Highlights from the 2025 European Society for Medical Oncology Congress

Phillip Koo, MD [00:00:00] Hi, this is Phillip Koo from the Prostate Cancer Foundation. Recently we started a new series of webinars focusing on the data that is presented at large national and international meetings, just because there's so much information there that really is going to change how prostate cancer care is practiced across the board. So, most recently, there was a meeting held in Berlin called ESMO, and we have with us today, Dr. Zach Klaassen, who's associate professor at Wellstar MCG Health. So, Zach, thank you very much for joining us.

Zachary Klaassen, MD, MSc [00:00:36] Oh, of course Phil. Always good chatting with you.

Phillip Koo, MD [00:00:37] So, first off, tell us what ESMO is.

Zachary Klaassen, MD, MSc [00:00:41] Yeah, ESMO is the European Society of Medical Oncology meeting. And it's basically one of three big meetings we have where a lot of advanced prostate cancer and even high-risk localized prostate cancer data is presented. And so, we have the American Society of Clinical Oncology with the American Society of Clinical Oncology with a genitourinary focus. That's our second meeting, and we also have the European Society of Medical Oncology. So, it's a big gathering of urologists, medical oncologists, radiation oncologists, etc. etc. So, it's a big academic meeting with a lot of important data presented, a lot of important data presented specifically at this meeting, which makes this discussion really exciting.

Phillip Koo, MD [00:01:21] Yeah, I will say this year for ESMO, there was so much excitement around prostate cancer, various trials that were reported. But today we're gonna focus on those that are closest to being able to translate into the clinics. So, let's, I'll turn it over to you and sort of take us step by step through the trials that you selected.

Zachary Klaassen, MD, MSc [00:01:40] Absolutely. So, the first trial was the ENZARAD trial. And this is a New Zealand Australian trial looking at high-risk localized prostate cancer. So, the top left is the trial design. We can see that these were men that were eligible, criteria included localized prostate cancer, suitable for radiation therapy, high risk of recurrence. And so, your Gleason 8 to 10s, your T3, T4 disease, PSA greater than 20. And they were randomized one to one to two different arms. So, the sort of traditional or standard of care arm was radiotherapy for 16 to 24 weeks, treated with an LHRH agonist, such as Lupron, which some men may be on that are listening to this webinar, as well as six months of a non-steroid antiandrogen. So, this is a standard of care arm.

The experimental arm was exactly the same radiotherapy, exactly the same LHRH agonist, except for 24 months of enzalutamide. So, can we super treatment-intensify these patients to see if there's a benefit for them? And so, what we found here that primary endpoint of metastasis-free survival by conventional imaging, so this is CT-bone scan, MRI, was no different between the two groups. And so, what that tells us is whether we gave men extra treatment intensification with enzalutamide or just treated them with the standard of care we had right now, there was no difference.

What we did see though, and in a subgroup analysis, and this is sometimes what happens in these big trials, is we don't see an overall effect, but is there a group that may benefit? And we see that the clinical N1 patients, so these are patients that have lymph nodes

enlarged on their CT scan before therapy. Did these patients have a benefit? And it turns out they kind of did. And we look at the ENZARAD study, the hazard ratio here is 0.43, which is very comparable to STAMPEDE that looked at abiraterone. So, this was a trial that's already been published. STAMPEDE abiraterone therapy is sort of standard of care in this disease space. And you can see here these hazard ratios are quite similar. So, perhaps in this trial of ENZARAD, there's a clinical benefit for CN1 patients. And I like this figure that I pulled out for the bottom right. This was in the discussion of this trial at ESMO.

And it sort of gives us a roadmap for treatment paradigm and who we could maybe think about combining pelvic radiotherapy, abiraterone, enzalutamide. And if you look at the first three, so N1 by conventional imaging, N1 by PSMA PET, or clinical N0, which means the lymph nodes are not enlarged, but their STAMPEDE criteria very high-risk, we could treat them with either abiraterone or enzalutamide and pelvic radiotherapy. If their clinical N1 STAMPEDE very high-risk, but a little more similar to ENZARAD, so this is getting a little bit in the weeds. Probably we don't have a benefit to adding enzalutamide or abiraterone. We could just treat them with two years of ADT and pelvic radiotherapy. If they're sort of regular risk, clinical N1, we've been treating them with two years of ADT and radiotherapy. That's probably reasonable to continue to do it that way.

