Technology Guidance

[GUIDANCE IS OUTDATED AND HAS BEEN WITHDRAWN ON 12 JULY 2022.]

Tyrosine Kinase Inhibitors

for treating ALK mutation-positive advanced 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:

- ✓ Brigatinib 30 mg, 90 mg and 180 mg tablets; and
- ✓ Ceritinib 150 mg capsule

for treating locally advanced or metastatic anaplastic lymphoma kinase (ALK) mutation-positive non-small-cell lung cancer (NSCLC) in line with specific clinical criteria.

Subsidy status

Ceritinib 150 mg capsule is recommended for inclusion on the MOH Standard Drug List (SDL), and brigatinib 30 mg, 90 mg and 180 mg tablets are recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication with effect from 4 January 2022.

SDL subsidy and MAF assistance does not apply to alectinib 150 mg capsule, crizotinib 200 mg and 250 mg capsules, and lorlatinib 25 mg and 100 mg tablets when used to treat ALK mutation-positive NSCLC.

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

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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; alectinib, brigatinib, ceritinib, crizotinib and lorlatinib) for treating anaplastic lymphoma kinase (ALK) 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 all TKIs 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 their appropriate and effective use based on the available clinical evidence.

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; and
- 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. The Committee noted that up to 40 patients are diagnosed with ALK mutation-positive advanced NSCLC each year in Singapore and there was a clinical need to consider TKIs for subsidy to improve treatment affordability and ensure appropriate patient care.

2.2. <u>Newly diagnosed advanced ALK mutation-positive NSCLC</u>
Locally TKIs are standard of care for treating newly diagnosed, advanced ALK mutation-positive NSCLC, in line with international clinical practice guidelines. However, none of the TKIs are currently included in the MOH List of Subsidised Drugs, representing a therapeutic gap. The Committee noted that all patients with non-squamous NSCLC are routinely tested for the presence of oncogenic markers prior to starting treatment, and up to 5% of patients in Singapore have ALK mutation-positive NSCLC.

2.3. Advanced ALK mutation-positive NSCLC after disease progression

The Committee heard from the clinical experts that subsequent treatment choices after disease progression depend on the prior therapy received. Patients who start with crizotinib will most often switch to a 2nd or 3rd generation TKI (alectinib, brigatinib, ceritinib or lorlatinib) after disease progression, while patients who start with alectinib will usually switch to lorlatinib.

Clinical effectiveness and safety

3.1. Newly diagnosed advanced ALK mutation-positive NSCLC

Ceritinib and crizotinib (versus chemotherapy)

The Committee reviewed three randomised controlled trials (RCT) which compared ceritinib and crizotinib with chemotherapy in patients with newly diagnosed advanced ALK mutation-positive NSCLC. While all trials consistently showed no statistically significant overall survival (OS) benefit for ceritinib or crizotinib compared with chemotherapy, there was significant crossover from the chemotherapy arms to the TKI arms leading to uncertainty about the true treatment effect of the TKIs. The Committee noted that all trials showed progression free survival (PFS) benefits favouring TKIs compared to chemotherapy.

3.2. **Alectinib and brigatinib (versus crizotinib)**

The Committee reviewed two RCTs which compared alectinib with crizotinib (ALEX and ALESIA) and one RCT which compared brigatinib with crizotinib (ALTA-1L). The Committee noted that alectinib showed an improvement in 5-year overall survival compared with crizotinib in the ALEX trial; however, OS data remained immature. While median OS was not reached for either brigatinib or crizotinib after a median follow up of 40.4 months in the ALTA-1L trial, the Committee noted that the OS result may have been confounded by crossover since nearly half of the patients who received crizotinib initially crossed over to brigatinib in the study, whereas the ALEX trial did not allow treatment crossover between arms. The Committee heard that all three head-to-head trials showed superior PFS benefits for alectinib and brigatinib compared with another TKI, crizotinib.

3.3. The Committee noted all the TKIs were associated with different safety and tolerability profiles.

3.4. The Committee acknowledged results from TKI evaluations of newly diagnosed ALK mutation-positive NSLCLC conducted by overseas HTA agencies. In particular in the absence of head to head randomised controlled trials, they considered an indirect treatment comparison (ITC) reviewed by NICE (UK) which showed that ceritinib appeared to be more effective than crizotinib at extending PFS; and conclusions made by the PBAC (Australia) which considered the claim of non-inferior PFS of brigatinib compared with alectinib was reasonable based on an ITC of the ALEX and ALTA-1 trials using crizotinib as a common reference, whereas for OS, data was immature

from both trials, and comparison of OS outcomes was potentially confounded by indirect nature of the comparison, differences in the duration of follow up and difference in practice between trials.

