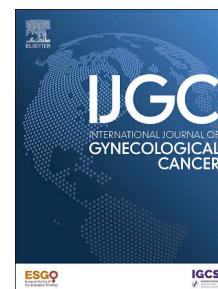


First-line lenvatinib plus pembrolizumab versus chemotherapy for advanced endometrial cancer: 1-Year follow-up after final analysis of the ENGOT-en9/LEAP-001 phase 3 trial



Christian Marth^{a,b,*}, Richard G. Moore^c, Mariusz Bidziński^{d,e}, Vanda Salutarì^{f,g}, Özden Altundag^{h,i}, Maria Jesús Rubio^{j,k}, Tally Levy^{l,m}, Alison Stillieⁿ, Christof Vulsteke^{o,p}, Ralf Witteler^{q,r}, Kazuya Ariyoshi^s, Xiaohua Wu^t, Sophia Frentzas^u, André Mattar^v, Brian M. Slomovitz^{w,x}, Stephanie Lheureux^y, Xiaojun Chen^z, Kosei Hasegawa^{aa}, Manuel Magallanes^{ab}, Chel Hun Choi^{ac}, Mariia Shalkova^{ad}, Diego Lucas Kaen^{ae}, Karen Cadoo^{af}, Lili Yao^{ag}, Jodi McKenzie^{ah}, Chinyere E. Okpara^{ai}, Robin Meng^{aj}, Robert Orlowski^{ak}, Lucy Gilbert^{al}, Vicky Makker^{am}

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ABSTRACT

Objective: The phase 3 ENGOT-en9/LEAP-001 trial (NCT03884101) comparing first-line lenvatinib+ pembrolizumab with carboplatin+ paclitaxel did not meet pre-specified statistical criteria for overall survival or progression-free survival in participants with advanced/recurrent endometrial cancer. We report results after an additional year of follow-up (overall median 54.5 [range; 46.5–69.0] months).

Methods: Eligible participants were adult females with stage III to IV or recurrent, histologically confirmed endometrial cancer. Measurable or non-measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and radiographically apparent disease per blinded independent central review was required. Participants were randomly allocated 1:1 to lenvatinib+ pembrolizumab or chemotherapy (paclitaxel+ carboplatin). The primary end points were overall survival and progression-free survival per RECIST version 1.1 by blinded independent central review. Secondary end points included objective response rate per RECIST version 1.1 by blinded independent central review and safety.

Results: The median overall survival (95% confidence interval [CI]) was 30.9 (range; 25.4–37.6) months with lenvatinib+ pembrolizumab versus 29.4 (range; 26.2–34.8) months with chemotherapy in mismatch repair–proficient endometrial cancer (hazard ratio [HR] 0.99, 95% CI 0.82 to 1.21), 37.9 (range; 32.2–43.0) versus 32.3 (range; 27.2–35.7) months in all-comers (HR 0.91, 95% CI 0.77 to 1.09), and not reached in either treatment group in mismatch repair–deficient endometrial cancer (HR 0.60, 95% CI 0.39 to 0.93). Corresponding results for progression-free survival were 9.6 (range; 8.2–11.9) versus 10.2 (range; 8.4–10.5) months (HR 1.01, 95% CI 0.83 to 1.22), 12.5 (range; 10.3–15.1) versus 10.2 (range; 8.4–10.4) months (HR 0.92, 95% CI 0.77 to 1.10), and 31.8 (22.5 to not reached) versus 9.0 (range; 8.2–17.1) months (HR 0.62, 95% CI 0.41–0.93). Objective response rates were 50.6% versus 54.7%, 55.7% versus 55.5%, and 72.0% versus 58.0%, respectively. No new safety signals were identified. The results were consistent with those at the final analysis.

Conclusions: The mismatch repair–proficient, all-comer, and mismatch repair–deficient populations continued to demonstrate antitumor activity for lenvatinib+ pembrolizumab after an additional year of follow-up. These results should be interpreted with caution due to the exploratory nature of the analysis. Trial registration: [ClinicalTrials.gov](https://clinicaltrials.gov) No. NCT03884101.

Keywords:

Endometrial Cancer; Chemotherapy; Lenvatinib; Pembrolizumab

WHAT IS ALREADY KNOWN ON THIS TOPIC

The phase 3 ENGOT-en9/LEAP-001 trial compared first-line lenvatinib plus pembrolizumab (lenvatinib+ pembrolizumab) versus carboplatin+ paclitaxel in participants with advanced endometrial cancer. The trial did not meet the pre-specified statistical criteria for the primary end points of overall survival or progression-free survival. We report the results after an additional year of follow-up.

WHAT THIS STUDY ADDS

In mismatch repair–proficient endometrial cancer, overall survival, progression-free survival, progression-free survival on next-line of therapy, and response rates were similar between lenvatinib+ pembrolizumab and chemotherapy, with a numerically longer median duration of response in the lenvatinib+ pembrolizumab group. In mismatch repair–deficient endometrial cancer, efficacy numerically favored lenvatinib+ pembrolizumab across all end points. There were no new safety signals with longer follow-up. Overall, the results were consistent with those at the final analysis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

Although the ENGOT-en9/LEAP-001 trial did not meet its primary end points, participants with advanced endometrial cancer continued to demonstrate antitumor activity for lenvatinib+ pembrolizumab after an additional year of follow-up.

