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NCCN Guidelines Panel: Non-Small Cell Lung Cancer

Tepotinib for advanced non-small cell lung cancer (NSCLC) with *MET* amplification

On behalf of EMD Serono, I respectfully request the NCCN NSCLC Panel to consider the enclosed clinical evidence[1-3] in support of Tepotinib with or without an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) as a treatment option for patients with metastatic NSCLC harboring mesenchymal-epithelial transition (MET) amplification.
Suggested Changes: Please consider the following update:

- **NSCL-I: "Emerging Biomarkers to Identify Novel Therapies for Patients with Metastatic NSCLC"**
  - For MET amplification: Add "Tepotinib ± EGFR TKI"
  - Based on the VISION[2] and INSIGHT[3] clinical studies

FDA Clearance[1]: Tepotinib (TEPMETKO®) is a kinase inhibitor indicated for the treatment of adult patients with metastatic NSCLC harboring MET exon 14 skipping alterations.

Rationale Summary:

- *MET* amplification is an oncogenic driver associated with a poor prognosis and limited effective therapeutic options. Furthermore, a subgroup of these patients has acquired resistance to previous EGFR therapy.
- Tepotinib is a highly selective, oral, once daily MET inhibitor that has demonstrated efficacy in patients with advanced NSCLC with *MET* amplification when used as monotherapy and in combination with an EGFR TKI for patients with acquired EGFR resistance in the Phase 2 VISION[2] and Phase 1b/2 INSIGHT[3] clinical trials.
- Substantial objective response rates (ORR) were observed for Tepotinib monotherapy as first-line (71.4%) and subsequent therapy (28.6%-30%).[2]
- When combined with an EGFR TKI, Tepotinib significantly improved OS (37.3 v 13.1 months) and PFS (16.6 v 4.2 months) compared with chemotherapy.[3]
- Tepotinib monotherapy and combination therapy were well tolerated, and the overall safety profile was consistent with its known safety profile.[2-5]
- The safety and efficacy of Tepotinib with or without an EGFR TKI support the request for inclusion as a targeted therapy for patients with *MET* amplification.

Supporting Literature:

The phase 2 VISION clinical trial enrolled a cohort of patients (N=24) with advanced EGFR/ALK wild-type NSCLC with *MET* amplification and no *MET* exon14 skipping mutation.[2] Tepotinib was administered first line to 7 patients, second line to 10 patients, and third line to 7 patients.

The primary outcome measure was objective response rate (ORR), and secondary outcome measures were 9-month event-free survival for progression-free survival (PFS) and event-free duration of response (DOR); all values were determined by independent-review committee (IRC). The overall ORR was 41.7% (95% CI, 22.1–63.4) with the highest response in patients receiving Tepotinib as a first-line therapy (71.4%; 95% CI, 29.0–96.3). The response rates in patients receiving second-line and third-line therapy were 30.0% (95% CI, 6.7–65.2) and 28.6% (95% CI, 3.7–71.0), respectively. In the overall population, the 9-month event-free survival for PFS was 40% (95% CI, 19–61) with a median PFS of 4.2 months. The 9-month event-free survival for PFS by line of therapy was 51% in first line, 58% in second line, and not evaluable (NE) in third line. The overall 9-month event-free DOR was 67% (95% CI, 28–88) with a 60% response in first-line therapy, 100% response in second-line therapy, and NE in third-line therapy.

The Phase 1b/2 randomized INSIGHT trial examined the use of Tepotinib as combination therapy for advanced NSCLC *MET* overexpression or amplification in patients (N=73) with acquired resistance to EGFR inhibition. Patients were randomized to receive Tepotinib combined with an EGFR TKI (gefitinib) or standard platinum doublet chemotherapy. The primary endpoint was PFS with secondary endpoints of overall survival and safety with pre-planned subgroup analyses for *MET* amplification. In the Phase 2 subgroup of patients with *MET* amplification and EGFR acquired resistance (n=19), the ORR was 67% (90% CI, 39.1–87.7) in patients receiving Tepotinib plus an EGFR TKI and 43% (90% CI, 12.9–77.5) in the patients who received Tepotinib plus chemotherapy (odds ratio, 2.67 [90% 0.37 – 19.56]); median DOR was 8.7 months (90% CI, 4.2–19.9) and 2.8 months (90% CI, 2.8-5.3), respectively. Median PFS was significantly improved with Tepotinib plus gefitinib versus chemotherapy (16.6 v 4.2 months; HR, 0.13; 95% CI, 0.04-0.43)). Median OS was also significantly longer with Tepotinib plus gefitinib (37.3 v 13.1 months; HR, 0.08; 95% CI, 0.01–0.51).

The adverse-event profiles for the VISION and INSIGHT trials were similar to prior studies of Tepotinib.[4,5] The most common grade ≥3 treatment-related adverse events (TRAEs) in the VISION trial were peripheral edema (8.3%), generalized edema (8.3%), and increased transaminases (4.2%).[2] Five patients discontinued treatment due to adverse events that were unrelated to Tepotinib. In the INSIGHT trial, the most common grade ≥3 TRAEs were increased amylase (16%), increased lipase (13%), diarrhea (10%), and rash (6.5%).[3] In total, only 1 patient reported a grade 4 TRAE.[2,3]

Based on these findings, we respectfully request the NCCN Non-Small Cell Lung Cancer Panel to consider the inclusion of Tepotinib with or without an EGFR TKI for the treatment of advanced or metastatic NSCLC with *MET* amplification.

Respectfully submitted,

DocuSigned by:
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3. Wu Y-L, Cheng Y, Zhou J, et al. 2020.Tepotinib plus gefitinib in patients with EGFR-mutant non-small-cell lung cancer with MET overexpression or MET amplification and acquired resistance to previous EGFR inhibitor (INSIGHT study): an open-label, phase 1b/2, multicentre, randomised trial. Lancet Resp Med. 8(11):P1132-1143.
4. Falchook GS, Kurzrock R, Amin HM, et al. First-in-man phase I trial of the selective MET inhibitor Tepotinib in patients with advanced solid tumors. Clin Cancer Res 2020; 26: 1237-46.
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