9 in renal, and more.



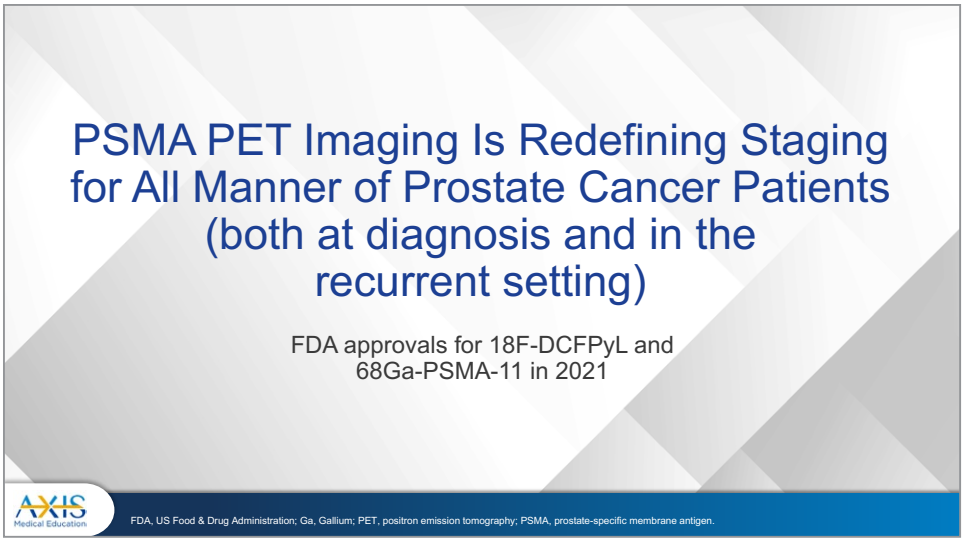
- So, today, it's really about PSMA, a transmembrane protein, the majority of which is on the extracellular surface, and a portion, by the way, of which is in the cytoplasmic domain, and it turns out that PSMA gene expression is very high in prostate, including prostate cancer, relative to other tissues.



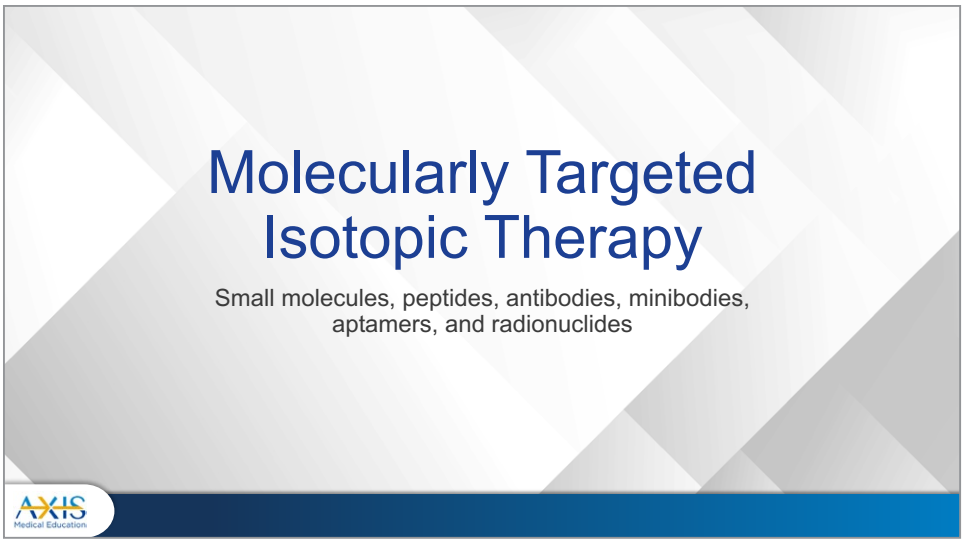
- Now, it is not absolutely unique to prostate. It's present within the central nervous system. It's present within the proximal tubules. It can be present in neovasculature. But prostate is really the high level of expression, and that's what we're going to be exploiting.



- Now, in the theranostics paradigm, Dr. Kendi covered PSMA PET, and this molecular imaging is really a disruptive force across the spectrum of prostate cancer. FDA approved in the context of either high risk disease at the time of diagnosis, or recurrent disease after a definitive therapy—either radical prostatectomy or radiation.

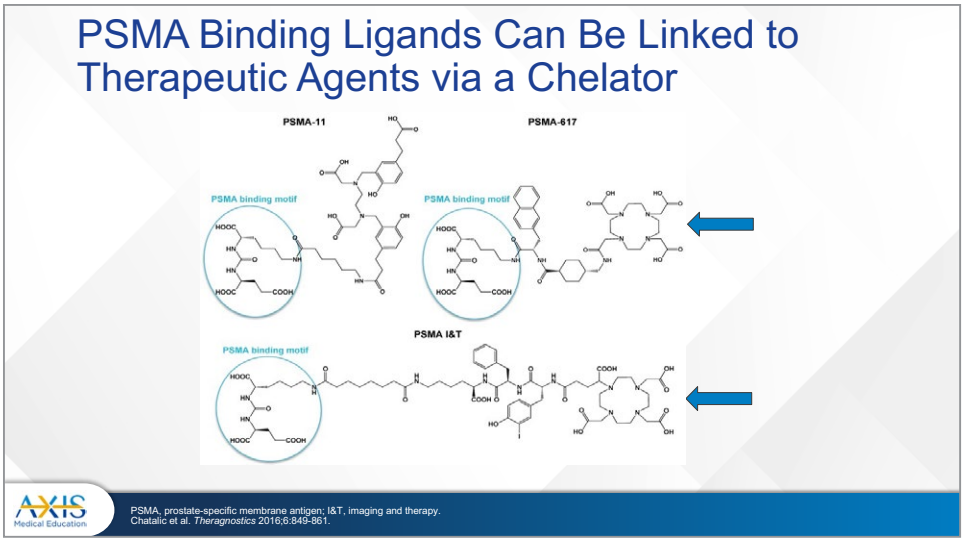


- We also know that it can serve as a predictive biomarker in terms of systemic therapy, with things like PSMA lutetium. So the whole concept of PSMA theranostics is built around seeing the tumor, treating the tumor, and understanding the diversity. Now, as Dr. Kendi mentioned, there is a little more to the story, because not every tumor is PSMA PET-positive. Nevertheless, it's a key tenet in our field. If you're going to treat with PSMA, you ought to be able to see it with PSMA PET. Now, we all know about the FDA approvals for DCFPyL and PSMA-11, either F18 or gallium-68, and this really sets the stage for the molecularly targeted isotopic therapy.



- And we have small molecules, there's also a lot of discussion around peptides, and antibodies, and maybe minibodies, and even naked radionuclides. So, there's a lot to talk about when it comes to this broad field of therapeutic aspects of theranostics.

.



- The PSMA binding ligands that we're going to be particularly discussing are PSMA-617 and PSMA-I&T, and both of these are being used therapeutically. Both of them have a chelator to which you can attack a therapeutic agent, and this therapeutic agent may be something like lutetium or actinium, and this ability to target the PSMA expressions, of course is critically important.

Large Number of Beta Emitters in Human Studies

Radionuclide	Half-life	Maximum Energy (MeV)	Mean Energy	Average Penetration
Strontium-89	50.5 days	1.46	0.58	2.4 mm
Samarium-153	1.9 days	0.81	0.22	0.5 mm
Phosphorus-32	14.3 days	1.71	0.69	3.0 mm
Ytrium-90	2.7 days	2.27	0.93	4.0 mm
Lutetium-177	6.7 days	0.49	0.14	0.3 mm
Iodine-131	8.0 days	0.61	0.19	0.8 mm
Rhenium-186	3.8 days	1.07	0.33	1.0 mm
Rhenium-188	0.7 days	2.12	0.64	3.8 mm
Holmium-166	1.1 days	1.84	0.67	3.3 mm
Tin-117m*	13.6 days	0.15	0.14	0.2 mm

AXIS Medical Education

* Conversion electron

- Now, there are actually a lot of beta emitters in human studies. Lutetium is the one we're going to focus on today, but there's also been already a mention of alpha emitters, such as actinium, and I'm going to cover a little bit about alpha emitters as well. Within the large number of beta emitters currently in human study, things like strontium-89, samarium-153, are actually FDA-approved for bone metastatic prostate cancer and for palliation, but they don't prolong survival. On the other hand, the PSMA lutetium-177 does prolong survival, and that's very, very important.

PSMA Targeted Therapy: The Beginning

Radiation Dosimetry and First Therapy Results with a $^{124}I/^{131}I$-labeled Small Molecule (MIP-1095) Targeting PSMA for Prostate Cancer Therapy

Christian M Zechmann, Ali Afshar-Oromieh, Tom Armor, James B Stubbs, Walter Mier, Boris Hadaschik, John Joyal, Klaus Kopka, Jürgen Debus, John W Babich, Uwe Haberkorn

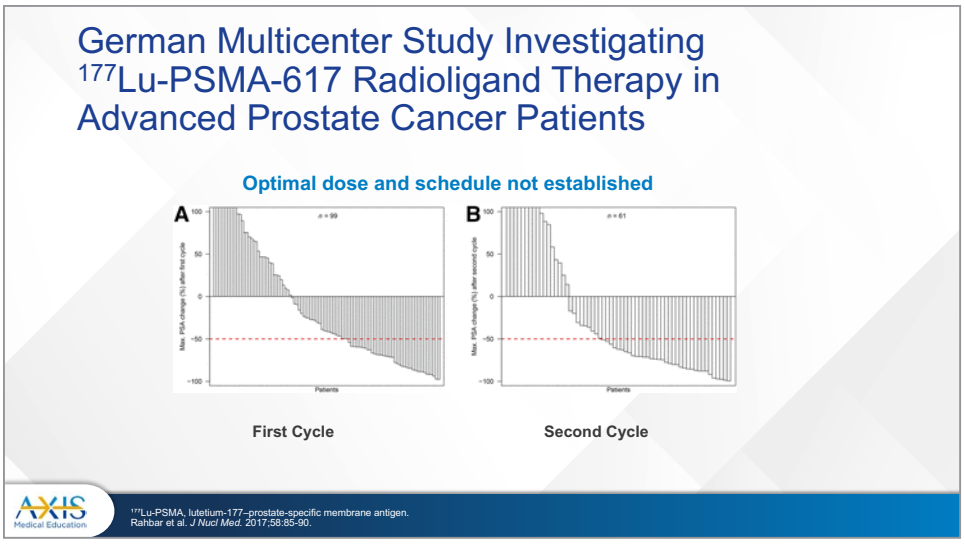
PSMA-Based Radioligand Therapy for Metastatic Castration-Resistant Prostate Cancer: The Bad Berka Experience Since 2013

Harshad R. Kulkarni, Aviral Singh, Christiane Schuchardt, Karin Niepsch, Manal Sayeg, Yevgeniy Leshch, Hans-Juergen Wester and Richard P. Baum