Phillip Koo, MD [00:04:43] You know, Zach, this is really, you know, interesting. Clearly, this space is an unmet need. We know these patients come in; they have high-risk disease. And how do we sort of treat them more aggressively, so they don't recur, they don't develop, let's say, metastases or whatnot. So, this is really compelling. And it's also interesting for the listeners to see how these trials are designed.

Zachary Klaassen, MD, MSc [00:05:03] Right.

Phillip Koo, MD [00:05:04] You're trying to keep everything the same and just make one thing different with just having one variable. And then when you design it that way, the best as possible, you see these interesting results of them where you could tease out little subgroups as well. So, this is really promising. And hopefully, you know, we'll, you know, we'll be able to provide these types of options for patients who have more aggressive disease. But again, we just need to know who those patients will be.

Zachary Klaassen, MD, MSc [00:05:28] Right. The one thing I'll add, Phil, too, is, it's important too, we want to treatment intensify. We know there's potential additional side effects for those patients. So, it has to make a clinical benefit, clinically meaningful benefit as well. So, clearly the overall population didn't see a benefit. Perhaps those clinical N1 patients, there may be a benefit. Small subgroup, so more work needs to be done, but at least we have an answer that okay, all comers, we don't necessarily need to give enzalutamide to all these patients.

Phillip Koo, MD [00:05:55] Great. All right, so let's go on to the next study.

[00:05:58] Great. So, this is the EMBARK trial. And so, people that are astute listeners of our webinars at PCF or they're on UroToday, we have covered a lot of EMBARK over the last couple of years. It's been a revolutionary trial. And so, I'll just sort of briefly go through the EMBARK study design. So, this is patients that had high-risk biochemical recurrence, which means their PSA was going up after either radiotherapy or radical prostatectomy. And then they were imaged with conventional imaging. This trial took place a long time ago, and it was before the PSMA PET era. And so, sort of briefly, these men were randomized one to one to one. So, the first group at the top there in red was enzalutamide

monotherapy. The next group in yellow was leuprolide. And the second group was or third group was enzalutamide plus leuprolide. So, you have three different arms, big trial over a thousand patients. What's interesting is that, and we won't talk about this tonight, but if men were on this for 37 weeks and their PSA came down to less than 0.2, they got a treatment break until it started to go up. So, a very adaptive study design. The primary endpoint was presented a couple of years ago, was positive for both the combination and the enzalutamide monotherapy for metastasis-free survival. So, that means that whether we gave leuprolide plus enzalutamide versus ADT or just enzalutamide versus ADT, both of those endpoints hit at metastasis-free survival.

So, this has been in our clinics now for a couple of years. Regulatory approval essentially across the board, certainly FDA approval.

What we hadn't had until ESMO was overall survival, which was a key secondary endpoint. And so obviously we want men to live as long as possible, we want a survival benefit. But these trials take a long time to get to that completion point where we can say whether there's a survival benefit or not. So finally, many years of follow-up. They looked at the survival benefit as a key secondary endpoint. You can see on the left here; this is the enzalutamide combination therapy versus ADT alone or the leuprolide alone. We see a hazard ratio of 0.597. Basically, there's a 40% reduction in mortality for enzalutamide plus leuprolide versus leuprolide alone in this high-risk biochemical recurrent population. What we see here is the enzalutamide monotherapy did not have a survival benefit. So, there's a 17% reduction in mortality, not statistically significant.

And so, when I talk to patients about this, I say, listen, both of these work for metastasis-free survival. It's probably beyond the scope of tonight's discussion, you know, side effects of each of these regimens. But now we know with extensive follow-up, we have the first overall survival benefit in this disease space of high-risk biochemical recurrence. And again, high-risk biochemical recurrence, PSA doubling time less than 10 months, excuse me, less than nine months. And so, this is after therapy, PSA is going up. It's doubling every nine months or less. And so, this is not for everybody. It's for those really high-risk patients. The first time we've seen overall survival benefit.

