6.01 DURVALUMAB, Solution concentrate for I.V. infusion 120 mg in 2.4 mL, Solution concentrate for I.V. infusion 500 mg in 10 mL, Imfinzi®, AstraZeneca Pty Ltd

OLAPARIB, Tablet 100 mg, Tablet 150 mg, Lynparza®, AstraZeneca Pty Ltd

1 Purpose of submission

1.1 The Category 2 submission requested Section 100 (Efficient Funding of Chemotherapy), Authority Required listing for durvalumab in combination with platinum-based chemotherapy (paclitaxel + carboplatin [PC]), followed by maintenance treatment with or without olaparib for the treatment of advanced, metastatic or recurrent (A/R) endometrial cancer (EC). A General Schedule listing for olaparib for the treatment of proficient mismatch repair (pMMR) advanced, metastatic or recurrent EC was also requested.

1.2 Listing was sought for two populations:

- dMMR: Listing of durvalumab + PC (initiation) followed by maintenance durvalumab monotherapy (referred to henceforth as durvalumab + PC) was requested on the basis of a cost-minimisation approach versus dostarlimab + PC (initiation) followed by dostarlimab (maintenance) for patients with deficient mismatch repair (dMMR) EC.
- pMMR: Listing of durvalumab + PC (initiation) followed by durvalumab + olaparib (maintenance) (referred to henceforth as durvalumab + PC + olaparib) was requested on the basis of a cost-effectiveness analysis versus PC for patients with pMMR EC.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description	
	dMMR	**pMRR**
Population	Patients with advanced, metastatic or recurrent endometrial cancer who have not received systemic therapy or whose disease has progressed following systemic therapy in the (neo) adjuvant setting.	
Intervention	Durvalumab by IV infusion in combination with platinum-based chemotherapy (paclitaxel + carboplatin) on Day 1 of 21 Day cycles for up to 6 cycles followed by:	
	- maintenance durvalumab IV infusion until disease progression (i.e. durvalumab + PC).	- maintenance durvalumab IV infusion in combination with oral olaparib until disease progression (i.e. durvalumab + PC + olaparib).
Comparator	IV platinum-based chemotherapy (paclitaxel + carboplatin) on Day 1 of 21-day cycles for up to 6 cycles followed by maintenance placebo (i.e. PC)	
	Dostarlimab by IV infusion in combination with platinum-based chemotherapy on Day 1 of 21 Day cycles for up to 6 cycles, followed by maintenance dostarlimab IV infusion. (i.e. dostarlimab + PC)	
Outcomes	Primary outcomes: PFS by Investigator Secondary outcomes: OS, PFS2, ORR, DoR, TFST, TSST, HRQoL and safety	
Clinical claim [a]	Compared with dostarlimab + PC, durvalumab + PC has: - non-inferior efficacy; and - non-inferior safety. Compared with PC alone, durvalumab + PC has: - superior efficacy; and - non-inferior safety.	Compared to PC alone, durvalumab + PC + olaparib has: - superior efficacy; and - inferior safety.

Source: Table 1.1, p23 and Section 2.2.5, p52 of the submission.
DoR = duration of response; EC = endometrial cancer HRQoL = health-related quality of life; ORR = objective response rate; OS = overall survival; PFS = progression free survival; PFS2 = time to second PFS; TFST = time free from subsequent therapy; TTST = time to subsequent therapy

2 Background

Registration status

2.1 TGA status at the time of PBAC consideration: The submission was made under the TGA/PBAC Parallel Process. At the time of the PBAC consideration the TGA Clinical Evaluation Report (CER), round 2, and the TGA Delegate's Overview (DO) were available. The TGA Delegate, in their preliminary view, was inclined to approve the registration of durvalumab for the dMMR EC population, that is for the following indication: durvalumab 'in combination with PC is indicated for the first-line treatment of adult patients with advanced or recurrent EC followed by maintenance treatment with durvalumab as monotherapy in EC that is dMMR'.

2.2 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. The TGA advised that durvalumab and olaparib for pMMR EC would be considered at a future Advisory Committee on Medicines meeting.

2.3 The pre-PBAC response requested that the PBAC provide separate recommendations for the dMMR and pMMR populations.

2.4 On 14 June 2024, the US Food and Drug Administration (FDA) approved durvalumab with carboplatin plus paclitaxel followed by single-agent durvalumab for adult patients with primary advanced or recurrent endometrial cancer that is dMMR. The FDA did not approve durvalumab for use in combination with olaparib in any patients with EC or use of durvalumab for any patients with pMMR EC.

2.5 On 27 June 2024, the European Committee for Medicinal Products for Human Use (CHMP) recommended use of durvalumab in combination with carboplatin and paclitaxel for the 1L treatment of adults with primary A/R EC who are candidates for systemic therapy, followed by maintenance treatment with durvalumab in combination with olaparib (in pMMR EC) and durvalumab monotherapy (in dMMR EC). The indication recommended by the CHMP was consistent with the requested PBS listing for durvalumab and olaparib for the treatment of EC.

Previous PBAC consideration

2.6 Durvalumab has not previously been considered by the PBAC for the requested restriction of use in A/R EC.

2.7 Dostarlimab in combination with PC (referred to as dostarlimab + PC from herein) was recommended by the PBAC at the November 2023 meeting for the treatment of patients with primary advanced or first recurrent EC that is dMMR.

2.8 Pembrolizumab + lenvatinib was recommended by the PBAC at the March 2022 meeting for the treatment of patients with advanced EC who have disease progression following prior systemic therapy regardless of biomarker status.

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Max. qty packs	Max. qty units	№. of Rpts	Dispensed Price for Max. Qty	Available brands
OLAPARIB					
olaparib 100mg tablet, 56	2	112	5	Published $6,632.11 Effective: $[redacted]	Lynparza AstraZeneca Pty Ltd
olaparib 150mg tablet, 56	2	112	5	Published $6,632.11 Effective: $[redacted]	Lynparza AstraZeneca Pty Ltd
MEDICINAL PRODUCT medicinal product pack	**Max Amount**		**№. of Rpts**	**Dispensed Price for Max. Amount**	**Available brands**
DURVALUMAB - initiation [a]					
durvalumab 120mg, 1 vial for IV infusion	1200 mg		5	Effective: TBD Public: $2,624.26 Private: $2,704.41 [c]	Imfinzi AstraZeneca Pty Ltd
durvalumab 500mg, 1 vial for IV infusion 1					
DURVALUMAB - maintenance [b]					

durvalumab, 500mg,1 vial for IV infusion	1500 mg	5	Effective: TBD Public: $3,393.93 Private: $3,441.45 [c]	Imfinzi AstraZeneca Pty Ltd

Source: Table 1.3 and 1.4, p33 of the submission and Attachment 3.1_Economic evaluation.xlsx.
a Durvalumab initiation dose is comprised of 1120 mg (1 x 120mg + 2 x 500 mg). The DPMQ shown is for the total dose.
b Durvalumab maintenance treatment is comprised of 1500 mg (3 x 500 mg). The DPMQ shown is for the total dose.
c The submission provided published (public) DPMQ for durvalumab for each individual vial strength only (rather than by total dose for initiation or maintenance). For the durvalumab 120 mg vial the published prices were $996.43 (public) and $1,053.79 (private). For the durvalumab 500 mg vial, the published prices for 2 x 500mg vials were $7,642.63 (public) and $7,793.04 (private), and the published prices for 3 x 500 mg vials were $11,418.88 (public) and $11,622.15 (private).

