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Case Consult: Treatment Strategies for HER2-Positive Platinum-Resistant Ovarian Cancer

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Dr. Salani:
Welcome. This is CE with GLC. I'm Ritu Salani. I'm a GYN oncologist at UCLA, where I'm also Division Director, and I'm pleased to be joined with Dr. Moore.

Dr. Moore:
Hi, I'm Dr. Kathleen Moore. I'm the Deputy Director and Director of Phase One Clinical Research at the Fred and Pamela Buffett Cancer Center in Omaha, Nebraska, and we're going to start this discussion with a case.

This is a patient who was diagnosed with stage IIIC high-grade serous ovarian cancer in June of 2022. Excellent performance status at the time she was diagnosed. She had molecular profiling sent and was *BRCA* wild-type, but HRD positive.

So her treatment course had primary cytoreduction, no gross residual, received paclitaxel/carboplatin for 6 cycles, had bevacizumab added cycle two, and then proceeded in January of '23 to receive what we call the PAOLA regimen, so continued bevacizumab and added on olaparib.

And then June of '25 unfortunately recurs with peritoneal disease and an elevated CA-125. So we launched carboplatin, PLD—pegylated liposomal doxorubicin—and bevacizumab as her next line of therapy, and launched tissue testing for all of the IHC. So she received 6 cycles of carbo/PLD, went on to maintenance bevacizumab, but right at that 6-month mark unfortunately progressed. And at that biomarker reassessment, we knew now she was HER2 2+, she's folate high. She's CPS 0.

So we could use T-DXd per NCCN guidelines. FDA is 3+, NCCN is 2+. We could use MIRV per FDA approval. I'm probably going to use all of them, Dr. Salani, at some point in some order. But what am I going to pick now? And why might it be T-DXd? I'll turn it over to you to discuss.

Dr. Salani:
Yeah, and I think it's just a wonderful thing that we have options now, right? So, before it was single-agent chemotherapy, and now we have things that are so much better.

And not that there's a single option that's wrong on there, but I'm going to just talk about trastuzumab deruxtecan, which I'm going to refer to as T-DXd moving forward. So, most of you, especially the medical oncologists, have probably been using trastuzumab

deruxtecan, or T-DXd, much longer than I have been, but we all know it's a monoclonal antibody targeting HER2, and this has a topoisomerase I inhibitor payload.

I'd like to just highlight the HER2 expression that we see in gynecologic cancers across the board. IHC 3+, you can see, is actually pretty rare in ovarian cancer at 2% to 5%, a little bit higher in our other cancer types, cervical and endometrial. But IHC 2+, you'll see in about 8% to 18% of patients. And as we're testing more ubiquitously, we'll kind of get a better handle of what that number is.

We've talked about this before, but testing early on, at the time of NGS, getting IHC added on, oftentimes this is something we can do at our institutions as well, so you don't need a third-party company to do this. It's important to have this information, even if it doesn't make a difference at frontline. You may have that information, which can help you kind of think and strategize moving forward.

So let me show the data from the phase 2 DESTINY-PanTumor02 trial. This was looking at T-DXd in HER2-expressed metastatic tumors, and this was in the recurrent setting. This was a basket trial, and they had different cohorts. I'm going to focus on the ovarian cancer population here, and this was using T-DXd at 5.4 mg/kg every 3 weeks. The primary endpoint was objective response rate, but I'm going to show you some of the really impressive secondary endpoints of duration of response, PFS, and OS.

Here you can see patient characteristics.

So, when we look at the objective response rate by IHC, you can see that we saw a pretty profound objective response rate at 45% in all patients. Those patients who had IHC 3+ by central testing, there was an objective response rate of 63%. And in the IHC 2, you saw it at 36.8%, so a little bit less impressive, but for platinum-resistant ovarian cancer, pretty impactful numbers that we're seeing. And you can see also that if patients had one prior regimen versus greater than two prior regimens, there was a difference in response rate, but still an impressive response rate across the board.

