News Release

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European Commission Approves TEPMETKO® (tepotinib) for Patients with Advanced NSCLC with *MET*ex14 Skipping Alterations

- **TEPMETKO is the first and only oral MET inhibitor to be approved in the European Economic Area for treating adult patients with advanced NSCLC harboring alterations leading to *MET*ex14 skipping, who require systemic therapy following prior treatment**
- **Approval is based on Phase II results from VISION, the largest interventional study to date of patients with advanced NSCLC with *MET*ex14 skipping alterations**
- **TEPMETKO demonstrated consistent responses across lines of therapy in the VISION study**

Darmstadt, Germany, February 18, 2022– Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced today announced that the European Commission (EC) has approved once-daily oral TEPMETKO® (tepotinib) as monotherapy for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harboring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (*MET*ex14) skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.

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"The approval of TEPMETKO provides a much-needed targeted treatment option for patients with advanced non-small cell lung cancer with *MET*ex14 skipping alterations," said Professor Egbert Smit, a VISION study investigator at the Netherlands Cancer Institute. "TEPMETKO has demonstrated durable and consistent response rates and has the potential to help patients with this challenging cancer."

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. Data from the primary analysis of the VISION study were previously published online in *The New England Journal of Medicine*.[1]

"The approval of TEPMETKO in Europe helps to address the need for targeted treatment options for people with lung cancer who have received prior treatment and whose tumors harbor *MET*ex14 skipping alterations," said Dr. Anne-Marie Baird, President of Lung Cancer Europe. "It is vital that biomarker testing is made consistently available and utilized across Europe to ensure people with advanced lung cancer receive an accurate diagnosis and optimal treatment."

In Europe, lung cancer is estimated to be the second most common cancer and the leading cause of cancer-related mortality, responsible for 388,000 deaths in 2018.[2] Alterations of the MET signaling pathway, including *MET*ex14 skipping alterations, are found in 3% to 4% of NSCLC cases and are associated with advanced disease and poor prognosis.[3-7]

"With the European Commission's approval of TEPMETKO, we are now able to bring this important medicine to more patients with this hard-to-treat and aggressive form of lung cancer," said Andrew Paterson, Chief Marketing Officer for the Healthcare business sector of Merck KGaA, Darmstadt, Germany. "As pioneers in the targeting of the MET signaling pathway, we will now be working on ways to bring this medicine to patients in Europe who may benefit."

About the VISION Study
VISION (NCT02864992) is an ongoing pivotal Phase II, multicenter, multi-cohort, single-arm, non-randomized, open-label study investigating tepotinib as monotherapy. Based on the 01 February 2021 data cut, 275 patients with a median age of 72.6 years with advanced or metastatic NSCLC with *MET*ex14 skipping alterations have been analyzed.

About TEPMETKO® (tepotinib)

TEPMETKO is a once-daily 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.
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. In February 2021, the U.S. Food and Drug Administration granted accelerated approval to TEPMETKO, making it the first and only once-daily oral MET inhibitor approved for patients in the U.S. with metastatic NSCLC with *MET*ex14 skipping alterations. Tepotinib is available in a number of countries, and under review by various other regulatory authorities globally. To meet an urgent clinical need, tepotinib is also available in a pilot zone of China in line with the government policy to drive early access for innovative medicines approved outside of China.
Merck KGaA, Darmstadt, Germany is also investigating the potential role of tepotinib in treating patients with NSCLC and acquired resistance due to *MET* amplification in the Phase II INSIGHT 2 study of tepotinib in combination with osimertinib in *MET* amplified, advanced or metastatic NSCLC harboring activating EGFR mutations that has progressed following first-line treatment with osimertinib.

Important Safety Information from the US FDA-Approved Label
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.
Commitment to Cancer

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Merck KGaA, Darmstadt, Germany, is a science-led organization dedicated to delivering transformative medicines with the goal of making a meaningful difference in the lives of people affected by cancer. Our oncology research efforts aim to leverage our synergistic portfolio in oncogenic pathways, immuno-oncology, and DNA Damage Response (DDR) to tackle challenging tumor types in gastrointestinal, genitourinary, and thoracic cancers. Our curiosity drives our pursuit of treatments for even the most complex cancers, as we work to illuminate a path to scientific breakthroughs that transform patient outcomes. Learn more at www.emdseronooncology.com. Follow us on Twitter: @EMDOncologyUS and LinkedIn: EMD Serono, Inc.

References

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About Merck KGaA, Darmstadt, Germany

Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across healthcare, life science and electronics. Around 58,000 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 2020, Merck KGaA, Darmstadt, Germany, generated sales of € 17.5 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 Electronics. 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.