Requested restriction – durvalumab, initial and continuing treatment

Category / Program: Section 100 (Efficient Funding of Chemotherapy)
Prescriber type: ☒Medical Practitioners
Restriction Type: ☒ Authority Required STREAMLINED
Severity: Advanced, metastatic or recurrent
Condition: Endometrial cancer
Indication: Advanced, metastatic or recurrent endometrial cancer
Treatment Phase: Initial treatment covering the first 6 treatment cycles
Clinical criteria: Patient must have evidence of mismatch repair status: either deficient mismatch repair (dMMR) OR proficient mismatch repair (pMMR), as determined by immunohistochemistry test **AND** The condition must be unsuitable for at least one of: 1) Curative surgical resection AND/OR 2) Curative radiotherapy **AND** The treatment must be in combination with platinum-containing chemotherapy **AND** The condition must be, at treatment initiation with this drug, either: Untreated with systemic therapy **OR** Treated with adjuvant systemic therapy, but the cancer has recurred or progressed **AND** Patient must not have received prior treatment with a programmed cell death-1 (PD-1) or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition **AND** Patient must have, at the time of initiating with this drug, a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status no higher than 1
Treatment Phase: Continuing treatment
Clinical criteria: Patient must have received previous PBS-subsidised treatment with this drug for this condition **AND** **Clinical criteria:** Patient must not have developed disease progression while receiving treatment with this drug for this condition **AND** The treatment must be as monotherapy if patient has dMMR EC **OR** The treatment must be in combination with olaparib if patient has pMMR EC unless the patient has a contraindication to olaparib or develops an intolerance to olaparib and requires a temporary or permanent discontinuation of olaparib.

Source: Table 1.5, p 36, Table 1.6, p 37 of the submission.

Requested restriction – olaparib, initial and continuing treatment

Category / Program: GENERAL – General Schedule
Prescriber type: ☒Medical Practitioners
Restriction Type: ☒ Authority Required STREAMLINED
Severity: Advanced, metastatic or recurrent
Condition: Endometrial cancer
Indication: Advanced, metastatic or recurrent endometrial cancer
Treatment Phase: Initial and continuing
Clinical criteria: Patient must have proficient mismatch repair (pMMR) endometrial cancer, as determined by immunohistochemistry test **AND** The treatment must be in combination with durvalumab **AND** For initial treatment with this drug, patient must be in partial or complete response to the immediately preceding platinum-based chemotherapy and durvalumab regimen **OR** For continuing treatment with this drug, patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition

Source: Table 1.7, p 38 of the submission.

Requested restriction – durvalumab, grandfathering

Category / Program: Section 100 (Efficient Funding of Chemotherapy)
Prescriber type: ☒Medical Practitioners
Restriction Type: ☒ Authority Required STREAMLINED
Severity: Advanced, metastatic or recurrent
Condition: Endometrial cancer
Indication: Advanced, metastatic or recurrent endometrial cancer
Treatment Phase: Transitioning from non-PBS to PBS subsidised treatment – Grandfather treatment
Clinical criteria: Patient must have evidence of mismatch repair status: either deficient mismatch repair (dMMR) OR proficient mismatch repair (pMMR), as determined by immunohistochemistry test **AND** The patient must have received non-PBS subsidised treatment with this drug for this condition prior to (PBS list date) **AND** The condition must be, prior to initiation of non-PBS subsidised treatment with this drug, unsuitable for at least one of: 1) Curative surgical resection AND/OR 2) Curative radiotherapy **AND** The treatment must be, at initiation of non-PBS-subsidised treatment with this drug, used in combination with platinum-containing chemotherapy **AND** The condition must be, prior to initiation of non-PBS-subsidised treatment with this drug, either: Untreated with systemic therapy **OR** Treated with adjuvant systemic therapy, but the cancer has recurred or progressed **AND** Patient must not have developed disease progression while receiving non-PBS subsidised treatment with this drug for this condition **AND**

Patient must have had, at the time of initiating with this drug, a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status no higher than 1
Note: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria
Note: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

Source: Table 1.8, p 39 of the submission.

Requested restriction – olaparib, grandfathering

Category / Program: GENERAL – General Schedule
Prescriber type: ☒Medical Practitioners
Restriction Type: ☒ Authority Required STREAMLINED
Severity: Advanced, metastatic or recurrent
Condition: Endometrial cancer
Indication: Advanced, metastatic or recurrent endometrial cancer
Treatment Phase: Transitioning from non-PBS to PBS subsidised treatment – Grandfather treatment
Clinical criteria: Patient must have evidence of proficient mismatch repair (pMMR) endometrial cancer, as determined by immunohistochemistry test **AND** The patient must have received non-PBS subsidised treatment with this drug for this condition prior to (PBS list date) **AND** The treatment must be in combination with durvalumab **AND** For initial treatment with this drug, patient must be in partial or complete response to the immediately preceding platinum-based chemotherapy and durvalumab regimen **OR** For continuing treatment with this drug, patient must not have developed disease progression while receiving treatment with this drug for this condition
Note: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria
Note: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

Source: Table 1.9, p 40 of the submission.

3.1 The proposed durvalumab initiation criteria requires that treatment must be in combination with PC, which excludes patients who are unable to receive chemotherapy from receiving durvalumab for EC.

3.2 The requested patient population was narrower than the proposed TGA indication as there is no World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status restrictions in the proposed TGA indication. The requested PBS restrictions were also not consistent with the pivotal DUO-E trial which did not stratify the durvalumab + PC and durvalumab + PC + olaparib arms by MMR status.

3.3 While the dostarlimab PBS restriction required that the "(p)atient must not be undergoing continuing PBS-subsidised treatment where this benefit is extending treatment beyond 36 cumulative months from the first administered dose, once in a lifetime", the submission's proposed restriction did not include a maximum duration of durvalumab therapy. Further, a 36-month maximum duration of durvalumab treatment was not included in the economic model base case or the financial estimates but was included in the cost-minimisation approach (CMA). The ESC

considered that the proposed restriction for durvalumab should mirror that of dostarlimab and include a 36-month stopping rule. The pre-PBAC response agreed that a 36-month stopping rule should be included in the restriction.

3.4 The restriction proposed in the Pre-Sub-Committee Response (PSCR) requires that olaparib must be used (in combination with durvalumab) in pMMR EC patients unless the patient has a contraindication to olaparib or develops an intolerance requiring discontinuation of olaparib. This is narrower than the TGA indication proposed by the sponsor in the second round CER, which would allow durvalumab maintenance as monotherapy in all patients regardless of MMR status and contraindication/intolerance to olaparib.

3.5 The submission requested a grandfathering listing and anticipated there will be approximately <500 patients with pMMR EC who will be grandfathered to PBS supply after receiving durvalumab (with or without) olaparib in a sponsor patient access program.

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 (uterine corpus). 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). The outcomes for advanced or recurrent disease remain poor, with 5-year overall survival (OS) rates of 20-25% (Oaknin 2022).

