Technology Guidance

Durvalumab with or without olaparib

for treating 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 not recommended durvalumab in combination with platinum-based chemotherapy, then as maintenance with or without olaparib, for inclusion on the MOH List of Subsidised Drugs for patients with untreated primary advanced or recurrent endometrial cancer. The decision was based on the uncertainties surrounding the magnitude of clinical benefit compared with chemotherapy, and unfavourable cost-effectiveness compared with chemotherapy and dostarlimab.

Clinical indication, subsidy class and MediShield Life claim limit for durvalumab and olaparib 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 two treatment regimens involving durvalumab, with or without olaparib, for untreated primary advanced or recurrent (A/R) endometrial cancer (EC). These regimens were 1) durvalumab in combination with carboplatin and paclitaxel (CP) followed by durvalumab as monotherapy ("durvalumab plus CP") for mismatch repair deficient (dMMR) primary A/R EC, and 2) durvalumab with CP followed by durvalumab with olaparib ("durvalumab plus OCP") for mismatch repair proficient (pMMR) primary A/R EC. 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 durvalumab and olaparib.

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. EC is the most common gynaecological malignancy in women. Approximately 230 new patients are diagnosed with primary A/R EC each year in Singapore, with the majority expected to receive first-line systemic therapy. Of these patients, approximately 25% have dMMR tumours, while the remaining 75% have pMMR tumours.

2.2. The current subsidised first-line treatment options for patients with dMMR primary A/R EC include chemotherapy with CP alone, and dostarlimab in combination with CP followed by dostarlimab as monotherapy ("dostarlimab plus CP"). The Committee noted that the proposed regimen of durvalumab plus CP would provide an alternative treatment for this subgroup.

2.3. For patients with pMMR primary A/R EC, CP is the only subsidised treatment available. The Committee acknowledged the clinical need to consider durvalumab plus OCP for funding to improve treatment affordability and ensure appropriate care. However, they also noted that other programmed cell death protein-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitors are approved for use in combination with CP for this indication, including dostarlimab plus CP, and pembrolizumab in combination with CP followed by pembrolizumab monotherapy ("pembrolizumab plus CP").

2.4. The submission nominated CP and dostarlimab plus CP as comparators for the dMMR subgroup, and CP and pembrolizumab plus CP as comparators for the pMMR subgroup. The Committee deemed the exclusion of dostarlimab plus CP as a comparator for the pMMR subgroup to be inappropriate.

2.5. The Committee considered four testimonials from local patient experts about how living with EC had negatively impacted their ability to carry out daily activities due to side effects such as body aches, numbness in the feet, fatigue, poor appetite, and breathlessness. The Committee noted that the condition also had a profound effect on the patient's mental and emotional well-being, and affected their ability to work because they needed to take time off to receive treatment. The Committee noted that the patient experts previously received chemotherapy, immunotherapy and radiotherapy, which led to side effects including constipation, nausea, a tingling sensation in the hands and feet, joint pain and hair loss. While the patient experts were unfamiliar with durvalumab and olaparib, they considered any new treatment options for endometrial cancer should be more affordable, have fewer side effects, improve quality of life and stop the cancer from worsening.

Clinical effectiveness and safety

3.1. The Committee reviewed the clinical evidence for durvalumab and olaparib, which was based on a phase III randomised controlled trial (RCT; DUO-E) that compared durvalumab plus CP, durvalumab plus OCP, and CP alone in patients with primary A/R EC. The Committee noted that the submission relied on results from prespecified subgroup analyses to inform the clinical claim, which was aligned with the company's requested listing and registered indication.

3.2. At the first interim analysis of the DUO-E trial (data cut-off: 12 April 2023), durvalumab plus CP led to improvements in progression-free survival (PFS) and overall survival (OS) compared to CP in the dMMR subgroup (Table 1). However, both PFS and OS data were immature. The interpretation of the results was further limited by the small sample size, high censoring rates, and wide confidence intervals (CI). Overall, the Committee considered the magnitude and sustainability of clinical benefit from durvalumab plus CP in the dMMR subgroup to be uncertain.

