6.08 PEMBROLIZUMAB, Solution concentrate for I.V. infusion 100 mg in 4 mL, Keytruda®, MERCK SHARP & DOHME (AUSTRALIA) PTY LTD.

1 Purpose of submission

1.1 The Category 2 submission requested a Section 100 (Efficient Funding of Chemotherapy Program) Authority Required (STREAMLINED) listing for pembrolizumab in combination with platinum-based chemotherapy, followed by pembrolizumab monotherapy, for primary advanced or recurrent (A/R) endometrial cancer (EC), regardless of mismatch repair (MMR) status.

1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) for two populations:

- Mismatch repair deficient (dMMR): compared to dostarlimab in combination with chemotherapy, followed by maintenance dostarlimab treatment, which was PBS-listed on 1 May 2024; and
- Mismatch repair proficient (pMMR): compared to either:
  - dostarlimab in combination with chemotherapy, however this was not recommended at the May 2025 PBAC meeting; or
  - durvalumab in combination with chemotherapy followed by durvalumab and olaparib maintenance (durvalumab + olaparib). However, this was deferred for the pMMR population at the November 2024 PBAC meeting, as the TGA Delegate (at the time the Delegate's Overview was prepared) was not satisfied that the efficacy and safety of durvalumab and olaparib were established for the pMMR component of the requested indication (paragraph 7.18, durvalumab and olaparib PSD, November 2024 PBAC meeting). The ESC noted that at the time of the ESC meeting, durvalumab was TGA-registered for the following indication: durvalumab 'in combination with carboplatin and paclitaxel, followed by durvalumab monotherapy, is indicated for the first-line treatment of patients with primary advanced or recurrent endometrial cancer' (i.e. durvalumab monotherapy had been TGA-registered regardless of MMR status).

1.3 The Pre-Sub-Committee Response (PSCR) acknowledged that if neither dostarlimab nor durvalumab + olaparib were recommended, then the most appropriate comparator would be platinum-based chemotherapy alone followed, in a proportion of patients, by second line (2L) pembrolizumab + lenvatinib. Given the submission did not include an economic evaluation versus this comparator, the PSCR stated that if neither dostarlimab nor durvalumab + olaparib were recommended, the sponsor

'would request a recommendation for the dMMR population on the basis of non-inferiority to dostarlimab' (page 2).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients with primary advanced or first recurrent endometrial cancer (either dMMR or pMMR) that has a low potential for cure by radiation therapy or surgery alone or in combination.
Intervention (both dMMR and pMMR	First six cycles: pembrolizumab (200 mg) + carboplatin-paclitaxel every 3 weeks. Subsequent cycles: pembrolizumab (400 mg) every 6 weeks for up to 2 years or until disease progression, whichever occurs first.
Comparator/s dMMR population	First six cycles: dostarlimab (500 mg) + carboplatin-paclitaxel every 3 weeks. Subsequent cycles: dostarlimab (1,000 mg) every 6 weeks for up to 3 years or until disease progression, whichever occurs first. OR First six cycles: durvalumab (1120 mg) + carboplatin-paclitaxel every 3 weeks Subsequent cycles: durvalumab (1,500 mg) every 4 weeks until disease progression.
Comparator/s pMMR population	First six cycles: dostarlimab (500 mg) + carboplatin-paclitaxel every 3 weeks. Subsequent cycles: dostarlimab (1,000 mg) every 6 weeks for up to 3 years or until disease progression, whichever occurs first. OR First six cycles: durvalumab (1120 mg) + carboplatin-paclitaxel every 3 weeks Subsequent cycles: durvalumab (1,500 mg) every 4 weeks + olaparib 300mg twice daily until disease progression.
Outcomes	Progression free survival, overall survival [a], progression free survival 2, objective response rate, duration of response, safety.
Clinical claim	dMMR population: In patients with primary advanced or first recurrent dMMR endometrial cancer, pembrolizumab plus platinum-containing chemotherapy followed by pembrolizumab monotherapy maintenance is non-inferior in terms of efficacy and safety compared to dostarlimab or durvalumab plus platinum-containing chemotherapy followed by dostarlimab or durvalumab monotherapy maintenance. pMMR population: In patients with primary advanced or first recurrent pMMR endometrial cancer, pembrolizumab plus platinum-containing chemotherapy followed by pembrolizumab monotherapy maintenance is: • non-inferior in terms of efficacy and safety compared to dostarlimab plus platinum-containing chemotherapy followed by dostarlimab monotherapy maintenance; and • non-inferior in terms of efficacy and superior in terms of safety compared to durvalumab plus platinum containing chemotherapy followed by durvalumab and olaparib maintenance.

Source: Table 1.1-1, p12 of the submission
Abbreviations: dMMR = mismatch repair deficient; pMMR = mismatch repair proficient
[a] A statistically significant incremental overall survival benefit was not demonstrated in NRG-GY018. The submission claimed this was due to unblinding following positive interim analysis 1 results which led to many patients in the placebo arm receiving immunotherapy in combination or monotherapy following unblinding. The efficacy claim was based on PFS, PFS2, response data, and supportive overall survival analysis, which was adjusted for subsequent immunotherapy +/- lenvatinib.

2 Background

Registration status

2.1 Pembrolizumab was TGA registered on 31st January 2025 for the following indication:

'Pembrolizumab, in combination with carboplatin and paclitaxel, followed by pembrolizumab as a single agent, is indicated for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma'.

Previous PBAC consideration

2.2 Pembrolizumab has not been considered previously by the PBAC for 1L A/R EC, though it was recommended at the March 2022 PBAC meeting for use in combination with lenvatinib for patients with A/R EC who have disease progression following prior systemic therapy regardless of biomarker status.

2.3 Dostarlimab was PBS listed in May 2024 for the dMMR A/R EC population, but was not recommended for use in the pMMR population at the May 2025 PBAC Meeting.

2.4 Durvalumab was recommended for the dMMR A/R EC population at the November 2024 PBAC meeting. However, the PBAC deferred making a recommendation in November 2024 for durvalumab + olaparib in the pMMR population due to ongoing TGA considerations.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

MEDICINAL PRODUCT, form	Maximum amount (units)	No. of repeats	Price	Dispensed price for maximum amount (DPMA)	Proprietary name and manufacturer
Pembrolizumab 100mg injection, 1 vial	200mg	5 (initial)	List Price	$7,886.48 (private) $7,736.12 (public)	KEYTRUDA MSD Australia Pty Ltd
	400mg	3 (continuing)	List Price	$15,641.04 (private) $15,383.62 (public)	
Category / Program: Section 100 – Efficient Funding of Chemotherapy}					
Prescriber type: ☒Medical Practitioners					
Restriction type: ☒Authority Required (STREAMLINED)					
Severity: Advanced, metastatic or recurrent					
Condition: Endometrial carcinoma					
Indication: Advanced, metastatic or recurrent endometrial carcinoma					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised Applications for authorisation under this restriction may be made in real-time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333					
Treatment Phase: Initial treatment					
Clinical criteria: The condition must be unsuitable for at least one of the following: (i) curative surgical resection, (ii) curative radiotherapy AND The treatment must be initiated in combination with platinum-containing chemotherapy AND The condition must be, at treatment initiation with this drug, either: (i) untreated with systemic therapy, (ii) treated with neoadjuvant/adjuvant systemic therapy, but the cancer has recurred or progressed after more than 6 months from the last dose of systemic therapy, AND Patient must not have previously been treated with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) for this condition, prior to commencing treatment with this drug for this condition AND Patient must have a World Health Organisation (WHO) performance status score no higher than 1 prior to treatment initiation.					
Treatment Phase: Continuing treatment					
Clinical Criteria Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition.					
Treatment criteria: Patient must not receive more than 24 months of combined PBS-subsidised and non-PBS-subsidised therapy.					

Source: Table 1.4-1 pp28-29 of the submission

Note: The effective price for the dMMR and pMMR populations is not known and will only be shared with the sponsor in the event of a positive PBAC recommendation.

The submission incorporated the following fees into the dispensed prices: public dispensing fees – preparation fee ($90.13); private dispensing fees –preparation fee ($90.13), diluent fee ($5.59), distribution fee ($30.05) and ready prepared dispensing fee ($8.67). A flat 1.4% mark-up applied in the private hospital setting.

3.1 The submission did not propose an effective price and stated that published prices were used given the sponsor was not aware of the effective prices of the comparator/s.

3.2 The ESC noted that the PSCR requested consideration of the dMMR population given the submission did not include an economic evaluation versus the appropriate comparator in the pMMR population. Thus, the ESC considered that the restriction should be amended to align with the dostarlimab restriction in dMMR patients.

3.3 The continuing treatment criteria were aligned with the circumstances of use in the NRG-GY018 clinical trial which allowed treatment with pembrolizumab for up to 20 total cycles (or approximately 24 months).

3.4 Differences between the eligibility criteria for the pivotal NRG-GY018 trial and the requested restriction included:

- Patients with carcinosarcomas were excluded from NRG-GY018 but would be eligible to initiate treatment under the proposed restriction. As such, the efficacy of pembrolizumab in patients with carcinosarcomas was uncertain; and
- Patients required a European Cooperative Oncology Group (ECOG) score of 0, 1 or 2 to be eligible for NRG-GY018, while the proposed restriction required patients to have a World Health Organisation (WHO) performance status score no higher than 1. Nonetheless, only around 3% of patients (6/222, 2.7% in dMMR and 18/597, 3% in pMMR) in NRG-GY018 had an ECOG score of 2 therefore the evaluation considered this was unlikely to lead to any applicability issues.

3.5 The submission stated that there are up to 50 pMMR EC patients anticipated to be Grandfathered onto PBS therapy upon listing, and that the submission's proposed restriction would enable Grandfathered patients to access PBS therapy.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 EC is a malignancy of the endometrium, the inner lining of the uterus. EC accounts for about 95% of all cases of uterine cancer, the most common gynaecological cancer diagnosed in Australian women (AIHW 2022a; Cancer Council 2021). EC typically has been considered to impact women 60-65 years, however the submission stated that the increase in the prevalence of obesity, a risk factor for EC, has led to an increasing number of younger women being diagnosed with uterine cancer (AIHW, 2024).

4.2 EC has been broadly classified into two subtypes based on histology. Type I is the most common subtype, accounting for approximately 70-80% of cases and are typically low-grade oestrogen-dependent endometrioid adenocarcinomas. Conversely, Type II

tumours comprise the remaining 20-30% and are more likely to be high grade, usually a papillary, serous, clear cell histology, undifferentiated carcinomas or carcinosarcomas, which confer a poorer prognosis (Morice et al., 2016; Passarello et al., 2019). In NRG-GY018, patients with tumours of carcinosarcoma histology were excluded.

4.3 EC may be classified based on the MMR status, as pMMR or dMMR tumours. MMR status can be assessed indirectly by immunohistochemistry (IHC) staining to determine the presence of four MMR proteins: MLH1, MSH2, MSH6, and PMS2. The PBAC previously considered that dMMR accounts for 27% of A/R EC (paragraph 4.2, dostarlimab PBAC Minutes, November 2023), with the remaining 73% classified as pMMR. dMMR tumours can develop microsatellite instability (MSI), which is a change in the length of repetitive sequences in tumour DNA compared with normal DNA. Therefore, MSI-H is the observable characteristic (phenotype) displayed when errors occur in the DNA MMR system (Luchini, 2019). The complement to this subgroup, pMMR EC, are also referred to as microsatellite stable (MSS).

4.4 The PBAC has previously considered it was plausible that MMR status may be a treatment effect modifier for another PD-1/PD-L1 inhibitor dostarlimab (and may also apply to pembrolizumab), as patients in GARNET Cohort A1 (dMMR A/R EC) appeared to have better outcomes compared to those in Cohort A2 (pMMR A/R EC) when treated with dostarlimab (paragraph 6.25, dostarlimab PSD, March 2022 PBAC meeting). The PBAC has also previously noted that the PFS benefit in the pMMR population was much smaller than in the dMMR population in patients treated with dostarlimab compared with placebo in RUBY-1 (paragraph 7.20, dostarlimab PSD, November 2023 PBAC meeting).

4.5 Pembrolizumab is an anti-PD-1 monoclonal antibody, which is an immune checkpoint receptor that limits the activity of T lymphocytes in peripheral tissues.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 For the dMMR population, the submission nominated dostarlimab as the main comparator. The evaluation and the ESC considered that this was reasonable and consistent with the PBAC's consideration of durvalumab in dMMR A/R EC at the November 2024 PBAC meeting. Dostarlimab was listed on the PBS for the dMMR patient population in May 2024 and was considered the current standard of care for patients with dMMR 1L A/R EC. In addition, the submission nominated durvalumab as a secondary comparator as it received a positive recommendation at the November 2024 PBAC Meeting.

5.2 For the pMMR population, the submission assumed that either dostarlimab or durvalumab + olaparib would have received a positive PBAC recommendation prior to the July PBAC 2025 meeting and therefore would be the therapies most likely replaced in clinical practice. As outlined in paragraph 1.3, the PSCR acknowledged that if neither

dostarlimab nor durvalumab + olaparib were recommended, then the most appropriate comparator would be platinum-based chemotherapy alone followed, in a proportion of patients, by second line (2L) pembrolizumab + lenvatinib. Given the submission did not include an economic evaluation versus this comparator, the PSCR requested consideration of the dMMR population only.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from two organisations via the Consumer Comments facility on the PBS website. The comments highlighted that one of the key benefits of listing pembrolizumab (in the dMMR population) would be that it would provide an alternative treatment option. The comments outlined that people living with dMMR endometrial cancer experience pain, fatigue, reduced functional capacity and premature menopause following treatment. The comments described an inability to work, financial stress and the impact of the condition on family members and carers. The comments outlined that use of concurrent chemotherapy was associated with significant side effects including nausea, vomiting, hair loss and fatigue; however, the PBAC considered that these adverse effects were not expected to change with the proposed new treatment.

6.3 The Medical Oncology Group of Australia (MOGA) expressed its strong support for the pembrolizumab submission, categorising it as one of the therapies of "high priority for PBS listing" on the basis of the NRG-GY018 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for pembrolizumab, which was limited to 3 or 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement) based on a comparison with placebo.[1]

Clinical trials

6.4 The submission was based on three randomized clinical trials which were used to inform a Bucher indirect treatment comparison (ITC) between pembrolizumab and dostarlimab and durvalumab ± olaparib using placebo as the common comparator (all therapies were in combination with platinum-based chemotherapy during the induction phase). The three trials were:

[1] Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017

- NRG-GY018 (pembrolizumab compared to placebo, n=222 for dMMR patients and n=597 for pMMR patients);
- RUBY-1 (dostarlimab compared to placebo, N=494, n=118 for dMMR patients and n=376 for pMMR patients); and
- DUO-E (durvalumab ± olaparib compared to placebo, N=718, n=143 for dMMR patients and n=575 for pMMR patients).

6.5 The submission also presented supplementary evidence in the form of a Bayesian network meta-analysis (NMA). The network of evidence for PFS in the dMMR and pMMR populations comprised seven studies, all with placebo as the comparator arm. The studies (in brackets, intervention assessed) included in the NMA were: AtTEnd (atezolizumab); DUO-E (durvalumab ± olaparib); LEAP-001 (pembrolizumab + lenvatinib); MITO END-3 (Avelumab); NRG-GY018 (pembrolizumab; RUBY-1 (dostarlimab); and RUBY-2 (dostarlimab + niraparib). For the network of evidence for OS in the dMMR and pMMR populations, RUBY-2 was not included due to OS not being reported by MMR subgroups.

6.6 The PSCR stated that NRG-GY018 was the only clinical trial of an immunotherapy in A/R EC that was powered to assess PFS across both dMMR and pMMR subpopulations. In RUBY-1 and DUO-E, the pMMR subpopulation was an exploratory subgroup analysis.

