Technology Guidance

Dostarlimab

for treating dMMR or MSI-H primary advanced or recurrent endometrial cancer

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

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

- ✓ Dostarlimab 500 mg concentrate for solution for infusion, in combination with carboplatin and paclitaxel, followed by dostarlimab as monotherapy for untreated mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) primary advanced or recurrent endometrial cancer. Treatment with dostarlimab should be stopped at 3 years, or earlier if disease progresses.

Funding status

Dostarlimab 500 mg concentrate for solution for infusion is recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication from 1 April 2025.

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

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Factors considered to inform the recommendations for funding

Company-led submission

1.1. At the July 2024 meeting, the MOH Drug Advisory Committee ("the Committee") considered the evidence submitted by the company and a review of the submission by one of ACE's evidence review centres for the technology evaluation of dostarlimab, when used in combination with carboplatin and paclitaxel, for mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) primary advanced or recurrent endometrial cancer.

1.2. Expert opinion was obtained from the MOH Cancer Drug Subcommittee and patient experts from local patient and voluntary organisations, who assisted ACE to ascertain the clinical value of dostarlimab.

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. The Committee heard that endometrial cancer is the most common gynaecological malignancy in women. dMMR or MSI-H tumours account for around 25% of endometrial cancers. Approximately 60 patients are diagnosed with dMMR or MSI-H primary advanced or recurrent endometrial cancer each year in Singapore.

2.2. In local practice, most patients who have dMMR or MSI-H primary advanced or recurrent endometrial cancer are treated with carboplatin plus paclitaxel. While carboplatin and paclitaxel are already subsidised, the Committee acknowledged the clinical need to consider dostarlimab for funding, to improve treatment affordability and ensure appropriate patient care. However, they noted that more treatment options, including other programmed cell death protein-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitors, are expected to receive regulatory approval for this indication.

2.3. The submission nominated carboplatin plus paclitaxel as the sole comparator. However, the Committee considered the appropriate comparators were not limited to carboplatin plus paclitaxel. Other near-market PD-1 or PD-L1 inhibitors were also relevant.

2.4. The Committee considered the testimonial from a local patient expert about how living with endometrial cancer had negatively impacted her physical well-being, causing fatigue, poor appetite and breathlessness which also impacted her ability to exercise. The Committee noted that the condition also had a profound effect on her mental and emotional well-being, leading to feelings of anxiety and stress. The Committee noted that she had previously received chemotherapy but stopped after the third cycle due to side effects such as numbness of extremities, and hair loss which affected her self-confidence and social life. They acknowledged that she was unfamiliar with dostarlimab but considered any new treatment options for endometrial cancer should be more affordable, have fewer side effects, and be taken orally for improved convenience.

Clinical effectiveness and safety

3.1. The Committee reviewed the clinical evidence in the submission, which was based on a phase III randomised controlled trial (RUBY) that compared dostarlimab with placebo in patients with primary advanced or recurrent endometrial cancer, who were also receiving carboplatin plus paclitaxel. While the submission relied on results of subgroup analyses in patients with dMMR or MSI-H endometrial cancer to inform the clinical claim, the Committee noted that this was aligned with the company's requested listing and the approved HSA indication.

3.2. The submission presented results of the dMMR or MSI-H subgroup from the first interim analysis of RUBY (September 2022 data cut-off). At a median follow-up of 24.8 months, dostarlimab led to a statistically significant improvement in progression-free survival (PFS) compared with placebo (Table 1). While overall survival (OS) was not formally tested for statistical significance, the results suggested a trend towards OS benefit in favour of dostarlimab. However, OS data was immature. The Committee noted that the company had recently released updated OS results from the RUBY trial. However, they were unable to verify the findings as the results were not included in the submission. Overall, the Committee considered that uncertainty remained about the long-term survival resulting from treatment with dostarlimab in combination with carboplatin and paclitaxel.

