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State of the Union: Advances in the Management of mUC

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Dr. Balar:
Welcome to the Metastatic Urothelial Cancer educational series. In this first chapter, we’re going to be setting the stage for this series in its entirety.

This is CME on ReachMD. My name is Arjun Balar. I’m a medical oncologists and director of the GU Medical Oncology Program at NYU Langone Health’s Perlmutter Cancer Center. And I’m joined for this session by Dr. Daniel Petrylak, professor of medicine at Yale Cancer Center. Welcome, Dr. Petrylak.

Dr. Petrylak:
Morning, Arjun, how are you today?

Dr. Balar:
I’m great. Thanks for joining me.

So let’s get started. I want to start off, Dr. Petrylak, by inviting you to just give us a brief overview of bladder cancer and the novel therapeutic options and just quickly cover, just briefly, a little bit about the disease and some of the advancements that we’ve made over the last few years.

Dr. Petrylak:
Thank you, Arjun. So, bladder cancer is the sixth most common cancer in the United States. 83,730 patients will be diagnosed in the year 2021 with approximately 17,200 deaths. The average age of diagnosis is 73 years. It’s predominantly males who are diagnosed with this disease; it’s a 3:1 ratio. And we’ve identified risk factors for urothelial carcinoma. These are those that will cause damage to the cells, such as smoking as well as chemicals, particularly the aromatic amines of the aniline dyes. When bladder cancer’s diagnosed, predominantly it’s superficial in 75% to 80% of cases. About a quarter of these patients have muscle invasive disease, and then 5% of patients are diagnosed with metastatic disease initially. So it’s not as common to be diagnosed with metastatic disease but predominantly non-muscle invasive and superficial bladder cancer.

So there are a number of different targets that we’re now beginning to evaluate in bladder cancer, and these include the PD-L1, PD-1 access FGFR3 which is expressed in approximately 20% of urothelial carcinoma specimens. Paradoxically, it’s expressed at a higher rate in the non-muscle invasive disease. These are markers that we check, and we’ll go into that in the next section, at various points in the treatment of urothelial carcinoma.

But there are other targets that really don’t need to be checked, which are fairly prominent in this disease and these are targets for

treatment in advanced disease. These include nectin, which we have an antibody-drug conjugate [ADC] called enfortumab vedotin which targets nectin, and also sacituzumab govitecan, which targets a target called TROP-2 which is expressed in a variety of different epithelial cells. So the disease advanced in terms of treatment over the last several years. It's been a rapid explosion in the targets and therapeutic modalities available to treat those patients.

Dr. Balar:
Fantastic. One of the key questions here at this point is what is the role for biomarker testing in advanced urothelial cancer? And one of the questions that we often get is, you know, what biomarkers do we use, and when do we test for them? Dr. Petrylak, I'm sure you're aware of PD-L1 expression testing that we do routinely, and also you kind of alluded to the role for FGFR testing. I'll quickly cover that, you know, as per NCCN guidelines – and we had erdafitinib which was approved in April of 2019 on the basis of the BLC2001 study – that biomarker testing has a pivotal role in the treatment of advanced urothelial cancer. But it should be done in unique clinical settings. I want to quickly review those.

So PD-L1 expression testing is really restricted for patients in the first-line metastatic urothelial cancer testing where patients who are ineligible for cisplatin-containing chemotherapy and you're making a decision between carboplatin-based treatment or first-line immunotherapy with either atezolizumab or pembrolizumab. In that setting the FDA label suggests that PD-L1 expression testing can be of value. Patients who are positive for PD-L1 expression using the companion diagnostic for either atezolizumab or pembrolizumab, those patients may be eligible for treatment with pembrolizumab or atezolizumab. However, patients who are absent or low levels of PD-L1 expression in that context really should not be offered first-line immunotherapy and rather should be treated with platinum-based chemotherapy. There is a clinical scenario where PD-L1 expression testing really doesn't have value, but – and that's really for patients who are entirely ineligible for platinum-containing chemotherapy. You know, Dan, you and I see these patients all the time. These are the late octogenarians, the nonagenarians, they're very elderly and very frail patients with very poor performance status and very poor renal function who are really not candidates for multi-agent chemotherapy, and in this context, really, immunotherapy is probably one of the only safe options for them. And there, you just give the immunotherapy and PD-L1 expression testing really has no value.