6.7 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
NRG-GY018	A Phase III Randomized, Placebo-controlled Study of Pembrolizumab (MK-3475, NSC #776864) in Addition to Paclitaxel and Carboplatin Measurable Stage III or IVA, Stage IVB or Recurrent Endometrial Cancer (KEYNOTE-868/NRG-GY018) Clinical Study Report (CSR) Interim Analysis 1 [NRG-GY018 CSR IA1] (Dec 2022 data cutoff)	Clinical study report 5 December 2023
	A Phase III Randomized, Placebo-controlled Study of Pembrolizumab (MK-3475, NSC #776864) in Addition to Paclitaxel and Carboplatin for Measurable Stage III or IVA, Stage IVB or Recurrent Endometrial Cancer (KEYNOTE-868/NRG-GY018) Efficacy and Safety Update [NRG-GY018 EUR] (Aug 2023 data cutoff)	Clinical study report No report date
	Eskander RN et al. Pembrolizumab plus chemotherapy in advanced or recurrent endometrial cancer: overall survival and exploratory analyses of the NRG GY018 phase 3 randomized trial [Data on file]	Nature Medicine 2025
	Eskander RN et al. Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer.	N Engl J Med. 2023; 388(23):2159-2170.
	Eskander, R.N. et al. LBA43 Updated response data and analysis of progression free survival by mechanism of mismatch repair loss in endometrial cancer (EC) patients (pts) treated with pembrolizumab plus carboplatin/paclitaxel (PBC) as compared to PBC plus placebo (PBO) in the NRG GY018 trial.	Conference abstract Annals of Oncology 2023; S1284
	Eskander, R,N et al. Overall survival and progression-free survival by PD-L1 status among endometrial cancer patients treated with pembrolizumab plus carboplatin/paclitaxel as compared to carboplatin/paclitaxel plus placebo in the NRG GY018 trial	Conference abstract Gynecol Oncol 2023; 190 (1); S5
RUBY-1	JEMPERLI (dostarlimab) in combination with carboplatin and paclitaxel, the treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy	European Public Assessment Report 12 December 2024
	JEMPERLI (dostarlimab) in combination with platinum-containing chemotherapy the treatment of adult patients with mismatch repair deficient (dMMR)/ microsatellite instability-high (MSI-H) primary advanced or recurrent endometrial cancer (EC) 12 October 2023	European Public Assessment Report 12 October 2023
	Mirza MR et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer.	N Engl J Med 2023; 388(23):2145-2158.
	Powell MA et al. Efficacy and safety of dostarlimab in combination with chemotherapy in patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer in a phase 3, randomized, placebo-controlled trial (ENGOT-EN6-NSGO/GOG-3031/RUBY).	Gynecol Oncol. 2024; 192:40-49.
	Powell et al. MA Dostarlimab plus chemotherapy in primary advanced or recurrent endometrial cancer (pA/rEC) in the RUBY trial: Overall survival (OS) by MMR status and molecular subgroups	Conference abstract Annals of Oncology 2024; (5), 103557
	Mirza et al., Post hoc analysis of progression-free survival (PFS) and overall survival (OS) by mechanism of mismatch repair (MMR) protein loss in patients with endometrial cancer (EC) treated with dostarlimab plus chemotherapy in the RUBY trial.	Conference abstract J Clin Oncol 2024; 42(16), 5606
DUO-E	IMFINZI (durvalumab) in combination with LYNPARZA for the maintenance treatment of adult patients with newly diagnosed advanced or recurrent endometrial cancer following treatment with Imfinzi and platinum based chemotherapy, based on results from pivotal Phase III study, (DUO-E).	European Public Assessment Report 27 June 2024
	Westin SN et al. Durvalumab Plus Carboplatin/Paclitaxel Followed by Maintenance Durvalumab With or Without Olaparib as First-Line Treatment for Advanced Endometrial Cancer: The Phase III DUO-E Trial.	J Clin Oncol 2024; 42(3):283-299.
	Baurain, JF et al. Durvalumab plus carboplatin/paclitaxel followed by durvalumab with or without olaparib as a first line treatment for endometrial cancer: Overall survival and additional secondary efficacy endpoints by mismatch repair status in the DUO-E/GOG-3041/ENGOT-EN10 Trial	Conference abstract Gynecol Oncol 2024; (62-63) 20

Source: Tables 2.2-1, 2.2-2 and 2.2-3 of the submission.
Blue shaded cells indicate information previously considered by the PBAC.

6.8 The key features of the included randomised trials are summarised in Table 3. The duration of treatment in the randomised trials is shown in Table 4.

Table 3: Key features of the included evidence

Trial	N	Design/ median OS follow-up	Risk of bias	Patient population	Outcomes	Use in CMA
Pembrolizumab + PBC versus PBC						
NRG-GY018	dMMR:222 pMMR:597	Phase III DB MC RCT IA1: 13.6 months (dMMR), 8.7 months (pMMR) EUR: 19.2 months (dMMR), 15.3 months (pMMR)	Low for IA1, high post IA1 [a]	1L A/R EC	PFS, OS, safety	AEs
Dostarlimab + PBC versus PBC						
RUBY-1	ITT:494 dMMR:118 pMMR:376	Phase III DB MC RCT IA1 24.8 months (dMMR), 25.7 months (pMMR) IA2 36.6 months (dMMR), 37.5 months (pMMR)	Low for all-comers and dMMR. High for pMMR [b]	1L A/R EC	PFS, OS, safety	Not used
Durvalumab +PBC (± olaparib) versus PBC						
DUO-E	ITT:718 dMMR:95 [c] pMMR:383 [d]	Phase III DB MC RCT IA1 18.4–19.1 months (dMMR), 18.2-18.6 months (pMMR)	Low for all-comers. High for dMMR & pMMR subgroups [e]	1L A/R EC	PFS, OS, safety	AEs

Source: Constructed during evaluation using Table 2.4-18 and 2.4-20, pp117-119 of the submission
Abbreviations: 1L = first line; AEs = adverse events; A/R = advanced recurrent; CMA = cost minimisation analysis DB = double blind; dMMR = mismatch repair deficient; EC = endometrial cancer; EUR = efficacy update report; IA = Investigator assessment; MC = multi-centre; OS = overall survival; PBC = platinum-based chemotherapy; PFS = progression-free survival; pMMR = mismatch repair proficient; RCT = randomised controlled trial;
[a] Following the publication of positive PFS results at IA1 (Median F/U dMMR~13.6 months) the NRG-GY018 study was unblinded.
[b] PFS and OS in the pMMR population was not formally tested.
[c] Including only DUR + PBC (n=46) and PBO +PBC (n=49).
[d] Including only DUR+PBC+OLA (n=191) and PBO+PBC (n=192).
[e] In DUO-E, the dMMR and pMMR subgroup analyses were exploratory.

Table 4: Duration of treatment in NRG-GY018, RUBY-1 and DUO-E

	dMMR population		pMMR population	
NRG-GY018	**PEM+PBC**	**PBO+PBC**	**PEM+PBC**	**PBO+PBC**
Interim Analysis 1 (Duration on therapy, months [a])				
Mean (SD)	9.4 (6.4)	6.1 (4.5)	6.0 (4.8)	5.2 (4.2)
Median (range)	7.7 (0, 23)	5.2 (0, 21)	5.2 (0, 24)	4.2 (0, 21)
Efficacy Update Report Anti-PD-1/PD-L1 ToT (months)				
Mean (SE)	14.4 (0.8)	6.5 (0.5)	9.9 (0.5)	6.1 (0.3)
Median (95% CI)	16.1 (11.53, 20.76)	5.6 (4.17, 5.78)	7.6 (7.03, 8.77)	5.5 (4.47, 5.55)
RUBY-1	**DOS+PBC**	**PBO+PBC**	**DOS+PBC**	**PBO+PBC**
Interim Analysis 1 Anti-PD-1/PD-L1 ToT (months)				
Mean (SD)	16.4	NA	NA	NA
Median (range)	17.6 (0.69-34.59)	7.3 (0.69-35.21)	NA	NA
Interim Analysis 2				
Mean (SD)	NA	NA	NA	NA
Median (range)	17.6 (0.69-44.32)	7.3 (0.69, 44.44)-	9.0 (0.69-43.89)	8.3 (0.48-43.04)
DUO-E	**DUR+PBC**	**PBO+PBC**	**DUR+PBC+OLA**	**PBO+PBC**
Interim Analysis 1 Anti-PD-1/PD-L1 ToT (months)				
Mean (SD)	14.4 (8.72)	9.3 (7.34)	12.7 (7.45)	10.3 (5.95)
Median (range)	14.8 (0.69-31.76)	6.7 (0.69-27.46)	12.2 (0.16-33.21)	9.6 (0.16-32.91)
Olaparib/placebo ToT (months) (Maintenance)				
Mean (SD)	12.2 (7.24)	8.7 (7.29)	10.1 (6.48)	7.3 (5.29)
Median (range)	12.29 (1.84-27.18)	7.89 (0.44-23.11)	9.2 (0.32-28.77)	5.55 (0.21-28.61)

Source: Table 2.4-9, Table 2.4-10 and Table 2.4-11 of the submission; Table 10-5 and Table 10-6 of IA1 NRG-GY018 clinical study report.
Abbreviations: dMMR = mismatch repair deficient; DUR = durvalumab; OLA = Olaparib; PBC = platinum-based chemotherapy; PBO = placebo; PEM = pembrolizumab; pMMR = mismatch repair proficient; SD = standard deviation; ToT = time on treatment
[a] The extracted durations of treatment from IA1 NRG-GY018 were converted from days to months to allow comparison.

6.9 Data from NRG-GY018 were available at two timepoints:

- interim analysis 1 (IA1) (data cutoff), 6 December 2022 for pMMR; 16 December 2022 for dMMR); and
- efficacy update report (EUR) (data cutoff August 2023) which included approximately 9-months of additional follow-up, released in response to a request by European regulators. The EUR included data post treatment switching (see paragraph 6.10). This was not a planned analysis, and the results are descriptive in nature with nominal p-values.

6.10 In NRG-GY018, on 6th February 2023 upon the reporting of a positive PFS benefit in the pembrolizumab arm (in both the dMMR and pMMR populations) at IA1, regulators notified investigators to unblind the trial, requesting the investigators make patients aware of the study outcome and their treatment assignment. Consequently, the majority (99.2%) of patients in the placebo arm discontinued study treatment and many subsequently received immunotherapy (the majority of which was pembrolizumab ± lenvatinib).

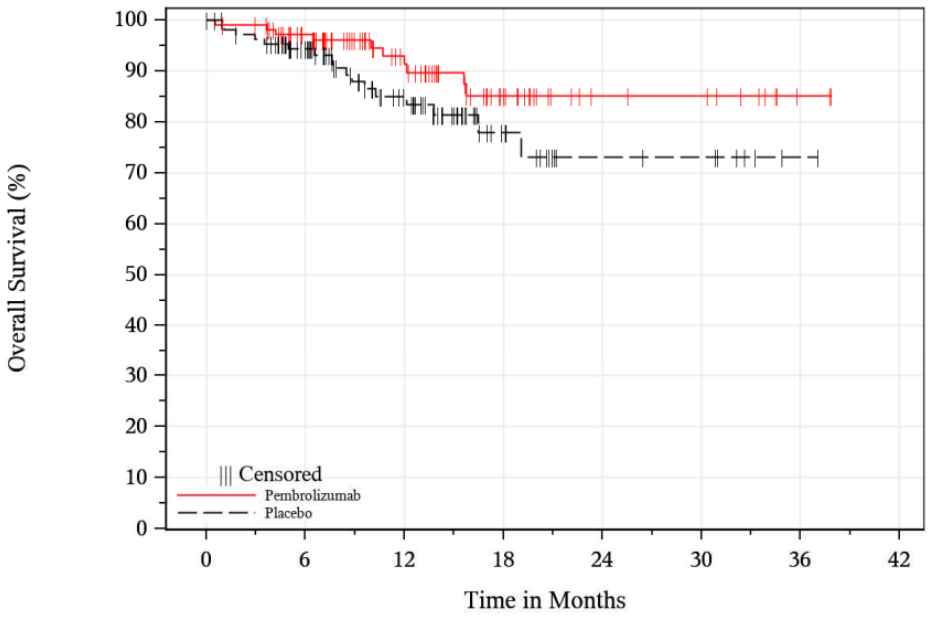
6.11 After unblinding, some patients who were randomised to placebo commenced immunotherapy prior to disease progression, however the number of patients for whom this was the case was not available. Therefore, the submission claimed that the EUR analyses conducted after the unblinding may be confounded, leading to

potentially biased estimation of hazard ratios in favour of the placebo group. On the other hand, a proportion of patients in the pembrolizumab arm also received 2L immunotherapy (10% [11/110] and 16.8% [50/294] in the dMMR and pMMR populations, respectively) in the EUR analysis, which does not reflect Australian practice (the PBS restrictions limit use to one PD-(L)1 inhibitor per lifetime) and would favour the pembrolizumab arm. The overall impact of confounding due to differences in subsequent therapy was unclear, as *post hoc* adjustments for treatment switching using inverse probability of censoring weights (IPCW) did not result in statistically significant OS hazard ratios (HR) (see paragraph 6.17). Further, differences in subsequent immunotherapy use may contribute to transitivity issues which may preclude the ITC being informative. This is discussed further in paragraph 6.27.

Comparative effectiveness

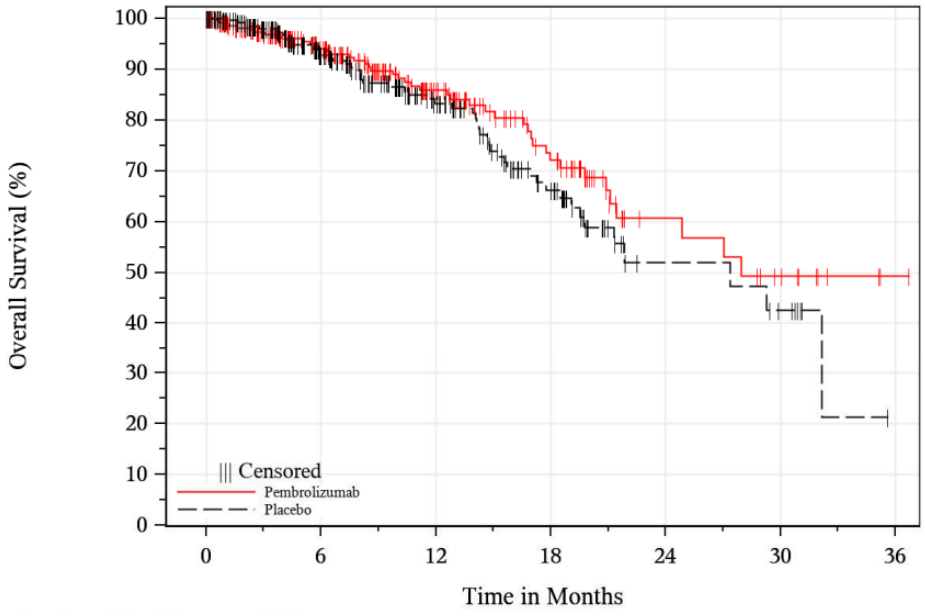
6.12 Figure 1 shows the OS KM results at IA1 for the NRG-GY018 dMMR (above) and pMMR (below) cohorts. NRG-GY018 did not present data for all-comers (i.e. dMMR combined with pMMR). Table 5 presents a summary of the OS results in NRG-GY018.

Figure 1: NRG-GY018 KM plot for OS in the dMMR (above) and pMMR (below) cohorts



Number of Participants at Risk

Pembrolizumab	110	88	55	29	12	11	2	0
Placebo	112	87	52	18	8	7	1	0



Number of Participants at Risk

Pembrolizumab	294	179	97	51	16	10	1
Placebo	294	174	94	46	11	7	0

Source: Figure 11-13 and 11-14, p134 and 137 NRG-GY018 CSR 2022
Note: IA1 Database Cutoff Date 16 DEC 2022, median follow up 13.6 months (dMMR) and 8.7 months (pMMR).

Table 5: OS results in NRG-GY018

	Treatment	N	Number of events (%)	Number censored (%)	Median OS (Months) (95% CI)	OS rates at 24 months % (95% CI)	Hazard Ratio (95% CI)	p-value
dMMR population								
IA1[a]	PEM+PBC	110	10 (9.1)	100 (90.9)	NR (NR, NR)	85.1 (73.2, 92.0)	0.55 (0.25, 1.19)	0.0617
	PBO+PBC	112	17 (15.2)	95 (84.8)	NR (NR, NR)	73.0 (56.4, 84.1)		
EUR [b]	PEM+PBC	110	17 (15.5)	93 (84.5)	NR, (NR, NR)	80.7 (70.3, 87.7)	0.57 (0.31, 1.04)	0.0323
	PBO+PBC	112	27 (24.1)	85 (75.9)	42.7 (NR, NR)	70.9 (59.8, 79.4)		
pMMR population								
IA1[a]	PEM+PBC	294	45 (15.3)	249 (84.7)	28.0 (21.4, NR)	60.7 (47.5, 71.5)	0.79 (0.53, 1.17)	0.1157
	PBO+PBC	294	54 (18.4)	240 (81.6)	27.4 (19.5, NR)	52.0 (38.4, 64.0)		
EUR [b]	PEM+PBC	298	77 (25.8)	221 (74.2)	28.9 (26.8, NR)	63.0 (54.5, 70.3)	0.80 (0.59, 1.08)	0.0683
	PBO+PBC	299	92 (30.8)	207 (69.2)	28.7 (24.0, 34.6)	58.3 (50.1, 65.6)		

Source: Table 2.5-3 and 2.5-7, p130 and p143 of the submission
Abbreviations: CI, confidence interval; NA, not available; NR, not reached
[a] Data cutoff date 16 December 2022, median follow up 13.6 months (dMMR) and 8.7 months (pMMR).
[b] Data cutoff date 18 August 2023, median follow up 19.2 months (dMMR) and 15.3 months (pMMR)
Note: In NRG-GY018 the number of patients included in ITT analysis increased from IA1 (N=588) to EUR (N=597). Nine patients in the pMMR population were randomised after the IA1 data cutoff and therefore were not included in the IA1 ITT OS analysis.

6.13 OS data in the dMMR population were not mature at the time of data cut-off for IA1 (Information Fraction 18%; median follow-up 13.6 months) and at the EUR data cut-off (Information Fraction 29.3%; median follow-up 19.2 months). At IA1, patients randomised to pembrolizumab demonstrated a positive numerical trend compared to patients randomised to placebo with a 45% lower risk of death (OS HR 0.55 (95% CI 0.25, 1.19)), however the 95% CI upper bound crossed 1.0 suggesting that there may be no difference between pembrolizumab and placebo. There was no clear divergence of the dMMR OS KM curves. At EUR, the OS HR in the dMMR population was similar to IA1 (HR = 0.57, 95% CI 0.31, 1.04).