AXIS Medical Education

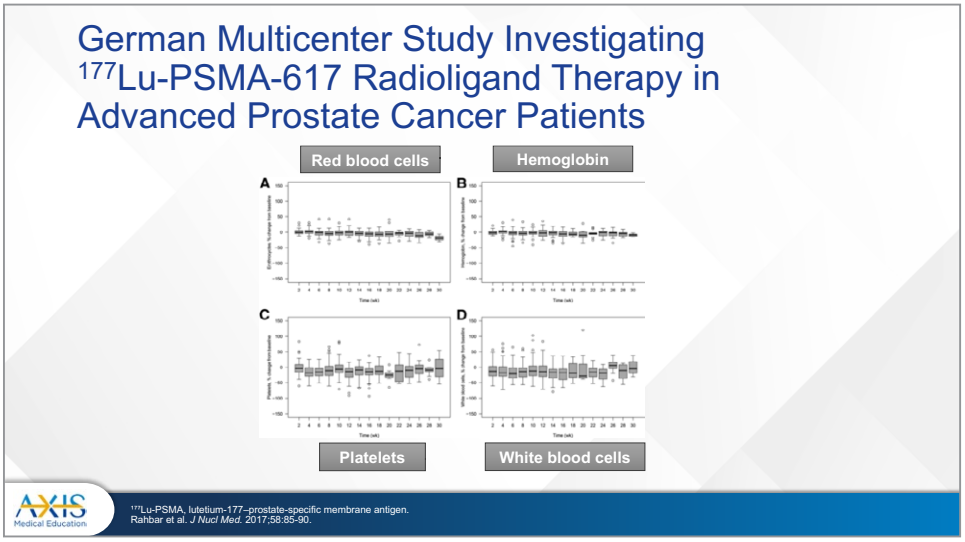
PSMA, prostate-specific membrane antigen.
Zechmann et al. *Eur J Nucl Med Mol Imaging* 2014;41:1280-1292; Kulkarni et al. *J Nucl Med*. 2016;57(suppl 3):97S-104S.

- Now, if we were to go back to the beginning of PSMA-targeted therapy, it actually starts with a small molecule called MIP-1095. And MIP-1095 doesn't bind lutetium, it actually binds iodine. And the therapeutic aspects of this molecule were being addressed with I-131, in some early studies in Germany. And what I'll say is this helped get the field rejuvenated and excited about moving forward.



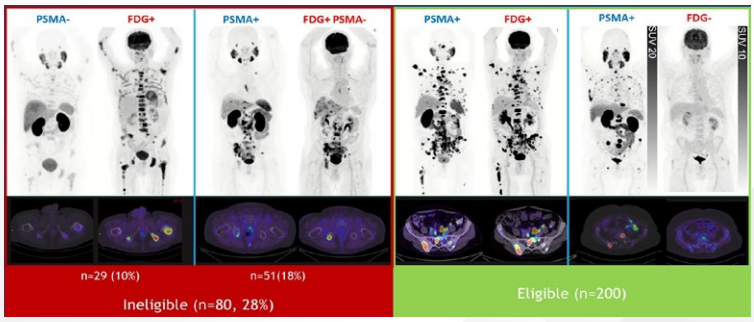
- And then, the first lutetium-based therapies were actually done at Bad Berka by Richard Baum, and he published his experiences going way back to 2013. So, even though it may appear as though PSMA-based theranostics is new, this work has been ongoing for a number of years, and in particular, since 2013.

  In the German experience, I think it was very valuable to be able to compilate a whole series of German centers, and to publish their data as a whole. And here, you see Kambiz Rahbar senior author Bernd Krause, looking at first cycle PSA declines, second cycle PSA declines, on a whole wide variety of doses and schedules. And what you can see is you've got a lot of patients that are responding, of course some that do not.



- One of the other interesting things about these early German studies was the fact that there was very little myelosuppression. The concern over using lutetium was that you would damage the bone marrow. But here, on this slide, from the *Journal of Nuclear Medicine* article in 2017, you can see that platelets, red cells, white cells, really do not suffer much in the way after this therapy, so that was a very important finding.

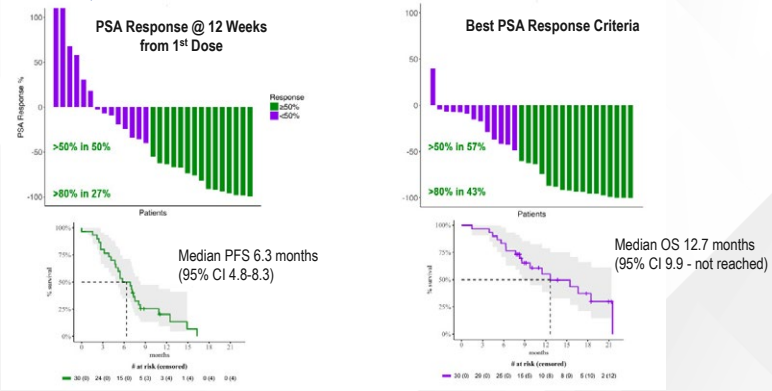
Patient Selection in Australian PSMA 617 Trials: PSMA and FDG PET/CT



PSMA, prostate-specific membrane antigen; FDG PET/CT, fluorodeoxyglucose-positron emission tomography.
Hofman et al. *J Clin Oncol*. 2020;38(15):5500.

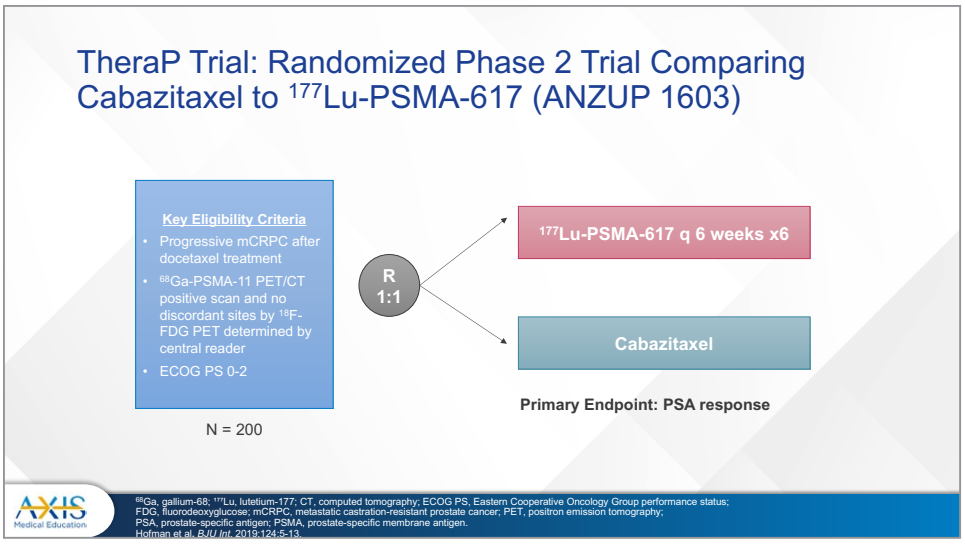
- Now, next—a hats off to the Australian group based at Peter Mac, partly led by Michael Hofman, but a number of very important collaborators at Peter Mac began to prospectively explore the PSMA-617 lutetium. They chose their patients in a way that was a little more complex than just using PSMA uptake. They were also looking at FDG uptake and looking for concordance and discordance. If the PSMA was positive, and there was no FDG uptake, well that patient was fine. If the FDG was positive, and there was no PSMA, well that patient would not be treated with a PSMA ligand. And if there was discordance between the scans, then the eligibility was in question, and typically for those individuals with FDG-positive lesions that were PSMA-negative, they did not want them to go on study.

LuPSMA Trial: ^{177}Lu-PSMA-617 in a Single-arm, Single-center, Phase 2 Trial

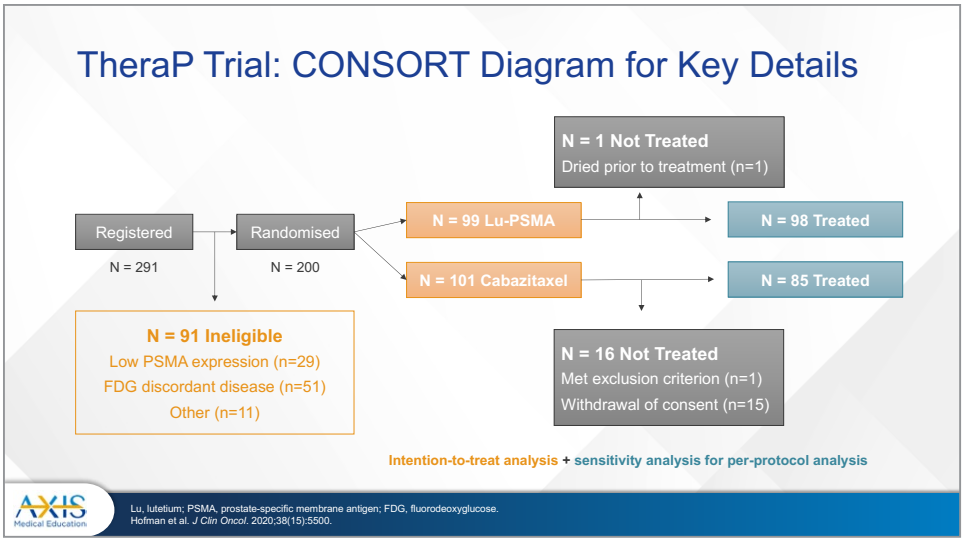


^{177}Lu-PSMA, lutetium-177–prostate-specific membrane antigen; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen.
Adapted from Hofman et al. *Lancet Oncol*. 2018;19:825-833.

- This is the original prospective phase 2 data, and you can see that on the left-hand side, PSA response—12 weeks from the first dose is really quite good. The best PSA response is very strong. Median time to progression was about 6.3 months, and that's quite good. This was an important study, defining the dose that was given, treating patients in a prospective manner.

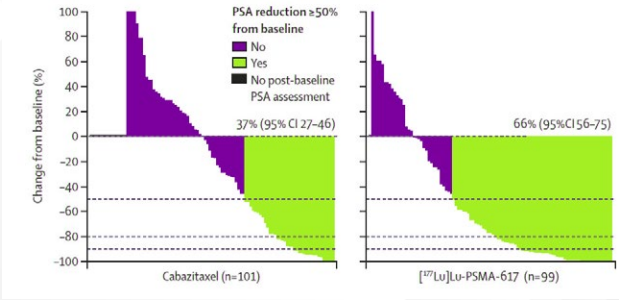


That, in turn, led the Australians to go to another trial. This was a randomized phase 2, that they call the TheraP trial. And here, they took individuals who were PSMA PET-positive, did not have FDG discordant lesions, all of whom had progressed after docetaxel and a novel hormone, and randomized them to either lutetium or the cabazitaxel, the primary endpoint of PSA response.



Well, it turned out that using the selection criteria in this particular trial, that they screened 291 patients to enroll 200, but 91 patients were excluded, either for low PSMA expression or FDG discordant disease, or a few other reasons. But you can see that low PSMA expression, in 10%—29 out of 291, and FDG discordant disease—51 out of 291—so there's a significant number of patients excluded from this particular trial.

