

# Exploring the Horizons in Advanced or Recurrent Endometrial Cancer - Practical Considerations and Future Directions for New Treatment Strategies



## CEC Podcast Transcript

### **Kathleen N. Moore, MD, MS, FASCO:**

Hello. On behalf of CE Concepts, I would like to welcome you to today's educational activity entitled, *Exploring the Horizons in Advanced or Recurrent Endometrial Cancer: Practical Considerations and Future Directions for New Treatment Strategies*. This activity is supported by an educational grant from Merck & Company in Rahway, New Jersey. This activity may include discussions of products or devices that are not currently labeled for use by the U.S. Food and Drug Administration (FDA). As a way of introduction, my name's Dr. Kathleen Moore. I am the Deputy Director and Director of Phase I Clinical Trials research at the Fred and Pamela Buffett Cancer Center at the University of Nebraska Medical Center in Omaha. And I am very excited to be joined by my friend, and I'm excited to say former colleague, but we're still colleagues at heart, Jaclyn Shaver. Jaclyn, will you introduce yourself, please?

### **Jaclyn Shaver, APRN, CNP, WHNP:**

Yes, Dr. Moore. Thank you for that. I'm excited to be here. We all miss you here at Stephenson Cancer Center. But my name is Jaclyn Shaver. I'm a nurse practitioner, lead nurse practitioner, here in the gynecologic oncology department. I've been here for quite a while now, since 2011. And I'm so just excited to be here.

### **Kathleen N. Moore, MD, MS, FASCO:**

Wonderful. I'm so excited to have you here. And, yes, we did used to work together and really brought a lot of medications that we're going to talk about today from clinical research now to FDA approval so that they can be used by patients within our practice. You take care of a lot of our patients and have brought a lot of these medications into safe use in the clinic. We'll talk about that today. We have three learning objectives for this exercise, and we'll review those on this slide. The first is to interpret the clinical evidence on new and emerging therapies to define their role in the current and evolving treatment paradigms for advanced or recurrent endometrial cancer. The second is to talk about how we manage treatment-related adverse events using evidence-based strategies to maintain treatment continuity and ensure patient safety. And the third objective is to implement or talk about how we implement multidisciplinary and patient-centered strategies to overcome all sorts of barriers, access barriers, access to these novel therapies, address disparities, how we incorporate patient education, patient-reported outcomes, and communication with the multidisciplinary team into the care of patients with advanced or recurrent endometrial cancer to ideally help them live long and high-quality lives.

We have had five phase III clinical trials that have read out in the last little less than 3 years. The first readout was in 2023. That was the inflection point when...it's kind of rare when you're at a meeting and data are shown and the next day how you treated patients changed. It was unethical to not change your behavior the next day. The manuscripts came out and we were changing care, and I'm going to show you why in a moment. But these are the five studies, and we'll go through them so you can see the very consistent...I don't know if it took five studies, but we've got five studies to show us very consistently the expectation of benefit that we obtain with the addition of immune checkpoint inhibitors in advanced or recurrent endometrial cancer. And it is gated or stratified the amount of benefit by biomarker, and we'll talk about that.

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So, let's talk about it. We'll spend the most time talking about the RUBY study and what we call NRG GY018, and I'll mention the other two a little bit as well. But let's start with RUBY because RUBY was really the first study to report out to mature completely. They all started about the same time. RUBY, we call it RUBY Part 1, but the RUBY study enrolled patients with advanced or recurrent endometrial cancer. They could have received prior chemotherapy in the adjuvant setting, meaning maybe they had stage I disease in the past that was felt to be high risk for recurrence, or maybe they had node-positive endometrial cancer, what we now call 3C1 or 3C2 disease that had been resected. And so they're not starting with any evidence of disease, and the expectation of treatment is cure. Well, that's treatment in the adjuvant setting where you use chemotherapy for a set number of cycles with the intent to cure. RUBY allowed those patients with prior chemotherapy to enroll, and that's noteworthy. That's why I'm making such a big deal about this, because prior to this generation of clinical trials, clinical trials that we did in the advanced or recurrent setting excluded any history of chemotherapy. This allowed them, as long as patients hadn't recurred within the first 6 months after completion of that chemotherapy, they could not have received prior chemotherapy in the metastatic setting. Patients could have tumors that were either deficient or proficient in mismatch repair proteins, but we had to know it coming on because it was a key stratification factor.

RUBY did allow patients with tumors that were classified as carcinosarcomas, which differed across the clinical trials. And so, by virtue of the fact that it allowed patients with carcinosarcoma and it allowed a 6-month window from prior chemotherapy, and about 20-ish percent of patients came on with prior chemotherapy, this group of tumors were relatively higher clinical risk than some of the other studies that I'm going to present. Patients were randomized one-to-one to receive paclitaxel/carboplatin, placebo, and placebo maintenance, or paclitaxel/carboplatin, both for six cycles, with the immune checkpoint inhibitor dostarlimab, and then dostarlimab maintenance. The primary endpoints were progression-free survival and overall survival, first in the deficient mismatch repair and then in the intention-to-treat population. I do want to call out that this study was not powered to look specifically at the proficient mismatch repair population, that was looked at in an exploratory fashion. So what I'm showing you here is the progression-free survival data. You can see the overall population on the left-hand side with a very notable hazard ratio, which is how we like to talk about Kaplan-Meier curves. The hazard ratio was 0.64. And so that's statistically and clinically relevant. But what's of more interest is when we look at this by biomarker. So if you'll see the cohort of patients whose tumors were deficient in mismatch repair proteins. In this population, the hazard ratio is 0.28.