6.14 OS data in the pMMR population was not mature at the time of data cut-off for IA1 (Information Fraction 27.2%; median follow-up 8.7 months) and at EUR data cut-off (Information Fraction 46.3%; median follow-up 15.3 months). At IA1, patients randomised to the pembrolizumab arm reported a directionally favourable improvement in reducing the risk of death by 21% with a hazard ratio of HR 0.79 (95% CI: 0.53, 1.17), however the upper bound of the 95% CI crossed 1.0 suggesting that there may be no difference between groups. The median OS by KM estimation was similar for patients randomised to pembrolizumab compared with patients randomised to placebo (28.0 vs 27.4 months). The pMMR KM OS curves were overlapping until approximately 14 months, and no clear separation was observed. At

EUR, the OS HR in the pMMR population was similar to IA1 (HR = 0.80, 95% CI 0.59, 1.08).

6.15 The submission noted the higher rate of subsequent anti-PD-(L)1 therapies in the placebo group (37.5% [42/112] and 48.2% [54/112] at IA1 and EUR, respectively) compared with the pembrolizumab (9.1% [10/110] and 10% [11/110] at IA1 and EUR, respectively), and claimed this difference could confound the OS results. However, as discussed in paragraph 6.11, if the results of NRG-GY018 were to be applied directly to the Australian setting, in which PBS-subsidised immunotherapy would not be available to patients treated with 1L pembrolizumab but would be available to patients treated with 1L chemotherapy only, the results of NRG-GY018 may overestimate the OS benefit.

6.16 To address the use of subsequent immunotherapies, the submission also included OS results adjusted for subsequent immunotherapy use using the IPCW and 2 Stage methods. These were *post hoc* adjustments included in the NRG-GY018 EUR. These adjusted results were included because of the submission's claim that a greater proportion of patients received subsequent immunotherapy in NRG-GY018 than otherwise would have been expected to occur in clinical practice.

6.17 The *post hoc* adjusted HRs for OS in the dMMR and pMMR populations using the IPCW method were:

- dMMR: 0.54 (95% CI 0.22, 1.69 2-sided p-value based on IPCW log-rank test nominal p=0.1602); and
- pMMR: 0.68 (95% CI 0.39, 1.26 2-sided p-value based on IPCW log-rank test nominal p=0.1231).

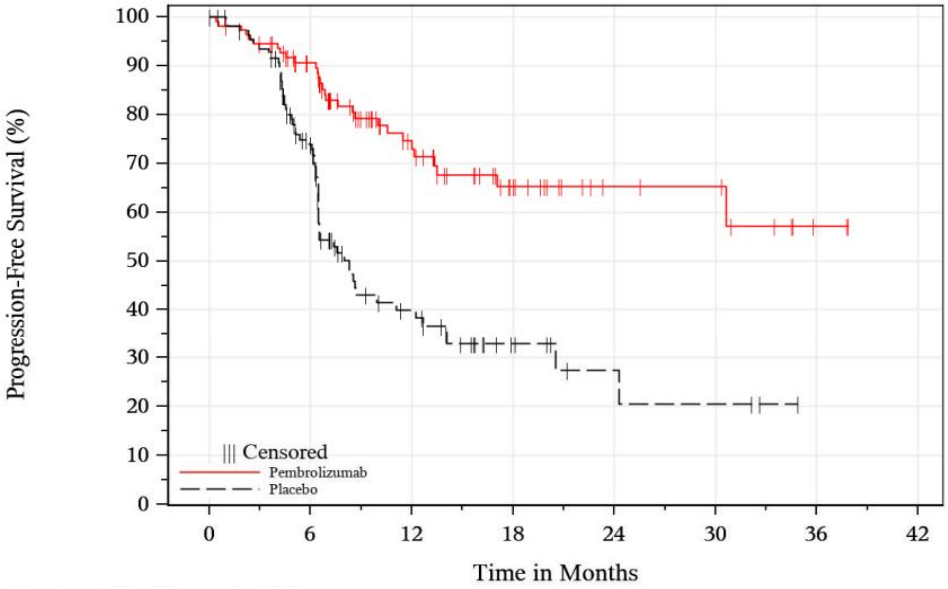
The IPCW adjusted OS HRs still reported a 95% CI which included 1 and a nominal p value which did not suggest any difference between treatment arms.

6.18 Due to the sparse occurrence of OS events among participants in the dMMR population, the first stage parametric survival model was not stable for the dMMR population. Consequently, the 2-Stage model result for the dMMR population was not reported. Using the 2-Stage model for adjustment for treatment switchover in the pMMR population resulted in an adjusted HR of 0.70 (95% CI 0.50, 0.98).

6.19 Neither the IPCW nor 2-stage model results were used in the submission's Bucher ITC, though they were tested as sensitivity analyses in the submission's NMA.

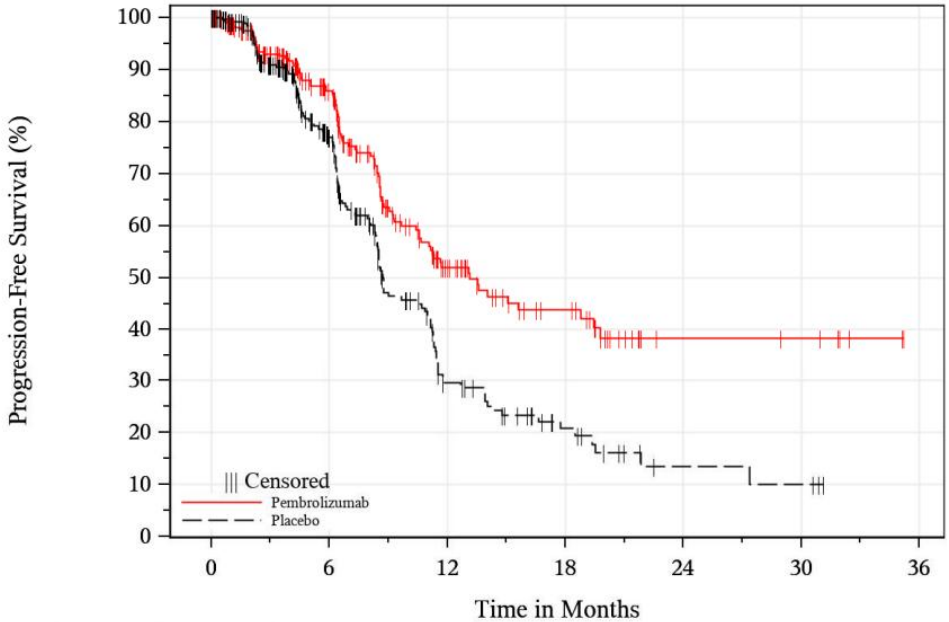
6.20 Figure 2 shows the PFS Kaplan-Meier (KM) results at IA1 for the NRG-GY018 dMMR (above) and pMMR (below) cohorts. Table 6 presents a summary of the PFS results in NRG-GY018.

Figure 2: NRG-GY018 KM plot for PFS in the dMMR (above) and pMMR (below) cohorts



Number of Participants at Risk

Pembrolizumab	110	85	45	24	10	9	2	0
Placebo	112	69	25	9	4	3	0	0



Number of Participants at Risk

Pembrolizumab	294	162	57	29	7	6	0
Placebo	294	144	36	15	4	3	0

Source: Figures 11-1, p104 and 11-3, p109 NRG-GY018 CSR 2022
Note: IA1 Database Cutoff Date 16 DEC 2022, median follow up 13.6 months (dMMR), and 8.7 months (pMMR).

Table 6: PFS based on investigator assessment in NRG-GY018

	Treatment	N	Number of events (%)	Number of Censored (%)	Median PFS (Months) (95% CI)	PFS rates at 24 months % (95% CI)	Hazard Ratio (95% CI)	p-value
dMMR population								
IA1[a]	PEM+PBC	110	29 (26.4)	81 (73.6)	NR (30.7, NR)	65.2 (52.7, 75.2)	**0.34 (0.22, 0.53)**	<0.0001
	PBO+PBC	112	60 (53.6)	52 (53.6)	8.3 (6.5, 12.3)	27.4 (15.2, 41.1)		
EUR[b]	PEM+PBC	110	36 (32.7)	74 (67.2)	NR (30.7, NR)	64.0 (53.0, 73.2)	0.35 (0.23, 0.52)[c]	<0.0001[c]
	PBO+PBC	112	70 (62.5)	42 (37.5)	8.3 (6.5, 12.7)	31.1 (21.7, 40.9)		
pMMR population								
IA1[a]	PEM+PBC	294	95 (32.3)	199 (67.7)	13.1 (10.6, 19.5)	38.3 (28.8, 47.7)	**0.57 (0.44, 0.74)**	<0.0001
	PBO+PBC	294	138 (46.9)	156 (53.0)	8.7 (8.4, 11.0)	13.5 (6.9, 22.2)		
EUR[b]	PEM+PBC	298	163 (54.7)	131 (55.4)	11.4 (10.9, 15.1)	34.1 (27.5, 40.8)	0.74 (0.60, 0.91)	0.0022
	PBO+PBC	299	187 (62.5)	107 (36.4)	10.6 (8.7, 11.3)	21.2 (15.0,28.1)		

Source: Table 2.5-1, 2.5-6 p125 and p138 of the submission

Abbreviations: CI = confidence interval; NA = not available; NR = not reached; PFS = progression free survival; PEM = pembrolizumab; PBC = platinum based chemotherapy; DOS = dostarlimab; DUR = durvalumab

[a] Data cutoff date 16 DEC 2022, median follow up 13.6 months (dMMR) and 8.7 months (pMMR).

[b] Data cutoff date 18 AUG 2023, median follow up 19.2 months (dMMR) and 15.3 months (pMMR)

[c]. The analysis was descriptive as statistical significance was met in prior IA.

Values in bold indicate statistically significant differences

Note: In NRG-GY018 the number of patients included in ITT analysis increased from IA1 (N=588) to EUR (N=597). Nine patients in the pMMR population were randomised after the IA1 data cutoff and therefore were not included in the IA1 ITT PFS analysis.

6.21 At the time of IA1 with a median 13.6 months of follow-up in the dMMR group, patients randomised to pembrolizumab reported a risk of progression or death which was 66% lower than patients randomised to placebo, with a statistically significant HR of 0.34 (95% CI 0.22, 0.53; stratified log-rank test p-value <0.0001). Median PFS was not reached in the pembrolizumab arm compared to 8.3 months in the placebo arm. At IA1, a clear separation of the KM curves was observed from approximately four months. At the time of EUR with a median follow up of 19.2 months in the dMMR group, the PFS HR was similar to IA1 (HR = 0.35 (95% CI 0.23 to 0.52, nominal p-value <0.0001). Median PFS was not reached in the pembrolizumab arm compared to 8.3 months in the placebo arm. Results reported from the unplanned EUR analysis were exploratory and as such not considered statistically significant.

6.22 At the time of IA1 with a median 8.7 months of follow-up in the pMMR group, patients randomised to pembrolizumab reported a risk of progression or death which was 43% lower than patients randomised to placebo, with a statistically significant HR of 0.57 (95% CI 0.44, 0.74, stratified log-rank test p-value <0.0001). Consistent with the results reported in the dMMR population, the KM curves demonstrated early separation at 3-4 months. The separation of the KM curves in the pMMR population was heavily

censored and observed to be markedly less pronounced than in the dMMR population.

6.23 The submission noted that the EUR (data cut-off August 2023) showed a smaller magnitude of PFS benefit in the pMMR population compared to IA1 (HR 0.74 95% CI 0.60 to 0.91). The submission claimed that this may be partly due to unblinding of patients following IA1, as patients in the placebo arm commenced immunotherapy, even before investigator's declared progression. Without information on the number of patients that commenced immunotherapy prior to disease progression, it was unclear whether this was a plausible explanation for the worsening of PFS benefit over time.

6.24 NRG-GY018 reported other secondary outcomes including time from randomisation to disease progression by investigator assessment or death (whichever occurs first) on subsequent anticancer therapy (PFS2) and objective response rate. Patient reported outcomes (not reported in the submission) were collected for pMMR patients only. In brief, PFS2 and ORR results in NRG-GY018 were consistent with the OS and PFS results and favoured pembrolizumab. The difference in quality of life between treatment arms measured by the Functional Assessment of Cancer Therapy –Endometrial Trial Outcome Index (FACT-En-TOI), which was a validated assessment tool for patient QoL in EC, was not considered to be clinically meaningful at up to week 54 in the NRG-GY018 clinical study report.

6.25 The evaluation considered that, even though no such clinical claim was made, it was reasonable to conclude that pembrolizumab was superior to placebo in pMMR for the outcome of PFS (but not OS) based on direct evidence from NRG-GY018.

Indirect comparisons

6.26 Landmark OS and PFS percentages from NRG-GY018, RUBY-1 and DUO-E are shown in Table 7.

Table 7: Landmark survival estimates in NRG-GY018, RUBY-1 and DUO-E

Therapy and trial ID	NRG-GY018 EUR N=222 (dMMR) N = 597 (pMMR)		RUBY-1 IA1 N=118 (dMMR) N = 376 (pMMR)		DUO-E IA1 N=95 (dMMR) N = 383 (pMMR)	
OS Follow-up (median)	22.5 months (dMMR), 18.3 months (pMMR) [a]		24.8 months (dMMR) 25.7 months (pMMR)		18.4-19.1 months (dMMR), 18.2-18.6 months (pMMR) [b]	
PFS Follow-up (median)					10.2-15.5 (dMMR) 12.8-15.2 months (pMMR) [c]	
PFS (dMMR)	**PEM+PBC**	**PBO+PBC**	**DOS+PBC**	**PBO+PBC**	**DUR+PBC**	**PBO+PBC**
6 month PFS	90.8%	74.7%	80.2%	59.7%	90.6%	73.1%
12 month PFS	75.2%	41.0%	63.5%	24.4%	67.9%	43.3%
18 month PFS	67.8%	32.9%	61.4%	17.9%	67.9%	31.7%
24 month PFS	64.0%	31.1%	61.4%	15.7%	NR	
OS (dMMR)	**PEM+PBC**	**PBO+PBC**	**DOS+PBC**	**PBO+PBC**	**DUR+PBC**	**PBO+PBC**
12 month OS	91.7%	85.7%	86.8%	79.9%	91.2%	74.4%
18 month OS	82.3%	73.9%	86.8%	67.3%	86.1%	65.8%
24 month OS	80.7%	70.9%	82.8%	54.1%	NR	
PFS (pMMR)	**PEM+PBC**	**PBO+PBC**	**DOS+PBC**	**PBO+PBC**	**DUR+PBC+OLA**	**PBO+PBC**
6 month PFS	85.5%	79.9%	NR		NR	
12 month PFS	47.7%	36.8%	NR		59.4%	40.8%
18 month PFS	38.0%	27.4%	NR		42.0%	20.0%
24 month PFS	34.1%	21.2%	28.4%	18.8%	NR	
OS (pMMR)	**PEM+PBC**	**PBO+PBC**	**DOS+PBC**	**PBO+PBC**	**DUR+PBC**	**PBO+PBC**
12 month OS	83.8%	81.2%	NR		87.3%	81.0%
18 month OS	72.9%	67.1%	NR		76.9%	69.9%
24 month OS	63.0%	58.3%	67.7%	55.1%	NR	

Source: Table 2.3-6, 2.6-2, p168 and Table 2.6-4, p170 of the submission, Table 6 and Table 17 of NRG-GY018 EUR

Abbreviations: EUR = efficacy update report; IA1 = first interim analysis; DOS = dostarlimab; PEM = pembrolizumab; PBC = platinum based chemotherapy; DUR = durvalumab; PFS = progression free survival

[a] For the ITC, the submission presented a 'theoretical follow-up time' for NRG-GY018 (dMMR 22.5 months; pMMR 18.3 months) which was longer than the follow-up time reported in the EUR (dMMR 19.2 months; pMMR 15.3 months). The submission claimed that the theoretical follow-up time was defined as the time between the date of randomisation until the date of database cutoff, for all patients, and that this definition was the same as RUBY-1. This was in place of the NRG-GY018 definition: the time between the date of randomisation until the date of death or the date of database cutoff for patients without documented death at the time of database cutoff. The theoretical follow-up time could not be independently verified during evaluation.

[b] The median OS duration of follow-up was 18.4 months for DUR+PBC+OLA (dMMR), 19.1 months for PBO+PBC (dMMR), 18.2 months for DUR+PBC (pMMR) and 18.6 months for PBO+PBC (pMMR)

[c] The median PFS duration of follow-up was 10.2 months for PBO+PBC (dMMR), 15.5 months for DUR+PBC (dMMR), 12.8 months for PBO+PBC (pMMR) and 15.2 months for DUR+PBC+OLA (pMMR)

6.27 The evaluation and the ESC noted the differences in event rates between the dMMR common comparator arms (placebo), with a larger proportion of patients randomised to placebo in NRG-GY018 remaining progression free at 24 months (31.1%) compared to RUBY-1 (15.7%). Similarly, a larger proportion of patients randomised to placebo in NRG-GY018 remained alive at 18 months (73.9%) compared to RUBY-1 (67.3%) and DUO-E (65.8%). The evaluation and the ESC considered this may indicate that there was poor exchangeability in the dMMR population between these trials and the results of an ITC based on these results may be uncertain. In the pMMR population, differences in event rates between the common comparator arms (placebo) were less pronounced.

