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Advancing Endometrial Cancer Care: How the Treatment Landscape Has Evolved

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 changing therapeutic landscape for endometrial cancer is Dr. Linda Duska, who's a gynecologic oncologist at UVA Health in Charlottesville. Dr. Duska, thanks for being here today.

Dr. Duska:
Thank you so much for inviting me to be here today.

Dr. Turck:
So to get us started, Dr. Duska, let's take a look at some of the most recent advances in endometrial cancer treatment. What can you tell us about the RUBY and GY018 studies?

Dr. Duska:
Well, let's start that conversation by talking about the design of these two trials because they're very similar studies, but they also have important differences.

So, first, the similarities: both of the studies were randomized phase three trials in advanced or recurring endometrial cancer. Both of them randomized subjects to paclitaxel plus carboplatin alone, which is the standard of care, versus that same standard of care plus immunotherapy followed by immunotherapy maintenance.

So in a nutshell, that was what both studies were: very similar trials, but with some important differences to note. First of all, the two studies used different immunotherapies. So, GY018 used pembrolizumab, and RUBY used dostarlimab. They're both PD-1 inhibitors, but they're different drugs, so important to note.

The second important thing to note is that they use different inclusion criteria, and a big example of that is that RUBY allowed endometrial carcinosarcomas, but GY018 did not.

And then finally, and this was in part because of the COVID pandemic, GY018 was unblinded during the course of the trial so that patients who were on placebo didn't have to come to the site to get their placebo during COVID. Some people argue that might make it a little more difficult to interpret the overall survival data for GY018, but we'll see. We're still waiting for those final results.

Dr. Turck:
And what did we learn from these studies?

Dr. Duska:
So we've seen two really important publications for both trials in 2023 in the New England Journal of Medicine. But we also saw updated overall survival data for both studies in 2024 at the Society of GYN Oncology, so I'm going to talk about GY018 first. I already told you this one used pembrolizumab and this study was run by the National Cancer Institute. We already knew from the 2023 paper that the addition of IO, or immunotherapy, to the chemotherapy backbone resulted in a statistically significant improvement in progression-free survival, or PFS, in both the dMMR and the pMMR subjects.

There was also a statistically significant improvement in overall response rate and duration of response, so that's really exciting. But then we saw updated data at SGO in 2024, and we saw the overall survival data. Now, remember that this is very early in the course of this study, so these data are not mature. However, for both pMMR and dMMR, we saw a trend for overall survival improvement in the group that got the immunotherapy. For pMMR, the hazard ratio was 0.79, and the hazard ratio was even better in the dMMR group—0.55—not statistically significant, but really exciting, and we're waiting for that data to mature.

Based on the flattening that we saw in the Kaplan-Meier curves, particularly in the dMMR group, it would appear that the benefit of IO, or immunotherapy, is sustained. So really exciting, and we're waiting for the updated results.

RUBY, on the other hand, as we already said, allowed carcinosarcomas, and interestingly, almost 10 percent of patients that entered RUBY had carcinosarcomas. So that's really important to note. For the RUBY trial, again, we already knew that the addition of dostarlimab improved PFS in the dMMR group and in the overall population. When you looked at the whole population, you saw an improvement in PFS and, in particular, in the dMMR population.

We also saw an early overall survival trend at the first interim analysis. But then, at SGO, we saw the updated OS data and we saw a statistically significant overall survival benefit in the overall population with a hazard ratio of 0.69. That was statistically significant, but it was most likely driven by the dMMR population. So this difference was most substantial in the dMMR population with a hazard ratio of 0.32. This is really remarkable, and at the presentation, it was actually called unprecedented. This is the first time we've seen such a remarkable difference in overall survival in endometrial cancer.

In the MMRp group, the difference in OS was not statistically significant, but there was a trend with a hazard ratio of 0.79, and there was also a seven-month difference in the median overall survival in those patients with MMR proficient disease. So provocative data again, even in that group.

I already alluded to the unblinding of GY018, which allowed crossover. There was also crossover in RUBY. So once people came off study, they did cross over, and about 38 percent of the whole population on RUBY who did not receive IO then received IO subsequently. Interesting, and still, we see this tremendous difference in OS. I think it's fair to say that, in summary, these studies have really revolutionized and changed the management of advanced and recurrent endometrial cancer.

Dr. Turck:
And what about the AtTEND trial? Would you tell us about those findings?

