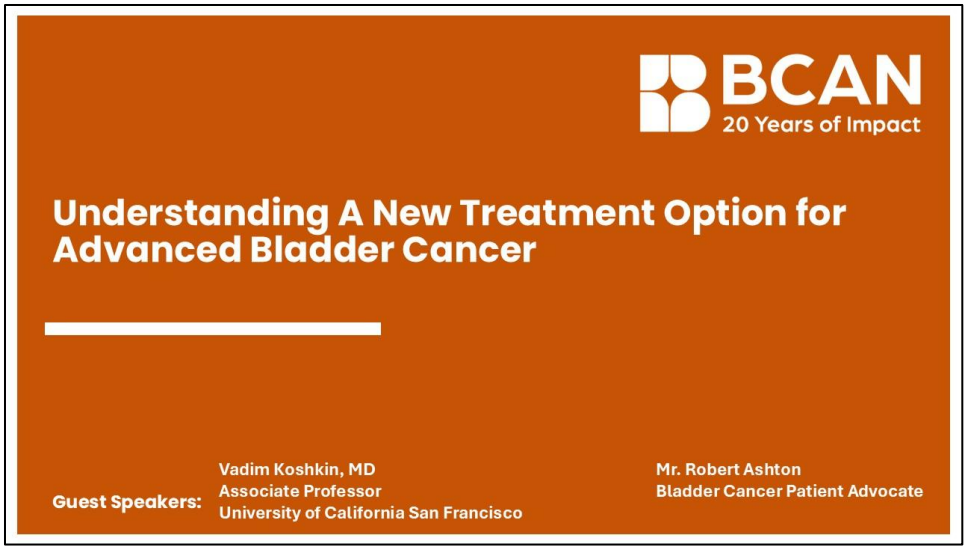

Patricia Rios:

Thank you for sharing that. I have a follow-up question, but I'm going to; I'm looking at all the questions on the Q&A box, so I'm going to go through all of those because there's a lot coming through and so, just a few … We will go a little bit over our scheduled time. And so, please stick around. So one of the questions from one of the participants is why doesn't the cancer that has metastasized to the adrenal gland respond to EV-pembro?

Dr. Vadim Koshkin:

Well, I mean, to my knowledge, that's not, you know, usually the case. I mean, you know, the different cases are different, so there may be situations where, you know, in particular cases that metastasis did not respond to treatment. But, I mean, I can certainly think of, you know, patients who I've had that did have that metastasis and it did respond.

So I don't think there's anything kinda specific about that location that, you know, indicates this therapy doesn't work as well. To my knowledge, there isn't really … I mean we have looked at this actually, looking at are there sort of specific situations in which it wouldn't work as effectively like based on the spread of disease or something else, and we're not really finding a lot.

I would say just the situations where maybe we're not as sure about, you know, the efficacy of this regimen are in bladder cancers that are not of the typical urothelial histology. So basically a slightly different subtype of bladder cancer that maybe doesn't express the target of the drug, of enfortumab vedotin, called nectin-4 as much. But even in many of those cancers, we still do see responses with this therapy.

Patricia Rios:

Good to hear. What is the maintenance protocol after the tumor has been eliminated? You talked about complete response and response ... What's the surveillance and just maintenance?

Dr. Vadim Koshkin:

Yeah. So at this point it's really quite variable, I would say. So usually if a patient has been on, you know, treatment with this for a few months, have had a complete response, meaning, you know, you have tumors on scans before treatment, then, you know, after starting on treatment, you get the same scans and the tumor isn't there, right.

So then we usually, you know, still continue treatment with both drugs for at least some time. There isn't, I would say at this point, a magic number or time when we can definitely say like this is, you know, this is the limit of it. At least we don't have that data yet. So because of that uncertainty, we usually continue it for some time, but keeping in mind the side effects, right? Because, again, you know, a patient has responded to treatment completely, but if they start, you know, developing more neuropathy, I would be probably more aggressive about, you know, stepping off of the treatment and maybe stopping at least one of the drugs, like enfortumab, in that situation.

Then oftentimes the ... To address the question directly, the maintenance ends up being pembrolizumab alone. So we stop enfortumab, the drug that probably causes more side effects and continue the immunotherapy drug that still is sort of working on your immune system, but usually doesn't cause as much side effects and we continue that for a bit longer.

