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NEW DATA FOR LENVIMA®▼ (LENVATINIB) PLUS KEYTRUDA® (PEMBROLIZUMAB) COMBINATION PRESENTED AT ESMO SHOW PROMISING RESULTS ACROSS SEVEN TUMOUR TYPES

Eisai and Merck present important new results for previously treated advanced cancer patients including those who have progressed on anti-PD-1-based therapy, with high unmet needs[1,2]

HATFIELD, ENGLAND & Kenilworth, NJ, Sept. 20, 2020 – Eisai Europe Ltd and Merck, Co., Inc., Kenilworth, N.J., U.S.A. (known as MSD outside the United States and Canada), today announced new data from the LEAP (LEnvatinib And Pembrolizumab) clinical trial programme evaluating Eisai's oral multiple receptor tyrosine kinase inhibitor, lenvatinib, in combination with Merck's anti-PD-1 therapy, pembrolizumab. In the ongoing Phase 2 LEAP-004 trial, the combination demonstrated an objective response rate (ORR) of 21.4% (22/103 patients) (95% CI: 13.9-30.5) in patients with unresectable or advanced melanoma who had previously progressed on anti-PD-1/PD-L1 therapy,[1] while the exploratory analysis showed that in patients whose disease progressed after an anti-PD-1/L1 plus anti-CTLA-4 therapy, the ORR was found to be 31% (9/29 patients) (95% CI: 15.3-50.8). Median overall survival (OS) was 13.9 months (95% CI: 10.8-not reached [NR]), and the nine-month OS rate was 65.4% (95% CI: 55.2-73.8).[1] In the ongoing Phase 2 LEAP-005 trial, the combination demonstrated an ORR that ranged from 9.7-32.3% (95% CI: 2.0-51.4) in previously treated patients with triple-negative breast cancer (TNBC), ovarian cancer, gastric cancer, colorectal cancer (non-microsatellite instability-high [MSI-H]/mismatch repair proficient [pMMR]), glioblastoma multiforme (GBM), and biliary tract cancer (BTC).[2] The safety profile for both studies was as expected based on prior studies involving each monotherapy. Results from LEAP-004 (Abstract #LBA44) and LEAP-005 (Abstract #LBA41) were accepted as late-breaking abstracts and are being presented in proffered paper presentations at the European Society for Medical Oncology (ESMO) Virtual Congress 2020.

"Patients with advanced cancer who have already failed on standard therapies can be incredibly difficult to treat. This is why these new combination studies, using two drugs with different mechanisms of action, are needed to provide patients with a potentially effective treatment

option where very few currently exist," said Associate Professor Zarnie Lwin, principal investigator of LEAP-005 trial and medical oncologist, Royal Brisbane and Women's Hospital.

"We believe that this first look at the lenvatinib and pembrolizumab combination data at ESMO represents important progress, particularly in advanced cancer types where treatment options can be severely limited for patients, leading to a high unmet need", said Miguel Marcão, Vice President, Eisai EMEA Oncology Business Group. "We remain committed to delivering on our strategic collaboration with Merck and exploring the potential of lenvatinib across multiple tumour types, to ensure we can help as many patients as possible. This year at ESMO we are celebrating this commitment through a decade of Eisai's work in oncology and the patients who have been treated with the innovative medicines that Eisai has discovered and developed."

Over the last ten years in oncology, Eisai has gained five oncology indications, across the region which includes Europe, the Middle East and Australia, plus Russia. Eisai is currently conducting studies across various tumour types and is presenting 12 abstracts across a broad range of tumour types at ESMO.

- **Ends -**

Notes to editors

Eisai EMEA Media Enquiries
Eisai Europe Ltd
Helena Symeou
+44 (0) 7507 309895
Helena_Symeou@eisai.net

Merck Media Relations
Pamela Eisele: (267) 305-3558
Rebecca Newberry: (484) 678-2952

About LEAP-004 (Abstract #LBA44)[1]

LEAP-004 (ClinicalTrials.gov, NCT03776136) is an ongoing Phase 2, single-arm, open-label trial evaluating pembrolizumab in combination with lenvatinib in patients with unresectable or advanced melanoma who had progressed on an anti-PD-1/PD-L1 therapy within 12 weeks. Patients were treated with lenvatinib 20mg orally once daily in combination with pembrolizumab 200mg intravenously every three weeks until unacceptable toxicity or disease progression for up

to 35 cycles (approximately two years). The primary endpoint is ORR per Response Evaluation Criteria In Solid Tumours (RECIST) v1.1 as assessed by blinded independent central review (BICR). Secondary endpoints include progression-free survival (PFS) and duration of response (DOR) per RECIST v1.1 by BICR, overall survival (OS) and safety.

