Dr. Oliver Sartor: Hi, I'm Dr. Oliver Sartor.

I'm the Chief of GU Cancers Disease Group and the Director of Radiopharmaceutical Trials at the Mayo Clinic. Been around the space for a little bit. And one of the things that is really nice about tonight is we have two real experts here to join us. and I think we're going to have an absolutely fabulous discussion.

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Louise Emmett, I don't know how many people know Louise; I've known Louise for a long time. Incredibly impressive career in theranostics, she's the Director of Theranostics & Nuclear Medicine at St Vincent's Hospital in Sydney, Australia. Has been a true leader in the field. She has a variety of academic appointments, but I think more impressive is just her accomplishments and she has led us forward in new understandings for a variety of clinical trials, radioisotopes. She's very sensitive to the patient needs and I think is a fabulous physician and delighted to have you here, Louise.

Probably well known to most everybody on the call, Dr. Michael Morris. He heads the prostate cancer section at Memorial Sloan Kettering Cancer Center. And in addition, is the chief medical officer for the Prostate Cancer Clinical Trials Consortium. Mike has been deeply involved with the radiopharmaceuticals really from the beginning. Leadership role in the VISION trial, helped to lead the CONDOR and OSPREY trials of PSMA PET imaging, extremely well published and has an interesting and recent new appointment as co-director of Clinical Trials Innovation Unit at the National Cancer Institute. We really are going to look forward to hearing from Mike.

I'm going to give a very brief introduction to the field. Maybe not everybody is familiar, but I suspect that many of you are…I have about eight slides as an introduction, and then we're going to turn it over for discussion on a couple of cases, Louise will be leading that and then we're all going to participate in the discussion…

So targeted radiopharmaceuticals and prostate cancer…here's the very basic concept. We're going to call it theranostics. By the way, we could call it a variety of other things as well; targeted radiation is also a popular term. If we think about cancer cells, it turns out that they will express a variety of proteins and even other molecules that might serve as targets for our therapy. And if we were to design a particular type of therapy that would exploit the radionuclide, we might have something called a ligand and that would bind to the target on the surface of the cancer cell. And then a little linker, maybe a chelator, we would then have a radionuclide. Now that radionuclide, that radioisotope, could either be one that is used for diagnosis or used for therapy or maybe even used for both imaging and therapy. And I think Dr. Emmett will present a little bit of examples of each. Now, this concept is really simple, but it's taken a while to refine. Now, I believe that we're in

the rapid progress period of theranostics and it's not only developing in prostate cancer, but also a variety of other cancers as well…

There are a variety of targets that we might be able to discuss.

But it turns out that PSMA, prostate specific membrane antigen, is the one we're going to focus on because there we have proven success with the isotopes. So even though there's a laundry list of other targets. They're not going to really be discussed much tonight…

PSMA is a transmembrane protein. We have a little cartoon. We see this sort of lipid bilayer represented by those little balloons and tethers. That's the membrane of the cell. And it turns out that PSMA is going to be the protein that is transmembrane, and it has a portion on the outside that we can bind our little ligands to, our little radioisotopes, to. And that allows us to target the cancer cell…

Now it turns out that PSMA, even though its name "prostate specific," is not absolutely specific. And when we look at the scans, we're going to see areas of scans where the uptake is not in the prostate. We can see salivaries, we are going to see a little liver, we are going to see a little spleen, a little bit of GI, we going to see a bladder, a little bit of kidney. So it turns out that it's not absolutely specific, but it's specific enough for us to exploit…

Molecularly targeted isotopic therapy. There are a variety of targeting molecules that are in exploration, these small molecules, peptide antibodies, camelid antibodies, minibodies, nanobodies, aptamers, they're all out there. But,… it turns out that a couple of these molecules are very, very well explored. The PSMA 617, the PSMA I&T, and I have little arrows that are pointing to what we call a chelator. That's where the isotope could be held and trapped. And then we have a little PSMA binding motif and I've circled that on each of the molecules, that's going to guide it into that PSMA protein. And the PSMA 11 is one of the agents we use for imaging. And there we're going to be using Gallium 68 as a imaging biomarker. And the PSMA 617, depending on the isotope that we put in place, we can either image or treat with it. And by the way, I&T from PSMA I&T, means image and treat.

That is all the slides that I have for the introduction. So I'd like to turn it over now to Louise, who's going to be leading us through a couple of cases and having a bit of a dialog. Louise, delighted to have you here.

Dr. Louise Emmett: Oliver, thanks so much for the introduction and that's a great overview of radionuclide therapy with PSMA PET for prostate cancer. So I am going to go through a few cases which I hope will give us, you know, some idea as to how we use it, how effective it's going to be, and possibly also some of the side effects that we can expect. And we're going to start with the first case.