Phillip Koo, MD [00:08:53] Great. So, I think, you know, patients can calculate those doubling times themselves, or you know, their treating team can calculate that. And again, if it's less than nine months, you get categorized as high-risk.

Zachary Klaassen, MD, MSc [00:09:02] Right.

Phillip Koo, MD [00:09:03] So, from your perspective, you know, clearly there's that overall survival benefit getting ENZA plus ADT. Are there ever any instances in which, you know, that ENZA-only treatment would apply and would be beneficial for patients?

Zachary Klaassen, MD, MSc [00:09:18] Yeah, it's a great question. And I give both these options to my patients. I've been doing it for two years. I still give them both, even after this data was presented a few weeks ago at ESMO. The reason it's important, there's a very known side effect profile for ENZA plus ADT. And that's obviously fatigue, there may be a little bit of brain fog with the enzalutamide. There's certainly going to be bone mineral density issues, you know, obesity. We know how to use this combination. We've been using it in advanced disease for a long time. And some men say, listen, I want that overall survival benefit. I know that gives it to me. We're gonna go with the combo. There's men that may be younger men, that may be older men that don't want the sexual dysfunction

side effects that we know we're not gonna get as significantly with enzalutamide monotherapy. We're not decreasing the testosterone like we are with the combination. The one thing I will say there's certainly a proportion of these men that will get gynecomastia or breast pain from the monotherapy. So, there's a whole discussion on what's your goals from an efficacy standpoint, but what's also your, you know, what's your risk aversion for side effects as well? So, it's still a conversation. We just have another data point. It's great to have OS data, but if the side effect profile fits for the monotherapy, men may choose that still.

Phillip Koo, MD [00:10:27] You know, I think that's a great point. Overall survival is very exciting. I think it's wonderful that EMBARK has that. But you're right, patient preferences and their goals are vitally important. So, thanks for reminding us about that. All right, so let's go on to the next trial.

Zachary Klaassen, MD, MSc [00:10:40] Yeah, so this is the PRESTO trial. So, a very similar population to EMBARK. This is high-risk biochemical recurrence. All these patients had their prostate removed. So, the EMBARK trial had prostatectomy or radiotherapy failures. This was just prostatectomy. So, that they had to have a biochemical recurrence with a PSA greater than five, again, PSA doubling time less than or equal to nine months. So high-risk biochemical recurrence. These patients were also staged on conventional imaging.

And they were randomized again, one to one to one, to three arms. So, arm A, LHRH analog, like leuprolide, arm B, the LHRH analog plus apalutamide, another one of the second generation ARPIs. And then arm C was sort of the super treatment intensification arm. This is LHRH analog plus apalutamide plus abiraterone acetate plus prednisone. And so, when we looked at the final result of PRESTO, and so they've had a couple of other presentations. I just pulled out time to mCRPC because I thought it was most representative. They looked at a lot of different outcomes.

What it tells us here, and I know the font's a little bit small, on the left here is LHRH agonist versus LHRH agonist plus apalutamide. We have a hazard ratio here of 0.55, benefiting the treatment intensification arm of leuprolide plus apalutamide. What we see on the right here in that sort of arm C, the super treatment intensification arm versus arm A. We also see a benefit versus leuprolide alone. But the benefit's very minimal compared to what we see on the left side here. So, what that tells me is we can add apalutamide to ADT and get a benefit. If we add apalutamide to ADT plus abiraterone, we get a benefit, but it's not that much drastic. That's not drastically different from just adding apalutamide itself. So, it tells us apalutamide on its own is doing a great job. We don't have to add the abiraterone. This is this also played out in the adverse events you can see here, especially grade three or four adverse events. Arm A 22%, arm B 26%. So very similar. When we add that abiraterone, we get up to 41%. And so, the risk-benefit profile starts to lose a little bit of appeal when we know we're getting good treatment efficacy from ADT plus apalutamide alone.

