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Recent Progress in Metastatic Castration-Resistant Prostate Cancer

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Dr. Saad:
Hello, and thanks for joining our discussion of some of the highlights at ASCO 2022, that was finally held in person in Chicago. So, I'm Fred Saad, Urological Oncologist from the University of Montreal, and I'm joined by Rana McKay. You're a medical oncologist from the University of California in San Diego. And we'll start talking about some of the highlights of Metastatic Castration-Resistant Prostate Cancer which, unfortunately, is still around, and is still the cause of death from Prostate Cancer.

So clearly looking forward to making strides and improving outcomes of these patients that are unfortunately all destined to die of Prostate Cancer. So, some of the interesting data that was presented, there was work looking at a simple Biomarker like Alkaline Phosphatase. And how it goes up or down on Radium 223, and how this correlates to overall survival. So, the reassured data, is a large study ongoing in patients on Radium capturing as much data in the real world as possible. And what the study found, at least in terms of Alkaline Phosphate, confirms what was seen earlier in smaller size studies. That Alkaline Phosphate is really what we need to be looking at when we treat patients with a drug like Radium. PSA is not a Biomarker that's useful for telling us whether patients are responding or not. But Alkaline Phosphate clearly, the patients who get a decline in Alkaline Phosphate, after as early as 12 weeks, are the ones that are really getting the best in terms of overall survival advantage. So a simple biomarker, and in my practice, I actually teach patients to stop looking at PSA when they're on Radium, and to focus on Alkaline Phosphate. So, it's very funny when residents are in the room, and they see patients asking what is my Alk-Phos level. And they're surprised that patients actually are able to switch thought process when they're on a drug that isn't really targeting PSA progression. So, I think in important information to know whether we're going in the right direction, or unfortunately not in the right direction, looking at a simple biomarker that's cheap, like Alkaline Phosphates, after three or four cycles you should get a signal that Alkaline Phosphate is going down.

So, Rana, there's other more exciting data coming out, with other Radioligand Therapy like Lutetium. And so maybe some thoughts on what was presented?

Dr. McKay:
Yeah. I mean, I have to say stepping back, you know, we wouldn't be here where we are today with Lutetium PSMA, if it wasn't for Alsympca, and wasn't for Radium 223, entering into the treatment landscape. You know, as a the first, you know, Radioligand Therapy to actually improve overall survival for any disease. And so just kind of I think that study and the results of the impact of Radium for people with Metastatic CRPC, were really critical to get us to where we are today.

So, you know, as you said, Fred, patients with Metastatic CRPC, it's a fatal condition. And we know, that actually PSMA expression, is high in patients with Metastatic Castration Resistant Disease, and actually increases in the context of patients having CRPC. Lutetium PSMA, is a Radioligand Therapy, that delivers Beta Particle Radiation to PSMA expressing cells, and the surrounding micro-environment. So how it differs a little bit from Radium, is that it's a Beta particle, not an Alpha particle. And radium is just sort of bone

targeting, whereas the Lutisium PSMA is PSMA targeting. So it targets a specific protein on the cell surface of tumor cells. And we were, last year, at last year's plenary, we heard Dr. Michael Morris present the results of the Phase Three Vision Trial, which were really groundbreaking. It was a international open label study of Lutetium PSMA 617 in adults with PSMA positive metastatic CRPC, that had previously received one AR, at least one AR agent, and at least one prior taxing. And based on the results of that study, this drug became FDA approved for use. Though, I think still hasn't fully got been integrated into clinical practice yet. So we actually saw updated data from the vision trial, looking at adverse event profiles. Really demonstrating that over 50% of patients with Metastatic CRPC had received five to six cycles of Lutetium PSMA 617. So most patients were actually able to complete therapy. And if you look at the treatment related adverse events across each of the cycles they were pretty similar between cycles one through five, there was more toxicity seen in cycle six. And it's really kind of cumulative over the longer duration of treatment.

