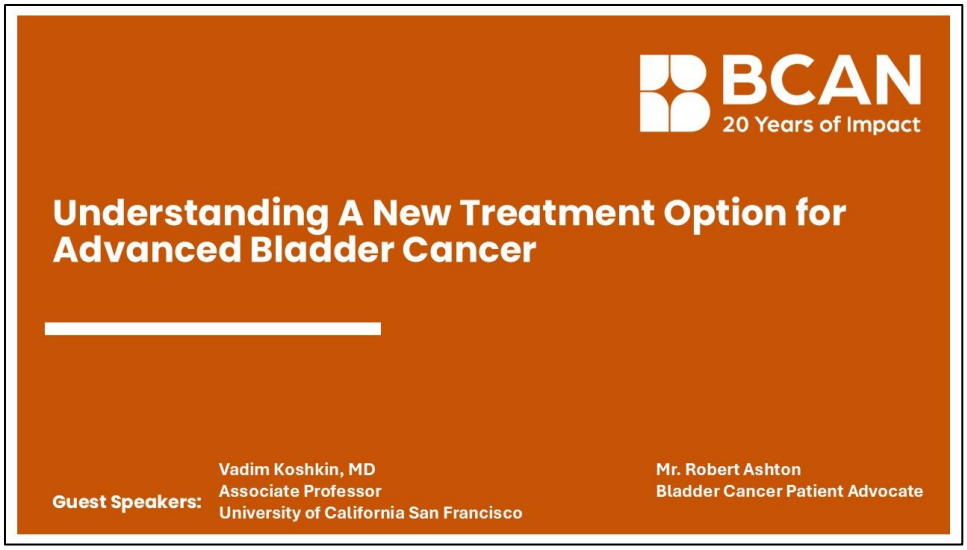


Patricia Rios:

I want to welcome you once again to the Bladder Cancer Advocacy Network Patient Insight Webinar Series. My name is Patricia Rios, and I am your host for today's program on understanding a new treatment option for advanced bladder cancer.

A combination treatment that includes EV plus pembrolizumab is changing the way advanced bladder cancer is treated today. This powerful combination is designed to help the body target and fight cancer cells more effectively. By doing so, it is offering new hope to patients and families.

To help us understand what is EV plus pembrolizumab, how it works, who it may benefit, and what patients can expect, we have invited Dr. Vadim Koshkin, genitourinary oncologist at the University of California San Francisco, where he co-leads the bladder cancer clinical program.

Dr. Koshkin received his medical degree from the University of Chicago Pritzker School of Medicine and completed his oncology fellowship at the Cleveland Clinic. His research interest at UCSF focuses on clinical trials, targeted agents, and biomarkers in bladder cancer. Clinically, he focuses on taking care of patients with advanced bladder cancer.

Joining Dr. Koshkin is his patient Robert Ashton, who will share his real-world experiences and insights with this therapy. Mr. Ashton resides in the San Francisco Bay Area, but is originally from Nashville, Tennessee. He has over 30 years of experience in healthcare and is currently consulting part-time to pharmaceutical biotech companies. Mr. Ashton sees each day as an opportunity to learn more about living with bladder cancer and in his free time, he enjoys traveling, cooking, hiking, music, and spending time with family and friends.

We'll get to hear more from Robert after Dr. Koshkin's presentation. But without further ado, I'm going to hand over the screen now to Dr. Koshkin for today's webinar on understanding a new treatment option for advanced bladder cancer.

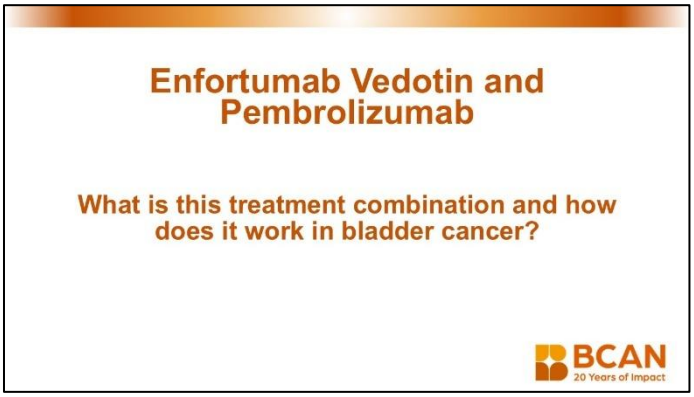
Dr. Vadim Koshkin:

Thank you, Patricia, for the very nice introduction. I really appreciate the ... Well, BCAN putting on this event and the opportunity to really you know, share what I think is really very important data and very important information about this new treatment regimen that we have for, for patients with advanced bladder cancer.

