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Expert Panel: Integrating and Optimizing ADCs in the Treatment of Urothelial Cancer

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Dr. Grivas:
Hello, I'm Dr. Petros Grivas. I'm a medical oncologist in Seattle. I'm a professional and the Clinical Director of Genitourinary Cancers Program at the University of Washington for Fred Hutch Cancer Center. I'm very excited today to host two wonderful individuals who have made major contributions in the field of genitourinary cancers. We have Dr. Shilpa Gupta, who's an associate professor and also the director of the Genitourinary Oncology Program at Cleveland Clinic and the co-chair of the Hoosier Cancer Research Network. Hello, Shilpa.

Dr. Gupta:
Hello Petros. Thanks for the invitation. Really excited to be here.

Dr. Grivas:
Thanks Shilpa. We're also very excited to have Dr. Vadim Koshkin. Dr. Koshkin is an assistant professor at the University of California San Francisco UCSF and doing great work in the field. Hello Vadim.

Dr. Koshkin:
Hi Petros and Shilpa. Very, very nice to be here. My pleasure.

Dr. Grivas:
Great to see both of you. We had the wonderful ESMO meeting, and a lot of data came up there, but I would like to focus our discussion today how the antibody-drug conjugates feeding the current paradigm of urothelial cancer treatment landscape. And maybe I will ask Shilpa first and with the data we have. Let's start with in, Shilpa. if you can give us your take in the current role of this horrible drug conjugate. For example, the FDA approved indication in the, based on the V-21 and V-301 trial to start us off.

Dr. Gupta:
So, antibody-drug conjugates like enfortumab vedotin have really advanced the treatment paradigm for metastatic urothelial cancer patients. As you know after planning, we were using immunotherapy for platinum-refractory disease, but response rates were modest at about 20% or so. And then with your and Tom Paul's work, Petros and the entire team for Javelin Plata 100 maintenance avelumab is now the standard of care in frontline after platinum therapy for patients who don't progress. However, a lot of people still progress or don't respond and for them, the antibody-drug conjugate has really now the changed the treatment options. We saw then enfortumab vedotin improved overall survival compared to salvage chemotherapy, investigators choice chemotherapy in the EB-201 phase three trial AB-301 phase three trial, I'm sorry. And that is now the current standard and that is for enfortumab vedotin can and then the other antibody drug conjugate cetuximab. Again, you've been instrumental in that work with the tropics study is also X-rated approval by the FDA to be used after immunotherapy and chemotherapy. So currently that is also an option for our patients who don't respond to

enfortumab vedotin or for whatever reason, cannot get enfortumab vedotin in the platinum and immunotherapy refractory treatment era. And as far as the frontline treatment goes it's not currently approved. However, we've seen remarkable data in the frontline setting from EV-103 study cohort K and the thing alarm study that we just published in the JCO and cohort K that was presented at Desmo. So that is currently under consideration by the FDA ineligible patients.

Dr. Grivas:
Thank you, Shilpa. Excellent overview, this ties very nicely with the previous episode that Dr. Koshkin did, and he nicely described how this data pan out and, Vadim, how do you integrate, and you optimize the use of antibody-drug conjugates in your treatment paradigm in clinic. Shilpa gave us a wonderful overview. How do you practice that?

Dr. Koshkin:
Yeah, that's a great question and of course a great overview by Miss Shilpa of the enfortumab and cetuximab data. We do know that both drugs, both antibody-drug conjugates are active in treatment-refractory bladder cancer. Arguably the data is a bit stronger for enfortumab and there's also more data for enfortumab Enfortumab had a large phase two study and two different cohorts that we outlined in one of the prior episodes. There was also a phase three study in patients post platinum and immune checkpoint inhibitors. That was again the EV-301 that Shilpa mentioned that demonstrated benefit of enfortumab relative to chemotherapy. So, the data for enfortumab is pretty well established and usually in the treatment-refractory setting. So, post platinum, post immune checkpoint inhibitor that is the drug we, well I go to first and I think the practice of most other physicians who see a lot of bladder cancer is pretty consistent with that as well. With cetuximab, we have also pretty robust data from the trophy study that's in patients post platinum and immune checkpoint inhibitor. The response rates were arguably a little bit lower. If you compare across trials to enfortumab, it was, you know almost 30% around 27% relative to really low 40s or so that we see with enfortumab. But there's certainly patients who respond and who do well with cetuximab and of course the large phase three tropic study, it will read out in the near future as well. So currently I would say I go to enfortumab first and then use cetuximab subsequently. However, there are certain patients for whom probably going to cetuximab first would make more sense and that really probably would be driven more by their comorbidities and the respected toxicities and side effects of the drugs as just as an example as enfortumab does cause quite a bit of neuropathy. And this is a patient population where who potentially already are experiencing a lot of neuropathy having been exposed to platinum previously. I would say for patients with severe neuropathy for instance when making a choice between, let's say, enfortumab and cetuximab potentially going to cetuximab would make more sense. But overall I would say it's just a tremendous advance over the past, really, just the past two to three years that previously in a space where we did not have a standard of care really to post platinum post immunotherapy space for metastatic urothelial patients now we have multiple antibody drug conjugates available and who really have robust activity and it's just been, you know, phenomenal to see this, these advances happen.