The other thing I will note is that if you look at the vertical bar at 12 months in that lower right-hand Kaplan-Meier curve, you'll see that before 12 months, in about 30% of patients, even with deficient mismatch repair, tumors recur. We still have to figure out why that is and why weren't they cured. But after 12 months, that line is flat. We are not seeing an event rate. So, not only is the rate of progression significantly, significantly slower, but we're actually not seeing progression events anymore or recurrence events after that 12-month mark, which does raise the possibility of cure in a population where we have never seen cures before. So, that's exciting. You see the exploratory analysis of the mismatch repair proficient (pMMR) cohort, which was a substantial part of the study. Here, the hazard ratio is 0.76, so a 24% reduction in the rate of progression events with the addition of dostarlimab versus placebo, so, here, a more modest signal of benefit of the immune checkpoint inhibitor but still a clinically relevant endpoint. Slowing progression events are always important for patients. This was felt to be not significant statistically, but significant clinically.

This slide shows you the overall survival. Remember, I told you the primary endpoints here were both progression-free and overall survival. What you can see on the left-hand side of this slide is the overall survival

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for the entire population. And here you can see that the improvement in the hazard ratio for the entire population is 0.69, so a 31% reduction in the rate of death events for patients in the entire study who are randomized to dostarlimab versus no dostarlimab. But even more noteworthy, if you look at the top now, you see the overall survival for the deficient mismatch repair population. This is mature data. The hazard ratio is 0.32, so, again, a 68% reduction in the rate of death events for patients who are randomized to dostarlimab versus chemotherapy with a very flat curve out there where we are not seeing patients die even out to 3 years, which is very different.

You can even see it in the control arm here. The number of patients alive at 3 years is about 50% in that placebo arm and we're at over 80% in the dostarlimab, so clearly a strong signal for survival. In the pMMR group, in the lower right-hand side, you see a pretty nice trend towards an improvement in survival with a hazard ratio of 0.79, so a 21% reduction in the rate of death events for patients who were randomized to dostarlimab versus no dostarlimab. This is, again, not a statistical endpoint. It's just a trend. Clearly it looks a little better than placebo, and we take that, and so this was approved by the FDA – paclitaxel, carboplatin, dostarlimab for both groups. Clearly the most benefit is in the deficient mismatch repair population, but there's benefit in the proficient population. The FDA felt that was enough to warrant approval for all-comers in this population, and that has been available for the last few years. Now, I've said a couple times in the pMMR group, and this is going to be true across every study I show you, there is clinical benefit to the addition of immune checkpoint inhibitors. It's modest, at best, probably not curing more patients, probably just a modest improvement in progression-free survival, and we'll see if the improvement in overall survival holds, which doesn't mean it's not important, but it just tells us as clinical trialists that we can do better. So, how can we do better while we're trying other things?

That brings us to RUBY Part 2. I'm not going to talk too much about it. It's a little bit of a hard study to interpret but it asks the question, and I'm going to show you another study that asks this question as well, in patients with advanced or recurrent endometrial cancer, specifically those with tumors that are proficient mismatch repair, we're not seeing this profound improvement in progression-free and overall survival. If I add a PARP inhibitor, which is an oral anti-cancer agent that we use commonly in ovarian cancer, if I add a PARP inhibitor to the immune checkpoint inhibitor, would that work better in a proficient mismatch repair population? And the rationale behind this comes from preclinical hypotheses generating studies that say, if I induce DNA damage with a PARP inhibitor, that's how they work, that leads to something called cytosolic DNA. Cytosolic DNA, among other things, activates the STING pathway. If we upregulate the STING pathway in the microenvironment of the tumor, would that make immune checkpoint inhibitors work better in a tumor that otherwise is a little bit more hostile to immune checkpoint inhibitors, like a proficient mismatch repair tumor? That's the theory.

RUBY Part 2 asked that question. It randomized consenting patients to either chemotherapy, not chemotherapy-dostarlimab, unfortunately, just chemotherapy alone for 6 cycles versus chemotherapy-dostarlimab for six cycles, and then dostarlimab plus niraparib, which is a PARP inhibitor, maintenance. And it said, "Is that better than chemotherapy alone?" The answer was yes. You can see it here. The median progression-free survival went from 8.3 months to 14.5 months in the all-comer population. In the proficient mismatch repair population, it was about the same, 8.3 to 14.3. The hazard ratio is 0.63. What we don't know, and the missing arm in this study is, what we don't know is how much better dostarlimab and niraparib was versus just dostarlimab. How much more did the niraparib add? And we can't answer that from this question. So, this one is an interesting study but it didn't really change practice. But I'll come back to...remember that hazard ratio of 0.63, because I'm going to come back to that in another study.

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Okay. Let's go back just to immune checkpoint inhibitors alone. We're going to talk about NRG GY018. I'm going to call it 018 from now on. This study is, I'm just going to say not qualitative, but it's probably the strongest study because it has nothing to do with the checkpoint inhibitor; it's just the design. This study was a very large study and it was fully powered to look at the deficient mismatch repair tumors and the proficient mismatch repair tumors as unique cohorts. RUBY looked at dMMR and then it looked at the intention to treat altogether. And that's fine. This one looked at dMMR and pMMR as fully-powered statistical endpoints. So we could really ask, statistically, did we drive improvement, particularly in a pMMR population? The answer is yes, this really proved it. These studies came out simultaneously. What you can see here is the dMMR cohort is on the left and the hazard ratio is 0.34, so a 66% reduction. In the pMMR, the hazard ratio is 0.57, so a 43% reduction in the rate of progression events with the addition of pembrolizumab to paclitaxel-carboplatin and to follow versus paclitaxel-carboplatin alone. Both of these are statistically and clinically relevant improvements in progression-free survival, again, in both the dMMR and the pMMR, clearly stronger in the dMMR, but in both groups, which supported regulatory approval of pembrolizumab in this setting as well.

