Technology Guidance

Sotorasib

for previously treated KRAS G12C-mutated locally advanced or 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 not recommended sotorasib for inclusion on the MOH List of Subsidised Drugs for previously treated Kirsten Rat Sarcoma glycine-to-cysteine at Codon 12 (KRAS G12C)-mutated locally advanced or metastatic non-small-cell lung cancer. The decision was based on lack of clinical- and cost-effectiveness of sotorasib compared with docetaxel, and the unacceptable price-volume agreement proposed by the company.

Clinical indication, subsidy class and MediShield Life claim limit for sotorasib are provided in the Annex.

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Company-led submission

1.1. At the June 2025 meeting, the MOH Drug Advisory Committee ("the Committee") considered the technology evaluation of sotorasib for previously treated, locally advanced or metastatic ("advanced") KRAS G12C-mutated non-small-cell lung cancer (NSCLC). The evaluation included the company's evidence submission and a review by one of ACE's evidence review centres.

1.2. Expert opinion obtained from clinicians from public healthcare institutions and the MOH Cancer Drug Subcommittee, and patient experts from local patient and voluntary organisations assisted ACE in ascertaining the clinical value of sotorasib.

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. Patients with KRAS G12C-mutated NCSLC typically have poorer survival outcomes compared to those with wild-type KRAS NSCLC. In Singapore, approximately 25 patients are diagnosed annually with advanced NSCLC harbouring the KRAS G12C mutation. The current standard of care involves initial treatment with an immune checkpoint inhibitor (ICI), either alone or in combination with a platinum-based chemotherapy. Upon disease progression, patients typically receive docetaxel monotherapy. The Committee noted that sotorasib would likely replace docetaxel monotherapy in local clinical practice.

2.2. The Committee considered testimonials from 13 local patients and carers about their lived experiences with lung cancer and the different treatments received. They acknowledged that lung cancer significantly impacted patients' emotional health, with both prognostic uncertainty and symptoms affecting their ability to work, socialise and perform daily activities.

2.3. The Committee noted that ten respondents were receiving targeted therapies which they felt worked well, were easy to take and had manageable side effects. They noted that while none of the respondents were familiar with or taking sotorasib, most would be willing to accept the side effects of a new treatment if it effectively reduced disease progression and was affordable. The patients considered that any new treatment for lung cancer should be more affordable, prolong their lifespan, stop the cancer from worsening, and have manageable side effects.

Clinical effectiveness and safety

3.1. The Committee reviewed the clinical evidence, presented in the company's submission, from an open-label, phase III randomised controlled trial (CodeBreaK 200) that compared sotorasib with docetaxel in patients with previously treated, advanced KRAS G12C-mutated NSCLC who had received both an ICI and platinum-based chemotherapy.

3.2. The company requested a listing for patients with advanced KRAS G12C-mutated NSCLC who have received at least one prior systemic therapy. This aligned with the HSA-approved indication but was broader than the CodeBreaK 200 trial population. Local clinicians considered the risk of inappropriate use to be low, as ICI combined with chemotherapy is commonly used as initial treatment for advanced KRAS G12C-mutated NSCLC.

3.3. The Committee heard that at a median follow-up of 16.3 to 17.7 months in the CodeBreaK 200 trial (August 2022 data cut-off), sotorasib showed a marginal benefit in progression-free survival (PFS), as assessed by blinded independent central review (BICR), over docetaxel. However, the PFS benefit did not translate into a significant and meaningful overall survival (OS) benefit. There was no statistically significant improvement in OS compared with docetaxel, with or without adjustments for treatment crossover (Table 1).

Table 1: Results of PFS and OS in CodeBreaK 200 trial

August 2022 data cut-off	Sotorasib (N=171)	Docetaxel (N=174)
PFS by BICR		
Events, n/N (%)	122/171 (71.3)	101/174 (58.0)
Median PFS (95% CI)[a], weeks	5.6 (4.3 to 7.8)	4.5 (3.0 to 5.7)
Hazard ratio (95% CI)[b], p-value[c]	**0.66 (0.51 to 0.86), p=0.002**	
Unadjusted OS		
Events, n/N (%)	109/171 (63.7)	94/174 (54.0)
Median OS (95% CI)[a], weeks	10.6 (8.9 to 14.0)	11.3 (9.0 to 14.9)
Hazard ratio (95% CI)[b], p-value[c]	1.01 (0.77 to 1.33), p=0.530	
Adjusted OS		
Two-stage approach adjusted hazard ratio (95% CI) (all crossover)[b]	0.82 (0.32 to 1.31)	
Two-stage approach adjusted hazard ratio (95% CI) (per protocol crossover)[b]	0.89 (0.17 to 1.33)	
RPSFTM adjusted hazard ratio (95% CI)[b]	1.01 (0.66 to 1.49)	
IPCW adjusted hazard ratio (95% CI)[b]	0.99 (0.73 to 1.34)	

Abbreviations: BICR, blinded independent central review; CI, confidence interval; IPCW, inverse probability of censoring weighting; OS, overall survival; PFS, progression-free survival; RPSFTM, rank preserving structural failure time model.
Bold indicates statistically significant result.
[a] Medians estimated using the Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.
[b] HR and 95% CIs estimated using a stratified Cox proportional hazards model.
[c] p-value is calculated using a stratified log-rank test.