Of course, in addition to me speaking about this today, one of my patients, Mr. Ashton, will join us as well and discuss the patient perspective here, which I think is, is really especially, especially critical.

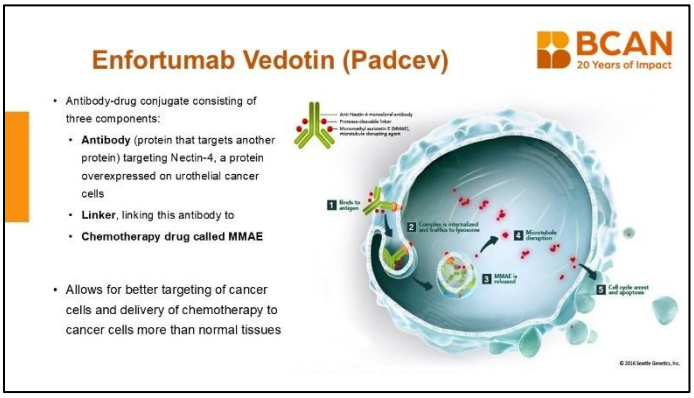
Dr. Vadim Koshkin:

So the treatment we're talking about, of course, is enfortumab vedotin and pembrolizumab. We will focus on what is this treatment and how does it work in bladder cancer. Of course this treatment combination consists of two very different drugs, right, and they're drugs that work quite differently as well. So one is enfortumab vedotin, which I'll discuss first.



Dr. Vadim Koshkin:

So this is a type of drug called an antibody drug conjugate, which is a new and a very different class of drugs than what we've had historically for bladder cancer and historically for cancers. It is really only over the last several years that we've seen these drugs sort of gradually become introduced into clinical practice across many different cancers. And in bladder cancer, this drug in particular was approved initially in about 2019.



Now there are several of these drugs approved across the oncology landscape, so not just in bladder cancer but for the treatment of other tumors, and they've been really, I would say, nothing short of revolutionary in, treating patients with cancer and in oncology. Then bladder cancer in particular, this drug, I would say, has been absolutely transformative as well.

So what is new and different about these drugs? Well, we conventionally used to give you know, chemotherapy by just infusing the chemotherapy drug into the patient's vein, and then where it goes all over the body, and affects, of course, cancer cells, hopefully, and hopefully destroys them, but it can affect other normal cells and normal organs as well. That accounts for a lot of the toxicity, a lot of the side effects associated with chemotherapy and, as a result, can limit both the how much a patient can tolerate a given treatment and also really how effective it can be.

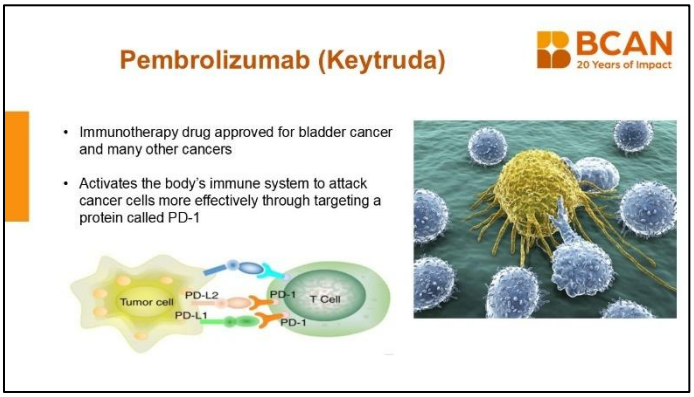
Well, these drugs, antibody drug conjugates, allow for a targeted delivery of chemotherapy specifically to the cancer cell. So these are complex drugs. They consist of at least three major components, as shown in the screen here. So an antibody, which is a protein that targets another protein. It usually is specific for another protein on the surface of cancer cells in the way that a key is specific to a lock. So it fits directly in and fits only you know for that lock.

And so, this drug consists of an antibody that targets nectin-4, a protein that's expressed in urothelial cancer cells, and it is linked via a linker molecule to a chemotherapy drug. In this case it's a chemotherapy drug called MMAE. There are different types of chemotherapy drugs that work differently, but this particular chemotherapy drug, when it enters the cancer cell, it affects the ability of the cell to divide and eventually leads to its demise. That's how it is able to you know destroy cancer cells and destroy tumors.