This is the overall survival, which at the time this was presented wasn't quite mature, so not statistically significant yet. We anticipate seeing updates on this relatively soon. But certainly the trends are in the right direction. You can see in the dMMR the hazard ratio for OS, not statistically significant but immature, but 0.55, so a 45% reduction in the rate of death events for those who received pembrolizumab. And in the pMMR, 0.79, so a 21% reduction in the rate of death events in the pMMR population. Other than it being a bigger study and fully powered, the other differences between RUBY and NRG GY018 is that 018 did not allow patients with carcinosarcoma. It did allow prior chemotherapy, just like RUBY did, but they had to be at least a year from prior chemotherapy to come on 018. So, it's still very high clinical risk. These are patients with advanced recurrent disease, but a slightly less risky clinical risk population. If you look at the medians, just keep that in mind that we really want to compare hazard ratios.

So, on the basis of RUBY Part 1 and 018, the FDA approved both dostarlimab and pembrolizumab with chemotherapy and to follow as maintenance for 2 years in all-comers with advanced recurrent endometrial cancer. That very much changed the standard of care. I want to mention a couple of other studies, just for consistency's sake. One is called the AtTEnd study. This was really similar to RUBY. It was looking at the addition of atezolizumab, again, with paclitaxel and carboplatin versus paclitaxel and carboplatin alone. It was randomized two to one rather than one to one, first looking at the progression-free survival in the overall and the dMMR population. The pMMR population was an exploratory endpoint, very similar to RUBY. The results were very similar. So just consistency, just to let you see, in the dMMR population you can see that we had that same kind of profound improvement with a flattening of the curve, again, speaking to the potential for cure.

And the last study I want to talk about is DUO-E because I mentioned PARP with RUBY Part 2 and that it was hard to really interpret RUBY Part 2 because it didn't have the single-arm dostarlimab. Well, DUO-E addressed that. DUO-E randomized patients, all-comers, with advanced recurrent endometrial cancer. They could have prior adjuvant therapy; it just had to be more than 12 months prior. It did allow carcinosarcoma, so a mix in clinical risk from RUBY and 018. But it randomized patients to receive paclitaxel-carboplatin for six cycles with placebo. Paclitaxel, carboplatin, durvalumab, durvalumab maintenance, and paclitaxel, carboplatin, durvalumab, durvalumab plus olaparib maintenance. And olaparib is a PARP inhibitor. This is a result of that clinical trial. Did olaparib-durvalumab do better than control, just paclitaxel-carboplatin alone? Well, yes, that's obvious. You're not surprised by that. The hazard ratio is 0.55. The next statistical question was paclitaxel-carboplatin-

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durvalumab versus just chemotherapy alone. And that was better with a hazard ratio 0.71, so about a 30% reduction in the rate of progression events with durvalumab.

What wasn't powered statistically, and we all kick ourselves, is statistically, was durvalumab-olaparib better than durvalumab? You can see in the upper right-hand side the progression-free survival curves. Clearly, the curve for durvalumab-olaparib is better than durvalumab, but we don't have statistical testing around that comparison, which makes interpretation difficult. However, in Europe, through the European Medicines Agency (EMA), they have authorized this regimen for proficient mismatch repair. In the deficient mismatch repair population of DUO-E, the addition of olaparib did nothing. Absolutely nothing, so we do not recommend it. But in the proficient group, you did see the hazard ratios that I'm showing you here, and then EMA has authorized this for consideration in that population. The U.S. FDA has not yet given an opinion on this, likely waiting for more mature overall survival data. And that's what you see on the bottom right. This is not mature just yet. We're still waiting on overall survival. And so I think that's really what will be pending before we get a regulatory opinion on this particular clinical trial. But it is interesting and may lend itself to a new opportunity for our patients, but not yet on-label in the United States.

So, that was a lot of data, and you've seen the slides, lots of statistics. But, Jaclyn, we changed practice. We all came back from Society of Gynecologic Oncology (SGO) in 2023. We changed practice the Tuesday we were back in clinic. So, you've been using this really since March of 2023.

**Jaclyn Shaver, APRN, CNP, WHNP:**

Yes.

**Kathleen N. Moore, MD, MS, FASCO:**

For 3 years we've had this available for patients. Tell me a little bit about what this looked like for you as the person who sees our patients in clinic and is following them. Efficacy-wise, what did this mean to our patients?

**Jaclyn Shaver, APRN, CNP, WHNP:**

I mean, like you said, it was a total game changer. It was like, one day we were treating with chemotherapy and next day we're treating with this immunotherapy, and it's been great for our patients. I mean, I've had patients on 018 who had stage 4 endometrial cancer. And before this clinical trial, they would've probably not been here today. But as of today, I've had patients who are still alive who were on this trial and there is no evidence of disease. So, it's just a testament to what being put on a clinical trial can do for those patients. It has just been amazing for our patient population to have that extra time with their family, time with their loved ones, and still have that quality of life as well, because when you add the immunotherapy to the chemotherapy we do have some immunotherapy-related toxicities, which I'll talk about in a minute. But overall, they tolerated this combination actually really well. There are specific things that we will address here in a little bit to talk about and just be aware of. But I mean, overall, these patients are doing much better. They're living much longer. And it has just been a real game changer.

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**Kathleen N. Moore, MD, MS, FASCO:**

Yes, I agree. Well, let's move to the safety. But the other thing I wanted to just ask you: pre- and post-March 2023, before this came out we were treating with chemotherapy and complete responses were very infrequent and people still had tumors, so remind me, were we just continuing chemotherapy? Were we stopping? Were patients getting a chemotherapy-free break? Because I feel like that's a big difference now.

