Technology Guidance

Toripalimab

for first-line systemic treatment of recurrent or metastatic nasopharyngeal carcinoma

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended toripalimab in combination with chemotherapy for inclusion on the MOH List of Subsidised Drugs for first-line systemic treatment of recurrent or metastatic nasopharyngeal carcinoma. The decision was based on the unfavourable cost-effectiveness of toripalimab plus chemotherapy compared with chemotherapy alone, and the unacceptable price-volume agreement proposed by the company.

Clinical indication, subsidy class and MediShield Life claim limit for toripalimab plus chemotherapy 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 toripalimab in combination with chemotherapy for first-line systemic treatment of recurrent or metastatic nasopharyngeal carcinoma. 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 toripalimab. Local patient and voluntary organisations were also invited to provide their lived experiences to inform the evaluation.

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. Approximately 270 patients are diagnosed with nasopharyngeal carcinoma each year in Singapore. For patients who have recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma (RM-NPC), the current standard first-line systemic therapy is gemcitabine-cisplatin (GP) chemotherapy. However, as the prognosis for these patients remains poor, the Committee acknowledged the clinical need for more effective treatment options.

2.2. The Committee noted that two programmed cell death protein 1 (PD-1) inhibitors, toripalimab and tislelizumab, were recently approved by the Health Sciences Authority (HSA) for use in combination with GP for first-line systemic treatment of RM-NPC.

2.3. The Committee considered 16 testimonials from local patient experts and carers about the negative impact of nasopharyngeal carcinoma on their physical, mental and emotional well-being. They noted that the fear of disease recurrence was a major concern. Most patients were treated with chemotherapy, either alone or in combination with radiotherapy. While some patients felt that their treatments worked well, all of them experienced treatment side effects which had a significant negative impact on their daily lives. These side effects included xerostomia, dysphagia, neck and jaw spasms, hearing loss, burns and mouth ulcers. The Committee noted that patients were concerned about the high cost of treatments as well as costs associated with specialist outpatient care and supplementary interventions to manage treatment side effects.

2.4. The Committee acknowledged that none of the respondents were familiar with toripalimab, but most of them would be willing to accept the side effects of a new treatment if it could stop the cancer from worsening. However, they would be less willing to pay more for a new treatment without survival benefits. Overall, they considered that any new treatment for nasopharyngeal carcinoma should prevent recurrence, stop the cancer from worsening, extend survival, improve quality of life, have manageable side effects, and be more affordable.

Clinical effectiveness and safety

3.1. The Committee noted the company's submission for toripalimab appropriately nominated GP (current standard of care) as the comparator. The Committee also considered tislelizumab to be a relevant comparator as it had achieved HSA approval for the same indication as toripalimab. However, no comparative evidence against tislelizumab was included in the submission.

3.2. The Committee reviewed the clinical evidence from a phase III randomised controlled trial (JUPITER-02) that investigated toripalimab as first-line systemic therapy for RM-NPC. Patients in the trial were randomised to receive toripalimab or placebo, both in combination with GP, every 3 weeks for up to 6 cycles. This was followed by maintenance treatment with toripalimab or placebo until disease progression, intolerable toxicity, or a maximum of 2 years of treatment was reached.

3.3. The primary endpoint was progression-free survival (PFS) as assessed by a blinded independent central review. At the final analysis, toripalimab improved PFS compared with placebo (hazard ratio [HR] 0.52; 95% confidence interval [CI] 0.37 to 0.73), with median PFS of 21.4 and 8.2 months, respectively.

3.4. At a median survival follow-up of 36 months, results showed that toripalimab improved overall survival (OS) compared with placebo (HR 0.63; 95% CI 0.45 to 0.89). The median OS was not reached in the toripalimab arm (95% CI 38.7 months to not estimable), while it was 33.7 months in the placebo arm (95% CI 27.0 to 44.2 months).

3.5. In terms of safety, the incidence of grade ≥3 treatment-emergent adverse events (TEAEs) and serious TEAEs were similar between the two treatment arms. However, a higher proportion of patients treated with toripalimab had TEAEs leading to treatment discontinuation, immune-related TEAEs, and events of hypothyroidism, pneumonia, and pruritus compared with those who received placebo.

3.6. The submission described toripalimab plus GP as superior in clinical effectiveness, and non-inferior in safety, compared with GP alone. The Committee considered that the claim of superior effectiveness was supported, although the magnitude of the OS benefit from toripalimab remained uncertain given the immaturity of the data. In terms of safety, the Committee considered a claim of inferior safety was more appropriate for toripalimab plus GP versus GP alone based on the trial evidence. The Committee also considered that the clinical effectiveness and safety of toripalimab versus tislelizumab could not be ascertained due to the unavailability of comparative evidence between the two treatments.

