Transcript Details

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Keeping Pace in Women's Cancer: Clinical Considerations for Endometrial Cancer—Global Perspectives

Announcer:
Welcome to CME on ReachMD. This activity, entitled "Keeping Pace in Women's Cancer: Clinical Considerations for Endometrial Cancer—Global Perspectives" is provided by AGILE and Prova Education.

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Dr. Penson:
Immunotherapy has emerged as a potential paradigm changer for the treatment of women with recurrent or advanced endometrial cancer. This is great news, as we're all too aware that women facing such a diagnosis have endured a grim survival prognosis for far too long.

This is CME on ReachMD, and I'm Dr. Richard Penson. Today, I'm talking with Dr. Ana Oaknin about the global perspective surrounding the recent emergence of immunotherapy agents in the management of recurrent or metastatic endometrial cancer. We'll also be looking at the critical role molecular testing can play in how we select which patients receive a particular therapeutic strategy.

Dr. Oaknin, welcome to the show.

Dr. Oaknin:
Thank you for having me.

Dr. Penson:
Dr. Oaknin, before we begin to address the potential benefits that immunotherapy brings to the management of recurrent or metastatic endometrial cancer, let's get some background. Can you explain for our listeners the importance of knowing if the tumor in question is microsatellite instable-high, microsatellite stable, or mismatch repair deficient? This all relates back to the emergence of the ProMisE molecular risk classifier. That molecular classification is at the heart of our subsequent discussions.

Dr. Oaknin:
DNA mismatch repair proteins are involved in DNA repair of genetic sequence code. In normal cells, the mismatch repair pathway identifies and corrects genetic mismatch errors during DNA replication. A deficient mismatch repair, dMMR, pathway leads to a cumulation of mismatches insertions and deletions in microsatellite repetitive sequences resulting in microsatellite instability. There are 4 key proteins involved in the mismatch repair pathway, namely MLH1, MSH2, MSH6, or PMS2. The absence of 1 of the 4 of these proteins can serve as an important biomarker for serial cancer diagnosis. In addition, a dMMR pathway can be caused by somatic or inherited pathogenesis. As you are aware, recent data show that dMMR MSI analysis is effective as a predictive biomarker for the effect of immuno checkpoint inhibitors including anti-PD-1, anti-PD-L1 antibodies. Indeed, pembrolizumab is approved for the treatment of adult and pediatric patients with unresectable or metastatic MSI-high or dMMR tumors.

In summary, I want to stress that mismatch repair deficiency, MSI-high tumors have the highest response rate to PD-1 inhibitors for any

cancer type so far. Then it's quite important to identify these characteristics in endometrial cancer patients to bring or to give them the best treatment available.

Dr. Penson:
Fabulous. Let's turn our attention now to another example of how that system has been applied. Dr. Oaknin, can you give us an overview of the key findings from the KEYNOTE-146/Study 111 of lenvatinib plus pembrolizumab in patients with advanced endometrial cancer?

Dr. Oaknin:
As you know, the KEYNOTE-146 is a phase 1b/2 study that analyzes the combination of pembrolizumab/lenvatinib across different solid tumor types. However, today, I will review with you the data on the recurrent metastatic endometrial cancer cohort.

In this particular cohort, patients must have received [no more than] 2 lines of therapy and they must have measurable disease by immune RECIST. All patients received lenvatinib 20 mg per day plus pembro every 3 weeks. Patients were eligible regardless of mismatch repair status. Indeed, 108 patients were enrolled, and 87% of the population, that is to say, 94 patients were not MSI-high or not dMMR, and only 11 patients were MSI-high or dMMR. In addition, I would like to point out that 49% of the patients were PD-L1 positive. The primary endpoint of the study was objective response rate at 24 weeks evaluated by the investigator following immune RECIST. Secondary efficacy endpoints included duration of response, progression-free survival, and overall survival.

Well, at the data cutoff with a median follow-up of 8.7 months, we observed a clinically meaningful response rate with the combination. Indeed, 38% of overall response rate in the whole population. When we look at the not MSI-high, non-dMMR group, the overall response rate was 36%. In the mismatch repair deficiency, MSI-high population, the overall response rate was 63%. However, I would like to stress here that the sample size was too small – as you recall, only 11 patients were mismatch repair deficient. For previously treated patients regardless of tumor MSI status, the median duration of response was 20.2 months, median PFS was 7.4 months, and median overall survival was 16.7 months.

I should highlight that the treatment-related adverse events were common, leading to dose reduction of lenvatinib in 64% of the patients and dose interruption in 70% of patients. And in addition, 18 patients discontinued therapy due to treatment-related adverse events. But I would like to summarize saying that lenvatinib plus pembrolizumab show promising antitumor activity in patients with advanced endometrial carcinoma who have experienced disease progression after prior systemic therapy, regardless of tumor MSI status.

In light of this compelling efficacy, on September 17, 2019, the FDA granted accelerated approval to pembrolizumab plus lenvatinib for the treatment of patients with advanced endometrial carcinoma that is not MSI-high or not dMMR and who have disease progression following prior systemic therapy but are not candidates for curative surgery or radiation.