**Jaclyn Shaver, APRN, CNP, WHNP:**

Oh, a total difference. I mean, they may get six, maybe nine, cycles and they still had disease. And at that point we didn't have anything else. We would just put them on surveillance. We would see them back. "Let's see you back in 3 months. Repeat your scan." And ultimately, we knew in a few scans we were going to have progression of disease or recurrence of disease, where now these patients are in maintenance. Immunotherapy, coming back, continues to be no abnormality detected (NAD), feeling good, doing well. So it really is just a huge game changer.

**Kathleen N. Moore, MD, MS, FASCO:**

Yes. It's a completely different world from even 4 years ago.

**Jaclyn Shaver, APRN, CNP, WHNP:**

Oh, 100%.

**Kathleen N. Moore, MD, MS, FASCO:**

Yes, which is great. We love that. That's why we do clinical research. But let's talk about...so we're happy they're responding. We're happy we can stop chemotherapy and put them on something that may be curative in dMMR and hopefully will stabilize and keep us off chemotherapy for longer. What do you see in terms of safety and tolerability from your standpoint? Why don't you talk about that a little bit?

**Jaclyn Shaver, APRN, CNP, WHNP:**

So, with the immunotherapies, of course we're turning on our body's own immune system. With that, you're going to have some different toxicities than that you would see with traditional chemotherapies. And so you could think about it and cancel the patients on, you can have an inflammation of basically anything in your body. But there are some common things and some not-so-common things that can happen with the immunotherapy. One of the big ones is rash. They can get a rash with the immunotherapy. It can be as small as even starting out as just itching, all the way to a localized spot on their body with a little bit of rash too, a global generalized rash. And we treat those individualized, the spread and the grade of the rash, so if you have a rash or some itching that's very mild, grade 1, you can treat those with antihistamines. You can do some local, just topical steroids. But if you're getting into the grade 2 rashes, we need to hold treatment and start them on some oral steroids and taper them down until we get back to that grade 1 stage.

So, education is key to immunotherapy. There is diarrhea. You can get colitis with immunotherapy. It's really important to ensure that those patients, again, are educated about that; get a baseline count of how many times you're having diarrhea stools each day. Grade 1, it would be suspicious, especially if they're on



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maintenance therapy, but if you're on an upfront first regimen with chemotherapy and immunotherapy, it could be the chemotherapy that's causing the grade 1 diarrhea. So, just be suspicious. Also think about ruling out some infectious causes. If you start to get to grade 2, we're going to have to hold treatment and, again, start them on some oral steroids with then tapering them off that. Be looking for that.

Another thing that's really common is thyroid dysfunction. They can become hyperthyroidism at the beginning and then move into more of a hypothyroidism. You can continue to treat through your thyroid abnormalities, generally speaking. Start them on some thyroid replacement. If need be, if it's a challenging case, always make sure that you refer out to endocrinology in that regards as well. Some other things that can happen can be hepatitis. You can get an inflammation of the kidney, so nephritis. You can get pancreatitis. All those things we would be looking for in lab values. You'll continue to monitor those just like you would in a maintenance setting as long as a chemotherapy setting.

Most generally, the immune toxicities are going to be seen early on with the first few months, few cycles, of the immunotherapy. And then as you progress into maintenance, it's really tolerated very, very well. You really don't see a whole lot of toxicity from the immunotherapy when you get into maintenance. They usually feel great. They're doing well. They're tolerating treatment well. And they can live their lives as they would if they weren't on treatment. The only thing is, is you do have to come back in that maintenance setting every 6 weeks for office visits and you have to come back for lab work, that can be burdensome to the patient and the patient's family, especially if they live far away. We live in an area in Oklahoma City where we treat a lot of the outlying areas, so patients may drive hours just to come see us. That can be a financial toxicity to those patients who have to drive far. They have to take off work; their family members have to take off work. So, it's something to consider and something to be aware of. Occasionally, we may need to do some telemedicine visits to accommodate some of those issues, or reach out to social work and they may have the ability to get help with getting rides to and from our clinic visits. But, overall, I think it's tolerated pretty well. There are just some specific things that we need to be watching out for.

Another one of the big ones is watching out for pneumonitis. And so, again, educate your patients on having any changes of cough or shortness of breath, and make sure that they notify the office about that. If that occurs, it could be a pneumonitis and we'll need to do a special computed tomography (CT) scan, a high-resolution CT scan, to ensure that you don't have pneumonitis. If we suspect pneumonitis, we'll need to hold the drug and then, again, start them on some oral steroids and/or refer them out to pulmonology as well. So, there's a lot of things to consider that we didn't consider before when using chemotherapy. It was a whole mindset change, learning new toxicities, learning how to manage those toxicities. But over the course of the few years, we've become more comfortable in doing that. But it was a change for us learning how to do those toxicities.

Like I was discussing, as we incorporate immunotherapy into frontline treatment for advanced and recurrent endometrial cancer, it's important to recognize the safety and delivery of these regimens into a multidisciplinary approach, like I said, referring to dermatology, when needed, or endocrinology, the gastrointestinal (GI) team. If there's something that is not fixing itself with our taper, then we need extra help outside of our clinic, then we definitely do use them and do that. There are multiple people we need to engage in with regards to, again, educating our staff, making sure they're aware of all of our toxicities from our treatments.