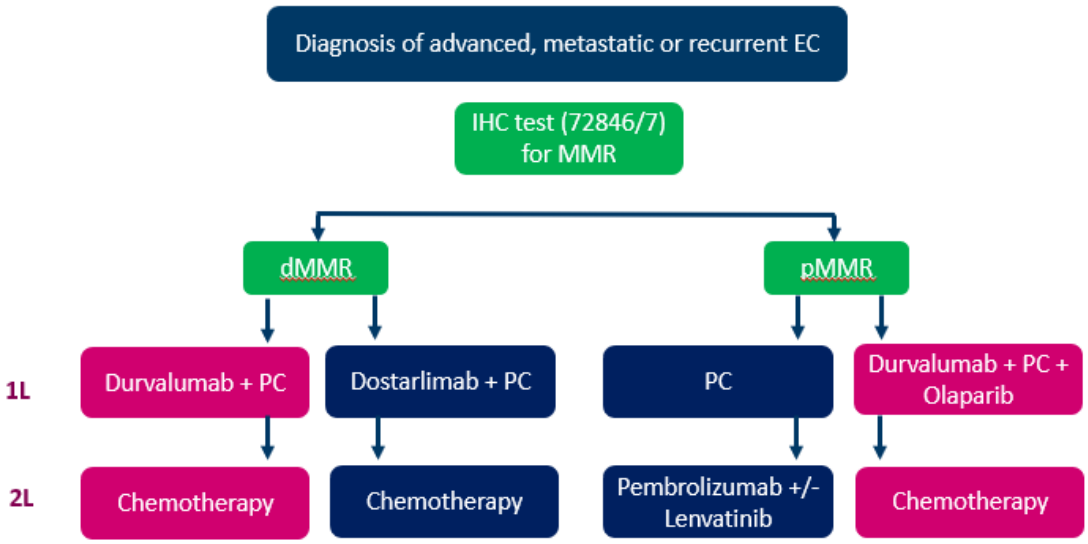
4.2 ECs may be classified based on the MMR status, as pMMR or dMMR tumours. The PBAC and DUSC have previously considered that around 27% of patients with EC have the dMMR sub-type (paragraph 7.11, dostarlimab Public Summary Document (PSD), March 2022 PBAC meeting). dMMR tumours can develop microsatellite instability (MSI), which is a change in the length of repetitive sequences in tumour DNA compared with normal DNA. Therefore, MSI high (MSI-H) is the observable characteristic (phenotype) displayed when errors occur in the DNA MMR system (Luchini, 2019).

4.3 The submission stated that MMR testing via immunohistochemistry (IHC) is considered routine clinical practice when patients are diagnosed with EC (accessed via MBS code 73354) as previously acknowledged by the PBAC (paragraph 4.3, dostarlimab PSD, November 2023 PBAC meeting).

4.4 Figure 1 shows the current and proposed treatment algorithms presented in the submission. Since the PBS listing of dostarlimab for patients with dMMR EC in May 2024, the A/R EC treatment algorithm has been differentiated by MMR status. Patients with dMMR EC can receive dostarlimab + PC with maintenance dostarlimab used until disease progression for a maximum duration of three years. Given there is a once in a lifetime PBS access rule for programmed cell death ligand 1 (PD-L1) or

programmed cell death protein 1 (PD-1) inhibitors in EC, these patients could receive chemotherapy (taxane based) in second-line (2L) but not pembrolizumab + lenvatinib. Under the proposed treatment algorithm, durvalumab would provide an additional treatment option for patients with dMMR EC and would replace the current standard of care of PC followed by 2L pembrolizumab + lenvatinib for patients with pMMR EC.

Figure 1: Proposed treatment algorithm for advanced/recurrent endometrial cancer



Source: Figure 1.7, p28 of the submission.
dMMR = deficient mismatch repair; EC = endometrial cancer; IHC = immunohistochemistry; MMR = mismatch repair; PC = platinum-based chemotherapy; pMMR = proficient mismatch repair
Notes: (1) The current treatment algorithm is shown in dark blue and the proposed additional treatment algorithm is shown in purple.
(2) The dostarlimab PBS restriction criteria allows its use for 36 months, defined as "36 cumulative months from the first administered dose".
(3) Patients who receive first-line durvalumab would not be eligible to receive 2L pembrolizumab + lenvatinib under its PBS restriction.

4.5 Durvalumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). Olaparib is an orally active inhibitor of human poly ADP-ribose polymerase (PARP) enzymes, including PARP-1, PARP-2 and PARP-3. PARP enzymes are involved in normal cellular functions, such as DNA transcription and repair of DNA single strand breaks. Olaparib is currently PBS-listed for the treatment of patients with confirmed BRCA mutation (high grade ovarian, fallopian tube or peritoneal cancer, early breast cancer and castration resistant metastatic prostate cancer) or homologous recombination deficiency (high grade ovarian, fallopian tube or peritoneal cancer).

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

5 Comparator

5.1 The submission nominated the following comparators:

- dMMR A/R EC population: The comparators for durvalumab + PC were: (i) dostarlimab + PC; and (ii) PC;

- pMMR A/R EC population: The comparator for durvalumab + PC + olaparib was PC alone.

dMMR population

5.2 The ESC considered that, in the dMMR population, dostarlimab + PC was the appropriate comparator as:

- Dostarlimab was listed on the PBS for primary A/R EC that is dMMR on 1 May 2024. The PBAC has accepted that dostarlimab provides, for some patients, a significant improvement in efficacy over platinum-containing chemotherapy alone (paragraph 7.1, dostarlimab PSD, November 2023 PBAC meeting);
- Dostarlimab and durvalumab are both immune checkpoint inhibitors acting on the PD-1/PD-L1 pathway. As such, dostarlimab would be the therapy most likely replaced in practice if durvalumab was to become available; and
- The submission noted that dostarlimab + PC is the current preferred 1L treatment for dMMR EC and chemotherapy is only a 2L treatment. The requested listing for durvalumab + PC is also in the 1L setting.

pMMR population

5.3 The ESC considered that PC, the nominated comparator for the pMMR A/R EC population, was reasonable and was consistent with the PBAC's consideration of dostarlimab in the all-comers A/R EC population at the November 2023 PBAC meeting (paragraph 7.19, dostarlimab PSD, November 2023). However, the ESC also noted that for a subgroup of patients, following progression on chemotherapy, 2L pembrolizumab + lenvatinib may be used. Under the current PD-1/PD-L1 listings, patients who are treated with durvalumab + olaparib + PC in the 1L setting would not be eligible to receive pembrolizumab + lenvatinib in the 2L setting, and as such, durvalumab + olaparib + PC will replace 1L chemotherapy plus 2L pembrolizumab + lenvatinib in some patients, making 1L chemotherapy plus 2L pembrolizumab + lenvatinib a comparator for a proportion of patients with pMMR EC. The relative efficacy of this comparison was not discussed in the submission, and the ESC noted that comparative efficacy for this treatment algorithm was unknown.

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

6 Consideration of the evidence

Sponsor hearing

6.1 A written clinician statement was provided for this item. The clinician supported the proposed listings, describing the natural history of the disease and MMR sub-populations, relevant clinical trial evidence, and contextualisation of the results in the Australian setting. The clinician stated that the results of dMMR patients in DUO-E were comparable to dostarlimab patients in RUBY. The clinician also discussed the results of DUO-E in the pMMR population, stating that the results were a substantial

improvement over current standards of care. The clinician also outlined the rationale for the combination of durvalumab and olaparib in the pMMR population.