Again, attaching this chemotherapy to the antibody that fits specifically to a marker on the surface of the cancer cell is what's really kinda transformative here, allows us to deliver you know chemotherapy specifically to the tumor in a more targeted way, and allows, at least in theory, for a much more effective treatment.

Now, of course, you know, in real life, and certainly in the human body, things don't work quite as cleanly. Oftentimes this chemotherapy drug can still fall off the molecule and cause side effects elsewhere in the body. But in the majority of cases, it is delivered to the area where we want it to go.

Dr. Vadim Koshkin:

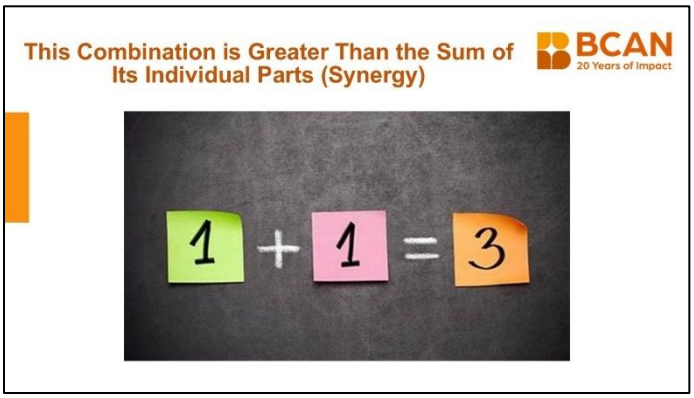


The other drug that's part of this combination is pembrolizumab or also known as Keytruda. This is a very different type of medication, so it's an immunotherapy drug approved for bladder cancer, but also for many other types of cancers. The late President Carter actually was treated with this for melanoma, a very different type of cancer, and you know lived for 10 years in a situation that you know previously was highly lethal. And so, this is a drug that's effective

for a number of cancers, but is also specifically approved in the treatment of bladder or urothelial cancers.

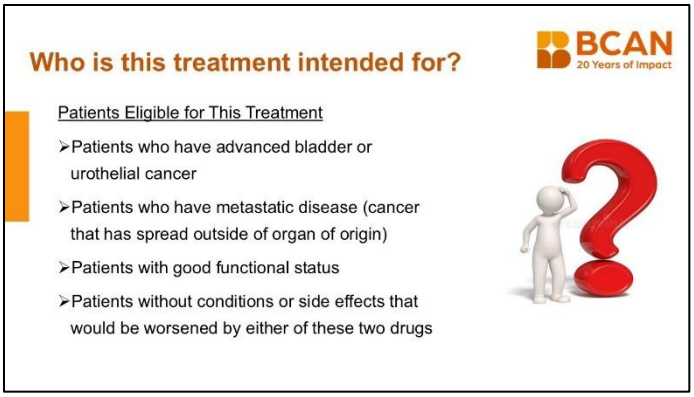
It works very differently not by attacking the cancer cell directly, but by activating the immune system, revving it up in a way, to then attack the cancer. That, we think, allows for often more durable responses to treatment, because in a way it trains your immune system. It conditions it to recognize tumors better and to really go after them more aggressively.

Dr. Vadim Koshkin:



What's really, I would say, transformative about this combination of these two drugs, which, again, work very, very differently, is that they have true synergy. What I mean by synergy is that the combination of their individual components, or the combination of these two drugs, is greater than the sum of their individual components. So each drug makes the other one work better and, as a result, we have a very effective new therapy for advanced bladder cancer.

Dr. Vadim Koshkin:



So, who is this treatment actually intended for? It's important to you know, really specifically highlight who is this treatment right for at this time. So this is a treatment for patients who have advanced bladder or urothelial cancer.

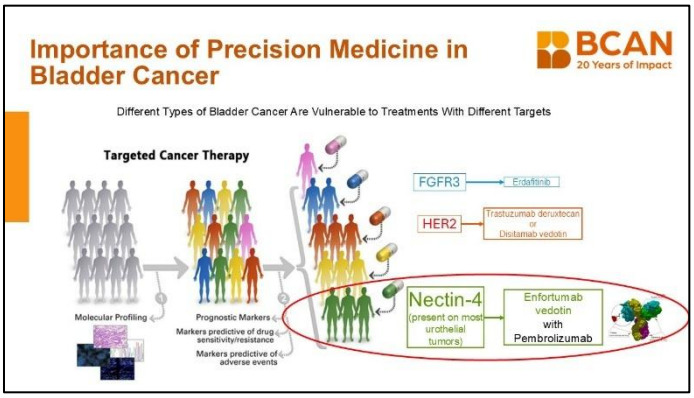
Bladder and urothelial cancer are words we often use interchangeably, but they're actually a little different. Urothelial just refers to the type of cell that lines both the bladder but also the rest of the genitourinary system, so including the ureter, so the tubes that lead to from the bladder to the kidneys, and even the entrance to the kidney is lined by these cells. So these cells, when they become abnormal and cancerous, can lead to urothelial cancer arising anywhere, not just the bladder but anywhere in genitourinary tract.