6.28 Overall, the evaluation and the ESC considered there were significant exchangeability issues with the trials included in the ITC. In addition, comparisons in the pMMR population were reliant on exploratory subgroup analyses of RUBY-1 and DUO-E, and therefore were associated with a higher degree of uncertainty.

6.29 The ESC considered a key reason for the different event rates in the common comparator arms was the early treatment switching in the NRG-GY018 trial after IA1 (median follow-up of 13.6 months), with higher rates of subsequent anti-PD-(L)1 use in the placebo arm of NRG-GY018 than the other trials (e.g. EUR 48.2% versus RUBY-1 IA1 38.5%, in the dMMR subpopulations).

6.30 The evaluation identified a range of other factors that may have impacted the comparability of treatment efficacy between trials, though the ESC considered these were less relevant than the early cross-over in NRG-GY018. These factors included:

- NRG-GY018 was the only trial powered to detect PFS differences in the dMMR and pMMR populations;
- The median duration of follow-up for PFS varied between NRG-GY018 EUR (dMMR: 19.2 months, pMMR: 15.3 months), RUBY-1 (dMMR: 24.8 months, pMMR: 25.7 months) and DUO-E (dMMR 10.2–15.5 months; pMMR: 12.8–15.2 months). A longer duration of follow-up was likely correlated to more PFS and OS events and more certainty in the data;
- The frequency of tumour assessments differed across the three trials;
- The proportion of Asian patients was substantially lower in NRG-GYO18 (dMMR: 3.2%, pMMR: 5.4%) and RUBY-1 (dMMR: 1.7%, pMMR: 3.5%) compared with DUO-E (dMMR: 30.5%, pMMR: 30.0%). Kim et al 2024, a meta-analyses of immunotherapy trials in A/R EC, reported that Caucasian patients appear to have better PFS outcomes (PFS HR 0.52; 95% CI: 0.43, 0.63) from checkpoint inhibitors than non-Caucasian patients (PFS HR 0.67; 95% CI: 0.42, 1.07);
- Patients with carcinosarcoma histology were excluded from NRG-GY018, however were included in RUBY-1 and DUO-E. In addition, more pMMR patients in NRG-GY018 and DUO-E had endometroid histology compared to RUBY-1 (52.1% [311/597] versus 54.4% [313/575] versus 45.2% [170/376], respectively);
- In NRG-GY018, 10.8% (24/222) of dMMR patients and 9.9% (59/597) of pMMR patients had adenocarcinomas not otherwise specified (NOS) histology. There were no patients with adenocarcinoma NOS in RUBY-1, and DUO-E did not report any patients with this histology. Adenocarcinomas are classified as Type I tumours, which are typically low grade and have a better prognosis than Type II tumours;

- Patients were required to have a disease-free interval of ≥12 months to be eligible for NRG-GY018 and DUO-E, whereas RUBY-1 allowed patients with a disease-free interval of ≥6 months to enrol. There is some evidence that longer progression-free intervals after primary chemotherapy treatment may be a predictor of improved survival after recurrence in A/R EC and as such, patients in RUBY-1 may have, on average, a poorer prognosis than patients in NRG-GY018 and DUO-E; and
- In the dMMR population, the proportion of patients with an ECOG PS score of 0 was higher in NRG-GY018 (64% [142/222]) compared with either RUBY-1 or DUO-E (57% [67/118] and 58% [83/143], respectively). In the pMMR population, the proportion of patients with an ECOG PS score of 0 was lower in RUBY-1 (63.3% [238/376] compared with either NRG-GY018 or DUO-E (67.2% [401/597] and 68.7% [395/575]).

6.31 Table 8 summarises the Bucher ITC and NMA results in the dMMR populations of NRG-GY018, RUBY-1 and DUO-E.

Table 8: Summary of Bucher ITC and NMA Results dMMR population

Arm of the trial	Event n/N (%)	Median PFS (months)	HR (95% CI)	Indirect comparison Bucher Fixed effects [b] HR (95% CI) p-value	Indirect comparison Bayesian NMA Fixed effects [c] HR (95% CI)
Progression Free Survival					
NRG-GY018 EUR: 22.5 months median FU (same definition as RUBY-1)				**PEM+PBC vs DOS+ PBC**	
PEM+PBC	36 (32.7)	NR	0.35 (0.23, 0.52)	1.24 (0.62, 2.49) p=0.549	1.25 (0.62, 2.51) [b]
PBO+PBC	70 (62.5)	8.3			
RUBY-1 IA1: 24.8 months median FU					
DOS+PBC	19 (35.8)	NR	0.28 (0.16, 0.50)		
PBO+PBC	47 (72.3)	NR			
NRG-GY018 EUR 22.5 months median FU				**PEM+PBC vs DUR+PBC**	
PEM+PBC	36 (32.7)	NR	0.35 (0.23, 0.52)	0.83 (0.39, 1.77) p=0.623	0.83 (0.39, 1.79) [b]
PBO+PBC	70 (62.5)	8.3			
DUO-E-1 IA1 DUR+PBC 15.4 vs PBO+PBC 10.2 months median FU					
DUR+PBC	15 (32.6)	NR	0.42 (0.22, 0.80)		
PBO+PBC	25 (51.0)	7.0			
Overall Survival					
NRG-GY018 EUR: 22.5 months median FU (same definition as RUBY-1)				**PEM+PBC vs DOS+ PBC**	
PEM+PBC	17 (15.5)	NR	0.57 (0.31, 1.04)	1.77 (0.73, 4.34) p=0.209	1.79 (0.73, 4.35)
PBO+PBC	27 (24.1)	42.7			
RUBY-1 IA2: 36.6 months median follow-up					
DOS+PBC	12 (22.6)	NR	0.32 (0.17, 0.63)		
PBO+PBC	35 (53.8)	31.4			
NRG-GY018 EUR 22.5 months median follow-up				**PEM+PBC vs DUR+PBC**	
PEM+PBC	17 (15.5)	NR	0.57 (0.31, 1.04)	1.67 (0.56, 4.96) p=0.356	1.69 (0.58, 4.99)
PBO+PBC	27 (24.1)	42.7			
DUO-E-1 IA1 DUR+PBC 18.4 vs PBO+PBC 18.6 months median FU					
DUR+PBC	7 (15.2)	NR	0.34 (0.13, 0.79)		
PBO+PBC	18 (36.7)	23.7			

Source: Table 2.6-3, p169 and 2.6-5, p171 of the submission; p 72 Attachment 9_ITC_NMA_Report

Abbreviations: EUR = efficacy update report; IA1 = first interim analysis; FU = follow up; DOS = dostarlimab; PEM = pembrolizumab; PBC = platinum based chemotherapy; DUR = durvalumab; NMA = network meta analysis; HR = hazard ratio; PFS = progression free survival

[a] The proportional hazards assumption for PFS may have been violated in the RUBY-1 trial, because the Grambsch and Therneau test p-value was less than 0.05. Therefore, an NMA involving this trial under the assumption of proportional hazards may be inappropriate.

[b] The ITCs were conducted under a fixed effects model, which may not be reasonable given the heterogeneity between trials. The PBAC guidelines (v5.0, p45) indicate that a random effects model should be used for pooling data.

Note: ITC hazard ratios less than 1.0 favour PEM+PBC, and, if greater than 1.0, favour the comparator.

6.32 Table 9 summarises the Bucher ITC and NMA results in the pMMR populations of NRG-GY018, RUBY-1 and DUO-E.

Table 9: Summary of Bucher ITC and NMA Results pMMR population

Arm of the trial	Event n/N (%)	Median PFS (months)	HR (95% CI)	Indirect comparison Bucher Fixed effects [b] HR (95% CI) p-value	Indirect comparison Bayesian NMA Fixed effects [b] HR (95% CI)
Progression Free Survival					
NRG-GY018 EUR: 18.3 months median FU (same definition as RUBY-1)				**PEM+PBC vs DOS+ PBC**	
PEM+PBC	163 (54.7)	11.4	0.74 (0.60, 0.91)	0.97 (0.70, 1.35) p value = 0.859	0.97 (0.70, 1.35) [b]
PBO+PBC	187 (62.5)	10.6			
RUBY-1 IA1: 25.7 months median follow-up					
DOS+PBC	116 (60.4)	9.9	0.76 (0.59, 0.98)		
PBO+PBC	130 (70.7)	7.9			
NRG-GY018 EUR 18.3 months median follow-up (same definition as RUBY-1)				**PEM+PBC vs DUR+PBC+OLA**	
PEM + PBC	163 (54.7)	11.4	0.74 (0.60, 0.91)	1.29 (0.93, 1.80) p value= 0.125	1.30 (0.94, 1.80) [b]
PBO+PBC	187 (62.5)	10.6			
DUO-E-1 IA1 DUR+PBC+OLA 15.2 vs PBO+PBC 12.8 months median FU					
DUR+PBC+OLA	108 (56.5)	15.0	0.57 (0.44, 0.73)		
PBO+PBC	148 (77.1)	9.7			
Overall Survival					
NRG-GY018 EUR: 18.3 months median follow-up (same definition as RUBY-1)				**PEM+PBC vs DOS+PBC**	
PEM+PBC	77 (25.8)	28.9	0.80 (0.59, 1.08)	1.01 (0.67, 1.52) p value=0.975	1.01 (0.67, 1.52)
PBO+PBC	92 (30.8)	28.7			
RUBY-1 IA2: 37.5 months median follow-up					
DOS+PBC	97 (50.5)	34.0	0.79 (0.60, 1.04)		
PBO+PBC	109 (59.2)	27.0			
NRG-GY018 EUR 18.3 months median follow-up (same definition as RUBY-1)				**PEM+PBC vs DUR+ PBC+OLA**	
PEM + PBC	77 (25.8)	28.9	0.80 (0.59, 1.08)	1.15 (0.71, 1.87) p-value=0.566	1.16 (0.71, 1.88)
PBO+PBC	92 (30.8)	28.7			
DUO-E-1 IA1 18.2 months minimum median follow-up					
DUR+PBC+OLA	46 (24.1)	NR	0.69 (0.47-1.00)		
PBO+PBC	64 (33.3)	25.9			

Source: Table 2.6-7, p174 and 2.6-8, p176 of the submission; p 72 Attachment 9_ITC_NMA_Report

Abbreviations: EUR = efficacy update report; IA1 = first interim analysis; FU = follow up; DOS = dostarlimab; PEM = pembrolizumab; PBC = platinum based chemotherapy; DUR = durvalumab; NMA = network meta analysis; HR = hazard ratio; PFS = progression free survival

[a] The proportional hazards assumption may have been violated in LEAP-001 and DUO-E, as the Grambsch and Therneau test p-values were less than 0.05. Therefore, an NMA involving these trials under the assumption of proportional hazards may be inappropriate.

[b] The ITCs were conducted under a fixed effects model, which may not be reasonable given the heterogeneity between trials. The PBAC guidelines (v5.0, p45) indicate that a random effects model should be used for pooling data.

Note: ITC hazard ratios less than 1.0 favour PEM+PBC, and, if greater than 1.0, favour the comparator.

6.33 No non-inferiority margin was proposed in the submission. The evaluation noted the wide confidence intervals (e.g. in dMMR, the HR for OS was 1.67 (0.56, 4.96) for the Bucher ITC between pembrolizumab versus durvalumab) and considered the claim of non-inferiority was not adequately supported.

6.34 The Bayesian NMA demonstrated consistent results to the Bucher analysis with respect to the HR and 95% CI. This was to be expected given the same studies were included for each of the treatments in both the Bucher ITC and the NMA.

6.35 Overall, the evaluation considered the results of the Bucher ITCs in the dMMR and pMMR populations were uncertain with wide CIs, and considered that no reliable conclusions on comparative treatment efficacy could be drawn. Moreover, the evaluation considered that without a non-inferiority margin, no assessment of non-inferiority based on the evidence presented could be reasonably conducted.

6.36 Nonetheless, given that pembrolizumab and dostarlimab are both PD-L1 inhibitors that have demonstrated PFS benefit in combination with chemotherapy versus chemotherapy alone, the evaluation considered that it was biologically plausible that pembrolizumab may be non-inferior to dostarlimab and durvalumab in terms of effectiveness as a 1L treatment in dMMR A/R EC.

6.37 However, the evaluation considered that such an argument could not be made for pMMR A/R EC as:

- The PBAC has previously considered that the benefit of dostarlimab in pMMR EC was unclear (paragraph 7.17, dostarlimab PSD, November 2023), and as such, even if non-inferiority of pembrolizumab to dostarlimab in pMMR could be established, it may not be sufficient to establish the benefit of pembrolizumab in pMMR A/R EC in the Australian clinical setting; and
- durvalumab + olaparib includes maintenance olaparib which belongs to a different drug class (a poly ADP ribose polymerase (PARP) inhibitor) with no direct equivalent in the proposed pembrolizumab regimen.

Comparative harms

NRG-GY018 (pembrolizumab versus placebo)

6.38 A summary of the frequency of adverse events (AEs) in NRG-GY018 in the all-comers population at IA1 is presented in Table 10. The submission only presented safety results for NRG-GY018 from the EUR which had approximately 9 additional months of data from IA1. However, as the majority (>99%) of placebo patients discontinued treatment following the unblinding of the trial at IA1, the EUR results may be confounded by reduced adherence to the assigned treatment in the placebo arm. Therefore, information from NRG-GY018 IA1 was extracted during the evaluation for estimations of relative risk (RR) and risk differences (RD).

Table 10: Summary of adverse events in NRG-GY018 IA1 (patients as treated)

Adverse Events, n (%)	All-comers		RR (95% CI)	RD (95% CI)
	PEM+PBC (N=382)	PBO+PBC (N=377)		
One or more adverse events	376 (98.4)	375 (99.5)	0.99 (0.98, 1.00)	-1.0 (-2.5, 0.4)
Drug-related adverse events	365 (95.5)	358 (95.0)	1.01 (0.97, 1.04)	0.6 (-2.4, 3.6)
Grade 3-5 adverse events	225 (58.9)	174 (46.2)	**1.28 (1.11, 1.46)**	**12.7 (5.7, 19.8)**
Grade 3-5 drug-related adverse events	172 (45.0)	120 (31.8)	**1.41 (1.18, 1.70)**	**13.2 (6.3, 20.1)**
Serious adverse events	132 (34.6)	73 (19.4)	**1.78 (1.39, 2.29)**	**15.2 (9.0, 21.4)**
Serious drug-related adverse events	82 (21.5)	43 (11.4)	**1.88 (1.34, 2.65)**	**10.1 (4.8, 15.3)**
Death	6 (1.6)	4 (1.1)	1.48 (0.42, 5.20)	0.5 (-1.1, 2.1)
Death due to a drug-related adverse event	1 (0.3)	2 (0.5)	0.49 (0.04, 5.42)	-0.3 (-1.2, 0.6)

Source: p16 and p17 of NRG-GY018 CSR IA1; Table 55, p 86 of Pembrolizumab EPAR 2024. The relative risks were analysed during the evaluation using the numbers in Table 2.5.10. This was performed using the statistical methods for deriving RR and RD by Gardner & Altman 1997

Abbreviations: PEM = pembrolizumab; PBC = platinum based chemotherapy; PBO = placebo; dMMR = mismatch repair deficient; pMMR = mismatch repair proficient

Database cutoff date 16 DEC 2022 for dMMR and 06 DEC 2022 for pMMR

Bold indicates values where the 95% CI did not include '1'

6.39 The proportion of patients reporting Grade ≥3 drug-related AEs was approximately 10 to 15% higher in the pembrolizumab arm compared to placebo (RD: all comers 13.2%; dMMR 15.3%; pMMR: 12.4%). Serious drug-related AEs were approximately 10% higher in the pembrolizumab arm compared to the placebo arm (RD: all comers 10.1%; dMMR 10.9%; pMMR: 9.7%). The differences in AEs were generally comparable across the dMMR and pMMR population (≤5% difference).

6.40 In NRG-GY018, six patients who received at least one dose of study intervention in the pembrolizumab arm experienced a fatal AE (five in pMMR group and one in dMMR group) of which one in the pMMR group was considered related to study treatment as assessed by the investigator (cardiac arrest). The updated safety data (data cutoff of 18 August 2023) showed that a total of 10 patients with a fatal AE in the pembrolizumab group (four additional deaths from IA1) had been reported, of which three were considered drug related (two due to cardiac arrest and one due to sepsis).

6.41 Table 11 summarises serious adverse events (SAEs) occurring in > 1% of patients in NRG-GY018 at IA1 in the all-comers population.