[^{177} Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial

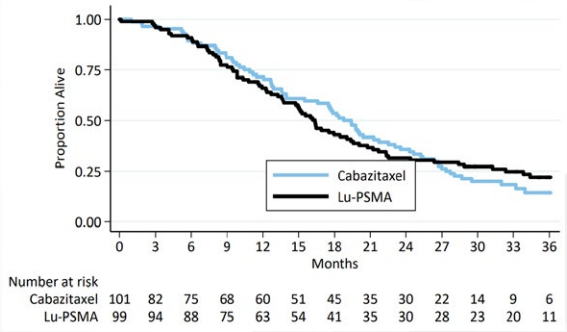


^{177}Lu, lutetium-177; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.
Adapted from Hofman et al. *Lancet* 2021;397:797-804.

- Now, this data has now been published in *Lancet* 2021, and you can see in this TheraP trial that there is a superiority of the PSA declines, with regard to PSMA lutetium, as compared to cabazitaxel.

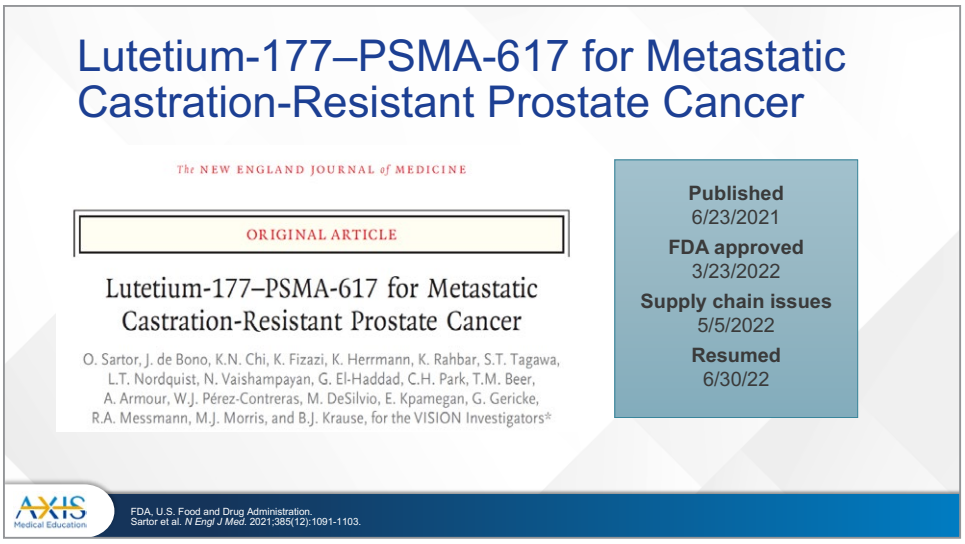
Survival in TheraP After 3 Years

- HR 0.97
- (95% CI, 0.70-1.4)
- *P* = .99
- Median not stated but approximately 17 months for ^{177}Lu-PSMA and approximately 20 months for cabazitaxel

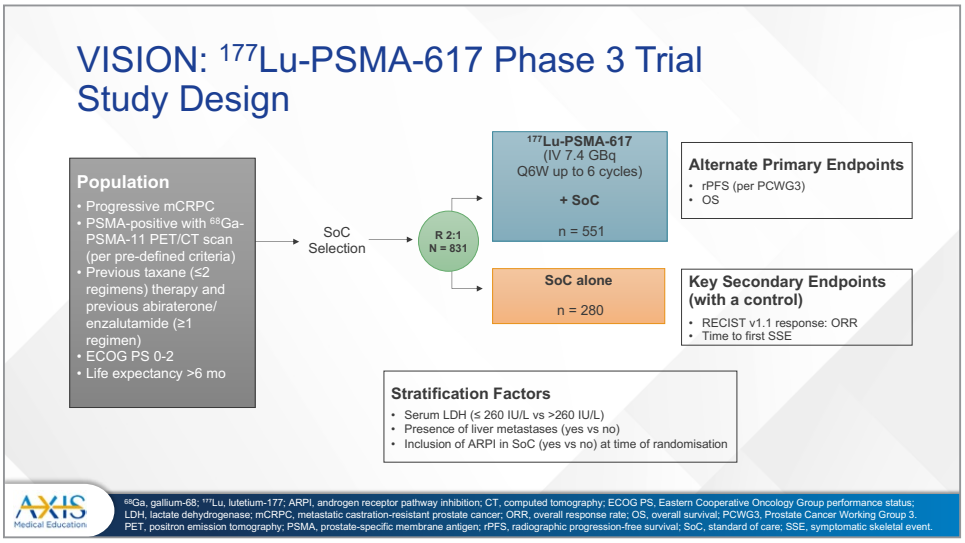


^{177}Lu, lutetium-177; PSMA, prostate-specific membrane antigen.
Hofman et al. *J Clin Oncol*. 2022;40(16):5000.

- But what we also know, very recently and presented at ASCO 2022, is that the survival between cabazitaxel and lutetium were essentially identical. Now this is a phase 2 trial. It's not really intended to be able to assess survival, and if you wanted to do formal trials for survival, you really would need larger numbers. But nevertheless, you can see in this particular trial after 3 years, that there really was not a distinction between the survival—between the lutetium PSMA and the cabazitaxel. Now, I will say that there was less side effects with the PSMA lutetium, and the authors concluded that the PSMA lutetium is preferable, given the superior adverse event profile.

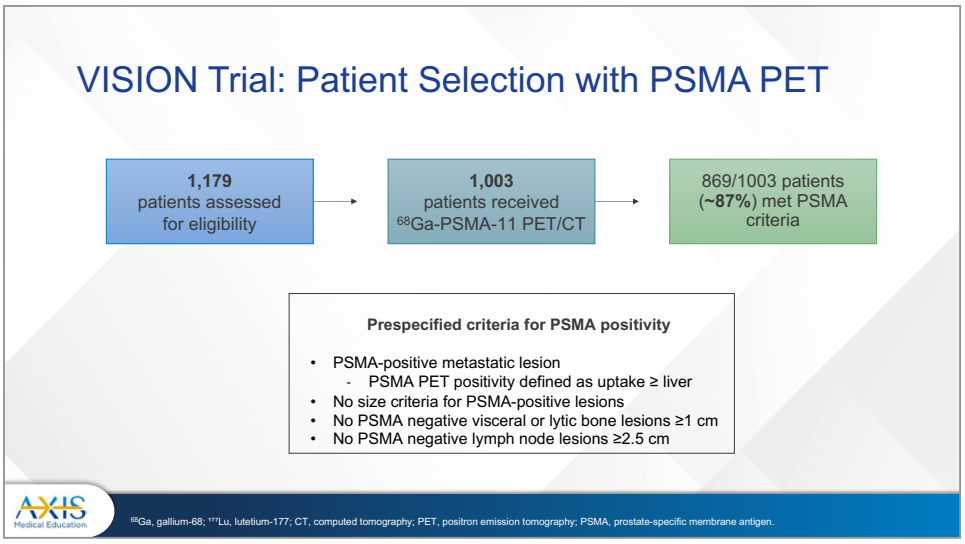


- Now, we now are going to go on to the phase 3 trial called the VISION trial. I was the co-PI, along with Bernd Krause, whom I mentioned earlier from Germany, and this was published June 23rd, leading to an FDA approval on March 23rd of 2022. But I should also make note of some supply chain problems, that came in the United States on May 5th. So, it's not all perfect here.



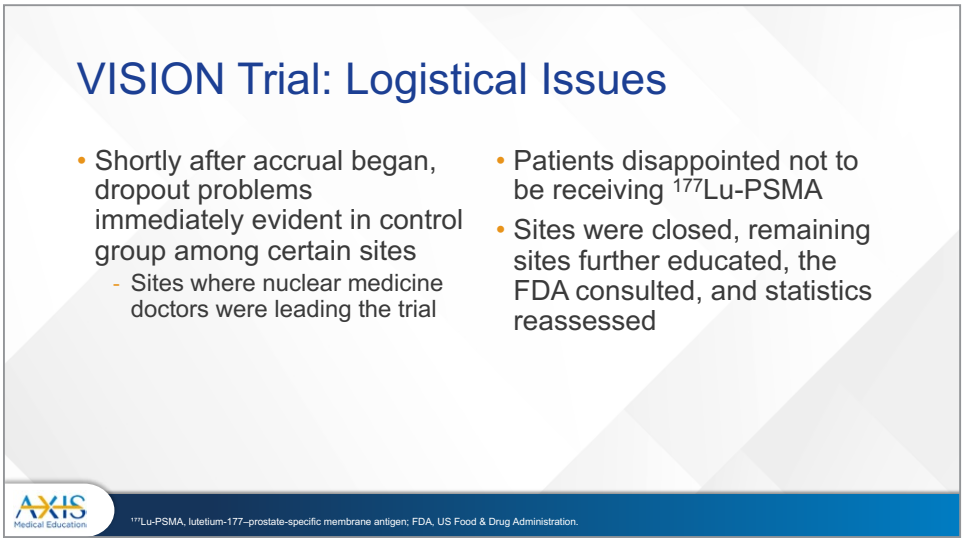
- Let's discuss the VISION trial, and how it was designed and what patients were included. First of all, everybody had to have metastatic CRPC by conventional imaging, and it had to be progressive. There had to be PSMA PET positivity with a gallium-68 PSMA-11 PET scan, and I'll come back to that in a second. There had to be treatment with at least 1 prior taxane, but up to 2, and at least 1 prior novel hormone, such as abiraterone and enzalutamide, and an ECOG performance status of 0 to 2, and a life expectancy of 6 months or more.

  The patients were randomized, 2 to 1, to receive the lutetium plus standard of care, or standard of care alone. And the standard of care selection was prespecified by the investigators. By the way, I should mention, this was a protocol-specified standard of care, and typically would consist of either abiraterone or enzalutamide, despite the prior exposure. There were alternate primary end points of rPFS and OS—radiographic progression-free survival—and a variety of secondary events as well, and then a variety of stratification factors.



So, if we look at the selection by PSMA PET, there were 1,179 patients assessed for eligibility, and 1,003 patients got the gallium-68 PSMA-11 PET scan. Of these patients, 87% met the PSMA PET criteria. And what did that mean? They had to have a PSMA PET-positive metastatic lesion, with uptake greater than liver, and there was no size criteria for the PSMA PET positivity. They could have no PSMA-negative, visceral, or lytic bone lesions greater than a centimeter. So, remember there's a CAT scan also being done.

If you had a liver lesion that was 1.5 centimeters, and on PSMA PET that was cold, then that meant less than liver, what you really needed to do was to exclude that patient, and the same thing was true for the lytic bone lesions, the same thing is true for PSMA-negative lymph node lesions greater than 2.5 centimeters. So very importantly, not only were patients chosen by PSMA PET, they were excluded if they were PSMA PET-negative and the CT scan showed a lesion.



Now, shortly after accrual began, dropout problems were immediately evident on the control side. So, it's typically in sites where nuclear medicine docs were leading the trial. Patients were disappointed not to be receiving the PSMA lutetium, and it actually turned into a bit of a mess. Sites had to be closed. The remaining sites were educated more. The FDA was consulted, and the statistics had to be reassessed.