Cost effectiveness

4.1. The Committee reviewed the submission's cost-utility analysis (CUA) that compared toripalimab plus GP versus GP alone based on JUPITER-02 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 recurrent or metastatic nasopharyngeal carcinoma
Outcomes	Total and incremental direct medical costs; total and incremental LY gained; total and incremental QALYs; ICER
Perspective	Singapore healthcare system
Type of model	Partitioned survival analysis
Time horizon	10 years in the model base case Lifetime time horizon modelled in sensitivity analysis
Health states	Progression-free survival (PFS); post-progression survival (PPS); death
Cycle length	One week
Extrapolation methods used to generate results	Derived from the PFS and overall survival (OS) Kaplan-Meier (KM) curves from the JUPITER-02 trial for both treatment arms. The PFS and OS curves were extrapolated by fitting parametric models (exponential, generalised gamma, Weibull, Gompertz, log-normal and log-logistic) to the KM data based on goodness of fit (visual inspection and AIC/BIC values). A piecewise approach for extrapolation was employed when standard parametric models did not provide good fits to the observed KM data. The proportion of patients in the PFS health state was directly estimated from the PFS curve, the proportion of patients in the PPS health state was estimated as the difference between the OS and PFS curves, and the proportion of patients transitioning to the death health state was estimated as 1-OS.
Health-related quality of life	The health state utility values (EQ-5D) applied in the base case were sourced from a published trial (CheckMate 141) for nivolumab in patients with recurrent or metastatic head and neck squamous cell carcinoma. • PFS health state: 0.68 • PPS health state: 0.66
Types of healthcare resources included	• Drug and drug administration • Disease management cost • Subsequent treatment costs • AE management costs • End-of-life costs

Abbreviations: AE, adverse event; AIC, Akaike information criterion; BIC, Bayesian information criterion; EQ-5D, EuroQol 5-Dimension; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

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 toripalimab plus GP compared with GP alone. However, the Committee considered the ICER to be highly uncertain and likely underestimated, mainly due to the following methodological errors and uncertainties in survival extrapolation:

- The submission applied hospice care costs to the cumulative number of patients in the death health state at the end of each cycle, instead of only to those who died in each cycle, leading to inflated total costs.

- The costs of subsequent treatments had not considered treatment durations and were applied to patients in the post-progression survival (PPS) health state until transition to the death health state. This effectively assumed that all progressed patients would receive subsequent treatment until death, which was not reasonable.

- The submission's choice of parametric models used to extrapolate OS for the two treatment arms predicted implausibly high proportions of patients who remained alive at 10 years.

4.3. The Committee considered the revised base case which had rectified the methodological errors and applied more plausible OS extrapolations for both treatment arms. The results showed an increased ICER of between SG$165,000 and SG$205,000 per QALY gained. Across all scenario analyses, the ICERs remained unfavourably high.

4.4. Overall, the Committee considered that, at the price proposed by the company, toripalimab did not represent a cost-effective use of healthcare resources when used in combination with GP for first-line systemic treatment of RM-NPC.

Estimated annual technology cost

5.1. The Committee considered that the company's financial estimates and proposed price-volume agreement (PVA) caps for toripalimab were high. This was mainly because the submission overestimated the incidence of nasopharyngeal carcinoma in Singapore, and inappropriately assumed that patients would receive the maximum number of 34 cycles of toripalimab in 2 years (as opposed to using 20.4 cycles based on the mean treatment duration in the JUPITER-02 trial).

5.2. The above issues were addressed in the revised budget impact model. The annual cost impact to the public healthcare system was estimated to be between SG$3 million and SG$5 million over the first five years of listing toripalimab on the MOH List of Subsidised Drugs for treating RM-NPC.

Recommendations

6.1. Based on available evidence, the Committee recommended not listing toripalimab in combination with chemotherapy on the MOH List of Subsidised Drugs for first-line systemic treatment of RM-NPC. The decision was based on the unfavourable cost-effectiveness of toripalimab plus chemotherapy compared with chemotherapy alone, 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
Toripalimab concentrate for solution for infusion (240 mg/6 mL)	Toripalimab in combination with chemotherapy for first-line systemic treatment of recurrent, not eligible for local-regional or curative treatment, or metastatic nasopharyngeal carcinoma. Maximum treatment duration with toripalimab is 2 years.	Not recommended for subsidy	Not recommended for MediShield Life claims

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

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