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Establishing the Role of Immunotherapy in Microsatellite Instability-High (MSI-H) or Mismatch Repair-Deficient (dMMR) Endometrial Cancer

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Establishing the Role of Immunotherapy in Microsatellite Instability-High (MSI-H) or Mismatch Repair-Deficient (dMMR) Endometrial Cancer” is provided by Prova Education.

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Dr. Coleman:
Microsatellite instability and mismatch repair deficiency are important biomarkers for predicting responses to immunotherapy and guiding treatment selection for endometrial cancer. Are you testing for this biomarker in your patients with endometrial cancer?

This is CME on ReachMD, and I'm Dr. Robert Coleman. Here with me today are Dr. Susana Campos and Dr. Ana Oaknin.

Dr. Campos:
Hi, good morning, and thank you for having me today.

Dr. Oaknin:
Hello, this is Ana Oaknin. I'm very happy to join Rob and Dr. Campos to discuss this interesting topic that is endometrial cancer, the MSI, dMMR status.

Dr. Coleman:
Wonderful, thank you so much for being here. So let's get started. Dr. Oaknin, to set the stage for this chapterized course, can you outline the molecular genomic classification of endometrial cancer for our listeners?

Dr. Oaknin:
For sure, this is a very important topic. I would say that the main progress in endometrial cancer has been driven by the TCGA [The Cancer Genome Atlas] project. In this, TCGA provided a comprehensive molecular classification which segregate endometrial cancer in 4 subtypes based on genomic abnormality. The POLE or ultramutated, MSI high or hypermutated, copy number low, and copy number high or serous-like. While TCGA is a milestone in endometrial cancer classification, as you know, it requires complex methodology. Therefore, we have developed a simplified molecular classification to have the potential for implementation in our daily practice. And this classification identifies 4 molecular subtypes that are analogous but not identical to the TCGA subtype. That is to say, POLE mutant, mismatch repair deficient, p53 abnormal, and SMP. And I would like to add that each of these molecular subgroups has a different prognosis, and in addition, this knowledge really provides us with an opportunity to tailor treatment for our patients with endometrial cancer.

Dr. Coleman:
Yeah, that's so important. Thank you for that description.

Dr. Campos, what impact does endometrial subtype have on prognosis and therapy selection?

Dr. Campos:
No, it's a very good question. You know, historically, we would think of endometrial cancer as a type 1 and a type 2 disease state. Type 1 was the endometroid histologies, and the type 2 were the more clear cell carcinosarcoma and the uterine PAP serous. But in 2013, through the work of many investigators, the TCGA data really identified 4 molecular subtypes of endometrial cancer, and these had distinct prognostic outcomes. One of them was a POLE mutation which was this ultramutated uterine cancer which actually tended to have a favorable prognosis. Second was an MSI-high cohort which are responsive to immunotherapy. The third cohort is the p53 abnormality group, which were the ones that actually had more of a poor prognostic element. These are like the uterine PAP serous. And then there was the "not otherwise specified," which were more like the microsatellite-stable. So this new classification, the TCGA data, and then there's been another more pragmatic classification called the PROMISE data. This actually helped us reorganize our thoughts on endometrial cancer, so we're no longer thinking about it in terms of a type 1 or a type 2; we're really thinking about it as a POLE mutation, MSI-high, MSS, or p53 aberrations.

Dr. Coleman:
Yes, thank you. So yeah, I think if you look at this, you know, we have this new kind of classification scheme that is aligning tumor biology with potential therapies. And of course, we've already seen this with the immune checkpoint inhibitors, which is so exciting. But you know, as we continue to develop, even out that cohort of patients that have no specific molecular abnormality, we're starting to find some nuances even in that group of patients, for which we might have some new therapies that will be further subdividing even that category into potential treatment groups. So this is just a fascinating development and evolution in endometrial cancer, and we're so excited to have this in front of us.

So in Chapter 2, we'll be defining MSI-high and dMMR endometrial cancer and considering the principles of testing, so stay tuned.

