The Promise of Lenvatinib/ Pembrolizumab for Endometrial Cancer

BY DIBASH KUMAR DAS, PhD

Endometrial cancer is the most common type of gynecologic cancer in the U.S. and an estimated 67,000 new cases will be diagnosed in 2021. Patients diagnosed with endometrial cancer face low survival rates when diagnosed at an advanced stage or at recurrence—particularly those whose disease progresses after platinum-based therapy and is no longer responsive to curative surgery or radiation.

In 2019, the FDA granted accelerated approval of the combination of lenvatinib—the orally available multikinase inhibitor of VEGFR1, VEGFR2, and VEGFR3 kinases—plus the anti-PD-1 antibody pembrolizumab for treatment of women with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation. The approval was based on the Phase II KEYNOTE-146/ Study111 data (NCT02501096).

Recently, the results of Phase III KEYNOTE-775/Study 309 (NCT03517449), the confirmatory trial for KEYNOTE-146, were presented at the 2021 Society of Gynecologic Oncology Annual Meeting on Women's Cancer. The multicenter, open-label KEYNOTE-775/ Study 309 trial evaluated the combination of pembrolizumab plus lenvatinib for the treatment of certain patients with advanced, metastatic, or recurrent endometrial cancer after a prior platinum-based regimen in any setting.

Of the 827 patients enrolled, the majority (n=697) had mismatch repair-proficient tumors (pMMR); the remainder (n=130) had dMMR. Researchers randomly assigned 411 women (median age, 64 years; range 30-82) to pembrolizumab (200 mg intravenously every 3 weeks for up to 35 cycles) in combination with lenvatinib (20 mg orally once daily). The other 416 women (median age, 65 years; range, 35-86) received chemotherapy of physician's choice of either doxorubicin at 60 mg/m^2 every 3 weeks up to a maximum cumulative dose of 500 mg/m^2 or paclitaxel at 80 mg/m^2 on a 28-day cycle.

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The study met the dual primary endpoints of progression-free survival (PFS), as assessed by blinded independent central review (BICR) per RECIST v1.1, and overall survival (OS). It also met the secondary endpoint of objective response rate (ORR) in the all-comer population (which included patients with pMMR and dMMR tumors) and in the pMMR subgroup.

Within the all-comer subgroups, the team reported comparable benefits in PFS and OS by age, race, region, MMR status, history of pelvic radiation, histology, and prior lines of therapy. The pMMR subgroup experienced a similar benefit as all-comers with the combination versus standard therapy.

At a median follow-up of 11.4 months, in the all-comer population, results showed statistically significant and clinically meaningful benefit with lenvatinib/pembrolizumab compared with the control arm with regard to PFS (median, 7.2 months vs. 3.8 months) leading to a 44 percent reduction in the risk of disease progression or death (HR, 0.56; 95% CI, 0.47-0.66; p<.0001).

Additionally, a statistically significant and clinically meaningful improvement in OS was seen in the all-comer population. The corresponding median OS with lenvatinib/pembrolizumab was 18.3 months versus 11.4 months, for a 38 percent reduction in the risk of death (HR, 0.62; 95% CI, 0.51-0.75; p <.0001). The secondary efficacy endpoint of ORR was also improved with lenvatinib/pembrolizumab (31.9% vs. 14.7%; p <.0001), with higher rates of CR (6.6% vs. 2.6%) and partial response (25.3% vs. 12%). For patients who responded, the median duration of response was 14.4 months for patients who received the combination versus 5.7 months for patients who received chemotherapy.

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The safety profile of the lenvatinib/pembrolizumab combination appeared consistent with the established safety profiles of the individual monotherapies. In the entire cohort, the most common any-grade adverse effects (AEs) occurring in more than 30 percent of patients assigned lenvatinib/pembrolizumab included hypertension (64%), hypothyroidism (57.4%), diarrhea (54.2%), nausea (49.5%), decreased appetite (44.8%), vomiting (36.7%), weight decrease (34%), fatigue (33%), arthralgia (30.5%), proteinuria (28.8%), anemia (26.1%), constipation (25.9%), and urinary tract infection (25.6%).