So this is a 70 year old patient who was diagnosed with prostate cancer in 2008, had a radical prostatectomy and then the disease recurred, had metastatic disease. We started on hormone therapy in 2015, and then 2021 it got more aggressive, the metastatic disease. So he was treated with

docetaxel chemotherapy and also an antigen receptor signaling inhibitor, abiraterone, that controlled the disease for a while, but not quite for long enough. And he actually developed brain metastasis, which is pretty unusual in prostate cancer. It shows it's a very aggressive clone that he has. So he had surgery and then radiotherapy to that brain metastasis and presented to us for consideration for PSMA targeted radionuclide therapy. So at the time that he presented to us, his PSA was 168 nanograms per mL, so pretty elevated. But he had no marrow compromise. He wasn't anemic, his platelets were okay and his other bloods were fine…

So what we do when we're considering patients for Lutetium PSMA therapy is, an important start of that, is to look at the PSMA scan, the PET scan. So this is, as Oliver explained it, Gallium PSMA 11 PET scan. And we inject the patient and we take the images one hour later and it gives us a very good idea as to how much uptake there is at all the sites. And so maybe I can ask Oliver and Mike, what do you think about this PSMA PET scan?

Dr. Oliver Sartor: I'll start off a little bit, Louise, you know, I'm looking at very extensive bony disease. I'm looking at a skeleton and I've got little spots almost everywhere. Now, I see some things other than cancer of the bone. I'd just like to briefly point this out, but you got a couple of dots where the eyes are, those are the lacrymal glands, you've got a couple of parotid glands that are salivary tissue. And you see that salivary uptake. You see some kidneys in there, then you see a bladder at the bottom. So it's not absolutely specific, but this is a high-burden patient. A lot of bone mets. I don't know, does that cover it, Mike? Are there other things you want to point out?

Dr. Michael J. Morris: Yeah. You know, I think that I would just add to what you just said. The reason that we know that this is such a high-burden is that we're seeing prostate cancer in the usual places in the body, and that's in the skull, in the shoulders, in the ribs, the spine and the pelvis. But this patient also has disease in the arms and the legs. And that suggests that it's moved out of its usual places because those places are so occupied with cancer. The bone marrow has now begun to move out of its usual places. And usually the prostate cancer is chasing the marrow. And in this case it's moved into the long bones, where we usually don't see prostate cancer. So this is someone with quite a bit of disease. And that's, I think, why Louise was pointing out, that despite that, his bone marrow was uncompromised. But we see that it's pressured here from a from a scan perspective.

Dr. Louise Emmett: Absolutely. It's something that you definitely want to look at very carefully. And one of the things I find in these patients who've got very, very high-volume disease, we do have to baby them through the first dose a little bit. These patients have—he has very bright disease. So I'm hopeful that he will have a good response. We look at two things, or a number of things: where the disease is, but also how bright the disease is on the scan in terms of trying to gauge how well they're going to respond to treatment. So if we have very bright disease at each of the sites, then we expect we'll get a good dose of radiation into each of those cells, and we expect that those patients will get a better response. So, I would put this patient into a category of nice,

bright disease. It's extremely extensive, but we're hopeful that this patient will have a good response.

Dr. Oliver Sartor: Louise, let me ask you a question. So, you call it bright. In this case, it's actually dark. Do you like to compare that to liver? To parotid? What sort of your gauge with the process, if you will?

Dr. Louise Emmett: Yes. So there's a number of ways that you can do it and there's a number of published ways that you can do it. So a lot of people will use either liver, so VISION criteria was using the liver, whether it was above liver. And you can see the liver here just above the kidneys. Just about all of this disease in the bones is above liver. So everything is above liver. And then if you look to see how bright the parotids are, it looks similar to the parotids. So that is a good intensity of uptake at all sites of disease that we can see at the moment

Dr. Michael J. Morris: It might be worth pointing out to our audience that those black spots are PSMA-expressing cancer. So it's not just cancer, but it's cancer that's visualized by virtue of having a lot of PSMA on the cell surface, just like Oliver was talking about.

Dr. Louise Emmett: And I'll also point out, I call it bright, because when we report it, the spots are yellow and we look at blue as a normal color. So we can…one of the lovely things about being an imager is we can see a rainbow when we report. And so, yes, you're right, Oliver, it is dark, but when we normally look at it, it's usually bright gold…

So the patient started with dose one in March 2022 and we give a slightly higher dose than usual, 8.5 Gbq. We give that standard, so a little bit higher than was given in some of the trials, the larger trials. And in this particular case it's because the patient’s got a high volume of disease and we really want them to get a good treatment response. So this patient had six doses that was given 6 to 10 weekly from March 2022, until February 2023. So he was able to receive all six doses. He had quite severe fatigue at the time that we injected him for the first dose. That improved very significantly with the reduction in his disease volume. He was able to go back to work. He didn't have a lot of pain even at baseline, which is surprising given the volume of disease that you see on his scan. He did get mild dry mouth with the treatment. So that means that he had a dry mouth at night, often need to keep a glass of water by his bed and have a sip at night sometimes. And if eating very dry food like bread, would need to keep water and have a sip of water while he's eating dry food. He also got mild—

Dr. Oliver Sartor: Well, wait.

Dr. Louise Emmett: Yes.

