Technology Guidance

Tyrosine Kinase Inhibitors

for treating MET mutation-positive metastatic non-small-cell lung cancer

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Tepotinib 225 mg tablet

for treating metastatic mesenchymal epithelial transition exon 14 skipping (METex14sk) mutation-positive non-small-cell lung cancer (NSCLC) in line with specific clinical criteria.

Funding status

Tepotinib 225 mg tablet is recommended for inclusion on the MOH Cancer Drug List (CDL; MAF with MediShield Life monthly claim limit of $1,600) for the abovementioned indication from 1 September 2022.

CDL listing **does not** apply to any formulations or strengths of capmatinib for treating metastatic METex14sk mutation-positive NSCLC.

Clinical indications, subsidy class and MediShield Life claim limits for all drugs included in the evaluation are provided in the Annex.

Published: 31 August 2022

Factors considered to inform the recommendations for funding

Technology evaluation

1.1. The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of mesenchymal-epithelial transition (MET) tyrosine kinase inhibitors (TKIs; capmatinib and tepotinib) for treating metastatic mesenchymal epithelial transition exon 14 skipping (METex14sk) mutation-positive non-small-cell lung cancer (NSCLC). The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from the public healthcare institutions. Published clinical and economic evidence for capmatinib and tepotinib was considered in line with their registered indications. Additional expert opinion was obtained from the MOH Oncology Drug Subcommittee (ODS) who assisted ACE ascertain the clinical value of the TKIs under evaluation and provided clinical advice on its appropriate and effective use based on the available clinical evidence.

1.2. The use of crizotinib for treating metastatic METex14sk mutation-positive NSCLC was outside the scope of the evaluation as it was not approved locally or overseas for this indication at the time of evaluation.

1.3. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.4. Additional factors, including social and value judgments, may also inform the Committee's funding considerations.

Clinical need

2.1. The Committee noted that approximately 50 patients are diagnosed with metastatic METex14sk-mutation positive NSCLC each year in Singapore. The Committee acknowledged the lack of approved alternatives for this condition and the high clinical need to consider MET TKIs for funding to improve treatment affordability and ensure appropriate patient care.

2.2. Locally, MET TKIs are the preferred upfront treatment for metastatic METex14sk-mutation positive NSCLC and immunotherapy would be reserved as subsequent treatment, in line with international clinical practice guidelines. However, none of the

MET TKIs are currently included in the MOH List of Subsidised Drugs, representing a therapeutic gap. Currently immunotherapy with or without chemotherapy (not specifically approved for treating METex14sk-mutation positive NSCLC) are used as upfront treatment, and pembrolizumab with or without chemotherapy was the most commonly used immunotherapy. The Committee noted that all patients with metastatic NSCLC are routinely tested for the presence of oncogenic markers prior to starting treatment, and up to 4% of patients in Singapore have METex14sk-mutation positive NSCLC.

Clinical effectiveness and safety

3.1. **Capmatinib versus tepotinib**
The Committee reviewed two phase II, single-arm, open-label trials which investigated the efficacy and safety of capmatinib and tepotinib in patients with stage IIIB or IV METex14sk-mutation positive NSCLC (GEOMETRY-MONO1 and VISION respectively). The Committee noted there was significant heterogeneity in the trial populations and trial designs.

3.2. The Committee acknowledged that head-to-head evidence between both MET inhibitors were lacking. Given the significant between-trial heterogeneity, indirect comparisons were likely to be associated with much uncertainty and naïve comparisons of the results might be associated with significant bias. As both MET inhibitors had shown high response rates and long progression-free survival in their respective trials, the Committee accepted that they could be considered clinically comparable.

3.3. **Capmatinib and tepotinib (versus immunotherapy)**
The Committee noted that head-to-head evidence comparing the MET inhibitors with pembrolizumab regimens were lacking. The Committee acknowledged conclusions made by Australia's PBAC, which considered the claim of non-inferiority of tepotinib compared with pembrolizumab with chemotherapy based on a matching adjusted indirect comparison (MAIC) submitted by the manufacturer. Based on the MAIC, PBAC considered that, overall, tepotinib was likely to have non-inferior efficacy and safety compared with pembrolizumab with chemotherapy for treating advanced METex14sk-mutation positive NSCLC.

Cost effectiveness

4.1. The Committee agreed that a cost-minimisation approach was appropriate to assess the cost-effectiveness of the MET inhibitors. The Committee reviewed an in-house cost-minimisation analysis (CMA) conducted by ACE for capmatinib, tepotinib and pembrolizumab with or without chemotherapy, which considered duration of treatment, cost of drug and administration, as well as the cost of testing for METex14sk mutation. The analysis showed that tepotinib was associated with the lowest treatment cost in the base case and scenario analyses.

4.2. The Committee noted that both the manufacturers of capmatinib and tepotinib offered price reductions. The manufacturer of tepotinib also agreed to enter into a confidential price volume agreement (PVA) which reduced the uncertainty of the overall budget impact and further improved cost-effectiveness. Therefore, the Committee considered that tepotinib was likely to represent a cost-effective option for treating metastatic METex14sk-mutation positive NSCLC, and recommended a line agnostic listing.

Estimated annual technology cost

5.1. Based on local epidemiological rates and estimated drug utilisation in the public healthcare institutions, the annual expenditure to the public healthcare system in the first year of listing tepotinib on the Cancer Drug List (CDL) for treating metastatic METex14sk-mutation positive NSCLC was estimated to be SG$1 million to <SG$3 million.

Recommendations

6.1. Based on available evidence, the Committee recommended tepotinib 225 mg tablet be listed on the MAF and CDL (MediShield Life monthly claim limit of $1,600) for treating metastatic METex14sk-mutation positive NSCLC, given its clinical need and favourable cost-effectiveness.

6.2. Based on available evidence, the Committee recommended not listing capmatinib on the CDL in view of its unacceptable cost-effectiveness compared with tepotinib and pembrolizumab regimens.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Clinical indications	Subsidy class (implementation date)	MediShield Life claim limit per month (implementation date)
Tepotinib 225 mg tablet	Treatment of metastatic non-small cell lung cancer (NSCLC) with mesenchymal-epithelial transition factor gene exon 14 skipping (METex14sk) alterations.	MAF (1 Sep 2022)	$1600 (1 Sep 2022)
Capmatinib 150 mg and 200 mg tablet	Treatment of metastatic non-small cell lung cancer (NSCLC) with a mesenchymal-epithelial transition factor gene exon 14	Not recommended for subsidy	Not recommended for MediShield Life claims

	skipping (METex14sk) mutation.		

Abbreviations: MAF, Medication Assistance Fund.