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<https://reachmd.com/programs/cme/reviewing-the-latest-bladder-cancer-practice-guidelines/32675/>

Released: 02/21/2025

Valid until: 02/21/2026

Time needed to complete: 28m

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### Reviewing the Latest Bladder Cancer Practice Guidelines

#### Announcer:

Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

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#### Dr. Plimack:

Hi. This is CME on ReachMD, and I'm Dr. Elizabeth Plimack, Deputy Director and GU Medical Oncologist at Fox Chase Cancer Center in Philadelphia. I'm going to be reviewing the latest updates to the guidelines for metastatic bladder cancer.

So, first, let's start with locally advanced and metastatic urothelial cancer first-line therapy. So, platinum-based therapy has been standard for decades. Common regimens are gemcitabine and cisplatin, gemcitabine and carboplatin, and dose-dense MVAC. But better understanding of underlying mechanisms of the disease has led to advances with effective immunotherapies, which have really been sweeping oncologic therapies across tumor types in the last decade. So, we've seen absolutely improved outcomes when chemotherapy and immunotherapy are used together, and even more so when some of the newer antibody drug conjugates are used with immunotherapy. And I'll go through some of that data in our time today.

So, in terms of chemotherapy, we know based on the JAVELIN studies that chemotherapy followed by maintenance immunotherapy is an effective strategy. And up until recently, this was the first-line standard of care.

Chemotherapy is typically gemcitabine and cisplatin, gemcitabine and carboplatin or dose-dense MVAC for 4 or sometimes, 6 cycles followed by a maintenance immunotherapy. Studies have supported immunotherapy with avelumab as well as pembrolizumab.

The immune checkpoint inhibitors, as folks probably know by now, stimulate T cell mediated killing of tumor cells by blocking recognition of tumor cells as antigens. We have immunotherapies targeting CTLA-4, PD-1 and PD-L1. This is not new information.

What's a little more novel, are the antibody drug conjugates. So, antibody drug conjugates, or ADC's, combine a monoclonal antibody directed against a very specific antigen expressed by the tumor with a cytotoxic drug or payload attached to the antibody by a linker. In all three components of this, the antibody has a specific target, the payload and the linker that attaches it determine the characteristics and potency of the ADC.

We have ADC's targeting HER2, Trop-2 and Nectin-4, all of which have been used in bladder cancer. And payloads commonly used are microtubule inhibitors or topoisomerase inhibitors.

So, now let's get to the relatively new data that has redefined the first-line standard of care in bladder cancer. Enfortumab/vedotin, which is an antibody drug conjugate targeting nectin-4 with a payload of MMAE, which is like a taxane, plus the PD-1 inhibitor, pembrolizumab. We like to say EV/Pembro, for short. This combination was studied in the EV302 study, which is a 1 to 1 randomized study of EV plus pembrolizumab versus that standard chemotherapy I mentioned, in this case, limited to gem/carbo or gem/cisplatin. Maintenance immunotherapy was allowed and encouraged, but not part of this study. This study met its primary endpoint with improvements in progression-free survival and overall survival, as well as pretty tremendous response rates.

The guidelines now have put EV/Pembro in the frontline, and that's because the progression-free survival in EV302 was 12.5 months compared to 6.3 with chemotherapy. Overall survival doubled: 31.5 months versus 16.1 months with chemotherapy. The overall response rate was 67.7% with EV/Pembro compared to 44% with chemotherapy. And what we really were happy to see – we're happy to see all these things, but – is the complete response rate of almost a third of patients, 29% versus 12.5% with chemotherapy. So, based on these unequivocal findings of superiority, EV/Pembro is now the first-line standard of care for all patients, really, regardless of whether they would be cisplatin eligible or not.

Now, let's talk a little bit about a newer agent more recently approved for all tumors with IHC staining for HER2 at high levels, either 3-plus or 2-plus. And that's trastuzumab/deruxtecan. So, this is an antibody drug conjugate targeting HER2. The payload is deruxtecan, and the results for bladder cancer show an overall response rate of 56% for patients with IHC 3-plus expression and 35% for patients with IHC 2-plus expression. And this is now available for patients whose tumors express HER2 at the 2-plus or 3-plus level. Importantly, if you're sending NGS testing or other testing for HER2, we aren't looking at overexpression, we aren't looking for mutations in HER2, we're really looking for this IHC staining in order to match it to the patients who benefited from trastuzumab/deruxtecan in the basket study.

It looks like our time is up today. Thank you so much for listening to CME on ReachMD.

**Announcer:**

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