Dr. Oliver Sartor: I'm sorry. I need to ask you a question because you gave him six doses. Then you stop it. His PSA was still 20. I mean, why not give him 20 doses and hope he gets PSA gets down to zero?

Dr. Louise Emmett: Yeah, it's a really interesting question.So-and we'll have a look at the scans. We could continue it—we could request for it to

be continued beyond the six doses. And I think we have—we clinically have done that in some patients. The question is how long do you continue to treat with one treatment? Is it sometimes better to stop and use another treatment or to attack the clone a different way? And I'll show you what—I can discuss what we did. We'll have a look at the scans as well. So he had mild anemia—

Dr. Michael J. Morris: Just really quick.

Dr. Louise Emmett: Yeah.

Dr. Michael J. Morris: Might we just want to explain on that first bullet point, we dose this drug by how much energy is being injected into the patient. A gigabecquerel, that GBQ, is a is a measure of radiation energy. Of course, how much of the dose is treating the tumor is by virtue of how bright the PSMA scan is, but this is how much was injected into the patient.

Dr. Louise Emmett: Yeah, absolutely, so the dose that’s injected is quite different to the dose that’s delivered because it's dependent on how many receptors there are on each cancer cell.

Dr. Michael J. Morris: And that's why it's so important when we think about who to treat. We want patients to have a lot of PSMA on their cancer.

Dr. Louise Emmett: Yeah, totally. So another common side effect is mild anemia. And this patients certainly got that. Their hemoglobin went down a little bit, not too dangerous levels that didn't need any transfusions, but they did have mild anemia in response to this treatment. And the PSA progressively went down with each dose. So 168 nanograms per mil at dose one and then at dose six, it had dropped to 20 nanograms per mil. And that's from March 2022 to February 2023. So 11 months that this patient was treated for with the six doses. And in response, Oliver, to your question, as to why we didn't keep treating six doses, six weekly, we actually gave the first few doses and then we stretched out the last few doses so that we did keep controlling the disease, but we tried to make it last as long as possible with the six doses. So it's almost a year of disease control for him.

Dr. Oliver Sartor: At some point we may come back to some of the FDA rules, which could be a little different. But let's keep going with the case.

Dr. Louise Emmett:…So what we're going to have a look at next is this other image. So this image is what we call a SPECT scan. And Oliver was talking about how we can image with multiple different agents to see what the PSMA receptor is looking like. And this is the therapy itself. So, this is an image that we derive from the injection of the lutetium PSMA and this is what he looked like with his first injection. And you can see all the spots there that we saw with the PET scan before we had the injection…

So what you can see here is the difference between the first dose and we can see the images. We can see exactly where the lutetium has landed and we can see how bright those cells are with the first dose and then with the sixth dose there you can see that—this gentleman still has quite a lot of disease involvement, but the volume of disease or the volume of cancer cells that are expressing the PSMA receptor have gone down very significantly. So we've controlled the disease. He hasn't got more extensive disease. The PSA has gone down very nicely, but he still has disease that's there. So this patient's had a good response to six doses of Lutetium PSMA…

So this is what—so in Australia we have Australian Kelpie dogs and I do explain a lot to my patients in terms of how they're going to respond based on dog types. So we have we have a few different dog types, we have white fluffy dog types. They're patients who have a really, really good response to treatment. They don't need a lot of doses in order to get very good disease control and can have disease control for a very long time with just a few doses. So white fluffies don't need to be on a lead. Very well-behaved. Kelpies are super bright, but they can be quite naughty so they need to be controlled. So this kind of cancer that patients need to keep on treatment and I think this patient is a very good example of this. Six doses continuing to treat keeping the disease controlled for the period of time that they're on treatment. And about a third of our patients have this kind of disease.

Dr. Michael J. Morris: Maybe worth mentioning here, Louise, that in the US—this is what Oliver was alluding to—in the US six doses is all you're permitted to receive.

Dr. Louise Emmett: Totally.

Dr. Michael J. Morris: And for much of our audience, this would be the end of therapy.

Dr. Louise Emmett: Absolutely. And, you know, I think it's a really interesting question. If you've had what you have left and what you have available as to whether we should give more, whether we should keep treating this patient or not, what would you do, Oliver? If you had—if you were in a free world?

Dr. Oliver Sartor: No, I think if I had free will, I would consider treating more. You know, I look at the target, that's the PSMA, looking at that scan on the right. And there's still plenty of target left. And you mentioned you had a continue of decrease in the PSA with each clinic to administer—excuse me, PSMA lutetium administration. And I'd probably get a little more. His anemia is notable, but it's not severe. So if I had free will, I might want to get more. But going back to Mike's point, very important in the FDA regulations and in the trial, the VISION trial that was run that generated that FDA recommendation, there was a limitation of six doses. And so we did not really have an option of going further in the U.S., perhaps in a clinical trial, but not as part of conventional care he had a mild anemia. By the way, we also dose it a little differently using the 8.5 Gbq, we use 7.4, and it turns out that we use about every six weeks on a fixed dose schedule instead of

stretching it out. But again, that's basically part of the VISION trial to get carried forth into the regulations, get a little more flexibility in Australia and by the way, we like your flexibility and we're enjoying this good response here. And that kelpie dog, I didn't think he was naughty. I thought he was just pretty smart.