* Correspondence to Dr Christian Marth, Department for Gynecology and Obstetrics, Medical University of Innsbruck, Anichstr. 35, 6020 Innsbruck, Austria; christian.marth@tirol-kliniken.at (C. Marth)

INTRODUCTION

The phase 3 ENGOT-en9/LEAP-001 trial compared first-line lenvatinib+pembrolizumab with carboplatin+paclitaxel for the treatment of advanced endometrial cancer.¹ The trial did not meet the pre-specified statistical criteria for improvement in the primary end points of overall survival or progression-free survival. However, a longer duration of response was observed with lenvatinib+pembrolizumab.² No new safety signals were identified compared with previous data for lenvatinib+pembrolizumab and the chemotherapy combination.³⁻⁶ The safety profile of lenvatinib+pembrolizumab was consistent, regardless of mismatch repair status.² We report the results after an additional year of follow-up.

METHODS

The methods for ENGOT-en9/LEAP-001 (ClinicalTrials.gov, NCT03884101) were previously described¹ and are detailed in the online protocol. Participants were adult females with stage III to IV or recurrent, histologically confirmed endometrial cancer. Measurable or non-measurable disease per RECIST version 1.1 and radiographically apparent disease per blinded independent central review were required.

Participants were randomly allocated 1:1 to lenvatinib 20 mg orally once daily plus pembrolizumab 200 mg intra-venously every 3 weeks or paclitaxel 175 mg/m²

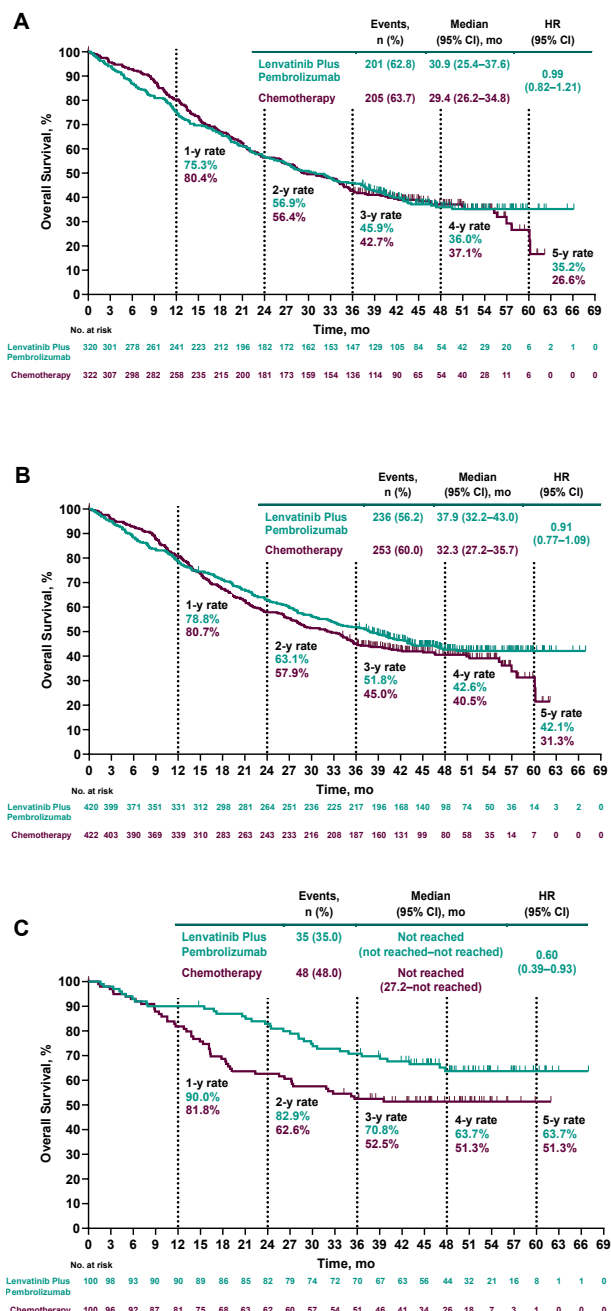


Figure 1 Efficacy and response. Overall survival in the (A) pMMR, (B) all-comer, and (C) dMMR populations. CI, confidence interval; dMMR, mismatch repair–deficient; HR, hazard ratio; pMMR, mismatch repair–proficient.

