

MSI-H/dMMR Endometrial Cancer

Endometrial cancer (EC) is the most common gynecologic cancer, with a 1% increase in incidence and mortality in the last year. Approximately 2%–5% of EC cases have a defective germline DNA mismatch repair system (dMMR) attributed to Lynch syndrome. Somatic mutations in dMMR proteins have been reported in up to 30% of all EC in the recurrent setting. Universal testing is now recommended on endometrial tumors for defects in the MMR system. The dMMR proteins cause cellular hypermutations and high microsatellite instability, making them receptive to inhibitors of programmed cell death-1 (PD-1) and its ligand, PD-L1.

PD-1 is a negative regulator of T-cell activation and proliferation, meaning it “turns the immune response off,” essentially acting as a brake. This type of inhibitory role is necessary to prevent excessive immune reaction and autoimmunity. For this reason, PD-1 and other regulators acting in this manner are known as immune checkpoints. We now understand that some tumors can exploit the PD-1 pathway, enabling them to evade the immune response.

Recent clinical trials have shown that patients with EC may have improved objective response rates and progression free survival when given pembrolizumab (Keytruda®), an anti-PD-1 receptor monoclonal antibody checkpoint inhibitor that blocks the inhibitory pathway and allows increased immunogenicity of tumors. Pembrolizumab is approved for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability high (MSI-H) or dMMR.

The phase 1b KEYNOTE-028 study enrolled a cohort of 24 patients with PD-1 positive, advanced or metastatic endometrial cancer. After a median follow-up of 10.9 months, 3 patients (13%) achieved a partial response, and the median duration of response had not been reached. Three patients (13%) achieved stable disease with a median duration of 24.6 weeks. The safety profile was consistent with other pembrolizumab clinical trials, with 13 patients (54.2%) experiencing treatment-related adverse events, including fatigue, pruritus, pyrexia, and decreased appetite in >10% of patients. Grade 3 adverse events were reported in 4 (16.7%) patients, including asthenia and back pain, pyrexia, anemia, hyponatremia, and hyperglycemia.

Of the 24 patients enrolled, 19 had tumor samples evaluable for MSI status. Only 1 patient (5.3%) had MSI-H tumor, and 18 patients (94.7%) were non-MSI-H. Of the 3 patients achieving PR as best response, 1 had a non-MSI-high tumor but was found to have a polymerase E (POLE) mutation, 1 had non-MSI-high status, and 1 had unknown MSI status. The single patient classified as MSI-H had a best response of progressive disease.

Although this was a small cohort of patients, it indicates that pembrolizumab shows promise as a treatment for advanced or metastatic endometrial cancer. An overall response of 13% is comparable to those seen with cytotoxic chemotherapy.

RESOURCES

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- Ott PA, Bang YJ, Berton-Rigaud D, et al. Safety and antitumor activity of pembrolizumab in advanced programmed death ligand 1-positive endometrial cancer: results from the KEYNOTE-028 study. *J Clin Oncol.* 2017;35:2535-2541.