Dr. Coleman:
Welcome back. We were just discussing the significance of endometrial subtype when it comes to prognosis and therapy selection and POLE and MSI phenotypes. Dr. Oaknin, how do we define microsatellite instability-high, or MSI-H, and deficient mismatch repair, or dMMR, endometrial cancer?

Dr. Oaknin:
Thank you, Rob, for this important question. I think this is a concept that we should clarify. Firstly, we need to know what are microsatellites. Let me explain in a brief manner. Microsatellites are repetitive DNA sequences that are distributed along the genome. And these DNA sequences are particularly sensitive to DNA mismatch repair errors, which can occur during DNA replication.

Secondly, the point is what is mismatch repair? Mismatch repair is a mechanism used to restore DNA integrity after the occurrence of mismatch errors, including single-base mismatches or short insertions or deletion. So this pathway counts on 4 genes that play a critical role, namely MLH1, MSH2, MSH6, and PMS2. Then how can we define MSI? MSI is a condition of genetic hypermutability, resulting from defective DNA mismatch repair. So what is the dMMR tumor? A dMMR tumor is a tumor with a defective mismatch repair pathway. It's a tumor that accumulates some sense of mutation, particularly cluster in microsatellite and consisting in repeat length alteration resulting in MSI.

In conclusion, MSI is a marker of dMMR. So the presence of MSI represents phenotypic evidence that mismatch repair bandwidth is not functioning normally. Hopefully it's clear enough for you; otherwise, I can repeat in another way.

Dr. Coleman:
Oh, my gosh, that was so wonderful. I thought it was done very, very well. Congratulations on such a clear explanation.

I think it's important to review that topic because what I'm going to ask Dr. Campos to do is to tell us how we find these patients or these tumors that have this niche. So we want to know how do we test for microsatellite instability high, or MSI-H, and mismatch repair, or dMMR, endometrial cancer?

Dr. Campos:
It's a very important question, and there are multiple ways that one can test, but most institutions will test for immunohistochemistry [IHC] using a panel of stains for the DNR, MMR proteins. They're going to look at MLH1, they're going look at MSH2, MSH6, and PMS2. So most institutions do IHC testing. You can also look for microsatellite instability by doing PCR [polymerase chain reaction], and of course you can do next-generation sequence. But most pathologists will favor the IHC. There's a high concordance between IHC and PCR testing.

Dr. Coleman:

Thank you, Dr. Campos. You know, as we see that these are so important to understand, and we'll get into that, into the emerging evidence of how we take advantage of this abnormality in these tumors when we find them, we have this opportunity to start to put this into our normal algorithm for how we evaluate endometrioid – particularly endometrioid endometrial cancer so that we can now define a new algorithm that will take advantage of that for treatment. So this will be, I think, really an important aspect, a foundation to talk about where endometrial cancer treatment is going in the future.

So thank you both. In Chapter 3, we'll be discussing how to apply current and emerging evidence to the treatment selection for endometrial cancer. So stay tuned.

Dr. Coleman:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Rob Coleman, and here with me today are Drs. Campos and Oaknin. We're discussing the role of immunotherapy in microsatellite instability-high or mismatch repair-deficient endometrial cancer.

Welcome back. We've been discussing MSI-high and dMMR endometrial cancer, and now we're shifting gears to focus on guidelines and emerging treatments.

So first, Dr. Campos, can you break down what the current NCCN guidelines are to advise for the treatment of endometrial cancer?

Dr. Campos:
So, the current guidelines for treating endometrial cancer are divided into systemic therapies or biomarker-driven systemic chemotherapies.

And in this particular section of the NCCN guidelines, recur or metastatic disease, we list the chemotherapies that are appropriate, such as carboplatin and paclitaxel. But in that particular cohort, we also talk about the biomarker-driven therapies, and that includes pembrolizumab based on the KEYNOTE-158 study, pembrolizumab and lenvatinib based on the KEYNOTE-146 study and the KEYNOTE-775 study. We list dostarlimab based on the GARNET data for deficiency in MMR, and there are some additional options there, such as nivolumab and avelumab, that were smaller studies looking at both of those compounds independently in uterine cancer, and it showed a modest activity. So the guidelines are really formulated to systemic therapies and also biomarker-driven systemic therapies, if appropriate.