Dr. Louise Emmett: Oh super smart, super smart, but you do need to keep telling them what to do, right?

Dr. Oliver Sartor: Okay, got it.

Dr. Michael J. Morris: It may be worth reminding people that—the natural question would be, well, why did the FDA limit the dose to six doses? And regulators tend to only be able to evaluate data that's submitted to them, and the trials that have been done or prospective regulatory review used six doses. So they can't really say that it's safe to go beyond six doses. And there are no real formal clinical trials to inform us as to the risks and benefits of going beyond six doses. And that's why.

Dr. Oliver Sartor: But Mike explain to the group why six was chosen. What was the concern that was the limitation to six? Because I think that's also part of what people need to understand.

Dr. Michael J. Morris: Sure. And I think Louise also as a nuclear medicine physician, would have a lot to say about this as well. So this is injected systemic radiation therapy. And so there are normal organs that are subject to radiation. Here are the bone marrow, the kidneys and other organs. So when there is a consideration of what are the long time safety implications, frequently that relates to how much radiation are the normal organs getting and what are the side effects, not only in the short term, from dose to dose for example, but in the long term as well. And of course, depending on where the person is in their disease, sometimes the long term is the short term. But as we think about moving these therapies ever earlier, the long term is a long term. And so the number of doses one gets may directly—*may* directly—relate to how much in the way of long term normal organ damage might be seen. Louise, do you have anything you want to add to that?

Dr. Louise Emmett: Yeah, no, I do. So when you start a treatment so PSMA targeted radionuclide therapy, and we're trying to decide what the doses are to the other organs, to the salivary glands, to the kidneys. They've used a proxy when they decided on the six dose and that proxy is external beam radiotherapy doses. We don't know exactly whether that's correct. So I think six doses is conservative and safe. I think we need to get a lot of information based on whether we actually are making the right calculations when we do our physics. And it could be that patients can safely get a lot more or that we need to be very careful as we move it earlier. I think this is a space that we're working in…

So this is case two. This is a 72 year-old, extremely well 72 year-old, who was diagnosed with prostate cancer in 2010. He was treated with hormones and abiraterone. And then when that stopped working, he swapped to enzalutamide. He was considered or asked to be considered for Lutetium-PSMA rather than chemotherapy. This was a personal choice for

him. He was a very busy businessman. He didn't want to undergo the side effects from chemotherapy. He was what we would call a PSA under-secreter. So his PSA was fairly low. But the volume of disease that we see on the scans and he didn't have any symptoms at the time that he was being considered. And this is his gallium PSMA PET scan here. And once again, I'm going to ask the experts in the room, what you think.

Dr. Oliver Sartor: Mike?

Dr. Michael J. Morris: Well, as we can see, he has less PSMA expressing disease than the patient before. We can again see that he has the salivary glands lit up quite well. So we know that the scan is actually localizing to PSA. Well, and he has a number of lesions that are brighter than his liver. And those are kidney shaped, kidney shaped structures. Those are his kidneys. And, you know, he ha—he is a little bit different than the patient that we saw by virtue of the third bullet point here. Our previous patient was treated with ADT, which stands for androgen deprivation therapy, which is testosterone lowering agents. This patient was also treated with abiraterone, just like the last patient, but the last patient received docetaxel chemotherapy. And in fact, that's where we have regulatory approval for Lutetium. So this patient in the—by virtue of the European and the American regulatory authorities, this patient would actually not be receiving Lutetium as part of standard of care because he had not received chemotherapy. So this is why I think this is an interesting case that Louise is showing and take it away.

Dr. Louise Emmett: Right. So looking at that. So first of all, I completely agree with you. This patient has not had chemotherapy and that would be the natural next progression for this patient in terms of recommended treatments. When we look at the scan, you can see that there's lots of small spots. So there's nowhere very big, no big sites of prostate cancer. It's all in bone, but there's quite a few of them. So there's at least 20 spots of disease there. And when you compare it to the liver, so the liver's just above the kidneys there, we would say that these spots are "above liver," so the patient would be suitable for consideration of treatment for lutetium PSMA just from an imaging point of view and we would expect that this patient based on this, should have a reasonable response to treatment. And because of their desire, a strong desire, because of a previous problem with family, his family having received chemotherapy, they were busy. We agreed to give them 2 doses of lutetium PSA to see whether in fact they had a good treatment response or not…

So we do give slightly higher doses of Lutetium PSMA than you give on the VISION. And I guess we do have a little bit more flexibility on that because we don't have funded treatment in Australia and we can choose to give slightly higher doses of standard. We gave 8.5 Gbq in the TheraP trial as a decreasing dose. So we are slightly used to higher doses of Lutetium PSMA. This patient received dose one, 8.0 Gbq Lutetium PSMA in June 2021 and 8.0 Gbq Lutetium PSMA six weeks later…