Table 1: Results for PFS and OS in the RUBY trial (September 2022 data cut-off)

	Dostarlimab (N=53)	Placebo (N=65)	HR (95% CI), p value
PFS by investigator assessment			
Patients with event, n (%) Progression Death	19 (35.8) 16 (30.2) 3 (5.7)	47 (72.3) 44 (67.7) 3 (4.6)	-
Median PFS, months (95% CI)	NR (11.8 to NR)	7.7 (5.6 to 9.7)	**0.28 (0.162 to 0.495), p<0.0001**
OS			
Patients with event, n (%)	7 (13.2)	24 (36.9)	-
Median OS, months (95% CI)	NR (NR to NR)	NR (23.2 to NR)	0.30 (0.127 to 0.699)

Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival.
Bold indicates a statistically significant result.

3.3. The Committee noted the small patient numbers for the dMMR or MSI-H subgroup and considered that the imbalance in patient characteristics between study arms in the trial was likely to bias the results in favour of the dostarlimab arm. Notably, patients in the placebo arm had higher mean body mass index compared to those in the dostarlimab arm, and body mass index was associated with poorer prognosis in endometrial cancer. The Committee also noted that generalisability of the RUBY trial's results to the local setting was limited, as the mean body mass index at baseline and the proportion of patients who had not received neo-adjuvant or adjuvant chemotherapy were higher than observed in clinical practice.

3.4. In terms of safety, the Committee heard that, compared with placebo, dostarlimab was associated with a higher incidence of grade ≥3 treatment-emergent adverse events (TEAEs; 70.5% vs 59.8%), serious adverse events (37.8% vs 27.6%) and immune-related TEAEs (56.8% vs 35.8%). More patients in the dostarlimab arm also experienced TEAEs leading to study drug discontinuation (23.7% vs 16.7%).

3.5. In patients with dMMR or MSI-H primary advanced or recurrent endometrial cancer, the submission described dostarlimab in combination with carboplatin and paclitaxel as superior, in terms of effectiveness, and acceptable, in terms of safety, compared with carboplatin plus paclitaxel. While the claim of superior effectiveness was found to be reasonable, the Committee concluded that the magnitude and sustainability of long-term clinical benefit provided by dostarlimab was uncertain. In terms of safety, the Committee considered that the addition of dostarlimab to carboplatin plus paclitaxel resulted in an inferior safety profile.

Cost effectiveness

4.1. The submission presented an economic evaluation for patients with dMMR or MSI-H primary advanced or recurrent endometrial cancer, based on the RUBY trial. Dostarlimab with carboplatin plus paclitaxel was compared with carboplatin plus paclitaxel, using a cost-utility analysis. 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 dMMR or MSI-H primary advanced or recurrent endometrial cancer
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 model
Time horizon	15 years in the model base case, based on a median follow-up of 24.8 months in the RUBY trial
Health states	Progression-free; post-progression; death
Cycle length	1 week
Extrapolation methods used to generate results	Time-to-event data (PFS, OS, TTD) was informed by the RUBY trial. The submission used flexible, non-parametric models to extrapolate PFS outcomes, whereas parametric models were utilised to extrapolate OS and TTD outcomes. No treatment effect waning was applied in the base case. • For PFS, the odds distribution with 2 knots was used for extrapolation in both arms. • OS was based on a piecewise approach that utilised all available KM data followed by parametric extrapolation beyond the trial period. The exponential distribution was used for the CP arm, whereas OS in the dostarlimab plus CP arm was informed by applying a constant hazard ratio of 0.32 to the CP arm. • TTD in the CP arm utilised TTD data directly from the RUBY trial up to a maximum of 18 weeks, whereas TTD in the dostarlimab plus CP arm was based on a piecewise approach that utilised all available TTD data followed by Weibull distribution for extrapolation beyond the trial period, up to a maximum of 3 years.
Health-related quality of life	• Progression-free health state utilities were based on the RUBY trial = 0.758 • Post-progression health state utilities were based on the RUBY trial = 0.710
Types of healthcare resources included	• Drug and drug administration • Disease management cost • Healthcare resource use • Subsequent treatment costs • AE management costs

Abbreviations: AE, adverse event; CP, carboplatin plus paclitaxel; dMMR, mismatch repair deficient; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; LY, life year; MSI-H, microsatellite instability-high; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TTD, time-to-treatment discontinuation.

