



**LENVIMA® ▼ (LENVATINIB) PLUS KEYTRUDA® ▼ (PEMBROLIZUMAB) COMBINATION
SHOWS ANTI-TUMOUR ACTIVITY IN ADVANCED ENDOMETRIAL CANCER
IRRESPECTIVE OF BIOMARKER STATUS**

**Final results from the endometrial cohort of KEYNOTE-146/Study 111 presented today at
the ESMO 2019 Congress**

HATFIELD, ENGLAND & Kenilworth, NJ, Sept. 29, 2019 – Eisai and Merck, Co., Inc., Kenilworth, N.J., U.S.A. (known as MSD outside the U.S.A. and Canada), today announced the final results from KEYNOTE-146/Study 111 evaluating lenvatinib, an oral receptor tyrosine kinase (RTK) inhibitor discovered by Eisai, plus pembrolizumab, Merck’s anti-PD-1 therapy, in a subset of patients with advanced endometrial cancer. The study demonstrated that the combination had an anti-tumour effect in patients with advanced endometrial cancer who received at least one prior therapy, irrespective of the biomarker status of their cancer.¹ The findings are being presented today in an proffered paper presentation (Abstract #994O) at the European Society for Medical Oncology (ESMO) 2019 Congress.¹

Data showed an objective response rate (ORR) at week 24 of 38.0% (95% CI: 28.8, 47.8) in the total study population (N=108), as assessed by investigators per immune-related Response Evaluation Criteria in Solid Tumors (irRECIST). In patients whose cancer was not microsatellite instability-high (MSI-H) or mismatch-repair deficient (dMMR) (N=94), genetic pre-dispositions that contribute to resistance to standard therapies, the ORR at week 24 was consistent with the wider study population at 36.2% (95% CI: 26.5, 46.7).¹ In patients whose tumours were MSI-H or dMMR (N=11) ORR at week 24 was 63.6% (95% CI: 30.8, 89.1). The overall safety profile of lenvatinib plus pembrolizumab was similar to previously reported profiles of each monotherapy. Incidence of hypothyroidism in this study was higher than previously reported profiles of each monotherapy.¹

“The results of this pembrolizumab plus lenvatinib study are a welcome development in the treatment of patients with advanced endometrial cancer, a patient group with an unmet medical need,” said Dr. Vicky Makker, principal investigator and medical oncologist, Memorial Sloan Kettering Cancer Center.

“Eisai is dedicated to finding effective treatments for multiple tumour types and our strategic collaboration with Merck has given us an opportunity to help even more people with cancer across the world”, said Pam Ganju PhD, VP Oncology Marketing, EMEA. “We look forward to continuing our research to realise the full potential of this combination in other cancer types.”

The overall ORR data in patients whose tumours were not MSI-H or dMMR (N=94), as assessed by independent imaging review (IIR) per RECIST version 1.1, served as the basis for the approval of this combination in the U.S., Canada, and Australia earlier this month for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation. Continued approval for this indication, including submission to the

European Medicines Agency, may be contingent upon verification and description of clinical benefit in the confirmatory trial.²

Endometrial cancer is the sixth most commonly occurring cancer in women, accounting for more than one in 20 female cancers in Europe, and the incidence of this disease is set to rise.^{3,4} Following the positive results of this trial, the LEAP-001 Phase III study is now underway to investigate the potential of lenvatinib and pembrolizumab as a first-line treatment for advanced/metastatic endometrial cancer.⁵

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Notes to editors

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About KEYNOTE-146/Study 111 (Abstract #9940)

KEYNOTE-146/Study 111 (ClinicalTrials.gov, [NCT02501096](https://clinicaltrials.gov/ct2/show/study/NCT02501096)) is a Phase 1b/2, multi-cohort, multi-center, open-label, non-randomised, single-arm trial of 108 patients with metastatic endometrial carcinoma that had progressed following at least one prior systemic therapy, with a median follow-up of 18.7 months. Patients were treated with pembrolizumab 200 mg intravenously every three weeks in combination with lenvatinib 20 mg orally once daily.

