Technology Guidance

Tisagenlecleucel

for relapsed or refractory B-cell acute lymphoblastic leukaemia

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

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

- ✓ Tisagenlecleucel cells dispersion for infusion for treating patients between two to 25 years of age (both ages inclusive) with B-cell acute lymphoblastic leukaemia that is refractory, in relapse post-transplant or in second or later relapse.

Funding status

Tisagenlecleucel cells dispersion for infusion is recommended for inclusion on the MOH Cell, Tissue and Gene Therapy Product (CTGTP) List for the abovementioned indication from 1 August 2024.

Tisagenlecleucel should be used in line with the additional clinical criteria listed in the Annex.

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Factors considered to inform the recommendations for funding

Technology evaluation

1.1. At the March 2024 meeting, the MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia (ALL). The Agency for Care Effectiveness (ACE) conducted the evaluation based on the evidence submitted by the company, in consultation with clinical experts from public healthcare institutions and patient experts from local patient and voluntary organisations.

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 funding considerations.

Clinical need

2.1. Approximately three paediatric and young adult patients are diagnosed with relapsed or refractory ALL each year in Singapore. In local clinical practice, most patients will receive blinatumomab (main comparator, listed on the Medication Assistance Fund), whereas salvage chemotherapy is less commonly used. The primary treatment goal is to achieve complete remission to undergo haematopoietic stem cell transplantation (HSCT).

2.2. Tisagenlecleucel is a one-time, chimeric antigen receptor T-cell (CAR-T) therapy. The Committee acknowledged the clinical need to consider tisagenlecleucel for funding, to improve affordability and ensure appropriate patient care.

2.3. The Committee considered two testimonials from local carers of patients about their experiences with ALL. They heard that the condition had a significant, negative impact on patients and their carers, affecting them physically, socially, mentally and emotionally. The Committee noted the carers' greatest concerns were financial burden and treatment side effects. One patient who received chemotherapy and HSCT had experienced severe side effects that required additional treatments. The Committee heard that the carers considered tisagenlecleucel would reduce the treatment burden for their children and were willing to let them receive the treatment if there was a possibility they could achieve remission. Overall, the carers considered that any new treatment for relapsed or refractory ALL should improve the quality of life for patients and carers and stop the cancer from worsening.

Clinical effectiveness and safety

3.1. In the absence of direct comparative evidence, the Committee reviewed indirect comparisons based on three single-arm trials for tisagenlecleucel (B2101J, ELIANA and ENSIGN), a single-arm trial for blinatumomab (MT103-205) and a retrospective observational study for salvage chemotherapy (von Stackelberg et al. 2011). The Committee heard that tisagenlecleucel was associated with improved overall response rate and overall survival when compared to blinatumomab and salvage chemotherapy.

3.2. The Committee noted that the results were based on the full analysis set (FAS; excluding patients assigned to the tisagenlecleucel arm who did not receive it) which biased the indirect comparisons in favour of tisagenlecleucel. The Committee agreed that results from the intention-to-treat population would be more appropriate in assessing the comparative efficacy.

3.3. Overall, the Committee considered that the naïve comparison was subject to bias due to differences in study designs and patient characteristics across the studies. The results from matching-adjusted indirect comparisons were also uncertain, given that (i) treatment effect modifiers and prognostic factors may not be fully accounted for, (ii) effective sample sizes were reduced after matching and (iii) the matched population may not be applicable to the local setting.

3.4. In terms of safety, the Committee heard that compared with blinatumomab, tisagenlecleucel was associated with a higher incidence of grade ≥3 adverse events and potentially fatal adverse events including cytokine release syndrome, neurological adverse reactions, febrile neutropenia and decreased platelet count. The Committee acknowledged that the available evidence was inadequate to support a reliable assessment of the comparative safety between tisagenlecleucel and salvage chemotherapy.

3.5. Based on the available evidence, the Committee considered that tisagenlecleucel was superior in terms of effectiveness compared with blinatumomab and salvage chemotherapy but the magnitude of the treatment effect remained uncertain. In terms of safety, the Committee considered tisagenlecleucel to be inferior to blinatumomab, and inconclusive compared with salvage chemotherapy. In addition, the Committee noted uncertainty regarding the long-term survival benefit and safety associated with tisagenlecleucel.

