

## Understanding A New Treatment Option for Advanced Bladder Cancer

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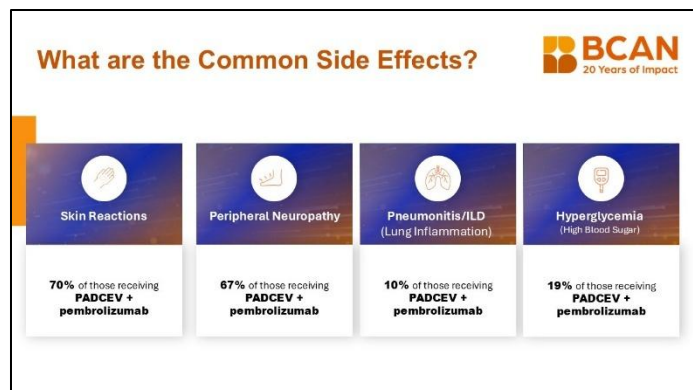
### Dr. Vadim Koshkin:

But, of course, the flip side of any treatment are the side effects. And so, there are specific side effects to this combination as well that any patient starting on this, and of course their physicians who are prescribing this, should be very aware of and actually should monitor.

So a common early side effect or toxicity are skin toxicities or skin

reactions that mostly are pretty manageable. They usually present as rashes that we can manage with steroid creams or things like that and really continued treatment. But in rare situations, these can be more severe skin side effects, sometimes even life-threatening. So that's certainly something we pay very close attention to and keep an eye on.

Over time, in particular as patients stay on the treatment longer, many patients develop peripheral neuropathy. What I mean by that is that's a side effect that really affects the tips of the nerves, and specifically the tips of the nerves in the extremities, so in the hands or in the feet. Usually it starts as not as noticeable a side effect, usually as a mild numbness and tingling that, you know, does not affect the patient's day-to-day, but, over time, that really can change substantially such that if you have significant neuropathy in your feet, for instance, and you're having really trouble feeling the floor, that will affect your balance and that can affect your gait and even basic walking, right.



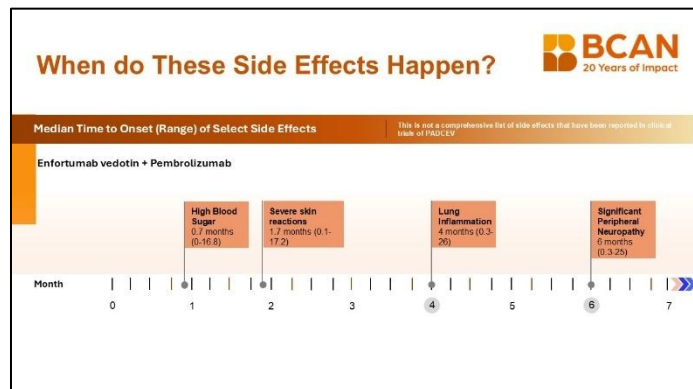
Neuropathy that's in the fingertips and that eventually progresses, can affect a myriad of things that we do with our fingers, right, things like buttoning shirts and tying shoelaces and holding utensils and writing, really things that often we take for granted but that are critical for day-to-day. And so, neuropathy is usually something that develops later after a while on this treatment. It's specifically related to enfortumab, so the antibody drug conjugate, rather than to pembrolizumab. And it is something we need to keep a close eye on because it often then later on requires dose reductions of this drug to manage it effectively.

Other side effects that are perhaps not as common, both that we monitor also carefully and that we pay close attention to, include lung inflammation, also known as pneumonitis. That's not as frequent with this combination, thankfully so, but can be more significant, right, because that's something that affects your lungs, your ability to breathe. We don't want it to get to that point either. That's usually, we initially appreciated on scans, so just as patients who basically get CT scans while on treatment and we see changes in the lungs, before symptoms develop. But it's critical to withhold the medication before further development of these symptoms.

Additionally, many patients who start on this treatment have high blood sugars as well or develop high blood sugars. This includes many patients who already have diabetes. So high blood sugar is a baseline, but actually many who do not and develop basically a new diabetes while on this therapy. That's also very important and critical to keep an eye on and in fact, every time that patients come in for treatment with these medications, we in addition to checking other labs, also check their blood sugars.

### Dr. Vadim Koshkin:

In terms of the timing of these side effects, as shown here and as we were just alluding to as well, something like high blood sugars, usually if it happens, happens early on. Skin reactions usually happen early on. Even severe skin reactions usually happen within the first couple of months, meaning that if you're on treatment with this, it's been several months, that's a side effect that's less likely to develop, but it can still develop at any point.



Sensory neuropathy, that's again, that's a numbness and tingling in the fingertips or feet. Significant side effects with that usually happen after about six months of treatment. But earlier and more indolent side effects like that can happen after about two to four months and that's when it's important to really start paying attention to this because, again, it's important to take action and do something before it develops to this significant neuropathy. It's important to not let it get to that point. And then lung inflammation really also can happen at any point, but, on average, it's after about four months of treatment.