Table 1: Outcomes for durvalumab plus CP and CP alone in the dMMR subgroup of the DUO-E trial

Outcome	Durvalumab plus CP (N=46)	CP (N=49)
PFS		
Events, n (%)	15 (32.6)	25 (51.0)
Median PFS, months (95% CI)	NR (NR to NR)	7.0 (6.7 to 14.8)
HR (95% CI) vs. CP	0.42 (0.22 to 0.80)	
OS		
Events, n (%)	7 (15.2)	18 (36.7)
Median OS, months (95% CI)	NR (NR to NR)	23.7 (16.9 to NR)
HR (95% CI) vs. CP	0.34 (0.13 to 0.79)	

Abbreviations: CI, confidence interval; CP, carboplatin and paclitaxel; dMMR, mismatch repair deficient; HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival.

3.3. In the pMMR subgroup, durvalumab plus OCP also led to an improvement in PFS compared to CP. However, for OS, the data were immature and the upper limit of the CI of the OS hazard ratio included one (Table 2). Therefore, the Committee found the OS benefit in the pMMR subgroup to be uncertain.

Table 2: Outcomes for durvalumab plus OCP and CP alone in the pMMR subgroup of the DUO-E trial

Outcome	Durvalumab plus CP plus olaparib (N=191)	CP (N=192)
PFS		
Events, n (%)	108 (56.5)	148 (77.1)
Median PFS, months (95% CI)	15.0 (12.4 to 18.0)	9.7 (9.2 to 10.1)
HR (95% CI) vs. CP	0.57 (0.44 to 0.73)	
OS		
Events, n (%)	46 (24.1)	64 (33.3)
Median OS, months (95% CI)	NR (NR to NR)	25.9 (25.1 to NR)
HR (95% CI) vs. CP	0.69 (0.47 to 1.00)	

Abbreviations: CI, confidence interval; CP, carboplatin and paclitaxel; HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair proficient.

3.4. In terms of safety, the Committee noted that, compared with chemotherapy, durvalumab plus CP had higher rates of immune-mediated adverse events (AEs; 28.1% versus 6.8%) and AEs leading to dose interruption (54.5% versus 50.0%). The Committee also acknowledged that adding olaparib to durvalumab plus CP resulted in the highest incidence of AEs across most safety endpoints.

3.5. In terms of clinical effectiveness for the treatment of primary A/R EC, the submission described durvalumab plus CP and durvalumab plus OCP as superior when compared with CP for the dMMR and pMMR subgroups, respectively. While the submission's claims of superior effectiveness were considered reasonable, the Committee found the magnitude of benefit to be uncertain in both subgroups given the immaturity of data.

3.6. In terms of safety, the Committee considered durvalumab plus CP to be inferior to CP, and highlighted that the addition of olaparib to durvalumab plus CP further worsened its safety profile.

3.7. In the absence of direct comparative evidence, the Committee reviewed Bucher indirect treatment comparisons (ITCs) informed by data from the DUO-E trial (durvalumab plus CP/OCP) and another phase III RCT, RUBY (dostarlimab plus CP). Results of the ITCs showed no significant difference between durvalumab plus CP and dostarlimab plus CP in the dMMR subgroups for PFS (hazard ratio [HR]: 1.32; 95% CI: 0.57 to 3.05) and OS (HR: 0.94; 95% CI: 0.32 to 2.78). Similarly, no significant difference was observed between durvalumab plus OCP and dostarlimab plus CP in the pMMR subgroups for PFS (HR: 0.75; 95% CI: 0.52 to 1.07) and OS (HR: 0.95; 95% CI: 0.57 to 1.57). The Committee considered that, while these results suggest comparable efficacy, there were uncertainties in the ITCs due to baseline differences between the DUO-E and RUBY trials, such as distribution in disease stage and time since completion of adjuvant therapy.