This combination is appropriate for actually patients with tumors arising anywhere in the GU tract. However, patients have to have metastatic disease, at least at this point, to receive this treatment to actually benefit from this treatment. That may change actually just in the very near future, and we'll talk about that in a little bit, a bit later in my talk.

But to tolerate this treatment, it's also important to keep in mind the patients have to have a good functional status. What I mean by that is this is a treatment that can have, of course, side effects. You have to be in reasonably good shape to be able to withstand that. That's why that's a very critical consideration for any you know, doctor who, of course, treats patients with this disease.

Then, of course, if a patient already has some of the side effects that can be worsened by some of these drugs, and we'll discuss what these side effects are a little bit later, then we're also pretty cautious about administering this treatment.

Dr. Vadim Koshkin:



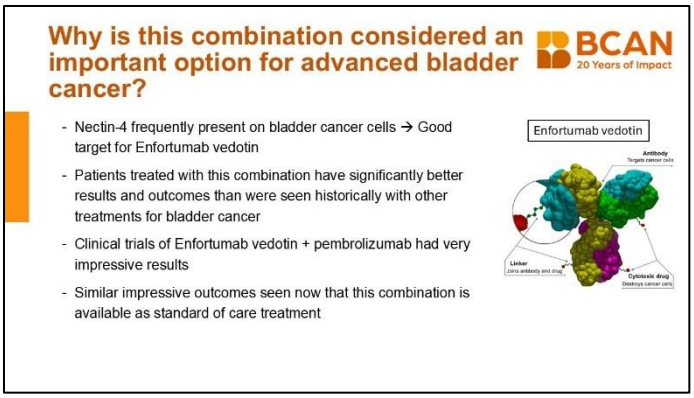
Before moving further, I also want to discuss the importance actually of precision medicine in cancer in general and in bladder cancer in particular. What I want to highlight is that you know, the entity, we call it cancer certainly, or even the entity we call bladder cancer, encompasses a whole wide variety of tumors, and each tumor is, in particular, pretty different from the next. Each tumor has a unique pattern of mutations that's almost like a fingerprint that may make it more or less vulnerable to certain treatment.

And so, with certain tumors, they have, for instance, expression of certain proteins like HER2, which makes them vulnerable to certain medications, which means we could you know effectively treat them with those drugs. Other tumors have mutations like in a protein called FGFR3 shown here, which, again, make it vulnerable to another type of drug.

But really across the board, many of the urothelial or bladder tumors have expression of this protein called nectin-4. That is the target of enfortumab vedotin, and that's what in particular makes this such a useful combination. We don't actually even have to test the tumors for expression actually of this protein to start this combination treatment because most urothelial or bladder cancers we know will express nectin-4.

Dr. Vadim Koshkin:

So why is this combination considered such an important option for advanced bladder cancer? Well, as I just mentioned, nectin-4 is very commonly present on the surface of bladder cancer cells, and it is a great target for enfortumab vedotin. Enfortumab vedotin works very well specifically in this situation.

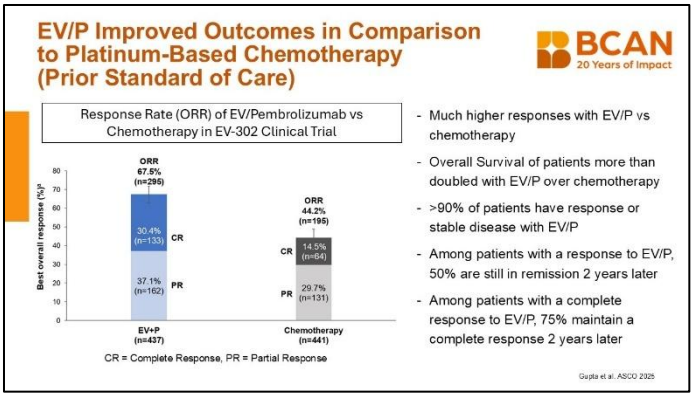


Patients treated with this combination have significantly better results and outcomes than historically we've seen with prior treatments for bladder cancer, in particular with, for instance, chemotherapy. The prior standard of care in bladder cancer before the advent of this combination was chemotherapy with a drug called cisplatin or carboplatin, and that was the standard of care for several decades, for about 20 to 30 years, until this trial of enfortumab vedotin and pembrolizumab was able to demonstrate the superiority of this combination to chemotherapy.

