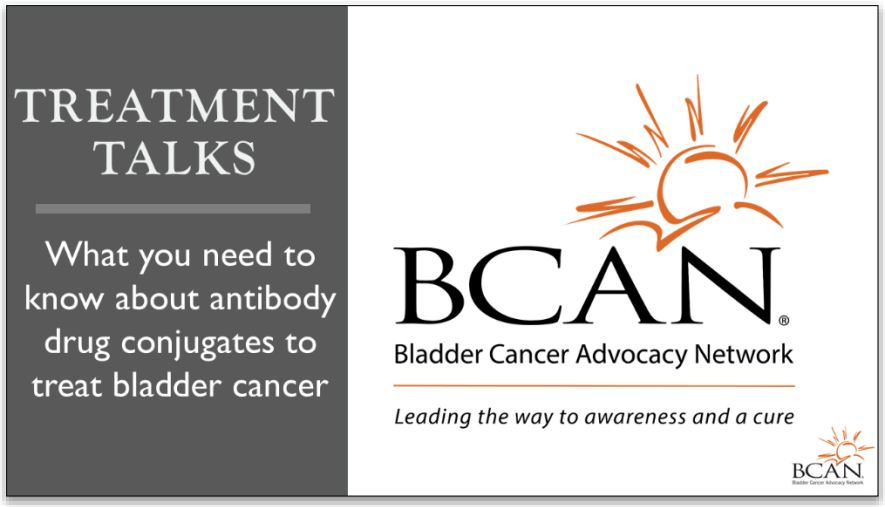

Question & Answer

Stephanie Chisolm: So let me ask a couple of questions that are coming in from the audience. So I know you mentioned that Enfortumab Vedontin is also available now and now we've just had the second approval, so that I think answers the one question. Yes, it is available, but another question that I'm seeing from participants: **Do patients need to have a particular genetic mutation to be successful with Antibody-Drug Conjugates?**

Dr. Gupta: No, they don't. And the targets against which these Antibody-Drug Conjugates are directed, they are ubiquitously expressed on the bladder cancer urothelial cancer cells, so we don't need to have a biomarker and that makes these drugs even more appealing that they can be used for pretty much everybody.

Stephanie Chisolm: **So are there other things that would preclude them from using this if all of their bladder cancer concerns fit the typical patient, but are there other comorbidities that might knock them out of consideration for using this type of treatment?**

Dr. Gupta: Yes. So that's a great question Stephanie. Enfortumab Vedontin it's key toxicity is peripheral neuropathy, and for patients who either have bad neuropathy at baseline from diabetes or other issues, or who've had prior platinum chemotherapy and have grade two or higher neuropathy, you will be very cautious with using it. I mean, you can still use it at very low doses, and more spaced out schedule, but that would be a big concern, and for patients with uncontrolled diabetes that's another concern because it can lead to hyperglycemia, lipase elevation. So they need to be monitored closely.

Stephanie Chisolm: **Is there anybody doing any research to look into whether Antibody-Drug Conjugates could be used for non muscle invasive bladder cancer?**

Dr. Gupta: That's a great question Stephanie. After seeing the success of Enfortumab Vedontin in metastatic disease, it is already moved into neoadjuvant treatment paradigms, and we are doing several

trials using that combination with pembrolizumab, but non-muscle invasive disease is certainly an attractive strategy, but it has not been looked at it yet.

Stephanie Chisolm: Okay. So outside of a clinical trial: **Do you have to have the chemotherapy or immunotherapy before you could receive the Antibody-Drug Conjugates**? Is that sort of a prerequisite that you have to not respond to chemo and immunotherapy before you can have it?

Dr. Gupta: That's the current FDA label for this, but there are many patients who for example, have had chemotherapy and are not candidates to receive immunotherapy. If let's say they have auto immune disease, or they are on immune suppressants. So we could use this then too, and we saw a recent data presented that patients who have received prior immunotherapy, but not chemotherapy, those who are cisplatin eligible, this drug has a very good efficacy too. So the strict label is yes, for those who've received prior platinum and immunotherapy, but in the real world there may be scenarios where not everybody has had both.

Stephanie Chisolm: Okay. **In the clinical trial you're looking at the combination of the EV and Pembro, how do you know which one is the most effective?** Is there a way to get that information so that you know where the real benefit for that patient is? Is it because of the pembrolizumab or because of Enfortumab Vedontin? What is it that's causing a good response? How do you know that as an investigator?

Dr. Gupta: Yeah, that's a great question Stephanie. And I think these two drugs do act in synergy and from our past experience with pembrolizumab, we know that for liver metastasis, it is not as effective as a single agent, and we know that Enfortumab as a single agent really exquisitely works well in liver metastasis. There's something with the biology and the mechanism of action, which left us really pleasantly surprised when we saw the initial data. So I think the key driver here is the Enfortumab Vedontin with the benefits we see with immunotherapy.

