Transcript Details

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Employing Immunotherapy and ADCs in Advanced Endometrial and Cervical Cancers: Current and Emerging Therapies

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Employing Immunotherapy and ADCs in Advanced Endometrial and Cervical Cancers: Current and Emerging Therapies” is provided by Prova Education.

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Dr. Coleman:
The recent addition of immunotherapy to treat endometrial and cervical cancers has shifted the treatment landscape. How are you using current and emerging clinical data to treat your patients with endometrial or cervical cancer?

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

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

Dr. Lorusso:
Hello, thank you for having me. It's my pleasure to be here.

Dr. Coleman:
Let's get started. Dr. Campos, to set the stage for this chapterized course, can you start by outlining the NCCN guidelines for the treatment of endometrial cancer?

Dr. Campos:
Sure, thank you. The guidelines for metastatic endometrial cancer, as it pertains to immunotherapy really is divided into systemic chemotherapy or biomarker-directed second-line therapy. And in the biomarker-directed second-line therapy there are several choices here that we listed, and they’re based on some very key studies. For example, pembrolizumab for patients that are deficient in MMR or MSI-high, and this really emanates from a very pivotal study, the KEYNOTE-158. We also list, on the NCCN guidelines, pembrolizumab and lenvatinib for patients that are MSS stable. And that is based on the work of Vicky Makker and based on the KEYNOTE-146 and also the more pivotal trial which was the KEYNOTE-775, which showed a progression-free survival as well as an overall survival benefit with the use of lenvatinib and pembrolizumab. Now listed also in the NCCN guidelines is dostarlimab, and dostarlimab is FDA-approved as a result of the GARNET study. We also list nivolumab and avelumab, just so these were smaller studies, but did show activity in uterine cancer. So the guidelines are centered on systemic therapies and are also subdivided into biomarker-directed therapies.

Dr. Coleman:
Thank you, Dr. Campos.

Dr. Lorusso, can you discuss the current approved immunotherapies for the treatment of endometrial cancer?

Dr. Lorusso:
Oh, it's a very important moment and also exciting moment for treating endometrial cancer. We discovered that endometrial cancer is not a single disease, but at least 4 different tumors. And in particular, we discovered that around 30% of endometrial cancer presents microsatellite instability which confers to this tumor a higher possibility to respond to immunotherapy. In fact, when we use immunotherapy as a single agent in this biomarker-selected patient, we obtained response – up to 50% with pembrolizumab or 45% with dostarlimab of single agent – in patients who have failed 1 or 2 prior chemotherapy lines. So no doubt that for these patients, the immunotherapy single agent is the best option. And also, the response were very durable with 84% of patients still in control of disease after 2 years of starting treatment.

But we have also an opportunity for patients without microsatellite instability. And in particular, we discovered that when we combine immunotherapy plus a TKI inhibitor with an antiangiogenic profile as for instance, lenvatinib, we obtain increased progression-free and overall survival with respect to non-platinum chemotherapy in second- and third-line treatment of advanced or recurrent endometrial cancer. And in this moment, the combination of pembro lenvatinib is an opportunity for our patients, which demonstrates in the KEYNOTE-775 trial to significantly increase progression-free, overall survival, response rate, and duration of response over [doxorubicin] or weekly paclitaxel of physician's choice. So I have no doubt this is the new standard in second-line treatment in patients without MSI instability.

Dr. Coleman:
Well, thank you both. So I heard a couple important points. First, endometrial cancer is evolving. It's evolving to consider molecular characterization, and this is a significant departure from our kind of classic thoughts of a type 1 versus a type 2 endometrial cancer. We're now actually testing the tumor to find out potential molecular drivers of disease, and that's important for our basic understanding of the biology of the cancer. But what I also heard was that these particular biomarkers actually may be ones that we could capitalize on for selection of therapy.

So, moving from a prognostic kind of category into a predictive category, where we find that these patients that carry these alterations can be aligned with better outcomes if they get a treatment that is actually targeted towards that. So that is one tremendous, important key message that I heard from this discussion.