Consumer comments

6.2 The PBAC noted and welcomed the input from 3 organisations via the Consumer Comments facility on the PBS website. The PBAC noted the comment received from Royal Australian and New Zealand College of Obstetricians and Gynaecologists expressing support for listings that would help improve the affordability of medications available to women in Australia. Rare Cancers Australia supported the submission, stating that durvalumab is a targeted therapy with demonstrated clinical benefits. Rare Cancers Australia described that patients living with endometrial cancer currently undergo a range of surgeries, chemotherapy, and radiation therapy. Additionally, patients who self-fund treatment experience an added financial burden. The comments noted the high unmet need for effective and tolerable treatment options in the pMMR setting to provide a clinically relevant improvement in efficacy and a reduction in toxicity over chemotherapy and other treatment options.

6.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the durvalumab submission, categorising it as one of the therapies of "highest priority for PBS listing" on the basis of the DUO-E trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for durvalumab, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[1], based on a comparison with platinum-based chemotherapy. The MOGA also noted that the highest benefit was seen in the dMMR population.

Clinical trials

6.4 The submission was primarily based on one head-to-head randomised trial (DUO-E) comparing (i) durvalumab + PC; (ii) durvalumab + PC + olaparib; and (iii) PC. The primary outcome was the dual primary progression free survival (PFS) endpoint comparisons (per RECIST 1.1 as assessed by Investigator) of the:

- durvalumab + PC arm compared with the PC arm; and
- durvalumab + PC + olaparib arm compared with the PC arm.

Comparisons between durvalumab + PC and durvalumab + PC + olaparib were exploratory only. See paragraph 6.13.

6.5 Subgroup data from the pMMR subgroup of patients in DUO-E was used to inform the comparison between durvalumab + PC + olaparib with PC, while indirect treatment

[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]

comparisons (ITCs) were used to inform the comparison between durvalumab + PC with dostarlimab + PC in patients with dMMR AR/EC.

6.6 The ITCs between durvalumab + PC and dostarlimab + PC for the treatment of patients with dMMR A/R EC were based on the dMMR subgroup of DUO-E plus one head-to-head randomised trial (RUBY) comparing (i) dostarlimab + PC and (ii) PC. (The RUBY trial also had two other treatment arms investigating the addition of niraparib compared to placebo during maintenance, which were not included by the submission.) PC was the common comparator.

6.7 Details of the DUO-E trial presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission (durvalumab)

Trial ID	Protocol title/ Publication title	Publication citation
DUO-E/GOG-3041/ENGOT-EN10 trial NCT04269200	A Randomised, Multicentre, Double-blind, Placebo-controlled, Phase III Study of First-line Carboplatin and Paclitaxel in Combination with Durvalumab, Followed by Maintenance Durvalumab with or without Olaparib in Patients with Newly Diagnosed Advanced or Recurrent Endometrial Cancer (DUO-E)	Clinical Study Report, Version 1, 21 September 2023
	Westin S 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.	Journal of Clinical Oncology 2023; 42: 283-299
	Westin S et al. LBA41 Durvalumab (durva) plus carboplatin/paclitaxel (CP) followed by maintenance (mtx) durva ± olaparib (ola) as a first-line (1L) treatment for newly diagnosed advanced or recurrent endometrial cancer (EC): Results from the phase III DUO-E/GOG-3041/ENGOT-EN10 trial.	Conference abstract Annals of Oncology (2023) 34 Supplement 2 (S1282-S1283)
	Westin S et al. DUO-E/GOG-3041/ENGOT-EN10: A randomized phase III trial of first line carboplatin (carb) and paclitaxel (pac) in combination with durvalumab (durva), followed by maintenance durva with or without olaparib (ola), in patients (pts) with newly diagnosed (nd) advanced or recurrent endometrial cancer (EC).	Conference abstract Journal of Clinical Oncology 2020; 38:15

Source: Table 2.3, p 46 of the submission.

6.8 Details of the RUBY trial presented in the submission used to inform the ITC are provided in Table 3.

Table 3: Trials and associated reports presented in the submission (additional trial for comparison vs dostarlimab)

Trial ID	Protocol title/ Publication title	Publication citation
ENGOT-EN-6-NSGO/GOG-3031/RUBY	Mirza M et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer.	N Engl J Med 2023; 388:2145-2158
	Powell M et al. Overall survival in patients with primary advanced or recurrent endometrial cancer treated with dostarlimab plus chemotherapy in Part 1 of the ENGOT-EN6-NSGO/GOG-3031/RUBY trial	Annals of Oncology. 2024 Jun 10:S0923-7534(24)00721-X.
	Mirza M et al. Dostarlimab in combination with chemotherapy for the treatment of primary advanced or recurrent endometrial cancer: a placebo-controlled randomized phase 3 trial (ENGOT-EN6-NSGO/GOG-3031/RUBY) (LBA 11).	Abstract Gynecologic oncology, 2023, 176, S43-S44
	Mirza M et al. VP2-2023: Dostarlimab+chemotherapy for the treatment of primary advanced or recurrent (A/R) endometrial cancer (EC): A placebo (PBO)-controlled randomised phase III trial (ENGOT-EN6-NSGO/GOG-3031/RUBY).	ESMO virtual plenary abstract 34 (5), P500-501, May 2023.
	Mirza M et al. 740MO Dostarlimab + chemotherapy for the treatment of primary advanced or recurrent endometrial cancer (pA/rEC): Analysis of progression free survival (PFS) and overall survival (OS) outcomes by molecular classification in the ENGOT-EN6-NSGO/GOG-3031/RUBY trial.	ESMO abstract 34(2), S507, October 2023

Source: Table 2.6, p50-51 of the submission.

6.9 The key features of the included randomised trials are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ median follow-up	Risk of bias	Patient population	Outcomes	Use in CUA/CMA
Durvalumab + PC with or without olaparib vs. PC						
DUO-E	718 ITT; 383 pMMR [a]	R, DB, MC; 10.2 months (PC); 15.5 months (durvalumab + PC); 19.2 months (durvalumab + PC + olaparib)	High for dMMR and pMMR subgroups	1L newly diagnosed (stage III/stage IV) or recurrent EC [a]	PFS, OS, safety	CUA: PFS, OS and TTD Kaplan-Meier data, safety, 2L treatment; utilities
ITC in dMMR EC: Durvalumab + PC vs. dostarlimab + PC (PC used as common comparator)						
DUO-E	718 ITT; 95 dMMR [b]	R, DB, MC 15.5 months (durvalumab + PC)	High for dMMR subgroup	1L newly diagnosed (stage III/stage IV) or recurrent EC [c]	PFS, OS, safety	Not used (assumed same as dostarlimab)
RUBY	494 ITT; 118 dMMR/ MSI-H	R, DB, MC 24.8 months (dMMR/ MSI-H)	High for dMMR subgroup	1L advanced/ recurrent EC	PFS, OS	CMA: Duration of treatment [d]

Source: Sections 2.3, 2.4, Table 3.39, pp53-63, 71-74, 179 of the submission.