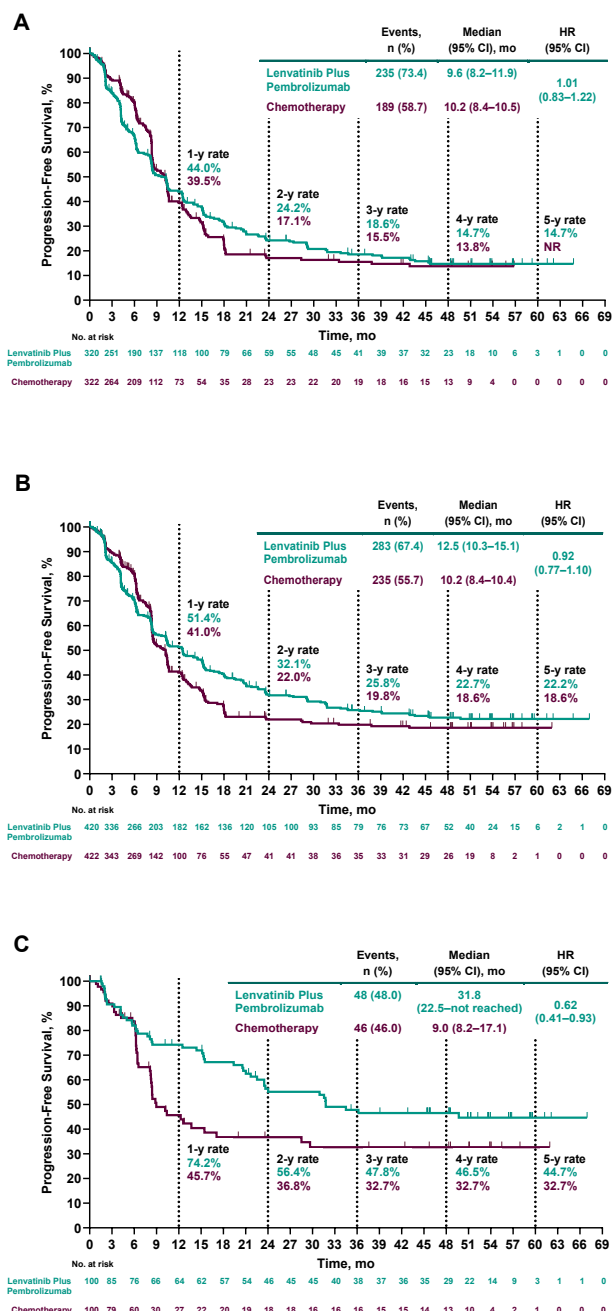


Figure 2 Progression-free survival per RECIST version 1.1 by blinded independent central review in the (A) pMMR, (B) all-comer, and (C) dMMR populations. CI, confidence interval; dMMR, mismatch repair–deficient; HR, hazard ratio; pMMR, mismatch repair–proficient; RECIST, Response Evaluation Criteria in Solid Tumors.

plus carboplatin area under the concentration–time curve 6 mg/mL/min every 3 weeks. Participants received ≤ 35 cycles of pembrolizumab; lenvatinib treatment could continue after discontinuation of pembrolizumab. Participants received ≤ 7 cycles of paclitaxel–carboplatin; those with ongoing clinical benefit could continue beyond 7 cycles after sponsor consultation. Treatment continued for the specified duration or until progressive disease, unacceptable toxicity, or withdrawal of consent.

Participants in the lenvatinib+pembrolizumab group who achieved stable disease or better and stopped pembrolizumab treatment after completing 35 infusions for reasons other than disease progression or intolerance or those who achieved a complete response and stopped pembrolizumab treatment after ≥ 8 infusions (≥ 2 after the complete response was achieved) may be eligible for a second course (an additional 17 cycles of pembrolizumab, with or without lenvatinib) after experiencing disease progression.

The protocol was approved by an institutional review board/ethics committee at each institution. All participants provided written informed consent.

Primary end points were overall survival and progression-free survival per RECIST version 1.1 by blinded independent central review. Secondary end points included objective response rate per RECIST version 1.1 by blinded independent central review and safety. Duration of response and progression-free survival 2 (time from randomization to investigator-assessed progressive disease on next line of treatment or death, whichever occurred first) were exploratory end points.

Mismatch repair status was assessed at a central laboratory (Neogenomics) by immunohistochemistry (VENTANA MMR RxDx Panel, Ventana) using archived tumor tissue or a fresh biopsy before randomization. The VENTANA anti-MLH1 (clone M1, mouse), anti-PMS2 (clone A16-4, mouse), anti-MSH2 (clone G219-1129, mouse), and anti-MSH6 (clone SP93, rabbit) monoclonal primary antibodies were used for immunohistochemical staining. The presence of staining for all mismatch repair protein markers (MLH1, PMS2, MSH2, and MSH6) in the tumor sample indicated mismatch repair–proficient status, and absence of staining in any mismatch repair protein marker indicated mismatch repair–deficient status.

Efficacy was assessed in all randomly allocated participants (intention-to-treat) and safety in all randomized and treated participants. Overall survival, progression-free survival, progression-free survival 2, and duration of response were evaluated using the Kaplan-Meier method. Hazard ratios (HRs) and 95% confidence intervals (CIs) for overall

survival, progression-free survival, and progression-free survival 2 were based on a Cox regression model, with the Efron method of tie handling and treatment as a co-variate; stratified models were applied to the mismatch repair–proficient and all-comer populations. No alpha was assigned to this analysis.

In accordance with the journal's guidelines, we will provide our data for independent analysis by a team selected by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

RESULTS

Overall, 842 participants were randomly allocated to lenvatinib+pembrolizumab ($n = 420$) or chemotherapy ($n = 422$); 642 had mismatch repair–proficient and 200 had mismatch repair–deficient tumors (Fig. S1). The median time from randomization to data cutoff (February 5, 2025) was 54.5 (range; 46.6–69.0) and 54.6 (range; 46.5–68.8) months in the lenvatinib+pembrolizumab and chemotherapy groups, respectively. Demographics/baseline disease characteristics were similar between the treatment groups (Table S1).