Table 11: Most Common SAEs occurring in >1% of patients in NRG-GY018 (IA1, all-comers)

N, (%)	NRG-GY018		RR (95% CI)	RD (95% CI)
	PEM+PBC N=382	PBO+PBC N=377		
Any	132 (34.6)	73 (19.4)	**1.78 (1.39, 2.29)**	**15.2 (9.0, 21.4)**
Anaemia	16 (4.2)	13 (3.4)	1.21 (0.59, 2.49)	0.7 (-2.0, 3.5)
Febrile neutropenia	11 (2.9)	5 (1.3)	2.17 (0.76, 6.19)	1.6 (-0.5, 3.6)
Urinary tract infection	8 (2.1)	6 (1.6)	1.32 (0.46, 3.76)	0.5 (-1.4, 2.4)
White blood cell decreased/neutropenia	8 (2.1)	4 (1.1)	1.97 (0.60, 6.50)	1.0 (-0.7, 2.8)
Dyspnoea	7 (1.8)	0	-	**1.8 (0.5, 3.2)**
Hyperglycaemia	7 (1.8)	0	-	**1.8 (0.5, 3.2)**
Neutrophil count decreased	7 (1.8)	7 (1.9)	0.99 (0.35, 2.79)	0.0 (-1.9, 1.9)
Pulmonary embolism	7 (1.8)	8 (2.1)	0.86 (0.32, 2.36)	-0.3 (-2.3, 1.7)
Sepsis	7 (1.8)	5 (1.3)	1.38 (0.44, 4.32)	0.5 (-1.3, 2.3)
COVID-19	6 (1.6)	0	-	**1.6 (0.3, 2.8)**
Diarrhoea	6 (1.6)	3 (0.8)	1.97 (0.50, 7.83)	0.8 (-0.8, 2.3)
Embolism	6 (1.6)	1 (0.3)	5.92 (0.72, 48.95)	1.3 (0.0, 2.7)
Hypokalaemia	6 (1.6)	2 (0.5)	2.96 (0.60, 14.58)	1.0 (-0.4, 2.5)

Source: Table 69, Pembrolizumab EPAR. The relative risks were analysed during the evaluation using the statistical methods for deriving RR and RD by Gardner & Altman 1997

Abbreviations: EPAR = European public assessment report; PEM = pembrolizumab; PBC = platinum based chemotherapy; PBO = placebo; RD = risk difference; RR =relative risk

Note: For NRG-GY018, reporting of unrelated serious adverse events between 30 and 90 days of last dose are not required

Bold indicates values where the 95% CI did not include '1'

6.42 The rates of any SAE were approximately 15% higher in patients who received at least one dose of study intervention in the pembrolizumab arm compared to placebo.

6.43 No new indication-specific, immune-mediated AEs causally associated with pembrolizumab were identified in NRG-GY018. Most indication-specific, immune-mediated AEs remained nonserious, Grade 1 or 2 in severity, and manageable with standard clinical practice, such as administration of systemic corticosteroids and/or treatment interruption/discontinuation.

6.44 The TGA Delegates Overview, which reviewed the NRG-GY018 IA1 data cutoff, stated that while the incidence of the most common drug-related AEs was generally higher in the pembrolizumab group, the AEs that occurred were consistent with the known safety profile of pembrolizumab monotherapy and chemotherapy regimens individually. No new toxicity was identified in the pembrolizumab plus chemotherapy combination group.

Indirect Comparisons of Safety

6.45 The submission presented unanchored indirect comparisons of AEs between NRG-GY018, RUBY-1 and DUO-E. As such, the evaluation considered that any potential inferences regarding the comparative safety of pembrolizumab, dostarlimab and durvalumab ± olaparib are highly uncertain, as differences between the rates AEs in the placebo arm in each of the trials were unaccounted for. As AEs were consistently reported for the combined dMMR and pMMR population (all-comers populations) across all three studies, only the safety outcomes for the combined dMMR and pMMR

populations were presented. The unanchored indirect comparisons used AE data from the NRG-GY018 EUR.

6.46 A summary of treatment-emergent AEs (TEAEs) and related AEs across the NRG-GY018, RUBY-1 and DUO-E safety analysis sets is shown in Table 12. A summary of key Grade 3 or higher TEAEs and immune-related TEAEs is shown in Table 13.

Table 12: Summary of Treatment-emergent and related AEs across NRG-GY018, RUBY-1 and DUO-E

	NRG-GY018 EUR		RUBY-1 IA1		DUO-E (chemo+maintenance) IA1		
	PEM+PBC N=391	**PBO+PBC N=388**	**DOS+PBC N=241**	**PBO+PBC N=246**	**PBO+PBC N=236**	**DUR+PBC N=235**	**DUR+PBC +OLA N= 238**
Any AE	388 (99.2)	387 (99.7)	241 (100)	246 (100)	236 (100)	232 (98.7)	237 (99.6)
Any Drug-related AE	379 (96.9)	373 (96.1)	236 (97.9)	243 (98.8)	NA	NA	NA
Grade ≥3	257 (65.7)	191 (49.2)	170 (70.5)	147 (59.8)	133 (56.4)	129 (54.9)	160 (67.2)
Drug-related Grade≥3	195 (49.9)	132 (34.0)	122 (50.6)	114 (46.3)	NA	NA	NA
Serious AEs	155 (39.6)	82 (21.1)	91 (37.8)	68 (27.8)	73 (30.9)	73 (31.1)	85 (35.7)
Drug-related Serious AEs	98 (25.1)	49 (12.6)	44 (18.3)	30 (12.2)	NA	NA	NA
Any TEAE Leading to treatment discontinuation	71 (18.2)	28 (7.2)	57 (23.7)	41 (16.7)	44 (18.6)	49 (20.9)	58 (24.4)
Any immune related TEAE	155 (39.4)	102 (26.3)	137 (56.8)	88 (35.8)	16 (6.8)	66 (28.1)	56 (23.5)
Any TEAE Intervention or PBO related irAEs	NA	NA	92 (38.2)	38 (15.4)	NA	NA	NA
Any infusion-related outcomes	74 (18.9)	72 (18.6)	44 (18.3)	49 (19.9)	24 (10.2)	15 (6.4)	14 (5.9)
Led to death	10 (2.6)	4 (1.0)	5 (2.1)	0	8 (3.4)	4 (1.7)	5 (2.1)
Drug-related AEs leading to death	3 (0.8)	2 (0.5)	2 (0.8)	0	NA	NA	NA

Source: Table 2.5-11, p151 of the submission
Abbreviations: AE = Adverse event; DCO = data cut-off; TEAE = treatment emergent adverse event; DUR = durvalumab; DOS = dostarlimab; OLA = Olaparib; PBC = platinum based chemotherapy; PEM = pembrolizumab
Note: Following IA1 in NRG-GY018 the majority >99% of PBO+PBC patients discontinued study treatment as a result of unblinding.

Table 13: Summary of TEAEs ≥ Grade 3 in ≥5% patients and most frequently occurring immune-related TEAEs

	NRG-GY018 EUR		RUBY-1 IA1		DUO-E (chemo+maintenance) IA1		
Grade ≥3 TRAE n (%) occurring in ≥5% of patients							
	PEM+PBC N=391	**PBO+PBC N=388**	**DOS+PBC N=241**	**PBO+PBC N=246**	**PBO+PBC N=236**	**DUR+PBC N=235**	**DUR+PBC+OLA N=238**
Any	257 (65.7)	191 (49.2)	170 (70.5)	147 (59.8)	133 (56.4)	129 (54.9)	160 (67.2)
Anaemia	66 (16.9)	45 (11.6)	36 (14.9)	40 (16.3)	34 (14.4)	37 (15.7)	56 (23.5)
Neutrophil count decreased	55 (14.1)	56 (14.4)	20 (8.3)	34 (13.8)	55 (23.3)	51 (21.7)	64 (26.9)
Neutropenia	NA	NA	23 (9.5)	23 (9.3)	-	-	-
White blood cell decreased	36 (9.2)	30 (7.7)	16 (6.6)	13 (5.3)	13 (5.5)	11 (4.7)	15 (6.3)
Lymphocyte count decreased	27 (6.9)	19 (4.9)	13 (5.4)	18 (7.3)	5 (2.1)	5 (2.1)	3 (1.3)
Hypertension	22 (5.6)	20 (5.2)	17 (7.1)	8 (3.3)	7 (3.0)	5 (2.1)	6 (2.5)
Any grade occurring in ≥1% of patients							
Any	155 (39.6)	102 (26.3)	137 (56.8)	88 (35.8)	16 (6.8)	66 (28.1)	56 (23.5)
Hypothyroidism	54 (13.8)	15 (3.9)	27 (11.2)	8 (3.3)	6 (2.5)	34 (14.5)	28 (11.8)
Hyperthyroidism	32 (8.2)	10 (2.6)	8 (3.3)	1 (0.4)	2 (0.8)	5 (2.1)	4 (1.7)
Infusion related rection	60 (15.3)	56 (14.4)	31 (12.9)	30 (12.2)	24 (10.2)	15 (6.4)	14 (5.9)
Pneumonitis	5 (1.3)	2 (0.5)	NA	NA	0	2 (0.9)	5 (2.1)
Anaphylactic reaction	4 (1.0)	0	NA	NA	3 (1.3)	1 (0.4)	2 (0.8)

Source: Table 2.5-13, p155, Table 2.5-15, p161 of the submission; Table 2.7.4 p37 NRG-GY018 Safety Update
Abbreviations: AE = Adverse event; DCO = data cut-off; TEAE = treatment emergent adverse event; DUR = durvalumab; DOS = dostarlimab; OLA = Olaparib; PBC = platinum based chemotherapy; PEM = pembrolizumab
Note: Following IA1 in NRG-GY018 the majority >99% of PBO+PBC patients discontinued study treatment as a result of unblinding.

6.47 dMMR: The submission claimed that in the dMMR population the unanchored ITC of AEs between NRG-GY018 and RUBY-1 supported the claim of noninferior safety between pembrolizumab versus dostarlimab and durvalumab. The evaluation considered the conclusions of non-inferior comparative safety were not adequately supported as the AE data were difficult to interpret given it was based on an unanchored indirect comparison. However, the evaluation considered that, given that pembrolizumab and dostarlimab are both PD-1 inhibitors with known and manageable safety profiles, a non-inferiority safety claim was biologically plausible.

pMMR

6.48 The submission claimed that in the pMMR population the unanchored ITC of AEs between NRG-GY018 and the DUO-E supported the claim of superior safety between pembrolizumab vs durvalumab + olaparib. The submission claimed:

- While the overall incidence of any grade AEs and Grade 3 adverse events were similar between durvalumab + olaparib (DUO-E) and pembrolizumab (NRG-GY018), the addition of olaparib led to numerically higher incidence of Grade 3, serious anaemia, neutropenia as well as higher rate of any grade pneumonitis compared to durvalumab; and

- Given the higher rate of hospital related costs associated with managing durvalumab + olaparib in clinical practice, the cost associated with managing haematological adverse events and pneumonitis should be factored into the derivation of the cost-minimised price of pembrolizumab.

6.49 The evaluation considered that the unanchored ITC was likely insufficient to determine superior safety of pembrolizumab compared with durvalumab + olaparib. Nonetheless, the evaluation considered it may be biologically plausible that the addition of olaparib would lead to an inferior safety profile for the durvalumab + olaparib regimen. However, the magnitude of the difference (if any) in safety could not be accurately informed by the unanchored ITC, as there were differences in duration of treatment and follow-up between the studies, and the unanchored nature of the comparison increased the uncertainty of any findings.

6.50 The submission included the crude difference in the rate of ≥ grade 3 anaemia and neutropenia/decreased white cell count in the CMA of pembrolizumab to durvalumab + olaparib. The submission claimed that:

- In DUO-E, there was an 6.6% higher rate of anaemia for patients receiving durvalumab + olaparib compared to patients in NRG-GY018 receiving pembrolizumab. However, the rate of anaemia reported in placebo patients in DUO-E was also higher (+2.8%) compared to placebo patients in NRG-GY018; and
- In DUO-E, a 12.8% higher rate of neutropenia/decreased white cell count was observed in patients receiving durvalumab + olaparib compared to patients in NRG-GY018 receiving pembrolizumab. However, the rate of neutropenia for placebo patients in DUO-E was also 8.9% higher than placebo patients in NRG-GY018.

These differences in the placebo arm AEs were not accounted for in the unanchored ITC of AEs and likely favoured pembrolizumab.

6.51 In addition, the drug exposure for the durvalumab + olaparib in DUO-E at IA1 (mean 13.4 months for durvalumab and 10.5 months for olaparib) was longer than pembrolizumab in NRG-GY081 (mean 9.57 months), and the pMMR durvalumab + olaparib arm had a longer median follow-up of 18.4 months, approximate three months longer than pMMR pembrolizumab (median follow-up 15.3 months). This difference would further bias any safety signals in favour of pembrolizumab as shorter follow-up and exposure likely correlated to fewer reported AEs.

Benefits/harms

6.52 A benefits and harms table was not presented as the submission made a claim of non-inferiority.

Clinical claim

dMMR population

6.53 For dMMR A/R EC, the submission described pembrolizumab as non-inferior in terms of effectiveness and safety compared with dostarlimab and durvalumab.

6.54 The evaluation considered that the claims of non-inferior effectiveness versus dostarlimab and durvalumab in dMMR EC were not adequately supported by the evidence presented due to:

- the multiple sources of heterogeneity in the trial and patient characteristics, and the differences in event rates between the common comparator arms;
- the immature data at the NRG-GY018 EUR cut-off (OS information fraction 29.3% [dMMR], 46.3% [pMMR]);
- the wide confidence intervals associated with the Bucher ITC ; and

6.55 the lack of non-inferiority margins provided.

6.56 The PSCR stated 'the wide confidence intervals may reflect the small, pooled sample size and exchangeability/transitivity issues between studies and are likely driven by NRG-GY018 being subsequently unblinded to allow pembrolizumab access in the standard of care arm.'

6.57 Overall, the evaluation considered that, given that pembrolizumab, dostarlimab and durvalumab are PD-(L)1 inhibitors that have demonstrated PFS benefit versus platinum-based chemotherapy alone, it was biologically plausible that pembrolizumab may be non-inferior to dostarlimab and durvalumab in terms of effectiveness.

6.58 The claim of non-inferior safety was based on unanchored indirect comparisons that were difficult to interpret. Nonetheless, the evaluation and the ESC considered that, given pembrolizumab, dostarlimab and durvalumab are PD-(L)1 inhibitors with known and manageable safety profiles, a non-inferiority safety claim was biologically plausible.

6.59 Overall, the ESC acknowledged the issues with the indirect comparisons (e.g. transitivity issues, differences in event rates between the common comparator arms and wide confidence intervals), but considered that the claim of non-inferior efficacy versus dostarlimab and durvalumab was biologically plausible and likely reasonable in the dMMR population. Further, the ESC considered that the claim of non-inferior safety was likely reasonable in the dMMR population given: the rates of adverse events in the unanchored indirect comparison were similar; there were no new safety signals; and non-inferior safety was biologically plausibility.

6.60 The PBAC considered that the claim of non-inferior efficacy versus dostarlimab and durvalumab was not adequately supported by the information provided in the submission.

6.61 The PBAC considered that the claim of non-inferior safety versus dostarlimab and durvalumab was likely reasonable in the dMMR population.

pMMR population

6.62 For the pMMR population, the submission described pembrolizumab as non-inferior in terms of effectiveness compared with dostarlimab and durvalumab + olaparib. The submission claimed non-inferior safety versus dostarlimab and superior safety versus durvalumab + olaparib.

6.63 The evaluation considered that the claim of non-inferior effectiveness versus dostarlimab and durvalumab + olaparib in pMMR EC was not adequately supported by the evidence presented. The confidence intervals associated with the Bucher ITC were wide. Results from the NMA were also broadly similar to the Bucher ITC. As with other comparisons, the evaluation considered the results of the ITC and the NMA were uncertain due to transitivity issues. Additionally, no non-inferiority margins were provided. Importantly, the evaluation noted that the PBAC has previously considered that the benefit of dostarlimab in pMMR EC was unclear (paragraph 7.17, dostarlimab PSD, November 2023). The ESC considered there may be efficacy in a small subset of the pMMR population, however it was unclear which patients this may be. The ESC further noted that the PBAC did not recommend dostarlimab in A/R pMMR EC due to an unclear clinical benefit with the PBAC considering "it was possible that these patients may benefit more from second-line treatment with pembrolizumab in combination with lenvatinib" (dostarlimab web outcomes, May 2025 PBAC meeting). Overall, the evaluation and the ESC considered that, even if non-inferiority versus dostarlimab could be established in pMMR, it was unlikely to be sufficient to establish the benefit of pembrolizumab in the Australian clinical setting.

6.64 In its the November 2023 consideration of dostarlimab in the pMMR population, the PBAC considered 'that in the context of the much smaller demonstrated PFS benefit in the pMMR population compared with the dMMR population, and the uncertain OS benefit, the clinical place for dostarlimab as 1L treatment for pMMR EC was unclear (paragraph 7.20, dostarlimab PSD, November 2023). The ESC considered that these issues also apply to pembrolizumab in the pMMR population.

6.65 The evaluation noted that, in the head-to-head trial versus placebo (NRG-GY018), pembrolizumab was not associated with a statistically significant difference in OS in either the dMMR or pMMR populations, even with adjustments for treatment switching.

6.66 The claim of non-inferior safety versus dostarlimab was based on unanchored indirect comparison that was difficult to interpret. Nonetheless, the evaluation considered that, given that pembrolizumab and dostarlimab are PD-(L)1 inhibitors with known and manageable safety profiles, a non-inferiority safety claim was biologically plausible.

6.67 The claim of superior safety versus durvalumab + olaparib was also based on an unanchored indirect comparison that the evaluation considered was likely insufficient to determine superior safety. However, the evaluation considered it may be biologically plausible that the addition of olaparib would lead to an inferior safety profile for the durvalumab + olaparib regimen. However, the magnitude of the difference (if any) in safety could not be accurately informed by the information presented in the submission.