1L = first-line; 2L = second-line; CMA = cost minimisation analysis; CUA = cost utility analysis; DB = double blind; dMMR = deficient mismatch repair; EC = endometrial cancer; ITC = indirect treatment comparison; MC = multi-centre; MSI-H = microsatellite instability-high; OS = overall survival; PC = paclitaxel + carboplatin; PFS = progression-free survival; pMMR = proficient mismatch repair; R = randomised; TTD = time to discontinuation.

a including only durvalumab + PC + olaparib arm (n=191) and PC arm (n=192)

b including only durvalumab + PC (n=46) arm and PC arm (n=49)

c Naïve to 1L systemic anti-cancer treatment. For patients with recurrent disease only, prior systemic anti-cancer treatment was allowed only if it was administered in the adjuvant setting and there was at least 12 months from date of last dose of systemic anti-cancer treatment administered to date of subsequent relapse.

d Based on Table 18, dostarlimab PSD, November 2023 PBAC meeting.

6.10 DUO-E enrolled a total of 718 patients who were randomised in a 1:1:1 ratio to one of the following treatment arms:

- Arm A (PC): Patients received PC every three weeks (Q3W) for a maximum of six cycles;
- Arm B (durvalumab + PC): Patients received PC plus 1,120 mg durvalumab (IV) Q3W for a maximum of six cycles. Following completion of chemotherapy treatment, patients without objective disease progression received maintenance 1,500 mg durvalumab (IV) Q4W; and
- Arm C (durvalumab + PC + olaparib): Patients received PC plus 1,120 mg durvalumab (IV) Q3W for a maximum of six cycles. Following completion of chemotherapy treatment, patients without objective disease progression received maintenance 1,500 mg durvalumab (IV) Q4W with 300 mg olaparib (tablets) twice daily orally.

6.11 Maintenance treatment was continued until disease progression. Placebo patients randomised to Arm A or Arm B received placebo 'durvalumab' and/or 'olaparib' to maintain double blinding.

6.12 DUO-E did not include a PC + olaparib arm, and as such, the evaluation and the ESC noted that the trial did not provide information as to the incremental value of adding durvalumab to PC + olaparib. The pre-PBAC response stated that the DUO-E trial did not contain a PC + olaparib arm because, at the time the trial was designed, there was no evidence to suggest this regimen would provide patients with the same or greater efficacy than PC alone.

6.13 A pre-specified exploratory analysis comparing durvalumab + PC + olaparib versus durvalumab + PC was undertaken in DUO-E. However, hypotheses testing for this comparison were not predefined and given the lack of adjustment for multiplicity, these analyses may be associated with a higher risk of bias and should be interpreted with caution.

6.14 During the evaluation of dostarlimab for the treatment of primary A/R EC, it was observed that while it was reasonable to conclude a low risk of bias for the all-comers population in the RUBY trial, the dMMR population was prone to a higher risk of bias given the smaller sample size (23.9% of the all-comers population, n=118) and RUBY was not powered for the outcome of OS in this subgroup (paragraph 6.8, dostarlimab PSD, November 2023). Similarly, in DUO-E, while the intention to treat (ITT) population (referred to as the full analysis set [FAS] by the submission) may be associated with a low risk of bias, the analysis of results based on MMR status was likely to be associated with a higher risk of bias due to reduced patient numbers and should therefore be interpreted with caution. Moreover, the multiple testing procedure in DUO-E did not include adjustments for MMR status and may increase the risk of false positives.

6.15 The submission reported that in DUO-E, 7/48 (14.6%) patients with dMMR EC and 40/191 (20.9%) patients with pMMR EC who were randomised to receive durvalumab + PC + olaparib did not receive the olaparib component of the regimen, largely due to patients not being well enough to receive the additional therapy. These patients were

assessed as part of the durvalumab + PC + olaparib treatment group to which they were randomised. The submission claimed that this was likely to be a reasonable proxy for what will happen in practice if durvalumab + olaparib is PBS listed. Although the proposed restriction stated that patients with pMMR EC must receive durvalumab in combination with olaparib (i.e. there was no option for maintenance with durvalumab monotherapy), the revised restriction presented in the PSCR would permit durvalumab monotherapy in patients who were unable to tolerate olaparib in the maintenance therapy setting.

Comparative effectiveness

Progression free survival – DUO-E trial

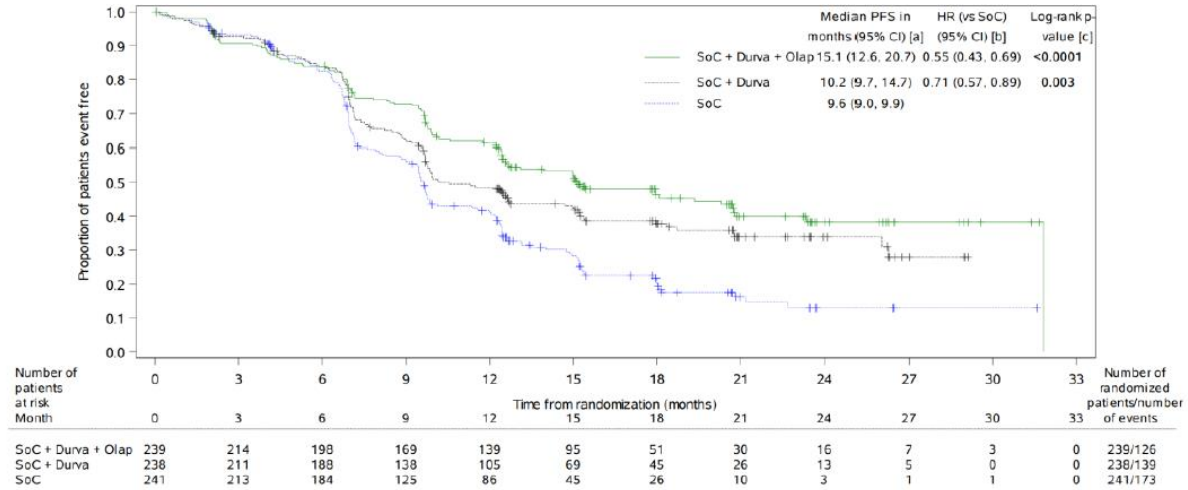
6.16 At the time of the primary analysis of PFS, the investigator assessed PFS data in the FAS were 61% mature across the three treatment arms (438 events/718 patients). The PFS results for DUO-E based on the FAS (ITT analysis) are presented in Table 5. Figure 2 provides the DUO-E Kaplan Meier (KM) curve for PFS.

Table 5: PFS based on investigator assessment (FAS), DUO-E

Measure	PC (N=241)	durvalumab + PC (N=238)	durvalumab + PC + olaparib (N=239)
Median PFS, months (95% CI)	9.6 (9.0, 9.9)	10.2 (9.7, 14.7)	15.1 (12.6, 20.7)
HR versus PC (95% CI)	-	**0.71 (0.57, 0.89)**	**0.55 (0.43, 0.69)**
P value versus PC	-	0.003	<0.0001
HR versus durvalumab + PC (95% CI)	-	-	0.78 (0.61, 0.99)
P value versus durvalumab + PC	-	-	NR
% patients progression free at			
6 months (95% CI)	82.5 (76.9, 86.8)	83.8 (78.4, 88.0)	83.9 (78.6, 88.0)
12 months (95% CI)	41.1 (34.6, 47.5)	48.5 (41.8, 54.9)	61.5 (54.9, 67.4)
18 months (95% CI)	21.7 (16.0, 27.9)	37.8 (31.0, 44.5)	46.3 (39.2, 53.0
Median range of follow-up (months)	12.6	15.4	15.4

Source: Table 2.14, p76 of the submission and Table 28 of the DUO-E CSR.
CI = confidence interval; FAS = full analysis set; HR = hazard ratio; PC = paclitaxel + carboplatin; PFS = progression free survival
Text in bold indicate statistically significant differences.