Dr. Coleman:
Thank you. Dr. Oaknin, what are the recent data telling us about immunotherapy treatment for endometrial cancer?

Dr. Oaknin:
Thank you, Rob. Because you know, I mean, the data that we have with IO [immunotherapy] in endometrial cancer are really, really exciting. This year in ESMO and ASCO, we have presented the latest data with IO in endometrial cancer either as monotherapy, namely pembrolizumab from KEYNOTE-158 and dostarlimab from the GARNET trial, and the combination of pembrolizumab plus lenvatinib from the MK-775 [KEYNOTE-775] trial.

I will start in a very short manner to summarize the latest data from the KEYNOTE-158. As you know, in ESMO this year, Dr. O'Malley had presented the data with a median follow-up around 54 months. And with 94 patients treated, all these patients were dMMR endometrial cancer patients who had progressed at least after 1 prior line of therapy. And what we have learned is that pembrolizumab as monotherapy provide with a 50% – five-zero – overall response rate with 15 complete responses and 32 partial responses. And interestingly, the duration of response is quite long. When we look at the percentage of patients who were still a response of 3 and 4 year, it was 66%. And moreover, when we look at the overall survival of 3 or 4 years, it was 59%. It means amazing results for our patients with endometrial cancer.

Looking at the GARNET trial that, as you know, is a phase 1B/2 with different cohort, and I will be focused on the cohort A1, it means those patients with dMMR tumor. This year in ASCO, we presented the data for 143 patients treated with dostarlimab, and with a median follow-up of 26.6 months. What have we learned? We have learned that dostarlimab produced 45.5% overall response rate. I mean, 23 complete responses and 42 partial response is very, very amazing, the duration of response. We can say that the median duration of response has not yet been reached. And in addition, reading it a different way, 83% of the patients who had response were still in response after a median follow-up of 24 months. It means a variable response rate and durable responses providing a great benefit for our patients.

But these 2 trials are mainly focused on dMMR patients. What about pMMR (mismatch repair proficient) and all-comers? I mean, this population has been very nicely addressed by the MK-775 [KEYNOTE-775], as you well know, published this year by Dr. Makker et al. in The New England Journal of Medicine, providing a benefit in terms of PFS [progression-free survival] and overall survival in favor of the pembro/lenva for those patients who were pMMR and all-comers. Although in the US, the combination is only approved for those

patients in whose tumor were pMMR. This year in ESMO, Dr. Makker presented the final overall survival with a longer follow-up of 60 months. In this final overall survival, the data were confirmed. The combination of pembro/lenva was superior in terms of overall survival than the standard chemotherapy, namely doxorubicin or weekly paclitaxel, in the pMMR population and all-comers population. And in addition, we saw this benefit in overall survival despite some patients were closed to pembrolizumab/lenvatinib in the chemotherapy arm. Interestingly, I mean just a kind of summary, the median overall survival was 12 months in the population treated with chemotherapy, compared to almost 19 months in those patients treated with pembrolizumab and lenvatinib.

Dr. Coleman:
Yes, thank you so much. Incredible progress being made with this type of therapy. As you mentioned, we have these 2 immune checkpoint inhibitors that have demonstrated their single-agent activity in patients that are annotated by this deficient MMR status or the MSI-high status. And that's been very exciting for us because it allowed us to continue the development of immune checkpoint inhibitors in this disease. And you shared with us some very important data with respect to KEYNOTE-775, which is bringing the combination of lenvatinib and pembrolizumab in patients in an intent-to-treat population, demonstrating this activity even in patients that have a proficient MMR status or a non-MSI-high status.