Dr. Duska:
So AtTEND, similar to the studies we already talked about, was in advanced and recurrent endometrial cancer, and like RUBY, AtTEND allowed carcinosarcomas. In AtTEND, patients were randomized two-to-one to receive the platinum-based backbone that we've just talked about with atezolizumab or the standard of care alone.

Now, atezolizumab and also durvalumab are PDL-1 inhibitors, not PD-1 inhibitors. But they're checkpoint inhibitors, and they work in a similar way. The results from AtTEND showed that the atezolizumab group had significantly improved PFS in both the dMMR group and the overall population. The PFS advantage in the overall population was driven by the dMMR group in this study. However, in the MMRp group, there was no difference in PFS.

Dr. Turck:
So how might the novel therapies these trials examined help address present unmet needs for patients with challenging subtypes, like tumors that are mismatch repair deficient?

Dr. Duska:
That's a really good question, but in the dMMR subtest, it seems very clear that the addition of IO to the chemotherapy backbone in advance or recurrent setting leads to both PFS and OS improvement. The OS improvement in one of the studies, as we already said, was unprecedented. My opinion, and the opinion of many others, is that all patients with dMMR advanced or recurrent endometrial cancer should be treated with paclitaxel-carboplatin plus IO, assuming, of course, that there are no contraindications in that individual to IO therapy.

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. Linda Duska about how the therapeutic landscape for endometrial cancer is evolving.

Now, Dr. Duska, clearly, we're making some exciting advances in the treatment of endometrial cancer, so if we look ahead for just a moment, would you walk us through some of the ongoing clinical trials and most promising therapies we can look forward to?

Dr. Duska:
There's a lot of excitement about selinexor in the p53 normal or the NSNP group, and there's currently a randomized phase three trial looking at randomizing patients to the re-treatment with carboplatin-paclitaxel versus carboplatin-paclitaxel plus a selinexor maintenance. And so we're really looking forward to the results of that study because that will give an option to those patients who may not benefit as much from the checkpoint inhibitors.

We're also really excited about antibody-drug conjugates in this space. So, we already know about T-DXd from the DESTINY-PanTumor trial that patients with endometrial cancer; there were multiple solid tumors on that study, but the patients with endometrial cancer had the most remarkable overall response rate on the study. And so it's really exciting that we have this option for our patients now; it was FDA-approved very recently, but there are also multiple other ADCs under development for endometrial cancer, including TROP2 ADCs, among others. And so we're really excited about further development in that space.

I also want to put in a plug for next-generation sequencing in endometrial cancer because it can identify potentially targetable mutations. We have a couple studies open here at the University of Virginia that target ARID1A mutations, which are relatively common in endometrial cancer, and give a novel opportunity for patients for treatment.

There are also studies looking at hormone combinations because hormones work well in some types of endometrial cancer, and there are lots of studies looking at hormonal combinations as well as studies looking at the PI3 kinase pathways.

Dr. Turck:
So with everything we've discussed today, Dr. Duska, do you have any final thoughts on the impact these therapies could have on quality of life and outcomes of patients with endometrial cancer?

Dr. Duska:
Well, thanks for asking the quality of life question because I did not mention that. So we talked about RUBY and GY018; these studies have really changed how we manage advanced and recurrent disease, particularly in the dMMR groups. As I've already said, checkpoint inhibitors should definitely be used in this group, but also RUBY and GY018, as well as the other studies, included quality of life questionnaires and obviously a lot of safety work and found that patient's quality of life was not significantly impacted by adding IO to the chemotherapy backbone. So, that's really important.

And so I think immunotherapy has really changed the landscape. It's been a really exciting 2 years for endometrial cancer, and I think the future is very bright as we study more and more, not just immunotherapy, but targeted agents; as we sort through how to give immunotherapy and how we think about women with this disease, we're going to have lots and lots of options.

I just think about 15 years ago when we thought chemotherapy didn't work in this cancer. And now, think about all the wonderful options that we have for these patients.

Dr. Turck:
Those are great comments for us to think on as we come to the end of today's discussion, and I want to thank my guest, Dr. Linda Duska, for joining me to discuss the evolving therapeutic landscape for endometrial cancer. Dr. Duska, it was great having you on the program.

Dr. Duska:
Thanks so much for having me, particularly with so much good news to give.

Announcer
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