Cost effectiveness

4.1. The Committee considered the results of a cost-utility analysis that compared tisagenlecleucel with blinatumomab (main comparator) in paediatric and young adult patients with relapsed or refractory ALL. Key components of the company's 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	Paediatric and young adult patients 2 to and including 25 years of age with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse
Outcomes	Total and incremental direct medical costs; total and incremental LY gained; total and incremental QALYs; ICER
Perspective	Singapore healthcare system
Type of model	Decision tree with partitioned survival model
Time horizon	88 years in the base case
Health states	EFS; post-progression; death
Cycle length	Monthly (30.44 days)
Extrapolation methods used to generate results	Transitions were informed by EFS and OS curves of tisagenlecleucel and blinatumomab. Survival curves were from pooled from B2101J, ELIANA and ENSIGN for tisagenlecleucel and MT103-205 for blinatumomab. These survival curves were extrapolated using standard parametric distributions and flexible spline method on a weighted basis (by AIC) in the base case. 88% of the LYs and 85% of the QALYs gained occurred in the extrapolated period.
Health-related quality of life	The health state utility values were informed by EQ-5D-5L (cross walked to 3L) with the data from ELIANA. • Progression-free=0.81 • Post-progression=0.69
Types of healthcare resources included	• CAR-T cost • Drug costs • Administration cost • Disease management cost • Adverse events cost

Abbreviations: AIC, Akaike information criterion; ALL, acute lymphoblastic leukaemia; CAR-T, chimeric antigen receptor T-cell; EFS, event-free survival; EQ-5D-5L, 5-level EuroQol 5-dimensional questionnaire; ICER, incremental cost-effectiveness ratio; LY, life years; OS, overall survival; QALY, quality-adjusted life-year.

4.2. The Committee considered the company's base-case incremental cost-effectiveness ratio (ICER) of between SG$45,000 and SG$75,000 per quality adjusted life-year (QALY) gained to be uncertain, because of the following:

- Once a cure was assumed, the model did not allow patients in the event-free survival health state to transition to death until the progressed disease health state was exhausted. In addition, although patients progressed, they were only exposed to a mortality rate that was marginally higher than that of the general population.

- In terms of healthcare resource use, the treatment costs of blinatumomab were overestimated, and the duration of intravenous immunoglobulin use for B-cell aplasia following tisagenlecleucel infusion was underestimated, both of which biased the incremental costs in favour of tisagenlecleucel.

4.3. The Committee noted that the ICER further increased and remained high in the revised base case, which accounted for changes in the cure assumptions and applying healthcare resource use parameters to reflect local practice. The Committee acknowledged other uncertainties associated with the ICER were due to (i) the limitations associated with the indirect comparisons between tisagenlecleucel and blinatumomab and (ii) the treatment benefits of tisagenlecleucel being accrued over a long time horizon, despite the short follow up from the tisagenlecleucel studies.

4.4. Following pricing negotiations, the Committee agreed that tisagenlecleucel was likely to represent an acceptable use of healthcare resources in the local setting, considering the improved ICER and prices in overseas reference jurisdictions. The proposal was also adequate to manage the uncertainty of the overall budget impact.

Estimated annual technology cost

5.1. The Committee considered that the company's estimates were high due to an overestimation of eligible patients. Based on the revised budget impact model, the annual cost impact to the public healthcare system was estimated to be less than SG$1 million, following inclusion on the MOH Cell, Tissue and Gene Therapy Product (CTGTP) List.

Recommendations

6.1. Given the clinical need, acceptable clinical effectiveness compared with current treatment options, and that tisagenlecleucel is considered to be an acceptable use of healthcare resources, the Committee recommended tisagenlecleucel cells dispersion for infusion, to be included on the MOH CTGTP List, for treating patients between two to 25 years of age (both ages inclusive) with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse.

6.2. The Committee also recommended that tisagenlecleucel be used in line with additional clinical criteria (listed in the Annex) to govern appropriate use in local practice. The criteria were developed in consultation with local clinical experts and are consistent with the pivotal trial population and overseas reimbursement criteria.

Annex

Clinical criteria for tisagenlecleucel for relapsed or refractory B-cell acute lymphoblastic leukaemia

Tisagenlecleucel cells dispersion for infusion for treating patients between two to 25 years of age (both ages inclusive), with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse, who also satisfy the requirements below:

- if the patient is <16 years of age, that patient is assessed to have a Lansky performance status of ≥50;
- if the patient is ≥16 years of age, that patient is assessed to have a Karnofsky performance status of ≥50;
- if the patient has Philadelphia-positive (PH+) B-cell ALL, that patient must:
  - (i) be assessed to be intolerant to tyrosine kinase inhibitor (TKI) therapy;
  - (ii) have failed at least two lines of TKI therapy; or
  - (iii) be assessed to be contraindicated for TKI therapy;
- the patient must have been assessed according to a morphologic assessment to have ≥5% lymphoblasts and CD19 ALL positivity in the patient's bone marrow;
- the patient must not have any of the following:
  - (i) isolated extramedullary ALL relapse;
  - (ii) any uncontrolled infection, including but not limited to HIV, active hepatitis B or active hepatitis C;
  - (iii) any active central nervous system (CNS) involvement by ALL;
  - (iv) any uncontrolled secondary CNS disease; or
  - (v) any secondary CNS disease that is anticipated to be uncontrolled at the time of lymphocyte infusion;
- the patient must have sufficient organ function (e.g. renal, cardiac, and pulmonary function); and
- the patient must not have received any prior chimeric antigen receptor T-cell (CAR-T) treatments for B-cell ALL.

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

Agency for Care Effectiveness, Ministry of Health, Singapore
Email: ACE_HTA@moh.gov.sg

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