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The Evolving Landscape of Endometrial Cancer Treatments

Announcer:
You're listening to *Project Oncology* on ReachMD. Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss the therapeutic landscape for endometrial cancer is Dr. Susana Campos. She's the Vice Chair of the NCCN Committee for Uterine and Cervical Cancer and an Assistant Professor of Medicine at the Dana Farber Cancer Institute in Boston.

Dr. Campos, thanks for being here today.

Dr. Campos:
Thank you very much for having me.

Dr. Turck:
Now to start us off, Dr. Campos, would you give us an overview of how the treatment landscape for endometrial cancer has evolved in recent years?

Dr. Campos:
Yes, I will. It's very exciting to actually talk about this because it has changed dramatically in the last year and year and a half. Back in 2023, at the SGO meetings, there were two very pivotal trials that were presented. That was the NRG-018 that studied the role of pembrolizumab plus chemotherapy in patients with advanced or recurrent disease. This particular trial led to the FDA approval of pembrolizumab with carboplatin and paclitaxel for advanced and recurrent disease. It showed a progression-free survival benefit.

In a likewise fashion, although a different trial, the RUBY 01 trial utilized dostarlimab in combination with carboplatin and paclitaxel. And once again, this particular study showed a progression-free survival in patients that were deficient in MMR in the overall patient population.

There is another trial called the DUO-E trial, which was presented by Dr. Westin and colleagues and now subsequently published in the *JCO*. In this particular trial, the authors looked at durvalumab plus chemotherapy, carboplatin, and paclitaxel for advanced endometrial cancer. And once again, this particular study showed a progression-free survival benefit of durvalumab plus chemotherapy in patients that were deficient in MMR. So all these three trials have very uniting themes, and that is that IO, whether it be pembrolizumab, dostarlimab, or durvalumab, have a role in the upfront management of advanced or endometrial cancer.

One question that's come to light specifically in patients that are deficient in MMR is whether or not chemotherapy remains important. Can we utilize simply IO therapy in the deficient MMR cohort? And there are two pivotal trials that are actually looking at this. One of them is the C93 data, which is looking at pembrolizumab versus chemotherapy. And the other trial is the DOMENICO trial, which is looking at dostarlimab versus chemotherapy. Specifically, these two trials are studying this combination in deficient MMR. So it's been very exciting in the last several years, and hopefully, in the next several years, we can narrow down the treatment of patients, especially for those that are deficient in MMR.

Dr. Turck:
Now you started to talk about some of this, but zeroing in on one therapeutic modality in particular, I was wondering if you would continue going over some of the key efficacy and safety data associated with immunotherapy?

Dr. Campos:

Absolutely. If we take each trial one by one, if we look at the NRG-018, which was pembro plus chemotherapy, the hazard ratio in the deficient MMR group was 0.3. This was a 70 percent difference in relative risk. The hazard ratio in the proficient MMR was 0.54. In the RUBY 1 data, which used dostarlimab, the hazard ratio in the dMMR was 0.28. Again, quite fruitful. And in the overall population, it was 0.64. The DUO-E trial, which was durvalumab plus chemotherapy, the hazard ratio in the deficient MMR was 0.42, and the proficient was 0.77. So there's a key term, and there's a key line here in that what we're seeing is amazing hazard ratios with the addition of immunotherapy to the backbone of chemotherapy.

In terms of safety, regardless of whether the drug was pembrolizumab, dostarlimab, or durvalumab, I mean, one has to be mindful of the potential toxicities of immunotherapy. And that really can be an inflammation of any grade in any organ system. And the idea and the purpose is to recognize it early and to actually mitigate those side effects, either with withdrawing the drug or the institution of steroids. So it has been tremendously beneficial. One has to be mindful of the side effect profile of IO.

Dr. Turck:
And looking specifically at durvalumab, how does it work to treat patients with advanced or recurrent endometrial cancer that is mismatch repair deficient?

Dr. Campos:
Sure. What durvalumab is, is a human immunoglobulin monoclonal antibody. And in this particular case, it blocks the interaction of the programmed cell death ligand 1, the PD-L1, with PD-1. So it's a bit different than that of pembrolizumab and dostarlimab.

Dr. Turck:
And as a follow up to that, are there any side effects specific to durvalumab that we should be aware of?

Dr. Campos:
I think all of them is more of a class effect. I think we have to really think about the fact that all of these drugs, all of these IOs have very common side effects, and that's an inflammation in any organ. So we think about pneumonitis, hepatitis, colitis, nephritis. We just have to be mindful of this. There's also endocrinopathies associated with some of these IOs, if not all of them. So again, it's a matter of recognizing them, having a really good rapport with your patients so that they tell you what these side effects are, and then instituting a treatment plan for basically mitigating the side effects.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Susana Campos about the treatment landscape for endometrial cancer.

So, Dr. Campos, given that immunotherapy, or IO, options like durvalumab have shown promising results in tumors with specific genetic changes like mismatch repair deficiency, what are some best practices for using biomarker testing?

Dr. Campos:
Oh, I think all tumors should be tested for a deficient MMR or proficient at first blush, and that will really help navigate the patients with advanced or recurrent endometrial cancer. So I think that is a must. And I do think all institutions are doing that, and that's quite important. That's probably the major ones.

Dr. Turck:
And just to bring this all together before we close, Dr. Campos, big picture, what kind of impact could biomarker testing in the evolving endometrial cancer therapeutic landscape have on our patients?

Dr. Campos:
I think it will be tremendous. I think it's quite important, as we mentioned before, that all patients should be tested to see whether or not they're deficient in MMR or proficient. That certainly guides the therapy in the upfront management of patients with endometrial cancer and in some studies, settings in the recurrent settings. I think depending on the results of the DOMENICA trial and the C93 data, I'm hopeful that perhaps we can use IO therapy alone in patients with deficient MMR. So I'm eagerly awaiting those results. So having that information would be extremely of paramount importance.

I think also thinking of other elements, like tumor mutational burden because pembrolizumab is indeed approved for patients with a high mutational burden. And we talk a lot about deficient MMR, proficient MMR, but there are other biomarkers, like HER2/neu, which can actually guide the clinicians in treating patients with HER2/neu disease. For example, there's a wonderful trial, the NRG-026, that is actually studying the role of HER2/neu-targeted therapy in patients with uterine serous carcinoma of the ovary. And then most recently, we have the DESTINY-PanTumor02 trial, which showed us the benefit of trastuzumab DXd in two-plus and three-plus uterine cancer. It was pretty remarkable objective response rates and pretty impressive progression-free survival. And other biomarkers include PI3

kinase, and let's not forget that estrogen receptor is also a biomarker in many cases and can also help navigate therapy.

So I think it really brings to the attention how very important it is to understand the subtypes of endometrial cancer so that you can start targeting this in a very different way.

Dr. Turck:
Well, with those reflections in mind, I want to thank my guest, Dr. Susana Campos, for joining me to discuss the evolution of the treatment landscape for endometrial cancer. Dr. Campos, it was great having you on the program.

Dr. Campos:
Thank you.

Announcer:
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