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Positive Quality Intervention: Tepotinib (Tepmetko®) for Non-Small Cell Lung Cancer with MET Exon 14 Alterations

Description: Tepotinib is an oral tyrosine kinase inhibitor (TKI) designed specifically to target mesenchymal epithelial transition exon 14 skipping alterations (METex14) in non-small cell lung cancer (NSCLC).[1] This PQI will discuss safety, efficacy, strategies for dosing, and side effect management.

Background: Tepotinib is indicated as a first-line option for patients with NSCLC with METex14 skipping alterations. Patients with METex14 mutations tend to be older (median 72 years old), former smokers (~60%), and PDL-1 positive (63%). METex14 patients are not the typical oncogenic driver patients like those with EGFR, ROS, and ALK. In the VISION trial, an open-label phase 2 study, tepotinib demonstrated durable clinical activity.[2-4] The VISION phase 2 nonrandomized clinical trial was a multicohort, open-label, multicenter study that enrolled patients with METex14-skipping advanced/metastatic NSCLC (cohorts A and C).[4] Cohorts A and C included 313 patients (50.8%female, 33.9% Asian; median age 72 years). The objective response rate (ORR) was 51.4% (95% CI, 45.8%-57.1%) with a median duration of response (mDOR) of 18.0 (95% CI, 12.4-46.4) months, mPFS of 11.2 (95 %CI, 9.5-13.8) months, and mOS of 19.6 (95% CI, 16.2-22.9) months. In cohort C (n = 161), an ORR of 55.9% (95% CI, 47.9%-63.7%) with an mDOR of 20.8 (95% CI, 12.6-not estimable (NE)) months was reported across treatment lines, comparable to cohort A (n = 152). In treatment-naive patients (cohorts A and C; n = 164), ORR was 57.3% (95% CI, 49.4%-65.0%) and mDOR was 46.4 (95% CI, 13.8-NE) months. In previously treated patients (n = 149), ORR was 45.0% (95% CI, 36.8%-53.3%) and mDOR was 12.6 (95%CI, 9.5-18.5) months. Rates of adverse events (AE) were broadly consistent irrespective of prior therapies.[4] Among patients with NSCLC with a confirmed METex14+ skipping alteration, tepotinib demonstrated meaningful activity across subgroups by prior therapies and brain metastases, with a manageable safety profile and few treatment discontinuations indicating that results were favorable.[3,4]

PQI Process: Upon receipt of a new prescription for tepotinib:

- Dosing:[2]
  - Starting dose is 450 mg by mouth once daily with food until progression or unacceptable toxicity
  - Discontinue in patients unable to tolerate 225 mg daily

Dose Reductions from 450 mg Starting Dose	
Interstitial lung disease (ILD)/Pneumonitis	**Intervention**
Suspected	Hold
Confirmed	Discontinue permanently
Hepatoxicity	**Intervention**
Increase ALT/AST without increased tbili Grade 3	Hold until recovery to baseline • Recovery ≤ 7 days: resume at same dose • Recovery >7 days: reduce dose to 225 mg daily
Increase ALT/AST without increased tbili Grade 4	Permanently discontinue
ALT/AST >3x ULN with total bilirubin >2xULN in absence of cholestasis or hemolysis	Permanently discontinue
Increase tbili without increased ALT/AST Grade 3	Hold until recovery to baseline • Recovery ≤ 7 days: resume at same dose • Recovery >7 days: permanently discontinue
Increase tbili without increased ALT/AST Grade 4	Permanently discontinue
Other adverse reactions	**Intervention**
Grade 2	Maintain dose – if intolerable consider holding and restart at 225 mg
Grade 3	Hold until resolved, resume at 225 mg
Grade 4	Permanently discontinue

- Side Effects[1]
    - Most common (≥20%): edema, increased creatinine, increased alk phos/AST/ALT, lymphopenia, anemia, fatigue, nausea, diarrhea, musculoskeletal pain, and dyspnea
    - Clinically relevant (<10%): ILD/pneumonitis, rash, fever, dizziness, pruritus, and headache
    - Serious adverse reactions occurred in 45% of patients;
        - Grade 3/4 adverse reactions in >2% of patients included: pleural effusion (7%), pneumonia (5%), edema (3.9%), dyspnea (3.9%), pulmonary embolism (2%), and musculoskeletal pain (2%)
        - Fatal adverse reactions included hepatic failure (0.4%), pneumonitis (0.4%), and dyspnea from fluid overload (0.4%)
- Monitoring[2]
    - Monitor LFTs prior to start, then every 2 weeks for the first 3 months, then monthly or as clinically indicated
    - Monitor for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (ex: dyspnea, cough, fever)
    - Monitor WBC, CMP, and creatinine prior to start and then monthly or as clinically indicated
- Drug Interactions:[1]
    - CYP3A inducers/inhibitors and P-gp substrates
    - If concomitant use is unavoidable, reduce the substrate dose if recommended in product labeling

Patient-Centered Activities:

- Provide Oral Chemotherapy Education (OCE) Sheet
- Ensure patient knows dosing schedule
- Counsel patient on how to take tepotinib and the most common side effects
- Instruct patient that tepotinib should be taken with food at the same time each day
- Counsel patient on embryo-fetal toxicity and use of effective contraception
- Advise patient not to make up a missed dose within 8 hours of the next scheduled dose
- Instruct patient to report any adverse events such as swelling, nausea, diarrhea, dyspnea, or cough
- Patient Assistance: NCODA Financial Assistance Tool

References:

1. *Met inhibitor: Tepmetko® (tepotinib) HCP*. MET Inhibitor | TEPMETKO® (tepotinib) HCP. https://www.tepmetko.com/us-en/home.html.
2. TEPMETKO® (Tepotinib) [Prescribing Information].
3. Paik PK, Felip E, Veillon R, et al. Topotinib in non-small-cell lung cancer with MET exon 14 skipping mutations. *New Engl J Med*. 2020; 383: 931-943.
4. Mazieres, Julien, et al. "Tepotinib Treatment in Patients with MET Exon 14–Skipping Non–Small Cell Lung Cancer: Long-Term Follow-up of the VISION Phase 2 Nonrandomized Clinical Trial." JAMA Oncology, 4 June 2023, jamanetwork.com/journals/jamaoncology/fullarticle/2805800, https://doi.org/10.1001/jamaoncol.2023.1962. Accessed 3 Aug. 2023.
5. NCCN Clinical Practice Guidelines in Oncology (NCCN guidelines®) for Non-Small Cell Lung Cancer.