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Case Consult: Targeting CDH6 in Platinum-Resistant Ovarian Cancer

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Dr. Moore:
Welcome. This is CE with GLC. I'm Dr. Kathleen Moore, Deputy Director and Director of Phase One Clinical Research at the Fred and Pamela Buffett Cancer Center in Omaha, Nebraska.

Dr. Salani:
And hi, I'm Ritu Salani. I'm a GYN oncologist at UCLA, where I'm also Division Director.

So I have a patient who's 61 years old, and she was diagnosed with advanced high-grade serous ovarian cancer. Her molecular profiling at the time of diagnosis was HRD negative, MSS, low tumor mutational burden, HER2 1+, and folate receptor alpha 20%. She was initially treated with neoadjuvant carboplatin/paclitaxel with bevacizumab and underwent interval debulking surgery. She then completed her chemotherapy regimen with bevacizumab maintenance.

Unfortunately, she developed metastatic disease, or recurrent disease, 9 months after platinum-based chemotherapy. Since she was platinum-sensitive, I started her on second-line carboplatin/liposomal doxorubicin. She received 4 cycles, but was noted to have progression of disease.

She was then started on a third-line regimen of cyclophosphamide, pembrolizumab, and bevacizumab, which is based on phase 2 data, and this was before we had B96 as an FDA label. She received 3 cycles, and imaging was done, and it showed disease progression. At this time, she expressed she was interested in all options, particularly clinical trials, and we found a trial that she was a great candidate for, which was the REJOICE-Ovarian01 trial. This is a trial that's using raludotatug deruxtecan as an option.

So, Dr. Moore, can you show us some of the data on this drug?

Dr. Moore:
Sure. So R-DXd, or raludotatug deruxtecan, is an antibody-drug conjugate that targets cadherin 6, or CDH6, and we'll talk about the drug in a moment.

CDH6, kind of like folate receptor alpha, is a target that we've been interested in for a long time in ovarian cancer, and also here in renal cell cancers. It's almost ubiquitously expressed to the point that we don't even have to test for it as a gate to have access to the medication, whether or not it's important level-wise for responses we'll talk about a little bit, but it's very common. You can see here in

high-grade serous, over 70% are going to have some cadherin 6. And we find it not uncommonly in other subtypes as well. And so this is a target that we know exists, and so we now have a medication that hopefully will exploit that to the benefit of our patients.

And so if we talk about just the drug R-DXd, or raludotatug deruxtecan, it's similar to trastuzumab deruxtecan, same payload, it's a deruxtecan payload, so topoisomerase payload. Linkers are similar, but here the antibody is targeting CDH6 or cadherin 6. And it went through phase 1 testing, which I'm just going to say I was involved with, so had early experience with the efficacy of this medication that led to its launch into a pivotal phase 2/3 study called REJOICE-Ovarian01.

And you can see this has two parts. There's a phase 2 part and a phase 3 part. The phase 2 part was a very intentionally designed dose optimization study to evaluate the three doses that we came to in the phase 1 that were effective and appeared to be safe, to really pick which one was the best. And then based on the phase 2, the phase 3 would launch with the appropriate dose.

And so we can look at just the phase 2 result now because we've actually seen the phase 2 readout. And so this was presented, not quite yet published yet, but 107 patients across 3 dose levels. You can see the demographics that are listed here, and it's a very characteristic population for platinum-resistant ovarian cancer. And we looked at membrane positivity of CDH6, and any positivity was in 94% of samples, and this wasn't selected. It's just what was found when the patients came on. So this is a very prevalent biomarker.

So, if we look at the antitumor activity, you can see these are the 3 dose levels: 4.8, 5.6, and 6.4 mg/kg. Overall, all patients, 107, the response rate is a little over 50%. Across the 3 dose levels, all were felt to be active.