The study also looked at different subgroup analyses. Whether there was prior or no prior HER2 therapy, you could see that these patients had a pretty impressive response rate. And same thing applies to prior topo I inhibitor therapy. So I think this kind of shows that this drug works regardless of what you had seen before, if you had that HER2 2+ or 3+ expression.

And then same thing, you can see by molecular markers, *BRCA1* or *2* mutation detection or not, you still had good response rates, although it was notably more impressive in the *BRCA1* and *2*-mutated carriers. And then same thing with HRD, a little bit more response with those who had HRD status, or HRR as they determined it here. CA-125 number did not also make a significant difference in response rates because both groups had impressive response rates. And once again, just highlighting really a provocative response across the board.

So now I'm going to show you the PFS and OS data, which is described here by HER2 expression level, and this data is really impactful. First, the PFS. IHC 3+ is depicted by the dark blue line, and the median PFS was 12.5 months. When you look at the purple line, that's IHC 2+, a median PFS of 4.1, and the green line, kind of the combination of the 2. Really, the IHC 3+ really does carry the kind of significant responses here, but we are seeing meaningful responses in the IHC 2+.

What's really powerful is the overall survival data. In the IHC 3+, we see a 20-month median overall survival. These are kind of data that we haven't seen across the board for ovarian cancer in quite some time. So this is a very meaningful biomarker. With the IHC 2+, you're seeing a median overall survival of 13 months, still very impactful, but you can see that it does correlate with IHC expression. So, this is a really great option for some of these patients who have IHC 2+ and really 3+ expression of HER2.

But along with these results, it's important to recognize adverse events. With the use of T-DXd, we do see myelotoxic responses: anemia, neutropenia, and thrombocytopenia, which may require dose reductions or dose delays, and then management, including GCSF and transfusions. We also know this is a high emetogenic regimen, and so managing nausea, vomiting with preventative or prophylactic antiemetic regimens is really key.

One of the more significant adverse events that we should realize is interstitial lung disease. One of the keys about this is recognition, and we want to catch this actually in the asymptomatic case or phase, and so actually imaging is going to be a key part of monitoring these patients for interstitial lung disease. If you see incidental findings on a scan, you will have to hold therapy, but it's also important to talk to patients and make sure that they are not having new symptoms: worsening cough, dyspnea, shortness of breath, fever, that might

also elicit a finding of interstitial lung disease, and not only holding therapy, but sometimes even stopping therapy when they are truly symptomatic.

So now that I reviewed this data, Dr. Moore, tell me how you're going to incorporate T-DXd into your patient practice.

Dr. Moore:
My priority for someone with platinum-resistant disease right now is to look at the available options and make sure that I'm giving them access to a topoisomerase I ADC because they just work so well. So I think this is going to change with time and new approvals, but right now, if I find HER2 2+ or 3+, then T-DXd is on the menu for my patient, and then we consider the best place with the available data that we have to use it.

My patient, though, is a cellist. Like that's her life, and she needs to feel her fingers, and she cannot tolerate any visual disturbances because she has to read music. And so for her you have the data, and then you have to look at the patient in front of you and meet them where they are and meet their expectations and what's important to them. So for her that was the best choice, no neuropathy, no ocular toxicities. Of course, we have to follow all of the adverse events that you so nicely reviewed, but it bumped up to the top because of that shared decision-making. So, I think that's what all of us know as physicians actually happens. You take the data and integrate it, but I might have made different decisions with a different patient based on their priorities.

Dr. Salani:
And I think it's important to recognize that it may not be unlikely that the patient may see both options, and so does it matter if you do mirvetuximab first and then T-DXd or vice versa? So I think these are always really great discussions where you're taking side effects as kind of the primary kind of motivator for your decision-making, and in conjunction with the patient's goals and desires.

Dr. Moore:
Absolutely, yeah. It's good. It's good. This is a challenge, but it's a good challenge to have, because it means we have options now and options coming and choices for our patients, which they've never had. They've had choices. They're bad choices. They have reasonable choices now, and hopefully even better choices. So this is why we do what we do. So.

Dr. Salani:
Couldn't say it better myself. So with that, our time is up. We hope this quick case-based discussion is helpful to your practice, and we thank you for listening.

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