We are engaging in the patients, making sure that they have the education they need. We are looking at the pathologists. Like Dr. Moore says, we need to know, are they MMR proficient? Are they MMR deficient? There are a lot of playing different parts with these patients, but just make sure that we are getting the whole team

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together to ensure that we assess either toxicity or what's the next phase in treating these patients. So, we'll go into our case study. Dr. Moore, do you want to take that case study?

## **Kathleen N. Moore, MD, MS, FASCO:**

Sure. This is, I'm probably going to see her this week, a 63-year-old patient who has newly diagnosed metastatic endometrial cancer. She feels fine. She has really no...performance status (PS) is zero. But she's working, doing everything, gets a biopsy, and was sent reflex right out of the gates for testing. We know that her tumor is deficient mismatch repair and microsatellite instable. They ran a PD-L1 immunohistochemistry as they do, and she's got a 10% tumor proportion score (TPS). She's TP53. Her tumor is TP53 wild-type and HER2-negative. And so the question is, how are we going to start treatment for this patient? The answer right now is really clear. This patient, a tumor with dMMR overtakes any other potential biomarker at this point. So, the treatment is paclitaxel-carboplatin, and you can pick any of the three that are FDA-approved. I didn't mention in my discussion earlier that durvalumab is also FDA-approved just for dMMR. So I could use dostarlimab and paclitaxel-carboplatin, pembrolizumab and paclitaxel-carboplatin, or durvalumab and paclitaxel-carboplatin. Any of those. And then whatever I picked, use that as maintenance for 2 years. And so that is the treatment for her.

There's no difference that we can tell based on efficacy, and they're probably never going to be compared head-to-head. There are no data that would suggest one immune checkpoint inhibitor is better than another immune checkpoint inhibitor. And many times, it's based on formulary requirements at institutions or through insurances. And so I don't really want to say this is my favorite or that is my favorite, because it may not be someone's choice. Which one they use and whichever one they get is going to be quite good. I think the only distinguishing feature of the three is that carcinosarcomas were allowed in the RUBY trial. And so I've heard people say, for carcinosarcoma, they always go to dostarlimab, but I don't think you're restricted from a registration standpoint against using pembrolizumab.

In the future, there are two studies that finished accruing and we're waiting to see the results. One of them is a study with pembrolizumab called KEYNOTE-C93. And the other one is a study with dostarlimab in a dMMR population comparing immunotherapy alone, so dostarlimab or pembrolizumab alone versus chemotherapy. But we're all asking whether or not we need the chemotherapy, or can we just move to an immune checkpoint inhibitor? At this point, we do not know. So, we do not recommend that approach. It is a chemotherapy immune checkpoint inhibitor world for this patient. And our expectation is that she's going to do very well. That setting, we're still, I think, as we collect data, getting estimates, but that's probably 30-ish percent of the patients who will walk through your door. The remainder are going to be, we say pMMR, but really they're just not dMMR, because pMMR is probably four or five different diseases that we're all trying to figure out at this point. So, I think the landscape is going to continue to change for the better.

So, let's have another case. This would be a 71-year-old. She has newly diagnosed advanced endometrial cancer, metastatic. She also has a pretty good performance status. She's 71, so a little bit older, but nothing that precludes standard of care. Her tumor is tested and it is not dMMR. Her tumor proportion score is negative, less than 1%. She's also TP53 wild-type, again. And again, HER2-negative. And so here, what would be my treatment? My treatment's actually not going to be different than what I said for dMMR, although my counseling for this patient will change because the prognosis is different. I think we have to be always, I mean, I think oncologists in general are optimistic, and I'm always optimistic that things are going to work, but the benefit here is a little more modest. But here, the standard of care would be paclitaxel-carboplatin. Durvalumab



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is not an option here because the tumor's not dMMR. So, you could either use dostarlimab-chemotherapy, or pembrolizumab-chemotherapy and maintenance. That would be one of the options that I recommend for this patient. I would also talk to this patient about chemotherapy alone. And I think that's something we have to talk to patients about.

We do not have evidence yet that there's overall survival benefit. There is a, I think, clinically relevant but modest progression-free survival benefit. It comes at a cost of visits and potentially toxicity. So, I do think patients need to be offered both. But I feel quite good about offering them chemotherapy and an immune checkpoint inhibitor. I think that's how I would counsel this patient, prioritizing an immune checkpoint inhibitor related, including therapy. So with that, I'll turn it back over to Jaclyn and we can have a little bit more of a discussion.

## **Jaclyn Shaver, APRN, CNP, WHNP:**

Okay. Before we move on, here are a few questions from the community related to first-line decision-making. Is there any role for PD-L1 to guide decision-making?

## **Kathleen N. Moore, MD, MS, FASCO:**

No, I really do not think so. Certainly not TPS, which is what we've been talking about. TPS is what's used with pembrolizumab. And there really isn't any...this was actually published by Dr. Eskander in an exploratory way. So, it wasn't a pre-specified endpoint, but an exploratory way. There really wasn't a signal amongst the either group, pMMR or dMMR, that it made this tremendous difference. Measuring PD-L1 with a different assay on the DUO-E study, we did see differences, but that just speaks to some of the risks of putting too much weight on exploratory non-analytic endpoints as you can get really misled. So, at this point, I would say in endometrial cancer there's absolutely no role for use of PD-L1 to gate use or not use of dostarlimab or pembrolizumab, but would not use it.

## **Jaclyn Shaver, APRN, CNP, WHNP:**

Okay. Our last one. Who should receive maintenance intensification with a PARP inhibitor?