After first-line treatment, PD-L1 expression testing has no real role because we know in the platinum refractory and beyond setting, single-agent immunotherapy is better than the standard of care, which is single-agent taxane or vinflunine in the European union. So, you know, beyond the first-line setting, PD-L1 expression testing has little value. Now, next-generation sequencing, FGFR, can be tested at any time, but once you've tested for it, you don't need to keep testing for it. And right now, the FDA label for erdafitinib includes gene fusions or translocations in FGFR2, translocations in FGFR3, and these are the so-called, activating gene fusions, such as the TACC3 FGFR gene fusion and then also activating point mutations in FGFR3. Now, we're still understanding the role for FGFR signaling in advanced bladder cancer, and perhaps there may be larger net to cast, so to speak, but other trials are still underway. But right now, approximately 20%, as you mentioned, are potentially eligible for erdafitinib. But again, I think we're still learning about the true role of FGFR signaling in advanced disease.

And certainly, survey results demonstrate now that we're using biomarker testing in various lines of treatment, but we do need to do a better job in terms of how patients are both counseled about the role for biomarker testing and how we're implementing them in practice.

Now, I want to pivot over a little bit to our most recent meeting at ASCO 2021, which just wrapped up in June. A lot of trials were presented in the GU space and in particular bladder cancer. So, Dr. Petrylak, do you want to comment about any trials that really stood out to you that you thought were noteworthy?

Dr. Petrylak:
Well, well there were 3 presentations which I thought were extremely important. Firstly, there was a presentation that looked at single-agent pembrolizumab for those patients who are platinum-ineligible in the frontline setting. This evaluated this drug, and we now have 5-year data with this particular study. The objective response rate overall was 29%, the median duration of response is actually pretty impressive at 33.4 months, and the overall survival is consistent with the originally presentations, 11.3 months. Another issue, which was not unexpected, was the fact that those patients who had a CPS score of more than 10 were more likely to respond than those patients who had a CPS score of less than 10, and these responses were durable. And this supports the FDA indication for pembrolizumab as a frontline treatment for those patients who are platinum ineligible – or cisplatin ineligible, excuse me. Overall, the objective response rate for those patients with a CPS of greater than 10 was 47.3% and 20.7% for those patients with a CPS of less than 10. Really no different safety signals were identified, and this supports the use of pembrolizumab in those patients who are cisplatin ineligible with locally advanced or metastatic urothelial carcinoma.

Moving forward to some combinations for cisplatin-ineligible patients, it makes logical sense to combine enfortumab vedotin, which is the antibody-drug conjugate that I mentioned before, and a checkpoint inhibitor. So there's been a phase 1 trial, EV-103, that has been

evaluating that combination. Slightly different dosage of enfortumab is administered. It's 1.25 mg/kg given on day 1, day 8. The FDA approval right now for enfortumab is day 1, day 8, and day 15 of a similar dose. Pembrolizumab is administered 200 mg q 3 weeks. The response rates are very impressive. The confirmed objective response rate, which was updated at the ASCO meeting, was 73.3%. These responses were generated irrespective of PD-L1 status. So PD-L1-negative patients responded; PD-L1-positive patients responded. What I think is impressive is the updated survival data with a median follow-up of nearly 25 months, the median overall survival is 26.1 months. I think that's actually the highest response rate I've seen – or survival rate I've seen in patients who are platinum ineligible or for any combination therapy. It sure beats gem/carbo or other single agents. So this is impressive data. Really no new safety signals were generated with this update. And again, randomized trials are needed to see whether this is the right combination to use in platinum-ineligible patients. This is currently, as part of EV-103, a randomized trial comparing enfortumab to enfortumab combined with pembrolizumab.