### Dr. Vadim Koshkin:

So, what kind of monitoring do patients need while on treatment with this combination? Well, it's really just monitoring for the things that we were just discussing as the major side effects, this means monitoring for skin rashes and other skin side effects. Again, particularly early on in treatment, which is when we start. As most side effects, they usually start to a

more limited extent, but then, you know, can get worse and exacerbate quite quickly. The key is to act before that happens, and certainly before more severe skin reactions happen.

It's important to monitor for progression of neuropathy. As I was mentioning, this is definitely something that usually starts out in a more indolent way, something that doesn't bother patients, but then can get significantly worse. We don't want it to get to that point. We want to act before that happens.

It's critical to monitor blood sugars every time patients are come in for treatment. These are both infusion medications. So every time they come into infusion, we check their blood sugars. It is also critical to monitor functional status and things like appetite and potential weight loss and weight trends in general. This is, of course, done during doctor visits, but it's also done by patients and family members at home. In particular for elderly patients, with this combination, I also do see more of an effect on appetite and potentially subsequent weight loss. So definitely something to keep an eye on as well.

Again, especially critical, and I can't highlight this enough, is really listening to the patient, is of course critical for the doctors and the healthcare teams, but also you know for family members and caregivers. That's why in particular, I think, for a webinar like this, it's very important to have a patient voice here today as well, which I'm glad that we do.

### Dr. Vadim Koshkin:

A question that patients very frequently ask about this treatment, certainly me and I know others as well, is, "How long am I expected to stay on this, right?" That's a very good and a very reasonable question to ask, right. You know, historically, for many of our other treatments, the chemotherapy that I was alluding to earlier, it had a finite course, simply because it has a lot of side effects. Patients just really can't stay on it longer than usually the fixed four to six cycles.

### What Kind of Monitoring do Patients Need While on Treatment With EV/P?

**BCAN**  
20 Years of Impact

- Monitor for skin rashes and other skin side effects
- Monitor for progression of neuropathy
- Monitor blood sugars
- Monitor functional status, appetite, weight trends
- Listen to the patient

### How Long do Patients Stay on Treatment with Enfortumab vedotin and Pembrolizumab?

**BCAN**  
20 Years of Impact

- No fixed treatment course
- Patients usually receive
  - EV and Pembrolizumab on Day 1
  - EV only on Day 8
  - In a 21-day cycle
- In the real-world setting most patients stay on treatment for at least several months.
- Longer time on treatment = treatment is likely working
- But side effects (esp. neuropathy) accumulate over time as well

**Median cycles in EV+P arm**

Population	Median Cycles (range)
Overall population (n=440)	9 (1-54)
CR+PR (n=295)	12 (1-54)
CR (n=133)	13 (1-50)
Overall population (n=440)	11 (1-35)
CR+PR (n=295)	17 (1-35)
CR (n=133)	27 (1-35)

Treatment cycle = 3 weeks  
CR: Complete Response  
PR: Partial Response

Gupta et al. ASCO 2025

With this, it's a little bit different, but because, you know, in the clinical trial of this combination, really these drugs were given indefinitely, that is what we do in the real world as standard of care practice now as well. But of course most patients also don't stay on any treatment indefinitely, right.

In general, with this treatment, it's given in 21-day cycles, and in a given 21-day cycle, patients receive both drugs. So in enfortumab vedotin and pembrolizumab on day one and then only enfortumab vedotin on day eight. For the remaining two weeks, they don't get treatment, and then we repeat the whole thing again.

In the real-world setting, most patients can expect to stay on treatment for at least several months. This is, of course, assuming that you go on treatment and the treatment is working, which is, again, the case for over 90% of patients. So you can say that that's probably how you can expect things to go.

But I think the information from clinical trials is important to tell us in general, on average, how long patients there stayed on this treatment before, you know, coming off, usually often due to side effects, maybe sometimes due to other things like patient preference. What we see is that, on average, patients stayed on enfortumab vedotin for about nine cycles. Nine 21-day cycles is about six to seven months. They stayed on pembrolizumab, the immunotherapy drug that doesn't have as maybe prominent a side effect profile, for a little bit longer, for about 11 cycles. That equates to about eight months.

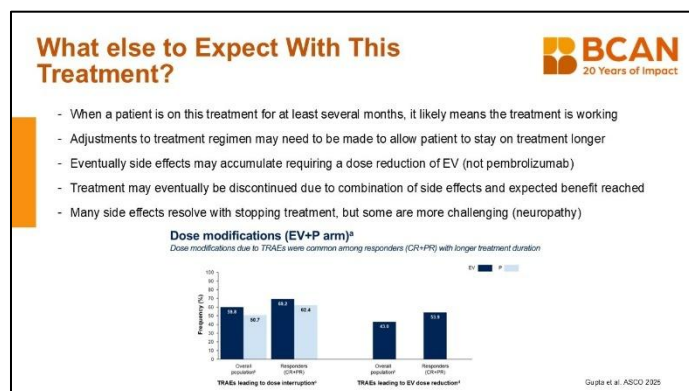
Now if patients are responding to treatment, they have a complete or partial response as shown here. They stay on either drug longer. If they have had a complete response in a clinical trial, they stay on treatment the longest. Then that, of course, makes sense, because if the treatment is working, they generally would stay on it.