A second is, of all of the therapies that we have available to us, we have been using relatively a blunt stick with chemotherapy. But now that we have been able to identify patients' tumors that actually carry the alterations that would imply or hopefully make immunotherapy more active, we've been able to apply that as a single agent and in combinations in this disease, and it made really tremendous strides in our ability to not only improve the progression-free survival, but as you heard, also the overall survival for these patients. So this is tremendous progress after decades of making very little progress, and I think it really speaks to personalized medicine, where we're actually able to align treatment with biology in order to effect lasting and better treatment for our patients.

In Chapter 2, we'll be reviewing the NCCN guidelines and approved immunotherapies for the treatment of cervical cancer. Stay tuned.

Dr. Coleman:
Welcome back. We were just reviewing the NCCN guidelines for the approved immunotherapies of endometrial cancer. I'm going to start by outlining the NCCN guidelines for the treatment of cervical cancer.

The current NCCN guidelines for recurrent metastatic cervix cancer include both immunotherapies and the antibody-drug conjugates, what we would call the ADCs, in that setting. There are 2 drugs, pembrolizumab and nivolumab, that are approved in this disease site.

Pembrolizumab actually has 3 different indications. The first involves the patients who have tumors that express PD-L1. And those particular patients are eligible for pembrolizumab or nivolumab. The second indication is a much rarer subgroup, would be those patients that do not express PD-L1, but have a high TMB or are microsatellite instable. And the third situation where pembrolizumab is approved is in combination with platinum-based chemotherapy, with or without bevacizumab.

I'm going to discuss the current approved immunotherapies and antibody-drug conjugates for the treatment of cervical cancer. But before I get to that, I think it would be good to have some context as to where cervix cancer treatment has really evolved.

We've spent decades moving and evaluating new therapies in the recurrent setting with the intent of trying to move them into earlier and earlier lines of therapy. And that process has been successful, but it's taken a long time. What we have found is that drugs like platinum, paclitaxel, and topotecan demonstrated their merit, usually in combination, for patients that had recurrent or advanced metastatic cervical cancer. And what we saw over the years, the decades, was that we were basically able to incrementally improve overall survivorship expectations.

In that process, we also started to understand a little bit more about the biology. Now, back in the day, we didn't really understand very

well about the immunology, although we knew that cervix cancer was a virus-inducing disease, and we would expect that because of that, it should have an immune response, but we really didn't have the agents to go after that particular aspect. We also knew that cervix cancer was a disease driven by angiogenesis. We knew this because in the precancer state, we often identify the high-risk precancer or preinvasive lesions with aberrant blood vessels. So we applied that thought with a targeted therapy, and in came bevacizumab.

So, GOG 240 was a trial that demonstrated the merit of adding bevacizumab to chemotherapy in patients with recurrent and a metastatic cervix cancer. And in doing so, essentially doubled our expectation for overall survivorship, and that was an amazing advance. Now along the way, we were also starting to understand and have availability of how immune checkpoint inhibitors could work as a way of bringing this therapy into the fold. A really groundbreaking trial published in The New England Journal of Medicine was KEYNOTE-826, and we've discussed this a bit.

Now 826 allowed us to look at the addition of this immune-based therapy that is targeting, as I mentioned before, the immune microenvironment in cervix cancer, and this particular trial demonstrated substantial improvement in every biomarker in every category that we evaluated, starting from progression-free survival, overall survival, and objective response. And what was really important about this trial is that we were able to see this combination both with and without bevacizumab. So the current guidelines now allow us platinum-based therapies, platinum-based therapies with bevacizumab, platinum-based therapies with immunotherapy, and platinum-based therapies with immunotherapy and bevacizumab. And all of this came from the very important successive evaluation of these agents targeted towards biological principles that drive this disease.