Now that this combination has been approved, at least in the United States, for some patients, it's been approved for over two years now, really since April of 2023, and across the broader spectrum of patients with urothelial cancer, it has had a full FDA approval since December of 2023. So now for almost a, well, soon it'll be two years, we've had a lot of experience also with this combination in a real-world setting, so outside of clinical trials, which, of course, is a very different, you know, group of patients than those patients who are in clinical trials. But we've seen the same impressive outcomes, and this really suggests that this is a very, very effective treatment.

Dr. Vadim Koshkin:

Here's what I mean by this. We see actually much higher responses with enfortumab vedotin and pembrolizumab in comparison to platinum-based chemotherapy. What I mean by responses here is a reduction in tumor size or tumor volume that we see on scans after starting treatment relative to before treatment.



In oncology, there are specific definitions of what a response means, but suffice it to say, it means a significant reduction in tumor size. With enfortumab vedotin and pembrolizumab combination, we see this significant reduction in more than two thirds of patients treated. In another probably 20 to 25%, we also see stable disease, meaning the tumor shrinks a little bit, but maybe not significantly, but at

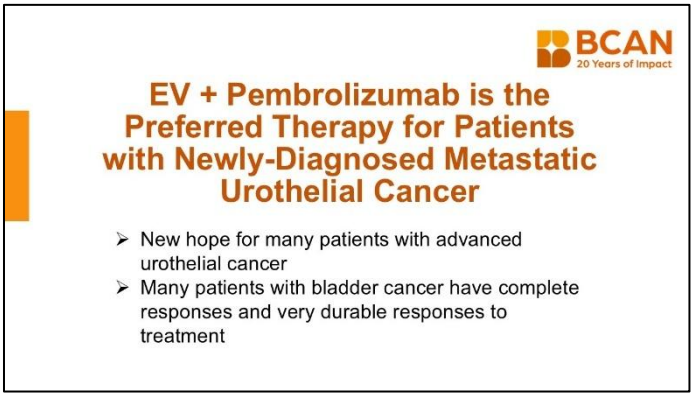
least it doesn't continue growing. Only a minority of patients who start this combination of enfortumab vedotin and pembrolizumab, actually less than 10% of patients, does the tumor continue to grow even as they're being treated and, as a result, we have to switch to something else.

So these are numbers that are much better and superior to what we've seen historically with platinum-based chemotherapy. We saw responses of about under 50% and probably disease control rate or basically clinical benefit, meaning response, and stable disease probably in the 60 to 70% range. So we see much higher responses with enfortumab vedotin and pembrolizumab versus chemotherapy that was used previously.

The overall survival is more than double with this combination also relative to chemotherapy. As I mentioned, more than 90% of patients with enfortumab vedotin-pembrolizumab have response or stable disease after they start treatment. Among those who have a response, that's this 68% almost of patients, about half, or actually a bit more than half, are still in remission about two years later.

Among those patients who have a complete response … And what I mean by complete response is a complete disappearance of tumor on scans, and that's almost a third of patients here, so 30% who start enfortumab vedotin and pembrolizumab, which by itself is a, you know, much higher number than what we've seen previously. But among those patients with a complete response, three-quarters, so 75%, maintain a complete response two years later.

Dr. Vadim Koshkin:



Based on all this, enfortumab vedotin and pembrolizumab is the preferred therapy for patients with newly diagnosed metastatic urothelial cancer. It represents a new hope for many patients with this advanced disease, and because of these very durable and deep responses that we see, many of these patients potentially are actually cured. It may be a bit soon to say that just because there have only been a few years of this data, but it really gives us a lot of hope that for many of these patients that have had complete responses, the cancer had gone away and hopefully will not come back.

It's the fact that we see these very durable responses that is … As we sometimes do specifically with treatment regimens that include immunotherapy like this one, that's what really, I think, is really exciting and encouraging here.

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