Additionally, during the presentation, they had data looking at PSMA based biomarkers of response to therapy. So looking at PSMA mean, PSMA max, and various other imaging based biomarkers to help inform, you know, who are the patients that are most apt to response. And I think those are still exploratory at the current time. We haven't really defined what's the, you know, they haven't necessarily been robustly validated. But I think we're going to start to see integration and more imaging based biomarkers to help inform treatment. And kind of segment, like piggybacking on that, we saw the results of the therapy trial that were presented by Dr. Hoffman. Therapy was a little bit different from vision, in that, it actually randomized patients to cabazitaxel, as opposed to, you know, just standard of care. And these were patients who had progression post docetaxel. So we saw the updated follow up data. You know, I think what's interesting that was reported from this trial, was that the median overall survival of patients who were excluded because of not meeting the PSMA FDG criteria, was really, you know, low. This is an unmet need that we still need to figure out how best to treat these patients. But nonetheless, you know, the therapy demonstrated that patients had lower adverse events, higher response rates and improved patient reported outcomes.

The study primary endpoint was PSA response. It wasn't really powered for OS. OS was similar between the therapy patients and the cabazitaxel patients. But, really the primary endpoint was powered around PSA response, rather than overall survival. It was a smaller study. But you know, these two trials are really going to change the way we treat patients with metastatic CRPC, with the introduction of targeted Radioligand Therapy. So, what's different about Butisium, is that it is a targeted Radioligand, as opposed to radium which is just an alpha emitter.

Dr. Saad:
Yeah. And, but it is interesting because, you know, I think it's important for our patients. I mean, in terms of overall survival, even though we can say it wasn't powered, we didn't see any difference. So in countries or people who can't get access to Lutetium, they don't have to feel like they're being shortchanged If they go onto cabazitaxel, which I think is reassuring, because sometimes, you know, you hear these exciting data, and then you say, I'm dying because I didn't get it, but there are alternatives. So I think now it confirms that calbazi, is a good alternative, even though the study was really designed in PSMA avid patients who were more likely to respond to Lutetium, than if they had accepted all comers like envision. So, I think informative as it is. And what is interesting is we've had the opportunity to treat patients with Lutetium pre and post-radium. And they've done very well. So, I wouldn't exclude Radium in the landscape of patients. It's just knowing, are we going to give it before or after? But, we found it to be safe both before and after in terms of Lutetium, whether patients had been exposed to Radium. And we've created patients after Lutetium with Radium and have had good experience.

Maybe just as a last study in these patients is looking at the, you know, up some updated safety analysis from the PROpel Study that combines olaparib with abiraterone. So the study is still continuing to mature in terms of overall survival. Clearly, a large improvement in Radiographic progression-free survival, whether or not you had DNA repair defects or HRR mutations detected. But what's reassuring, is that in terms of tolerability, the addition of a lapure, at least in first-line MCRPC, where patients still have a relatively good bone marrow. The grade three, four adverse events were really quite low, the highest being anemia at 15%, but all the others are under 5%, and overall patients were able to stay on therapy for a long period of time. So I think reassuring combination, and looking forward to other studies that are looking at combinations in first-line MCRPC, with data from magnitude that was also reported, and continued to update. And TelePro, too. So, this is a field that's continuing to grow also.

So, I think overall, I think it's exciting that we're still working on MCRPC. This disease state is not about to disappear. And so, we need to continue finding ways, like you said. For those patients that don't express PSMA, that are newer endocrine, and we receive more and more of those patients, as they progress through lines of therapy, integrating biomarkers. So, very exciting. And I think good news for our patients. But obviously, if we can get them to be treated appropriately earlier, then we might be able to make this state extinct.

Dr. McKay:
Yeah.

Dr Saad:
Which would I think be both of our objectives.

Dr. McKay:
Yeah, no, there's a lot of interesting data. I know we don't have the time to go through every single study. But a lot of interesting data from several phase ones that are ongoing of PSMA CAR-T therapy from the Placid Study. There's Bispecifics, we saw data get presented around that. ADCs targeting B7-H3, you know, Emmanual Enterocus presented data around that. So I think there's a lot of really interesting novel compounds, with also novel delivery mechanisms, you know, not just oral pills and chemo. But we're talking antibody-drug kinds against cellular immunotherapies. So, a lot of things that I think, in the future, I think, we're going to be seeing more of.

Dr. Saad:
Right. So, thanks a lot. And I hope everyone found this informative, whether you were at ASCOR or not. There's just too much being presented. So, hopefully, this was informative as being some of the highlights that we thought were important for clinical practice.

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