So what we do routinely as well is we take these images of the patient when they get the Lutetium. So this is the image that we got of the patient for dose one, and it shows us exactly where the treatment has

landed, as such. Gives us an idea as to how bright each of the spots are, how big each of the spots are. And we use that in conjunction with the PSA to decide how the treatment's doing. So at the first dose, the patient had a PSA of 5.6ng/mL,and then at the second dose it had risen up to 15ng/mL. We sometimes see that in patients that we get a rise between dose one and dose two. And some of those patients actually subsequently have quite a good treatment response. So we gave the second dose…

And if you look here, it's the images that you get from the SPECT—or just from the physics of it. They're a bit more granular. They're not quite as uniform as you see on the PET scan, but it gives us a good idea as to what's happening. We know that the PSA is rising. It's gone from 5.6 to 15ng/mL. Is that a real rise? Is that due to disease progression or is it because the patient's just having a flare? And what we see on the second scan is more spots of disease. So between the first and the second dose, we can see that there are more spots of disease than we can see on the first dose. We don't use that on its own. We also use ongoing PSA response. So this patient had another PSA at nine weeks after treatment started and the PSA had risen to 40ng/mL. So we've gone from 5.6 up to 40 with two injections of Lutetium PSMA. So I'm going to hand over—Mike? Oliver? What do you think?

Dr. Oliver Sartor: Well, I want to ask—well first of all, I'm disappointed for this patient. I'm sure he's much more disappointed than I am. But help me understand, Louise. You presented a great response in case one and now this patient really didn't respond. What percentage of patients fall into the "do not respond" category? I think that's important for our audience to have some sense of, you know, we don't respond all the time. So what percentage do you see this type of lack of response?

Dr. Louise Emmett: So I think we can quite nicely divide treatment response into thirds. One third of patients have a really good response, a great response, one third of patients have a good response. So they're going to have a good PSA response. They have a duration of disease control, and about a third of patients don't have as good a treatment response as we would like. But patients who have disease progression with no stopping - the PSA continues to rise like you didn't give them anything at all. And they also have new lesions on their second scan. Quite a few new lesions is quite rare. It's about 5 to 10% of the patients who we inject.

Dr. Oliver Sartor: Thank you.

Dr. Louise Emmett: I think in the—you know, about 10 to 15% of patients will have new lesions. But they'll also have response in some of the other lesions. And they might have a short-lived PSA response. But this kind of marching through is quite rare. So, you know, I think this is—this patient hasn't had—yet had chemotherapy. What would you recommend, Mike?

Dr. Michael J. Morris: Well, like you said, I'm reluctant to terminate therapy unless I really have a triumvirate of or a constellation of symptoms and signs that indicate progression. A rise in PSA? Yes, he has

one. Worsening scans? Yes, he has. The question is, does he feel well or not? And that's information that we don't have. But presuming that everything is hanging together, at—looking like it's getting worse here, I would switch over to chemotherapy…

Dr. Oliver Sartor: I agree. I agree.

Dr. Louise Emmett: Absolutely. And I think that this patient's had a trial of Lutetium PSMA. They wanted to avoid chemotherapy, but they also want to live, you know. They—we need something that's going to improve overall survival. And so after discussion with the patient, they did, in fact, start chemotherapy at this stage. We can get scans in patients that look like they're going to have a good treatment response. And certainly when I look at his baseline scan as a nuclear medicine physician with the gallium PSMA 11 I would say this patient's going to have a reasonable response, at least a two thirds chance of a reasonable response. But what we don't know in these patients is how radiation sensitive their disease is, and that's not something that we can measure it for upfront. And I think in this patient they have particularly radiation resistant disease and Lutetium PSMA is not the best treatment for them, and it gives them the opportunity to move to something else that will be effective. And that's exactly what we did.

So next case. So case three is an 83 year-old man. He'd been diagnosed with metastatic prostate cancer from the beginning, so four years previously presented with metastatic disease. This was treated both with abiraterone and with androgen deprivation therapy. So testosterone control. He'd also had two lines of chemotherapy, had docetaxel and cabazitaxel in his four years. So he had very aggressive disease. He also had significant pain, severe fatigue that meant spent a lot of time in bed and was having hospital visits to manage these symptoms. His PSA at the time that he was referred to us was 2220. And at the time he was referred to us, he was also mildly anemic with the hemoglobin a little bit lower than normal…

So this is his PSMA PET scan. And once again, I'm going to ask you to tell me what you think.

Dr. Oliver Sartor: Lots of cancer, pretty sizable lesions, I’m mainly looking at bone, in my estimation, although I like—to see it travel around a little bit, probably have some lymph nodes in there as well. Uptake is plentiful. You know, I'm looking at the liver, far greater than the liver, equivalent to the salivaries. You know, I am thinking this is going to be a good responder. He's bright, or dark, whatever your terminology might be. I'm hopeful for this patient. So let's see what happens, Mike any comments?