Phillip Koo, MD [00:12:53] You know, that's interesting. And this goes back to what we talked about earlier. If you are going to add more and treatment intensify, you want to make sure, you know, the benefits outweigh any of those adverse events. So, explain to us what time to CRPC means and how significant is that?

Zachary Klaassen, MD, MSc [00:13:09] Yeah, time to mCRPC is, I really like that as an endpoint because it's a very trial-relevant endpoint. It's also a very clinically relevant

endpoint. What that means is, if we start you on a medication today, how much time does it take for that medication to not work and for you to develop metastases, you know, prostate cancer outside the prostate or the area where we initially treated and become resistant to the therapy. So, we know that at that point the therapy is not working. So, we know for a couple of things. This is now getting into the potential lethal form of prostate cancer, but it also means we've got to change therapies. Patients don't want to get to that next step of mCRPC. They also don't want to change therapies. So, it's a very relevant endpoint for us as trialists, but also clinically when we speak to our patients.

Phillip Koo, MD [00:13:56] Great. And is it safe to assume that at some point we'll see overall survival data from this trial reported?

[00:14:02] It's a good question. It's the final results for the trial. So, I don't believe they're gonna continue to follow them up for overall survival benefit. It takes a lot of time and money to continue following patients in a trial setting. So, unlike EMBARK, which had a big trial, lots of big funding, not that PRESTO didn't, but I think this is the final results for this trial.

Phillip Koo, MD [00:14:20] All right, great. Thank you. So, let's go on to the next trial. And I know this has garnered a lot of attention.

Zachary Klaassen, MD, MSc [00:14:27] Yeah, so the next trial is the CAPItello trial. So, this is a metastatic hormone-sensitive prostate cancer, CAPItello-281. We've known for decades that the androgen receptor is very key to prostate cancer progression. You can see it here on the left-hand side of the screen. But we've become more adept at sort of seeing is their other ways that prostate cancer can sort of get out of control? And one of them certainly is the PI3K/AKT signaling pathway. PTEN loss is certainly key. We know that men that have PTEN loss tumors generally do quite poorly.

And so, I'll flip over to the right side of the screen. This is the CAPItello-281 trial design. So, all of the men in this trial had to have a PTEN deficiency. And there's a couple different ways to measure this beyond the scope of this discussion, probably, but there had to be a loss of expression of PTEN. What's important here is to get to those 1,012 patients that they randomized, they had to screen 6,200 men to get down to that 1,000 that actually had a PTEN loss. So, it's not that this is uncommon, but it's not a super common a mutation that we see in prostate cancer.

What's really important here is that those men were then randomized to capivasertib versus plus abiraterone plus ADT versus placebo plus abiraterone plus ADT. So, again, as you mentioned earlier, we have a very similar arm, but we're just adding one thing. So, this is the inhibitor of this pathway here on the left. Capivasertib was the sort of experimental treatment in this situation. So, this was a positive trial. The primary endpoint was radiographic progression-free survival. This is in the bottom right of the screen. And you can see here the hazard ratio was 0.81. So, a 19% reduction in mortality or radiographic progression, statistically significant, about an overall seven-month benefit. And so, this was a huge deal because we actually have a biomarker influencing assessment before randomization and then testing the treatment versus sort of standard of care. And we saw an improvement in radiographic progression-free survival.

So, I think, as you mentioned, a lot of interest garnered here, a lot of sort of downstream effects about testing these patients, importance of that. And so, I think we'll continue to

see additional follow-up from this trial, which will be really important for hopefully getting regulatory approval, but also learning more about the subsequent outcomes.

Phillip Koo, MD [00:16:55] You know, Zach, this was really interesting because I love the fact that, you know, this takes us even deeper into this idea of precision medicine.

Zachary Klaassen, MD, MSc [00:17:02] Yes.

Phillip Koo, MD [00:17:02] So, what you know, how do you detect PTEN loss and what advice do you have for patients to, you know, again, this isn't FDA approved, but sort of the approach, that what it could look like if it was FDA approved.

