

Durvalumab in combination with tremelimumab for treating unresectable hepatocellular carcinoma

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

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

- ✓ Durvalumab 120 mg/2.4 mL and 500 mg/10 mL concentrate for solution for infusion, and tremelimumab 300 mg/15 mL concentrate for solution for infusion, to be used according to the STRIDE regimen (single-dose tremelimumab in combination with regular-interval durvalumab) for treating unresectable hepatocellular carcinoma. Patients must not have received prior systemic therapy and must have adequate liver function as assessed by the Child-Pugh scoring system.

Funding status

Durvalumab 120 mg/2.4 mL and 500 mg/10 mL concentrate for solution for infusion, and tremelimumab 300 mg/15 mL concentrate for solution for infusion, are recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication from 1 August 2025.

Clinical indication, subsidy class and MediShield Life claims eligibility for durvalumab and tremelimumab are provided in the Annex.

Factors considered to inform the recommendations for funding

Company-led submission

- 1.1. At the November 2024 meeting, the MOH Drug Advisory Committee (“the Committee”) considered the technology evaluation of durvalumab in combination with tremelimumab for treating unresectable hepatocellular carcinoma (uHCC) in patients who have not received prior systemic therapy. 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 assisted ACE in ascertaining the clinical value of durvalumab in combination with tremelimumab. Local patient and voluntary organisations were also invited to provide their lived experiences to inform the evaluation, however, no submissions were received.
- 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. In Singapore, approximately 330 new patients with uHCC will require first-line systemic treatment in 2025. The currently subsidised first-line treatment options are atezolizumab plus bevacizumab, as well as monotherapy with lenvatinib or sorafenib.
- 2.2. The Committee noted that durvalumab plus tremelimumab (termed STRIDE regimen) is an alternative for patients with uHCC and may serve the need of some patients who are at high risk of bleeding and unable to receive atezolizumab plus bevacizumab. The STRIDE regimen is administered as a single priming dose of tremelimumab in combination with regular-interval durvalumab that is given until disease progression or unacceptable toxicity.

- 2.3. The Committee noted the submission for STRIDE appropriately nominated sorafenib monotherapy and atezolizumab plus bevacizumab as comparators. While the submission did not present comparative evidence versus lenvatinib, the Committee deemed it reasonable as lenvatinib has previously been considered to be clinically comparable to sorafenib for treating uHCC.

Clinical effectiveness and safety

STRIDE versus sorafenib

- 3.1. The Committee reviewed the clinical evidence, presented in the company's submission, from a phase III randomised controlled trial (RCT; HIMALAYA) that compared STRIDE with sorafenib in patients with uHCC who had not received prior systemic therapy and had Child-Pugh class A.
- 3.2. Results showed that STRIDE improved the primary outcome of OS compared with sorafenib (hazard ratio [HR] 0.78; 95% confidence interval [CI] 0.67 to 0.92), with median OS of 16.4 and 13.8 months respectively.
- 3.3. The Committee noted that, among patients in the STRIDE arm who experienced disease progression, only a small proportion (7.6%) received one-time retreatment with tremelimumab plus regular-interval durvalumab. Hence, the Committee considered the clinical benefit of retreatment after disease progression to be uncertain.
- 3.4. For safety outcomes, the trial reported that the STRIDE regimen had a higher incidence of serious treatment-related adverse events (TRAEs) compared to sorafenib (17.5% vs. 9.6%), but a lower incidence of grade 3 or 4 TRAEs (25.8% vs. 36.9%).
- 3.5. The submission described STRIDE as superior to sorafenib in both clinical effectiveness and safety. While the Committee agreed that the claim of superior effectiveness was reasonable, they considered STRIDE to be non-inferior to sorafenib in safety.

STRIDE versus atezolizumab plus bevacizumab

- 3.6. The Committee heard that no head-to-head trial was conducted comparing STRIDE with atezolizumab plus bevacizumab. Hence, they reviewed a matching-adjusted indirect comparison (MAIC) from the submission, that was informed by trial data from HIMALAYA (for STRIDE) and IMbrave150 (for atezolizumab plus bevacizumab). In IMbrave150, atezolizumab plus bevacizumab was compared with sorafenib in patients with uHCC who had not received prior systemic therapy and had Child-Pugh class A.