Figure 2: Kaplan Meier Curve for PFS (FAS)



Source: Figure 2.6, p76 of the submission
FAS = full analysis set; HR = hazard ratio; SoC = paclitaxel + carboplatin; PFS = progression free survival

6.17 Patients randomised to durvalumab + PC reported a statistically significant improvement in PFS compared to patients randomised to PC, with a 29% reduction in the risk of disease progression or death: HR = 0.71 (95% CI: 0.57, 0.89, p=0.003). Patients who were randomised to durvalumab + PC + olaparib reported a statistically significant improvement in PFS compared to patients who were randomised to PC, with a 45% reduction in the risk of disease progression or death: HR = 0.55 (95% CI: 0.43, 0.69, p<0.0001).

6.18 In an exploratory analysis, patients randomised to durvalumab + PC were compared to patients randomised to durvalumab + PC + olaparib. The PFS hazard ratio (HR = 0.78, 95% CI: 0.61, 0.99) was more favourable towards the durvalumab + PC + olaparib arm with the upper 95% confidence interval excluding the null.

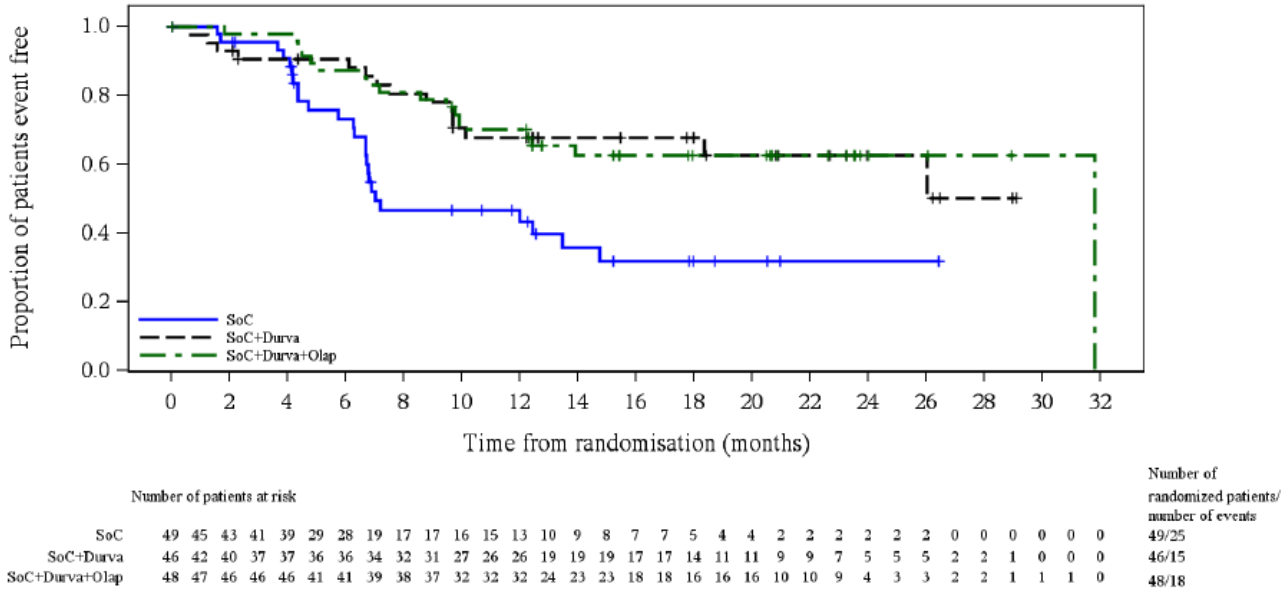
6.19 Table 6 summarises the DUO-E PFS results by MMR status. Figure 3 and Figure 4 provide the KM curves for PFS in the dMMR and pMMR subgroups, respectively.

Table 6: PFS by investigator by MMR status (FAS)

dMMR	**PC (N=49)**	**durvalumab + PC (N=46)**	**durvalumab + PC + olaparib (N=48)**
Median PFS, months (95% CI)	7.0 (6.7, 14.8)	NR (NR, NR)	31.8 (12.4, NR)
HR versus PC	-	0.42 (0.22, 0.8)	0.41 (0.21, 0.75)
HR vs durvalumab + PC	-	-	0.97 (0.49, 1.98)
Median follow-up (months)	10.2	15.5	19.2
pMMR	**PC (N=192)**	**durvalumab + PC (N=192)**	**durvalumab + PC + olaparib (N=191)**
Median PFS, months (95% CI)	9.7 (9.2, 10.1)	9.9 (9.4, 12.5)	15.0 (12.4, 18.0)
HR versus PC	-	0.77 (0.60, 0.97)	0.57 (0.44, 0.73)
HR vs durvalumab + PC	-	-	0.76 (0.59, 0.99)
Median follow-up (months)	12.8	15.3	15.2

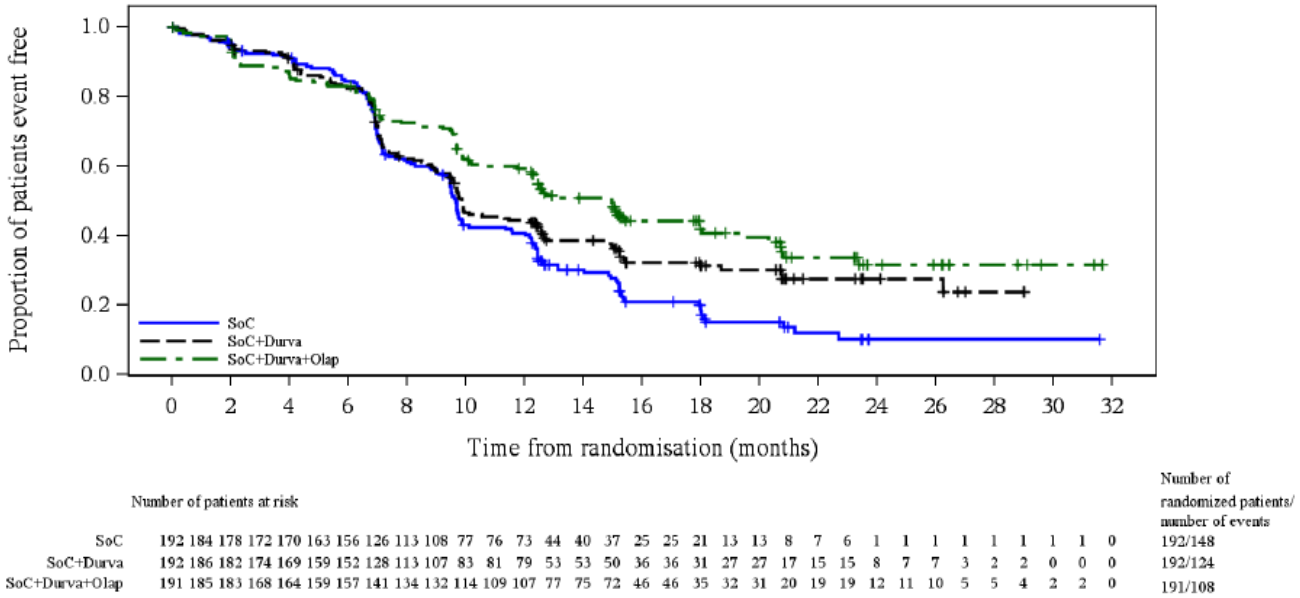
Source: Table 2.24, p97 of the submission.
dMMR = deficient mismatch repair; FAS = full analysis set; HR = hazard ratio; MMR = mismatch repair; NR = not reached; PC = paclitaxel + carboplatin; PFS = progression free survival; pMMR = proficient mismatch repair