An update of the EV-201 data was presented. This is the second cohort. Again, those patients who are cisplatin-ineligible, platinum-naïve, and who had had a prior checkpoint inhibitor. This is a presentation of 89 patients who were entered on arm 2 of the EV-201 study. And again, we're seeing the same high response rate with enfortumab vedotin, a confirmed objective response rate of 52% with 20% of patients having a complete response. What I think is also impressive about this data, and again, impressive about enfortumab vedotin in general, is the fact that patients with hepatic metastases have a high response rate. 10 of 21 patients with liver metastases responded for 48% response rate, and that's really higher than what we see with any single agent in this disease. And actually, combination therapy really does not yield that same response rate in liver.

So in summary, again, really an impressive overall median survival. No new safety signals were generated – or at least were presented at this particular poster, and again, randomized trials needed to confirm the role of enfortumab vedotin combined with pembrolizumab in platinum-ineligible patients with urothelial carcinoma.

Dr. Balar:
Thank you so much Dr. Petrylak. That was a wonderful rearview of really some of the high line data from ASCO 2021. Before we wrap up, just give us one key takeaway from ASCO 2021 – and just for this chapter in general before we move on to the next one.

Dr. Petrylak:
I think that the key take-aways that the future of urothelial cancer treatment is bright. We have new agents; we've really come a long way in the 8 years that that we've been working with checkpoints, and now we're looking at novel combinations of checkpoints plus ADCs and perhaps checkpoints with some of the other tyrosine kinase inhibitors as well. So there's a lot of work to be done in improving these agents to be superior to standard of care.

Dr. Balar:
Thank you so much. In Chapter 2, we'll be discussing 3 different patient cases to demonstrate the optimal therapy selection in the management of metastatic urothelial cancer, so please stay tuned.

[CHAPTER 2]

Dr. Balar:
Welcome back. In the first chapter, we covered novel therapeutic options for metastatic urothelial cancer based on the pertinent biomarkers. We also discussed recent clinical trial updates for metastatic urothelial cancer presented at ASCO 2021, and now, on to Chapter 2, we're going to be using 3 different patient cases to demonstrate the optimal therapy selection and sequencing and how we approach this disease. So let's start off with case number one.

Dr. Petrylak:
So, Fred's 68 years old and he has a history of, he was diagnosed with initially with metastatic urothelial carcinoma. Platinum eligible, he had creatinine clearance of 65, and he received 6 cycles of gemcitabine and cisplatin. And he had metastatic disease to lung and the treatment resulted in a partial response. We had a discussion with Fred about the use of maintenance checkpoint therapy after his initial response. We decided that he didn't want to go forth with further treatment at that point. We monitored the patient with CT scans every 3 to 4 months. And then 6 months after he stopped his chemotherapy, he developed disease progression in lymph nodes and was treated with a PD-L1 antibody. That response lasted 10 months, and he has now progression both in the liver as well as in the lung.

Dr. Balar:
Great. So, we encounter this patient all the time. You and I have met Fred so many times in our, in our clinical practices. And in this setting, you know, in the third-line setting, I think, you know, before the advent of antibody-drug conjugates, and importantly molecularly targeted agents, we most often would counsel a patient like this for best supportive care and often hospice because we didn't have