Zachary Klaassen, MD, MSc [00:17:17] Yeah, currently it's by partnering with our pathologist to get stains that tell us whether there's loss or not. So, it's definitely not just a quick, you know, write a script and we figure out if you have PTEN loss. It takes a little bit of work to get to that. I think, you know, we had a lot of discussions around this at the meeting and even at subsequent meetings at the PCF Retreat, just discussing is there ways to improve efficiency for detecting PTEN loss, whether that's with artificial intelligence, other ways of detecting it. So, I think we'll get better at detecting it, a lot more efficient. Currently it's an immunohistochemical stain, so it has to go to the pathologist to specifically look at that. But you're right, there's a lot of especially if this gets regulatory approval, which I really hope it does because it's a great option for patients that have PTEN loss, there's gonna be a lot of sorts of downstream effects that we'll have to work out some of those logistics.

Phillip Koo, MD [00:18:04] That's great. You know, I love that comment. I think having as many options and figure out which options are best at what time is really, really how we'll hopefully move that dial to improve the overall survival, improve clinical outcomes.

Zachary Klaassen, MD, MSc [00:18:18] Absolutely.

Phillip Koo, MD [00:18:18] So, let's shift to the next trial and this is interesting because it's a drug that we're familiar with. It's been FDA approved, but you know, it's being continually studied in different settings.

Zachary Klaassen, MD, MSc [00:18:30] Yeah, absolutely. So PSMAddition, again, going back to metastatic hormone-sensitive prostate cancer. We had lutetium already approved in the VISION trial. So, post-mCRPC, post-ARPI, post-docetaxel. This was several years ago. Just recently, we've had approval about six months ago, roughly, March, I think of 2025. PSMAfore looking at the same mCRPC patients, but pre-chemotherapy, post-ARPI. And now we're seeing a big phase three trial readout for metastatic hormone-sensitive prostate cancer. This is the PSMAddition trial. And so, you can see the trial design here, just briefly. This is essentially standard of care for mHSPC, which is typically an ADT plus an ARPI. That was the standard of care arm versus standard of care plus lutetium PSMA-617, radioligand therapy. And so, this has created a ton of buzz over the last several years, certainly for this trial as well. The primary endpoint here was radiographic progression-free survival. What's important though is if patients progressed in standard of care, they could then be eligible to receive lutetium after progression. So, that's a relevant point that I'll come back to in a minute.

When we look at the rPFS benefit here, this is radiographic progression free survival. This is the primary endpoint, positive trial. We see a hazard ratio of 0.72. This is a 28% reduction in radiographic progression or mortality. And so, this has benefited that sort of triplet therapy intensification with radioligand therapy. Because a lot of these patients did cross over to receive radioligand therapy after they progressed on standard care therapy, we don't have an overall survival signal yet. And we may not. I think when a lot of the patients are all getting the same treatment eventually, that may affect the overall survival. So, we don't have an overall survival benefit, but it's again positive trial, rPFS positive.

What's interesting though, we know there's side effects to everything we give, whether it's ADT, ARPI, Lutetium-617. And so, the discussion at the meeting and something we have in the clinics if this gets approved in this space is, what side effect profile are we willing to take earlier on with radioligand therapy versus waiting until later in disease therapy. Certainly, we see here any grade dry mouth, 45% with the lutetium arm, 3.7% in the control. Nausea, 34% versus 9.4. I'll go down to dysgeusia, which is sort of this the taste is a little bit off, 11.9% versus 4.1%. So not surprising, we do see some more side effects here. Again, this will be a discussion with our patients, and we know that this works later in lines of therapy. So, it'll be interesting to see how further follow-up from this trial sort of plays out with these two curves we see on the bottom of the screen and whether this gets regulatory approval from the FDA.

Phillip Koo, MD [00:21:23] You know, I think these are wonderful points. Side effects are vitally important to understand and for patients to understand, you know, what they could expect as a side effect of these drugs.

Zachary Klaassen, MD, MSc [00:21:35] Right.

Phillip Koo, MD [00:21:36] Oftentimes, when you treat patients earlier, some of these side effects become, in some ways, a bigger issue. Radiation exposure can become a bigger issue. And I know this drug now is available in multiple different spaces along the continuum of prostate cancer. So, what advice do you have for patients to sort of figure out when they should, you know, ask or discuss this treatment option along their course?