VISION Trial: Baseline Patient Characteristics

Characteristic	Analysis Set for Imaging-Based Progression-free Survival (N = 581)		All Patients Who Underwent Randomization (N = 831)	
	^{177}Lu-PSMA-617 plus Standard Care (N = 385)	Standard Care Alone (N = 196)	^{177}Lu-PSMA-617 plus Standard Care (N = 551)	Standard Care Alone (N = 280)
Previous prostatectomy – no. (%)	159 (41.3)	82 (41.8)	240 (43.6)	130 (46.4)
Previous androgen-receptor–pathway inhibitor – no. (%)				
One regimen	213 (55.3)	98 (50.0)	298 (54.1)	128 (45.7)
Two regimens	150 (39.0)	86 (43.9)	213 (38.7)	128 (45.7)
More than two regimens	22 (5.7)	12 (6.1)	40 (7.3)	24 (8.6)
Previous taxane therapy – no. (%)				
One regimen	207 (53.8)	102 (52.0)	325 (59.0)	156 (55.7)
Two regimens	173 (44.9)	92 (46.9)	220 (39.9)	122 (43.6)
Docetaxel	377 (97.9)	191 (97.4)	534 (96.9)	273 (97.5)
Cabazitaxel	161 (41.8)	84 (42.9)	209 (37.9)	107 (38.2)

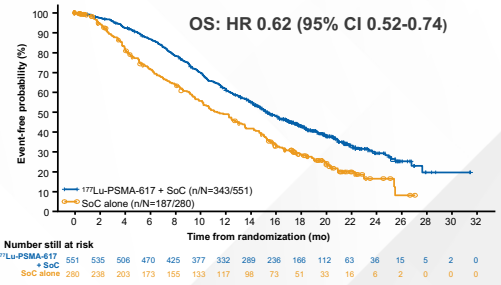
^{177}Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617.
Sartor et al. *N Engl J Med*. 2021;385:1091-1103.

And what this turns out—and if you go to the literature and you look at *The New England Journal*—what you see is two sets of patients. All of the patients who were randomized, and then a subsequent analysis for an image-based progression-free survival subset. All patients are 831, and the progression-free survival subset was 581. So, two different sets of patients, but for survival, it was really critical to do the intent-to-treat. And you can see here, these patients were heavily pretreated. Many of the patients had had 2 or even more than 2 regimens of androgen receptor pathway inhibitors—abiraterone, enzalutamide, apalutamide, et cetera. Around 40% of the patients had 2 regimens of taxane-based chemotherapy, and the second taxane was almost always cabazitaxel. So, these are very, very heavily pretreated patients.

VISION Trial: Primary Efficacy Outcomes Imaging-based OS

VISION met both primary endpoints of OS and rPFS

	^{177}Lu-PSMA-617 + SoC (n = 551)	SoC alone (n = 280)
Median OS, mo	15.3	11.3
HR (95% CI)	0.62 (0.52-0.74)	
***P*, one-sided**	<.001	



Note: OS positive (HR 0.63) in rPFS subset and rPFS positive (HR 0.43) in OS subset

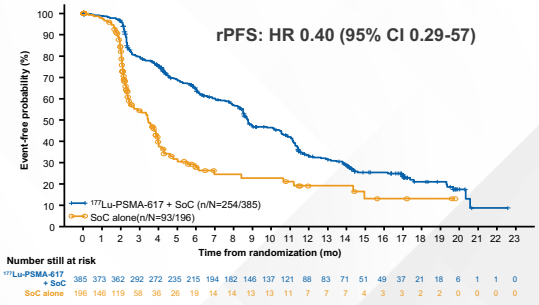
^{177}Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617; OS, overall survival; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival; SoC, standard of care.
Sartor et al. *N Engl J Med*. 2021;385:1091-1103.

Now, what was found? Remember, there are 2 primary endpoints. Primary endpoint number 1 is overall survival. Hazard ratio of 0.62. Confidence intervals not even close to 1—0.52 to 0.74.

VISION Trial: Primary Efficacy Outcomes Imaging-based PFS

VISION met both primary endpoints of OS and rPFS

	^{177}Lu-PSMA-617 + SoC (n = 385)	SoC alone (n = 186)
Median rPFS, mo	8.7	3.4
HR (95% CI)	0.40 (0.29-0.57)	
***P*, one-sided**	<.001	



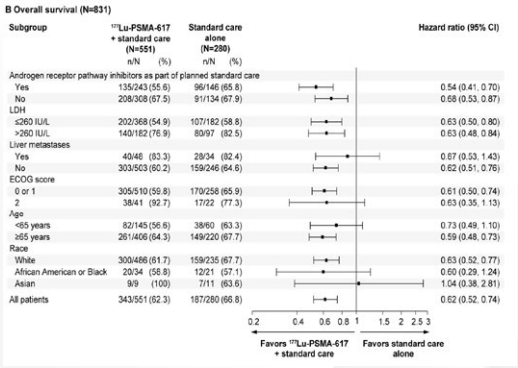
Note: OS positive (HR 0.63) in rPFS subset and rPFS positive (HR 0.43) in OS subset

^{177}Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617; OS, overall survival; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival; SoC, standard of care.
Sartor et al. *N Engl J Med.* 2021;385:1091-1103.

- The radiographic progression-free survival, and this was by criteria that was specified by the prostate cancer working group 2 and 3. The hazard ratio was 0.4. A positive trial on either endpoint.

  And by the way, if you look at the overall survival in that smaller rPFS subset, it's positive, with a hazard ratio of 0.63. And if you look at the rPFS in the overall survival subset, with this large group of patients, you still end up positive. So, it doesn't matter how you slice and dice the data. This is a positive trial.

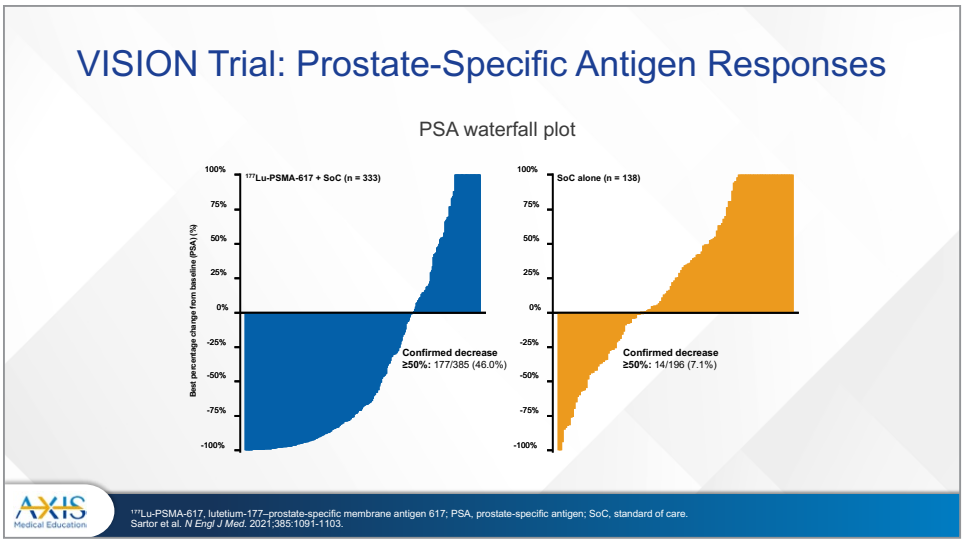
VISION Trial: Prespecified Subgroup Analyses of Imaging-based PFS and OS



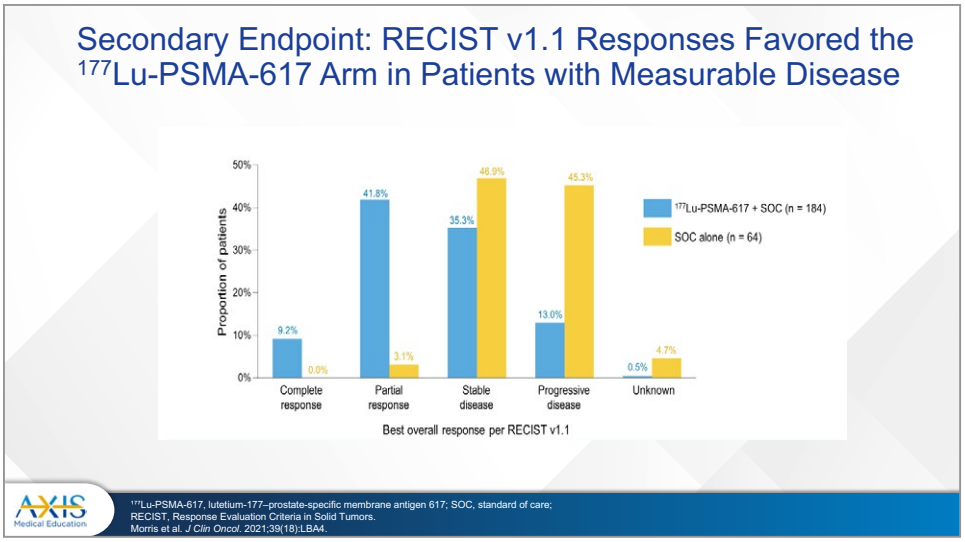
^{177}Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617; LDH, lactate dehydrogenase; ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival; OS, overall survival.
Sartor et al. *N Engl J Med.* 2021;385:1091-1103.

- Now when you look at overall survival, this is the Forest plot, and what you can see is by far the majority of the points are to the left of the 1.0 line, meaning they favored lutetium PSMA-617, but certain subsets were smaller, and not able to be fully analyzed. You know, you can see the confidence intervals were large when the number of patients in the treatment group were small. But, for instance, liver metastases, the hazard ratio was 0.87—not quite as good as those who had no liver metastasis. If you look at those less than age 65, it's a smaller subset. Hazard ratio of 0.73 is good. 0.59 in those more than 65 years old, or age 65.

  The Asian population was extremely small—only 20 patients. But there you can see that the hazard ratio is 1.04. I do not believe that is any relationship to lack of effect in Asians. I think it's just not poorly studied in the Asian population. Nevertheless, you can see that there is an overall survival benefit for all patients and most of the subsets clearly trend in the strong right direction.



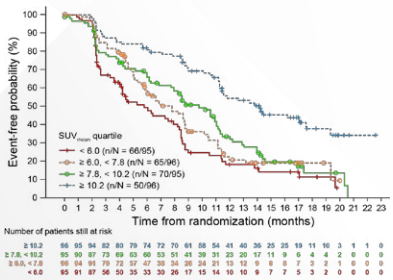
- For PSMA declines, as shown here on the PSA Waterfall plot, you can see PSA declines of more than 50% in 46% of the patients. Remember, this is not a therapy population. These patients all had cabazitaxel. The TheraP randomized trial was randomized with cabazitaxel and no prior pretreatments. These were a different group of patients, and you have to be clear about that. In the control group here, 7.1% of the patients had a PSA decline of 50% or more. There was also tumor shrinkage.