anything beyond checkpoint blockade. Now, granted, you know, checkpoint blockade only became available in 2016, so we can't even say that that is something that we've been doing for a very long time. You know, so in this setting, it's really important to understand that some of the most important critical things to think about here is a patient who is progressing like this in liver and lung, you know, the data from prognostic studies show that in the treatment refractory setting, patients with liver metastases in particular have a median survival of often 4 months. And so treatment options in this setting are a critical unmet need. What we didn't mention here in this case is molecular testing, next-generation sequencing, you know, what's the value here? Now whether it was done at the initial biopsy or biopsy at progression, at some point in time a portion of tumor tissue absolutely should be collected for next-generation sequencing and if, you know, one is not available or safely accessible during the course of treatment, then a liquid biopsy using ctDNA can also be used to identify targetable alterations. And so, here, we're going to look also for FGFR mutations and FGFR2 or FGFR3, and then that'll give you the sufficient information you need to make a treatment decision. And right now, we have 3 potential FDA-approved option for patients in this particular situation. Two that require no additional testing, that's both enfortumab vedotin and sacituzumab govitecan. Those are both antibody-drug conjugates. I should mention that enfortumab vedotin now has regular approval and has demonstrated a survival benefit on the basis of EV-301. And then sacituzumab govitecan, which targets TROP-2 – it's an antibody-drug conjugate with a payload called SN-38 – recently received accelerated approval on the basis of the TROPHY-U-01 study just earlier this year and had a 27% response rate in that study. But neither of these 2 drugs require any sort of biomarker testing and is readily-available in this clinical scenario. Erdafitinib, as I mentioned, does require biomarker testing and would be a very reasonable option, as well, in this patient, but again requires that the patient has a activating alteration and either FGFR2 and FGFR3. So that's how we would approach this patient in this clinical scenario. And again, Dr. Petrylak and I meet Fred all the time in this setting. And we're glad to say that we have those 3 available treatment options for this patient.

So now, let's jump ahead to the second patient case. And this is Beverly. She's an 81-year-old woman who's has chronic obstructive pulmonary disease, chronic kidney disease stage 3, and she presents with metastatic urothelial cancer to lymph nodes in the lung. This is also a woman that we meet often in our, our clinical practice. And I would say that we are seeing more and more of these patients now than we ever did before because of the advent of immunotherapy. And many of these patients could not safely receive multi-agent platinum-based chemotherapy just because of their advanced age and their medical frailty. And Beverly receives first-line immunotherapy with a PD-1 or PD-L1 antibody; she tolerates treatment well. She develops some mild pruritus, some grade 1 to grade 2 skin rash that we treat with topical steroids and antihistamines, but she develops a partial response that lasts over 12 months. And we do see this in clinical practice often.

Now she has developed, however, new disease progression and new liver metastases after 12 months of achieving a partial response. She still maintains a reasonable performance status at ECOG PS1. She still has stage 3 chronic kidney disease; this is something that accompanied her at the time of diagnosis and she still has it today. And she's a year older right? But she's still interested in receiving more treatment for her cancer. And so now you're presented with her, and now how do you approach treatment options in this setting? So, Dr. Petrylak, how do you approach Beverly and have these treatment discussions with her?

Dr. Petrylak:
So this patient is a cisplatin-ineligible, checkpoint-experienced patient, and there recently was an FDA approval for enfortumab vedotin for this particular group of patients. As we saw from the ASCO presentation, this patient has liver metastases and in the ASCO presentation it was noted that there's a higher response rate – 40% of patients respond who are treated with enfortumab vedotin with liver metastases. So enfortumab vedotin has FDA approval and would be my first-line choice for this patient. It certainly would – although there are no randomized trials comparing it, overall it seems that this has more activity than the combination of carboplatin with gemcitabine.

Now, there are clinical trials that are evaluating this patient group, but also of course, do FGFR3 mutational analysis to see if this patient would be eligible to receive erdafitinib. But there are other clinical trials and other agents that are being evaluated in this setting as well. There is a trial that is looking at sacituzumab govitecan which is a different ADC, it targets a different epitope and delivers a different payload which is SN-38, different from enfortumab vedotin which is an antitubulin agent called MMAE. So that trial is currently ongoing, accruing patients, and we'll see if sacituzumab govitecan has sufficient activity to be approved in this particular clinical setting.

So we have trials, we have standard of care, and certainly I think the patient should be offered these agents because they potentially can benefit.

Dr. Balar:
Excellent. And do you want to carry us to our third and final case?