- 3.7. The Committee noted several limitations with the MAIC including a reduced sample size for the HIMALAYA matched cohort, and differences between HIMALAYA and IMbrave150 (in terms of endpoint assessments and proportion of patients receiving subsequent anticancer treatments) which were not accounted for in the MAIC.
- 3.8. The results for OS showed no significant difference between STRIDE and atezolizumab plus bevacizumab, but the HR was imprecise (HR 1.09; 95% CI 0.80 to 1.48), and the point estimate was in favour of atezolizumab plus bevacizumab. For progression-free survival (PFS), there was also a treatment difference in favour of atezolizumab plus bevacizumab. Overall, the Committee considered that no definitive conclusions could be drawn from the MAIC due to its limitations and imprecise results.
- 3.9. In terms of safety, the Committee also noted the uncertainty in the MAIC results as the direction of effect was not consistent across outcomes. Compared with atezolizumab plus bevacizumab, STRIDE was associated with lower odds of grade 3 or 4 adverse events (AEs) but higher odds of serious AEs.
- 3.10. The submission described STRIDE as non-inferior in clinical effectiveness, as well as non-inferior or superior in safety, compared with atezolizumab plus bevacizumab. Based on the submitted evidence, the Committee concluded that the company's claims were not adequately supported, and the relative effectiveness and safety between STRIDE and atezolizumab plus bevacizumab remain uncertain.

Cost effectiveness

STRIDE versus sorafenib

- 4.1. The Committee reviewed the submission's cost-utility analysis (CUA) that compared STRIDE with sorafenib based on HIMALAYA trial data. Key components of the base-case economic evaluation are summarised in Table 1.

Table 1: Key components of the company-submitted base-case economic evaluation

Component	Description
Type of analysis	Cost-utility analysis
Population	Patients with unresectable hepatocellular carcinoma receiving first-line systemic treatment
Outcomes	Total and incremental direct medical costs; total and incremental LYs gained; total and incremental QALYs gained; ICER
Perspective	Singapore healthcare system
Type of model	Partitioned survival model
Time horizon	7 years in the base case Sensitivity analyses are presented using 4 and 15 years
Health states	Pre-progression; post-progression; death
Cycle length	Weekly
Extrapolation methods used to generate results	The submission used flexible spline models to extrapolate OS and PFS outcomes for STRIDE, and parametric survival analysis for TtTD for STRIDE, and all outcomes for sorafenib. Treatment waning was not applied. Modelling was based solely on the fitted curves (i.e. fitted curves were used for both the observed and extrapolated periods; KM data were not used in the model). Data from the 4-year follow-up analysis were used: median (95% CI) follow-up of 49.1 months (47.0–50.2) for STRIDE and 47.3 months (45.1–49.2) for sorafenib. 45.9% of QALYs and 13.6% of costs occur in the extrapolated period (i.e. between 4 and 7 years) in the submission base case.
Health-related quality of life	<ul style="list-style-type: none"> The health state utility values for pre- and post- discontinuation were estimated separately across arms, using EQ-5D-5L data from HIMALAYA trial data with Canadian preference weights. Disutility values due to AEs were not applied in the base case.
Types of healthcare resources included	<ul style="list-style-type: none"> Drug and administration costs Disease management costs Subsequent treatment costs AE management costs End-of-life costs

Abbreviations: AE, adverse event; EQ-5D-5L, EuroQol 5-Dimension 5-Level; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; LY, life year; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TtTD, time-to-treatment discontinuation

- 4.2. The base-case incremental cost-effectiveness ratio (ICER) in the submission was between SG\$75,000 and SG\$105,000 per quality-adjusted life year (QALY) gained for STRIDE compared with sorafenib. However, the Committee considered the ICER to be highly uncertain and likely underestimated, mainly due to the choice of health state utility values.
- 4.3. For the submission base case, treatment-specific EQ-5D-5L data collected from the HIMALAYA trial were used to derive health state utilities based on the Canadian value set. However, the derived utility values lacked face validity as they were higher than Canadian population norms and indicated a 'healthy cohort effect'. The submission also applied differential health state utility values across treatment arms, which was considered optimistic by the Committee, as this approach implied that treatment-related differences in quality of life seen in the clinical trial data were sustained over the longer-term, and beyond treatment discontinuation.

- 4.4. The revised base case applied health state utility values from a submission previously reviewed by UK National Institute for Health and Care Excellence (NICE) for lenvatinib, and also adjusted for various healthcare resource use parameters that were over- or under-estimated in the company's economic model. The Committee noted that these changes increased the ICER to between SG\$135,000 and SG\$165,000 per QALY gained.
- 4.5. The Committee noted the key drivers of the ICER included time horizon, and drug acquisition and administration costs of STRIDE. Across most of the scenario analyses, the ICERs remained unfavourably high.