- This was presented at ASCO by Michael Morris, and you can see that the CR rate for those receiving lutetium was about 9.2%, the PR rate about 41.8—added together, about 50% of the patients that were assessable actually had a decrease in their measurable disease by criteria dictated from RESIST.

rPFS by Whole-body SUVmean Quartiles (PFS-FAS)

Higher whole-body SUV_{mean} was associated with prolonged rPFS



SUV_{mean} quartile	Median rPFS (mo)
≥10.2 (highest)	14.1
≥7.8, <10.2	9.8
≥6.0, <7.8	7.8
<6.0 (lowest)	5.8

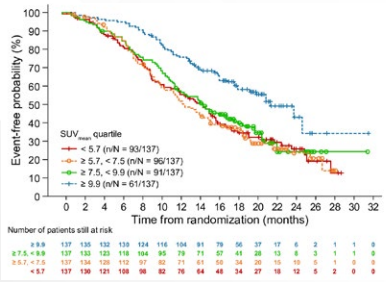
SUV_{mean}	rPFS
	HR [95% CI], *P*
Univariate analysis	**0.88** [0.84-0.91], <.001
Multivariate analysis	**0.86** [0.82-0.90], <.001

PFS-FAS, progression-free survival-full analysis set; rPFS, radiographic progression-free survival; SUV, standardized uptake value.
Kuo et al. *J Clin Oncol.* 2022;40:5002.

- Now, one of the things that's interesting is that when you look at whole body SUV mean, and this is looking at totality of the tumor uptake, that there is a pretty good correlation between the higher PSMA uptake—and this is by the PSMA PET scan—and the rPFS.

OS by Whole-body SUVmean Quartiles (FAS)

Higher whole-body SUV_{mean} was associated with improved OS



SUV_{mean} quartile	Median OS (mo)
≥9.9 (highest)	21.4
≥7.5, <9.9	14.6
≥5.7, <7.5	12.6
<5.7 (lowest)	14.5

SUV_{mean}	OS
	HR [95% CI], *P*
Univariate analysis	**0.92** [0.89-0.95], <.001
Multivariate analysis	**0.88** [0.84-0.91], <.001

FAS, full-analysis set; OS, overall survival; SUV, standardized uptake value.
Kuo et al. *J Clin Oncol.* 2022;40:5002.

- But if we look at the overall survival, the groups that were a little less avid by the SUV mean—remember, this is PSMA-11 SUV mean—that these were all pretty similar, whereas the highest quartile did extremely well, the median overall survival being 21.4 months for those with the highest PSMA uptake.

VISION Trial: Adverse Events

TEAEs Occurring in ≥5% of Patients, n (%)	Safety Set (N = 734)			
	All Grades		Grade 3-5	
	^{177}Lu-PSMA-617 + SoC (n = 529)	SoC alone (n = 205)	^{177}Lu-PSMA-617 + SoC (n = 529)	SoC alone (n = 205)
Fatigue	228 (43.1)	47 (22.9)	31 (5.9)	3 (1.5)
Dry mouth	205 (38.8)	1 (0.5)	0	0
Nausea	187 (35.3)	34 (16.6)	7 (1.3)	1 (0.5)
Anaemia	168 (31.8)	27 (13.2)	68 (12.9)	10 (4.9)
Back pain	124 (23.4)	30 (14.6)	17 (3.2)	7 (3.4)
Arthralgia	118 (22.3)	26 (12.7)	6 (1.1)	1 (0.5)
Decreased appetite	112 (21.2)	30 (14.6)	10 (1.9)	1 (0.5)
Constipation	107 (20.2)	23 (11.2)	6 (1.1)	1 (0.5)
Diarrhea	100 (18.9)	6 (2.9)	4 (0.8)	1 (0.5)
Vomiting	100 (18.9)	13 (6.3)	5 (0.9)	1 (0.5)
Thrombocytopaenia	91 (17.2)	9 (4.4)	42 (7.9)	2 (1.0)
Lymphopaenia	75 (14.2)	8 (3.9)	41 (7.8)	1 (0.5)
Leukopaenia	66 (12.5)	4 (2.0)	13 (2.5)	1 (0.5)

^{177}Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617; SoC, standard of care; TEAEs, treatment-emergent adverse effects.
Sartor et al. *N Engl J Med*. 2021;385:1091-1103.

If we look at the side effects from VISION—fatigue, dry mouth, nausea, some anemia, back pain and arthralgias—but please remember that the patients were observed for a longer time on the lutetium. They were alive longer, and took longer to progress, so some of these differences may be, in part, due to the fact that patients were followed for a longer period of time. Nevertheless, dry mouth is an unequivocal side effect from PSMA lutetium. Some of these patients can have nausea. Some can get anemia, some can be fatigued, and these are things that we need to be concerned about when treating our patients, as well as some thrombocytopenia.

What We Know From VISION

- ^{177}Lu-PSMA-617 is effective and well tolerated in heavily pretreated mCRPC
- The trial would have been positive without patient selection using PSMA PET
  - OS HR 0.62 (95% CI 0.52-0.74)
- Nuclear medicine sites not well partnered with oncology had difficulty managing the control group in this randomized trial
  - Multidisciplinary care is **required!!!**
- This therapy will be adopted rapidly after regulatory approvals and will be used earlier in the treatment paradigm
- March 2022: FDA approved lutetium-177 vipivotide tetraxetan for the treatment of adult patients with PSMA-positive mCRPC who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy

^{177}Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617; FDA, US Food & Drug Administration; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; SoC, standard of care.

Now, what do we know from VISION? We know that PSMA lutetium-617 is effective and well-tolerated in heavily pretreated patients. We know that, in all likelihood, the trial would have been positive, even without PSMA PET selection. We also know that nuclear medicine sites, not well-partnered with oncology, had difficulty managing the control group, and I believe that multidisciplinary care is required. This therapy will be rapidly adopted after regulatory approvals, and we have that now, and likely it will move earlier into the treatment paradigm, and there are trials looking at that now.

What We Do Not Know From VISION

- What is the optimal patient selection criteria when using PSMA PET? FDG PET?
- What is the optimal dose and schedule for this therapy?
- What is the relationship between PSA progression and/or response and survival benefit?
  - Extremely good!!!
- Can re-treatment at progression make a positive impact?
- Does treatment with "SoC" + ^{177}Lu-PSMA-617 add to that of the isotope alone?
- What about trials in the pre-chemotherapy space?
- What type of therapies might be synergistically combined with this therapy?

AXIS Medical Education

^{177}Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617; FDG, fluorodeoxyglucose; PET, positron emission tomography; PSA, prostate-specific antigen; SoC, standard of care.

Now what do we not know from VISION? I don't think we know yet the optimal PSMA PET selection criteria. We don't really know if FDG/PET should be used. Interestingly, we don't know the optimal dose and schedule for this therapy. We don't fully understand the relationship between PSA progression, PSA response, and survival. But I'm telling you, preliminary data look fairly good – wait till ESMO. We don't know anything about retreatment at progression. We don't know about standard of care, and to what extent standard of care really adds to the PSMA of lutetium. It did look a little better for those being treated with the combination of – of the advanced hormonal agents plus lutetium, as compared to lutetium alone, but that is a conjectural statement, not a definitive statement.

New Important Trials in Metastatic Prostate Cancers

Trial Name	Phase	Prostate Cancer Type	Details
PSMAfore	3	mCRPC	Open-label, Multi-Center, Randomized Study Comparing ^{177}Lu-PSMA-617 vs. a Change of Androgen Receptor-directed Therapy in the Treatment of Taxane Naïve Men With Progressive mCRPC
SPLASH	3	mCRPC	Open-Label, Randomized Study Evaluating Metastatic Castrate Resistant Prostate Cancer Treatment Using PSMA [Lu-177]-PNT2002 Therapy After Second-line Hormonal Treatment
ECLIPSe	3	mCRPC	Open-Label, Multi-Center, Randomized Trial Comparing the Safety and Efficacy of ^{177}Lu-PSMA-I&T Versus Hormone Therapy in Patients With mCRPC
PSMAddition	3	mHSPC	International Prospective Open-label, Randomized, Study Comparing ^{177}Lu-PSMA-617 in Combination With SoC, Versus SoC Alone, in mHSPC

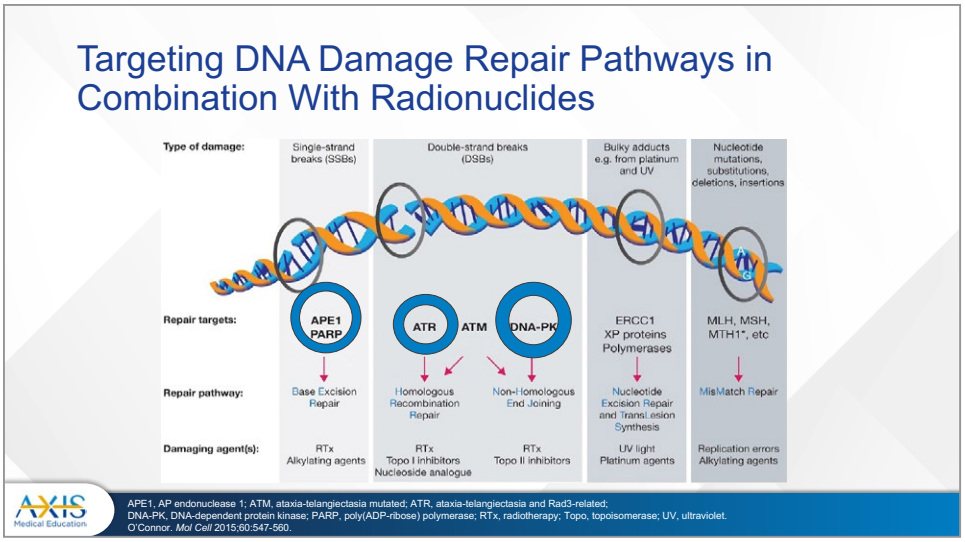
AXIS Medical Education

^{177}Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617; mHSPC, metastatic hormone-sensitive prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; SoC, standard of care.

We have trials that are ongoing in the pre-chemo space, but we don't know about that space yet. We don't know a lot about how we can combine this set of trials. Now we do have some important trials in the metastatic CRPC setting. PSMAfore, SPLASH and ECLIPSe are all looking at metastatic CRPC, PSMA PET-positive patients who are going to be getting PSMA lutetium versus a second-line hormonal agent, and all of these trials are in accrual right now.

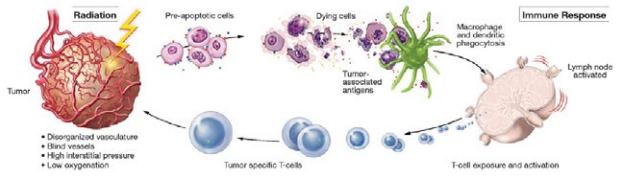
We also know that there is a trial called PSMAddition. And this is a prospective open-label study, looking at hormone-sensitive prostate cancer standard of care versus the PSMA lutetium plus standard of care. Very, very important trial for metastatic, hormone-sensitive patients, and this trial is now ongoing.

- We have many questions about synergistic opportunities for radiopharmaceuticals.



- Number 1, since the lutetium and other radiopharmaceuticals damage DNA, what would happen if you inhibited DNA repair pathways? What about a PARP inhibitor, an ATR inhibitor, an ATM inhibitor, or a DNA-P kinase inhibitor? And we really don't know about synergy in this setting. We think that there could be synergy, and there are now phase 1 studies that are ongoing with the PARP inhibitors, in particular, in combination with PSMA lutetium.