Economic analysis

6.68 Based on the non-inferiority efficacy claims for pembrolizumab versus dostarlimab in dMMR A/R EC and versus durvalumab + olaparib in pMMR A/R EC, a CMA was used. The key assumptions for the cost minimisation of pembrolizumab to dostarlimab and durvalumab + olaparib in the dMMR and pMMR populations, respectively, are summarised in Table 14.

Table 14: Key components and assumptions of the cost-minimisation approach proposed in the submission

Component	Claim or assumption
Therapeutic claim: effectiveness	In patients with primary advanced or first recurrent dMMR endometrial cancer: pembrolizumab + platinum-based chemotherapy (PBC) followed by pembrolizumab monotherapy maintenance is non-inferior to dostarlimab or durvalumab plus PBC followed by dostarlimab or durvalumab monotherapy maintenance based on indirect comparisons. In patients with primary advanced or first recurrent pMMR endometrial cancer: pembrolizumab + PBC followed by pembrolizumab monotherapy maintenance is non-inferior to dostarlimab or durvalumab + PBC followed by dostarlimab monotherapy or durvalumab + olaparib maintenance based on indirect comparisons.
Therapeutic claim: safety	dMMR: Pembrolizumab is non-inferior in safety to dostarlimab pMMR: Pembrolizumab is superior in safety to durvalumab + olaparib
Evidence base	An indirect treatment comparison of Phase III trials with chemotherapy as the common comparator: • pembrolizumab+PBC (NRG-GY018) versus dostarlimab+PBC (RUBY-1) • pembrolizumab+PBC (NRG-GY018) versus DUR+PBC+olaparib (DUO-E)
Equi-effective doses	Initiation (6 cycles): pembrolizumab 200mg Q3W = dostarlimab 500mg Q3W = DUR 1,120mg Q3W Maintenance: pembrolizumab 400mg Q6W = dostarlimab 1,000mg Q6W = DUR 1,500mg Q4W + olaparib 300mg bd Overall, the submission claimed the equi-effective doses, over a 12 month period would be: dMMR: pembrolizumab 3,479 mg = dostarlimab 8,696 mg pMMR: pembrolizumab 3,479 mg = DUR 19,537 mg + olaparib 143,550 mg
Direct medicine costs	Calculation of the equi-effective doses was based on the first full year of treatment, using the recommended treatment regimens for each respective therapy. Dose intensity and treatment durations from clinical trials were not considered. The cost of PBC was excluded in the CMA.
Other costs or cost offsets	dMMR population equivalent: In the event of a positive PBAC recommendation the cost minimised price per vial of pembrolizumab will be adjusted to reflect the difference in the duration of treatment (pembrolizumab 2 years vs dostarlimab 3 years) to deliver the same total cost to government (MBS+PBS), when the cost minimisation is performed on the basis on the effective dostarlimab PBS price. However, the evaluation considered it was unclear what this referred to and noted the submission had conducted the CMA based on equi-effective doses over a 12-month treatment duration for both pembrolizumab and dostarlimab. pMMR population equivalent: In the event of a positive PBAC recommendation the cost minimised price per vial of pembrolizumab will be adjusted to reflect the incremental costs associated with the management of Grade 3-4 adverse events (i.e. higher with durvalumab + olaparib maintenance) to deliver the same total cost to government (MBS+PBS), when the cost minimisation is done on the basis of the effective durvalumab and olaparib PBS price.

Source: Table 3.1-1, p193 of the submission

Abbreviations: CMA = cost minimisation analysis; dMMR = mismatch repair deficient; pMMR = mismatch repair proficient; DOS = dostarlimab; DUR = durvalumab; MBS = Medicare Benefits Schedule; PBAC = Pharmaceutical Benefits Advisory Committee; Q3W = three weekly; Q4W = four weekly; Q6W = six weekly.

Note: The submission stated that in the absence of the PBAC accepted mean time on treatment and effective prices for dostarlimab/durvalumab + olaparib the cost per patient per year was calculated using list prices for illustrative purposes. Once the mean time on treatment and effective prices are shared by the Department, MSD will work to update the cost-minimisation analysis.

dMMR population

6.69 The equi-effective doses proposed in the submission were based on the recommended treatment regimens, with a 100% dose intensity assumed. Therefore, the equi-effective doses for the dMMR population were:

- Initiation: pembrolizumab 200mg Q3W is equivalent to dostarlimab 500mg every three weeks (Q3W) for six cycles; and
- pembrolizumab 400mg Q6W is equivalent to dostarlimab 1,000mg every six weeks (Q6W).

6.70 The submission stated that since the treatment durations for pembrolizumab, dostarlimab and durvalumab + olaparib differed between trials and cohorts (dMMR vs pMMR), the CMA was based on the costs of the first full year of treatment only (i.e. complete initiation phase, then use maintenance until a full year of treatment was reached).

6.71 The evaluation considered that it was unclear whether the use of the first full year of treatment only for the estimation of equi-effective doses was appropriate as the clinical claim was based on results from the NRG-GY018, DUO-E and RUBY trials, therefore using the mean number of doses, extrapolated from each trial may have been more appropriate. Extrapolation of mean doses would be required as the (truncated) means reported in the trials would likely favour pembrolizumab as the duration of follow-up and the time on treatment was longer for dostarlimab in RUBY than for pembrolizumab in NRG-GY018 (refer to Table 4 and Table 7).

6.72 The submission's proposed equi-effective doses for the dMMR population are summarised in Table 15.

Table 15: Equi-effective doses over 12-month treatment duration (dMMR)

	Pembrolizumab			Dostarlimab		
	mg per infusion	Number of infusions	Total mg	mg per infusion	Number of infusions	Total mg
Induction	200	6.0	1,200	500	6.0	3,000
Maintenance	400	5.70 [a]	2,279	1000	5.70 [a]	5,696
Total	-	11.70	3,479	-	11.70	8,696

Source: CMA excel workbook, Attachment 11 to the submission

[a] Calculated by the submission as 1 year minus 18 weeks (6.0 Q3W cycles), divided by the 42 day (Q6W) dosing frequency for maintenance. Equi-effective doses would usually be calculated based on the actual number of doses received i.e. a dose at Week 18, 24, 30, 36, 42 and 48 for a total of six doses.

6.73 The CMA incorporated intravenous (IV) administration costs. The MBS fee for the administration of IV chemotherapy (MBS item code 13950, $123.05) was used.

6.74 The dostarlimab costs were based on the published ex-manufacturer prices

6.75 The submission calculated the total annual cost of dostarlimab by summing the initiation phase and maintenance phase of treatment, then the annual cost was used to calculate the cost-minimised price of pembrolizumab, as shown in Table 16.

Table 16: Cost-minimisation approach for pembrolizumab to dostarlimab (Total 52 week of treatment) - dMMR

Step	Description	Calculation	Result	
Initiation Phase				
A	Published AEMP 500 mg Q3W	-	$7,647.50	
B	Cost of dostarlimab for 6 cycles	A*6 (Q3W)	$45,885.00	
C	Cost of dostarlimab administration for 6 cycles	$123.05 [a] * 6	$738.30	
D	Total cost of dostarlimab for initiation phase (18 weeks)	B + C	$46,623.30	
Maintenance Phase				
E	Published AEMP 1000 mg Q6W	$7647.50 * 2	$15,295	
F	Cost of dostarlimab supply for 5.7 [b] cycles	E * 5.7 (Q6W)	$87,126.88	
G	Cost of dostarlimab administration for 5.7 [b] cycles	$123.05 [a] * 5.7	$700.95	
H	Total cost of dostarlimab for maintenance phase (34 weeks)	F + G	$87,827.82	
Total				
I	Cost of dostarlimab per year	B + F	$133,011.88	
J	Cost of dostarlimab administration per year	C + G	$1,439.25	
Cost-minimisation of pembrolizumab to dostarlimab				
K	Cost of dostarlimab per year		I + J	$134,451.12
L	Cost of pembrolizumab administration per year		J	$1,439.25
M	Cost of pembrolizumab per year		K - L	$133,011.88
N	Yearly dose of pembrolizumab (mg)		(200mg*6) + (400mg*5.70)	3479 mg
O	Cost of pembrolizumab per mg		M/ N	$38.24
P	**Cost minimised AEMP per 100mg vial pembrolizumab**		**O * 100**	**$3,823.75**
Q	Pembrolizumab cost per patient (per year)		L + (P*2*6) + (P*4*5.7)	$134,451.12

Source: Table 3.4-1, 3.4-2 and 3.4-4, pp197-199 of the submission; Attachment 11 to the submission 'vs dostarlimab'.
Abbreviations: AEMP = approved ex-manufacturer price; Q3W = three weekly; Q6W = six weekly
[a] MBS item 13950 $123.05
[b] Assuming 6.0 Q3W initiation doses (18 weeks), then 1 year minus 18 weeks = 34 weeks, divided by Q6W dosing = 5.7 maintenance doses.
Note: One year supply of pembrolizumab is equivalent to 6.0 x 200mg initiation doses and approximately 5.7 x 400mg maintenance doses.

6.76 The submission did not present any sensitivity analyses. As shown in Table 17, a sensitivity analysis was conducted during evaluation, using the same assumptions as were accepted for the CMA of dostarlimab to durvalumab in dMMR: i.e. a treatment duration of 20.5 months (based on the dostarlimab dMMR modelled treatment duration) and a relative dose intensity of 5.1 initiation doses and 12.0 maintenance doses (Table 18, dostarlimab PSD, November 2023 PBAC Meeting; Table 17, durvalumab PSD, November 2024 PBAC Meeting).

Table 17: Estimated equi-effective dose based on accepted dosage in durvalumab Nov 2024 submission

	Pembrolizumab			Dostarlimab		
	Mean treatment duration = 20.5 months (88.9 weeks)			Mean treatment duration = 20.5 months (88.9 weeks)		
	Milligrams per infusion	**Number of infusions**	**Total milligrams per course**	**Milligrams per infusion**	**Number of infusions**	**Total milligrams per course**
Induction	200	5.1	1,200	500	5.1	2,550
Maintenance	400	12	4,800	1,000	12	12,000
Total	-	17.1	5,820	-	17.1	14,550
Cost minimisation (sensitivity analysis)						
	Output			Calculation/Method		Result
A	Cost of dostarlimab per mg			$7,647.50/ 500 mg		$15.30
B	Cost of dostarlimab per course			14,550 x A		$222,542.25
G	Cost of pembrolizumab per mg			F / 5,820 mg		$38.24
H	Cost minimised AEMP per 100mg vial pembrolizumab			G * 100		**$3,823.75**

Source: Calculated during evaluation for sensitivity analysis. The dose equivalence for DUR was sourced from the PBAC outcomes for November 2024. The PBAC previously considered that over a mean duration of therapy of 20.5 months, durvalumab 32,712 mg was equivalent to dostarlimab 14,550 mg.
Abbreviations: AEMP = approved ex-manufacturer price
[a] Administration costs were not included in the table above as they do not impact the overall result.

6.77 For the CMA of pembrolizumab versus dostarlimab, the duration and dose intensity do not impact the CMA as long as they are assumed to be equal between arms (due to identical dosing frequency between arms).

pMMR population

6.78 The ESC noted that the submission did not present an economic analysis versus the appropriate comparator of platinum-based chemotherapy alone followed, in a proportion of patients, by second line (2L) pembrolizumab + lenvatinib, with the PSCR requesting consideration of the dMMR population only.

6.79 The submission assumed that either dostarlimab or durvalumab + olaparib would receive a positive PBAC recommendation for pMMR A/R EC prior to PBAC consideration of pembrolizumab. The submission stated that if dostarlimab were recommended before durvalumab + olaparib, then the submission will instead cost minimise to dostarlimab in the pMMR population, and that the equi-effective doses would remain consistent with those outlined for the dMMR population. The evaluation considered it may not be reasonable for the equi-effective doses in the pMMR population to be the same as in dMMR as differences in time on treatment were observed in NRG-GY018 for the dMMR and pMMR populations (see Table 4), and different durations of treatment depending on MMR status were also applied in submission's financial estimates.

6.80 The equi-effective doses for the pMMR population, as proposed by the submission, were:

- Initiation: pembrolizumab 200mg Q3W is equivalent to durvalumab 1,120mg every three weeks (Q3W); and
- Maintenance: pembrolizumab 400mg Q6W is equivalent to durvalumab 1,500mg every four weeks (Q4W) plus olaparib 300mg twice daily (bd).

6.81 The submission's proposed equi-effective doses are summarised in Table 18 for the pMMR population.

Table 18: Equi-effective doses over 12-month treatment duration (pMMR)

	Pembrolizumab			Durvalumab			Olaparib		
	Mg per infusion	Number of infusions	Total mg	Mg per infusion	Number of infusions	Total mg	Mg per day	Days on tx	Total mg
Induction	200	6.0	1,200	1120	6.0	6,720	-	-	-
Maintenance	400	5.70 [a]	2,279	1500	8.54 [b]	12,817	600	239.25 [c]	143,550
Total	-	11.70	3,479	-	14.54	19,537	-	239.25	143,550

Source: CMA excel workbook, Attachment 11 to the submission
Abbreviations: Tx = treatment
[a] Calculated by the submission as 1 year minus 18 weeks (6.0 Q3W cycles), divided by the 42 day (Q6W) dosing frequency for maintenance.
[b] Calculated by the submission as 1 year minus 18 weeks (6.0 Q3W cycles), divided by the 28 day (Q4W) dosing frequency for maintenance.
[c] 1 year minus 18 weeks of initiation therapy = 34 weeks.
Equi-effective doses would usually be calculated based on the actual number of doses received i.e. a dose at Week 18, 24, 30, 36, 42 and 48 for a total of six doses.

6.82 For the CMA of pembrolizumab to durvalumab + olaparib in the pMMR population, the submission included the costs associated with managing haematological grade ≥3 adverse events due to the addition of olaparib. However, the evaluation considered that the unanchored indirect comparison was unlikely to accurately inform the magnitude of difference (if any) between pembrolizumab and durvalumab + olaparib (see paragraphs 6.49 to 6.51) and may not be reliable. The difference in incidence of AEs was then multiplied by the cost of episode of care (based on AR-DRG codes and cost from the National Efficient Price for public hospital services 2024-25) to derive a total incremental cost of adverse event management per patient of $717.22.

6.83 The durvalumab and olaparib costs were calculated based on the published ex manufacturer prices (in other indications including non-small cell lung cancer and biliary tract cancer), as shown in Table 19.

Table 19: Cost-minimisation analysis of pembrolizumab to durvalumab + olaparib (Total 52 weeks of treatment)- pMMR

Step	Description	Calculation	Result
Initiation Phase			
A	Published AEMP durvalumab 500 mg	-	$3,776.25
B	Published AEMP durvalumab 120 mg	-	$906.30
C	Total published AEMP durvalumab 1,120mg	A*2 + B	$8,458.80
D	Cost of durvalumab for 6 cycles	C*6	$50,752.80
E	Cost of administration for 6 cycles	$123.05 [a] * 6	$738.30
F	Total cost of durvalumab for initiation (18 weeks)	D + E	$51,491.10
Maintenance Phase			
G	Total published AEMP durvalumab 1,500mg	A * 3	$11,328.75
H	Cost of durvalumab supply for 8.54 cycles	G * 8.54 [b]	$96,800.12
I	Cost of durvalumab administration per year for 8.54 cycles	$123.05 [a] * 8.54 [b]	$1,051.42
J	Total cost of durvalumab for maintenance (34 weeks)	H + I	$97,851.54
K	Published AEMP olaparib 150 mg (56 tablets)	-	$3,234.75
L	Cost of 600mg daily dose of olaparib	(K/56) * 4	$231.05
M	Cost of 34 week supply of olaparib	L * 239.25	$55,279.57
N	Total cost of durvalumab and olaparib for maintenance	J + M	$153,131.11
Adverse Events			
O	Incremental cost of AE management per patient per year	See paragraph 6.82	$717.22
-	Difference in incidence of anaemia x Cost per episode	6.6% [c] * $3,231.17 [d]	$213.26
-	Difference in incidence of neutropenia x Cost per episode	12.8% [c] * $3,937,19 [d]	$503.96
Total			
P	Total yearly cost of durvalumab and olaparib	F + N + O	$205,339.43
Cost-minimisation of pembrolizumab to durvalumab+olaparib			
Q	Cost of pembrolizumab administration per year	$123.05 [a] * (6+5.70)	$1,439.25
R	Cost of pembrolizumab per year	P - Q	$203,900.18
S	Yearly dose of pembrolizumab (mg)	(200*6)+(400*5.70)	3479 mg
T	Cost of pembrolizumab per mg	R / S	$58.62
U	**Cost minimised AEMP per 100mg vial pembrolizumab**	**T * 100**	**$5,861.61**
V	Pembrolizumab Cost per patient (per year)	Q + (U*2*6) + (U*4*5.7)	$205,339.43

Source: Table 3.4-6, pp197-202 of the submission

Abbreviations: AEMP = approved ex-manufacturer price; Q3W = three weekly; Q6W = six weekly

[a] MBS item 13950 $123.05

[b] Assuming 6.0 Q3W initiation doses (18 weeks), then 1 year minus 18 weeks = 34 weeks, divided by Q4W dosing = 8.54 maintenance doses.