Efficacy outcomes at interim analysis 2, final analysis, and after an additional year of follow-up (ie, current analysis) are summarized in Table S2. In the current analysis, 406 participants (63.2%) with mismatch repair–proficient endometrial cancer had died, with a median overall survival (95% CI) of 30.9 (range; 25.4–37.6) months in the lenvatinib+pembrolizumab group versus 29.4 (range; 26.2–34.8) months in the chemotherapy group (HR 0.99, 95% CI 0.82 to 1.21; Fig. 1A). Among all-comers, 489 participants (58.1%) had died, with median overall survival (95% CI) of 37.9 (range; 32.2–43.0) versus 32.3 (range; 27.2–35.7) months (HR 0.91, 95% CI 0.77 to 1.09; Fig. 1B). In mismatch repair–deficient endometrial cancer, 83 participants (41.5%) had died, with median overall survival not reached in either group (HR 0.60, 95% CI 0.39 to 0.93; Fig. 1C). The HRs for overall survival favored lenvatinib+pembrolizumab across most sub-groups in mismatch repair–deficient endometrial cancer (Fig. S2A–C).

In mismatch repair–proficient endometrial cancer, 424 participants (66.0%) experienced a progression-free survival event, with median progression-free survival (95% CI) of 9.6 (range; 8.2–11.9) months in the lenvatinib+pembrolizumab group versus 10.2 (range; 8.4–10.5) months in the chemotherapy group (HR 1.01,

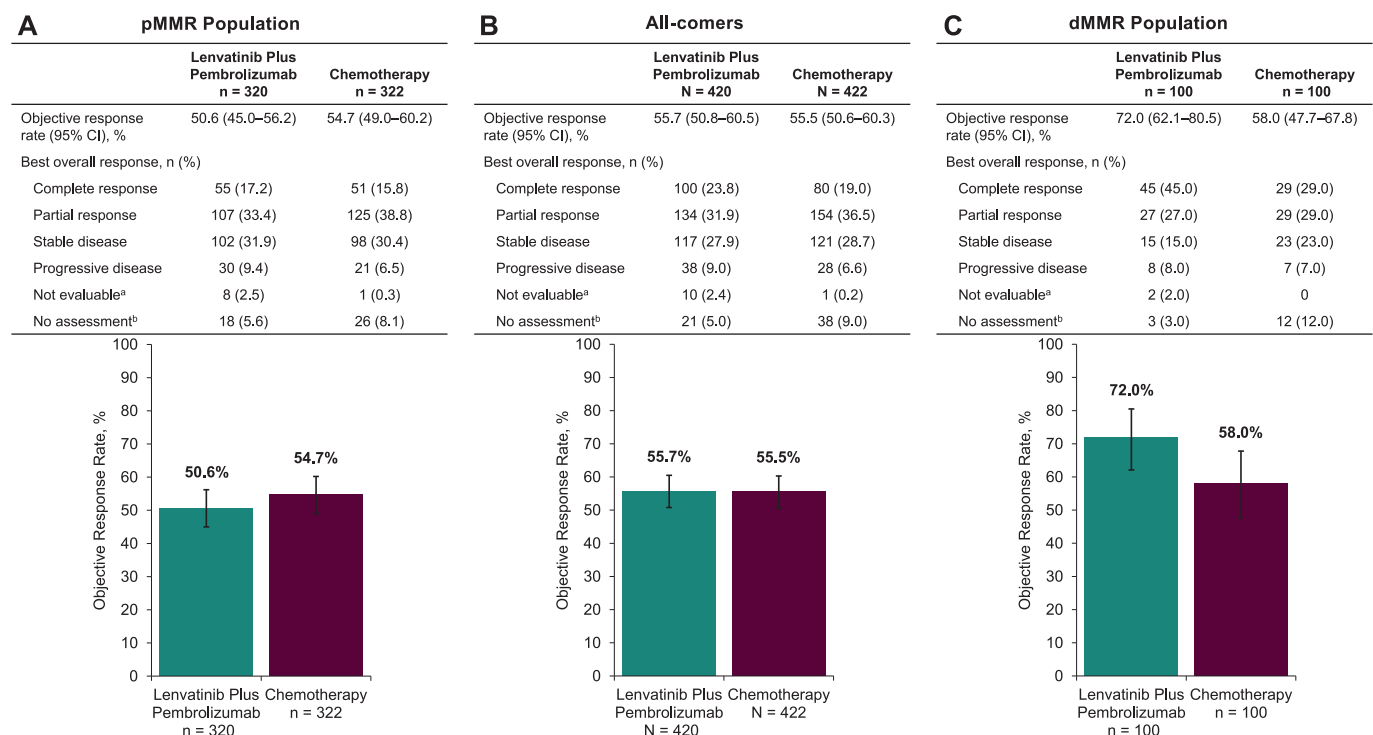


Figure 3 Objective response rate per RECIST version 1.1 by blinded independent central review in the (A) pMMR, (B) all-comer, and (C) dMMR populations.

^aPost-baseline assessment(s) available but not evaluable.