Antigen Release From Radiated Tumor: Synergy With Immunotherapies?



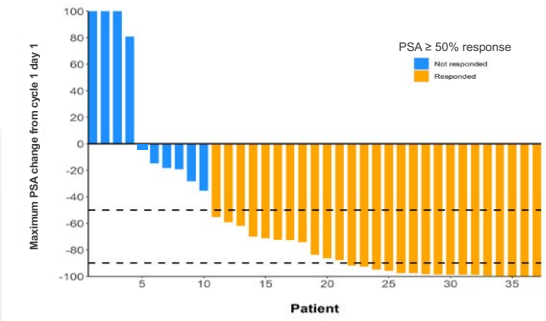
Systemic/local immune enhancement

- Vaccine
- Checkpoint Inhibitors
  - Anti-CTLA-4
  - Anti-PD-L1
  - Anti-PD-1
  - Anti-TIM3
- Co-stimulatory agonists
  - Anti-OX40
  - Anti-4-1BB
  - Anti-GITR
  - Anti-CD27
  - Anti-CD40
- Exogenous Cytokines
  - IL-2
  - IL-7
  - IL-12
  - IL-15
  - IL-21
  - GM-CSF

CTLA, cytotoxic T-lymphocyte–associated antigen; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1.
Kamrava et al. *Mol BioSyst* 2009;5:1249-1372.

- There is also a question about antigen release from radiated tumors, and potential synergy with immunotherapy.

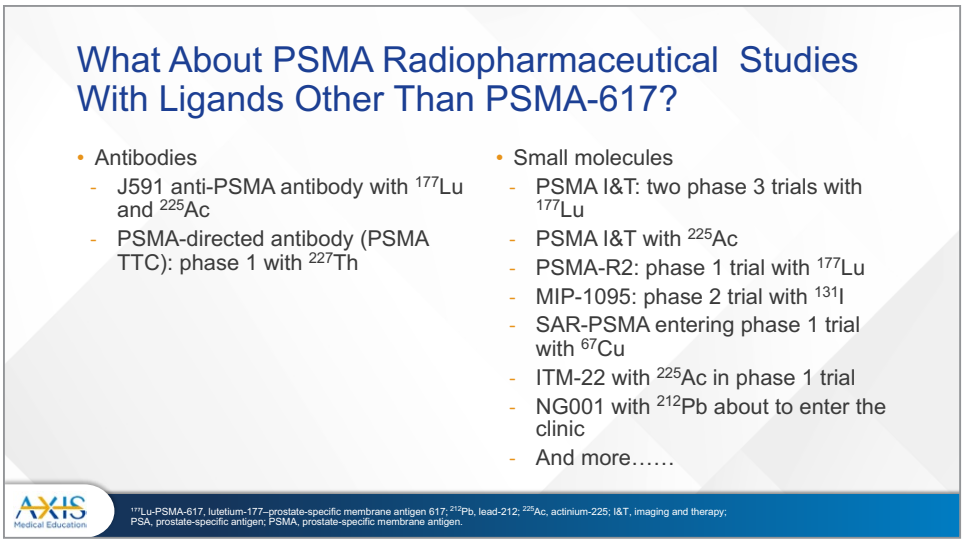
Waterfall Plot for PSA Declines on PRINCE Trial: ^{177}Lu-PSMA-617 + Pembrolizumab



This may be selection bias

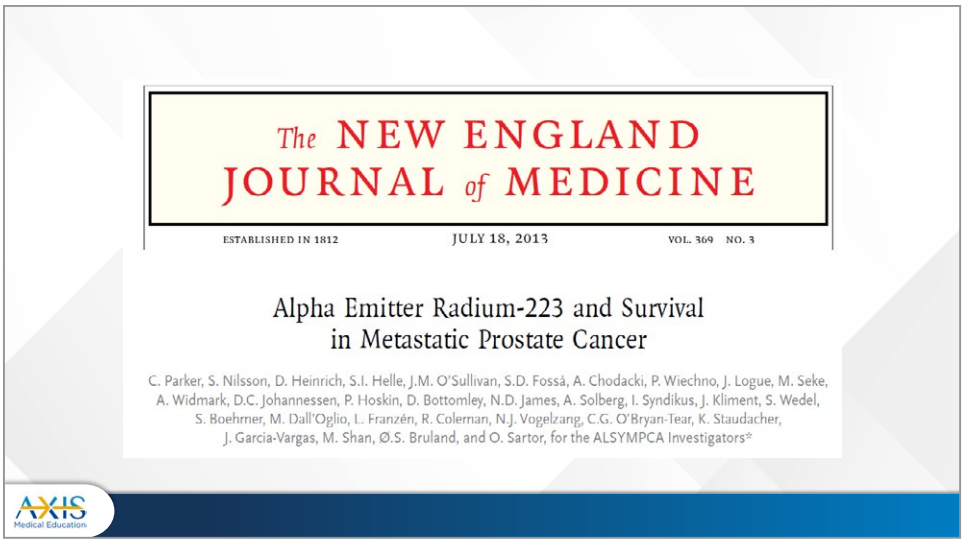
^{177}Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617; PSA, prostate-specific antigen.
Sandhu et al. *Ann Oncol.* 2021;32:S626-S677.

- As it turns out, that there are initial reports that look at the combination of PSMA lutetium and pembrolizumab, a PD-1 inhibitor in immunotherapy, but we don't really have comparative data, and I'm not willing to say at this point that this is better than PSMA lutetium alone. It's certainly better than pembrolizumab alone, but there could be some selection bias in the way the patients were chosen. So, small phase 2s always have to be interpreted with caution.

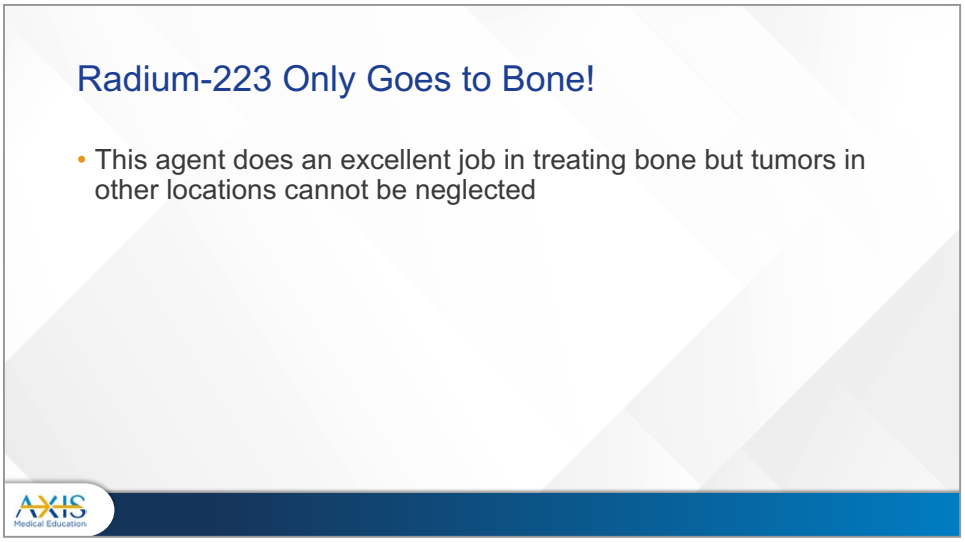


- Now, what about PSMA radiopharmaceutical studies with ligands other than PSMA-617? I mentioned the ECLIPSE trial and the SPLASH trial. Those are being conducted with PSMA I&T. But they're also antibodies, such as J591, and another antibody called PSMA-TTC, that have been looked at in phase 1. And then, in addition to PSMA I&T, there are also other small molecules, such as R2, 1095, an agent called SAR-PSMA, or ITM22 and NG001, and there are a variety of isotopes. And so, this is an interesting and rapidly evolving space.

- Now it turns out that Dr. Kendi had mentioned the alpha particles. I also wanted to mention alphas.



- This harkens back to the use of radium-223, which can prolong survival in metastatic prostate cancer, but here you're targeting only the bone.



- And because radium only goes to bone, the tumors in the other locations cannot be neglected. Yet, that's what we have with radium therapy alone.

Alphas

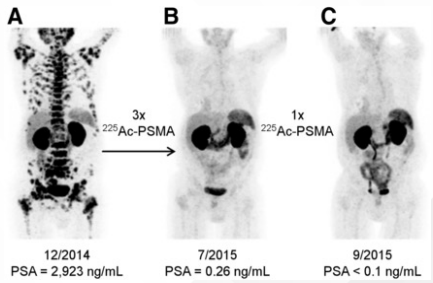
Radionuclide	Chelate	Half life	Total alpha	"Long lived" Intermediate	Final
Terbium-149	DOTA	4.1 hours	1 alpha		Nd-145
Astatine-211	Various	7.2 hours	1 alpha		Pb-207
Bismuth-212	C-DEPA/ DTPA/DOTA	61 minutes	1 alpha 1 beta		Pb-208
Lead-212	TCMC and more	10.6 hours	1 alpha 2 beta		Pb-208
Bismuth-213	C-DEPA/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

AXIS Medical Education

- Now, there are a whole series of alphas that are under investigation. Dr. Kendi had mentioned actinium-225, and that's one of my favorites as well. We've also done studies with thorium-227. By the way, radium-223 is very, very difficult to chelate, so we don't have a way of chelating radium at this time. But there are studies that are being planned with lead-212. There's studies that have been performed with bismuth-212. Terbium-149 and astatine-211 are also of potential interest.

