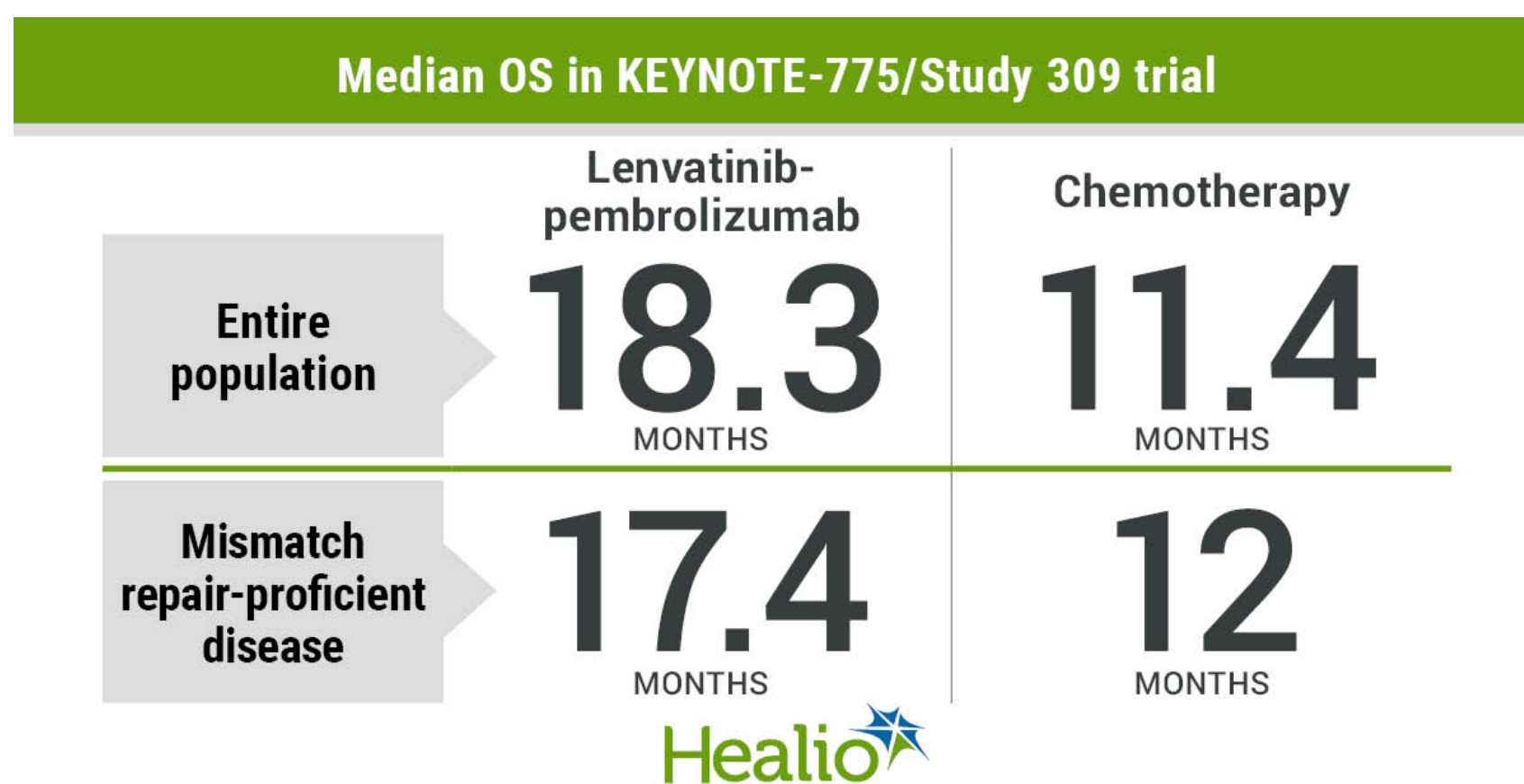


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## Lenvatinib-pembrolizumab combination extends PFS, OS in advanced endometrial cancer

Lenvatinib plus pembrolizumab improved outcomes vs. chemotherapy for women with advanced endometrial cancer, according to findings presented at the virtual Society of Gynecologic Oncology Annual Meeting on Women's Cancer.