At data cut off (June 10, 2020) in the interim analysis, a total of 103 patients were enrolled and treated. With a median duration of follow-up of 12 months (range: 8.7-15.6), pembrolizumab plus lenvatinib demonstrated an overall ORR by BICR of 21.4% (22/103 patients) (95% CI: 13.9-30.5), with a complete response rate of 1.9% (2/103 patients) and partial response rate of 19.4% (20/103 patients). In the total study population, median DOR was 6.3 months (range: 2.1+ to 11.1+), with 72.6% (95% CI: 46.2-87.6) of responses lasting for at least six months. Median PFS was 4.2 months (range: 3.5 to 6.3), with 73.8% of patients experiencing disease progression or death, and the nine-month PFS rate was 26.2% (95% CI: 17.4-35.9). Median OS was 13.9 months (range: 10.8-not reached [NR]), with death occurring in 44.7% of patients, and the nine-month OS rate was 65.4% (95% CI: 55.2-73.8).

The exploratory analysis showed that, in the 29 patients whose disease progressed after an anti-PD-1/L1 plus anti-CTLA-4 therapy, the ORR by BICR was 31% (95% CI: 15.3-50.8), with a complete response rate of 3.4 (1/29 patients) and partial response rate of 27.6% (8/29 patients), and the disease control rate (DCR) was 62.1% (95% CI: 42.3-79.3). In the total study population, the DCR by BICR was 65% (95% CI: 55.0-74.2).

Treatment-related adverse events (TRAEs) led to discontinuation of pembrolizumab and/or lenvatinib in 7.8% of patients. Grade 3-5 TRAEs occurred in 44.7% of patients (Grade 3: 39.8%; Grade 4: 3.9%; Grade 5: 1.0%), and serious TRAEs occurred in 18.4% of patients. The most common TRAEs of any grade occurring in at least 30% of the overall study population were hypertension (56.3%), diarrhea (35.9%), nausea (34.0%), hypothyroidism (33.0%) and decreased appetite (31.1%).

About LEAP-005 (Abstract #LBA41)[2]

LEAP-005 (ClinicalTrials.gov, NCT03797326) is an ongoing Phase 2, single-arm, open-label trial evaluating pembrolizumab in combination with lenvatinib in patients with select previously treated advanced solid tumours. The study cohorts are TNBC, ovarian cancer, gastric cancer,

colorectal cancer (non-MSI-H/pMMR), GBM or BTC. Patients were treated with lenvatinib 20mg orally once daily in combination with pembrolizumab 200mg intravenously every three weeks until unacceptable toxicity or disease progression for up to 35 cycles (approximately two years). The primary endpoints are ORR per RECIST v1.1 as assessed by BICR or Response Assessment in Neuro-Oncology (RANO) criteria (for GBM only) as assessed by BICR, and safety. Secondary endpoints include DCR per RECIST v1.1 by BICR or RANO (for GBM only) by BICR, DOR per RECIST v1.1 by BICR or RANO (for GBM only) by BICR, PFS per RECIST v1.1 by BICR or RANO (for GBM only) by BICR, and OS.[2,3]

At data cut off (April 10, 2020) in the interim analysis, a total of 187 patients were enrolled and treated. After a median duration of follow-up of 8.6 months (range: 1.9-13.1), the ORR ranged from 9.7-32.3% across six different tumour types. Additional efficacy and safety results from the interim study showed:

	2L/3L TNBC (n=31)	**4L Ovarian (n=31)**	**3L Gastric (n=31)**	**3L Colorectal (n=32)**	**2L BTC (n=31)**	**2L GBM (n=31)**
ORR, % (95% CI)	29.0 (14.2-48.0)	32.3 (16.7-51.4)	9.7 (2.0-25.8)	21.9 (9.3-40.0)	9.7 (2.0-25.8)	16.1 (5.5-33.7)
DCR, % (95% CI)	58.1 (39.1-75.5)	74.2 (55.4-88.1)	48.4 (30.2-66.9)	46.9 (29.1-65.3)	67.7 (48.6-83.3)	58.1 (39.1-75.5)
DOR, median (range), months	NR (0.0+ to 8.4+)	NR (1.5+ to 7.9+)	NR (2.1+ to 2.3+)	NR (2.1+ to 10.4+)	5.3 (2.1+ to 6.2)	3.2 (2.5 to 4.9+)
Grade ≥3 TRAEs, % (n)	55 (17)	68 (21)	42 (13)	50 (16)	48 (15)	35 (11)
Death due to TRAE, % (n)	3 (1)	3 (1)	3 (1)	3 (1)	0 (0)	3 (1)
Discontinued due to TRAE, % (n)	10 (3)	13 (4)	6 (2)	9 (3)	6 (2)	6 (2)

+, no progressive disease (PD) as of last disease assessment; DCR, disease control rate (best confirmed response: complete/partial response; stable disease); DOR, duration of response; NR, not reached.

The most common TRAEs of any grade occurring in at least 20% of the overall study population were hypertension (39.0%), fatigue (29.4%), diarrhea (26.7%), decreased appetite (25.1%), hypothyroidism (27.8%) and nausea (21.9%). The study is ongoing and will be expanded to enrol ≤ 100 patients in each cohort.

About Lenvima® (lenvatinib)

Lenvatinib is a multiple tyrosine kinase inhibitor that is indicated in Europe:

- As monotherapy for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI)[4]
- As monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy[4]
- In combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy[5]

Lenvatinib, discovered and developed by Eisai, is a multiple tyrosine kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib inhibits other kinases that have been implicated in pathogenic angiogenesis, tumour growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1-4, the platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET.[4] In syngeneic mouse tumour models, lenvatinib decreased tumour-associated macrophages, increased activated cytotoxic T cells, and demonstrated higher antitumor activity in combination with an anti-PD-1 monoclonal antibody compared to either treatment alone.[6,7]

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.[8]

Merck has the industry's largest immuno-oncology clinical research programme.[9] There are currently more than 1,200 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.

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 commercialize 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 have jointly initiated new clinical studies through the LEAP (LEnvatinib And Pembrolizumab) clinical programme and are evaluating the combination in 13 different tumour types (endometrial carcinoma, hepatocellular carcinoma, melanoma, non-small cell lung cancer, renal cell carcinoma, squamous cell carcinoma of the head and neck, urothelial cancer, biliary tract cancer, colorectal cancer, gastric cancer, glioblastoma, ovarian cancer and triple-negative breast cancer) across 19 clinical trials.

About Eisai EMEA

At Eisai, everything we do is dedicated to giving our first thought to patients and their families through our *human health care* (*hhc*) philosophy. We are the European hub of Tokyo-based Eisai Co. Ltd., forming part of a multinational team working across a global network of R&D facilities, manufacturing sites and marketing subsidiaries.

Our collective passion and dedication to patient care is the driving force behind our efforts to discover and develop innovative medicines in a variety of therapeutic areas in which a high unmet medical need remains, including oncology and neurology.

Our mission is clear: we strive to make a significant long-lasting contribution to society in an ethical, compliant and sustainable way by embodying our *hhc* philosophy in everything we do.

For further information please visit www.eisai.eu.

About Merck

For more than 125 years, Merck, 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 in pursuit of our mission to save and improve lives. We demonstrate our commitment to patients and population health by increasing access to health care through far-reaching policies, programmes and partnerships. Today, Merck continues to be at the forefront of research to prevent and treat diseases that threaten people and animals – including cancer, infectious diseases such as HIV and Ebola, and emerging animal diseases – as we aspire to be the premier research-intensive biopharmaceutical company in the world. For more information, visit www.merck.com and connect with us on Twitter, Facebook, Instagram, YouTube and LinkedIn.

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