4.2. The base-case incremental cost-effectiveness ratio (ICER) in the submission was between SG$15,000 and SG$45,000 per quality-adjusted life year (QALY) gained. However, the Committee considered the ICER to be highly uncertain and likely underestimated, given the following:

- Immature OS data resulted in substantial uncertainty in long-term survival estimates. The Committee noted that this had a large impact on cost-effectiveness, as the majority of the incremental QALYs were accrued during the extrapolated period.

- The submission assumed that the treatment effect of dostarlimab with carboplatin plus paclitaxel persisted over the time horizon even after discontinuation of treatment. Given the uncertainty in the sustainability of long-term clinical benefit provided by dostarlimab, the Committee considered that the lack of treatment effect waning was an optimistic assumption that overestimated the cost-effectiveness results.

- The submission's choice of extrapolations methods resulted in the PFS and OS curves intersecting at approximately 10 years from baseline. In particular, the use of flexible models with multiple knots increased the weight that the tail end of the PFS Kaplan-Meier curve had on extrapolation, even though it was informed by a small number of events. The Committee considered the modelled long-term outcomes to be clinically implausible and highly uncertain.

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 applying treatment waning and choice of OS and PFS extrapolations. These changes increased the ICER to between SG$75,000 and SG$105,000 per QALY gained.

4.4. Overall, the Committee considered that at the price proposed by the company, dostarlimab did not represent a cost-effective use of healthcare resources when used in combination with carboplatin and paclitaxel for treating dMMR or MSI-H primary advanced or recurrent endometrial cancer.

Estimated annual technology cost

5.1. The Committee considered that the submission's financial estimates and price-volume agreement (PVA) caps were high due to an overestimation of the number of vials required per treatment course and an optimistic uptake rate for dostarlimab, given the potential entry of other PD-1 or PD-L1 inhibitors.

5.2. Based on the revised budget impact model, the annual cost impact to the public healthcare system was estimated to be between SG$1 million and SG$3 million.

Recommendations (July 2024)

6.1. Based on the evidence submitted, the Committee recommended not listing dostarlimab on the MOH List of Subsidised Drugs, for use in combination with carboplatin and paclitaxel, for treating dMMR or MSI-H primary advanced or recurrent endometrial cancer. The decision was based on the uncertain extent of clinical benefit, the unfavourable cost effectiveness of dostarlimab, and the unacceptable PVA proposed by the company.

Updated recommendations (November 2024)

7.1. Following a negative recommendation at the July 2024 meeting, the company of dostarlimab submitted a revised proposal. The Committee noted that the revised proposal by the company resulted in an improved ICER and was adequate to manage the overall budget impact.

7.2. Hence, the Committee recommended dostarlimab 500 mg concentrate for solution for infusion be listed on the Medication Assistance Fund, for use in combination with carboplatin and paclitaxel, for treating dMMR or MSI-H primary advanced or recurrent endometrial cancer.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Clinical indication	Subsidy class (implementation date)	MediShield Life claim limit per month (implementation date)
Dostarlimab concentrate for solution for infusion (500 mg/ 10 mL)	Dostarlimab in combination with carboplatin and paclitaxel, followed by dostarlimab as monotherapy, for untreated mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) primary advanced or recurrent endometrial cancer. Treatment with dostarlimab should be stopped at 3 years, or earlier if disease progresses.	MAF (1 April 2025)	$1,800 (1 April 2025)

VERSION HISTORY

Guidance on dostarlimab for treating dMMR or MSI-H primary advanced or recurrent endometrial cancer

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.

1. **Publication of guidance**

Date of Publication	13 Sep 2024

2. **Guidance updated to include dostarlimab on the Cancer Drug List and Medication Assistance Fund**

Date of Publication	17 Feb 2025