3.8. In terms of safety, the ITC results showed that the odds ratios for selected safety outcomes favoured durvalumab plus CP over dostarlimab plus CP in the dMMR subgroups. However, the Committee observed that the CIs included the null value for some safety endpoints. They also highlighted that the analysis did not account for the time-dependent nature of AE occurrence, as the RUBY trial had a longer follow-up duration than DUO-E. The Committee further noted that no ITC was available for comparing safety in the pMMR subgroups.

3.9. Based on the submitted evidence, the Committee concluded that durvalumab plus CP may be considered non-inferior in both effectiveness and safety to dostarlimab plus CP in the dMMR subgroup. In the pMMR subgroup, the Committee concluded that, based on available evidence, durvalumab plus OCP may be considered non-inferior in clinical effectiveness to dostarlimab plus CP. However, the addition of olaparib to durvalumab is likely to result in an inferior safety profile.

3.10. The Committee also heard that the submission included a naïve indirect comparison of pMMR subgroups between durvalumab plus OCP and pembrolizumab plus CP, based on data from the DUO-E and phase III NRG-GY018 trials. The Committee considered this approach inappropriate due to methodological limitations, including concerns about trial heterogeneity, violation of transitivity, and the use of a later data cut-off in the NRG-GY018 trial, during which unblinding and initiation of post-study immunotherapy may have biased results against pembrolizumab plus CP.

3.11. The Committee noted that an ITC using data from the first interim analysis of the NRG-GY018 trial, conducted prior to unblinding, was instead performed during the evaluation. As the results showed no significant differences in PFS (HR: 1.00, 95% CI: 0.70 to 1.44) and OS (HR: 0.87, 95% CI: 0.51 to 1.51), the Committee concluded that durvalumab plus OCP may be considered non-inferior in effectiveness to pembrolizumab plus CP in the pMMR subgroup. In terms of safety, the Committee considered that durvalumab plus OCP is likely to be inferior to pembrolizumab plus CP.

Cost effectiveness

Cost-minimisation analysis

4.1. The Committee reviewed the company's cost-minimisation analysis (CMA), which relied on a clinical claim of non-inferiority between durvalumab plus CP and dostarlimab plus CP in the dMMR subgroup. The analysis indicated that durvalumab plus CP was associated with lower healthcare costs.

4.2. The Committee noted that the analysis was not appropriate due to differing assumptions regarding treatment duration which favoured durvalumab plus CP. In addition to drug and administration costs, the CMA included cost-offsets for AEs based on an assumed superior safety profile for durvalumab plus CP, which was not supported by the available evidence.

4.3. The Committee considered the revised analysis that included drug acquisition and administration costs only and assumed equal treatment durations for both arms. The results indicated that durvalumab plus CP was more costly than dostarlimab plus CP.

4.4. The Committee also noted that no additional CMAs were conducted for the pMMR subgroup, as the combination of two high-cost drugs (durvalumab and olaparib) would be dominated as it exceeds the cost of dostarlimab or pembrolizumab alone.

Cost-utility analysis

4.5. The Committee reviewed the submission's cost-utility analyses (CUA), which compared durvalumab plus CP and durvalumab plus OCP with CP alone based on DUO-E trial data. Key components of the base-case economic evaluation are summarised in Table 3.

Table 3: Key components of the company-submitted base-case economic evaluation

Component	Description
Type of analysis	Cost-utility analysis
Population	Newly diagnosed advanced or recurrent EC with dMMR or pMMR status
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	15 years
Health states	Pre-progression; post-progression; death
Cycle length	Patient tracking: monthly Drug administration: weekly
Extrapolation methods used to generate results	Kaplan-Meier data from DUO-E for PFS, OS and TDT were fitted using both standard parametric distributions and flexible spline models in the base case. <u>dMMR subgroup</u> • Durvalumab plus CP arm ▪ PFS: 2-knot spline-based normal distribution ▪ OS: log-logistic distribution ▪ TDT: exponential distribution • CP arm ▪ PFS: 1-knot spline-based normal distribution ▪ OS: log-normal distribution ▪ TDT: modelled using the average number of chemotherapy cycles from DUO-E <u>pMMR subgroup</u> • Durvalumab plus OCP arm ▪ PFS and OS: log-logistic distribution ▪ TDT: exponential distribution • CP arm ▪ PFS and OS: log-logistic distribution ▪ TDT: modelled using the average number of chemotherapy cycles from DUO-E
Health-related quality of life	Based on utility analysis of the DUO-E trial, ITT population (EQ-5D-3L, UK preference weights): Progression-free utility = 0.782 Progressed disease utility = 0.731 Total AE-related utility decrement per treatment arm: • Durvalumab plus CP arm: -0.013 • Durvalumab plus OCP arm: -0.018 • CP arm: -0.010
Types of healthcare resources included	• Drug and administration costs • Disease management costs • Subsequent treatment costs • AE management costs • End-of-life costs