The primary endpoint was ORR at week 24 as assessed by investigators per irRECIST. Key secondary endpoints include overall ORR, duration of response (DOR), progression-free survival (PFS), overall survival (OS), disease control rate (DCR), clinical benefit rate (CBR), safety and tolerability at the time of data cutoff (January 10, 2019). Tumour responses for primary and secondary endpoints were assessed by investigators per irRECIST. Pre-specified exploratory endpoints include independent imaging review (IIR) per irRECIST and RECIST version 1.1, and antitumor activity by PD-L1 status.⁶

In the total study population of 108 patients, as assessed by investigators per irRECIST, at data cutoff overall ORR was 38.9% (95% CI: 29.7, 48.7), with a complete response rate of 7.4% (N=8) and a partial response rate of 31.5% (N=34). Median DOR was 21.2 months (range 1.2+ to 35.6+).¹

In the 94 patients with tumours that were not MSI-H or dMMR, at data cutoff overall ORR was 37.2% (95% CI, 27.5, 47.8), with a complete response rate of 7.4% (N=7) and a partial response rate of 29.8% (N=28). Median DOR was not estimable (range: 1.2+ to 33.8+ months).

Additionally, in the 11 patients with tumours that were MSI-H or dMMR, at data cut off the overall ORR was 63.6% (95% CI: 30.8, 89.1), with a complete response rate of 9.1% (N=1) and a partial response rate of 54.5% (N=6). Median DOR was 21.2 months (range: 6.1+ to 35.6+).¹

In a pre-specified exploratory analysis, tumour responses also were assessed by independent imaging reviewers (IIR) per RECIST version 1.1. In the total study population of 108 patients, at data cutoff the ORR was 40.7% (95% CI: 31.4, 50.6), with a complete response rate of 10.2% (N=11) and a partial response rate of 30.6% (N=33). Median DOR was 14.8 months (range: 1.2+ to 35.6+). The median PFS was 7.5 months (95% CI: 5.0, 8.3), and the median OS was 16.7 months (95% CI: 15.0, NE).

In the 94 patients with tumours that were not MSI-H or dMMR, at data cutoff the ORR was 38.3% (95% CI: 28.5, 48.9), with a complete response rate of 10.6% (N=10) and a partial response rate of 27.7% (N=26). Median DOR was not estimable (range: 1.2+ to 33.1+ months). The median PFS was 5.4 months (95% CI: 4.4, 7.6), and the median OS was 16.4 months (95% CI: 13.5, 25.9).

In the 11 patients with tumours that were MSI-H or dMMR, at data cutoff the ORR was 63.6% (95% CI: 30.8, 89.1), with a complete response rate of 9.1% (N=1) and a partial response rate of 54.5% (N=6). Median DOR was not estimable (range: 2.1+ to 35.6+ months). The median PFS was 18.9 months (95% CI: 3.9, NE), and the median OS was not estimable (95% CI: 7.4, NE).

Treatment-related treatment-emergent adverse events (TEAEs) leading to discontinuation of pembrolizumab and/or lenvatinib occurred in 18.5% of patients (N=20). Both pembrolizumab and lenvatinib were discontinued in 9.3% of patients (N=10); lenvatinib was discontinued in 15.7% of patients (N=17), regardless of action taken with pembrolizumab; and pembrolizumab was discontinued in 13% of patients (N=14), regardless of action taken with lenvatinib. Treatment-related TEAEs leading to dose reduction of lenvatinib occurred in 64.8% of patients (N=70). Treatment-related TEAEs leading to interruption of pembrolizumab and/or lenvatinib occurred in 72.2% of patients (N=78). Interruption of both pembrolizumab and lenvatinib occurred in 27.8% of patients (N=30); interruption of lenvatinib occurred in 67.6% of patients (N=73), regardless of action taken with pembrolizumab; and interruption of pembrolizumab occurred in 39.8% of patients (N=43), regardless of action taken with lenvatinib.