But then, you know, if a couple of years down the line, or even less amount of time, we, you know, are still in a complete response, we could, you know, stop therapy altogether and then just monitor with scans. I do, though, you know, continue monitoring, and I want to emphasize that that's, in particular, important, right, you know, that we still ... Even patients who stop treatment, who are in, you know, that very good situation where they can stop treatment, we still watch things with scans every few months just to make sure that if there is a, God forbid, you know, recurrence of the cancer, that we can, you know, address it promptly and potentially restart treatment.

Patricia Rios:

This is kind of related, you talked about perhaps stopping EV. What, is there a recommended like low dosage where it may become ineffective, or is it stopping it altogether the best approach?

Dr. Vadim Koshkin:

Yeah. So we have, I would say, a pretty well-worked out protocol, again based on experience from clinical trials, of how to reduce dose. There are basically four different dose levels of

enfortumab that we use, starting with the highest dose, and then we can reduce it about three times before we have to stop it kinda completely.

But the decision to stop completely, at least in my practice, centers more around the side effect. So if we are getting to the point where I feel like, you know, we've gotten all the benefit, most of the benefit that we can from this and further treatment just, you know, causes more neuropathy, causes more discomfort for the patient, that is where I would probably step off and stop the drug.

Keep in mind that, again, you know, the cancer has never been able to progress and grow successfully on treatment, meaning that if there is a recurrence later, we can still retreat, right? retreat with this combination.

Patricia Rios:

I don't know if we had too much time to talk about how the medications are administered. And so, one of our listeners wants to know how is it dispensed in the body. Is it directly into the bladder or intravenously? That question is for both. Dr. Koshkin, if you can, you know, speak about how it is administered and, Robert, your experience with that piece.

Dr. Vadim Koshkin:

Yeah, I'll just say quickly that this ... So this specific combination that we're talking about here is given intravenously, because this is meant for treatment of metastatic or systemic disease, so cancer that's potentially anywhere in the body, places where we can see it on scans, but also other places where perhaps it's microscopic. So it goes in your vein and technically all over the body, right, not just inside the bladder as certain treatments do. When you're early on in the treatment course of bladder cancer, it's limited just to the bladder. Then in terms of how the experience goes with getting these drugs, that's, I mean, yeah, certainly something Robert can speak to more.

Robert Ashton:

Yeah. As Dr. Koshkin said, it is delivered IV. I do have a port, so it's delivered through my port. As I mentioned, it's an infusion on day one when you get both medications, about an hour total time because each drug is a 30-minute infusion. And so, they just access the vein as they typically would with any other IV drug, and then they, it's administered via the pump, and then you're on your way. So compared to several of the other therapies I've been on, this one's pretty easy to take.

Patricia Rios:

Good to know. Speaking of ... Well, there is a ... We talked about whether this is available in different settings, academic versus community. I'm curious to know in terms of coverage insurance, are there any limitations cost-wise that patients should be aware of?

Dr. Vadim Koshkin:

Yeah. Well, again, I think I'll probably address it maybe from my end, and then Robert, hopefully, can speak to this as well, just because this is another topic where I think the patient voice is probably a lot more critical than mine. I will say that when a therapy is FDA-approved like this, insurance should cover it, right. But of course that is a blanket statement that applies very differently, I think, to different people.

So, yeah, there should be no issue with getting this, you know, reimbursed by a coverage plan, because as long as, again, it's being used in the correct circumstance, which is for, you know, advanced bladder cancer, as I mentioned, it will probably be expanding to a broader population of patients based on, you know, additional trials that are coming out as positive in patients with muscle-invasive disease. That is not the case yet. So technically right now we would not be able to use it and for it to get reimbursed in that situation. But that's probably, probably coming down the line.

But, yeah, so from a physician end of things, I've not had, you know, situations where you order this regimen and the insurance company blocks it or rejects it because, again, it's an FDA-approved drug, the way that they can reject certain other things, even like scans or things like that. But, you know, these are very, very expensive drugs, I mean both of them. If this is something that someone would pay for out of pocket, which no one should, it's tens of thousands of dollars per dose, right. So not something anyone would really consider reasonable.

Then, of course, depending on your specific coverage and plan, that even a percentage of that, I think, can still hit a patient significantly. I don't know, if Robert, if you have more to add to that.

Robert Ashton:

No, I would only add that it's going to be variable by individual plan and what they cover. Fortunately, my insurance does cover it, so I have no out of pocket for the infusion cost or the drug itself. But as Dr. Koshkin said, it is, by their own, it is extremely expensive. However, it is an FDA-approved treatment and therapy. But it does go back to the individual plan and what they cover.