Abbreviations: AE, adverse event; CP, carboplatin and paclitaxel; CUA, cost utility analysis; dMMR, mismatch repair deficient; EC, endometrial cancer; EQ-5D-3L, EuroQoL-5 Dimension-3 Level; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LY, life years; OCP, olaparib + carboplatin + paclitaxel; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair proficient; QALY, quality-adjusted life year; TDT, time-to-discontinuation of treatment

4.6. The base-case incremental cost-effectiveness ratio (ICER) in the submission was between SG$45,000 and SG$75,000 per quality-adjusted life year (QALY) gained for durvalumab plus CP compared with CP in the dMMR subgroup. For the pMMR subgroup, durvalumab plus OCP was associated with an ICER between SG$285,000 and SG$325,000 per QALY gained compared with CP.

4.7. The Committee considered the ICERs to be uncertain and likely underestimated due to optimistic survival extrapolations and inappropriate assumptions regarding healthcare resource use that favoured the intervention. For the dMMR subgroup, the extrapolated OS and PFS curves intersected at around 50 months, which was considered clinically implausible and indicative of substantial model uncertainty.

4.8. The Committee reviewed the revised base case, which addressed these uncertainties. These changes increased the ICER to between SG$105,000 and SG$135,000 per QALY gained for the dMMR subgroup and between SG$325,000 and SG$365,000 per QALY gained for the pMMR subgroup.

4.9. Overall, based on the findings from the CUA and CMA, the Committee concluded that at the price proposed by the company, durvalumab plus CP and durvalumab plus OCP did not represent a cost-effective use of healthcare resources for treating dMMR and pMMR primary A/R EC, respectively.

Estimated annual technology cost

5.1. Using an epidemiological approach, the submission estimated that the annual cost impact to the public healthcare system would be between SG$1 million and SG$3 million in the first year, and between SG$5 million and SG$10 million in the fifth year of listing durvalumab and olaparib on the MOH List of Subsidised Drugs for untreated primary A/R EC.

5.2. The Committee considered that the submission's financial estimates were high due to an overestimation of the annual incidence growth of EC and the omission of relative dose intensity.

5.3. Based on the revised budget impact analysis, the annual cost to the public healthcare system was estimated to be between SG$1 million and SG$3 million in the first year, increasing to between SG$3 million and SG$5 million in the fifth year of listing.

Recommendations

6.1. Based on available evidence, the Committee recommended not listing durvalumab in combination with platinum-based chemotherapy, then as maintenance with or without olaparib, on the MOH List of Subsidised Drugs for patients with untreated primary A/R EC. The decision was based on the uncertainties surrounding the magnitude of clinical benefit compared with chemotherapy, and unfavourable cost-effectiveness compared with chemotherapy and dostarlimab.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Company-proposed clinical indication	Subsidy class	MediShield Life claim limit per month
Durvalumab concentrate for solution for infusion (500 mg/10 mL) Olaparib tablet (100 mg, 150 mg)	Durvalumab in combination with platinum-based chemotherapy is indicated for the first-line treatment of patients with advanced or recurrent endometrial cancer, followed by treatment with - Durvalumab as monotherapy in endometrial cancer that is mismatch repair deficient - Durvalumab in combination with olaparib in endometrial cancer that is mismatch repair proficient	Not recommended for subsidy	Not recommended for MediShield Life claims