Dr. Grivas:
Thank you, Vadim. Great overview as well. Shilpa, going back to you. So, let's say we have a patient who goes through platinum-based chemotherapy. And by the way, for the audience, you had a wonderful poster for ASCO 2022 annual meeting. Try to define the population who are not fit for any platinum system carbo unfit patients. And I know you're working on the manuscript but let's say a patient is fit for platinum most of our patients are system carbo maybe half of them are fit for platinum maybe another 40% fit for only for carbo ballpark. Let's say this patient get platinum-based chemo going on maintenance avelumab but as you mentioned is level-one evidence for the audience. Also, there is a wonderful trial that you are leading the main calf trial randomizing patients to carbonal avelumab versus avelumab So something to keep in the radar in the maintenance trial setting. Let's say this patient gets avelumab and has progression while being on avelumab maintenance let's say ten months later. What would be your next step there and how would you sequence the two antibody-drug conjugates that are FDA approved and how the comorbidities and the toxicity profile can help you optimize that sequence?

Dr. Gupta:
Thank you, Petros, for highlighting our collaborative work on platinum ineligibility and also our main cap trial of maintenance avelumab intensification which you're also championing for us through the ECOG-ACRIN group. So, for patients who get frontline platinums and those are 90% or more in my practice you know very few patients are actually platinum ineligible as you know. Those patients, if they do not progress on platinums we enroll on the main cap trial which is randomizing patients to avelumab versus avelumab cabozantinib And even if they get just avelumab as standard of care and then they progress, then my go-to drug is enfortumab vedotin, which is a very effective, and I would say, very rapidly works, you know, if it works you'll see the response within the first couple of cycles. Sometimes the challenge becomes, you know, if after platinum patients have residual grade two neuropathy and that's when I like to avoid enfortumab vedotin because the neuropathy with that drug as Dr. Koshkin mentioned is very disabling and we want to give patients time to recover before we can restart that agent. And if a patient cannot go to enfortumab vedotin for reasons of peripheral neuropathy or poorly controlled diabetes, then I go to cetuximab and if patient's diabetes is better controlled and neuropathy is

improving then I reserve enfortumab vedotin for later. And just to mention here that if a patient has a tumor that is in risk for FGFR alteration or mutations then we also have targeted therapy on a (indistinct).

Dr. Grivas:
Fantastic review, Shilpa. Very quickly. Maybe in the next few seconds, I will ask Shilpa first and then Vadim. If you have an FGFR three mutation or fusion and you have the option of erdafitinib, would you do that first before enfortunab or cetuximab or you will go to the ADCs first? Any comment on that, Shilpa? Would it be depend on the toxicity profile?

Dr. Gupta:
Yeah, so that's a great question Petros, and I think because we do not have any data on the sequencing, you know we need to learn more from trials, and we need to do trials to address this question. But I would go to either or depending on what comorbidities these patients have. There is really no right or wrong answer here. We want to be able to offer all the treatments to every patient in their journey and need to sequence it wisely.

Dr. Grivas:
Thank you, Shilpa. Vadim?

Dr. Koshkin:
Yeah, no, I broadly agree with Shilpa and her great answer. There is a four FGFR three altered patients. I really see this as basically additional ability to treat. There are now instead of these, two drugs available. Now there are three. So, it's really just a plethora of opportunities to hopefully have the patient respond to something. I would say, yeah, again there are multiple right answers here because we really, we don't have perspective data of how to appropriately sequence these patients. We do have retrospective data suggesting that FGFR three alter patients do respond to enfortumab. There's even limited data suggesting that those previously treated with erdafitinib still have responses to enfortumab. These are, you know, very small numbers so I don't want to sort of put too much emphasis on that but aside from just saying that enfortumab does work in FGFR three-altered patients there is limited data with cetuximab as well. And so, I mean generally speaking I would say among the three drugs I would be choosing probably between enfortumab and erdafitinib first there are important differences between the drugs even besides their toxicity. So erdafitinib is of course an oral medication. Enfortunab is an infusion so, you know, patient who lives far away doesn't want to come in for infusions or some patients who just don't want to come in for infusions. Like I've had patients like that. I would lean towards erdafitinib first and then have enfortumab as an option later and then again, you know, cetuximab is additionally probably an option for these patients after I would say probably these first two just because there's probably less data with cetuximab at least that's kind of how I would guide my practice in this situation.

Dr. Grivas:
Thank you, Shilpa and Vadim. Great discussion. You know it's great to have options for our patients. These agents did not exist four years ago so it's great to have enfortumab, cetuximab, erdafitinib, and of course, any new agent at this on clinical trials, we're looking into it. So very exciting to see this evolving landscape more options for our patients and hopefully we translate this in improved outcomes for our patients. So, I would like to thank both of you for all your contributions in the field. Great work. And also, for your time today. That was a great discussion. Thank you.

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