But I switched insurance companies, and it wasn't preapproved yet for the first dose that I got, but it was approved shortly thereafter. And in fact, they approved me for a total year. So they knew that once you start, you're probably going to be on this for a while, and they didn't want to have to go through this all the time. But it will be variable. But I haven't heard of any specific individuals that were rejected for it.

Patricia Rios:

Thank you for sharing that. So looking at the time, I have two questions for you, Robert, and one for you, Dr. Koshkin. One of the questions is the same one for both of you, but what I'll do

is; Robert, this question was directed to you. What advice or what would you say to a patient that's considered this treatment option?

Robert Ashton:

I'm sorry, Patricia, you broke up just a second.

Patricia Rios:

Oh, so sorry. Let me try again. This is a question from one of our audience participants who wants to know what piece of advice would you give to a newly diagnosed patient contemplating whether to receive this treatment or not?

Robert Ashton:

Yeah, I think if you've been newly diagnosed first, I would recommend you take a deep breath. The diagnosis is a lot to take in. But, second, my advice is just be curious. Learn as much as you can, not just about the treatment, but also about the disease. You know, Dr. Koshkin's overview was very helpful, talking about how it works, et cetera, and what is its benefits over others, as well as also what are some of the challenges with the medication.

So, learn as much as you can, as well as take advantage of all the resources you may have available and these include everything from your healthcare team, your oncologist to radiologist, the nurses, technicians, and all of the other healthcare professionals that you'll meet along the way. They manage this disease every day as well as work with this combination. I've always been impressed by how much knowledge they can share.

The other place I would look to is patient associations like the Bladder Cancer Advocacy Network. They offer a wealth of resources where information and help can be found on an easy-to-access website. Another place is your cancer support services that's may be offered through your local hospital, that will be … They can give information on some of the things that support you around the treatment of the disease, as well as speak with other patients that are going through this, and particularly those that are having the drug administered. You know, how are they responding to it? How are they tolerating it, et cetera?

I think it's a great combination. It has really kept my disease stable in majority of the cases, and much longer than I had anticipated personally. So I'm thankful it's here. It is relatively well-tolerated. I think Dr. Koshkin did a great job of covering what the side effects are. Just continue to learn more about it and speak with the experts who use it on a regular basis, and experts including patients.

Patricia Rios:

Thank you for the special recognition to BCAN. Dr. Koshkin, there's a lot of questions in the chat about dosage, restarting, and effectiveness. I'm curious to know if you have some sort of general advice to those who are joining us today, who need a little bit more guidance or information about how to proceed now that they either have started treatment, stopped, or are not sure, you know, if it's working.

Dr. Vadim Koshkin:

Yeah, all of these cases are so individualized, right, and so different, I think, from each other that it's hard to give like a blanket statement as guidance. In part, that's what, you know, clinical trials try to do is that everyone basically usually gets the same thing or there's a strict set of rules that guide sort of what you do if something happens. But then when this therapy becomes available for the broader population in the real world where we're using it for now thousands of patients, then it's you learn as you go along and you acquire those experiences.

So I would say, again, it's very variable what you do in different situations in terms of situations in which you would reduce dose or maybe stop the treatment and give patient a treatment break altogether, right.

And so, the key thing, again, I think for the patient to be aware of and to do, and I try to highlight that in my presentation as well, is just to be pretty candid about their side effects and what they're experiencing, right, because I mean sometimes, at least what I found, some patients are worried about endorsing side effects too much with a concern that this will, you know, ... a treatment that's working will be pulled back.

But it is really, again, just critical to do so because it allows us to, I think, more effectively dose the drug, right, and really, I think, help patients more and more effectively and not allow for the side effects to get worse and then impact really the treatment going forward. But aside from that, yeah, I mean I think in a lot of situations, even after a, you know, patient has been on this treatment and they take a break, we can resume treatment and it still works. We've seen that quite a bit.

We're also now learning we have other approaches and other biomarkers that we use. So not just CT scans, but things like tumor DNA. So that's a blood test that we also use to monitor therapy. Right now we mostly use it for patients actually with earlier stages of disease, so muscle invasive disease. But actually we can use it for monitoring on any immunotherapy regimen as well.

That's something that we're kinda using more and more and I think becomes a very useful adjunct to know when to discontinue treatment, when to resume it again. I think, you know, when we have this conversation two years from now, I think we'll know even more than today and have more guidance and more sense of how to do these things.

Patricia Rios:

Thank you for answering that, and I think that is something we're all looking forward to see where, what the future holds in terms of this therapy and how it can be used in other stages or types of bladder cancer.

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