[c] The submission applied the crude difference in the rate of ≥ grade 3 anaemia and neutropenia/decreased white cell count between PEM+PBC and DUR+PBC+olaparib (Refer to Table 13).

[d] Based the cost per episode of care for DRG codes Q61A, Q61B and Q61C for anaemia and Q60A and Q60B for neutropenia, using published cost weights and the National Efficient Price 2024-25 of $6,465.

Note: One year supply of pembrolizumab is equivalent to 6.0 200mg initiation doses and approximately 5.7 400mg maintenance doses.

6.84 The submission's cost minimised price for the pMMR population was higher ($5,861.61) than the dMMR population ($3,823.75) because in pMMR, pembrolizumab was compared with a two-drug regimen (durvalumab + olaparib) instead of a single drug (dostarlimab), and also due to the published prices used. Overall, the evaluation considered that a higher price in the pMMR population may not be appropriate given that the incremental benefit reported in NRG-GY018 at IA1 in the pMMR group (PFS HR=0.57, 95% CI 0.44, 0.74; OS HR = 0.79, 95% CI 0.53, 1.17) was lower than in the dMMR group (PFS HR=0.34, 95% CI 0.22, 0.53; OS HR = 0.55, 95% CI 0.25, 1.19).

6.85 For the pMMR CMA of pembrolizumab to durvalumab + olaparib, longer treatment durations (i.e. greater than one year) resulted in a higher cost-minimised price for pembrolizumab.

Drug cost/patient/course

6.86 Table 20 and Table 21 show the doses of pembrolizumab used in the submission and the resulting drug cost per patient course in the dMMR and pMMR populations, respectively based on published prices. The ESC noted the cost per patient will reduce once the effective price of the comparator is applied (in the dMMR population).

Table 20: Drug cost per patient for pembrolizumab treatment, dMMR (based on published prices)

	Trial dose and duration	CMA	Financial estimates
Pembrolizumab, mean total number of doses	12.9 [a]	11.7	13.4 [d]
Initiation (200 mg)	NR	6.0	6.0 [d]
Maintenance (400 mg)	NR	5.7	7.4 [d]
Pembrolizumab, duration of treatment	54.19 weeks [b]	52.14 weeks	62.57 weeks [c]
Total cost/patient/course	$151,420.50 [e]	$133,011.88	$159,068.00 [f]

Source: Compiled during evaluation using information from Section 3 & 4; and Table 4.1-1 Attachment 14 and 15 of the submission
[a] NRG-GY018 time on treatment data from Table 4.1-1 Attachment 14 to the submission
[b] Duration on pembrolizumab NRG-GY018, 379.3 days; Table 4.1-1 Attachment 14 to the submission
[c] Time on treatment estimated from NRG-GY018 using the non-parametric Kaplan-Meier (KM) product-limit method
[d] The submission assumed an average duration of treatment of 62.57 weeks (comprising 18 weeks initiation plus 44.57 weeks maintenance) in the dMMR financial estimates.
[e] Based on the cost minimised (to dostarlimab) price for 100mg pembrolizumab = $3,823.75. Therefore, ($3,823.75 * 6.0 * 2) + ($3,823.75 * 6.9 * 4). Assuming 6.0 initiation doses.
[f] Based on the cost minimised (to dostarlimab) price for 100mg pembrolizumab = $3,823.75. Therefore, ($3,823.75 * 6.0 * 2) + ($3,823.75 * 7.4 * 4)

Table 21: Drug cost per patient for pembrolizumab treatment, pMMR (based on published prices)

	Trial dose and duration	CMA	Financial estimates
Pembrolizumab, mean total number of doses	9.8 [a]	11.7	10.17 [c]
Initiation (200 mg)	NR	6.0	6.0
Maintenance (400 mg)	NR	5.7	4.17
Pembrolizumab, duration of treatment	36.81 weeks [b]	52.14 weeks	43.02 weeks [d]
Total cost/patient/course	$159,435.79 [e]	$203,900.18	$168,110.97 [f]

Source: Compiled during evaluation using information from Section 3 & 4; and Table 4.1-1 Attachment 14 and 15 of the submission
[a] NRG-GY018 time on treatment data from Table 4.1-1 Attachment 15 to the submission
[b] Duration on pembrolizumab NRG-GY018, 257.7 days; Table 4.1-1 Attachment 15 to the submission
[c] Calculated based on duration of treatment. Assuming 6.0 initial doses (18 weeks). Then 43.02 – 18 = 25.02 weeks, divided by Q6W dosing (42 days) = 4.17 maintenance doses. 6.0 + 4.17 = 10.17 total doses.
[d] Time on treatment estimated from NRG-GY018 using the non-parametric Kaplan-Meier (KM) product-limit method
[e] Base on the cost minimised (to durvalumab/olaparib) price for 100mg pembrolizumab = $5,861.61. Therefore, ($5,861.61* 6.0 * 2) + ($5,861.61* 3.8 * 4). Assuming 6.0 initiation doses.
[f] Based on the cost minimised (to durvalumab/olaparib) price for 100mg pembrolizumab = $5,861.61. Therefore, ($5,861.61* 6.0 * 2) + ($5,861.61* 4.17 * 4)

6.87 The durations of treatment were not consistent between NRG-GY018 (actual time on treatment during the trial), the CMA (assumed to be the first year of treatment), and the financial estimates (estimated time on treatment using the KM product-limit method). In addition, in the CMA and financial estimates, a dose intensity of 100% was assumed.

Estimated PBS usage & financial implications

6.88 This submission was not considered by DUSC.

6.89 The submission used an epidemiological approach to estimate the financial impact of listing pembrolizumab for the treatment of 1L A/R EC. Separate financial estimates were provided for the dMMR and pMMR populations. The submission stated that although a CMA submission would typically utilise a market-share approach, there was insufficient PBS utilisation data (< 12months) for dostarlimab or durvalumab to perform a market share approach.

dMMR population

6.90 As the financial estimates have already been established for dostarlimab in the dMMR population, the submission reasonably did not include a prevalent population but inappropriately excluded cost offsets.

6.91 The key data sources, parameters and assumptions used to estimate the financial impact of listing pembrolizumab for 1L dMMR EC are summarised in Table 22.

Table 22: Key inputs for financial estimates (dMMR)

Data	Value and Source	Comment from evaluation
Eligible population		
Incident *de novo* EC patient pool	Yr 1 (2025): 3,443 increasing to Yr 6 (2030): 3,921 Source: AIHW patients with Uterine Cancer (Long term Incidence Projections 2025+) Published August 2024. Calculated by the application of 95% (proportion of uterine cancer reported as EC) to estimated uterine cancer incident.	The evaluation considered this was reasonable. The method was different to the dostarlimab submission which applied a 3% growth rate to 2019-2022 AIHW incidence (Table 20, dostarlimab PSD, November 2023 PBAC meeting).
Stage III not for curative intent & Stage IV de novo metastatic	10% Source: SEER 2024 database and clinician feedback.	The evaluation considered this was reasonable. Previously used in 2L PEM+LEN (Table 15, pembrolizumab PSD, March 2022 PBAC meeting) and consistent with dostarlimab dMMR estimates (Table 20, dostarlimab PSD, November 2023 PBAC meeting).
Patients eligible to receive 1L platinum-based chemotherapy	90% Source: Assumption	The evaluation noted that, for dostarlimab, the PBAC had previously considered that the proportion of patients with ECOG 0-1 and expected to receive 1L PBC of 72% (80% x 90%) was reasonable. (Table 20, dostarlimab PSD, November 2023). The PSCR updated this parameter to 80%, consistent with the value previously accepted by the PBAC for dostarlimab.
ECOG 0-2	95% Source: Huepenbecker 2024 (this value could not be independently verified [a]) Updated to 80% in the PSCR.	
dMMR/pMMR proportion	dMMR: 27% Source: Gupta 2021 pMMR: 73% (complement of dMMR)	DUSC previously considered this may be reasonable (Table 14, dostarlimab PSD, March 2022 PBAC meeting).
Recurrence within 2 yrs of diagnosis	22% (Combined Stage I/II and resectable Stage III) Source: Vizza 2020	A recurrent rate of 19.5% (Vizza 2020) was used in 2L PEM+LEN (Table 15, pembrolizumab PSD, March 2022 PBAC Meeting).

Data	Value and Source	Comment from evaluation
	This value could not be independently verified. Vizza 2020 reported a recurrence rate of 19.5% for Grade IA – IIIB tumours. The time period for this recurrence rate is also not specified (i.e. may include recurrences beyond 2 years).	The rate of first recurrence in the dostarlimab dMMR submission was 13% for Stage I/II and 36% for Stage III curative. The PBAC previously considered a 30% recurrence rate for stage III patients would be appropriate (Table 20, dostarlimab PSD, November 2023 PBAC Meeting).
Proportion with distant recurrence	64% Source: Vizza 2020 Total recurrence proportion = 14.08% (64%*22%)	DUSC has previously considered for PEM+LEN that this proportion was likely underestimated as patients would be eligible for treatment if they were not suitable for curative treatment, rather than only if they had distant recurrence (Table 15 pembrolizumab PSD, March 2022).
Treatment utilisation		
Uptake rate	95% for the incident population Source: Assumption	DUSC previously considered 95% was reasonable for 2L PEM + LEN (Table 15, pembrolizumab PSD, March 2022).
Treatment duration	dMMR: 62.57 weeks (18 weeks initiation; 44.57 weeks continuing) Source: Estimated time on treatment from NRG-GY018 using product-limit (Kaplan-Meier) method.	The applied product-limit (Kaplan-Meier) method estimated mean time on treatment was longer than the reported duration on therapy for the EUR, which appeared to be due to differences in approach for handling censored data. The ESC considered the average treatment duration in the financial estimates should be consistent with that accepted for dostarlimab in dMMR for consistency with the CMA methodology used in the submission.
Patients eligible for 2L immunotherapy	49% Source: Miller 2012	DUSC previously considered this estimate may be reasonable for 2L PEM+LEN (Table 15, pembrolizumab PSD, March 2022 PBAC Meeting).
Costs		
Proposed medicine	Published cost per administration Public (28.10%) / Private (71.90%) 200mg: $7,737.63 / $7,889.37 400mg: $15,385.13 / $15,643.93 Source: Requested price, based on the published AEMP of $3,823.75 per 100mg vial	The requested list price was used in the submission's financial estimates in place of the cost minimised price.
Infusion costs	$123.05 Source: MBS 13950	The evaluation considered this was reasonable.

Source: Compiled during evaluation using information from pp204-211 of the submission; Attachment 14 and 15 of the submission, and the submission's financial workbooks (dMMR and pMMR).

Abbreviations: 1L = first-line; 2L = second-line; AEMP = approved ex-manufacturer price; AIHW = Australian Institute of Health and Welfare; A/R = advanced or recurrent; CMA = cost minimisation analysis; dMMR = mismatch repair deficient; DOS = dostarlimab; DUSC = drug utilisation sub-committee; DUR = durvalumab; EC = endometrial cancer; ECOG = Eastern Cooperative Oncology Group; MBS = Medicare Benefits Schedule; OLA = olaparib; PBC = platinum-based chemotherapy; PBS = Pharmaceutical Benefits Scheme; PEM+LEN = pembrolizumab + lenvatinib; PSD = public summary document; RPBS = Repatriation Pharmaceutical Benefits Scheme; SEER = Surveillance, Epidemiology, and End Results; Yr = year.

[a] Huepenbecker 2024 reported 83.5% of patients (272/326) treated with immune checkpoint inhibitors had an ECOG score of 0-2, and 72.9% (1,332/1,826) of patients that never received immune checkpoint inhibitors had an ECOG score of 0-2.

6.92 Table 23 presents the submission's estimate of the financial implications of listing pembrolizumab for the 1L treatment of dMMR EC over the first 6 years. However, the ESC considered these estimates were not informative and substantially overestimated as: published prices were used (as the effective prices of the comparators were not known to the sponsor and no effective price for pembrolizumab was proposed); and offsets for reduced use of dostarlimab/durvalumab or 2L pembrolizumab + lenvatinib were not included. The PSCR stated the financial estimates were intended to provide the PBAC with an estimation of the total cost of listing anti-PD-(L)1 for the treatment of 1L A/R EC. However, the ESC noted that estimates of offsets are required as part of the PBAC's consideration of the financial estimates.

6.93 If the cost per patient per course of pembrolizumab was no more than the cost of the comparators, inclusive of offsets for 2L pembrolizumab + lenvatinib, then the financial estimates would be expected to be at least cost neutral. The PSCR confirmed that the financial estimates are expected to be at least cost neutral compared to the RSA/s in place for dostarlimab and durvalumab (and 2L pembrolizumab plus lenvatinib).

Table 23: Estimated use and financial implications (published prices, without offsets for other anti-PD-(L)1s), dMMR

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimation of use						
Total initiating dMMR patients	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Number of scripts (PBS + RPBS), dMMR						
Initial 200mg Q3W [a]	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Continuing 400mg Q6W [b]	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Total scripts	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Estimated financial implications for the PBS/RPBS/MBS, dMMR						
Net cost to PBS/RPBS	$[redacted]3	$[redacted]4	$[redacted]4	$[redacted]4	$[redacted]4	$[redacted]4
Net MBS costs [g]	$[redacted]5	$[redacted]5	$[redacted]5	$[redacted]5	$[redacted]5	$[redacted]5
Net cost to PBS/RPBS/MBS	$[redacted]3	$[redacted]4	$[redacted]4	$[redacted]4	$[redacted]4	$[redacted]4
PSCR revised estimates (lower % of patients with relevant ECOG status)						
Total initiating dMMR patients	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Total scripts	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Net cost to PBS/RPBS	$[redacted]6	$[redacted]3	$[redacted]3	$[redacted]3	$[redacted]3	$[redacted]4
Net cost to PBS/RPBS/MBS	$[redacted]6	$[redacted]3	$[redacted]3	$[redacted]3	$[redacted]3	$[redacted]4

Source: Tables 4.2-1; 4.2-2; 4.2-3; 4.3-4; 4.3-5; 4.3-6; 4.3-7; 4.3-8; 4.3-9; 4.4-1; 4.4-2; 4.4-5; 4.4-7; 4.5-1; 4.5-2; 4.6-1; 4.6-2; 4.6-3; pp209 - of the submission.

Abbreviations: 1L = first-line; 2L = second-line; AIHW = Australian Institute of Health and Welfare; A/R = advanced or recurrent; dMMR = mismatch repair deficient; EC = endometrial cancer; ECOG = Eastern Cooperative Oncology Group; Govt = government; MBS = Medicare Benefits Schedule; PBC = platinum-based chemotherapy; PBS = Pharmaceutical Benefits Scheme; PEM+LEN = pembrolizumab + lenvatinib; RPBS = Repatriation Pharmaceutical Benefits Scheme; Yr = year.

Two minor issues were corrected during evaluation (refer to paragraph 6.95).

[a] Calculated using patient years of treatment using an 18 week initiation period. 17.33 scripts per year of treatment (52 weeks / (1 pack / (dosing of 1 pack / every 3 weeks))* 100% compliance.

[b] Calculated using patient years of treatment. dMMR estimated mean time on treatment NRG-GY018 14.4 months = 62.57 weeks. Assuming 18 weeks of initiation, then the remainder 44.57 weeks used as maintenance. With 8.67 scripts per year of treatment (52 weeks / (1 pack / (dosing of 1 pack / every 6 weeks))* 100% compliance.

[e] Pembrolizumab scripts calculated using patient years of treatment with a treatment duration of 44.07 weeks per the finalised 2L PEM+LEN pricing package. 17.33 scripts per year of treatment (52 weeks / (1 pack / (dosing of 1 pack / every 3 weeks))* 100% compliance.

[f] Lenvatinib scripts calculated using patient years of treatment with a treatment duration of 8.81 months per the finalised 2L PEM+LEN pricing package. This treatment duration could not be independently verified. 12 scripts per year of treatment (12 months / (30 pack / (dosing of 30 pack)* 100% compliance.

[g] Calculated by multiplying the number of administrations for pembrolizumab by the corresponding number of MBS items (MBS code 13950) and its allocated cost ($123.05).

The redacted values correspond to the following ranges:

[1] < 500

[2] 500 to < 5,000

[3] $30 million to < $40 million

[4] $40 million to < $50 million

[5] $0 to < $10 million

[6] $20 million to < $30 million

6.94 The evaluation noted the following points regarding the submission's financial estimates for the dMMR population:

- Offsets for reduced use of dostarlimab and durvalumab should have been included. As such, the net costs to the PBS/RPBS were overestimated and were not indicative of the actual cost of listing. As outlined in paragraph 6.92, the PSCR stated the financial estimates were intended to estimate the total cost of listing anti-PD-(L)1 for the treatment of 1L A/R EC. The ESC noted that the submission did not include any market share assumptions. The pre-PBAC response stated it anticipated a market share rate of 70% in first line dMMR;

- It was unclear why 2L pembrolizumab + lenvatinib offsets were not included in the dMMR population as 1L pembrolizumab would be expected to replace 1L PBC followed by 2L pembrolizumab + lenvatinib in a proportion of patients. This would have led to an overestimate in the cost in the dMMR population;
- There was potential double counting due to inclusion of ECOG 0-2 criteria (95%) and eligibility for 1L PBC (90%), as part of the eligibility requirements to commence 1L PBC are likely inclusive of an ECOG assessment;
- The number of recurrent EC patients was likely overestimated as the rate of 22% (Stage I/II and Stage III curative) could not be independently verified, and was greater than 19.5% reported in Vizza 2020, as used in 2L pembrolizumab + lenvatinib (Table 15, pembrolizumab PSD, March 2022 PBAC Meeting); and
- A compliance rate of 100% was assumed for the pembrolizumab scripts which was likely an overestimate.

