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News Release

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FDA Approves TEPMETKO® as the First and Only Once-daily Oral MET Inhibitor for Patients with Metastatic NSCLC with *MET*ex14 Skipping Alterations

- **TEPMETKO is approved for both treatment naïve and previously treated *MET*ex14 positive NSCLC patients**
- **TEPMETKO demonstrated consistent and durable responses in both treatment naïve and previously treated *MET*ex14 patients in the VISION study**
- **VISION is the largest clinical study to date of patients with metastatic NSCLC with *MET* exon 14 skipping alterations**

Darmstadt, Germany, February 3, 2021 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced that the US Food and Drug Administration (FDA) has approved TEPMETKO® (tepotinib) following Priority Review for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (*MET*) exon 14 skipping alterations. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

The approval is based on results from the pivotal Phase II VISION study evaluating TEPMETKO as monotherapy in patients with advanced NSCLC with *MET*ex14 skipping alterations.

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"*MET*ex14 skipping occurs in approximately 3% to 4% of NSCLC cases, and patients with this aggressive lung cancer are often elderly and face a poor clinical prognosis," said Paul K. Paik, M.D., VISION primary investigator and Clinical Director, Thoracic Oncology Service, Memorial Sloan Kettering Cancer Center. "There is a pressing need for targeted treatments that have the potential to generate durable anti-tumor activity and improve the lives of patients with this challenging disease. TEPMETKO offers an important and welcome new therapeutic option for patients with metastatic NSCLC harboring these genetic mutations."

"In recent years, the treatment of lung cancer has seen powerful progress in the understanding of the genetic mutations that lead to tumor growth, resistance and progression," said Andrea Ferris, President and CEO of LUNGevity. "The availability of a new precision medicine for NSCLC with *MET*ex14 skipping alterations advances patient access to targeted treatment and underscores the importance of routine comprehensive biomarker testing for patients with this challenging cancer."

TEPMETKO is the first and only FDA approved MET inhibitor that offers once-daily oral dosing and is administered as two 225 mg tablets (450 mg). Patients with metastatic NSCLC should be selected for treatment with TEPMETKO based on the presence of *MET* exon 14 skipping alterations.

"This approval of TEPMETKO by the FDA is an important milestone on our mission to significantly improve the treatment of cancer where MET plays a driving role," said Danny Bar-Zohar, M.D., Global Head of Development for the Healthcare business sector of Merck KGaA, Darmstadt, Germany. "Our focus now is to ensure TEPMETKO is accessible to patients in the United States and fully integrated into clinical practice given the important advance it represents for indicated patients as an oral once-a-day precision medicine."

EMD Serono, the healthcare business of Merck KGaA, Darmstadt, Germany in the US and Canada, is committed to providing patient access and reimbursement support for eligible TEPMETKO patients through its Oncology Navigation Center™ (ONC) program in the US. ONC provides a spectrum of patient access and reimbursement support services intended to help US patients receive appropriate treatment access. ONC may be reached at 1-844-662-3631 (844-ONC-EMD1)

between 8am-8pm Eastern Time, Monday through Friday, or by visiting OncNavigationCenter.com.

TEPMETKO was the first oral MET inhibitor to receive a regulatory approval anywhere in the world for the treatment of advanced NSCLC harboring *MET* gene alterations, with its approval in Japan in March 2020. The FDA completed its review of TEPMETKO under its Real-Time Oncology Review pilot program after previously granting the medicine Breakthrough Therapy Designation. The FDA also recently granted TEPMETKO Orphan Drug Designation (ODD).