Now, but I can't stop there because, obviously, we still have patients that succumb to this disease and we're going to try to figure out ways to better address that. And in doing so, we realized that many of our cervix cancer patients, their tumors express tissue factor. It's almost a ubiquitous expression of that biomarker. And we did an early study that demonstrated that patients who received an antibody-drug conjugate, namely tisotumab vedotin, which was an antibody-drug conjugate that brings a cytotoxic payload targeting tissue factor, was able to affect objective responses in a number of different solid tumors, but most importantly, and actually I think even to the greatest degree, in cervix cancer, we saw tremendous responses, and that's always a wonderful thing to see in a phase 1 trial. So of course, we rapidly developed the development plan for that particular agent and we demonstrated in a single-arm phase 2 trial that this drug produced objective response rates better than we expect with chemotherapy, around 24% now, with durable duration of response and ultimately led, again, to the footprint for further development. And that is what's actively ongoing right now, as we look at combinations with immune checkpoint inhibitors, bevacizumab, and really importantly now the potential to replace a cytotoxic agent in our most active regimen for recurrent metastatic cervical cancer, which is replace paclitaxel to add this drug with platinum, pembrolizumab, and bevacizumab. And that is active, ongoing research that would hopefully change the landscape of this disease once again.

In Chapter 3 we'll be discussing key investigational clinical data with immunotherapy and antibody-drug conjugates to treat cervical cancer. 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 Dr. Susana Campos and Dr. Ketta Lorusso. We're discussing employing immunotherapy and ADCs in advanced endometrial and cervical cancers, both current and emerging therapies.

Welcome back. After reviewing the NCCN guidelines and approved immunotherapy and antibody-drug conjugates for the treatment of cervical cancer, let's shift gears and discuss some key investigational clinical data from immunotherapy and antibody-drug conjugates to treat cervix cancer.

This is a fascinating area because it's undergone some tremendous changes, mostly because we're not only interested in looking at alternative ways to enhance the efficacy with our immune checkpoint inhibitors, but we're also looking at the adoption and incorporation of newer so-called chemotherapy agents, as we've mentioned before, with the antibody-drug conjugates.

So we started the story with trying to evaluate it in settings in previously treated patients, and we'll review that in just a second. But we have some data now emerging for the combination of carboplatin and tisotumab vedotin in the first-line setting in untreated patients.

And what we've seen with this combination that was recently reported and updated at the recent annual meetings, including ASCO, we have seen some objective response rates that seem to rival at least what we've seen with paclitaxel and carboplatin, now using a different, more targeted agent: tisotumab vedotin. And we're quite excited about this because if the strategy is to replace paclitaxel, we now have an opportunity based on the emerging data in the recurrent setting in previously treated patients to add not only pembrolizumab to this combination, but also to look at the 4-drug regimen, similar to what we've seen in the KEYNOTE-826 data with the combination of tisotumab vedotin, carboplatin, pembrolizumab, and bevacizumab. So this will be quite exciting to see how this plays

out in the months and years to come.

Dr. Campos, can you discuss some of the key clinical immunotherapy and antibody-drug conjugate data in the second-line treatment for cervix cancer?

Dr. Campos:
Oh, I would love to. Actually, it's been very exciting in that field. I think Dr. Coleman actually talked about one of the key studies using an antibody-drug conjugate called tisotumab vedotin, and he described the 204 study, which was a simple phase 2 study looking at this particular compound, tisotumab, which targets the tissue factor. This particular study reported an objective response rate of about 24% and has FDA approval for cervical cancer at this point in time. However, on the heels of that, there's been many different studies that are actually ongoing, some of which have actually been reported at ASCO 2022 and reviewed at ESMO. One particular study that we're very excited about is the innova 301, which is the study of tisotumab versus chemotherapy. And this is going to be an open-label, randomized phase 3 study looking at patients with cervical cancers, squamous cell, adenocarcinoma, adenosquamous, and patients are going to be randomized to tisotumab versus the investigator's choice, which would be systemic chemotherapy, which could be topotecan, vinorelbine, gemcitabine, irinotecan or pemetrexed. So that's the innova 301 study.

