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Case Consult: Personalizing First-Line Maintenance Therapy in Advanced Ovarian Cancer

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Dr. Moore:
Welcome. This is CE with GLC. 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.

Dr. Salani:
And I'm Dr. Ritu Salani. I'm at UCLA, where I'm Division Director of GYN Oncology. And it's a pleasure to be here with you today.

So, I have an interesting case. This is a 76-year-old patient who presents with abdominal pain. She undergoes imaging and is found to have an adnexal mass and findings concerning for ovarian cancer. She undergoes primary debulking surgery with optimal cytoreduction, and final pathology demonstrates FIGO stage IIIA high-grade serous ovarian cancer. She undergoes molecular testing of her tumor, and it demonstrates HRD positivity, wild-type *BRCA1* and *2*, microsatellite stability, and a tumor mutational burden of 8. She's initially treated with carboplatin and paclitaxel, and bevacizumab, and she has a complete response after completing 6 cycles of this first-line therapy. I then started maintenance olaparib and bevacizumab, and she continues on maintenance therapy with no evidence of progression to today. Our plan is to stop maintenance therapy after 2 years.

So, Dr. Moore, you've been really instrumental in some of this data, and I'm wondering if you can share some of the data that supports the use of PARP inhibitors as first-line maintenance therapy in advanced ovarian cancer.

Dr. Moore:
Absolutely. This is one of the places where we actually have quite a bit of data, including long-term data and overall survival data for use of PARP inhibitors in this setting.

So, let's go through the data. We'll start with SOLO-1, which was the first randomized phase 3 study to launch to evaluate PARP inhibitors in the frontline setting. It enrolled patients with *BRCA*-associated cancers. They had to be in response to their frontline chemotherapy, and then they were randomized 2:1 to receive up to 2 years of olaparib or placebo. And the primary endpoint was progression-free survival.

So, let's take a look at the progression-free survival, and this is actually an updated look at PFS that we did at 5 years. And you can see we have a hazard ratio of 0.33, so a 67% reduction in the rate of progression events for patients that were randomized to receive olaparib as compared to placebo.

So treatment was stopped at 2 years, and then we had this real plateauing of these two Kaplan-Meier curves demonstrating ongoing kind of treatment benefit beyond the 2-year treatment cap, leading to this substantial reduction in the rate of progression for patients treated with olaparib.

We can look at the interim analysis of overall survival next. This was a preplanned interim look at 7 years. What you can see here is a 45% reduction in the rate of death events for patients who were randomized to olaparib as compared to placebo. And this is even more remarkable when you consider that among the patients who were randomized to placebo, 44% of them at this point had appropriately crossed over to PARP inhibitor in a subsequent line of therapy. And so they didn't catch up in terms of overall survival, which I think answered the kind of question about should you wait and use a PARP inhibitor in the setting of recurrence? No, you should use it up front because you lose the overall survival advantage, and you'll see an update of this data coming up in the next short time period.

PAOLA-1 evaluated all-comers, so it did not matter what molecular subtype. Similar to SOLO, they had to be in complete or partial response to their frontline chemotherapy. They had to have had incorporation of bevacizumab into initially 3 of the however many cycles of paclitaxel and carboplatin had to contain bevacizumab. That was later amended to 2. Patients were stratified by *BRCA* status, not HRD, but by *BRCA*, and were randomized either continuing the bevacizumab for a year with placebo in place of olaparib, or continuing the bevacizumab, again for a year, or 2 years of olaparib.

And the primary endpoint was progression-free survival in the entire group, but really what we care about are the subsets, which we can show here in this next figure, where you can look at the 5-year progression-free survival just pulling out the HRD-positive subset, which includes *BRCA* and is largely driven by *BRCA*, but also includes about 20% of tumors that are *BRCA* wild-type HRD. PARP-bevacizumab versus bevacizumab, you have a hazard ratio of 0.41, so almost a 60% reduction in the rate of progression events when you add olaparib to bevacizumab as compared to bevacizumab alone in the HRD-positive subgroup. So, a substantial improvement in PFS. And then looking at the 5-year OS in the HRD-positive subgroups, this is in higher clinical-risk tumors, what you can see here is about a 30% improvement in the 5-year overall survival with the addition of olaparib.