Dr. Petrylak:
Sure. So Tony is a 72-year-old smoker, retired truck-driver. And he quit smoking approximately 20 years ago, and he recently was

noted to have gross hematuria. Subsequent evaluation and workup demonstrated muscle-invasive urothelial carcinoma on the basis of a TURBT and the extensive lymph node and lung metastases on CT imaging. His ECOG performance status was 1 and his creatinine clearance was 55, and he previously had an LAD stent placed for coronary artery disease approximately 6 years ago, but he has no other relevant medical history and is very, very active. So, Arjun, why don't you discuss this case for us? What would you do?

Dr. Balar:
Yeah. Absolutely. I think I can – just like Beverly and Fred before, you know, you and I meet Tony all the time as well. And this is your classic patient, a former heavy smoker who's just diagnosed with metastatic urothelial cancer. And he's a patient who is eligible for platinum-containing chemotherapy and is coming to you to have a treatment discussion. And he has the classic medical history that also accompanies patients who have developed this disease. And, you know, patient who are smokers have cardiovascular risk factors, have a little bit of renal dysfunction, little bit of a rough-and-tumble crowd. And so you have a lot of options for these patients across the board. And so, here, the first decision is that is this patient eligible for cisplatin-containing chemotherapy or not? And then if the patient is eligible for cisplatin-containing chemotherapy, we generally approach this patient for that because we know it's improved survival and in some patients it can be associated with cures. I want to point out that a GFR of 55 cc/min is a perfectly safe GFR to administer cisplatin-containing chemotherapy. I will point out, on the other hand, though, for regulatory purposes, the FDA considered a GFR of less than 60 to be considered ineligible for cisplatin-containing chemotherapy to allow patients to get on cis-ineligible trials, but in and of itself does not exclude patients to receive cisplatin-based treatment. So I think that's an interesting little wrinkle about how we approach clinical care from a practical standpoint but then also how the FDA looks at the regulatory definition of cis-ineligibility. And I think those two things are really, really distinct issues, and I think, Dr. Petrylak, you and I agree on that issue upfront is that a patient like this can probably safely receive cisplatin-based treatment and should be offered that as a first-line approach if they're willing to receive it.

Now, in a patients like this I think we would easily be able to administers cisplatin-based treatment. It could be reasonable to check for PD-L1 status. It could influence your decision-making if, let's say, there are other reasons why the patient couldn't receive cisplatin, and now you're having a conversation about carbo versus first-line immunotherapy, and then in that case, the PD-L1 expression status could be of some relevance. But in either case, if you move forward with platinum-based chemotherapy, then at that point, then you're having a conversation after the patient had hopefully achieved stable disease or better, which is very likely, then to have a conversation about maintenance immunotherapy following that – disease control versus waiting until progression and then using immunotherapy at the time of progression. But this is, again, a classic patient that we see receive in the first-line setting. I'll also point out that at the time of diagnosis, if you have TURBT tissue demonstrating muscle invasive disease, that is more than adequate to send for next-generation sequencings, so send that off from the outset. Or if you wanted to get a biopsy of the lung metastases in this patient, send that off also from the outset because it can take 6 to 8 weeks to get that information back, and you want to have that in your back pocket in the event that you have an FGFR mutation so that you have that available down the road if you want to use erdafitinib, for example.

So this has been a great discussion. Before we wrap up, Dr. Petrylak, like I asked you before, one additional key takeaway from this chapter before we move on to the next one?

Dr. Petrylak:
I think the key takeaway is that we have new agents that are available for the treatment of platinum-ineligible disease as evidenced by the recent FDA approval of enfortumab vedotin in this setting. So I think that patients should be offered all of possible treatments that are available. Carbo/gem is really now going by the wayside and again we need to molecularly phenotype all of our patients to evaluate whether they are eligible to receive an FGFR3 inhibitor during the course of therapy.

Dr. Balar:
So thanks so much Dr. Petrylak. In Chapter 3 we'll be discussing what to look for in the future for both early- to late-stage metastatic urothelial cancer, so please stay tuned.