Stephanie Chisolm: Okay. Thanks. Good. **So another question going about other conditions, if somebody is experiencing any kind of a compromise in their immune system, would they be eligible to be treated with Antibody-Drug Conjugates?**

Dr. Gupta: Yes. They can be treated with that. This doesn't work where the immune system... Depends on if they have adequate lab parameters which can be monitored. So unlike the immunotherapy, patients with autoimmune diseases can get this drug.

Stephanie Chisolm: Okay. And Dr. Gupta, this is a question really for you**. For patients that might have rare forms of bladder cancer, say Sarcoma or Squamous, are they being looked at in terms of is this effective for them as well, or is it just sort of a general category of bladder cancer?**

Dr. Gupta: Yeah. I think the traditional trials required a urothelial cancer component. So it has not been looked at in pure Sarcomatoid or pure Squamous cell or small cell, but I think those are the next steps for research to have this option looked at for patients with those rare variants.

Stephanie Chisolm: Okay. Good. That's good to know. So this is a question for you Guy. You mentioned having pain that disappeared in your stomach after the treatment. In terms of feeling like you feel good about now you've controlled your cancer again and as you said you had no evidence of diseases that may be microscopic. **So how is that mentally for you to feel the treatment has benefited you? How do you feel about that? Can you talk a little bit about that experience?**

Guy: Well, mentally it's a great relief because when your pain subsides then you know that the cancer has to be subsiding too. I mean, I would have pain after I ate supper, I had like heartburn pain, and even if I drank a glass of water would give me pain in my abdomen and to be relieved of that pain, that in itself... I mean, the pain was something that... You know people get cancer and you don't think about pain, but the treatment stopping the pain mentally has really meant a lot to me.

I mean, it makes me positive. I'm looking to the future and I'm seeing myself to be cancer-free as long as I'm getting this treatment and maybe when the treatment ends I'm looking to be cancer-free and live. I always tell my wife, I want to get 10 more years and then she gets mad and tells me, why do you say 10 years? Why don't you say 20 years? Oh yeah. 20 years would be great too. Yeah.

Stephanie Chisolm: Okay. **So is there a time perhaps where Guy doesn't have to be under treatment, but just under observation or is this something that the treatment is going to be going on for a really long time?** What are your thoughts Dr. Gupta?

Dr. Gupta: Yeah. I think there's a duration for up to 24 months, and we know with the Enfortumab at some point if neuropathy becomes a challenge, we can reduce the dose or drop that and continue the immunotherapy and we have seen from our past experience that patients who stop immunotherapy even afterwards they keep having the response because the immune system is already engaged especially for patients like Guy who had a complete response already, and even when we stopped treatment at some point he's expected to be deriving that benefit.

Stephanie Chisolm: That's great because that was actually one of my questions. **If somebody has an adverse event, they're having a reaction in some way, but they're also benefiting from the treatment because it's showing that it's actually working for them, what would you do as their doctor?** Do you lessen the dose? Do you stretch out the application of the treatment? How do you adjust to help manage those side effects?

Dr. Gupta: So it depends. If the side effect is thought to be from Enfortumab Vedontin like if he gets really bad neuropathy or bad rashes which we can't control with typical treatment, I will reduce the dose and then skip a cycle or two till his symptoms return to normal or baseline and then reintroduce, and if those symptoms recur then we'll just drop that drug and continue only immunotherapy or if he gets a significant side effect to immunotherapy which requires long-term use of steroids at higher doses, then as we have seen from our experience he'll still continue to respond even if he doesn't get immunotherapy for a while or doesn't get it ever. So I think having that jumpstart of a great response really is key, and then we can easily work on those adjustments without really worrying about what will happen to the cancer.

Stephanie Chisolm: So if you had a crystal ball, **do you see this being used in the future as standard of care?**

Dr. Gupta: I think that's the million dollar question and this study will help us address that, and I think with the combination the results that we have seen in the past, we may be in a spot down the line where this combination may be able to replace chemotherapy. That's the hope, and the trials will provide us the results to see if that happens.

Stephanie Chisolm: **If someone were to progress even after this, does having the Antibody-Drug Conjugate preclude or limit you in your choices of future treatments?** I know that there's so much exciting work that's being done in bladder cancer research today compared to 10 years ago. I know there's a lot of other things kind of being tested in the pipeline, but right now is being on this treatment going to preclude you from any other treatments down the road that we know about? Can you-

Dr. Gupta: Yeah. There's a lot of treatment options. For someone like Guy who's not really had platinum based chemo ever that remains a very valid option, and for patients who've had that and then also we have this new Antibody-Drug Conjugate that I talked about the Sacituzumab Govitecan. That remains an option for Guy and everyone who's had ADCs like Enfortumab, and if a patient's tumors show a certain kind of a mutation in the FGFR or fibroblasts growth factor receptor, then we have an approved therapy for that as well called Erdafitinib. So really getting this treatment does not precludes from any future treatments.

