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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, effective strategies for dosing, and side effect management.

Background: Tepotinib is indicated for patients with NSCLC with evidence of METex14 skipping alterations. Testing becomes even more important for identifying METex14 patients as they are older (median 72 years old), about 50% will be smokers/former smokers (59-65%), and 63% will be PDL-1 positive. METex14 patients are not the "typical" oncogenic driver patients like those with EGFR, ROS, and ALK who tend to be younger and never smokers. In the VISION trial (NCT02864992), an open-label phase 2 study, tepotinib demonstrated an objective response rate, by independent review, of 46% with a median duration of response of 11.1 months in patients expressing the METex14+ skipping mutation. The VISION trial showed durable clinical activity.[2,3] In a retrospective clinical study, outcomes were presented for clinically relevant subgroups of the VISION trial where they assessed efficacy and safety in predefined subgroups according to age, prior therapies (chemotherapy and immune checkpoint inhibitors), and brain metastases. An ad hoc retrospective analysis using Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria was used to assess intracranial activity. Overall, 152 patients were evaluable for efficacy. Overall, objective response rate (ORR) was 44.7% [95% confidence interval (CI): 36.7-53.0]. Patients aged <75 (n=84) and ≥75 (n=68) had ORRs of 48.8% (95% CI: 37.7-60.0) and 39.7% (95% CI: 28.0-52.3), respectively. Treatment-naïve (n=69) versus previously treated (n=83) patients showed consistent efficacy [ORR (95% CI): 44.9% (32.9-57.4) vs. 44.6% (33.7-55.9); median duration of response (95% CI): 10.8 (6.9-not estimable) vs. 11.1 (9.5-18.5) months]. Of 15 patients analyzed by RANO-BM (12 received prior radiotherapy), 13 achieved intracranial disease control; 5 of 7 patients with measurable brain metastases had partial intracranial responses. Of 255 patients evaluable for safety, 64 (25.1%) experienced Grade ≥3 treatment-related adverse events (TRAE), leading to discontinuation in 27 patients (10.6%). 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 age, prior therapies, and brain metastases, with a manageable safety profile and few treatment discontinuations indicating that results were favorable.[3,4]

PQI Process: Tepotinib is a first-line therapy option for NSCLC expressing the METex14+ skipping alteration.[5] It is available in 225 mg tablets. Upon receipt of a new prescription for tepotinib:

- Dosing:[6]
  - Starting dose is 450 mg by mouth once daily with food until progression or toxicity

Dose Reductions	
Interstitial lung disease (ILD)/Pneumonitis	**Intervention**
Suspected	Hold
Confirmed	Discontinue permanently
Hepatoxicity	**Intervention**
Grade 3	Hold until recovery to baseline • Recovery ≤ 7 days: resume at same dose • Recovery >7 days: reduce dose to 225 mg daily
Grade 4	Permanently discontinue
ALT/AST >3x ULN with total bilirubin >2xULN	Permanently discontinue

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Other adverse reactions	Intervention
Grade 2	Maintain dose – if intolerable consider holding and restart at 225 mg
Grade 3	Hold, resume at 225 mg, and permanently discontinue if unable to tolerate
Grade 4	Permanently discontinue

- Side Effects[1]
  - Most common (>20%): edema, 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. Serious 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%)
- Monitoring[2,6]
  - 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 and electrolytes prior to start and then monthly or as clinically indicated
- Drug Interactions:[1]
  - CYP3A4 inhibitors, P-gp inhibitors, and CYP3A4 inducers
  - If concomitant use is unavoidable, reduce the substrate dose if recommended and approved

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:

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