Radio-Conjugates: PSMA-Targeted Alpha Emitters (Actinium-225) as Ninth-Line Treatment

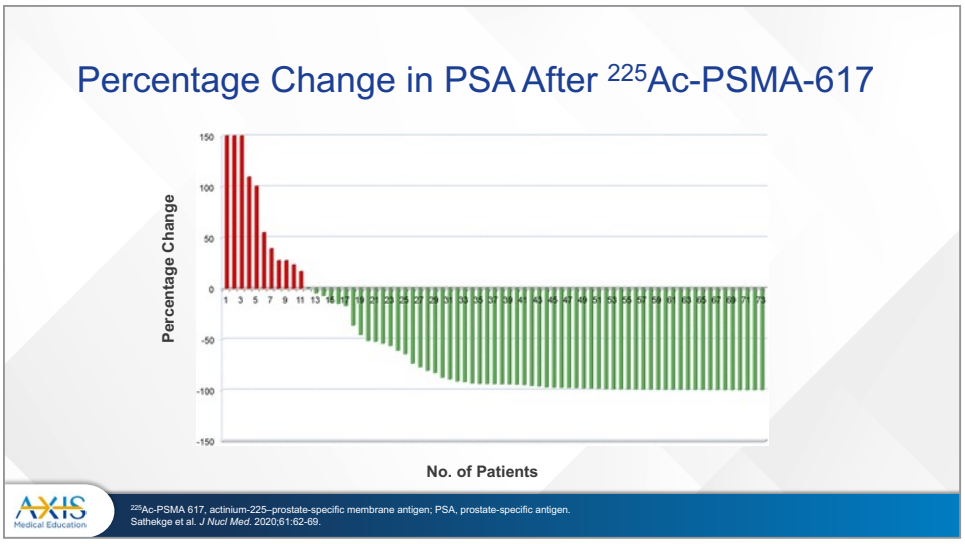
Patient A
Leuprorelin
Zoledronate
Docetaxel (50 cycles)
Carmustine/epirubicin in hyperthermia
Abiraterone
Enzalutamide
^{223}Ra (6 cycles)
Abiraterone reexposition
Estramustine



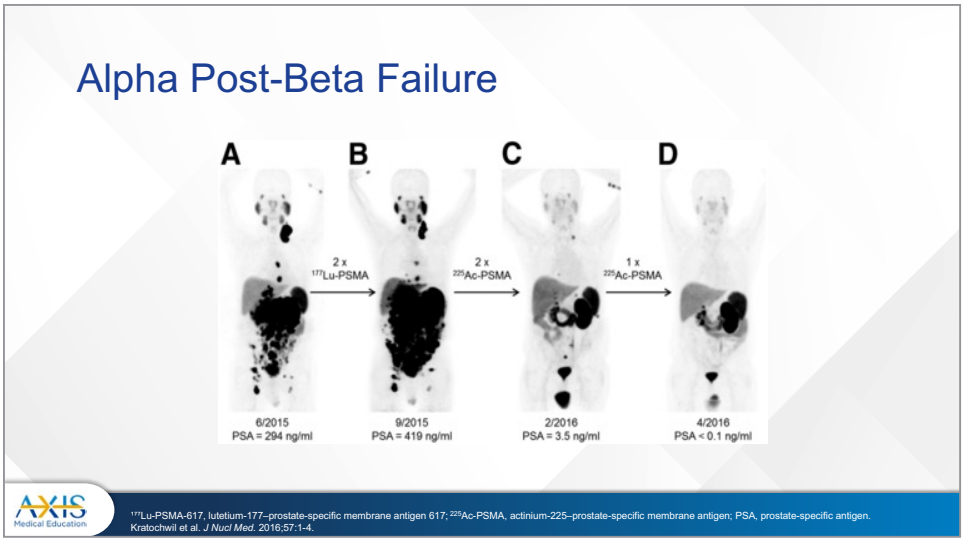
AXIS Medical Education

^{225}Ac-PSMA, actinium-225–prostate-specific membrane antigen; ^{223}Ra, radium-223; PSA, prostate-specific antigen.
Kratochwil et al. *J Nucl Med.* 2016;57:1-4.

- Now, it turns out that PSMA-targeted alpha therapy, with actinium-225 and here is PSMA-617, has the capacity to be very, very active in a subset of patients, but salivary gland toxicity has been rate limiting.



- There is also data from South Africa, and this is from University of Pretoria by Dr. Mike Sathekge, looking at the actinium-225, PSMA-617. It is highly active but again, there's some salivary issues, and these were not necessarily refractory patients. These were patients who may not have previously received chemotherapy or novel hormones.



- There was a mention of alphas post-beta failure, and here's an example from the German group at Heidelberg, using alphas after therapy had failed with PSMA lutetium, and getting an excellent response.

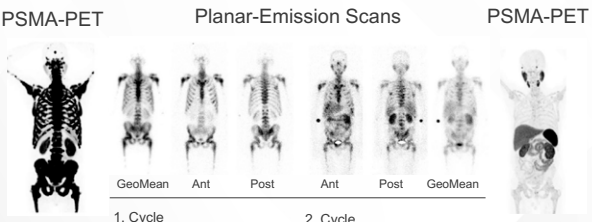
Current "Combination" Explorations

- Isotopes: Alphas and Betas in combination
- Isotopes and various hormonal therapies
  - Novartis "mHSPC" phase 3 trial
- Isotopes and PARPi and other inhibitors of DNA repair
- Isotopes and high-dose testosterone
- Isotopes and 5-FU infusion low dose (radiosensitizer)
- Isotopes and immunotherapy (anti-PD-1, etc)

5-FU, 5-fluorouracil; mHSPC, metastatic hormone-sensitive prostate cancer; PARPi, pol (ADP-ribose) polymerase inhibitor; PD-1, programmed cell death protein 1.

- And looking at combinations, which was also mentioned by Dr. Kendi. Alphas and betas in combinations, isotopes in various hormonal combinations, PARP inhibitors and other inhibitors of DNA repair. It's been an interesting concept around isotopes and high-dose testosterone. Isotopes in 5-FU infusion, which is radiosensitizer. Isotopes in immunotherapy, which I mentioned. So, lots of ways to project this into the future.

Alpha/Beta Combo



1. Cycle
[1.5 GBq ^{177}Lu-PSMA+ 8 MBq ^{225}Ac-PSMA]

2. Cycle
[2 GBq ^{177}Lu-PSMA+ 6 MBq ^{225}Ac-PSMA]

Lab test:
[prior PSMA-Tx]

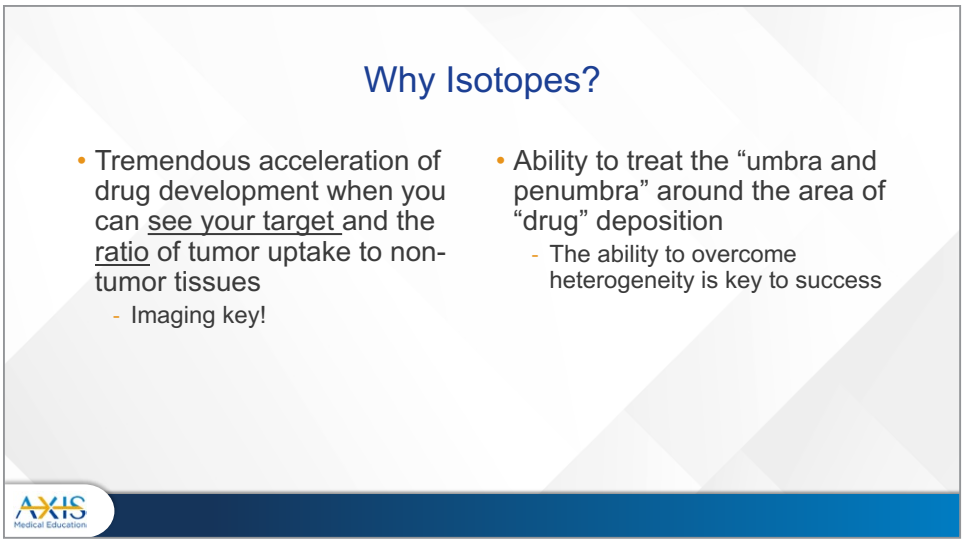
PSA 722.5 / AP 639
LDH 425 / PLT 55 / Hb 6.8
Leucoerythroblastic cell-count:
10% Progenitor cells (1% meta myelocytes, 7% myelocytes, 2% blasts)

Lab test:
[after PSMA-Tx]

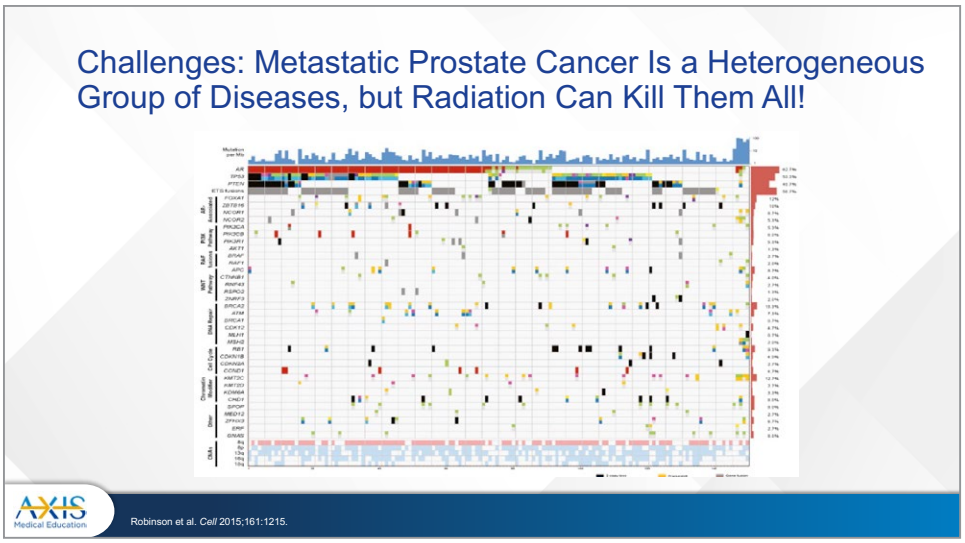
PSA 0.4 / AP 144
LDH 232 / PLT 146 / Hb 9.7
Leucoerythroblastic cell-count:
0% Progenitor cells

^{177}Lu-PSMA-617, lutetium-177–prostate-specific membrane antigen 617; ^{225}Ac-PSMA, actinium-225–prostate-specific membrane antigen; AP, alkaline phosphatase; Hb, hemoglobin; LDH, lactate dehydrogenase; PET, positron emission tomography; PLT, platelets; PSA, prostate-specific antigen; Tx, treatment.
Kratochwil et al. *Semin Nucl Med*. 2020;50:133-140.

- These alpha-beta combos are particularly interesting. Here, you can diminish the salivary damage, and hopefully provide some better effect than just the beta alone, but we need to think in more detail.



One of the things that I think needs to be addressed, is why isotopes? I think you can tremendously accelerate drug development when you can see your target and look at the ratio of tumor uptake to nontumor tissue. You can image your target, and then when you treat, it's not just the individual cell, but also what I call the umbra and penumbra—the area around the drug deposition site. This helps to overcome heterogeneity. When you use an isotope, you get into the tumor, and you can potentially kill the cell to which it binds, but you may also kill surrounding cells including the microenvironment in the stroma.



Metastatic prostate cancer is a heterogenous group of diseases, but radiation can kill them all, and that is one of the reasons why I've devoted a substantial portion of my own career to trying to improve patient care through the use of molecularly targeted radiation.

FACULTY DISCUSSION

Dr. Sartor: I might like to mention a case, that I think is quite interesting. As with any therapy, there are patients who do well, and patients who do less well. One of the more interesting patients I've seen and just completed three cycles of therapy with PSMA lutetium, was a patient who had a somatic *BRCA2* mutation, detected on his circulating tumor DNA. After his initial response, he had about a 90% decline in PSA, and after 2 treatments, he had a 99% decline in PSA, and it was now less than 1. As it turned out, we were looking at serial circulating tumor DNA markers. And what we could see was the disappearance of the *BRCA2* somatic clone. Now, we've all known that *BRCA2* mutations predispose to DNA damaging agents, and this type of therapy is going to be exploited with the use of things like carboplatin, cyclophosphamide. But now, we have clear evidence that lutetium-177 may be especially active in those individuals with *BRCA* mutations, which in turn predispose to damage from DNA-damaging agents. So, an interesting little vignette.

One of the things that I think is important is a team-based approach toward theranostics, when you're treating the advanced patient with prostate cancer. It turns out that advanced prostate cancer patients have many potential complications. They have issues with pain, anemia, thrombocytopenia, may have difficulty with bone metastasis, and as we have done at Tulane, I have found it most productive to work as a team with my colleagues, and I wonder if you might mention how that works at Mayo Clinic, because I know that you guys have a fantastic team up there as well.