Figure 3: Kaplan Meier curve for PFS, dMMR subgroup



Source: Figure 2.14, p98 of the submission.
Durva = durvalumab; dMMR = deficient mismatch repair; Olap = olaparib; PFS = progression free survival; SoC = standard of care

Figure 4: Kaplan Meier curve for PFS, pMMR subgroup



Source: Figure 2.15, p98 of the submission.
Durva = durvalumab; dMMR = deficient mismatch repair; Olap = olaparib; PFS = progression free survival; SoC = standard of care

6.20 The DUO-E CSR reported that the global interaction test indicated a quantitative interaction involving MMR status and region, suggesting numeric differences favouring durvalumab + PC versus PC of different magnitudes but in the same direction (p = 0.036). Whereas for the comparison of durvalumab + PC + olaparib versus PC, the global interaction test showed no evidence of treatment effect being different across the pre-specified subgroups (p=0.133).

6.21 The PBAC previously considered it was plausible that MMR status may be a treatment effect modifier for dostarlimab as patients in GARNET Cohort A1 appeared to have better outcomes compared to those in Cohort A2 (paragraph 6.25, dostarlimab PSD, March 2022 PBAC meeting). In November 2023, the ESC considered that based on the test for interaction with p=0.0061 for PFS, and a clear difference in response between the pMMR and dMMR subgroups, MMR status was likely to be a treatment effect modifier for dostarlimab (paragraph 6.24, dostarlimab PSD, November 2023 PBAC meeting). Moreover, while the dostarlimab submission requested listing in both the dMMR and all-comers A/R EC populations, the PBAC only recommended listing in the dMMR A/R EC population.

6.22 Among patients with dMMR EC there did not appear to be any difference in PFS between patients randomised to durvalumab + PC + olaparib and patients randomised to durvalumab + PC (HR = 0.97, 95% CI: 0.49, 1.98). Additionally, the PFS HRs were similar between patients randomised to durvalumab + PC and patients randomised to durvalumab + PC + olaparib compared to patients randomised to PC. The submission claimed that this indicated that the addition of olaparib had little impact on PFS in patients with dMMR EC. However, concerns regarding the additional toxicity of adding olaparib to durvalumab + PC were not specifically addressed in the submission. Additionally, the sample size in the dMMR subgroup was small (around 20% of the total DUO-E population, less than 50 patients in each arm) and the subgroup may not have been sufficiently powered to detect differences between durvalumab + PC and durvalumab + PC + olaparib.

6.23 For pMMR EC, patients randomised to durvalumab + PC + olaparib reported a median PFS of 15.0 months, compared with 9.7 months in patients randomised to PC and 9.9 months in patients randomised to durvalumab + PC. Though it was plausible that MMR status may be a treatment effect modifier for PD-L1 inhibitors (see paragraph 6.21), DUO-E endpoint analyses by MMR status were not included in the formal testing hierarchy, and analysis of results based on MMR status is likely to be associated with a higher risk of bias and should be interpreted with caution (see paragraph 6.14).

6.24 The PFS results for durvalumab + PC + olaparib vs durvalumab + PC were used to justify the proposed PBS-listing of durvalumab + PC + olaparib for the treatment of pMMR. However, it was unclear whether any additional incremental efficacy would outweigh the potential for additional adverse events with olaparib. The pre-PBAC response stated that the rationale for combining durvalumab and olaparib was based on the hypothesis that inhibition of PARP with olaparib would result in enhanced immunogenicity, which can be further enhanced with an immune checkpoint inhibitor like durvalumab, not by targeting BRCAm.

6.25 The submission reported results from a *post hoc* analysis (Nieuwenhuysen 2024) of PFS data which was conducted with the aim of assessing the impact of *BRCA1* and/or *BRCA2* pathogenic variation (*BRCAm*) status on the clinical outcomes in DUO-E as olaparib is usually used for the treatment of patients whose tumours have *BRCAm* (Table 7). For DUO-E, *BRCA* status was determined retrospectively.

Table 7: PFS by BRCAm status (ITT population)

		PC (N=241)	durvalumab + PC (N=238)	durvalumab + PC + olaparib (N=239)
All patients	Events n/N (%)	173/241 (71.8)	139/238 (58.4)	126/239 (52.7)
	Median, months (95% CI)	9.6 (9.0, 9.6)	10.2 (9.7, 14.7)	15.1 (12.6, 20.7)
	HR (95% CI) vs PC	-	0.71 (0.57, 0.89)	0.55 (0.43, 0.69)
	P value	-	P=0.003	P<0.0001
BRCAm	Events n/N (%)	17/22 (77.3)	10/24 (41.7)	13/30 (43.3)
	Median, months (95% CI)	9.5 (6.3, 12.3)	26.0 (9.6, NR)	31.8 (10.1, NR)
	HR (95% CI) vs PC	-	0.26 (0.10, 0.61)	0.27 (0.12, 0.58)
Non-BRCAm	Events n/N (%)	131/181 (72.4)	108/180 (60)	98/182 (53.8)
	Median, months (95% CI)	9.7 (8.3, 12)	10.5 (9.7, 15)	15.1 (12.6, 20.7)
	HR (95% CI) vs PC	-	0.73 (0.56, 0.94)	0.56 (0.43, 0.73)
Unknown	Events n/N (%)	25/38 (65.8)	21/34 (61.8)	15/27 (55.6)
	Median, months (95% CI)	9.5 (7.1, 11.6)	8.8 (7.1, 15.2)	9.9 (6.2, NR)
	HR (95% CI) vs PC	-	0.80 (0.44, 1.42)	0.77 (0.40, 1.45)

Source: Table 2.27, p102 of the submission.
BRCA = breast cancer gene mutation; dMMR = deficient mismatch repair; ITT = intention to treat; NR = not reached; PC = paclitaxel + carboplatin; PFS = progression free survival; pMMR = proficient mismatch repair

6.26 The median PFS results for the ITT population showed improvement in PFS for both durvalumab + PC and durvalumab + PC + olaparib versus PC, in both patients with confirmed *BRCAm* and confirmed non-*BRCAm* status. The PSCR noted that the proportion of patients with unknown *BRCA* status was small (99/718, 13.8%) and therefore results of the unknown *BRCA* status subgroup were highly uncertain.

