Tepotinib (Tepmetko®) as monotherapy for the treatment of patients with advanced non-small cell lung cancer (NSCLC)

General information [1]

Drug description	Indication
Tepotinib (Tepmetko®) is a mesenchymal-epithelial transition (MET) inhibitor, which blocks MET phosphorylation and MET-dependent downstream signalling.	Tepotinib (Tepmetko®) as monotherapy is indicated for the treatment of adult patients with advanced NSCLC harbouring alterations leading to MET factor gene exon 14 (METex14) skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.

Current treatment [2]

- There are currently no treatments approved by NICE to specifically target METex14 skipping mutation or c-MET gene amplification.
- The following treatments are recommended for first-line treatment of patients with advanced (stages IIIB and IV) NSCLC, and no specific modifications to the EGFR or ALK genes:
  - PD-L1 expression under 50%:
    - Atezolizumab plus bevacizumab, carboplatin and paclitaxel (non-squamous)
    - Pembrolizumab with pemetrexed and platinum chemotherapy (non-squamous)
    - Pemetrexed in combination with cisplatin (non-squamous)
    - Pembrolizumab with carboplatin and paclitaxel (squamous)
  - PD-L1 expression 50% or over
    - Pembrolizumab, with pemetrexed and platinum chemotherapy (non-squamous)
    - Pembrolizumab (squamous and non-squamous)
    - Pembrolizumab with carboplatin and paclitaxel (squamous).

Regulatory status

EMA	FDA [4]
Approval status for this indication: On 16 December 2021, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Tepmetko®.**UPDATE**: Date of issue of marketing authorisation valid throughout the European Union: 16/02/2022 The full indication is: ❖ Tepmetko® as monotherapy is indicated for the treatment of adult patients with advanced NSCLC harbouring alterations leading to MET factor gene exon 14 (METex14) skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy. **Other indications**: none ✓ Medicine under additional monitoring	**Approval status for this indication**: On 3 February 2021, the FDA granted accelerated approval to tepotinib (Tepmetko®) for adult patients with metastatic NSCLC harbouring METex14 skipping alterations. ✓ This indication is approved under accelerated approval based on overall response rate and response duration. **Other indications**: none

Costs

60 Tepmetko® tablets 225 mg = € 8,500.00 (ex-factory price) [5]

Posology [6]

- The recommended dose is 450 mg tepotinib (2 tablets) taken once daily. Treatment should continue as long as clinical benefit is observed.

Warnings and precautions

- **Assessment of METex14 skipping alterations status:**
  - When detecting the presence of alterations leading to METex14 skipping using tissue-based or plasma-based specimens, it is important that a well-validated and robust test is chosen to avoid false negative or false positive results.
- **Interstitial Lung Disease (ILD)/pneumonitis:**
  - Immediately withhold Tepmetko® in patients with suspected ILD/pneumonitis.
  - Permanently discontinue Tepmetko® in patients diagnosed with ILD/pneumonitis of any severity.
- **Hepatotoxicity:**
  - Monitor liver function tests.
  - Withhold, dose reduce, or permanently discontinue Tepmetko® based on severity.
- **QTc prolongation:**
  - QTc prolongation was reported in a limited number of patients. In patients at risk of developing QTc prolongation, including patients with known electrolyte disturbances or taking concomitant medicinal products known to have QTc prolongation effects, monitoring is recommended as clinically indicated (e.g. ECG, electrolytes).
- **Embryo-foetal toxicity:**
  - Tepmetko® can cause foetal harm.
  - Advise of the potential risk to a foetus and use of effective contraception.
- **Interaction with other medicinal products:**
  - Concomitant use of Tepmetko® with strong CYP and P-gp inducers or dual strong CYP3A and P-gp inhibitors should be avoided.
- **Interpretation of laboratory tests:**
  - In vitro studies suggest that tepotinib or its main metabolite inhibit the renal tubular transporter proteins organic cation transporter 2 and multidrug and toxin extrusion transporters 1 and 2. Creatinine is a substrate of these transporters, and the observed increases in creatinine may be the result of inhibition of active tubular secretion rather than renal injury. Renal function estimates that rely on serum creatinine (creatinine clearance or estimated glomerular filtration rate) should be interpreted with caution considering this effect. In case of blood creatinine increase while on treatment, it is recommended that further assessment of the renal function be performed to exclude renal impairment.
- **Lactose content:**
  - Tepmetko® contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Study characteristics [8-11]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
VISION NCT02864992	152 (safety) 99 (efficacy)	tepotinib at a dose of 500 mg once daily	-	confirmed objective response (defined as a complete or partial response)[1]	**ongoing**[2], open-label, phase 2 study	METex14	Merck	[10]

Efficacy (n=99)	**Safety** (n=152)
Objective response rate (according to independent review): 46% (95% CI, 36-57), all responses were partial. Response rate in the liquid-biopsy group: 48% (95% CI, 36-61) Response rate in the tissue-biopsy group: 50% (95% CI, 37-63)	**Any AE (all grades):** n=149/152 (98.0%) **Grade ≥3 AEs**: n=83/152 (54.6%)

[1] As determined according to RECIST, version 1.1, on the basis of an assessment by an independent review committee.