^bNo post-baseline assessment available for response evaluation.

dMMR, mismatch repair–deficient; pMMR, mismatch repair–proficient; RECIST, Response Evaluation Criteria in Solid Tumors.

95% CI 0.83 to 1.22; Fig. 2A). Among all-comers, 518 participants (61.5%) experienced a progression-free survival event, with median progression-free survival (95% CI) of 12.5 (range; 10.3-15.1) versus 10.2 (range; 8.4-10.4) months (HR 0.92, 95% CI 0.77 to 1.10; Fig. 2B). In mismatch repair–deficient endometrial cancer, 94 participants (47.0%) experienced a progression-free survival event, with median progression-free survival (95% CI) of 31.8 (22.5 to not reached) versus 9.0 (range; 8.2-17.1) months (HR 0.62, 95% CI 0.41 to 0.93; Fig. 2C). The HRs for progression-free survival favored lenvatinib+pembrolizumab across most subgroups in mismatch repair–deficient endometrial cancer (Fig. S2D-F). Progression-free survival 2 results were similar between treatment groups in mismatch repair–proficient endometrial cancer but favored lenvatinib+pembrolizumab in mismatch repair–deficient endometrial cancer (Fig. S3A-C).

The response rates were similar between treatment groups in mismatch repair–proficient endometrial cancer (50.6% vs 54.7% in the lenvatinib+pembrolizumab vs chemotherapy groups) and all-comers (55.7% vs 55.5%) and numerically higher for lenvatinib+pembrolizumab in mismatch repair–deficient endometrial cancer (72.0% vs 58.0%; Fig. 3A-C). The median duration of response was numerically longer for lenvatinib+pembrolizumab across all 3 populations (Fig. 4A-C). In the lenvatinib+pembrolizumab group, 92.6% and 95.9% of participants with mismatch repair–proficient and mismatch repair–deficient endometrial cancer, respectively, had a reduction from baseline in target lesion size (Fig. S4A and S4B). The duration of response for mismatch repair–proficient and mismatch repair–deficient responders treated with lenvatinib+pembrolizumab are shown in Figure S5A and S5B. The median time to a complete or partial response in all-comers was 2.1 months in both treatment groups. The treatment duration and time to response in all-comers treated with pembrolizumab for 35 cycles in the first course are shown in Figure S6. Of the 17 participants who received a second course of pembrolizumab with or without lenvatinib, best overall responses by blinded independent central review in the 5 participants with assessment during the second course were partial response ($n = 1$), stable disease ($n = 3$), and progressive disease ($n = 1$; Fig. S7); the remaining participants ($n = 12$) had no assessment because it was not required by protocol. In terms of disposition, 2 completed second-course treatment and 15 discontinued second-course treatment due to progressive disease ($n = 10$), study termination ($n = 2$), physician decision ($n = 1$), participant withdrawal ($n = 1$), and initiation of non-study anti-cancer therapy ($n = 1$).

Safety outcomes at the final analysis and after an additional year of follow-up are summarized in Table S2. Drug exposure and lenvatinib dose reductions are provided in Tables S3 to S5. The most frequent adverse events leading to lenvatinib dose reductions were hypertension (18.1%) and proteinuria (11.7%; Table S6). Adverse events led to interruption of any treatment in 74.3% and 41.1% of participants in the lenvatinib+pembrolizumab and chemotherapy groups, respectively, (Table S7) and discontinuation of any treatment in 48.3% and 19.5% (Table S8). Adverse events of interest and dose management in the lenvatinib+pembrolizumab group are summarized in Figure S8. The rate of exposure-adjusted adverse events was 141.0 and 220.4 events per 100 person-months of exposure in the lenvatinib+pembrolizumab and chemotherapy groups, respectively (Table S9). Serious adverse events occurred in 54.8% and 20.4% of participants, respectively (Table S10).

Most participants in the lenvatinib+pembrolizumab and chemotherapy groups (97.9% and 96.8%, respectively) experienced treatment-related adverse events (Fig. 5). The most frequent treatment-related adverse events were hypertension (62.6%) and hypothyroidism (58.6%) in the lenvatinib+pembrolizumab group and alopecia (52.6%) and anemia (48.2%) in the chemotherapy group. Adverse events of special interest for pembrolizumab are summarized in Table S11. The majority of participants in the lenvatinib+pembrolizumab group (96.0%) experienced clinically significant adverse events for lenvatinib (based on a list of terms specified by the sponsor and considered regardless of attribution by investigators; Table S12). In the lenvatinib+pembrolizumab group, 65.5% of participants experienced grade 3 to 5 clinically significant adverse events for lenvatinib, with 2.9% resulting in death. Subsequent anti-cancer treatment for eligible participants is summarized in Table S13.