## **Kathleen N. Moore, MD, MS, FASCO:**

This is a controversial question. In the United States, it's not approved. So, again, sitting here with you and talking to an audience of physicians and providers mainly in the United States, this is off-label. The DUO-E regimen of durvalumab-olaparib is off-label. It's now National Comprehensive Cancer Network (NCCN) listed, but category 2B, so that is not guaranteed and I would say probably unlikely to get insurance approvals. So, really, I would not recommend this right now because of the lack of that approval. And in the absence of overall survival data, I think the risk of doing things off-label, at the very least from a financial toxicity standpoint, if I'm going to cure more patients, I'm going to talk to patients about this and we'll deal with it.

If I'm not curing more patients and I'm putting them at risk for significant financial toxicity, I think we really have to be quite cautious at saying you should go out and try and get this for your patient at this point, were it approved. Then there's going to be clinical equipoise. How much more benefit did olaparib add to the durvalumab versus durvalumab alone? And it clearly looks a little better. So, you are probably bumping out that

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progression-free survival. And that, again, is important to patients clinically. They want another Christmas. They want to get a little bit farther out.

There's a lot of work being done right now on that clinical trial and others to try to figure out if there are any biomarkers that help us assess the tumors that are more likely to respond from PARP inhibitors or not. Shannon Westin, who's the principal investigator (PI) of that study, has presented at a few meetings some of that work. And thus far, surprisingly, there isn't a big signal about if there's a certain molecular subtype, TP53 mutated, we all thought it would be that. There really hasn't been a "smoking gun," so to speak, of a subgroup that seemed to benefit. They all seem to benefit about as much. So, we may be a little bit in a quandary. If this gets approved, is this a must for all of our patients? Is it a can-do? If it's a can-do, in whom?

And the other thing we have to think about is, what are the long-term toxicities that come with use of PARP inhibitors? Are they the same as we see in ovarian cancer? What does that mean for response to subsequent therapies? I think that's why you've seen the FDA not perhaps comment on this yet without overall survival data to see, so that we can really make sure if we're going to use this we're doing it in the safest way possible. So, the short answer is, right now, I think no one, because it's not FDA-approved.

## **Jaclyn Shaver, APRN, CNP, WHNP:**

Well, thank you, Dr. Moore, for answering those questions.

## **Kathleen N. Moore, MD, MS, FASCO:**

These are the questions that really matter for our patients in providing patient-centered care. We need to pivot, both add things and take things away as data come out so we can best take care of the patient in front of us. But with that, let's shift gears a little bit and talk about what happens after, right now, chemotherapy or chemotherapy immune checkpoint inhibitors. Well, this space is a place of active drug development right now. There are a lot of clinical trials in this space. Again, I've been doing this for 22 years now. Gosh. Lenvatinib-pembrolizumab (LENPEM) was approved I think in 2022. Before that, we had nothing in the second-line setting. If the tumor was dMMR late in the 2018-2019 timeframe, we got pembrolizumab, so we were able to rescue in that setting. Although once the tumors were recurrent, it wasn't as often curable, but it worked quite well. And outside of pembrolizumab in a dMMR, we had doxorubicin or weekly paclitaxel, where the expected response rate is 15% and the expected median progression-free survival is 3.4 months, very consistent across every failed phase III that had been done in that setting. That second-line metastatic setting in a non-dMMR was a very desperate place to be for patients because we did not have good things, until what we call LENPEM. And that's what you see on the screen. So, this is lenvatinib and pembrolizumab, we all shorten it to LENPEM.

And this was a randomized phase III study of patients whose tumors had recurred after chemotherapy, paclitaxel-carboplatin. They did not have prior immunotherapy. They were randomized to receive lenvatinib-pembrolizumab or investigator's choice chemotherapy, which was either doxorubicin or weekly paclitaxel. And it was statistically powered to look at progression-free and overall survival, both. You can see on this slide the progression-free survival data for the all-comer group. That's the first thing you see in the lower left-hand side of your slide, with a hazard ratio of 0.56, so a 44% reduction in the rate of progression events for patients randomized to lenvatinib-pembrolizumab versus chemotherapy. And then if you look at the upper right, you see the deficient mismatch repair population where the hazard ratio is 0.39, so a 61% reduction in the rate of progression events. And in the pMMR population, the hazard ratio is 0.60, so a 40% reduction in the rate of

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progression events. Then, if you look at overall survival, that was a primary endpoint, you can see here in the all-comer group and in both the dMMR and the pMMR, there was an improvement in overall survival, which was never shown before in endometrial cancer because nothing worked.

This was really a seed change in how we took care of patients in this second-line setting, so we're forever grateful for this work in Dr. Mecker's leadership. So, this has been FDA-approved for years and we use it. So, I'm going to turn it back over to you, Jaclyn. Well, now I'm here, but when I was there I put someone on LENPEM, I'd counsel them, and I'd see them for cycle 1, and then you'd see them for cycle 2. So, walk me through what you saw, what the toxicities were, and how you took care of our patients on LENPEM.

## **Jaclyn Shaver, APRN, CNP, WHNP:**

Yes, I want to go back a little bit before we even start cycle 1. With lenvatinib, one of the biggest toxicities is hypertension. So, we just need to make sure when we start patients on lenvatinib that their hypertension is in control. That's really important with this drug, ensuring that that is in control. If their primary care is managing it, or their cardiologist, we've got to get back with them to see them, or if they're not on anything, and they've had these labile hypertensive episodes in office we will need to start them on some hypertensive medications before we put them on there because it's only going to get worse.

The majority of these patients will develop hypertension on lenvatinib, so that's really important to address there. And then with the combination of the immunotherapy and the lenvatinib, they can have similar side-effect profiles. So which one is it? Is it the pembrolizumab? Is it the immunotherapy? Is it lenvatinib? With the lenvatinib, it's an oral drug, so you can actually hold that and see if the toxicity is lenvatinib or is it the pembrolizumab. If you're having grade 2 toxicity that you're having to hold for, likely you'll need to reduce your dose of lenvatinib. We don't start at the 20 milligram dose here at the University of Oklahoma. We usually start at 14 milligrams. It's just better tolerated and patients usually do much better with that dosing to begin with. It's just a trial and error and figuring out which one it is.