3.5. Advanced ALK mutation-positive NSCLC after disease progression

The Committee reviewed three RCTs (two studies compared ceritinib and alectinib with chemotherapy, and one compared two different doses of brigatinib) and one single arm study (for lorlatinib) to inform decisions about treatments for advanced ALK mutation-positive NSCLC after disease progression. The populations in the studies for ceritinib, alectinib and brigatinib included patients whose disease had progressed after one or more lines of therapy including crizotinib with or without chemotherapy. The population in the lorlatinib study included patients whose disease had progressed on prior ALK TKIs (such as ceritinib and alectinib). Results showed ceritinib and alectinib led to PFS benefits favouring the TKIs compared to chemotherapy. The study for brigatinib showed that it was effective for those who had progressed on crizotinib (with or without chemotherapy) with a median PFS of 15.6 months, while the single arm study for lorlatinib showed that it was effective for those who had progressed on other ALK TKIs, including ceritinib and alectinib with a median PFS of 7.4 months.

3.6. The Committee also noted the heterogeneity in the patient populations across studies, the single arm nature of the studies and lack of comparative evidence among the TKIs when used after disease progression.

Cost effectiveness

4.1. Newly diagnosed advanced ALK mutation-positive NSCLC

The Committee acknowledged that the price proposed by the manufacturer for ceritinib was comparable with overseas reference jurisdictions and considerably lower than the prices offered by manufacturers for the other TKIs, making it a cost-effective use of healthcare resources in Singapore. The price proposed by the manufacturer for crizotinib was higher than overseas reference jurisdictions and not considered to be cost-effective.

4.2. The Committee reviewed an in-house cost effectiveness analysis conducted by ACE for alectinib versus crizotinib in patients with newly diagnosed advanced ALK mutation-positive NSCLC. The analysis showed alectinib was associated with a base-case incremental cost effectiveness ratio (ICER) of more than S$105,000 per QALY gained compared with crizotinib.

4.3. The Committee agreed that a cost-minimisation approach was appropriate to assess the cost-effectiveness of brigatinib and alectinib for newly diagnosed ALK mutation-positive NSCLC. The Committee noted that the manufacturer of brigatinib agreed to lower their prices to be more aligned with overseas jurisdictions and 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 brigatinib to be more cost-effective than alectinib.

4.4. Advanced ALK mutation-positive NSCLC after disease progression
Given the absence of evidence showing superiority of any TKIs to treat advanced ALK mutation-positive NSCLC after disease progression, the Committee agreed that a cost-minimisation approach was appropriate to assess the cost-effectiveness of the TKIs, which showed ceritinib and brigatinib to be the cost-effective options 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 cost impact in the first year of listing ceritinib on SDL and brigatinib on MAF for treating advanced ALK mutation-positive NSCLC was estimated to be less than SG$1 million, and between SG$1 million to less than SG$3 million, respectively.

Recommendations

6.1. Based on available evidence, the Committee recommended ceritinib 150 mg capsules be listed on SDL, and brigatinib 30 mg, 90 mg and 180 mg tablets be listed on MAF for treating advanced ALK mutation-positive NSCLC (not restricted to specific line of treatment), in view of the current therapeutic gap in the MOH List of Subsidised Drugs and acceptable clinical effectiveness and cost effectiveness at the prices proposed by the manufacturers.

6.2. At the prices proposed by the manufacturers, alectinib and crizotinib were not recommended for listing on the MAF for newly diagnosed advanced ALK mutation-positive NSCLC due to unacceptable cost effectiveness compared with the other TKIs.

6.3. At the prices proposed by the manufacturers, alectinib and lorlatinib were not recommended for listing on the MAF for advanced ALK mutation-positive NSCLC after disease progression due to unacceptable cost effectiveness compared with the other TKIs.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Clinical indications	Subsidy class (implementation date)	MediShield Life claim limit per month (implementation date)
Alectinib 150 mg capsule	Treatment of locally advanced or metastatic ALK mutation-positive non-small-cell lung cancer.	Not recommended for subsidy	$2000 (1 Sep 2022)
Brigatinib 30 mg, 90 mg and 180 mg tablets	Treatment of locally advanced or metastatic ALK mutation-positive non-small-cell lung cancer.	MAF (4 Jan 2022)	$2000 (1 Sep 2022)
Ceritinib 150 mg capsule	Treatment of locally advanced or metastatic ALK mutation-positive non-small-cell lung cancer.	SDL (4 Jan 2022)	$1000 (1 Sep 2022)
Crizotinib 200 mg and 250 mg capsules	Treatment of locally advanced or metastatic ALK mutation-positive non-small-cell lung cancer.	Not recommended for subsidy	Not recommended for MediShield Life claims
Lorlatinib 25 mg and 100 mg tablets	Treatment of patients with locally advanced or metastatic ALK mutation-positive non-small-cell lung cancer whose disease has progressed after an ALK inhibitor other than crizotinib.	Not recommended for subsidy	$2000 (1 Sep 2022)

Abbreviations: SDL, Standard Drug List; MAF, Medication Assistance Fund