DISCUSSION

Summary of Main Results

After an additional year of follow-up, participants with mismatch repair–proficient endometrial cancer demonstrated similar overall survival, progression-free survival, progression-free survival 2, and objective response rates between the lenvatinib+pembrolizumab and carboplatin+paclitaxel groups, with a numerically longer

median duration of response among responders treated with lenvatinib+pembrolizumab. In mismatch repair–deficient endometrial cancer, the HRs were <1 in favor of lenvatinib+pembrolizumab for overall survival, progression-free survival, and progression-free survival 2, with 95% CIs that did not cross 1. In addition, in mismatch repair–deficient endometrial cancer, the response rate continued to be 14% higher with lenvatinib+pembrolizumab than with chemotherapy, and the median duration of response was still not reached among responders treated with lenvatinib+pembrolizumab. These results were seen despite a greater use of subsequent systemic anti-cancer therapy in the chemotherapy group in the mismatch repair–proficient and mismatch repair–deficient populations, including subsequent receipt of lenvatinib+pembrolizumab and programmed cell death protein 1 (PD-1) or programmed cell death ligand 1 checkpoint inhibitors. Notably, lenvatinib+pembrolizumab showed a longer progression-free survival in participants with previous neoadjuvant or adjuvant chemotherapy, and participants with a longer platinum-free interval were those with the greatest numerical benefit.

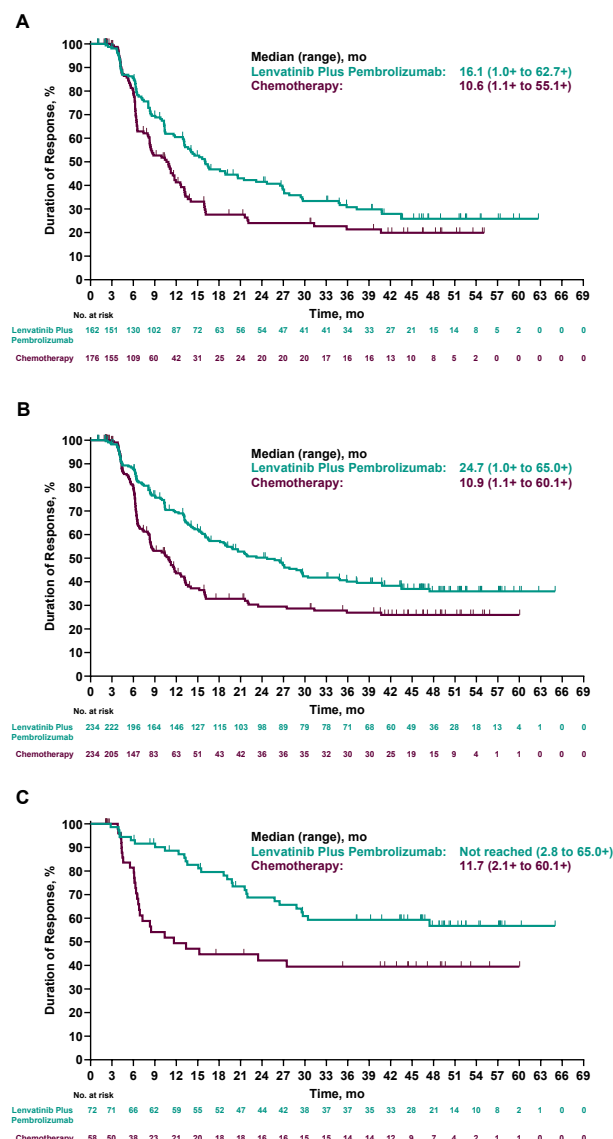


Figure 4 Duration of response per RECIST version 1.1 by blinded independent central review in the (A) pMMR, (B) all-comer, and (C) dMMR populations.

+, no disease progression by the time of the last disease assessment; dMMR, mismatch repair–deficient; pMMR, mismatch repair–proficient; RECIST, Response Evaluation Criteria in Solid Tumors.

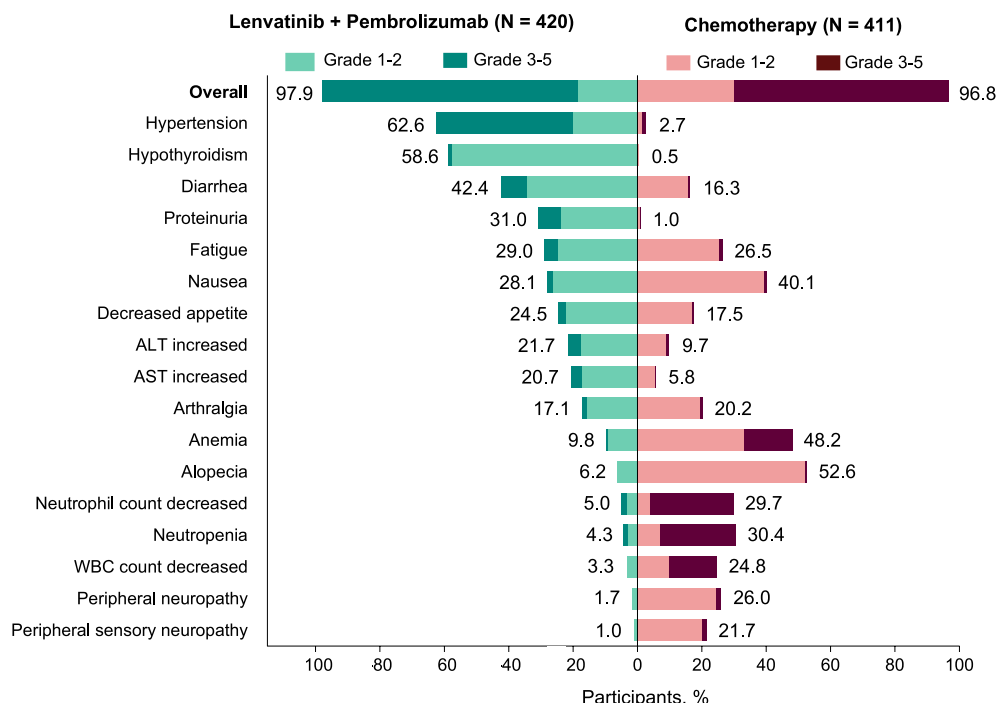


Figure 5 Tornado plot of the most frequent treatment-related adverse events ($\geq 20\%$ in either treatment group) in all participants in the safety analysis population.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell.