"[The regimen conferred] statistically significant and clinically meaningful improvements in OS, PFS and objective response rate ... regardless of mismatch repair status in endometrial cancer following platinum-based chemotherapy," researcher Vicky Makker, MD, medical oncologist at Memorial Sloan Kettering Cancer Center, said during a presentation.



Data were derived from Makker V, et al. Abstract 11512. Society of Gynecologic Oncology Annual Meeting on Women's Cancer (virtual meeting); March 19-25, 2021.

The PFS and OS benefits observed in the randomized phase 3 KEYNOTE-775/Study 309 trial appeared consistent across all analyzed subgroups, including those based on histology and number of prior therapies, Makker said.

The combination also exhibited a manageable safety profile, she added.

Endometrial cancer is the most common type of gynecologic cancer in the United States.

Survival typically is poor for women diagnosed at an advanced stage or who develop recurrence — particularly those whose disease progresses after platinum-based therapy and is no longer amenable to curative surgery or radiation, Makker said.

In 2019, the FDA granted accelerated approval of the combination of lenvatinib (Lenvima, Eisai) — a multiple receptor tyrosine kinase inhibitor — and the anti-PD-1 antibody pembrolizumab (Keytruda, Merck) for treatment of women with [advanced endometrial carcinoma](#) that was not microsatellite

instability-high or mismatch repair-deficient, and who progressed after prior systemic therapy and were not candidates for curative surgery or radiation.

The confirmatory multicenter, open-label KEYNOTE-775/Study 309 trial included 827 women with advanced, metastatic or recurrent endometrial cancer who received one prior platinum-based regimen in any setting. The majority (n = 697) had mismatch repair-proficient tumors; the remainder (n = 130) had mismatch repair-deficient tumors.

Researchers randomly assigned 411 women (median age, 64 years; range 30-82) to lenvatinib dosed at 20 mg orally once daily plus pembrolizumab dosed at 200 mg via IV every 3 weeks for up to 35 cycles.

The other 416 women (median age, 65 years; range, 35-86) received physician's choice of chemotherapy. This consisted either of doxorubicin (60 mg/m<sup>2</sup> via IV every 3 weeks for a maximum cumulative dose of 500 mg/m<sup>2</sup>) or paclitaxel (80 mg/m<sup>2</sup> via IV on a 28-day cycle, administered in a 3-weeks-on, 1-week-off schedule).

PFS as assessed by blinded independent central review and OS served as dual primary endpoints. ORR assessed by blinded independent review in the all-comers population and in the subgroup of patients with mismatch repair-proficient disease served as a secondary efficacy endpoint.

Median treatment duration was 231 days (range, 1-817) with lenvatinib-pembrolizumab and 104 days (range, 1-785) with chemotherapy.

Median follow-up was 11.4 months.

In the entire cohort, results showed significant benefit with [lenvatinib-pembrolizumab](#) with regard to PFS (median, 7.2 months vs. 3.8 months; HR = 0.56; 95% CI, 0.47-0.66) and OS (median, 18.3 months vs. 11.4 months; HR = 0.62; 95% CI, 0.51-0.75).

Researchers also reported a significantly higher ORR with lenvatinib-pembrolizumab (31.9% vs. 14.7%;  $P < .0001$ ), with higher rates of complete response (6.6% vs. 2.6%) and partial response (25.3% vs. 12%).

Median duration of response was 14.4 months with the combination vs. 5.7 months with chemotherapy.

Researchers reported similar results among women with mismatch repair-proficient disease.