And you can really see that here. The waterfall plot—this is all of the 100-plus patients. The colors denote each dose level. And this is the type of waterfall plot you want to see when you're taking care of your patient because my expectation—all the way on the left side there were maybe 8 patients where it just did not work, and that's unfortunate. But for the vast majority of patients there was some tumor shrinkage, with around 50% of patients having a RECIST-confirmed response rate. So evidence of efficacy, or at least signals of efficacy here, are quite strong.

Statistically thus far there's no correlation with the baseline CDH6 level and the patients who had response to this medication. So it may not be important, but it is being evaluated in the phase 3 as a stratification factor, and so we'll have definitive data on that when the phase 3 reads out.

The go-forward dose was the 5.6 mg/kg. The overall risk of pneumonitis was half the rate at the 5.6 dose. And so this is really felt to be the safest medication level to go forward.

And then you can see just the other adverse events in a granular fashion across the three dose levels. We did see less hematologic toxicity at 5.6 as well, which gives us the opportunity to use a medication without having to use required GCSF, for example, and without having to dose hold and do things for hematologic toxicities, and have a much lower risk of pneumonitis.

I want to just touch on ILD because this is such an important toxicity with a lot of the topoisomerase I ADCs. I think we have to be careful across the board. But we want to really catch these when they're CTCAE grade 1, which means they're completely asymptomatic. We have grace to hold these medications. Let grade 1 resolve so that we can restart in a safe manner. Because once it's grade 2, just like T-DXd, we have to permanently, unfortunately, discontinue.

And so based on the REJOICE-Ovarian01 phase 2 data, as I mentioned previously, the phase 3 is now launched with the go-forward dose of 5.6 mg/kg IV with stratification by cadherin 6 levels. This is an exciting opportunity to build on the breakthrough therapy designation for R-DXd by the FDA for that initial strong efficacy standpoint. We hope that this will translate into another winning medication for our patients.

Dr. Salani:
Yeah, and if I could just add, I'm really excited about this option. I think the data across the board, regardless of expression, is kind of compelling, especially when we see that HER2 really is kind of correlated with the expression level. This may kind of give us that same payload, which we believe is very active, but a better way of getting it to the tumor, especially since CDH6 is so widely expressed.

And so I think it really affords a really nice option for our patients. And although they're not exactly the same drug, I think the

management of toxicities we're more familiar with having that T-DXd experience. And so you mentioned ILD, the hematologic toxicities. I think we're getting more comfortable with those, so I feel like it adds a new option with better efficacy, but maybe not new toxicities. Still toxicities, but not new toxicities, which I think gives us that level of familiarity and comfort when using these drugs. I'm really excited about this clinical trial. I think this really has that potential to be game-changing.

Dr. Moore:
Yeah, and I am too. This is open and accruing now globally, and so this is why we really want to have clinical trials accessible to as many patients as possible across the US and across the globe, so they can have access to the opportunity.

Dr. Salani:
So, I think this study is really designed with patients' best intention, best outcome. It is randomized, but just like you said, that's the only way we're really going to know the impact in our patient population. Really exciting, though.

Dr. Moore:
The overlapping biomarkers may be important in picking which topoisomerase I ADC we pick when we have more than one available. Right now we have one, T-DXd, and so we're all fighting to use it in wherever we can. But when we have more than one, which we will, I think in the next 1 to 2 years based on clinical trial readouts, will the biomarker be important or not? I think is the next question. Or does topoisomerase I work in whatever biomarker setting, and then you just use the one that you think is safest and has the best schedule? So there's just a lot for us to suss out here as we get more of these into our hands.

Dr. Salani:
And we're getting into that world where we now have potential multiple targets for the same biomarker and similar payloads, different payloads. It's going to get very, very confusing, I think. But I think these programs are really helpful in helping to understand the data that we have today and what to look forward to in the future.

Dr. Moore:
Yeah, confusing right now, but it will get clearer as we get more data. But a little overwhelming right now.

But with that, our time is up. We hope this quick case-based discussion is helpful to your practice, and thank you so much for listening.

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