But some of the studies that actually were presented at the American Society of Clinical Oncology meeting by some of our European colleagues are quite interesting and actually great food for thought. And this was, again, the combination of tisotumab, which is the ADC, but it's in combination with other drugs. The 205 study was a study that had a dose escalation and a dose expansion. And this particular study looked at, for example, tisotumab plus pembrolizumab tisotumab plus pembrolizumab after 1 to 2 prior lines of therapy, and tisotumab plus carboplatinum. And it actually – it was rather inviting in terms of the actual responses. When the authors reported this, the combination of tisotumab and pembrolizumab – about 78% of patients had a reduced target lesion. When they looked at pembrolizumab and tisotumab in a later line, like second line and third line, once again it was a 74% of patients had a reduced target lesion size. And in a likewise fashion, although – albeit it was a small cohort of first-line tisotumab and carboplatinum – 32 patients – but 85% of patients had a reduced target lesion. So these are actually quite inviting studies, looking at this particular compound, and in combination with either pembrolizumab or that of a carboplatinum.

Now, there are other combinations that are also quite interesting. There were reports of the CheckMate 358 study, which looked at nivo or nivo plus ipi. And the dosages of nivo and ipi were different. And this combination of nivo and ipi proved to be actually quite instrumental in patients with cervical cancer, reporting in some cohorts a response rate of 30%.

Interestingly, that particular study, the [CheckMate] 358, also showed some activity of this combination in patients that were PD-L1 negative, albeit these were very small cohorts, so I think that that requires further delineation. But there have been many studies, just to recap, many studies looking at second-line therapies, looking at ADCs, and we base this on the innova 204 data, the upcoming TV 301, some of the data that we've been able to recollect from the 205 data, the CheckMate 358. So it's a very exciting time in cervical cancer.

Dr Coleman:
Thank you, Dr. Campos. I think it's safe to say that the historical success of treatment with patients with metastatic and recurrent cervical cancer patients has been iterative and slow, but 826 really set the standard for capitalizing, not only on our understanding of biological elements such as angiogenesis and immune therapy, but also on the opportunity to move this into a line of treatment that will have the greatest effect.

In review, we have seen that with the, at least at the median, we have been able to triple our expectation for overall survivorship in this disease from our historical benchmark of combination chemotherapy, which itself was an iterative change over single-agent treatment. So this has been a tremendous advance for us and it, again, lays the platform for our continued development of novel treatments, not only novel chemotherapies, but novel immunotherapies, as this field continues to move forward with identifying better and more lasting efficacious treatment.

In Chapter 4, we'll be discussing regional considerations based on the ESMO 2022 data. Stay tuned.

Dr Coleman:
Welcome. We just spoke about key clinical data from the immunotherapy and antibody-drug conjugates studies in patients with cervix cancer. Now let's talk about regional considerations.

Dr. Campos, what are some of the regional considerations to keep in mind based on the data released at ESMO 2022?

Dr. Campos:
I think that's a very important question, and I think when we think about cervical cancer cervical cancer is actually the fourth most common cancer in the world and the seventh most common cancer overall. When we look at statistics, there was about 604,000 new

cases of cervical cancer in 2020, and we tend to see cervical cancer mostly in patients that unfortunately don't have access to screening of cervical cancer. And when we look at some global statistics in 2020, some of these areas really include, like, east Africa, southern Africa, and then of course, South America and Central America. These tend to have the highest incidence of cervical cancer, and mostly, this is due to lack of access for screening.

Dr. Coleman:
Thank you. Well, this has certainly been a fascinating conversation. To summarize, the endometrial and cervical cancer landscape has changed tremendously and continues to evolve. It's actually pretty exciting, because for many years we had very little to talk about. Now these drugs are demonstrating their independent efficacy and in combination even more so. And so we're so excited to see how these new innovative strategies will annotate the landscape of cervix and endometrial cancer in the years to come.

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

Dr. Campos:
Thank you for having me, and thank you for the opportunity to review some of the key data on endometrial cancer. Thank you.

Dr. Lorusso:
Thank you, Robert. Thank you for having me. It was a very great and nice and interesting discussion. Thank you so much.

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