Dr. Michael J. Morris: What I think is interesting about this patient is that he's sort of on the other side of the spectrum of case two. He has much more advanced disease and he's symptomatic. And what we're looking for here is not only having a PSA go down or the scans improve, but this is somebody who has the potential to actually feel better, function better, and enjoy his quality of life more if he responds. And I would consider that to be a measure of response as well. A clinical benefit.

Dr. Louise Emmett: Totally agree. Very important that we can improve his quality of life. So when I look at this scan as a nuclear medicine physician, one of the things that I see is that I'll call them black spots, not bright spots, but all the black spots are similar in intensity. So that's what I would call "homogenous disease." They're all very, very similar in intensity. And it's also high volume. So that tells me two things. One, I am expecting that this patient will have a good response, but then I expected the first patient to have a good response as well. And two, it's high volume. So I'm expecting that this patient will have quite a few symptoms in the beginning. Quite often we see an increase in fatigue. Often we see, you know, a flare in pain in these patients in the first few days. And a lot of that is we're giving radiation to these cells. They do swell a little bit. They do release toxins into the…bladders there as they're dying. And that can very much cause increased symptoms…

So this patient was actually on a trial, prospective trial that we did at St Vincent's. It was a prospective trial of Lutetium PSMA. It was 617 in this case and a radiation sensitizer that we use to enhance treatment response. This patient was eligible for six doses of Lutetium PSMA 7.5 Gbq 6 weekly standard. So pretty well, exactly what is VISION trial and as you give that in the United States. So they received the first dose of Lutetium PSMA 7.4 gigs. At that stage the PSA was 2220 in October 2019, and six weeks later, as per trial protocol, came back and got a second dose of Lutetium PSMA. And it was very interesting when they came back, we didn't get the PSA back until after they'd had the injection, but the PSA had gone down from 2220 to 38ng/mL in November 2019.

The disadvantage of that, sometimes, I mean, that's a massive drop in PSA. And when we lose the target on the tumor, sometimes you actually get some of the radiation going to the other organs. And in this case, the patient got quite severe dry mouth as a result of that second injection. So—such severe dry mouth was so symptomatic from it that he actually removed himself from the trial and had no further treatment. So all that he was on was the androgen deprivation therapy. And in February 2020, it's interesting, the PSA continued to go down, even though we hadn't treated since November. PSA was 2.0ng/mL and he didn't get a rise in PSA subsequently until August 2020 with a rise of 15ng/mL…

And you remember how bright that disease was that we treated. And when we look on this scan from August 2020, which was actually part of the trial protocol, you can see this is a PSMA PET scan, we can see the liver, the kidneys, the salivary glands nicely, but very few spots remaining associated with that disease…

So we do get some patients who have exceptional responses and get marked dramatic responses to just a few doses of Lutetium PSMA. They are what I would call a white, fluffy dog cancer type. They're very well behaved. They're highly radiation sensitive. And you get these marked responses. And what we have on—we have the first PET on the left and the PET from August 2020 second. And then these images here that you can see are actually the SPECT images in the gold. So they're from the Lutetium of the first dose and the second dose, what you can see is if you look

between the first dose, where you see lots of cancer by the second dose that had all gone. So it's only a small percentage of patients who can get this kind of response, but it can be quite dramatic.

Dr. Michael J. Morris: I think that this also brings up another issue, Louise, and that is the dialog between the patient and the physician and…the value of expertise. You're one of the world's greatest experts in this therapy. And so you were looking for xerostomia - the dry mouth and talking to the patient. And even though the patient was having a really great response from a PSA and scans-standpoint, ultimately that dialog resulted in saying we're done with treatment, for now, at least because of the dry mouth. And that's why I think the scan and the PSA isn't the be all and end all of what measures response and the value of expertise as well. And a good doctor.

Dr. Louise Emmett: You know, it's super interesting. I said if—the patient didn't need more treatment, so it's not a question, but you know, we, possibly if…we've had that PSA back before we injected them, we could have looked at it—you know, the question is, should you dose reduce because of toxicity or should you dose reduce to, you know, to avoid toxicity? And that's really a step that we haven't done in a lot of our trials and we haven't done clinically, but we really need to think about.

Dr. Michael J. Morris: Yeah.

Dr. Louise Emmett: We should have thought about in this patient,

Dr. Oliver Sartor: Louise, I'm going to make a comment and then we're going to need to move over to the questions because we've got a big audience, over a thousand individuals online and there's no way we're going to answer all the questions. We want to give a shot. You presented these three different cases with three different outcomes, but in each case, looking at the scan itself, you would have predicted a pretty good response. And particularly in the second case, someone looked at it, said, “Hey, you know, that patient's going to do okay.” And he did. And I think it brings a very important point to the floor, and that is the scan is really helpful. But there's more to the story, and it's called cancer biology. Not every cancer is going to respond. And some of the cancers that don't respond are not the ones where you expect a non-response, and that's where resistance to radiation tumor biology comes to the floor. And we still have a lot of work to do, a lot of research, in order to understand who's going to do well, who's not going to do well, and how to optimately manage these patients going forward. So.

Dr. Louise Emmett: Yeah, I totally agree.