In the total study population (N=108), treatment-related TEAEs occurred in 97.2% of patients (N=105) who received the pembrolizumab plus lenvatinib combination. The most common treatment-related TEAEs (any grade) ($\geq 20\%$) were hypertension (60.2%), diarrhoea (52.8%), fatigue (51.9%), decreased appetite (47.2%), hypothyroidism (43.5%), nausea (39.8%), stomatitis (33.3%), arthralgia (31.5%), dysphonia (27.8%), vomiting (26.9%), palmar-plantar erythrodysesthesia syndrome (25.9%), decreased weight (25.9%), proteinuria (22.2%), and headache (20.4%). Treatment-related TEAEs (Grade 3-4) occurred in 69.4% of patients (N=75) receiving the pembrolizumab plus lenvatinib combination. The most common treatment-related TEAEs (Grade 3-4) ($\geq 3\%$) with the pembrolizumab and lenvatinib combination were hypertension (32.4%), fatigue (8.3%), diarrhea (6.5%), and proteinuria (3.7%).

In the total study population (N=108), immune-related TEAEs occurred in 57.4% of patients (N=62) who received the pembrolizumab plus lenvatinib combination. The most common immune-related TEAE (any grade) ($\geq 20\%$) was hypothyroidism (47.2%). Immune-related TEAEs (Grade 3-4) occurred in 13% of patients (N=14) who received pembrolizumab plus lenvatinib. The most common immune-related TEAE (Grade ≥ 3) ($\geq 3\%$) was severe skin reactions (4.6%).¹

About Endometrial Cancer

Endometrial cancer begins in the inner lining of the uterus, which is known as the endometrium, and is the most common type of gynecological cancer in the developed world.⁷ In 2018, there were more than 382,000 new cases and nearly 90,000 deaths from uterine body cancers worldwide (these estimates include both endometrial cancers and uterine sarcomas; more than 80% of uterine body cancers occur in the endometrium, so the actual numbers for endometrial cancer cases and deaths are slightly lower than these estimates).³

About Lenvima® (lenvatinib)

Lenvatinib, discovered and developed by Eisai, is an oral RTK inhibitor that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors (VEGFR1 (FLT1), VEGFR2 (KDR) and VEGFR3 (FLT4)), and fibroblast growth factor (FGF) receptors FGFR1, 2, 3 and 4 in addition to other proangiogenic and oncogenic pathway-related RTKs (including the platelet-derived growth factor (PDGF) receptor PDGFR α ; KIT; and RET) involved in tumour proliferation.⁸ Lenvatinib possesses a distinct binding mode (Type V) to VEGFR2, as confirmed through X-ray crystal structural analysis, and exhibits rapid and potent inhibition of kinase activity, according to kinetic analysis in pre-clinical models.⁹

Studies of lenvatinib are currently ongoing in several types of cancer including renal cell carcinoma (phase III) and endometrial cancer (phase III).^{10,11}

About Keytruda® (pembrolizumab)

Pembrolizumab is an anti-PD-1 therapy that works by increasing the ability of the body's immune system to help detect and fight tumour cells. Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, thereby activating T lymphocytes which may affect both tumour cells and healthy cells. There are currently more than 1,000 trials studying pembrolizumab across a wide variety of cancers and treatment settings. The pembrolizumab clinical program seeks to understand the role of pembrolizumab across cancers and the factors that may predict a patient's likelihood of benefitting from treatment with pembrolizumab, including exploring several different biomarkers.¹²

About the Eisai and Merck Strategic Collaboration

In March 2018, Eisai and Merck, known as MSD outside the United States and Canada, through an affiliate, entered into a strategic collaboration for the worldwide co-development and co-commercialisation of lenvatinib. Under the agreement, the companies will jointly develop, manufacture and commercialise lenvatinib, both as monotherapy and in combination with Merck's anti-PD-1 therapy pembrolizumab.

In addition to ongoing clinical studies evaluating the pembrolizumab plus lenvatinib combination across several different tumour types, the companies will jointly initiate new clinical studies through the LEAP (**LE**nvatinib **And P**embrolizumab) clinical program, which will evaluate the combination to support 11 potential indications in six types of cancer (endometrial carcinoma, hepatocellular carcinoma, melanoma, non-small cell lung cancer, squamous cell carcinoma of the head and neck, and urothelial cancer). The LEAP clinical program also includes a new basket trial targeting six additional cancer types (biliary tract cancer, breast cancer, colorectal cancer, gastric cancer, glioblastoma and ovarian cancer).

About Eisai Co., Ltd.