Results in the Context of Published Literature

Overall, results after an additional year of follow-up in the ENGOT-en9/LEAP-001 trial were consistent with those at final analysis.² No new safety signals were identified with longer follow-up,²⁻⁶ and the safety profile of lenvatinib+pembrolizumab was consistent, regardless of mismatch repair status. At the time the ENGOT-en9/LEAP-001 trial was initiated, standard of care for first-line treatment of advanced endometrial cancer was paclitaxel-carboplatin, which had been established based on results from the GOG209 study.⁷ However, after the completion of enrollment for the ENGOT-en9/LEAP-001 trial (March 25, 2021), results from the phase III NRG-GY018⁸ and RUBY⁹ trials of anti-PD-1 monoclonal antibodies pembrolizumab and dostarlimab in combination with chemotherapy became available. Subsequently, treatment guidelines for endometrial cancer were updated with revised recommendations for chemotherapy-based regimens, including combination chemotherapy plus immunotherapy, which are now the standard treatment approach for first-line therapy for patients with inoperable stage III to IV or recurrent endometrial cancer.¹⁰

Several first-line studies have recently read out positive with treatments that incorporated anti-PD-L1 therapy, with or without a poly(adenosine diphosphate-ribose) inhibitor, to standard-of-care chemotherapy (NRG-GY018,⁸ RUBY,⁹ and DUO-E¹¹). ENGOT-en9/LEAP-001 was a replacement rather than add-on treatment study and, therefore, faced a higher bar to show a meaningful improvement to an active comparator in paclitaxel-carboplatin. Notably, the antitumor effect with the combination of lenvatinib+pembrolizumab was substantially higher than would be expected with either given as monotherapy. In the second-line setting, lenvatinib has demonstrated an objective response rate of $\sim 15\%$ in the overall population (Study 204¹²) and pembrolizumab had an objective response rate of $\sim 10\%$ in the mismatch repair-proficient population (KEYNOTE-158¹³). An objective response rate of $>50\%$ and a duration of response of 16.1 months in the mismatch repair-proficient population in ENGOT-en9/LEAP-001 suggests potentiated activity when pembrolizumab and lenvatinib are used together. In the mismatch repair-deficient sub-group, pembrolizumab is expected to have substantial activity. However, it is notable that the early Kaplan-Meier curves for progression-free survival in ENGOT-en9/LEAP-001 are overlapping compared with another pembrolizumab monotherapy versus chemotherapy study in micro-satellite instability-high/mismatch repair-deficient colorectal cancer (KEYNOTE-177¹⁴), where the Kaplan-Meier curves initially favor chemotherapy due to the delayed effect of

immunotherapy. This suggests potential benefit for the lenvatinib component of the regimen. KEYNOTE-C93 (NCT05173987) will provide further information regarding pembrolizumab monotherapy benefit in first-line mismatch repair-deficient endometrial cancer in the future.

Strengths and Weaknesses

The ENGOT-en9/LEAP-001 trial was a phase 3 randomized controlled trial that compared a novel combination treatment strategy with the standard of care. No alpha was assigned to these long-term follow-up analyses that were exploratory, and, thus, the results should be interpreted with caution. In addition, because these analyses were exploratory, the findings are, therefore, best viewed as hypothesis-generating rather than confirmatory and may not be generalizable beyond the trial sample.

Implications for Practice and Future Research

The trial did not meet its primary end points for improvements in overall survival or progression-free survival in mismatch repair-proficient and all-comers populations²; however, the mismatch repair-proficient, all-comer, and mismatch repair-deficient populations continued to demonstrate antitumor activity with lenvatinib+pembrolizumab.

CONCLUSIONS

In this exploratory analysis of the ENGOT-en9/LEAP-001 trial in participants with advanced or recurrent endometrial cancer, first-line lenvatinib+pembrolizumab compared with paclitaxel-carboplatin was associated with similar overall survival, progression-free survival, and progression-free survival 2 in the mismatch repair-proficient and all-comer populations and improvement in the mismatch repair-deficient population after an additional year of follow-up. The median duration of response was numerically higher with lenvatinib+pembrolizumab in all 3 populations. There were no new safety signals, although there were more treatment interruptions and discontinuations due to adverse events in participants randomly allocated to lenvatinib+pembrolizumab. These results should be viewed as hypothesis-generating and interpreted with caution due to the exploratory nature of the analysis.