But, again, it's important to keep in mind that side effects, especially neuropathy, accumulate over time as well, in particular, you know, as the patient continues on treatment with enfortumab vedotin. That's when we often have to make critical adjustments.

### Dr. Vadim Koshkin:

So, with that, what do we expect with this treatment? Well, as I was mentioning, when a patient is on treatment for at least several months, it likely means that the treatment is working, right. We wouldn't keep going. If, of course, the tumor was growing, in that situation, we would switch to something else.

What that means is that, over time, side effects can accumulate as well. There is a cost, unfortunately, to that success of treatment. And so, it is, you know, in my experience at least, critical to highlight to patients from the very



beginning that, especially if things work and you're on this treatment for a while, we will eventually be reducing dose. We have to be you know very candid about your experience on the treatment, about the side effects you're experiencing to, you know, allow us to do that basically correctly and to allow you to stay on treatment longer and potentially benefit from it more.

Because many side effects can certainly improve and many can resolve with stopping treatment, but some are much more challenging, and neuropathy is such a side effect. If it gets really bad before we discontinue it, in many cases it won't improve all the way back to normal. That's why it's especially important to not let things get to that point.

But, again, we have some useful information from clinical trials to guide us in this situation. This suggests that treatment modifications or dose modifications, meaning reducing dose or maybe pausing treatment for a bit, occurred in the majority of patients. More than 50% of patients who start this treatment can expect to basically either reduce dose, interrupt treatment at some point.

Again, that is to be expected. It doesn't mean that anything really is going wrong. In fact, it happens more frequently in patients who have responded. It's probably because they're on treatment longer. But, again, doing this, adjusting dose, often decreasing dose of enfortumab does not necessarily compromise the efficacy of treatment. I know that's something that many patients worry about and so, I think that's, and rightfully so. I think that's an absolutely critical thing to highlight. Again, the fact that many patients, about 50% basically, will have a dose reduction. Among responders, that number is actually higher, it's over 50%.

### Dr. Vadim Koshkin:


It's also important to consider, despite this being such a promising and effective regimen, that it's not actually the right treatment for some patients. So which patients should not get this treatment? Well, certainly those who already have very significant neuropathy, and that can happen, neuropathy can happen for other reasons. It can happen due to prior

treatments. It can happen due to diabetes, that affects your nerves as well. Sometimes it happens for unclear reasons, many patients have what's called idiopathic neuropathy.

But if they already have a pretty significant neuropathy, starting on this treatment will certainly worsen it. So for those patients, we have to be pretty careful, and some of them actually, maybe we should look for other treatments that do not have the same side effect.

If they have a functional status that is impaired and not necessarily due to untreated cancer, so maybe patients who are significantly frail such that a more aggressive cancer therapy like

#### Which Patients Should not Get Treatment with EV + Pembrolizumab?



- Patients with significant pre-existing neuropathy
- Symptomatic neuropathy that interferes with activities of daily living (buttoning shirts, tying shoes, fine finger movements, balance)
- Poor functional status that is not due to untreated cancer (similar to many other cancer therapies)
- Patients who cannot be treated with immunotherapy drugs
- Patients with rheumatologic conditions whose immune system is being suppressed with medications such as steroids
- Patients with history of organ transplants whose immune system is suppressed to prevent rejection of the organ
- Patients with diabetes CAN receive EV/P but should be monitored carefully

this can actually make them a lot worse, that's a situation in which we should exercise significant caution as well.

Then important thing to consider in any treatment that includes an immunotherapy drug as part of the combination is that many patients actually cannot get immunotherapy drugs. So it's dangerous for them to get drugs that activate or rev up their immune system and that could be because they can have a condition where their immune system is already overactive or revved up. So, for instance, patients with poorly controlled rheumatoid arthritis or patients with inflammatory bowel disease, like ulcerative colitis or Crohn's disease, you know, giving them pembrolizumab will likely significantly worsen those and may not be worth it.

Then an important consideration, of course, with patients with history of organ transplants as well. These patients are generally already on immunosuppressive medications we're actually were trying to not make their immune system overactive, but actually tone it down so that it doesn't attack and reject the transplanted organ.

For such patients who are often on medications that actually suppress their immune system, if you give them a drug that actually enhances and revs up their immune system, they're for sure going to reject that organ, and we want to avoid that. For patients like that, we may be able to just consider enfortumab, for instance, and not the immunotherapy drug pembrolizumab.

Then an important considerations for patients with diabetes, as I mentioned, blood sugar control is an issue with this combination or can be an issue, but I will highlight that patients with diabetes can receive this therapy. Diabetes is pretty common, and it's pretty common in this population, unfortunately. It doesn't mean that it rules you out for this treatment, but such patients, of course, should be monitored pretty carefully.