This has been incredibly important because this therapy now has demonstrated its efficacy and allowed us to actually even challenge some of our more current standards of care, such as chemotherapy. And so as you know, in LEAP-001, we are looking at this combination of lenvatinib/pembrolizumab against combination chemotherapy. So we hope that will ultimately supplant chemotherapy in this potential patient cohort. But what's even more exciting is that we had the opportunity to move this type of therapy into annotated populations in combination with chemotherapy as a combination with maintenance, and also even to address a patient population that's considered high-intermediate risk. So our hope is that this type of therapy will effect lasting changes in the tumor microenvironment so that patients may actually be cured at a higher rate than we've seen in our traditional therapies in the past. So we're very, very excited about that.

And I think so, as we've look at what we've learned today in this session, we have some very active therapies that appear to be aligned with a predictive biomarker. And so this, I think, will be very important as we continue the clinical development of these agents in this disease.

So thank you. In Chapter 4, we'll be discussing regional challenges based on testing. Stay tuned.

Dr. Coleman:
Welcome back. Now that we have been discussing the guidelines and the emerging treatments for endometrial cancer, let's move on to some regional challenges.

Dr. Oaknin, what are some of the regional challenges that you see with access to testing and treatment?

Dr. Oaknin:
Thank you, Rob. I would like to say that, you know, we don't have any issue regarding testing because, I mean, you know, in our region and in our country, I mean in Spain, we use immunohistochemistry as a surrogate to TCGA to identify those patients who are either dMMR, pMMR, p53 abnormal. I don't think testing is a barrier. However, the access to immunotherapy is still a barrier. Because although EMA has already approved the combination of pembro/lenva for our patients with endometrial cancer who had progress after platinum therapy, this therapy is not yet available in our site. We can only access these drugs through the compassionate use. And, you know, all this paperwork sometimes precludes physicians from treating patients with a very effective regimen. However, for those patients with dMMR, we have access to pembrolizumab and dostarlimab.

But let me tell you something. For me, one of the main barriers is some medical oncologists or gyne/oncos who are only treating the patients with gyne, they are not used to working with immunotherapy. They are a little bit concerned about the side effects from this therapy. And this is a clear barrier. So I think we should increase the knowledge about how to manage these side effects in order to make physicians feel more comfortable with this therapy, because I don't think we should miss any patients who may benefit from IO just because the doctors are not used to working with these kind of drugs.

So testing is not a barrier. Regulatory issue is a transient barrier, because I hope that at the end of the year, hopefully as late as early next year, we will have the drugs in our pharmacy. But sure, I mean, the knowledge of management of side effects is still a barrier.

Dr. Coleman:
Yeah, I totally agree. And I think that the, you know, what we've tried to do in many places with the availability of these agents is to have a discussion with the pathologist so that these – a series of biomarkers can actually be addressed on the initial diagnosis, so that you get a more comprehensive view of what's going on in the tumor, and particularly with MSI testing. Obviously, this has an impact, also, for those relatively rare patients that actually have Lynch syndrome, so carry a germline mutation in one of the mismatch repair genes. And

those patients would require some additional counseling.

So we have now built this into our kind of routine reflex testing for endometrioid adenocarcinoma. But I think as the space develops, you know, we'll be getting additional information such as HER2, you know, the comprehensive AR endocrine markers themselves. And so there's a real opportunity to continue to expand the information that we can get right at the beginning.

Well, this has been a fascinating conversation. I'm so excited to have these 2 experts to join me and join us today. I think the kind of the take-home messages that we've heard today, one is that endometrial cancer's becoming much more complicated than just a kind of type 1, type 2 category that we used to use in the past. We've now been able to segregate this into different molecular subcategories. And while those have some biological significance and potentially some prognostic significance, importantly, some of them also have predictive significance, because we now have agents that we can align with that. And we've seen it through this discussion of efficacy that these immune checkpoint inhibitors have really changed the landscape for this disease. And we're so excited for the future, because we expect to see this migration of therapy to continue into earlier and earlier lines of therapy, hopefully providing even more benefit to our patients in the future.

So unfortunately, that's all the time we have today. So I want to thank our audience for listening and for both Dr. Campos and Oaknin for joining me and sharing all their valuable insights. It was great speaking with you today.

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