Eisai Co., Ltd. is a leading global research and development-based pharmaceutical company headquartered in Japan. We define our corporate mission as “giving first thought to patients and their families and to increasing the benefits health care provides,” which we call our *human health care* (hhc) philosophy. With over 10,000 employees working across our global network of R&D facilities, manufacturing sites and marketing subsidiaries, we strive to realise our *hhc* philosophy by delivering innovative products in various therapeutic areas with high unmet medical needs, including Oncology and Neurology.

As a global pharmaceutical company, our mission extends to patients around the world through our investment and participation in partnership-based initiatives to improve access to medicines in developing and emerging countries.

For further information please visit www.eisai.eu.

About Merck

For more than a century, Merck [& Co., Inc., Kenilworth, N.J., U.S.A.], a leading global biopharmaceutical company known as MSD outside of the United States and Canada, has been inventing for life, bringing forward medicines and vaccines for many of the world's most challenging diseases. Through our prescription medicines, vaccines, biologic therapies and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck [& Co., Inc., Kenilworth, N.J., U.S.A.] continues to be at the forefront of research to advance the prevention and treatment of diseases that threaten people and communities around the world - including cancer, cardio-metabolic diseases, emerging animal diseases, Alzheimer's disease and infectious diseases including HIV and Ebola. For more information, visit www.merck.com

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¹ Makker, V., et al. Lenvatinib (LEN) and Pembrolizumab (PEMBRO) in advanced Endometrial Cancer (EC) ESMO 2019 Oral Presentation #994O.

² FDA Approves KEYTRUDA® (pembrolizumab) plus LENVIMA® (lenvatinib) Combination Treatment for Patients with Certain Types of Endometrial Carcinoma. Available from: <http://eisai.mediaroom.com/pressreleases?item=122746>. Last accessed September 2019.

³ World Cancer Research Fund. Endometrial Cancer Statistics. Available from: <https://www.wcrf.org/dietandcancer/cancer-trends/endometrial-cancer-statistics>. Last accessed: September 2019

⁴ Bray, F., et al. Endometrial cancer incidence trends in Europe: underlying determinants and prospects for prevention. *Cancer Epidemiol Biomarkers Prev.* 2005 May;14(5):1132-42.

⁵ Clinical trials.gov. Pembrolizumab (MK-3475) plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for Endometrial Carcinoma (ENGOT-en9 / MK-7902-001) (NCT03884101). Available from: <https://clinicaltrials.gov/ct2/show/NCT03884101>. Last accessed: September 2019

⁶ Clinical trials.gov. Phase 1/2b Trial of Lenvatinib (E7080) Plus Pembrolizumab in Subjects With Selected Solid Tumors (NCT02501096). Available from: <https://clinicaltrials.gov/ct2/show/NCT02501096>. Last accessed: September 2019

⁷ Saso, S., Chatterjee, J., Georgiou, E., Ditre, A.M., Smith, J.R. and Ghaem-Maghami, S., 2011. Endometrial cancer. *Bmj*, 342, p.d3954.

⁸ LENVIMA Summary of Product Characteristics. Available from: https://www.ema.europa.eu/en/documents/product-information/lenvima-epar-product-information_en.pdf Last accessed September 2019

⁹ Okamoto K, et al. (2014) Distinct Binding Mode of Multikinase Inhibitor Lenvatinib Revealed by Biochemical Characterization. *ACS Medicinal Chemistry Letter.* 2015; 6:89-94

¹⁰ Clinicaltrials.gov. Lenvatinib/Everolimus or Lenvatinib/Pembrolizumab Versus Sunitinib Alone as Treatment of Advanced Renal Cell Carcinoma (CLEAR) Trial. Available from: www.clinicaltrials.gov/ct2/show/NCT02811861 Last accessed September 2019

¹¹ Clinicaltrials.gov. Lenvatinib in Combination with Pembrolizumab Versus Treatment of Physician's Choice in Participants With Advanced Endometrial Cancer (MK-3475-775/E7080-G000-309 Per Merck Standard Convention [KEYNOTE-775]) Available from: www.clinicaltrials.gov/ct2/show/NCT03517449 Last accessed September 2019

¹² KEYTRUDA Summary of Product Characteristics. Available from: <https://www.medicines.org.uk/emc/medicine/30602> Last accessed September 2019