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> —Rachel N. Grisham, MD, at Memorial Sloan Kettering Cancer Center Westchester

In all-comers, treatment-related AEs leading to discontinuation of therapy were observed in 18.7 percent with pembrolizumab, 30.8 percent with lenvatinib, and 14.0 percent with both. In the control group, discontinuation of chemotherapy due to AEs occurred in 8.0 percent. The scientists reported higher rates of grade 5 (5.7% vs. 4.9%) or grade 3 or higher (88.9% vs. 72.7%) treatment-emergent adverse events in the lenvatinib/pembrolizumab group.

Oncology Times chatted with Rachel N. Grisham, MD, Section Head of Ovarian Cancer and Director in Gynecologic Medical Oncology at Memorial Sloan Kettering Cancer Center Westchester. Her clinical expertise and research focuses on developing novel treatments and improving treatment strategies for women with gynecologic malignancies. Grisham provided us with her insights on using the combination of lenvatinib and pembrolizumab for advanced endometrial cancer.

Oncology Times: *In the Phase III KEYNOTE-775/Study 309 trial, the findings demonstrate a 38 percent reduction in risk of death regardless of mismatch repair (MMR) status in patients with advanced endometrial cancer using the combination of lenvatinib and pembrolizumab. Are these results practice-changing?*

Grisham: "This is a huge advance for the treatment of endometrial cancer. Immunotherapy has quickly become a standard second-line therapy for treatment of endometrial cancer, with studies ongoing

to see if it will move into our first-line treatment paradigm. While awaiting further FDA review of the data, I continue to recommend pembrolizumab in combination with lenvatinib for my patients with microsatellite stability recurrent disease following chemotherapy, and single-agent immune checkpoint inhibitor for my patients with MMR-deficient recurrent disease following chemotherapy."

Oncology Times: *The toxicities of this combination of lenvatinib/pembrolizumab are significant. What are some factors you would consider when choosing this combination to treat patients safely and effectively?*

Grisham: "I think we have learned a lot about how to better manage the toxicity of this combination over the past couple years of routinely using it in clinical practice. When starting the combination, I make sure that my patient has a blood pressure monitor at home and ask them to keep a daily log of their blood pressures. I give them parameters for when to call the office and also ask them to send me their log through our patient portal every week so that I can proactively manage any hypertensive complications by up-titrating anti-hypertensives quickly. I also let my patients know ahead of time that a significant percentage of patients will need a dose reduction in their lenvatinib, and that we may need to make multiple dose reductions over time depending on how they tolerate the regimen."

Oncology Times: *Black women have worse 5-year survival rates for endometrial cancer than White women and are diagnosed at later stages. Yet, for this trial, Black women accounted for only 4 percent on the lenvatinib/pembrolizumab arm and 3.4 percent on the control arm. In terms of cancer disparities, are there any studies underway or being considered to determine whether the efficacy or toxicity of lenvatinib/pembrolizumab is influenced by race?*

Grisham: "This is a really important question to ask and highlights the obligation that we as academic physicians have to actively work to make our population of patients enrolling to clinical trials more diverse and more representative of the population in general. Historically, the population of patients enrolled to gynecologic oncology clinical trials in the United States has been overwhelmingly Caucasian. This prevents us from being able to accurately assess if race affects outcomes in a controlled prospective fashion. Clinical trial enrollment needs to be more accessible to all patients with less geographic, financial, and logistical obstacles."

Oncology Times: *Right now, the indication for this regimen is strictly for patients with advanced endometrial carcinoma that is not microsatellite instability–high (MSI-H) or mismatch repair–deficient (dMMR), who have disease progression following prior systemic therapy, and are not candidates for curative surgery or radiation. Are there other difficult-to-treat cancers where you can see potential to explore this combination?*

Grisham: "Pembrolizumab in combination with lenvatinib has been a huge advance for the treatment of endometrial cancer and I am hopeful that it will be found to offer similar benefit in other gynecologic cancers. Diseases of particular interest include clear cell ovarian cancer and endometrioid ovarian cancer, which frequently arise from endometriosis and are histologically and molecularly similar to endometrial cancer." OT

Dibash Kumar Das is a contributing writer.

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Learning Objectives for This Month's Activity:

After participating in this activity, readers should be better able to: 1. Assess the results of the Phase III KEYNOTE-775/Study 309 trial evaluating the combination of pembrolizumab plus lenvatinib for the treatment of certain patients with endometrial cancer. 2. Summarize the implications of the Phase III trial results for treatments strategies for women with gynecologic malignancies.

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