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Keeping Pace in Women's Cancer: Focus on Endometrial Carcinoma

Announcer:
Welcome to CME on ReachMD. This activity, titled "Keeping Pace in Women's Cancer: Focus on Endometrial Carcinoma" is provided in partnership with Prova Education and is supported by an independent educational grant from Merck.

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Here's your host, Dr. Richard Penson.

Dr. Penson:
Women facing recurrent or metastatic endometrial cancer receive a grim survival prognosis, currently 12 to 15 months, following standard-of-care chemotherapy. As such, there remains a critical unmet need for effective therapies following recurrence.

This is CME on ReachMD, and I'm your host, Dr. Richard Penson. I'm joined today by Dr. Linda Duska, and we will be discussing the rapidly changing clinical landscape and exciting treatment options in the management of recurrent and metastatic endometrial cancer. More specifically, we'll be assessing the role of immunotherapy and targeted therapies in managing advanced endometrial cancers, as well as the importance of assessing the biomarker status of endometrial cancers.

Dr. Duska, welcome to the program.

Dr. Duska:
It is great to be here.

Dr. Penson:
So, let's begin. Dr. Duska, can you provide an overview of the challenges faced in managing recurrent or metastatic endometrial cancer? Historically, what treatment options have been offered to these women after recurrence and how successful have they been?

Dr. Duska:
Dr. Penson, as you note, patients with advanced or recurrent disease do not have a wonderful prognosis, and particularly women of color have a higher death rate in the United States, and this therefore represents a significant unmet need. I want to start by just briefly touching on first-line therapy. The NCCN Guidelines for advanced or recurrent endometrial cancer include chemotherapy and hormonal therapy in the first-line. The preferred chemotherapy regimen is carboplatin and paclitaxel, established by GOG 209, with an overall response rate of 51% and a median progression-free survival of 14 months. Dr. Fader's study also demonstrated an overall survival advantage for adding trastuzumab to patients with advanced or recurrent uterine papillary serous carcinoma who are HER2-positive. Still, there is clearly an unmet need including an improvement in front-line therapy.

There have been multiple different chemotherapy and targeted agents tested in the second line without significantly encouraging results. Chemotherapy results generally less than 15%, and targeted therapy, with the exception of letrozole and everolimus, less than 5%. In contrast, the response rate in KEYNOTE-158 with pembrolizumab is far higher than these and led to the approval of pembrolizumab in the second line for patients with microsatellite instable cancer in 2017. Specifically, in KEYNOTE-158, in 49 microsatellite-instable endometrial cancers, the overall response rate was 57%. Compare that to the GOG 209 response rate that I

mentioned earlier, with a median overall survival that's not reached. This is a remarkable response rate for patients in the second line.

This leads me to just touch on the molecular classification of endometrial cancer, which was developed from data from the Cancer Genome Atlas project, and it's really changing the way we think about this disease from a traditional type-1, type-2 dichotomy to a molecular classification that is more reproducible than traditional histology and is more predictive of response to therapy and potentially of prognosis. The molecular classification of endometrial cancer divides endometrial cancers into so-called "hot" tumors and "cold" tumors. The hot tumors are ultramutated, in the case of POLE, and hypermutated in the case of microsatellite instable. These hot tumors are expected to be responsive to immunotherapy. In endometrial cancer, about 25% to 30% of tumors will be microsatellite instable.

Dr. Penson:
I love what you say about the different approaches to the different disease subsets. Clearly, there is an unmet need for better therapy. So let's turn our attention now to the 2019 accelerated approval of the pembrolizumab and lenvatinib combination for patients with advanced endometrial cancer. Patients whose prior systemic therapy has failed them and who are not candidates for surgery or radiation, all again metastatic disease, you have disease that is not microsatellite instable-high or mismatch repair-deficient.

Dr. Duska:
So we talked about the patients who had microsatellite instable tumors and their excellent response to pembrolizumab, but what about those patients who have microsatellite stable tumors, and this will be the majority of them, about 70%. And to do this, we can try to combine immunotherapy with another agent, such as chemotherapy, radiotherapy, targeted therapy such as anti-angiogenesis molecules as an example, or other immunotherapy agents.

One approach that has proven to be successful is the combination of lenvatinib with pembrolizumab; the study was called KEYNOTE-146. The investigators combined lenvatinib, an oral multikinase inhibitor, with pembrolizumab in unselected patients. So these patients were not prescreened to be microsatellite instable. They had recurrent or advanced endometrial cancer, and were, in general, treated with less than or equal to two prior lines of therapy. The preliminary results of this study, published in *The Lancet* in 2019, showed a response rate of 40% at week 24 regardless of microsatellite instability status. So this is pretty remarkable and led to the accelerated FDA approval of the combination in 2019 for women with advanced endometrial cancer who had disease progression following first-line therapy and who have microsatellite stable tumors. What's really notable is the final efficacy results, which were presented at the Society of GYN Oncology Virtual Meeting in 2020 by Dr. Macker. I just want to remind you again, the majority of patients in this study had microsatellite stable tumors – a little over 90% of them. Despite this, the overall response rate was 38% for the entire population. Notably, it was 64% in the microsatellite instable group – so higher – but when Dr. Macker looked at only the microsatellite stable tumors, the response rate was still 36%. The median duration of response was 21 months for the total population, and for the microsatellite stable patients, the median overall duration of response was not reached. What was also really interesting was the response rate seen in the traditionally thought of as high risk, the copy number high cancers. Those serous cancers and clear-cell cancers, the overall response rate was 50%, and the median duration of response was not reached for any of these histologies. Truly remarkable for tumors that we traditionally think of as nonresponsive to therapy. In my opinion, this study has been practice changing.

