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Expanding Endometrial Cancer Treatment Options: A Look into Trial Data

Announcer:
You're listening *Project Oncology* on ReachMD. Today, we'll hear from Dr. Richard Penson, who's an Associate Professor of Medicine at Harvard Medical School and the Clinical Director of Medical Gynecologic Oncology at Massachusetts General Hospital. He'll be discussing the current unmet needs when it comes to treating endometrial cancer patients who have deficient mismatch repair tumors.

Let's hear from Dr. Penson now.

Dr. Penson:
So endometrial cancer is one of the few cancers in the U.S. today that is both increasing in instance and mortality. And all of endometrial cancers between 20 and 30 percent are going to have this type called deficient mismatch repair, or dMMR, and our understanding of that has really exploded. In the late 70s, we started to understand about things, and we could see these tiny, what's would call microsatellites, little clusters outside the DNA, and they were a consequence of that failed mismatch repair. And so certain drugs, hydroxyurea and cyclophosphamide, seemed to clear those up, and they were associated with a better prognosis. So first in colorectal, and then in endometrial cancer, it really looked like a potential for exploitation to advantage patients. And then there's this inflection point where the science takes off, and 2013 it becomes all the rage in the literature, and 2014 immunotherapy is proof for melanoma, 2015 for lung cancer, and then May 2017 pembrolizumab was approved as a monotherapy for tissue agnostic mismatch repair deficient tumors. And then, most recently, it's been very exciting with the approval of now three agents, which is really very exciting.

So the standard of care for patients now is informed by five trials; GY018 it looked at chemotherapy with or without pembrolizumab; RUBY was chemotherapy with or without dostarlimab; and then the DUO-E trial looked at durvalumab; and the AtTEnd and MITO END-3 trial looked at atezolizumab. And it's incredibly exciting that we now have three approved immunotherapies.

So the limitations are really that, to date, we've been looking at patients with recurrent disease, and so two years of pembrolizumab or three years of dostarlimab has become a standard for a while, and across the trials, the patients with deficient mismatch repair tumors seem to do really very similar with different drugs. But it's not a cure for recurrent disease.

And so there was a presentation of the ESMO 2023 meeting using neoadjuvant immunotherapy, and it was quite clear that when it's an acquired deficient mismatch repair with silencing of the genes, and so low-protein repair enzymes present, you don't get as good an outcome. And so the big challenge has been to get the biggest impact for the greatest number of patients.

And one of the exciting things has been the transition to first-line therapy. Can we really cure more patients? And so there was a presentation in 2024 of the Leap-001 trial, and some people might interpret it as a negative trial. Say it was pembrolizumab with lenvatinib, which alters the microenvironment and gets a better outcome, and that didn't look any different for all-comers against chemotherapy. But in the patients who'd had adjuvant chemotherapy before and then were re-challenged in that group, the patients randomized to lenvatinib/pembrolizumab appeared to do better, and it really spoke to the hope that we can both define a group of patients and modify our treatments to get the best the outcome, especially for deficient mismatch repair.

And so there are two upfront studies comparing pembrolizumab with chemotherapy and first-line therapy for patients with deficient mismatch repair tumors; KEYNOTE-C93, and then chemotherapy versus dostarlimab, again deficient mismatch repair tumors first-line in the DOMENICA trial.

Antibody-drug conjugates, trastuzumab deruxtecan has just been magnificent in terms of impact—more than 80 percent response rate

in HER3+ tumors, FDA-approved in that group in any tissue type—and then the NCCN approved for the two-plus and three-plus HER2-expressing tumors. But there are other targets, very exciting things, folate receptor, TROP2, as well as HER2. So the targets for antibody-drug conjugate's expanding and that is going to be used, and maybe the best outcomes we're going to see are in the patients with deficient mismatch repair tumors.

In the hormonally responsive subset of the no-specific mutational profile, a large number of endometrial cancer patients doing an aromatase inhibitor or SERMs, selective estrogen receptor modulating drug, with CDK inhibitor is getting great outcomes. Quite a few of those tried selinexor as a switch maintenance therapy in the p53 wild-type tumors, and then the integration of PARP inhibitors in DUO-E and RUBY 2 is one of those things that's really exciting. Maybe the p53-mutated tumors are going to be a mark of better outcomes.

So new and exciting options and patients living longer and better with cancer, and a real encouragement that we are rapidly finding ways that we can cure more patients from this terrible disease.

Announcer:
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