A Marketing Authorization Application for tepotinib for a similar indication was validated by the European Medicines Agency in November 2020. Applications have also been submitted in Australia, Switzerland, and Canada under the FDA's Project Orbis initiative, which provides a framework for concurrent submission and review of oncology medicines among international partners.[1]

VISION Study Pivotal Trial Results

VISION (NCT02864992) is an ongoing pivotal Phase II, multicenter, multi-cohort, single-arm, non-randomized, open-label study investigating tepotinib as monotherapy in 152 patients with a median age of 73 years with advanced or metastatic non-small cell lung cancer (NSCLC) with *MET* exon 14 (*MET*ex14) skipping alterations. Eligible patients were required to have advanced or metastatic NSCLC harboring *MET*ex14 skipping alterations, epidermal growth factor receptor (EGFR) wild-type and anaplastic lymphoma kinase (ALK) negative status, at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1. Patients received TEPMETKO 450 mg once daily until disease progression or unacceptable toxicity. The major efficacy outcome measure is overall response rate (ORR) according to RECIST version 1.1 as assessed by a blinded independent review committee (BIRC). An additional efficacy outcome measure was duration of response (DOR) by BIRC. Patients with symptomatic CNS metastases, clinically significant uncontrolled cardiac disease, or who received treatment with any MET or hepatocyte growth factor (HGF) inhibitor were not eligible for the study. Data from the primary analysis of the VISION study were previously published online in *The New England Journal of Medicine*.[2]

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In the study, TEPMETKO demonstrated an overall response rate of 43% (95% CI, 32–56) in treatment-naïve patients (n=69) and 43% (95% CI, 33-55) in previously treated patients (n=83). Median duration of response (DOR) was 10.8 months (95% CI, 6.9-NE) and 11.1 months (95% CI, 9.5-18.5) among treatment-naïve and previously treated patients, respectively. Duration of response of six months or more occurred among 67% of treatment-naïve patients and 75% of previously treated patients, and duration of response of nine months or more occurred among 30% of treatment-naïve patients and 50% of previously treated patients.[3]

The safety population included 255 patients with NSCLC positive for *MET*ex14 skipping alterations, who received TEPMETKO in the VISION study. Fatal adverse reactions occurred in one patient (0.4%) due to pneumonitis, one patient (0.4%) due to hepatic failure, and one patient (0.4%) due to dyspnea from fluid overload. Serious adverse reactions occurred in 45% of patients who received TEPMETKO. Serious adverse reactions occurring in >2% of patients included pleural effusion (7%), pneumonia (5%), edema (3.9%), dyspnea (3.9%), general health deterioration (3.5%), pulmonary embolism (2%), and musculoskeletal pain (2%). The most common adverse reactions (≥20%) in patients who received TEPMETKO were edema, fatigue, nausea, diarrhea, musculoskeletal pain, and dyspnea.

About Non-Small Cell Lung Cancer
With 2 million cases diagnosed annually, lung cancer (including trachea, bronchus and lung) is the most common type of cancer worldwide and the leading cause of cancer-related death, with 1.9 million mortality cases worldwide each year.[4] In the US in 2020, there were an estimated 228,820 new cases of lung cancer and more than 135,000 deaths from lung cancer.[5] Alterations of the MET signaling pathway, including *MET* exon 14 (*MET*ex14) skipping alterations, are estimated to occur in 3% to 4% of NSCLC cases.[6]

About TEPMETKO® (tepotinib)
TEPMETKO is an oral MET inhibitor that inhibits the oncogenic MET receptor signaling caused by *MET* (gene) alterations. Discovered and developed in-house at Merck KGaA, Darmstadt, Germany, TEPMETKO has a highly selective mechanism of action, with the potential to improve outcomes in aggressive tumors that have a poor prognosis and harbor these specific alterations.[7]
Additional Clinical Investigations: Tepotinib is also being investigated in the Phase II INSIGHT 2 study in combination with osimertinib in *MET* amplified, advanced or metastatic NSCLC harboring activating *EGFR* mutations that has progressed following first-line treatment with osimertinib, and in the Phase II PERSPECTIVE study in combination with cetuximab in patients with *RAS/BRAF* wild-type left-sided metastatic colorectal cancer having acquired resistance to anti-EGFR antibody targeting therapy due to *MET* amplification.

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Important Safety Information
TEPMETKO can cause **interstitial lung disease (ILD)/pneumonitis**, which can be fatal. Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (eg, dyspnea, cough, fever). Immediately withhold TEPMETKO in patients with suspected ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis are identified. ILD/pneumonitis occurred in 2.2% of patients treated with TEPMETKO, with one patient experiencing a Grade 3 or higher event; this event resulted in death.