Zachary Klaassen, MD, MSc [00:22:00] Yeah, great question. Let's assume this gets approval, which I think it probably will at some point. We're gonna learn more from PSMAddition over the next couple of meetings as well, I think.

To answer your question, but when should patients ask about it? They should ask about it at this initial visit. If they have metastatic hormone-sensitive prostate cancer, we now have several options we've talked about. And really, it's gathering information, understanding side effect profile, understanding what the, you know, we don't have a perfect sequence for every patient of how we should treat them, but knowing this is available, seeing what the benefit is, seeing what your clinician thinks. I

'm always a fan of second opinions. If your doctor doesn't talk about it, if you want to hear about it, find somebody who's you know familiar with it. But certainly, this is moving up. And I think it's exciting to have other options. We have great doublet options, you know, whether it's ADT plus darolutamide, apalutamide, enzalutamide, abiraterone. Is there a benefit to treat triple intensification with radioligand therapy? Probably for some patients, it's just figuring out who's gonna be the best, get the most benefit out of this in the earlier stage.

Phillip Koo, MD [00:23:05] Great. You know, just one last question. We often talk about overall survival as the gold standard. That's what we're shooting for. When you have trials that are treating patients earlier and earlier, it's really hard to get overall survival. You talked about crossover, which makes it a little bit more challenging to calculate the overall survival benefit. What advice do you have for patients? Because I'm sure they might sit down with their provider and they'll say, Oh, that, you know, we don't know the overall survival, but these endpoints are better. How do patients navigate that?

Zachary Klaassen, MD, MSc [00:23:34] Yeah, it's really hard. And it's honestly hard for us as clinicians sometimes sort of explain it properly. I think you look at the fact, there's two things. You look at what the primary endpoint for the trial was. The primary endpoint for this trial was radiographic progression-free survival. That was positive. It's a positive trial. We all would love overall survival benefit, but in a day and age where patients know about radioligand therapy, they may go get it down the road outside the trial. They'd rather have good clinical equipoise, meaning run a run a good trial where there's access to therapy after progression. That's why you see these patients cross over to get the actual treatment drug. And like you said, you can do a lot of fancy statistics, but at the end of the day, if there's a huge proportion of the control on getting the radioligand therapy, you're probably not going to see an overall survival benefit after that primary endpoint is met.

Phillip Koo, MD [00:24:24] Great. Thank you. So, let's go on. We talked a little bit about precision medicine, genetic testing, somatic testing, germline testing. We've had a lot of webinars about this. Very happy to show that we have a new resource on the PCF website that really outlines and educates on this topic. But Zach, any comments about this and how you see this helping patients?

Zachary Klaassen, MD, MSc [00:24:47] Yeah, this is really good to highlight, Phil. And I think, you know, Channing Paller is a medical oncologist that gave a great discussion at ESMO, and I covered it on UroToday. So, I think we can probably link this video to that discussion. But really just - and the ASCO guideline is just an example of how complicated this can be. I think it's super important for patients and their family members to understand just basically the difference between somatic and germline testing. We know germline is what is in your DNA of every cell, that's what you pass on to your children. Somatic is at the tumor level. And so, there's two differences there. But this kind of resource by PCF is fantastic because it really goes into explaining this at the patient understanding, because we're going to continue to see more of that.

We just talked about CAPItello-281, and these sorts of trials are going to continue to bring up the importance of understanding what your tumor biology looks like. And if you have a high risk-and and there's germline testing conversations, what that means and what it means to sort of your family members as well.

Phillip Koo, MD [00:25:48] Great. Thank you, Zach. And I do want to recognize the AUA and the Urology Care Foundation for working together on this project and also AstraZeneca for supporting it. And as Zach said, it's a great resource and it really helps patients learn more and feel empowered throughout this journey. So, thank you very much, Zach, for your time and for covering these important trials from ESMO.

Zachary Klaassen, MD, MSc [00:26:09] Absolutely, Phil. Great chatting with you. Hope it's helpful for our patients. Thank you.