Dr. Oliver Sartor: I think what final…comments from you, Louise, and then we're going to head off into the Q&A.

Dr. Louise Emmett: No, I just say that I totally agree. We need to know more about who will respond and how to make everyone respond well. And at this stage, we're not—we're not there, but we're working on it.

Dr. Oliver Sartor: Alright. Let's talk about some practical issues.And I'm looking at some questions coming in. Tell me about the injection itself. I mean, what happens to the patient? How long does it last? What kind of precautions are necessary? Or if people are radioactive, do you just send them out on the street? What do you do?

Dr. Louise Emmett: Actually, it's super interesting. It's a little bit different in each country. But yes, it's an injection. It's a very simple injection. We just have to be very careful to make sure that the cannula is in the vein so that it goes to the right place. And in our institution, our patients stay with us for about 4 hours. We get them to drink more water than they would normally drink so that they can flush the excess through, and they will have radioactive urine, particularly, for the first few days. So in fact, I ask a lot of people to sit when they wait so that they don't have a lot of radiation, you know, in their bathrooms. If they can have a separate bathroom from their family when they go home, I recommend that. They will be mildly radioactive to people around them, but it's really mildly radioactive, actually, with Lutetium PSMA. About 10% of it goes beyond the skin in terms of radiation weights. Most of it actually stays within a millimeter of where the tumor is itself. So they will give a low dose to their family. But there's a couple of papers that have shown that the dose to family and carers is very low. We do ask patients to sleep in a separate bed to other people for the first couple of nights because that's the time in which you are really close to someone for a long period of time.

Dr. Oliver Sartor: Got it. Thank you. Now, we've talked a little bit about disease biology and Mike, I want to make sure we get your thoughts on this. What about genetic testing? I mean, we do a lot of genetic testing. We look for PARP inhibitor sensitivity. We're looking for a variety of molecular defects. Might predict response to therapy. What about genetic testing for this type of therapy? Any lessons learned so far? Mike could you get the latest?

Dr. Michael J. Morris: Great question. So let's draw the lens back for just one second while we're looking at these scans. We've been talking about disease heterogeneity, and let's just explain what that really is. If you look at that picture on the left, you see all of these different black spots. Some of those black spots are darker than others and some are in bones, and some may be in lymph nodes. Each of those is really its own family of cancers. Each of those spots has a discrete biology, and some of those cells may be quite sensitive to radiation, and others may be resistant. Now, what confers resistance? We're just learning about this right now, to be honest. So in a number of laboratory and human experiments, it does seem like we have identified some candidate gene or gene patterns that characterize the more resistant clones or families of cancers. There are also general patterns that we think would—may lend exquisite sensitivity to radioligand therapy as well. So we're just learning about this. And I think that the importance of this is that there are really three different factors. When you think about the interaction of whether a given therapy such as this will work or not. One is the amount of target that's on the cells and that's PSMA. The other is the amount of radiation. And Lutetium is only one type of radiation, but it may be insufficient for some patients. And so we're looking at several

other types of more powerful radiation. And then the third is the patient's own biology and genetics, which lends itself to being resistant to this type of treatment. I guess an implicit fourth one is just drug delivery to the tumor within the body, and that's by virtue of the targeting agents as well. So within those realm of four things, you're talking about disease heterogeneity, the payload, the targeting agent, and the target.

Dr. Oliver Sartor: Yep, lots of factors. And it extends probably on the scans. Now, so if you presented us with some really nice, hot PSMA PET scans, bright, if you will. But not all the patients are going to be that way. We have neuroendocrine cancer. And by the way, if you do PSMA PET scan on like a small cell variant of the prostate cancer, you don't see it at all. I wonder if you might comment briefly about neuroendocrine and PSMA PET negative cancers because that's important.

Dr. Louise Emmett: Yeah, totally. And so there are a proportion of patients who will get screened and who don't really have enough PSMA expression for us to think that they're going to have a treatment response. And then, you know, what options does that patient have? They don't have a PSMA receptor. The alternatives are we can try and upregulate that receptor. That's really not been shown at this stage to be an option. We need to do more work in that, or using another agent. Now, Oliver, I'll take you back to radium. And if someone's got extensive bone disease and they don't have high PSMA expression it's not to say there aren't other radionuclides that might be effective. And then, so what do you think about using radium instead of using PSMA target radionuclide therapy if you don't have bright enough disease.

Dr. Oliver Sartor: We actually have a biomarker for radium as well. It's not PSMA PET, but it's the osteosclerotic changes on a bone scan. And I know bone scans are oh so 1995 but nevertheless, as uptake of radium is predicted on the basis of a bone scan. If you had good bone scan uptake, you can have good radium uptake and that could be an option. But then We also need to think about all those other systemic therapies that we use. I mentioned PARP inhibitors. We have second-line chemotherapies. We have other experimental therapies. So one of the things I actually want to come back Mike, the very, very important issue, is clinical trials. Now, Mike, you mentioned that we sometimes offer clinical trials really as the best option for a patient. How can patients access clinical trials? What advice might you give?