Stephanie Chisolm: Okay. So again just kind of recap, I know you spoke about all of the elements of the treatment, but now that Guy has got another scan coming up and it's going to be clear. Is he going to just sort of back off? What's the next predicted thing? **Is he going to continue with this treatment or does he take a break until he has another problem down the road?**

Dr. Gupta: Yeah. So I think for now our goal will be to continue as long as he's not having unmanageable side effects or progressing, but the clinical trial allows a lot of leeway about dose adjustments and skipping doses. So we want to... I think now that Guy has had a great response, focus on his quality of life is very important. So we'll only push it for as long as we can push it safely because the odds are that he continue to do well regardless.

Stephanie Chisolm: Great. So Guy, what else do you have to add about this? **What would you tell somebody else who said, my doctor said I should try this?** How would you advise them as a patient?

Guy: I would tell them to dive in. You know I see the cancer patients at the hospital and I can see the people getting chemo, and to me it seems like the chemo it practically has to kill you to kill the cancer, and this is more targeted and it's not killing me, it's not destroying regular healthy cells I don't believe as much as regular chemo does, and I think about... Like you were talking to Dr. Gupta about getting off the drug or cutting out the drug because I'm having good results maybe, to me it's like, no, don't stop anything. Keep it going while we got this stuff on the run, go after it and I can handle these side effects. Yeah. This is something I would get into in a heartbeat again if I could.

Stephanie Chisolm: Okay. So being in the clinical trial was a good experience for you and again, it probably... You said it made you feel better knowing that you were in the treatment arm. So that was probably a little boost of confidence that you started to respond and you found out you were getting the actual treatment so I think that that's a good thing. So we don't have a whole lot of additional... Well, wait a minute. There's one more question. What about the dosage reduction?

Dr. Gupta: I have to say does become a challenge at some point because patients eventually do develop neuropathy and we believe that we should be very prompt with decreasing the doses to one mcgs and even further down if needed or switching that schedule to day one day eight instead of day one, day eight, day 15. So a lot of strategies to keep patients getting the maximum benefit.

Stephanie Chisolm: Great. **I know that there was a question that just came in as far as how far you can reduce the dosage?** I don't know Dr. Gupta, if you have any kind of levels that you as a clinician are willing to go to in terms of reducing the dosage, or is this very individual and people just are still in that early trial and error trying to figure that out?

Dr. Gupta: I think I would be very proactive with reducing the dose to one and even 0.75 if patients start exhibiting neuropathy which is significant because that can be a real challenge, and also skipping the weekly schedule and maybe giving it every two weeks. As standard of care we can try out the lowest dose, lowest frequency schedule that the patient can tolerate.

Stephanie Chisolm: **Is there anything that could be done to help treat the neuropathy that might evolve?** You know if you are going to start to feel these tinglings in your fingers and feet, how could you help treat that and still stay on treatment? Is there anything you could do?

Dr. Gupta: Yeah. If patients have neuropathic pain there's several medications like Gabapentin and things like that, but really because the neuropathy can potentially be irreversible we just want to be very cautious because reducing the dose still works. You know giving it less frequently will still work, but neuropathy if it starts getting worse may not improve. So that's my general point.

Stephanie Chisolm: Great. Here's a good question. **Will this treatment be high cost or similar to chemotherapies?** For the high cost on more advanced treatments that are very expensive these days or is it similar to chemo which I think has a generally lower cost?

Dr. Gupta: Yeah. I think compared to chemo, this is certainly high costs because immunotherapy is expensive and so is this drug. I mean, chemo is the cheapest that could get. You know cisplatin and gemcitabine, but I think that is a key question for our regulators and pharma companies to really work on in the future.

Stephanie Chisolm: Okay. Well, this has been phenomenal. I want to thank you both. Guy thanks so much for sharing your story. It's really hard to just sort of come out there and talk about your experience with the disease and with the treatment, and we really do appreciate you doing that. Dr. Gupta, it's been really wonderful always to listen to you talk about all the trials that you're involved in, and you have so much enthusiasm and obviously a warm and informative nature that I hope comes through to the patients, and I think that in looking to just sort of summarize, if you were to tell patients who are listening, if this is something you're considering, how would they bring it up to their doctors if

say for instance they're not being seen in a large urology clinic at a big teaching hospital like you're at Cleveland Clinic? What if they're being seen in their communities, how would you suggest that they bring this up to their medical oncologist?

Dr. Gupta: Yeah. Thank you Stephanie for your kind words, and I would like to thank Guy also for taking time out and sharing his experience with us and everyone in the country who will be watching this later. So I think patients should always ask their oncologist like what other things can I do? Because this is not the era where chemo is all we have and patients... You know, a lot of them have heard about immunotherapy, but a lot of them have not and a lot of community oncologist may not have heard about new Antibody-Drug Conjugates drug.

So I think patients should always ask their doctors, okay, this is the standard treatment, what's new out there? Where can I go and get it? Is it feasible for me? Just having that information, and if they decide it's not feasible, that's okay but I think they have a right to know what's the latest that's going on, and I know BCAN has done so much work in getting that information to patient Stephanie that... The education efforts are very important for the patients to be able to make an informed decision with their doctors.

Stephanie Chisolm: Well, again, thank you so much both of you. This has been a phenomenal program.