[CHAPTER 3]

Dr. Balar:
For those just tuning in, you're listening to CME on ReachMD. I'm Arjun Balar. I'm here today with Dr. Daniel Petrylak. We're discussing recent advances in the management of metastatic urothelial cancer.

So welcome back. In Chapter 2, we walked through 3 unique patient case presentations that we commonly encounter in the clinic. And now, in Chapter 3, Dr. Petrylak and I, we're going to be discussing what the future holds in terms of novel therapeutics from early-stage to late-stage metastatic urothelial cancer, and I'm going to invite Dr. Petrylak to take it from here.

Dr. Petrylak:
So, Dr. Balar, let's get started. We've seen some impressive data from both ASCO GU and ASCO this year. What new data and

potential therapeutic options do you think we might see coming out at ESMO 2021 or even ASCO GU and ASCO in the year 2022?

Dr. Balar:
Thanks so much, Dr. Petrylak, for that question. I think it's probably a bit too early to say what we're going to see in 2021 and 2022 because, you know, like fine wine, it takes time for these studies to fully accrue and to age and mature and the endpoints to finally be ready to be presented. So I don't think we're going to see practice-changing data at the end of this year or next year. But there are a number of studies in both early-stage and late-stage bladder cancer that I'm really excited about that I think we may see in the years ahead. And I want to quickly run through those studies. And I'll break it down in terms of both early-stage bladder cancer and late stage.

I'll first begin with late stage because with that's been mostly what we've talked about today. I'll first talk about some of the exciting combinations that we are seeing with both immunotherapy and antibody-drug conjugates. Two studies that really stand out to me that I think are practice-changing and may completely change how we treat metastatic urothelial cancer in the first-line setting: Cohort K of EV-103, this is the randomized, first-line trial of EV/pembro versus EV alone in the first-line treatment of patients who have metastatic urothelial cancer that are ineligible for cisplatin-containing chemotherapy. The target enrollment is about 150 patients. We're almost there in terms of enrollment, and this is a study that I think will really understand what the role is for the combination and also understand the contribution of components, EV versus EV/pembro, and maybe even inform just how synergistic this combination is in the first-line setting and can inform to a larger degree, you know, what the role could be in in the broader patient population. The larger study's EV-302. This was initially designed as a 3-arm study that quickly tapered down to a 2-arm trial. And this study is probably the largest practice-changing trial that we should expect in the coming years. This is platinum gemcitabine, which includes cis/gem or carbo/gem versus EV plus pembro, all comers with first-line metastatic urothelial cancer, and this is the study that I think is going to completely redefine how we treat metastatic disease in the first line setting. This study is still early in its enrollment. I don't expect data for this study in the next several years because it has 2 co-primary endpoints, both PFS and OS, but I think most of us are going to be hanging our hat on the OS data, and that's going to take some time, especially since the OS data so far for the EV/pembro is so promising and there's also a lot of maintenance use of immunotherapy. And so that's also going to really influence potentially some of the outcomes in such a time-to event-analysis. So it's going to be several years before we see data from that study.

The other study to look out for is the TROPICS study, and this is the study that looks at sacituzumab govitecan versus single-agent dealer's choice chemotherapy in kind of the third-line setting after platinum-based chemotherapy and immunotherapy and looks at the role for this additional antibody-drug conjugate sacituzumab govitecan, which targets TROP-2, the payload is SN-38. It's linked through a hydrolyzable linker, and it adds to our armamentarium in addition to enfortumab vedotin. And again, we have more options now than we ever did before in metastatic urothelial cancer, and this drug recently received accelerated approval earlier this year. But we really need to understand, does it improve survival in this heavily treatment refractory setting? And this study is currently ongoing and we look forward to this data, and hopefully it will demonstrate a survival benefit much like enfortumab vedotin did in the EV-301 dataset.