And then if we look at the kind of lower clinical risk, we have a hazard ratio here of 0.31, and so this is a group that just did remarkably well with PARP inhibitors.

And then the other study that was run was called PRIMA. This was also an all-comers study, took patients with advanced ovarian cancer who were in response to chemotherapy and then were randomized 2:1 to either receiving niraparib monotherapy or placebo.

Primary endpoints here were PFS in the ITT, intention-to-treat, and then also the HRD test-positive group. And what you can see here in the PFS in the HRD-positive population, which is of course where we have an indication, is a hazard ratio of 0.51, so almost a 50% reduction in the rate of progression events with use of niraparib as compared to placebo.

But when we look at OS, we don't see a detriment, but we don't see an advantage to use in this particular population.

This is just a summary of the safety data across the phase 3 trials. I think we know the safety data of PARP inhibitors well. Common but low-grade GI toxicities. Anemia is a common grade 3 side effect. There are varying degrees of thrombocytopenia, and then the long-term kind of catastrophic toxicity that we worry the most about are treatment-related myeloid neoplasms, such as AML or MDS. But when we use these PARP inhibitors in the frontline for time-limited amounts, the rates of this admittedly catastrophic side effect—we can't underestimate that—but they're really low.

And so the summary is that's where we are right now. The big gap is HRD test-negative, where we don't have anything other than bevacizumab. And we have antibody-drug conjugates moving into the space, many in development, two in clinical trials and public domain: sacituzumab tirumotecan for all-comers, HRD test-negative but not selected by TROP2 status, and then trastuzumab deruxtecan in DESTINY-Ovarian01 in tumors that are HER2 1+, 2+, or 3+, both of these maintenance ADC plus bevacizumab versus bevacizumab. And I think we'll see more of these moving forward.

And that's sort of the rapid summary of the frontline space. I'll turn it back over to you, Dr. Salani.

Dr. Salani:

Thank you. So, I'm just curious, when you're selecting first-line maintenance, you said you kind of use molecular profiling first, so B-R-C-A, *BRCA* status, HRD status, and then what other factors could go into your decision-making?

Dr. Moore:
Well, at this point, that's it. When I'm thinking about a patient in frontline, there's decisions that you make before you know the molecular status of your patient. Often, you're deciding about bevacizumab before you have any testing back. And maybe I have a consult for a patient that had been started, and they come in to see me after neoadjuvant, for example. Then I'm incorporating there's something called the KELIM score, which is looking at logarithmic CA-125. I may look at that to see if the tumor is responding really well or not really well, because that might gate me adding on bevacizumab in a place where it hadn't been added.

But right now we don't really have great biomarkers for bevacizumab, so I'm getting that initial testing back and making my decisions for PARP. And then tumors that are HRD test-negative or unknown, I'm looking for trials right now. And as a part of frontline workup, I send my tumors out for testing, so I'm getting the whole panel back of HER2, folate, of course we get cyclin E amplification, which may be important in the future. But those are all things that are, I think, informing clinical trials right now, not so much changes in what I do right now in the frontline.

Dr. Salani:
Dr. Moore, one thing I often encounter is you'll see a patient who's referred to you who's maybe getting neoadjuvant chemotherapy. The biopsy was done, it was sent for molecular testing, and it'll say quantity not sufficient, and so you'll only be able to get some molecular testing, and sometimes the HRD status is written as unknown or not evaluated. What do you recommend in those scenarios?

Dr. Moore:
Yeah, that's a great question. Thank you. What I recommend is really going back and talking to the pathologist about what was sent, and asking them to send maybe another cut, another section of the block. Sometimes it's even worth trying to get another biopsy, because in absence of *BRCA*, this is the only opportunity for a patient to get a PARP inhibitor, and they can be, as I outlined, incredibly effective in tumors that are HRD positive, even with *BRCA* wild-type. And so I would make every effort possible to, at the very least, send another specimen for evaluation. If not, consider a biopsy if there's biopsiable disease, to make sure that you're lining your patient up for the most effective maintenance therapy available to them in this setting.

Dr. Salani:
And I will add, sometimes it's like you can think about, oh, we'll get more tissue at the time of tumor debulking if the patient's getting neoadjuvant, but it's a little bit risky because sometimes the patient may have such a profound response, or the tumor has gone through changes where it's not evaluable. So, I think getting that information up front can be really impactful.

So, 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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