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Where Do ADCs Fit in the Current Urothelial Cancer Treatment Paradigm?

Announcer:
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Dr. Koshkin:
Hello, everyone. My name is Vadim Koshkin. I'm a genitourinary medical oncologist and assistant professor at the University of California, San Francisco. This is episode three. Where DO antibody-drug conjugates fit in the current urothelial cancer treatment paradigm? This is a treatment landscape in metastatic urothelial carcinoma prior to 2019. So only a few years ago. At that time, the only options available were really platinum-based chemotherapy and then immune checkpoint inhibitors, which were recently approved at that time. This is the space in which the initial enfortumab vedotin trials were conducted.

EV-201 was a single-arm, pivotal phase two trial of enfortumab vedotin monotherapy. Patients were enrolled in two separate and non-sequential cohorts. There's cohort one of patients who had previously progressed on a platinum-based chemotherapy and an immune checkpoint inhibitor. That cohort finished enrollment first. Then there was cohort two of patients who were cisplatin-ineligible who had not received prior platinum-based chemotherapy but had progressed on a prior immune checkpoint inhibitor. In either case, in either cohort, I should say, patients were treated with enfortumab vedotin on days 1, 8, and 15 of a 28-day cycle. The primary endpoint was confirmed objective response rate by central review.

Cohort one, which I mentioned read out first. The confirmed objective response rate in these patients with prior exposure to platinum-based therapy and an immune checkpoint inhibitor was 44%, including 12% complete responses. Median progression-free survival was by 5.8 months. Median overall survival was almost 12 months. The response rate was considerably higher than the historical baseline to second line chemotherapy, which was at around 10% as opposed to 44% in this study. And this led to the accelerated approval of enfortumab vedotin in the post platinum-based chemo and post immunotherapy space, and this occurred late in 2019. Cohort two shown on the right side of the slide read out a bit later. These were again, patients who were not exposed to prior platinum-based therapy and progressed only on a prior immune checkpoint inhibitor. Here the response rate was 52%, just a little bit higher than in cohort one, including 20% complete response rates. Median progression-free survival was around six months. Median overall survival was 14.7 months. This led to the expansion of enfortumab's label to include progression only on one prior line of therapy.

EV-301 was an open-label phase three trial that was a confirmatory trial for EV-201 cohort one. These were patients with metastatic urothelial carcinoma who had previously progressed on platinum-based chemotherapy and an immune checkpoint inhibitor, but this was a randomized trial. They randomized these patients to be treated with enfortumab vedotin or a preselected chemotherapy regimen, which included either docetaxel, paclitaxel, or in Europe, vinflunine. The primary endpoint in this study was overall survival.

In EV-301, the investigator-assessed overall response rate was 41% in the enfortumab cohort as opposed to 18% with chemotherapy. The chemotherapy cohort arguably outperformed expectations a bit since historically expected response rates to chemotherapy in this setting we're about 10%. But despite that, the responses were still much higher more than twice as high with enfortumab. There was

additionally advantage in median progression-free survival with enfortumab relative to second line chemotherapy, which was statistically significant. And of course, for the primary endpoint in the trial of median overall survival, there was significant advantage of enfortumab at 12.9 months as opposed to chemotherapy at around nine months.

This led to the full approval of enfortumab vedotin in patients post platinum-based chemotherapy and immune checkpoint inhibitor after initially the drug again received accelerated approval based on the phase two trial data.

For sacituzumab govitecan, the approval of this antibody-drug conjugate was based on the data from the TROPHY-U-01 study whose design is shown here. This was a multicohort study, but we will focus only on cohort one including about a hundred patients. These were patients with metastatic urothelial carcinoma who progressed on prior platinum-based chemotherapy and an immune checkpoint inhibitor. These patients received sacituzumab on days one and day eight of a 21-day cycle. The primary endpoint was objective response rate by investigator review. Here were the results of this primary endpoint. The objective response rate in cohort one was 27%. Most patients did have significant reduction in tumor size as shown on the right-hand side of the slide. Median progression-free survival and overall survival in cohort one were 5.4 months and 10.9 months respectively. These numbers are pretty comparable to enfortumab numbers listed earlier. Arguably though, the objective response rate was a bit lower than the low forties that we see with enfortumab vedotin. For sacituzumab govitecan, there's also a phase three confirmatory trial known as TROPiCS-04. This trial randomizes patients with metastatic urothelial cancer, prior progression on platinum-based therapy and an immune checkpoint inhibitor to receive either sacituzumab govitecan or again, physician's choice of chemotherapy with either docetaxel, paclitaxel, or vinflunine in Europe. This trial is accruing right now, and the results are expected soon. This slide compares the clinical trial data of enfortumab vedotin and sacituzumab govitecan from the largest trials of these agents we have to date. For in enfortumab vedotin, there was the results of a large, randomized phase three study, which included over 300 patients treated with enfortumab. For sacituzumab, again, the approval was based on the non-randomized phase two study, specifically cohort one of TROPHY-U-01 study, which included 113 patients. In both cases, these were patients who are post platinum and an immune checkpoint inhibitor. Median follow-up was significantly longer with enfortumab in that trial. That was recently updated at around 24 months. With sacituzumab, the currently published data is with a median follow-up of only about nine months from that study. The response rates, which I alluded to earlier were a bit higher with enfortumab at 41% versus 27%. Median progression-free survival and median overall survival that is available thus far was overall pretty comparable. I would say across the two antibody-drug conjugates arguably a bit shorter with sacituzumab in terms of median overall survival. Common toxicities, which we did not discuss earlier, but are very important to discuss actually are also quite different between the two drugs. With enfortumab, the most common toxicities we look out for are skin toxicities, especially early on and neuropathy as a late toxicity. With sacituzumab, these are quite different. The most common side effects they experience are loose stool or cytopenias. And this difference in the common toxicities really affects potentially which patients these drugs can be offered to.

So, this brings us to the current treatment landscape in metastatic urothelial carcinoma using antibody-drug conjugates. Beyond platinum-based chemotherapy and an immune checkpoint inhibitors, there are now at least two antibody-drug conjugates available as standard of care in metastatic urothelial carcinoma. This includes sacituzumab govitecan, which is available after prior progression on platinum-based chemo and an immune checkpoint inhibitor. And enfortumab vedotin, which is available as an option after progression on only one line of therapy. So, after prior immune checkpoint inhibitor or even after prior platinum-based chemo, but also of course is available for treatment in patients who previously progressed on both chemotherapy and an immune checkpoint inhibitor.

There are a lot of ongoing questions with these recently approved drugs and of course future directions to pursue. One is of course, how to appropriately sequence treatments when these multiple drugs are available? Typically, nowadays we use in enfortumab before using sacituzumab as there's just more data for enfortumab use. But potentially for a subset of patients, sacituzumab should be used first. Potentially this can be driven by the comorbidity and the toxicity profile of the patients and drugs respectively. But really, we need retrospective studies and real-world data to help provide some of these answers. We also need more and better biomarkers predicting response to these treatments and there's work being done on this right now. Finally, these antibody-drug conjugates are increasingly moving into earlier treatment spaces. Frontline treatment space as we'll be discussing in some of the later episodes and also even as perioperative and neoadjuvant therapies. This concludes the episode. Thank you so much for your attention.

Announcer:
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