[2] The VISION trial is ongoing until 02/2023; Currently, primary analysis data is available.

Response rate (according to investigator assessment): 56% (95% CI, 45-66); 2 patients had a complete response and 53 patients had a partial response;
Response rate in the liquid-biopsy group: 56% (95% CI, 43-68)
Response rate in the tissue-biopsy group: 62% (95% CI, 48-74)
Tumour shrinkage: 89% by independent review; 88% as assessed by investigators
Responses were rapid, with onset usually within 6 weeks after the initiation of treatment
Median duration of response (by independent review) in the combined-biopsy group: 11.1 months (95% CI, 7.2-could not be estimated)
Median duration of response (by independent review) in the liquid-biopsy group: 9.9 months (95% CI, 7.2-could not be estimated)
Median duration of response (by independent review) in the tissue-biopsy group: 15.7 months (95% CI, 9.7-could not be estimated)
The results according to **investigator assessment** were similar.
Median duration of PFS by independent review in the combined biopsy group: 8.5 months (95% CI, 6.7 to 11.0)
Median duration of PFS by independent review in the liquid-biopsy group: 8.5 months (95% CI, 5.1-11.0)
Median duration of PFS by independent review in the tissue-biopsy group: 11.0 months (95% CI, 5.7-17.1)
(Similar results according to investigator assessment)
Median duration of OS: 17.1 months (95% CI, 12.0-26.8)

QoL:

- Completion rates for the EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L were more than 88% up to week 12.
- Mean changes from baseline in cough, as part of the EORTC QLQ-LC13 symptom score, exceeded the predefined minimally important difference (10 points), which indicated a reduction in symptoms; symptoms of dyspnea and chest pain showed stability.
- Scores for global functioning showed stability in the patients' reported QoL over time on the EORTC QLQ-C30 scale and the EQ-5D-5L.

UPDATE: Clinical outcomes in the VISION study by independent review committee assessment [6]
Overall population (n=275):
Objective response rate: 49.1% (95% CI, 43.0-55.2)
Median duration of response: 13.8 months (95% CI, 9.9-19.4)
Previously treated patients (n=138):
Objective response rate: 44.2% (95% CI, 35.8-52.9)
Median duration of response: 11.1 months (95% CI, 8.4-18.5)

AEs of grade ≥3 that were considered by the investigators to be related to tepotinib were reported: 28% of the patients (grade 3 in 25% and grade 4 in 2%)
Serious AEs that were considered to be related to tepotinib: 15%
Treatment-related AEs leading to permanent discontinuation: 11%
A total of 21 patients had **AEs leading to death** while they were receiving tepotinib; **1 death was considered by investigators to be related to tepotinib**.

ESMO-MCBS version 1.1

The ESMO-MCBS form 3 for single-arm studies is only applied in "orphan diseases" and for diseases with "high unmet need". Therefore, the ESMO-MCBS cannot be applied here.

Risk of bias - study level (case series)[12]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?

yes	yes	yes	yes	yes	yes	yes	yes	yes
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	unclear	yes	yes	unclear[3]	yes
Overall risk of bias: low								
First published: 01/2022 **Last updated**: 05/2022								

Abbreviations: AE=adverse event, ALK=anaplastic lymphoma kinase, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, EGFR=epidermal growth factor receptor, EMA=European Medicines Agency, EORTC-QLQ-C30=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, EQ-5D-5L= EuroQol Group 5-Dimension 5-Level questionnaire, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, HR=hazard ratio, I=intervention, ILD=interstitial lung disease, MET=mesenchymal-epithelial transition, METex14=MET factor gene exon 14, n=number of patients, NICE=National Institute of Health and Care Excellence, NSCLC=non-small cell lung cancer, OS=overall survival, PD-L1=programmed death ligand 1, PE=primary endpoint, PFS=progression-free survival, QoL=quality of life, SAE=serious adverse event,

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11. U.S. National Library of Medicine, ClinicalTrials.gov. Tepotinib Phase II in NSCLC Harboring MET Alterations (VISION). [Available from: https://clinicaltrials.gov/ct2/show/NCT02864992].

[3] Primary analysis data available; the VISION trial is currently ongoing.

12. Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist. Edmonton (AB): Institute of Health Economics; 2014. [Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about].