Author Affiliations

- ^aMedical University of Innsbruck, Department for Gynecology and Obstetrics, Innsbruck, Austria
- ^bAGO, Innsbruck, Austria
- ^cUniversity of Rochester, Wilmot Cancer Institute, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Rochester, NY, USA
- ^dPaństwowy Instytut Badawczy, Narodowy Instytut Onkologii im M Skłodowskiej – Curie, Department of Gynecological Oncology, Warszawa, Poland
- ^ePGOG, Warsaw, Poland
- ^fDepartment of Women, Children and Public Health Sciences, Gynecologic Oncology Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
- ^gMITO, Rome, Italy
- ^hBaşkent University Hospital, Medical Oncology, Ankara, Turkey
- ⁱTRSGO, Istanbul, Turkey
- ^jH. Reina Sofía de Córdoba, Córdoba, Spain
- ^kGEICO, Madrid, Spain
- ^lWolfson Medical Centre, Holon, Israel
- ^mISGO, Israel
- ⁿWestern General Hospital, Edinburgh Cancer Centre, CTG UK and Clinical Oncology, Edinburgh, UK
- ^oIntegrated Cancer Center Ghent, AZ Maria Middelaers, Ghent, Belgium
- ^pCenter for Oncological Research, Antwerp University, Antwerp, Belgium
- ^qUniversitätsklinikum Münster, Klinik für Frauenheilkunde und Geburtshilfe, Münster, Germany
- ^rNOGGO, Berlin, Germany
- ^sNational Hospital Organization Kyushu Cancer Center, Gynecology Service, Fukuoka, Japan
- ^tFudan University Shanghai Cancer Center, Department of Gynecologic Oncology, Shanghai, China
- ^uMonash Health & Monash University, Department of Medical Oncology, Melbourne, VIC, Australia
- ^vHospital da Mulher, Oncology, São Paulo, Brazil
- ^wMount Sinai Medical Center, Division of Gynecologic Oncology, Miami Beach, FL, USA
- ^xGOG Foundation, Philadelphia, PA, USA
- ^yPrincess Margaret Cancer Centre, Toronto, Ontario, Canada
- ^zFudan University, Obstetrics and Gynecology Hospital, Shanghai, China
- ^{aa}Saitama Medical University International Medical Center, Department of Gynecologic Oncology, Hidaka, Saitama, Japan
- ^{ab}Hospital Diomed, Mexico City, Mexico
- ^{ac}Samsung Medical Center, Sungkyunkwan University Seoul, Republic of Korea
- ^{ad}Communal Non-Profit Enterprise Regional Center of Oncology, Kharkiv, Ukraine
- ^{ae}Centro Oncologico Riojano Integral and National University of La Rioja, La Rioja, Argentina
- ^{af}Cancer Trials Ireland, St James's Hospital Dublin, Trinity St James's Cancer Institute, Trinity College Dublin, Dublin, Ireland
- ^{ag}Merck & Co., Inc., Rahway, NJ, USA
- ^{ah}Eisai Inc., Nutley, NJ, USA
- ^{ai}Eisai Ltd., Hatfield, UK
- ^{aj}Division of Gynecologic Oncology, Research Institute of the McGill University Health Centre, Gerald Bronfman Department of Oncology, McGill University, Montreal, QC, Canada
- ^{ak}Weill Cornell Medical College, Memorial Sloan Kettering Cancer Center, Gynecologic Medical Oncology Service, New York, NY, USA

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Author Contributions All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: CM, CV, XW, KH, MM, JM, RO. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: CM, CV, KH, MM, JM, RO, VM. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: LY. Administrative, technical, or material support: CM, RGM, MB, SF, SL, XC, KC. Supervision: CM.

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RGM: consulting or advisory role for Fujirebio Diagnostics Inc.

MB: None declared.

VS: Advisory boards for MSD, GSK, AbbVie, Menarini, Eisai, and AstraZeneca; invited speaker for MSD, GSK, AbbVie, Menarini, Eisai, AstraZeneca, and pharma; principal investigator for MSD, GSK, AstraZeneca, and AbbVie.

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AM: Employment, leadership, and stock ownership for Novo Nordisk; honoraria from DASA; consulting or advisory role for Lilly, AstraZeneca, Roche, Novartis, Fleury Group, Exact Sciences, and MSD Oncology; speakers bureau for Exact Sciences and Novartis; travel, accommodations, and expenses from Roche and MSD Oncology; other relationships with Genomic Health and Roche.

BMS: Consulting or advisory role for Seagen, AstraZeneca, MSD, Novocure, Aadi Biosciences, Regeneron, Immunocore, Gilead, Eisai, Genmab, Karyopharm, Beigene USA, Incyte, Daiichi Sankyo, GSK, and GOG Foundation.

SL: Honoraria from AstraZeneca, MSD, GSK, Roche/Genentech, and Eisai; consulting or advisory role for AstraZeneca, MSD, GSK, Shattuck Labs, Eisai, Roche/Genentech, Zai Lab, Repare Therapeutics, Seagen, Regeneron, Lilly, and AbbVie; research funding (all to institution) from AstraZeneca, Roche/Genentech, Regeneron, MSD, GSK, Schrodinger, Third Arc Bio, and Repare Therapeutics.

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Data Sharing Statement Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: <https://externaldatasharing-msd.com/>) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country- or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and

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