6.95 The following minor corrections were applied to the submissions financial model during the evaluation (though these do not appear to have been corrected in the PSCR's revised financial estimates):

- The duration of treatment group for the 50 grandfathered patients (pMMR) was corrected to maintenance (Q6W) patients instead of initiating (Q3W), as these patients were assumed by the submission to have completed half of their total treatment duration (and thus would be beyond the 18 weeks of initiation treatment); and
- The submission's MBS service volume calculation basis only included administration associated with initial scripts, which underestimated the total volume of drug administrations.

pMMR population

6.96 For the pMMR population, a prevalent and incident pool was included as the submission anticipated pembrolizumab to be PBS-listed in the same year as other immune checkpoint inhibitors (dostarlimab and/or durvalumab + olaparib). Cost offsets were included to account for the decreased utilisation of 2L pembrolizumab + lenvatinib (though these were not included in the dMMR population estimates).

6.97 The key data sources, parameters and assumptions used to estimate the financial impact of listing pembrolizumab in the 1L pMMR setting are summarised in

6.98 Table 24. Only inputs that differ to the dMMR setting are included in this table.

Table 24: Key inputs for financial estimates (pMMR)

Data	Value and Source	Comment from evaluation
Eligible population		
Prevalent EC patient pool (pMMR only)	Yr 1: 326 Source: Calculated by linear extrapolation of known EC patients based on AIHW data from 2021 to 2024 to estimate total prevalent patients in 2025, then calculated by assuming the following: • 95% (proportion of uterine cancer reported as EC) was applied; • 50 grandfather patients were subtracted; • 18% were assumed to be advanced or metastatic (Stage III SEER database); and • 1 year OS of 92.5% was assumed. This was reduced to 83.5% in the PSCR (as accepted for the 2L PEM+LEN submission). • 90% eligible for 1L PBC • 95% ECOG 0-2. Updated to 80% in the PSCR. • 73% pMMR	In the 2L PEM+LEN submission (March 2022 PBAC meeting), the percentage of patients assumed to be advanced or metastatic was reduced to 10% from 18% in the pre-PBAC response in response to DUSC advice to remove Stage III patients that would be treated with curative intent (Table 15 pembrolizumab PSD, March 2022 PBAC meeting). However, the PSCR maintained that 18% was consistent with the final estimates accepted for 2L PEM+LEN. The PSCR updated the estimated 1 year OS rate and the proportion of patients with ECOG 0 to 2 to be consistent with values previously accepted by the PBAC.
Treatment utilisation		
Uptake rate	95% for the incident population Source: Assumption 76% for the prevalent pMMR population Source: Not stated	DUSC previously considered 95% was reasonable for 2L PEM + LEN (Table 15, pembrolizumab PSD, March 2022). The evaluation considered it was unclear why the uptake was lower in prevalent patients compared to incident patients. The PSCR clarified that the treatment uptake rate of 75.8% (amended from 76%) was intended to reflect a 95% treatment uptake applied to the eligible patient number minus the [redacted][1] grandfathered patients, to avoid double counting.
Treatment duration	pMMR: 43.02 weeks (18 weeks initiation; 25.02 weeks continuing) Grandfathered: 21.51 weeks (corrected from initiation to continuing during evaluation) Source: Estimated time on treatment from NRG-GY018 using product-limit (Kaplan-Meier) method.	The applied product-limit (Kaplan-Meier) method estimated mean time on treatment was longer than the reported duration on therapy for the EUR, which appeared to be due to differences in approach for handling censored data.
Grandfathered patients (1L A/R pMMR EC)	[redacted][1] in Yr 1 Source: Sponsor estimate	The submission stated that half of the time on treatment was applied for grandfathered patients in the pMMR population. However, the DTG incorrectly applied the initiation treatment (200mg Q3W), instead of maintenance (400mg Q6W) which was inappropriate given these patients would be expected to have completed initiation. This was corrected during evaluation.

Source: Compiled during evaluation using information from pp204-211 of the submission; Attachment 14 and 15 of the submission, and the submission's financial workbooks (dMMR and pMMR).

Abbreviations: 1L = first-line; 2L = second-line; AEMP = approved ex-manufacturer price; AIHW = Australian Institute of Health and Welfare; A/R = advanced or recurrent; CMA = cost minimisation analysis; dMMR = mismatch repair deficient; DOS = dostarlimab; DUSC = drug utilisation sub-committee; DUR = durvalumab; EC = endometrial cancer; ECOG = Eastern Cooperative Oncology Group; MBS = Medicare Benefits Schedule; OLA = olaparib; PBC = platinum-based chemotherapy; PBS = Pharmaceutical Benefits Scheme; PEM+LEN = pembrolizumab + lenvatinib; PSD = public summary document; RPBS = Repatriation Pharmaceutical Benefits Scheme; SEER = Surveillance, Epidemiology, and End Results; Yr = year.

[a] Huepenbecker 2024 reported 83.5% of patients (272/326) treated with immune checkpoint inhibitors had an ECOG score of 0-2, and 72.9% (1,332/1,826) of patients that never received immune checkpoint inhibitors had an ECOG score of 0-2.

The redacted values correspond to the following ranges:

[1] < 500

6.99 Table 25 presents the submission's estimate of the financial implications of listing pembrolizumab for the 1L treatment of pMMR EC over the first 6 years. Published prices were used (as the effective prices of the comparators were not known to the sponsor and no effective price for pembrolizumab was proposed). Offsets for reduced use of dostarlimab/durvalumab were not included and as such, the evaluation and the ESC considered that the submission's estimate of the financial impact was not informative (substantially overestimated).

Table 25: Estimated use and financial implications in pMMR (published price, without 1L offsets)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated Estimation of use						
Total initiating pMMR patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
PBS/RPBS cost less co-pay						
pMMR [d]	$[redacted][2]	$[redacted][3]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Estimation of changes in use and financial impact of other medicines (PBS and RPBS)						
2L PEM+LEN scripts (pMMR) [e, f]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
PBS/RPBS cost less co-pay						
2L PEM+LEN (pMMR)	-$[redacted][6]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][6]
Estimated financial implications for the PBS/RPBS						
Net cost to PBS/RPBS (pMMR)	$[redacted][8]	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][9]
Estimated financial implications for the health budget						
Net MBS costs (pMMR) [g]	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]
Net cost to PBS/RPBS/MBS (pMMR)	$[redacted][8]	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][9]	$[redacted][3]
PSCR revised estimates						
Net cost to PBS/RPBS	$[redacted][8]	$[redacted][9]	$[redacted][9]	$[redacted][3]	$[redacted][3]	$[redacted][3]

Source: Tables 4.2-1; 4.2-2; 4.2-3; 4.3-4; 4.3-5; 4.3-6; 4.3-7; 4.3-8; 4.3-9; 4.4-1; 4.4-2; 4.4-5; 4.4-7; 4.5-1; 4.5-2; 4.6-1; 4.6-2; 4.6-3; pp209 of the submission.

Abbreviations: 1L = first-line; 2L = second-line; AIHW = Australian Institute of Health and Welfare; A/R = advanced or recurrent; dMMR = mismatch repair deficient; EC = endometrial cancer; ECOG = Eastern Cooperative Oncology Group; Govt = government; MBS = Medicare Benefits Schedule; PBC = platinum-based chemotherapy; PBS = Pharmaceutical Benefits Scheme; PEM+LEN = pembrolizumab + lenvatinib; RPBS = Repatriation Pharmaceutical Benefits Scheme; Yr = year.

Two minor issues were corrected during evaluation (refer to paragraph 6.95)

[d] The grandfathered patients DTG was corrected during the evaluation to the continuing (maintenance) patients as these patients were assumed to have completed half the total treatment duration and therefore would not be under initiation regimens. Half of the pMMR duration of treatment = 21.51 weeks. With 8.67 scripts per year of treatment (52 weeks / (1 pack / (dosing of 1 pack / every 6 weeks))* 100% compliance.

[e] Pembrolizumab scripts calculated using patient years of treatment with a treatment duration of 44.07 weeks per the finalised 2L PEM+LEN pricing package. 17.33 scripts per year of treatment (52 weeks / (1 pack / (dosing of 1 pack / every 3 weeks))* 100% compliance.

[f] Lenvatinib scripts calculated using patient years of treatment with a treatment duration of 8.81 months per the finalised 2L PEM+LEN pricing package. This treatment duration could not be independently verified. 12 scripts per year of treatment (12 months / (30 pack / (dosing of 30 pack)* 100% compliance.

[g] Calculated by multiplying the number of administrations for pembrolizumab by the corresponding number of MBS items (MBS code 13950) and its allocated cost ($123.05).

The redacted values correspond to the following ranges:

[1] < 500

[2] $100 million to < $200 million

[3] $70 million to < $80 million

[4] $80 million to < $90 million

[5] 500 to < 5,000

[6] $20 million to < $30 million

[7] $10 million to < $20 million

[8] $80 million to < $90 million

[9] $60 million to < $70 million

[10] $0 to < $10 million

Quality Use of Medicines

6.100 The submission stated that the Sponsor intends to develop materials to provide the latest information to physicians, nurses, pharmacists and patients about how to identify and manage potential treatment-related AEs, in particular immune-related AEs. In addition, the submission stated a number of education activities are planned

that will be supported by the Sponsor's medical team and representatives. The submission also noted access to the Sponsor's 1800 medical information service line to respond to questions from patients, carers and health care professionals about specific medicines.

Financial Management – Risk Sharing Arrangements

6.101 The submission stated that the Sponsor was willing to discuss and work through the parameters of any risk sharing arrangement (RSA) but did not provide further details.

6.102 There is an existing RSA that comprises both the 1L dMMR dostarlimab listing and also the 2L pembrolizumab + lenvatinib listing (all-comers). Paragraph 7.11 of the dostarlimab PSD, November 2023 PBAC meeting states: "(t)he PBAC considered that shared financial caps with 2L pembrolizumab + lenvatinib would be appropriate, given the substantial overlap in patient populations and because the cost-effectiveness for dostarlimab relies on cost offsets for 2L pembrolizumab + lenvatinib. The PBAC considered that the caps should be increased to account for additional patients treated 1L dostarlimab, with offsets for 2L pembrolizumab + lenvatinib."

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend pembrolizumab for the treatment of primary advanced or recurrent endometrial cancer in patients irrespective of their mismatch repair (MMR) status. The PBAC considered the claim of non-inferior effectiveness versus dostarlimab and durvalumab in mismatch repair deficient (dMMR) endometrial cancer was not adequately supported by the evidence presented due to wide confidence intervals for the progression-free survival (PFS) and overall survival (OS) hazard ratios (HRs) in the indirect treatment comparison, with point estimates that generally favoured the comparators. The PBAC considered that these results did not sufficiently rule out the possibility of a conclusion of inferiority. The PBAC also considered this was in the context of limited clinical need for additional treatment options in dMMR endometrial cancer (i.e. as dostarlimab and durvalumab are available in this setting). In the mismatch repair proficient (pMMR) population, the PBAC noted that the nominated comparators had not received positive recommendations, and thus the cost-minimisation approaches (CMAs) presented were not relevant.

7.2 The primary reason for this outcome was due to the comparative clinical evidence.

pMMR population

7.3 The PBAC noted that the submission had requested listing in both the dMMR and pMMR populations. Listing in the pMMR population was requested on a cost-minimisation basis versus dostarlimab and durvalumab + olaparib, which were both under PBAC consideration at the time the submission was made. However, since that time, neither therapy had received a positive PBAC recommendation in the pMMR

population: dostarlimab was not recommended at the May 2025 PBAC meeting; and durvalumab + olaparib was deferred at the November 2024 PBAC meeting due to ongoing TGA considerations (refer to paragraph 1.2). The PSCR acknowledged that if neither dostarlimab nor durvalumab + olaparib were recommended for pMMR, then the most appropriate comparator would be platinum-based chemotherapy alone followed, in a proportion of patients, by second line pembrolizumab + lenvatinib. Given the submission did not include an economic evaluation versus this comparator, the PSCR requested that the PBAC's consideration of this submission be limited to the dMMR population only.

dMMR population

7.4 The PBAC noted and welcomed the consumer comments, which were from two organisations. The comments highlighted that a key benefit of listing pembrolizumab (in the dMMR population) would be that it would provide an alternative treatment option. Overall, in the population with dMMR endometrial cancer, the PBAC considered the clinical need for new therapies was limited given dostarlimab and durvalumab are available. However, the PBAC acknowledged that an advantage of pembrolizumab compared with dostarlimab or durvalumab would be its shorter maximum treatment duration (two years for pembrolizumab versus three years for dostarlimab or durvalumab).

7.5 In the dMMR population, the PBAC noted that the submission nominated dostarlimab as the main comparator and durvalumab as a secondary comparator (as it received a positive recommendation at the November 2024 PBAC Meeting but was not listed at the time of PBAC consideration). The PBAC considered the comparators nominated by the submission were appropriate.

7.6 The clinical claim in the dMMR population was based on an indirect comparison between pembrolizumab (informed by NRG-GY018), dostarlimab (informed by RUBY-1) and durvalumab (informed by DUO-E) using placebo as the common comparator. The PBAC noted the confidence intervals were wide, for example the Bucher indirect comparison between pembrolizumab and dostarlimab reported a progression-free survival (PFS) hazard ratio (HR) of 1.24 (95% CI: 0.62, 2.49) and an overall survival (OS) HR of 1.77 (95% CI: 0.73, 4.34). The results versus durvalumab were similar with the Bucher indirect comparison between pembrolizumab and durvalumab reporting a PFS HR of 0.83 (95% CI: 0.39, 1.77) and an OS HR of 1.67 (95% CI: 0.56, 4.96). The PBAC considered that the wide confidence intervals, with point estimates generally favouring the comparators, did not sufficiently rule out the possibility of a conclusion of inferiority. Overall, the PBAC considered that the claim of non-inferior efficacy versus dostarlimab and durvalumab was not adequately supported by the information provided in the submission.

7.7 The PBAC acknowledged that event rates were different in the common comparator arms of the trials included in the indirect comparison, and that a key reason for this may have been the early treatment switching that occurred in the NRG-GY018 trial.

The NRG-GY018 trial was unblinded after interim analysis 1 (IA1, median follow-up of 13.6 months), which led to some placebo-randomised patients commencing immunotherapy prior to disease progression. The subsequent data-cut, referred to as the efficacy update report (EUR, median follow-up of 22.5 months per Table 8) analysis, was used in the indirect comparisons. The submission claimed the early crossover impacted the EUR analysis and may have biased the estimation of HRs (in the NRG-GY018 trial) in favour of the placebo group. The PBAC noted there were higher rates of subsequent PD-(L)1 inhibitor use in the placebo arm of NRG-GY018 than the other trials (e.g. EUR 48.2% versus RUBY-1 IA1 38.5%, in the dMMR subpopulations). However, overall, the PBAC considered the impact of confounding due to differences in use of subsequent therapies between the trials was unclear and introduced bias that could not be quantified. For example: the number of placebo-randomised patients who commenced immunotherapy prior to disease progression was not available; and a proportion of patients in the pembrolizumab arm also received second line immunotherapy in the EUR analysis (10% of patients in the dMMR population), which does not reflect Australian practice. Further, *post hoc* adjustments for treatment switching on the NRG-GY018 trial using the inverse probability of censoring weights (IPCW) method did not result in statistically significant OS HRs versus placebo (i.e. OS HR of 0.54 (95% CI 0.22, 1.69) for the dMMR population).

7.8 The PBAC considered that the claim of non-inferior safety versus dostarlimab and durvalumab was likely reasonable in the dMMR population given the rates of adverse events in the unanchored indirect comparison were similar and there were no new safety signals.

7.9 The PBAC considered that the CMA and financial estimates were not relevant as the clinical claim was not accepted.

7.10 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

MSD is disappointed by the PBAC's decision not to recommend pembrolizumab (KEYTRUDA®) plus chemotherapy for advanced/recurrent (A/R) dMMR endometrial cancer (EC) with the rationale that PBAC considered the results of the indirect comparisons did not sufficiently rule out the possibility that pembrolizumab would provide worse outcomes for patients than dostarlimab and durvalumab. The PBAC also considered this was in the context of limited clinical need for additional treatment options in the dMMR setting. This is notably paradoxical to MOGA which considered the submission to be a "high priority for PBS listing." NRG-GY018 was the only study to incorporate a dMMR specific cohort with independent and pre-specified formal testing. NRG-GY018 demonstrates a numerically better Hazard Ratio for PFS than the dMMR subgroup not formally tested in DUO-E. Further, MSD considers that NRG-GY018 is comparable to RUBY dMMR population in terms of PFS, OS, ORR and DOR. In summary, MSD concludes that the clinical data demonstrate that NRG-GY018 is the most well-designed study to evaluate benefit in the biologically distinct dMMR phenotype and MSD considered it demonstrates unequivocally non-inferior efficacy to RUBY/DUO-E, a finding further supported by the literature (Bartoletti et al, 2024).