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Dear NCCN Guidelines Panel Members,

On behalf of EMD Serono, Inc., I respectfully request the NCCN Non-Small Cell Lung Cancer Panel (NSCLC) to consider the recent FDA approval<sup>1</sup> and the pivotal clinical trial data<sup>2-5</sup> supporting the use of Tepotinib for the treatment of advanced or metastatic NSCLC with *MET* exon 14 skipping mutation.

**Suggested Changes:** We request the panel consider the following:

- **NSCL-28** – “*MET* exon 14 skipping mutation discovered prior to first-line systemic therapy”
  - **“First-line therapy”**: please add “Tepotinib” as preferred
  - **“Subsequent therapy”**: please add “Tepotinib” as preferred
- **NSCL-28** – “*MET* exon 14 skipping mutation discovered during first-line systemic therapy”
  - **“First-line therapy”**: please add “Tepotinib” as preferred
- **NSCL-I (1 of 2)** – “Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease”
  - **“*MET* Exon 14 Skipping Mutation”**: please add “Tepotinib” as preferred

**FDA Clearance<sup>1</sup>:** Tepotinib is a kinase inhibitor indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (*MET*) exon 14 skipping alterations. Tepotinib was previously granted orphan-drug designation by the FDA for the treatment of NSCLC with *MET* genomic aberrations.

**Rationale Summary:** Tepotinib is a once-daily, orally-dosed, *MET* kinase inhibitor approved by the FDA based on the VISION Phase 2 clinical trial in patients with advanced or metastatic NSCLC with a confirmed *MET* exon 14 skipping mutation. Tepotinib demonstrated efficacy in both treatment-naïve and previously treated patients, with or without brain metastases, as well as across histologic subtypes, including adenocarcinoma, squamous cell carcinoma, and sarcomatoid carcinoma. Overall response rate was 46% (55% for patients with brain metastases) with a median progression-free survival of 8.5 months and a clinically manageable safety profile.<sup>2,3</sup>

**Supporting Literature:**

The pivotal Phase 2 VISION clinical trial studied tepotinib in 152 adult patients with *MET* exon 14 skipping mutation determined by liquid biopsy and/or tissue biopsy who have advanced or metastatic NSCLC. All patients were negative for *EGFR* mutations and *ALK* rearrangement. Results have been published with at least 9 months of follow-up in the *New England Journal of Medicine*.<sup>2</sup> The overall objective response rate reported by the independent review committee (IRC) was 46% with no



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significant difference among patients based on prior number of therapy, including patients who had received immunotherapy. Stable disease was reported in 19.2% of patients for a disease control rate (DCR) of 65.7%. Median duration of response (DOR) was 11.1 months and median duration of progression-free survival (PFS) was 8.5 months. Tepotinib also showed significant efficacy in patients with brain metastases, with 55% ORR and 10.9 months median PFS.<sup>2</sup>

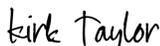
The above results were confirmed in the updated pre-planned analysis of 146 patients, with an ORR of 45.2% (57.1% for patients with brain metastases), median DOR of 11.1 months, and median PFS of 8.9 months as determined by the IRC.<sup>3,4</sup> In addition, patient-reported outcomes showed a meaningful improvement in symptoms of cough and stable dyspnea and chest pain during the 24-week treatment.<sup>5</sup>

Tepotinib was generally well-tolerated. In the published data set, grade 3 or higher treatment-emergent adverse events (TEAEs) occurred in 28% of patients, with peripheral edema being the most common (7%).<sup>2</sup> Treatment discontinuation rate due to adverse events was 11%. There were 21 patients who had adverse events leading to death while on treatment, with one treatment-related death by respiratory failure and dyspnea secondary to interstitial lung disease.<sup>2</sup>

Based on the FDA approval and study data, we request the NCCN Non-Small Cell Lung Cancer Panel to consider inclusion of tepotinib as a preferred option for the first-line and subsequent treatment of *MET* exon 14 skipping mutation NSCLC in patients with metastatic or advanced disease.

Respectfully submitted,

DocuSigned by:



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#### References:

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2. Paik et al. Tepotinib in Non-Small-Cell Lung Cancer with MET Exon 14 Skipping Mutations. *N Engl J Med.* 2020; 383:931-943
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