3.4. The Committee noted that the open-label design of CodeBreaK 200 could have introduced bias, particularly in assessing subjective outcomes such as health-related quality of life and adverse events (AEs). The Committee was also concerned about the study conduct, as there was a higher early dropout rate in the docetaxel arm compared to the sotorasib arm, censoring of patients who crossed over from the docetaxel arm to the sotorasib arm before BICR-confirmed progressive disease and imaging assessments of disease progression conducted by study investigators that favoured sotorasib.

3.5. In terms of safety, the Committee noted that the incidence of grade ≥3 treatment-emergent AEs, serious AEs and fatal AEs were consistently higher in patients receiving sotorasib compared with docetaxel. They also noted that while results of treatment-related AEs (TRAEs) appeared to favour sotorasib, these results were potentially biased as assessment of TRAEs was at the discretion of investigators who were not blinded to treatment allocation. The most common grade ≥3 TRAEs reported with sotorasib were diarrhoea, increased alanine transaminase (ALT) and increased aspartate aminotransferase (AST).

The Committee heard that at the time of funding consideration, the US Food and Drug Administration (FDA) had rejected the company's application for full regulatory approval of sotorasib, due to concerns regarding the reliability of results from the CodeBreak 200 trial. The FDA considered that the primary outcome of PFS by BICR lacked reliable interpretation, the observed PFS benefit of sotorasib was modest, and there was no OS benefit versus docetaxel.

3.6. The submission described sotorasib as superior in terms of effectiveness, with a more favourable safety profile compared with docetaxel in patients with previously treated, advanced KRAS G12C-mutated NSCLC. Based on the evidence submitted, the Committee concluded that the submission's claims were not supported given the issues with the study design and study conduct issues that undermined the reliability of the results of the CodeBreaK 200 trial.

Cost effectiveness

4.1. The Committee considered the results of the submission's cost-utility analysis that compared sotorasib with docetaxel for KRAS G12C-mutated advanced NSCLC. Key components of the base-case economic evaluation provided in the submission are summarised in Table 2.

Table 2: Key components of the company-submitted base-case economic evaluation

Component	Description
Type of analysis	Cost-utility analysis
Population	Patients with KRAS G12C-mutated locally advanced or metastatic NSCLC, who have received at least one prior systemic therapy.
Outcomes	Total and incremental costs, total and incremental LYs, total and incremental QALYs, ICER
Perspective	Singapore healthcare system
Type of model	Cohort-based partitioned survival model
Time horizon	5 years in the base case 3 years and 7 years modelled in sensitivity analysis
Health states	Progression-free, Post-progression, Death
Cycle length	1 week
Extrapolation methods used to generate results	• PFS: CodeBreaK 200 PFS KM data by IA fitted and extrapolated using a jointly fitted log-logistic model, for both sotorasib and docetaxel arms. • OS: sotorasib OS KM data from CodeBreaK 200 (fitted and extrapolated using an independently fitted log-normal model), with a HR (0.65) applied from a retrospective analysis of the Flatiron database to estimate docetaxel survival. Treatment waning of OS probabilities over 5 years, beginning at 3 years were used. • ToT: Multipliers derived from the proportion of patients remaining on treatment who were progression-free (by IA) in CodeBreaK 200, applied to the modelled PFS curves. • 60.8% of the incremental LYs gained were accrued in the extrapolated period.
Health-related quality of life	Time-to-death utility values (≥6 months, 3–6 months, 1–3 months and <1 month), which varied by treatment arm, was based on EQ-5D-5L data from CodeBreaK 200, using UK preferences. Disutilities for AEs and IV treatment were not included in the base case.