Now, let me pivot over to early-stage disease. This is where I think immunotherapy and antibody-drug conjugates have still the potential to have even more significant impact in muscle invasive early-stage disease. There were two concepts that are kind of prevailing in this setting. One is a neoadjuvant, adjuvant, or perioperative approach. Several trials are looking at the role of immunotherapy in combination with chemotherapy, multiple sponsors, it's impossible for me to go through all the trials. But in essence, many trials are looking at PD-1 access inhibitors in combination with cisplatin-based chemotherapy where we're essentially randomizing patients to cisplatin-based chemotherapy with or without a PD-1 access inhibitor followed by cystectomy with some adjuvant component of additional treatment afterwards to see if we can further improve outcomes in patients with localized muscle invasive bladder cancer, improve disease-free survival in overall survival and get more cures by adding immunotherapy to standard cisplatin-based chemotherapy and cystectomy.

There's also, for patients who are cis-ineligible, we're looking at the role for immunotherapy, as well, in this setting and also adding enfortumab vedotin in this setting. And there's a pivotal study – there's a 3-arm study of cystectomy alone versus pembro, cystectomy, followed by adjuvant pembro and a third arm of EV/pembro, cystectomy, followed by EV/pembro, as well, and I think this is one of the really exciting trials that may look at the role for ADCs plus pembrolizumab in the perioperative setting.

So, in summary, all of these trials are really exciting studies but are still maturing, and it will be several years before we see some of these studies read out in the future.

So let me hand it over back to you, Dr. Petrylak. I've covered a lot of studies that are currently ongoing, but we see these ADCs now are currently approved. They're used in clinical practice: enfortumab vedotin, Nectin-4 MMAE, sacituzumab govitecan, TROP-2, SN-38. These are very, very different drugs and have unique safety and efficacy profiles. Can you guide us through how clinicians should use them in clinical practice?

Dr. Petrylak:
So I think it's important, obviously, we have great clinical trial data, but it's important for clinicians in the community to be comfortable with using these drugs. And unfortunately, over 50% of clinicians are less than confident in using ADCs in second-line systemic therapy as opposed to the immune checkpoint inhibitors. And they're also less confident in using the ADCs in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinomas compared to gemcitabine and carboplatin. So, how can we improve the comfort level of physicians in using these drugs? Really, the issue comes down to the management of toxicities, which are different for erdafitinib, for enfortumab vedotin, as well as sacituzumab.

Now, in terms of which drug to use, we really don't have good data. Although the perception is 39% of clinicians will believe that erdafitinib is more effective than an ADC in those patients with locally advanced or metastatic urothelial carcinoma who harbor FGFR3 mutations. Unfortunately, we don't have randomized data, which either proves or disproves that hypothesis, but these drugs can be used in sequence. In fact, we have a case that was presented at the ESMO meeting a couple of years ago on the TROPHY trial where a patient received initially enfortumab vedotin, responded, and then progressed and received sacituzumab. Certainly, I've seen responses anecdotally to all 3 drugs, and I think that the patient should be offered the opportunity to receive these drugs if they are eligible. So we don't have randomized data that compares these agents, but certainly there are trials that are being considered that will answer this particular question.

Dr. Balar:
Thank you so much, Dr. Petrylak, and I think it's pretty clear that the field is rapidly evolving, and with all these new treatments that are currently available, I think the key takeaway here is that each drug is unique, whether it's erdafitinib, sacituzumab govitecan, or enfortumab vedotin, since each time the target is different, the mechanism of action is different. There's no reason to believe that these drugs are cross-resistant, so sequencing these drugs is ultimately a bit of an art of medicine, a little bit of the data, and just getting comfortable with the unique safety profiles and making sure that these patients have access to these drugs ultimately to improve clinical outcomes.

So this has been a wonderful discussion. This is unfortunately all the time we have today, but I wanted to thank our audience for listening in, thank you, Dr. Petrylak, for joining me and sharing all of your valuable insights. And it was great to speak with you today. Thanks so much for joining us.

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