## **Kathleen N. Moore, MD, MS, FASCO:**

Obviously, this is where having well-trained and embedded advanced practice providers in your oncology clinic is really key. If I'm in clinic a certain number of days of the week and there every day and can get calls from my patients and know them and day-to-day adjust these medications, it's the difference between safe utilization of oral medications and not, because patients need immediate answers to, "Do I dose? What do I do?" And that's hard to do, I think, without qualified help.

So, we've discussed LENPEM in that second-line metastatic setting, which was game-changing for us. But I'll remind you that that was approved. The study was done and it was approved in an era before we were using immune checkpoint inhibitors in the front line. So, there's a big question right now of whether or not this regimen is still the standard of care in a tumor that's progressed on or shortly after maintenance pembrolizumab or dostarlimab. Does this still work? Do you still go to this? Or do you pivot to something else? And something else in the reproved setting is still doxorubicin or weekly paclitaxel, so that's not great. I see a lot of my colleagues in the community still going to LENPEM post, but there's a lot of work being done right now to change that across a number of different mechanisms. But the main thrust of research is really around these antibody-drug conjugates.

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We do have one FDA approval and that is for trastuzumab deruxtecan (T-DXd). That is based on a basket study called DESTINY-PanTumor. It's an accelerated approval by the FDA for tumors, any tumor that's HER2 3+ expressing by gastric scoring. You can see the results of DESTINY-PanTumor here. These were 40 patient cohorts. A lot of work still needs to be done. But remember I told you in the second-line setting the benchmark is a response rate of 15%. Okay. Well, here, if I have any tumor that's HER2 2+ or 3+ that's endometrial, my response rate is almost 58%. If it's essentially confirmed 3+, my response rate was 84%. And if it's essentially confirmed 2+, it's 47%. I'm okay with any of those. I want to use any of those. I'm fine.

So, this is why we are testing universally now. We want to know HER2 immunohistochemistry (IHC) by gastric scoring so we can get availability to T-DXd in this second-line setting if indicated. It's FDA-approved for 3+. It's NCCN-listed category 2A for 2+ and 3+. And so this is an important add-on for tumors with 2+ or 3+, which are largely but not exclusively your TP53-mutated tumors. Not exclusively. So, you want to test everyone. But you're mostly going to find this in your TP53-altered tumors. And so what does that mean for everything else? Well, we're looking at a bunch of other antibody-drug conjugates in phase III clinical trials right now in endometrial cancer beyond HER2.

There are data with Trop-2 inhibitors. There are early-phase data for datopotamab deruxtecan. We have a phase III study. It's actually done accruing. So, we'll see hopefully soon for sacituzumab govitecan and sacituzumab tirumotecan, two different Trop-2–targeting antibody-drug conjugates, both with promising phase I expansion data, now with completed phase IIIs, that should read out maybe later this year, maybe early next year, I don't know. But they're not accruing. So, we may have that as an option beyond HER2. Folate. Folate receptor alpha is important in ovarian cancer, isn't important in endometrial cancer. We saw data last year at American Society of Clinical Oncology (ASCO) with rinatabart sesutecan, which is a folate-targeting antibody-drug conjugate with an exatecan payload in endometrial cancer with a response rate in only 22 patients, so we got to see this born out, but the response rate's 50%. And there are a bunch of these.

These are coming fast into the second-line setting. And we're even seeing clinical trials planned where we're moving them maybe into frontline maintenance in a pMMR population. And so you're going to see, I think, the landscape really shift with these incredibly active agents coming soon. Now, that's exciting. And there's no but to that. I'm excited about that. With a new class of drugs comes, just like immune checkpoint inhibitors, new opportunities for multidisciplinary care and how we think about the safety of utilizing these medications in different patient populations. As with any novel treatment drug, understanding the toxicity profile and the practical management considerations of these antibody-drug conjugates is really critical.

And this is different than immune checkpoint inhibitors, where I think we can all agree that their side-effect profiles are pretty much the same. Antibody-drug conjugates, that is not true. Even topoisomerase 1 conjugated, antibody-drug conjugates, exatecan, belotecans, SN-3, deruxtecans, they have common GI toxicities, and you can see that here on the slide. But some of them have higher rates of pneumonitis. Some of them have higher rates of mucositis. We're seeing neuropathy with some of them, alopecia with some of them. Some of them have much higher rates of significant hematologic toxicities than others and need for granulocyte-colony stimulating factor (G-CSF) prophylactically.

So, the nuances and really understanding that practical considerations of these individual drugs is going to be critical as we bring them into our practices to train our partners, including our advanced practice providers, so as they're seeing these patients they know what to look out for and can intervene early. And I think pneumonitis is really the poster child for that, wanting to identify that at grade 1, which is asymptomatic based on non-descript

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changes on a CT scan, that your antennas have to be up to call, hold the drug, and get worked up. These are the sorts of nuances that are going to help us utilize these safely in our practices.

With that, let's go to our last case of the day. This is a 66-year-old woman. She has metastatic endometrial cancer, previously received paclitaxel, carboplatin, pembrolizumab, and pembrolizumab maintenance. And then she got LENPEM after that, which happens all the time. And now she's progressed again. Her tumor's pMMR and was tested. She's HER2 IHC 1+. She has nothing else on her next-generation sequencing. Assuming access is not a limiting factor, what would I be thinking of here?