STRIDE versus atezolizumab plus bevacizumab

- 4.6. The submission presented a cost-minimisation analysis (CMA) between STRIDE and atezolizumab plus bevacizumab based on a claim of non-inferiority. The base case results indicated that the total healthcare costs over a 7-year time horizon were lower with STRIDE compared with atezolizumab plus bevacizumab.
- 4.7. The Committee considered that a CMA approach alone was not appropriate to compare STRIDE with atezolizumab plus bevacizumab, and the submission CMA results were highly uncertain. Besides drug and administration costs, the submission CMA also included additional resource uses (e.g. AE management and end-of-life costs), which amplified the uncertainty in the results.
- 4.8. The Committee noted that, in the revised base case, STRIDE was compared with atezolizumab plus bevacizumab based on drug and administration costs only, and over the mean treatment duration of STRIDE in the HIMALAYA trial. The results indicated that STRIDE was costlier than atezolizumab plus bevacizumab. The Committee considered that, as more bevacizumab biosimilars become available, the treatment cost of atezolizumab plus bevacizumab would reduce over time, thereby increasing the incremental cost of STRIDE.
- 4.9. Overall, based on the findings from the CUA and CMA, the Committee considered that STRIDE did not represent a cost-effective use of healthcare resources for treating uHCC at the prices of durvalumab and tremelimumab proposed by the company.

Estimated annual technology cost

- 5.1. The Committee considered that the company's financial estimates and proposed price-volume agreement (PVA) caps for durvalumab and tremelimumab were high, due to the use of optimistic uptake rates for STRIDE.

- 5.2. Based on the revised budget impact model that used more conservative uptake rates, the annual cost impact to the public healthcare system was estimated to be between SG\$1 million and SG\$3 million in the first year, and between SG\$3 million and SG\$5 million in the fifth year of listing durvalumab plus tremelimumab on the MOH List of Subsidised Drugs for treating uHCC.

Recommendations (November 2024)

- 6.1. Based on available evidence, the Committee recommended not listing durvalumab in combination with tremelimumab on the MOH List of Subsidised Drugs for treating uHCC in patients who have not received prior systemic therapy. The decision for durvalumab in combination with tremelimumab was based on its unfavourable cost effectiveness versus sorafenib, its uncertain clinical and cost effectiveness versus atezolizumab plus bevacizumab, and the unacceptable PVAs proposed by the company.

Updated recommendations (March 2025)

- 7.1. Following a negative recommendation by the Committee at the November 2024 meeting, the company of durvalumab and tremelimumab submitted a revised pricing proposal for funding consideration.
- 7.2. Based on the revised proposal, the Committee considered STRIDE to be an acceptable use of healthcare resources for treating uHCC. They also noted that the revised PVA proposals for durvalumab and tremelimumab were adequate to manage the overall budget impact.
- 7.3. Hence, the Committee recommended durvalumab 120 mg/2.4 mL and 500 mg/10 mL concentrate for solution for infusion in combination with tremelimumab 300 mg/15 mL concentrate for solution for infusion (STRIDE regimen), be listed on the Medication Assistance Fund (MAF) for treating uHCC. Patients must not have received prior systemic therapy and must have adequate liver function as assessed by the Child-Pugh scoring system.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Approved clinical indication	Subsidy class (implementation date)	Eligible for MediShield Life claims (implementation date)
Durvalumab 120 mg/2.4 mL and 500 mg/10 mL concentrate for solution for infusion Tremelimumab 300 mg/15 mL concentrate for solution for infusion	Durvalumab in combination with a single priming dose of tremelimumab for treating unresectable hepatocellular carcinoma in patients who have not received prior systemic therapy, and who have adequate liver function as assessed by the Child-Pugh scoring system.	MAF (1 Aug 2025)	Yes ¹ (1 Aug 2025)
Durvalumab 120 mg/2.4 mL and 500 mg/10 mL concentrate for solution for infusion	Treatment of unresectable hepatocellular carcinoma in patients who had received a priming dose of tremelimumab and have adequate liver function as assessed by the Child-Pugh scoring system.	MAF (1 Aug 2025)	Yes ¹ (1 Aug 2025)

Abbreviation: MAF, Medication Assistance Fund.

¹ Please refer to [MOH's website](#) for the MediShield Life claim limit starting from the implementation date.

VERSION HISTORY

Guidance on durvalumab in combination with tremelimumab for treating unresectable hepatocellular carcinoma

This Version History is provided to track any updates or changes to the guidance following the first publication date. It is not part of the guidance.

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|----|---|-------------|
| 1. | Publication of guidance | |
| | Date of Publication | 17 Feb 2025 |
| 2. | Guidance updated to include durvalumab and tremelimumab on the Cancer Drug List and Medication Assistance Fund | |
| | Date of Publication | 4 Jun 2025 |
| 3. | Guidance updated to reflect MediShield Life claims eligibility | |
| | Date of Publication | 1 Jun 2026 |

 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 <https://www.ace-hta.gov.sg/about-us/>

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