Dr. Michael J. Morris: Well, I think that the first place to start is your own oncologist - to have that discussion. Not everyone, of course, has the same access to clinical trials, depending on where they are and where are where they live and where their doctors practice. There are some online resources as well, in order to inform for the availability of clinical trials such as clinicaltrials.gov. in the U.S. There are patient related information sources such as PCF, American Cancer Society, and others that are informational resources for clinical trials. But the best way to both participate in answering some of the questions like why can't we give this therapy earlier? And what if we did get more radiation? Either through Lutetium or through other radioligands, one called Actinium, for example, or Lead-212 which are more powerful than Lutetium.

And the question of, well, how low can I go in terms of PSMA-directed therapy for the patient who may not have very much PSMA expression? Or why do I am I limited to six doses? All of these, all of these questions are currently being addressed in clinical trials. So it really is an issue of seeking those out. Generally, I think the best way to do that is through your own doctor or if your doctor is associated with a nearby cancer center, then having an opinion delivered there. I would say that it is hard to participate in clinical trials that are very far away from you geographically. Those are challenges in terms of both financial challenges and psychological and support challenges - to be disconnected from your support system, but within your community, I think is the best place to access clinical trials and through the resources I just mentioned.

Dr. Oliver Sartor: Thank you, Mike. Louise, I wanted to come back for a brief moment. You know, I look at that great responding patient and he just had a couple little spots left. What about considering external beam radiotherapy for these patients who may have exhausted their Lutetium options, but at the same time they still have disease, just not very much? What about external beam there?

Dr. Louise Emmett: So look, I think external beam for, you know, progressive disease where you just have a few spots is something that's definitely happening clinically. I think it's something that's also being looked at in trial and it's very appealing, isn't it? Yeah, but if you have a spot that's left and particularly if that symptomatic to use external beam radiotherapy just to finish that one off and give the patient a bit of time between needing other systemic treatments. So it's definitely something that we do. We didn't do that in this patient in that case, but it's always an option and that's one of the advantages of doing the imaging really, isn't it? That you can see not just what the PSA is doing, but you can also see where the diseases is, what it looks like and what the best therapy might be for that patient in terms of controlling the disease for as long as possible. I totally agree.

Dr. Oliver Sartor: I—we're going to have to wrap up pretty soon. And I'll tell you what, I'm going to ask some really quick questions and we'll try to get some really quick answers. Mike, what about insurance? Is insurance going to be covering this? What might you tell the patient who's saying, "Well, gosh, I'm interested in these therapies. Is my insurance going to cover it?"

Dr. Michael J. Morris: Sure. So, very quickly, insurance will depend on your health care system. And there are a thousand people on this call and presumably they're all not from the same country. So in some countries, they'll be covered by national insurance programs. In the U.S., though, within the label of the drug, most insurers will cover the dose and the dose duration, i.e. six doses for men who have progressed through either abiraterone, enzalutamide, or a drug like it, or one or two chemotherapy courses.

Dr. Oliver Sartor: Louise, quickly. The side effect of dry mouth, you mentioned it several times. Is it reversible and if so, how long does it take typically?

Dr. Louise Emmett: It's variable. It's usually—patients are usually left with mild dry mouth. I have to say with Lutetium, it is very manageable. In 95% of patients, they have a normal life, they eat normally. It's not a big concern. When we move to other agents like Alphas, it might be a different question, and that will be something we have to address.

Dr. Oliver Sartor: Right. So that last patient who you presented, who had to stop therapy because of their severe dry mouth, that's actually a very rare event.

Dr. Oliver Sartor: Very rare. Very unusual. As unusual as dropping your PSA from 2220, down to 38.

Dr. Sartor: Yep. Absolutely. One more comment before we wrap up. Medical contraindications to therapy. So you mentioned these people had good bone marrow function. You didn't talk about kidney function. Tell us quickly what type of patient should not receive Lutetium because it would be unsafe to do so.

Dr. Louise Emmett: To tell the truth, it's a really safe treatment to give, in the majority of cases, severe marrow dysfunction would be something that we would have to be very careful in terms of how we do it. Patients have received treatment on dialysis. It's not a contraindication. And if patients have severe renal impairment, it would require a very good conversation with their consultant and their doctors to see whether it would be suitable or not. But the vast majority of patients would be suitable.

Dr. Oliver Sartor: Good. With that, I'm going to thank Louise and Mike for a fabulous discussion. Louise, thank you for putting those cases together. Mike, thanks for adding wisdom, experience, and the context to these patients and how we view them. I hope that people have enjoyed the seminar this evening. I have enjoyed it. I always enjoyed talking to Mike and Louise, and with that I'll bid you goodnight. Thank you so much for attending this evening.

Dr. Michael J. Morris: Thank you for hosting, Oliver. Thank you, Louise, for doing such a great job presenting those cases and discussing your—sharing your expertise.

Dr. Louise Emmett: Such a pleasure to be on with you both. Thank you.

Dr. Oliver Sartor: See you, guys.