Tyrosine kinase inhibitors
(afatinib, erlotinib and gefitinib)

for the first-line treatment of locally advanced or metastatic EGFR mutation-positive non-small-cell lung cancer

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health’s Drug Advisory Committee has not recommended afatinib, erlotinib or gefitinib to be listed on the Medication Assistance Fund (MAF) for the first-line treatment of locally advanced or metastatic EGFR mutation-positive non-small-cell lung cancer due to uncertain clinically meaningful benefits for patients in the absence of overall survival gains and unacceptable cost-effectiveness compared to chemotherapy at the prices proposed by the manufacturers.

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Factors considered to inform the recommendations for subsidy

Technology evaluation

1.1 The MOH Drug Advisory Committee (“the Committee”) considered the evidence presented for the technology evaluation of tyrosine kinase inhibitors (TKIs: afatinib, gefitinib and erlotinib) compared with platinum-based chemotherapy for the first-line treatment of locally advanced or metastatic EGFR mutation-positive (EGFRM+) non-small-cell lung cancer (NSCLC). The Agency for Care Effectiveness conducted the evaluation in consultation with the MOH Lung Cancer Expert Working Group and the Oncology Drug Subcommittee (ODS) of the MOH Drug Advisory Committee.

1.2 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
- Estimated annual technology cost and the number of patients likely to benefit from the technology

1.3 Additional factors, including social and value judgments, may also inform the Committee’s subsidy considerations.

Clinical need

2.1 In local clinical practice, TKIs are routinely prescribed for the first-line treatment of advanced NSCLC with EGFR mutations in line with the Singapore Cancer Network (SCAN) clinical guideline on use of systemic therapy in advanced NSCLC. The Committee noted that all patients with non-squamous NSCLC are routinely tested for EGFR status prior to beginning treatment. The Committee heard that TKIs are not routinely used as maintenance treatment in Singapore, therefore use in this setting was outside of the remit for the evaluation.
Clinical effectiveness and safety

3.1 The Committee reviewed the clinical evidence for the TKIs and acknowledged that all trials consistently showed no overall survival (OS) benefit of afatinib, gefitinib, and erlotinib compared with platinum-based chemotherapy for the first-line treatment of locally advanced or metastatic EGFRM+ NSCLC. Head to head trial data comparing the TKIs also demonstrated no difference in OS for afatinib versus gefitinib, and erlotinib versus gefitinib.

3.2 The Committee heard that progression free survival (PFS) outcomes from published trials were inconsistent; however most studies indicated PFS gains favouring TKIs compared to chemotherapy. A statistically significant PFS benefit for afatinib compared to gefitinib was reported in a head to head trial (LUX-LUNG 7), however, the actual median PFS difference was small (12.8 months vs 11.2 months) but was not considered to be clinically significant. No statistically significant difference in PFS was observed for erlotinib versus gefitinib.

3.3 The Committee reviewed ACE’s network meta-analysis which directly compared PFS gains between the TKIs, and noted that a significant PFS benefit was only demonstrated for afatinib compared to gefitinib (HR 0.71; 95% CI: 0.51 to 0.98), which was consistent with published head to head data. All TKIs led to significantly better PFS compared to all platinum-based chemotherapy regimens except pemetrexed-cisplatin.

3.4 In the absence of robust evidence to indicate that prolonging PFS translates to clinically meaningful outcomes to the patients, the Committee agreed with advice from the ODS that there was considerable uncertainty about the comparative effectiveness of TKIs versus chemotherapy and agreed that results should be interpreted with caution.

3.5 The Committee acknowledged that TKIs were associated with an increased risk of rash, diarrhoea, liver and pulmonary toxicities, and the frequency of adverse effects varied between all 3 agents. However, they noted that the clinicians considered that the adverse reactions were manageable, and were less common than those associated with chemotherapy.
Cost effectiveness

4.1 The ACE technical team conducted an economic evaluation which modelled TKIs compared with pemetrexed-cisplatin chemotherapy as first-line treatment for advanced EGFRM+ NSCLC until disease progression.

4.2 The Committee noted from ACE’s analyses that the base-case incremental cost effectiveness ratios (ICERs) for afatinib, erlotinib and gefitinib compared with pemetrexed-cisplatin were all above $105,000 per QALY gained, and were not considered to be an acceptable use of healthcare resources at the prices proposed by the manufacturers. The Committee acknowledged that the ICERs were highly sensitive to the utility scores and time horizon, and exceeded $200,000 per QALY in some analyses.

4.3 The Committee acknowledged that although manufacturers were given the opportunity to propose price discounts for subsidy consideration through value-based pricing proposals, no price discounts were received. The Committee noted that, not taking into account consultation fees and monitoring tests, the cost of each TKI is already covered under the Medishield Life monthly claim limit ($3,000/month), and therefore there was no incentive for manufacturers to reduce their prices, even though they are not cost-effective.

4.4 The Committee heard that ACE’s cost-effectiveness results were consistent with published cost effectiveness analyses and subsidy of TKIs in other countries such as Australia and the UK was only recommended following considerable price discounts from the manufacturers.

Estimated annual technology cost

5.1 The Committee noted up to 300 subsidised patients with EGFRM+ NSCLC in Singapore would benefit from government assistance for erlotinib, gefitinib and afatinib. The annual cost impact was estimated to be in the range of $500,000 to $1 million for afatinib, less than $500,000 for erlotinib, or $1 to $3 million for gefitinib in the first year of listing on the MAF.
Additional considerations

6.1 The Committee acknowledged that existing patient assistance programs available in several public healthcare institutions in Singapore have also reduced the cost of the TKIs for patients.

Recommendation

7.1 On the basis of the evidence available, the Committee did not recommend afatinib, erlotinib or gefitinib for listing on the MAF for the first-line treatment of locally advanced or metastatic EGFRM+ NSCLC, due to uncertain clinically meaningful benefits for patients in the absence of overall survival gains, and unacceptable cost-effectiveness compared to chemotherapy at the prices proposed by the manufacturers.