In this subgroup, women assigned lenvatinib-pembrolizumab achieved longer median PFS (6.6 months vs. 3.8 months; HR = 0.6; 95% CI, 0.5-0.72) and longer median OS (17.4 months vs. 12 months; HR = 0.68; 95% CI, 0.56-0.84). They also were twice as likely to respond to treatment (30.3% vs. 15.1%;  $P < .0001$ ), achieve complete response (5.2% vs. 2.6%) or achieve partial response (25.1% vs. 12.5%).

Median duration of response in the mismatch repair-proficient subgroup also favored lenvatinib-pembrolizumab (9.2 months vs. 5.7 months).

The safety profile of the lenvatinib-pembrolizumab combination appeared consistent with the established profiles of each agent as monotherapy.

In the entire cohort, the most common any-grade treatment-emergent adverse events among women 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%).

The most common any-grade treatment-emergent adverse events in the chemotherapy group included anemia (48.7%), nausea (46.1%), neutropenia (33.8%), alopecia (30.9%) and fatigue (27.6%).

Among women assigned the combination, treatment-emergent adverse events prompted 30.8% to discontinue lenvatinib, 18.7% to discontinue pembrolizumab and 14% to discontinue both agents. Eight percent of women assigned chemotherapy discontinued treatment due to adverse events.

Researchers 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.

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### PERSPECTIVE



#### Ursula Matulonis, MD

Nearly 67,000 new cases of endometrial cancer will be diagnosed in the United States in 2021. Incidence has increased by about a 1% per year, driven by nonendometrioid subtypes.

There has been a paucity of drug approvals for endometrial cancer. Prior to the 2019 accelerated approval of pembrolizumab-lenvatinib, the last and only FDA approval for endometrial cancer came in 1971.

Was single-agent doxorubicin or paclitaxel the appropriate choice for a control arm? Other agents could have been used, such as endocrine therapy for ER-positive cancers, single-agent pembrolizumab for mismatch repair-deficient tumors, or the reuse of platinum. There also are emerging control-arm agents, such as CDK 4/6 inhibitors for ER-positive cancers or novel agents such as the WEE1 inhibitor adavosertib (AZD1775, AstraZeneca) for serous carcinomas.

Previous phase 3 trials showed that for single-agent doxorubicin or weekly paclitaxel, response rates are up to 25% or 27%, but there seems to be a lower overall response rate in the single-agent chemotherapy control arm in KEYNOTE-775. Future clinical trial designs will need to take into account molecularly targeted therapies as controls that are appropriate for specific histologies and their genetics.

How do we mitigate toxicities, and what is the optimal dose of lenvatinib? A previous phase 1B/phase 2 study established the dose of 20 mg lenvatinib combined with pembrolizumab. The trial started with 24 mg lenvatinib and found this dose too high; other doses below 20 mg were not explored.

In KEYNOTE-775, 66% of patients required dose reductions of lenvatinib, 59% required dose hold or interruption, and 31% of patients discontinued lenvatinib because of toxicities. For other cancers, other FDA-approved lenvatinib doses are used. For example, in hepatocellular cancer, there is a weight-based dosing that uses either 12 mg or 8 mg based on weight.

Black women are diagnosed at later stages than white women and have worse 5-year survival rates for endometrial cancer. Only 4% of women on the pembrolizumab-lenvatinib arm and 3.4% on the control arm were Black. There is a need to diversify accrual of future trials that will help answer important questions, such as whether the efficacy or toxicity of pembrolizumab-lenvatinib is influenced by race.

The results of this trial are indeed practice-changing for mismatch repair-proficient endometrial cancer. However, pembrolizumab remains the standard of care for recurrent mismatch repair-deficient endometrial cancer. The toxicities of this combination are significant. I strongly recommend studying lenvatinib dosing based on factors such as weight, performance status or comorbidities. Clinicians need objective criteria on how to select appropriate lenvatinib starting doses in order to safely and effectively treat patients.

This really represents the start of a new era in endometrial cancer drug development and improved patient outcomes.

**References:**

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**Disclosures:** Matulonis reports consultant roles with Merck, NextCure and Novartis, as well as a data safety monitoring board role with Advaxis.

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