ABOUT TEPMETKO® (TEPOTINIB)

TEPMETKO® (tepotinib) is indicated in the U.S. 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. TEPMETKO was discovered and developed in-house at Merck KGaA, Darmstadt, Germany.

TEPMETKO has been granted Orphan Drug Designation and Breakthrough Therapy Designation by the U.S. Food and Drug Administration (FDA).

THE ONLY ONCE-DAILY ORAL MET INHIBITOR FOR PATIENTS WITH *MET*EX14+ METASTATIC NSCLC[1]

TEPMETKO allows for a once-daily dosing schedule.[1] Patients with metastatic NSCLC should be selected for treatment with TEPMETKO based on the presence of *MET* exon 14 skipping alterations in plasma or tumor specimens. Testing for the presence of *MET* exon 14 skipping alterations in plasma specimens is recommended only in patients for whom a tumor biopsy cannot be obtained. If an alteration is not detected in a plasma specimen, re-evaluate the feasibility of biopsy for tumor tissue testing.[1]

The recommended dosage of TEPMETKO is 450mg (two 225 mg tablets) orally once daily with food until disease progression or unacceptable toxicity.[1]

Patients are instructed to take their dose at approximately the same time every day, swallow tablets whole and to not chew, crush or split tablets. Patients are advised to not make up a missed dose within 8 hours of the next scheduled dose. If vomiting occurs after taking a dose, patients are advised to take the next dose at the scheduled time.[1]

VISION PHASE II DATA

VISION is an ongoing, single arm, open label, multicenter, non-randomized, multicohort study in adult patients with advanced or metastatic non-small cell lung cancer (NSCLC) harboring *MET*ex14 skipping alterations.[1]

The major efficacy outcome measure was confirmed ORR according to RECIST v1.1 as evaluated by a BIRC. An additional efficacy outcome measure was DOR by BIRC.[1]

The primary analysis of the VISION study data was published in *The New England Journal of Medicine (NEJM)*.[2]

Consistent responses across lines of therapy (N=152)[1]

	TREATMENT NAÏVE (N=69)	PREVIOUSLY TREATED (N=83)
ORR by BIRC	**43%** (95% CI: 32.0, 56.0)	**43%** (95% CI: 33.0, 55.0)
mDOR by BIRC	**10.8 months** (95% CI: 6.9, NE)	**11.1 months** (95% CI: 9.5, 18.5)
	Patients with DOR ≥6 months, 67% Patients with DOR ≥9 months, 30%	Patients with DOR ≥6 months, 75% Patients with DOR ≥9 months, 50%

BIRC=Blinded Independent Review Committee; CI=confidence interval; DOR=duration of response; mDOR=median duration of response; mNSCLC=metastatic non-small cell lung cancer; ORR=overall response rate (confirmed); RECIST=Response Evaluation Criteria in Solid Tumors

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

IMPORTANT SAFETY INFORMATION (*continued on page 2*)

TEPMETKO can cause **interstitial lung disease (ILD)/pneumonitis**, which can be fatal. Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (e.g., 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% 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).

Click for full **Prescribing Information**.

HOW TEPMETKO® (TEPOTINIB) WORKS

MET activation is a primary oncogenic driver.[3,4] The MET pathway is susceptible to dysregulation that can drive the growth, survival and spread of NSCLC.[3]

Tepotinib is a kinase inhibitor that targets MET, including variants with exon 14 skipping alterations. Tepotinib inhibits hepatocyte growth factor (HGF)-dependent and independent MET phosphorylation and MET-dependent downstream signaling pathways. Tepotinib also inhibited melatonin 2 and imidazoline 1 receptors at clinically achievable concentrations.[1]

OTHER AREAS OF CLINICAL RESEARCH

Tepotinib is being investigated in additional settings:

- In combination with osimertinib in *MET* amplified, advanced or metastatic NSCLC harboring activating *EGFR* mutations that has progressed following first-line treatment with osimertinib.[5] (NCT03940703)
- 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.[6] (NCT04515394)

There is no guarantee that tepotinib, either alone or in combination with other therapies, will be found efficacious and safe in additional settings or tumor types.

IMPORTANT SAFETY INFORMATION *(continued)*

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 ALT (44%), increased 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.

Click for full **Prescribing Information**.

REFERENCES

1. TEPMETKO [prescribing information]. EMD Serono, Inc., Rockland, MA; 2021. **2**. Paik P, et al. *N Engl J Med*. 2020;DOI:10.1056/NEJMoa2004407. **3**. Drilon A, et al. *J Thorac Oncol*. 2017;12(1):15-26. **4**. Wu YL, et al. *Cancer Treat Rev*. 2017;61:70–81. **5**. A study of tepotinib plus osimertinib in osimertinib relapsed mesenchymal-epithelial transition factor (*MET*) amplified non-small cell lung cancer (NSCLC) (INSIGHT 2). https://clinicaltrials.gov/ct2/show/study/NCT03940703.
6. Study of tepotinib combined with cetuximab in participants left-sided metastatic colorectal cancer (mCRC) acquired resistance due to mesenchymal epithelial transition (*MET*) amplification. https://clinicaltrials.gov/ct2/show/NCT04515394?cond=NCT04515394&draw=2&rank=1.

About EMD Serono, Inc.

EMD Serono - the biopharmaceutical business of Merck KGaA, Darmstadt, Germany in the U.S. and Canada - is engaged in the discovery, research and development of medicines for patients with difficult to treat diseases. The business is committed to transforming lives by developing and delivering meaningful solutions that help address the therapeutic and support needs of individual patients. Building on a proven legacy and deep expertise in neurology, fertility and endocrinology, EMD Serono is developing potential new oncology and immuno-oncology medicines while continuing to explore potential therapeutic options for MS and other immunologic diseases. Today, the business has approximately 1,500 employees around the country with commercial, clinical and research operations based in the company's home state of Massachusetts. www.emdserono.com.

For media information on request:
Julissa Viana: julissa.viana@emdserono.com
Kristin Mulligan: kristin.mulligan@emdserono.com