Dr. Kendi: Thank you, Dr. Sartor. I echo with what you mentioned, especially the care of the patients at advanced stages with multiple comorbidities. You have to have the teamwork at any point, but that is most important in this patient population, and at Mayo Clinic, since the start of VISION trial, we formed already a team that we are working together, collaborating together, and this is going on after FDA approval as well. This team includes people from nuclear medicine with dedicated interest to nuclear therapies. This includes people from urology, radiation oncology, and also team members from medical oncology, as well as, if needed, from surgery, nephrology and orthopedics, depending on patient's condition and the needs. And we decided to have biweekly meetings to discuss patients. In our initial few meetings, we decided to have presentations about the treatment, and we make our protocols together, and we decided to move forward everything together with this – within these meetings with decisions made together. And after that, now we are reviewing cases with that needs discussions in these meetings with our colleagues together. This meeting is led by nuclear medicine team, but everybody from all the other departments are joining; these patients need care from all of us, and it is not like a one-sided approach. It is just combination of all the expertise coming together with the patient in the centers.

For example, these patients are coming after heavy treatments with other therapies. And with the chemotherapy and radiation therapy, immunotherapy, and we definitely look at the medications and recent history and we go through these in details. In addition, some of the patients – the burden of the disease can be concerning for possible fractures, or spinal canal compromise. We always review, we have some of our patients who needed extra review by orthopedics team to make sure we can proceed with the therapy and if needed to prevent any impending fractures, if there is any intervention is needed we get consults for these patients. In addition, sometimes lymph nodes and some of the pelvic disease may cause a urinary tract obstruction. You have to be careful about the kidney function as well as you should check the patency of the ureters, making sure there is no hydronephrosis. If there is hydronephrosis, you need to fix that with nephrostomy, or ureteral stent placement before moving with the treatment. These are a few things I wanted to mention.

Dr. Sartor: That's wonderful, and you're very fortunate to be able to have such a multidisciplinary team. And of course, I think we all know the reputation of Mayo Clinic and excellence in patient care, so thank you for sharing.

Dr. Kendi: Thank you so much, Dr. Sartor.

Dr. Sartor: Thank you very much.

REFERENCES

American Cancer Society. Cancer facts & figures 2022. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2022/2022-cancer-facts-and-figures.pdf.

American Cancer Society. January 12, 2022. Key statistics for prostate cancer. https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html

Chatalic KLS, Heskamp S, Konijnenberg M, et al. Towards personalized treatment of prostate cancer: PSMA I&T, a promising prostate-specific membrane antigen-targeted theranostic agent. *Theragnostics* 2016;6:849-861.

Evans JC, Malhotra M, Cryan JF, O-Driscoll CM. The therapeutic and diagnostic potential of the prostate specific membrane antigen/glutamate carboxypeptidase II (PSMA/GCPII) in cancer and neurological disease. *Br J Pharmacol.* 2016;173:3041-3079.

Ferreira G, Iravani A, Hofman MS, Hicks RJ. Intra-individual comparison of ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL normal-organ biodistribution. *Cancer Imaging* 2019;19(1):23.

Frangos S, Buscombe JR. Why should we be concerned about a "g"? *Eur J Nucl Med Mol Imaging* 2019;46:519.

Hofman MS, Lau WFE, Hicks RJ. Somatostatin receptor imaging with 68Ga DOTATATE PET/CT: clinical utility, normal patterns, pearls, and pitfalls in interpretation. *Radiographics* 2015;35:500-516.

Hofman MS, Lawrentschuk N, Francis RJ, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. *Lancet* 2020;395:1208-1216.

Hofman MS, Emmett L, Sandhu SK, et al. TheraP: a randomised phase II trial of ^{177}Lu-PSMA-617 theranostic versus cabazitaxel in metastatic castration resistant prostate cancer progressing after docetaxel: initial results (ANZUP protocol 1603). *J Clin Oncol.* 2020;38(15):5500.

Hofman MS, Violet J, Hicks RJ, et al. [^{177}Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. *Lancet Oncol.* 2018;19:825-833.

Hofman MS, Emmett L, Violet J, et al. TheraP: a randomized phase 2 trial of (177) Lu-PSMA-617 theranostic treatment vs cabazitaxel in progressive metastatic castration-resistant prostate cancer (Clinical Trial Protocol ANZUP 1603). *BJU Int.* 2019;124:5-13.

Hofman MS, Emmett L, Sandhu S, et al for the TheraP Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group. [^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. *Lancet* 2021;397:797-804.

Hofman MS, Emmett L, Sandhu S, et al. TheraP: ^{177}Lu-PSMA-617 (LuPSMA) versus cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel—Overall survival after median follow-up of 3 years (ANZUP 1603). *J Clin Oncol.* 2022;40(16):5000.

Jadvar H, Calais J, Fanti S, et al. Appropriate use criteria for prostate-specific membrane antigen PET imaging. *J Nucl Med.* 2022;63:59-68.

Kamrava M, Bernstrein MB, Camphausen K, Hodge JW. Combining radiation, immunotherapy, and antiangiogenesis agents in the management of cancer: the Three Musketeers or just another quixotic combination? *Mol BioSyst.* 2009;5:1249-1372.

Khreish F, Ebert N, Ries M, et al. ^{225}Ac-PSMA-617/ ^{177}Lu-PSMA-617 tandem therapy of metastatic castration-resistant prostate cancer: pilot experience. *Eur J Nucl Med Mol Imaging* 2020;47:721-728.

Kratochwil C, Bruchertseifer F, Giesel FL, et al. ^{225}Ac-PSMA-617 for PSMA-targeted α-radiation therapy of metastatic castration-resistant prostate cancer. *J Nucl Med*. 2016;57:1-4.

Kratochwil C, Haberkorn U, Giesel FL. ^{225}Ac-PSMA-617 for therapy of prostate cancer. *J Semin Nucl Med*. 2020;50(2):133-140.

Kulkarni HR, Singh A, Schuchardt C, et al. PSMA-based radioligand therapy for metastatic castration-resistant prostate cancer: the bad berka experience since 2013. *J Nucl Med*. 2016;57(suppl 3):97S-104S.

Kumar AS, Hofman MS. Mechanistic insights for optimizing PSMA radioligand therapy. *Clin Cancer Res*. 2020;26:2774-2776.

Kumar R, Shin WS, Sunwoo K, et al. Small conjugate-based theranostic agents: An encouraging approach for cancer therapy. *Chem Soc Rev*. 2015;44:6670-6683.

Kuo P, Hesterman J, Rahbar K, et al. [^{68}Ga]Ga-PSMA-11 PET baseline imaging as a prognostic tool for clinical outcomes to [^{177}Lu]Lu-PSMA-617 in patients with mCRPC: a VISION substudy. *J Clin Oncol.* 2022;40:5002.

Lawhn-Health C, Salavati A, Behr SC, et al. Prostate-specific membrane antigen PET in prostate cancer. *Radiology* 2021;299:248-260.

Miyahira AK, Pienta KJ, Babich JW, et al. Meeting report from the Prostate Cancer Foundation PSMA theranostics state of the science meeting. *Prostate* 2020;80:1273-1296.

Morris MJ, De Bono JS, Chi KN, et al. Phase III study of lutetium-177-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION). *J Clin Oncol*. 2021;39(18):LBA4.

Morris MJ, Rowe SP, Gorin MA, et al. Diagnostic performance of ^{18}F-DCFPyL-PET/CT in men with biochemically recurrent prostate cancer: results from the CONDOR phase III, multicenter study. *Clin Cancer Res*. 2021;27(13):3674-3682.

O'Connor MJ. Targeting the DNA damage response in cancer. *Mol Cell* 2015;60:547-560.

Parker C, Nilsson S, Heinrich D, et al. Alpha emitter Radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369:213-223.

Rahbar K, Ahmadzadehfar J, Kratochwil C, et al. German multicenter study investigating ^{177}Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients. *J Nucl Med*. 2017;58:85-90.

Rauscher I, Kronke M, Konig M, et al. Matched-pair comparison of ^{68}Ga-PSMA-11 PET/CT and 18F-PSMA-1007 PET/CT: frequency of pitfalls and detection efficacy in biochemical recurrence after radical prostatectomy. *J Nucl Med*. 2020;61:51-57.

Robinson D, Van Allen EM, Wu Y-M, et al. Integrative clinical genomics of advanced prostate cancer. *Cell* 2015;161:1215.

Sandhu SK, Joshua AM, Emmett L, et al. PRINCE: interim analysis of the phase Ib study of ^{177}Lu-PSMA-617 in combination with pembrolizumab for metastatic castration resistant prostate cancer (mCRPC). *Ann Oncol.* 2021;32:S626-S677.

Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med.* 2021;385(12):1091-1103.

Sathekge M, Bruchertseifer F, Vorster M, et al. Predictors of overall and disease-free survival in metastatic castration-resistant prostate cancer patients receiving ^{225}Ac-PSMA-617 radioligand therapy. *J Nucl Med*. 2020;61:62-69.

Schaeffer EM, Srinivas S, Armstrong AJ, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Prostate cancer. V.4.2022. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

Zechmann CM, Afshar-Oromieh A, Armor T, et al. Radiation dosimetry and first therapy results with a (124)I/ (131)I-labeled small molecule (MIP-1095) targeting PSMA for prostate cancer therapy. *Eur J Nucl Med Mol Imaging* 2014;41:1280-1292.

About AXIS Medical Education, Inc.

AXIS Medical Education, Inc. is a full-service continuing education company that designs and implements live, web-based, and print-based educational activities for healthcare professionals. AXIS provides convenient opportunities to engage learners based on their individual learning preferences through a full spectrum of educational offerings.

The executive leadership of AXIS combines 75 years of experience in adult learning theory, curriculum design/implementation/assessment, continuing education accreditation standards, and medical meeting planning and logistics. Our team has a deep understanding of the governing guidelines overseeing the medical education industry to ensure compliant delivery of all activities. AXIS employs an experienced team of medical and scientific experts, medical writers, project managers, meeting planners, and logistics professionals. This team is dedicated to meeting the unmet educational needs of healthcare professionals, with the goal of improving patient outcomes.

AXIS believes that partnerships are crucial in our mission to deliver timely, relevant, and high-quality medical education to healthcare professionals. To that end, AXIS partners with other organizations and accredited providers to offer added expertise and assist in expanding access to our educational interventions. AXIS also partners with numerous patient advocacy organizations to provide recommended patient education and caregiver resources in specific disease areas. AXIS finds value in these partnerships because they complement our core clinical curriculum with validated and relevant supplemental resources for busy clinicians and their patients.

The mission of AXIS is to enhance the knowledge, skills, competence, and performance of the interprofessional healthcare team to ensure patients receive quality care, resulting in improved patient outcomes. We engage healthcare professionals in fair-balanced, scientifically rigorous, expert-led certified educational activities designed to foster lifelong learning that is applicable to clinical practice and patient-centered care.

To learn more and to see our current educational offerings, visit us online at www.AXISMedEd.com.

AXIS
Medical Education