TEPMETKO can cause **hepatotoxicity**, which can be fatal. Monitor liver function tests (including ALT, AST, and total bilirubin) prior to the start of TEPMETKO, every 2 weeks during the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients who develop increased transaminases or total bilirubin. Based on the severity of the adverse reaction, withhold, dose reduce, or permanently discontinue TEPMETKO. Increased alanine aminotransferase (ALT)/increased aspartate aminotransferase (AST) occurred in 13% of patients treated with TEPMETKO. Grade 3 or 4 increased ALT/AST occurred in 4.2% of patients. A fatal adverse reaction of hepatic failure occurred in one patient (0.2%). The median time-to-onset of Grade 3 or higher increased ALT/AST was 30 days (range 1 to 178).

TEPMETKO can cause **embryo-fetal toxicity**. Based on findings in animal studies and its mechanism of action, TEPMETKO can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential or males with female partners of reproductive potential to use effective contraception during treatment with TEPMETKO and for one week after the final dose.

Avoid concomitant use of TEPMETKO with dual strong **CYP3A inhibitors** and **P-gp inhibitors** and strong **CYP3A inducers**. Avoid concomitant use of TEPMETKO with certain **P-gp substrates** where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, reduce the P-gp substrate dosage if recommended in its approved product labeling.

Fatal adverse reactions occurred in one patient (0.4%) due to pneumonitis, one patient (0.4%) due to hepatic failure, and one patient (0.4%) due to dyspnea from fluid overload.

Serious adverse reactions occurred in 45% of patients who received TEPMETKO. Serious adverse reactions in >2% of patients included pleural effusion (7%), pneumonia (5%), edema (3.9%), dyspnea (3.9%), general health deterioration (3.5%), pulmonary embolism (2%), and musculoskeletal pain (2%).

The most common adverse reactions (≥20%) in patients who received TEPMETKO were edema, fatigue, nausea, diarrhea, musculoskeletal pain, and dyspnea.

Clinically relevant adverse reactions in <10% of patients who received TEPMETKO included ILD/pneumonitis, rash, fever, dizziness, pruritus, and headache.

Selected laboratory abnormalities (≥20%) from baseline in patients receiving TEPMETKO in descending order were: decreased albumin (76%), increased creatinine (55%), increased alkaline phosphatase (ALP) (50%), decreased lymphocytes (48%), increased alanine aminotransferase (ALT) (44%), increased aspartate aminotransferase (AST) (35%), decreased sodium (31%), decreased hemoglobin (27%), increased potassium (25%), increased gamma-glutamyltransferase (GGT) (24%), increased amylase (23%), and decreased leukocytes (23%).

The most common Grade 3 to 4 laboratory abnormalities (≥2%) in descending order were: decreased lymphocytes (11%), decreased albumin (9%), decreased sodium (8%), increased GGT (5%), increased amylase (4.6%), increased ALT (4.1%), increased AST (2.5%) and decreased hemoglobin (2%).

A clinically relevant laboratory abnormality in <20% of patients who received TEPMETKO was increased lipase in 18% of patients, including 3.7% Grades 3 to 4.

For more information about TEPMETKO, please see full Prescribing Information, and visit www.TEPMETKO.com.

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Disclosure: Dr. Paik has provided consulting/advisory services for EMD Serono.

About Merck KGaA, Darmstadt, Germany

Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across healthcare, life science and performance materials. Around 57,000 employees work to make a positive difference to millions of people's lives every day by creating more joyful and sustainable ways to live. From advancing gene editing technologies and discovering unique ways to treat the most challenging diseases to enabling the intelligence of devices – the company is everywhere. In 2019, Merck KGaA, Darmstadt, Germany generated sales of € 16.2 billion in 66 countries.

The company holds the global rights to the name and trademark "Merck" internationally. The only exceptions are the United States and Canada, where the business sectors of Merck KGaA, Darmstadt, Germany operate as EMD Serono in healthcare, MilliporeSigma in life science, and EMD Performance Materials. Since its founding in 1668, scientific exploration and responsible entrepreneurship have been key to the company's technological and scientific advances. To this day, the founding family remains the majority owner of the publicly listed company.