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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

What Novel Combination Strategies Are Being Studied for Anti-Drug Conjugates in Urothelial Cancer?

Announcer:
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Dr. Grivas:
Hello, I'm Dr. Grivas. I'm a medical oncologist in Seattle, a professor at University of Washington, Fred Hutchinson Cancer Center. Welcome to our episode, "What Novel Combination Strategies Are Being Studied for Antibody-Drug Conjugates in Urothelial Cancer?" And I mentioned in the previous episode briefly about the Cohort A of the EV-103 trial. We already reviewed the data there. Just a reminder that this was a population of cisplatin-ineligible patients. Only 45 patients with a very impressive overall response rate, and this is control rate and a response rate in certain subsets of patients that definitely raised enthusiasm. This was about three years ago, frontline setting of cisplatin-unfit patients. And more recently, we saw validation of this data, with a combination of pembrolizumab plus enfortumab vedotin, and that combination is important to note that it was tested in about 76 patients or so in the frontline setting of cisplatin-ineligible patients, and had a 65% response rate, and 97% reduction in tumor size and most patients had significant benefit. And this subcommission combination, of course, we're waiting for the EV-302 trial, randomized phase 3, comparing enfortumab vedotin plus pembrolizumab versus chemotherapy. That trial allows maintenance of avelumab. We'll see how many patients end up getting cisplatin, and how many end up getting maintenance avelumab in that trial. But that's in the phase 3 trial. We await the results. That trial is finishing accrual, and we'll see what the results show in the future.

Of course, there is significant interest in high attention in other antibody-drug conjugates. Another example sacituzumab govitecan, that's antibody-drug conjugate against Trop-2. That's a different antibody, and this is different linker and different payload. This is an antibody-drug conjugate that carries SN-38, doubled up with irinotecan, and the target is Trop-2. We showed a very interesting data at ASCO GU 2022, with a combination of pembrolizumab and PD-1 checkpoint inhibition, plus sacituzumab govitecan in patients who are platinum-refractory in the second-line setting. That's why I put the red box around the Cohort 3. I want to point out there are multiple cohorts in that particular trial. Cohort 1 led to accelerate approval of sacituzumab advanced monotherapy, accelerated approval by the FDA after platinum-based chemotherapy after checkpoint inhibition. There is an ongoing TROPiCS-04 trial that tries to validate results of Cohort 1, sacituzumab govitecan monotherapy versus Taxane in US or Vinflunine in Europe. And that trial is ongoing and will finish accrual soon. We have Cohort 2 data that will be presented in the near future. And then ongoing Cohort 4, 5, and 6.

I'll focus my attention on Cohort 3. Again, this is combination of pembrolizumab plus sacituzumab govitecan. This is a very difficult to treat population. These were patients who have frequently, progression early on, on platinum chemotherapy. Low response rates on prior platinum and very short time on platinum chemo. Again, very poor prognosis in those patients. We need combinations to be tested in clinical trials to treat those patients, and that combination was tested here, sacituzumab plus pembrolizumab. We see a promising response rates of 34% with a 61% disease control rate. CR, PR stable this. And you see the most responses were partial on the right part of the slide. On the left part of the slide, usually, about 2/3 of the patients had some reduction in the tumor size, and those

responses usually in that trial were rapid in the first scan, first couple of months. Median duration of response was not reached. So, some responses are durable and again this is a single arm, not randomized trial. Median PFS 5.5 months. Median OS not reached. Again, grain of salt, because it's a single-arm study not randomized, but promising signal there. And this is on the left, the response rate by subgroup. You see in the lower part of the slide, patients with visceral metastasis had a 36% response rate. Patients with liver metastasis 42% response rate. And you see responses across the categories of Bellmunt risk factor groups, zero, one, and two. You still see responses in those groups in the lower part of the left corner. On the right part, you see the swimmer's plot, and you see that the number of responses were durable, and you see there that green as a responder, gray as the non-responders, and we're going to have updated data follow-up in the future from that study.

Toxicity always something to discuss across trials as you see on the left part. These are treatment-related adverse events, and any grade, diarrhea was about 70%, about half of the patient having a great nausea, and you see the rest of the potential side effects, neutropenia, anemia, fatigue, alopecia, anorexia, and pruritus. On the right part of the slide, you see that treatment-related grade 3-4 adverse events was present in 59% of the patients and 39% of the patients had some reduction with the sacituzumab dose because of treatment-related adverse event. There was no treatment-related death, and about the quarter of the patients had steroids and only 10%, one out of 10 patients, had oral steroids, which about the proportion you'll expect with pembrolizumab alone. So, the toxicity seemed predictable based on pembro alone and sacituzumab govitecan alone data. About 29% of patients had growth factor and if you give growth factor, you reduce significantly the chance of neutropenia and febrile neutropenia. So now we're moving towards utilization, more utilization of growth factor, G-CSF in patients who get sacituzumab govitecan for advanced urothelial cancer. And as you see, the rate of febrile neutropenia was 10%, and as you see, this was without prior growth factor.

To conclude that study, so the promising signal response rate 34%, this is control rate. Clinical benefit rate, let's say, 61%, and median duration of response, median OS not reached. This was a single-arm study. The toxicity profile was covered, and there was no new safety signal compared to what you expect from each drug alone. The combination, in my opinion, looks promising and merits further investigation in platinum-refractory, and maybe earlier settings of advanced urothelial cancer. And there are of course many other cohorts on TROPHY-01, and there is a TROPiCS-04 trial with SG monotherapy versus chemotherapy, Taxane or Vinflunine, that is going on accruing in the post-platinum and post-checkpoint inhibition.

Very few words about anti-HER2 and about drug conjugates. These are very promising agents. I'm going to put it in your attention. Disitamab vedotin was combined with anti-PD-I toripalimab. This study was done in China presented by Dr. Sheng and colleagues at ASCO 2022. Very promising data. You see confirmed response rate 72%. You see the breakdown here with CR and PR, and also you see responses also in patients with lower expression of HER2. This is an antibody-drug conjugates against HER2, the disitamab vedotin, combined with anti-PD-1. Again, median PFS about nine months. This is a single arm, not randomized comparison here, so take the PFS and OS with a grain of salt. But the data looked very promising, something to keep in our radar, and there are ongoing design of phase 2 and phase 3 trials, looking at these anti-HER2, antibody-drug conjugates, so something to keep in mind.

And also, to keep in mind that trastuzumab deruxtecan antibody-drug conjugates against HER2, you have seen a lot of data without agent in other cancers, like breast cancer, we saw the data at ASCO 2022. That's the table of Dr. Galsky, put together for the recent ASCO 2022 meeting. Look at different combinations. Obviously, these are different trials. You cannot compare across trials. Different population of patients, different treatment setting, so we cannot compare across trials, but you see a flavor of how the combinations look like, and I included the two anti-HER2 agents, trastuzumab deruxtecan plus nivolumab, and again post-platinum and disitamab vedotin and toripalimab as I mentioned in the patients who are 6% of them were treatment-naive. So again, different population patients but promising signals there with the antibody-drug conjugates against Nectin-4 as I mentioned before, enfortumab, Trop-2, sacituzumab, and anti-HER2 is coming in the future. Thank you so much for your attention. I hope you enjoyed our episodes.

Announcer:
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