Dr. Penson:
I want to touch on the conflicting advice people get when starting lenvatinib. Do they use the full 20 mg dose, or do they use a lower dose, say 14 mg, and escalate? People are often told that if a patient's fatigued, they could start at a lower dose or dose reduce. And there's actually a very useful metric. These tyrosine kinase inhibitors really change things in about three days, and so to watch blood pressure and start at a low dose and then escalate if the blood pressure does not go above 140/90 can be a nice strategy, particularly in older patients. It's not wrong, though, to start at full dose and dose reduce. And one of the drugs we found helpful for the weight loss that you get with lenvatinib is olanzapine.

So Dr. Duska, are there other data to discuss regarding immunotherapy and the second-line setting for patients with endometrial cancer?

Dr. Duska:
There's so much data to discuss, but there's one study that I want to just focus on, and that is the early results of the GARNET study, which were first presented at the Society of Gynecologic Oncology meeting this time in 2019. It was a study of dostarlimab, which is a different PD-1 inhibitor, but in the same population, in women with recurrent or advanced endometrial cancer who progressed after primary therapy. In the case of GARNET, both microsatellite stable and women with microsatellite instable tumors were allowed to go on study. In the 2019 analysis, the overall response rate for the entire population was 30%. It was 49% for the microsatellite instable tumors and a remarkable 20% for the microsatellite stable tumors. So this was somewhat unexpected, and there's a lot of excitement about these results. Additionally, similar to pembrolizumab, the responses were durable, with ongoing responses occurring in the

majority of patients described in the 2019 presentation. There was an update presented at the Society of GYN Oncology meeting this year that was specific to the microsatellite instable tumors, and the overall response rate in this group was 42%. Remarkably, there were nine complete responses, 21 partial responses. The responses were deep and durable, and again, the therapy was tolerable. We are really looking forward to the updated data regarding the microsatellite stable tumors from this trial.

I just want to mention the excitement about immunotherapy has encouraged us to move immunotherapy into the first-line. There are currently two trials ongoing. The RUBY trial, which combines taxel and carboplatinum with dostarlimab in the upfront setting, and the ongoing GOG-3018 study, similar trial with pembrolizumab in combination with carboplatin and paclitaxel. But even more interesting to me is the LEAP-001 trial. It randomizes women between lenvatinib plus pembrolizumab versus carboplatin and paclitaxel in the first-line. So lots of excitement about immunotherapy and immunotherapy combinations in this group of patients.

Dr. Penson:
The permutations of novel approaches to maximize the impact of immunotherapy are mind-bending. We haven't even touched on, sort of, passive immunotherapy with antibody drug conjugates, really trying to squeeze the biggest bang for your buck out of immunotherapy.

For those just joining us, this is CME on ReachMD. I'm Dr. Richard Penson, and I'm joined today by Dr. Linda Duska. Together, we are discussing the changing landscape of the management of the current metastatic endometrial cancer.

Dr. Duska:
Dr. Penson, how do emerging data regarding new drugs or treatments make their way into clinical practice? Can you comment on any differences there might be between academic and community practices, especially as related to the management of common gynecologic cancers such as endometrial cancer?

Dr. Penson:
In a world of fast and faster change, get educational information out about new standards of care in a better and more tailored way. World-class care on your doorstep is the mantra of community practice. CMEs, podcasts, and educational academic symposia mean that any distance between medical centers and community oncology practices are being reduced, and collaboratively, we can together offer the best care to all of our patients. I'm actually optimistic that at that point, the latest breakthroughs translate into meaningful improvements for our patients with endometrial cancer.

Dr. Duska:
Perhaps one of the benefits of the virtual meetings we've been experiencing this year is that more people can take part in them, and perhaps we'll see a better distribution to the community and to academic practices of new information by virtue of all of the virtual meeting we've been doing lately.

Dr. Penson:
That's such an important point. As we come to the close of our discussion today, Dr. Duska, what are the key take-home messages you have for our colleagues?

Dr. Duska:
First of all, we know that these patients have limited treatment options, and they represent a high unmet need. Secondly, I believe that in the coming years, we're going to see a shift to molecular classification rather than the traditional type 1 and type 2 classification that we've used in the past. Molecular classification is more reproducible, it better reflects tumor behavior, and perhaps most importantly, potential therapeutic response. Checkpoint inhibitor monotherapy is promising in MMR-deficient tumors, and pembrolizumab is approved in this setting in the second line. We're waiting excitedly to see the data from dostarlimab. There may be a role for checkpoint inhibitor monotherapy in microsatellite stable tumors. Clearly, combination therapy with immunotherapy is successful in microsatellite tumors in the case of pembrolizumab and lenvatinib. There are other combination studies that we didn't have time to discuss that also show promising results.

Dr. Penson:
Fabulous. It's marvelous. And now every patient with recurrent endometrial cancer has access to immunotherapy. Well, that brings us to the end of our discussion. I want to thank my guest, Dr. Linda Duska, for joining me and for sharing her insights on the changing management of recurrent metastatic endometrial cancer. Dr. Duska, it was great speaking with you today.

Dr. Duska:
It was my pleasure. It was great speaking with you as well.

Announcer:

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