<table>
<tr><th>Component</th><th>Description</th></tr>
<tr><td></td><td>
<table>
<tr><th>Health state</th><th>Utility</th><th>Nature of estimate</th></tr>
<tr><td><1 month to death</td><td>Sotorasib: 0.749
Docetaxel: 0.670</td><td rowspan="4">EQ-5D-5L, UK value set</td></tr>
<tr><td>1–3 months to death</td><td>Sotorasib: 0.719
Docetaxel: 0.638</td></tr>
<tr><td>3–6 months to death</td><td>Sotorasib: 0.628
Docetaxel: 0.534</td></tr>
<tr><td>≥6 months to death</td><td>Sotorasib: 0.501
Docetaxel: 0.433</td></tr>
</table>
</td></tr>
<tr><td>Types of healthcare resources included</td><td>• Drug acquisition and drug administration costs
• Disease management costs
• Subsequent treatment costs
• AE management costs
• Terminal care costs</td></tr>
</table>

Abbreviations: AE, adverse event; EQ-5D-5L, EuroQoL-5 Dimension-5 Level; HR, hazard ratio; IA, investigator assessment; ICER, incremental cost-effectiveness ratio; IV, intravenous; KM, Kaplan-Meier; LY, life year; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; ToT, time on treatment ; UK, United Kingdom.

4.2. The base-case incremental cost-effectiveness ratio (ICER) in the submission was between SG$105,000 and SG$135,000 per quality-adjusted life year (QALY) gained. However, the Committee considered the ICER to be highly uncertain and likely underestimated given:

- The submission used a hazard ratio from an external real-world study to model the OS for docetaxel. The Committee considered this approach was poorly justified and less reliable than directly using CodeBreaK 200 data.

- The submission assumed that treatment benefits would continue after treatment discontinuation, with waning of the OS effect implemented from Year 3. Given that the observed data only extended to 19 months, the Committee considered it more appropriate to implement treatment waning from this earlier timepoint, as it is unreasonable to assume benefits persist beyond treatment discontinuation.

- The submission modelled time on treatment using multipliers applied to the modelled curve for PFS by investigator assessment (an exploratory outcome used in CodeBreaK 200). The Committee considered this inappropriate, as the multipliers could not be verified and the approach underestimated sotorasib treatment duration after 6 months.

- The submission assumed that more patients receiving docetaxel would receive palliative care as part of best supportive care compared to those receiving sotorasib. The Committee considered this inappropriate as sotorasib would likely delay rather than reduce the need for palliative care.

- The submission applied utility values based on the length of time before death (time-to-death) using data collected from the trial. The Committee considered this approach was inappropriate as the utility data were collected only until 30 days post-treatment discontinuation and may not reflect the decline in utility that occurs following progression over the disease course. Moreover, the submission used utility values derived from EQ-5D-5L instead of EQ-5D-3L specified in ACE's reference case.

4.3. The Committee considered the revised base case, which accounted for several uncertainties in the company's model. Key changes to the economic model included implementing jointly-fitted restricted models for OS for both sotorasib and docetaxel, applying utility values by health states instead of time-to-death, and applying treatment waning from 19 months. These changes substantially increased the ICER for sotorasib to between SG$325,000 and SG$365,000 per QALY gained versus docetaxel.

4.4. The Committee noted that based on a one-way sensitivity analysis of the revised base case, the ICER was sensitive to the time horizon, OS extrapolation method and the approach for utility values.

4.5. Overall, the Committee considered that sotorasib did not represent a cost-effective use of healthcare resources for previously treated, advanced KRAS G12C-mutated NSCLC at the price proposed by the company.

Estimated annual technology cost

5.1. The Committee considered that the company's financial estimates were uncertain due to an overestimation of advanced NSCLC cases, an underestimation of sotorasib treatment duration and an optimistic uptake rate for sotorasib. Based on the revised budget impact model, the annual cost impact to the Singapore public healthcare system was estimated to be less than SG$1 million over the first five years of listing sotorasib on the MOH List of Subsidised Drugs for previously treated, advanced KRAS G12C-mutated NSCLC.

5.2. Additionally, the Committee considered the company's price-volume agreement (PVA) caps were unacceptably high compared to the revised financial estimates. The Committee considered that the company's use of assumptions that lacked sufficient justification resulted in significantly overestimated PVA caps, and does not provide budget certainty to payors.

Recommendations

6.1 Based on available evidence, the Committee recommended not listing sotorasib on the MOH List of Subsidised Drugs for previously treated, advanced KRAS G12C-mutated NSCLC. The decision was based on the lack of clinical- and cost-effectiveness of sotorasib compared with docetaxel, and the unacceptable PVA proposed by the company.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Company-proposed clinical indication	Subsidy class	MediShield Life claim limit per month
Sotorasib 120 mg tablet	Treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small-cell lung cancer, who have received at least one prior systemic therapy.	Not recommended for subsidy	Not recommended for MediShield Life claims

Abbreviation: KRAS G12C, Kirsten Rat Sarcoma glycine-to-cysteine at Codon 12.

Agency for Care Effectiveness - ACE Agency for Care Effectiveness (ACE)

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government funding decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

The guidance is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

Find out more about ACE at www.ace-hta.gov.sg/about

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