In addition, the clinical trial KEYNOTE-775 was launched acting as a confirmatory trial. 780 previously treated endometrial carcinoma patients were randomized either to lenvatinib with pembrolizumab or physician's choice chemotherapy, either doxorubicin or weekly paclitaxel. As you are quite aware, on December 2020, a press release informed that the trial was positive, having achieved the primary endpoint of PFS and OS. Moreover, the data had recently been presented at SGO conference at the end of March.

Dr. Penson:
This is truly an exciting story.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Richard Penson and here with me today is Dr. Ana Oaknin. We're discussing the global perspective of immunotherapeutic management of recurrent and metastatic endometrial cancer and how to select a particular therapy for each patient.

Continuing this theme, I think data from the GARNET study also provided an interesting perspective on the use of immunotherapy in women with recurrent or advanced mismatch repair-deficient endometrial cancer. Could you discuss those data for us?

Dr. Oaknin:
As you will note, GARNET is a phase 1, single arm study evaluating the anti-PD-1 antibody dostarlimab in multiple tumor types. We will focus on the endometrial cancer cohort today, namely in the mismatch repair-deficient cohort. And I would like to stress that mismatch repair status in this trial was determined by local immunohistochemistry. The primary endpoint for the GARNET trial was overall response rate by RECIST and duration of response. At data cutoff day, 126 dMMR patients had been enrolled and treated. And this makes up the safety population. For the efficacy population, only patients with at least 6 months of follow-up time in the study and with at least 1 measurable lesion at baseline were included. So 103 dMMR patients met these criteria. It should be noted that all patients have at least 1 prior line of platinum-based chemotherapy. The overall response rate was 42.3%. We observed 9 patients with a confirmed complete response, and we observed 20 patients who achieved a partial response. In addition, responses were durable. In

fact, with a median follow-up of 11.2 months, the median duration for response was not reached. When we look at the estimated likelihood of maintaining a response, it was 96% at 6 months and 77% at 12 months.

I have to say that the safety profile of dostarlimab is quite aligned with other anti-PD-1 agents. In fact, the most common grade 3 or higher treatment-related adverse events were anemia, just 2.9%, colitis 1.9%, and diarrhea 1.9%.

In summary, I would like to say that in this non-randomized trial, dostarlimab showed a clinically meaningful and durable antitumor activity with an acceptable safety profile for patients with dMMR endometrial cancer after prior platinum-based chemotherapy. In addition, this year at SGO we had presented an updated result from both endometrial cancer cohorts, namely dMMR and non-dMMR cohorts. And in both cohorts, dostarlimab has shown activity. However, this activity is greater in the dMMR cohort.

Dr. Penson:
Fabulous. I think there's a lot of chatter around this drug. Dr. Oaknin, we're discussing emerging data supporting the use of immunotherapy as both a safe and effective approach to managing a subset of women with advanced endometrial carcinoma, more specifically related to MSI, dMMR status. Not all agents are equally available in all regions. Let's consider, for example, the US, the EU, Latin America, and China. Even if the agent or agents are available, their use may be restricted and/or the physicians using them may not be familiar enough with them to deal with the immune-related adverse events that may occur. How do we address the issue of optimizing care for women in various regions?

Dr. Oaknin:
Thank you for bringing this important issue. So while the adverse events related to chemotherapy may significantly impact quality of life of our patients, these adverse events are at least well known, recognized, and understood by oncologists after decades of use in the field. Immunotherapy, on the other hand, may be accompanied by a spectrum of unknown, unrecognized, and poorly understood adverse events. In addition, immuno-related adverse events can affect any organ system and can have delayed onset plus a prolonged duration, making diagnosis challenging for clinicians. It's quite important to stress that this challenge in recognizing immuno-related adverse events was underscored by a study showing poor integrated agreement on immuno-related adverse event occurrences and grades.

So, because oncologists are less familiar with immuno-related adverse events than with adverse events from standard treatments, they may be more likely to misdiagnose them. Moreover, there are no prospective trials to define strategies to manage specific immuno-related adverse events. These challenges in recognition, diagnosis, and treatment of immuno-related adverse events underscored the need for further clinical education.

Dr. Penson:
Yes, And I think it's also true to say that medical clinicians are expanding into medical teams so that together with gastroenterologists or cardiologists, they can manage people with complications of immune treatment better.

Well, this has certainly been a fascinating conversation, but before we wrap up, Dr. Oaknin, can you please share one take-home message with our audience?

Dr. Oaknin:
I would say that in immunotherapy with checkpoint inhibitor is changing the face of oncology treatment for many tumors. Endometrial carcinoma may not be an exception. Since 1970 and thanks to immunotherapy, we have now been able to bring new efficacy agents for our patient with recurrent metastatic endometrial carcinoma. So I think it's crucial to identify the mismatch repair status for our patient with recurring endometrial carcinoma and to provide them with the best immunotherapy that we have on board, so far.

Dr. Penson:
Education is necessary so that people know how to choose and how to manage the toxicities of those treatments best. But a great message in terms of significant improvements for patients.

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

Dr. Oaknin:
Thank you for having me. It has been my real pleasure to share this conversation with you.

Announcer:
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