Transcript Details

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Released: 12/20/2024
Valid until: 12/20/2025
Time needed to complete: 1h 16m

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Clinical evidence driving guideline recommendations for frontline immunotherapy-based combination regimens in metastatic urothelial cancer

Announcer:
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Dr. Xu:
Hello, everyone. This is CME on ReachMD and I'm Dr. Vincent Xu.

Dr. Duran:
And I'm Dr. Ignacio Duran.

Dr. Xu:
Dr. Duran, what data support our guideline recommendations for frontline immunotherapy-based combination regimens in metastatic urothelial cancer?

Dr. Duran:
Well, thank you, Dr. Xu, for interesting question. I think is relevant to share with our audience that in 2024 immunotherapy-based combos have made it to the frontline of systemic treatment, and they should be the first consideration in that clinical scenario. So, in fact, we have data from three key studies to support that approach, and I'm going to try to summarize that data briefly. I think in order of relevance, we should probably first mention this study EV-302 that was published in March 2024 in *New England Journal of Medicine*. In EV-302, patients with either locally advanced or metastatic urothelial carcinoma were randomized to receive either a conventional platinum-based chemotherapy, or the antibody-drug conjugate (ADC) enfortumab vedotin (EV) combined with pembrolizumab.

I think the results of the trial were, what we could say, impressive, and they were presented at ESMO 2023 by Tom Powles, and I think are well known by the medical community. But let's just summarize and say that this combo doubled the results of the control arm PFS, 6 versus 12 for EV + pembro. Also, the OS data was almost 32 months, 31.5 for EV + pembro versus 16 for the chemo arm, and the hazard ratios were incredible, 0.45 and 0.47 respectively. In terms of response, this was also quite outstanding, and the responses were close to 70% for EV + pembro, including 30% of complete responses.

So, I think that data is quite striking, but it's also true that perhaps not all patients are suitable to receive EV + pembro. And this leaves an open space for other options such as platinum-based chemotherapy followed by maintenance avelumab, and this is based in JAVELIN 100 that we know well, since 2020 published. And another option is for those patients only cisplatin eligible cisplatin/gemcitabine/nivolumab, followed by nivolumab maintenance based on the data of CheckMate-901, recently published in *New England Journal of Medicine* and presented.

And that combination showed better outcomes than the conventional chemotherapy.

So, that's the data. So, Dr. Xu, can you talk about how these data informed current guidelines?

Dr. Xu:
Absolutely. I think I agree with you so much, Dr. Duran. This EV + pembro regimen has really revolutionized what we can tell patients for first-line metastatic urothelial bladder cancer. This near-doubling of overall survival and progression-free survival is a game changer for patients. And the NCCN guidelines really reflect this because EV + pembro is a preferred regimen, whether patients are cisplatin eligible or cisplatin ineligible. The majority of patients should really be getting EV + pembro. Again, it's a game changer.

However, there are very specific subsets of patients where you could consider other options. And when I think about this, I think about patients who for some reason or the other may not tolerate well EV + pembro. One difference between EV + pembro versus either the JAVELIN Bladder approach with maintenance avelumab after platinum doublet, or the CheckMate triplet with gem/cis/nivo. One of the key differences is that for platinum doublet, the number of cycles of chemotherapy is limited, whereas for EV + pembro people are continuing EV as long as they can tolerate it. So, there's some appeal to patients of having a limited course of chemotherapy.

And on the other hand, for very specific subsets, EV has very unique toxicities. For example, with EV, the doublet, there's a higher chance of sometimes life-threatening pneumonitis and higher chance of hyperglycemia, which can be a problem for people with really poorly controlled diabetes. Otherwise, skin and neurotoxicities can also be dose-limiting. Overall, absolutely true, most patients should get EV + pembro, and in very specific circumstances where they're not tolerating the platinum doublet with immunotherapy either up front or in maintenance is another potential option.

The other really interesting scenario is patients with lymph node-only disease. We know that this is a favorable prognostic sign in metastatic urothelial cancer, and we've long known that a small subset of patients with lymph node disease can have durable remissions even to cisplatin-based therapies alone, and even more so with addition of immunotherapy. I don't think any of these factors should change our recommendation to use EV + pembro in most patients, but it does require another scenario where we might consider cisplatin-based therapy.

Finally, the last thing I would mention is that we have recent data from ESMO from EV-302 showing that nectin-4 expression did not change the superiority of EV + pembro over platinum-based doublets. And so, this is despite EV being a nectin-4 targeted ADC.

It really is the standard of care in all patients, regardless of nectin-4 expression.

Dr. Duran, are there any circumstances where you use alternative treatments for these first-line patients?

Dr. Duran:
Well, thank you, Dr. Xu, you couldn't have done a better summary. I think you actually put everything into context. I think you've very well summarized that there is a paradigm change and we're moving towards utilizing EV + pembro in most of our patients. And there is some little details in patient selection based on comorbidities. You mentioned it very well. Diabetes, neuropathy, those are key determinants. Some immune diseases or autoimmune diseases, and some clinical circumstances where you can select for other regimes. Other than that, I think EV + pembro is currently the treatment of choice for most of our patients. And I think that's very well reflected in our NCCN guidelines.

I think we're running out of time, Dr. Xu, so I think we're going to have to close this fantastic discussion. I would like to thank our audience, and thank NCCN for organizing this CME activities. Thank you, everyone.

Announcer:
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