This for me is easy. This is clinical trial. I'm going to be looking for an antibody-drug conjugate. This is true in ovary as well. I have a lot of cool things. But my priority is to get patients access to a topoisomerase 1 conjugated, antibody-drug conjugate. We do not know yet which one of all those ones I listed is the best one, which biomarker should link to which drug. We don't know yet. We're going to figure that out over the next few years. And so that's a big black box, to be honest, other than HER2 positivity. That makes it a little bit easier. But outside of that, a 1+, should I try to get her T-DXd off-label? Should I be trying to get a clinical trial with one of the Trop-2s or folate or Cadherin-6? There are a number of them.

I think this is really where clinical trials and advocating for clinical trial access for your patient is key because those are really some of the most effective medications we've seen in this setting. And I would use them long before I was trying to use doxorubicin or weekly paclitaxel in this patient population. She deserves access to a trial. So, we've talked a lot today about what's really exciting in endometrial cancer. The inflection point with the incorporation of immune checkpoint inhibitors has been game-changing for our patients to varying degrees. The emergence of antibody-drug conjugates has really set the stage for another big inflection point in terms of how well our patients do.

We've talked quite a bit about how the incorporation of these new therapies has challenged us to be more communicative with our teams in terms of what to expect with adverse event expectations and management, as well as expanding our multidisciplinary teams to a way that I've never practiced in my career. I have cardio-oncologists, pulmonologists, dermatologists, and rheumatologists all on my team now trying to help us take exceptional care of patients. The one thing that you and I haven't talked about too much yet, which is weird because we practice in Oklahoma where this is such a thing, is just the big elephant in the room, which is, "Yeah, these are great, yeah they work, if your patient can access them" if they're being seen in a place with access to them, if they can get there. You mentioned, can they come in every 6 weeks? Can they come in every 3 weeks? Do they have financial barriers? Do they have social barriers?

The health inequities inherent to cancer in general but specifically around endometrial cancer are quite profound. It's sobering to remind everyone that the only solid tumor, when you look at the Surveillance, Epidemiology, and End Results (SEER) presentations and American Cancer Society facts and figures, everything's decreasing, incidence and mortality, except endometrial cancer. It's the only solid tumor increasing in incidence and mortality, so this is really the fire alarm in gynecology/oncology and I think in women's health in general. That increase in incidence and mortality isn't equanimous. It is at the expense primarily of Black women. Why this has been a really important area of discovery has been a lot of work to figure out and to report on this fact. Some of it is related to access to care, timely diagnosis, and inequities in the access to care and quality of care. But that's in delays. That's true. But it's not all that. There's something else there in the biology, whether it's environmental exposures or molecular characteristics, that is also driving this really disturbing trend of

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increased incidence and mortality that we're trying to get our hands around so that we can really start implementing some actions that reverse it.

I am quite hopeful to see the next round of seeing reports that will be post the immunotherapy era and post the incorporation of T-DXd to see if some of that reverses a little bit with therapeutics, but I am a little concerned that it will not be. This is really something that we are thinking hard about or are very concerned about and spend a lot of time and energy thinking about to try and make sure all of our patients have access to us, have access to the support, financial support, transportation support, housing support. In Oklahoma, Jaclyn knows we have a food bank, food inequities, to check that our patients are not getting the best care because of those features.

And this is an ongoing mission and looks different in different parts of the United States as to why these inequities exist and how to address them. But it is a big challenge for us in oncology to make sure we are addressing them to the best of our abilities so patients can access the care that they need. Which brings me to the last point, which is, how in our practices we're always unconsciously doing these things to try to improve process, to build out multidisciplinary teams, to improve communication, symptom triage. We're doing this all the time. But we can be more intentional around the processes.

It's always just helpful to review this mnemonic of SMART goals, goals that are smart. You're smart by making goals. But SMART goals are specific in that it means specific goals. Be specific about what your goals are. You want to improve how you do adverse event triage. You want to improve universal mismatch repair testing for every patient at your hospital that has uterine cancer or HER2. Whatever it is, be specific. Not "I just want to be better." I mean, that's a good goal too, but be specific. Pick something you can measure. Right now, we test 50%. We want to get to 100% over this time period. Be specific. Something you can measure. Something that's achievable.

If you're 20% and you want to be to 100%, well, yes, but you can't be there in 3 months. So, pick an achievable goal, achieve it, and then make another SMART goal. Make it relevant. Maybe you don't want to be 100% doing PD-L1 testing in endometrial because it doesn't matter. So, it's not relevant. But make sure you're doing dMMR testing, mismatch repair relevant to your tumor. That is something that's going to change practice. And then time-limited. Set a goal and give yourself a deadline, because we all work better under deadlines. And, again, make them achievable so that you can be successful, feel good, and then go to your next goal. It's a nice way to think about incorporation of a lot of things that we talked about: access, incorporation of novel therapeutics, educating your team, making sure that you're providing access to patients. These are nice ways to set up those goals. And I think it's just more type A. All of us are type A to get some things accomplished in our clinics.

I think with that we will call this session to a close. That's all the time we have today. For additional resources, please visit the CE Concepts website. To receive CME/CE credits for today's program, complete the post-test and evaluation online. I would, again, would really like to thank Jaclyn Shaver for her expertise, not only for my former practice in Oklahoma, her continued home. Our patients are so lucky to have her. But thank you for sharing your experience during this informative discussion. And I want to thank CE Concepts for their assistance in developing today's program. And with that, that will end *Exploring the Horizons in Advanced or Recurrent Endometrial Cancer: Practical Considerations and Future Directions for New Treatment Strategies*. Thank you for joining me.