6.27 Patients with *BRCAm* comprised only a small proportion (10.6%) of the total patient population. The ESC noted that although patients in the *BRCAm* subgroup experienced better outcomes than those in the non-*BRCAm* subgroup and the ITT population, the 95% confidence intervals overlapped. In addition, the ESC noted that the PFS hazard ratios for durvalumab + PC and durvalumab + PC + olaparib (compared to PC) were similar (i.e. the addition of olaparib did not appear to improve efficacy in *BRCAm* patients). However, the ESC also noted that, in the non-*BRCAm* subgroup, the point estimate of the hazard ratio for PFS was better in the durvalumab + PC + olaparib arm than in the durvalumab + PC arm. The ESC considered that these results appeared to be counter-intuitive and highlighted the uncertainties with the multiple *post-hoc* subgroup analyses that were conducted.

6.28 The ESC noted that at baseline, although the proportions of patients with *BRCAm* were similar across the arms (9-12%), patients in the durvalumab + PC + olaparib arm had a higher incidence of homologous recombination repair gene pathogenic variation (*HRRm*), which includes *BRCAm*, (16.3%), compared to the durvalumab + PC (10.9%) or PC (13.3%) arms.[2] The ESC considered that this also added to the uncertainty of the results as it may have biased the results in favour of the durvalumab + PC + olaparib

[2] Table 1, 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 - PMC (nih.gov)

arm (given patients in the *BRCAm* subgroup experienced better outcomes than those in the non-*BRCAm* subgroup and the ITT population).

6.29 The submission provided median PFS results for the pMMR EC subpopulation by *BRCA* status (Table 8). Given these represent data from subgroups of subgroups, there were small sample sizes (e.g. only 37 patients with *BRCAm* across all three arms) and the results should be considered with caution.

Table 8: PFS by BRCAm status (pMMR EC population)

		PC (N=192)	durvalumab + PC (N=192)	durvalumab + PC + olaparib (N=191)
All subjects	Events n/N (%)	148/192 (77.1)	124/192 (64.6)	108/191 (56.6)
	Median, months (95% CI)	9.7 (9.2, 10.1)	9.9 (9.4, 12.5)	15.0 (12.4, 18.0)
	HR (95% CI) vs PC	-	0.77 (0.60, 0.97)	0.57 (0.44, 0.73)
BRCAm	Events n/N (%)	11/13 (84.6)	4/10 (40)	7/14 (50)
	Median, months (95% CI)	9.9 (4.2, 12.5)	15.0 (8.7, NR)	15.2 (5.3, NR)
	HR (95% CI) vs PC	-	NC	NC
Non-*BRCAm*	Events n/N (%)	116/149 (77.9)	101/156 (64.7)	87/152 (57.2)
	Median, months (95% CI)	9.7 (8.8, 12)	9.9 (9.5, 12.6)	15.0 (12.4, 19.4)
	HR (95% CI) vs PC	-	0.77 (0.59, 1.00)	0.57 (0.43, 0.75)
Unknown	Events n/N (%)	21/30 (70)	19/26 (73.1)	14/25 (56)
	Median, months (95% CI)	9.5 (7.2, 11.6)	8.2 (6.6, 9.8)	9.9 (4.8, NR)
	HR (95% CI) vs PC	-	1.05 (0.56, 1.96)	0.74 (0.37, 1.45)

Source: Table 2.27, p102 of the submission.
BRCA = breast cancer gene mutation; dMMR = deficient mismatch repair; ITT = intention to treat; PC = paclitaxel + carboplatin; PFS = progression free survival; pMMR = proficient mismatch repair

6.30 Nieuwenhuysen 2024 also presented median PFS results for the dMMR EC population by *BRCAm* status. Data were limited in this subpopulation due to low patient numbers but in the dMMR subpopulation patients with *BRCAm* achieved similar median PFS results when they received durvalumab + PC (26.0 months; 95% CI: 7.1, NR) compared to durvalumab + PC + olaparib (31.8 months; 95% CI: 9.9, NR).[3] Hazard ratios for these treatment arms compared to PC could not be calculated.

6.31 The TGA evaluator in the CER (round 2) [redacted][4]

- [redacted][4]
- [redacted][4]

[3] Nieuwenhuysen et al. Durvalumab + carboplatin/paclitaxel followed by durvalumab ± olaparib as first-line treatment for newly diagnosed advanced or recurrent endometrial cancer in the DUO-E/GOG-3041/ENGOT-EN10 trial: results by BRCA1 and/or BRCA2 mutation status. Poster presented at the American Society for Clinical Oncology (ASCO) Annual Meeting, held on May 31–June 4, 2024.

[4] The redacted information relates to the TGA assessment of durvalumab and olaparib for the treatment of endometrial cancer. Details about the TGA assessment will be available in the TGA Australian Public Assessment Report for this assessment once it is published at www.tga.gov.au/resources/auspar.

- [redacted][5]

Overall survival – DUO-E trial

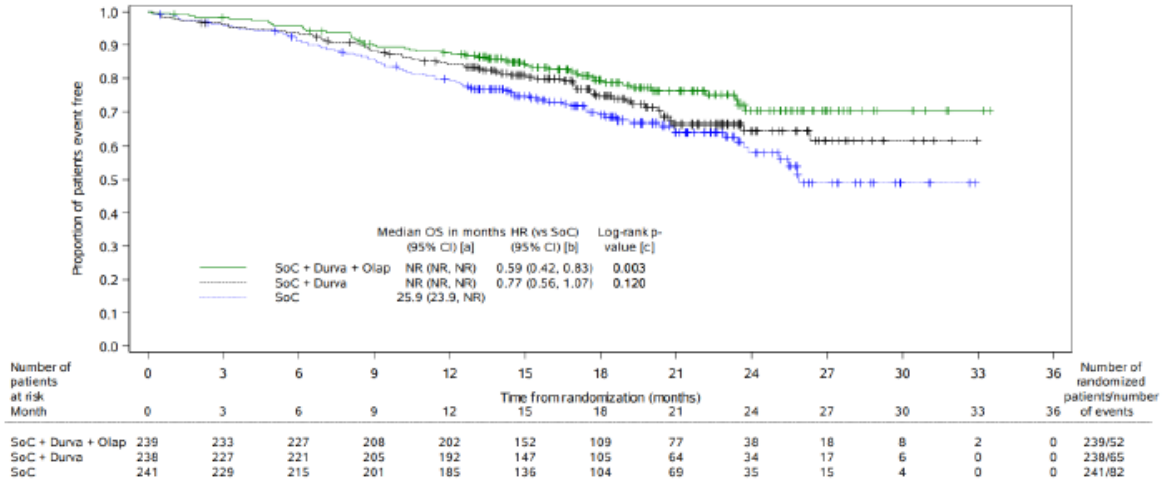
6.32 At the time of the study data cut off (DCO) the OS data in the FAS were 27.7% mature across the three treatment arms (199 events/718 patients). The results for OS in the FAS are summarised in Table 9 and the KM curve for OS is presented in Figure 5.

Table 9: OS Results for all treatment arms DUO-E (FAS)

Measure	PC (N=241)	durvalumab + PC (N=238)	durvalumab + PC + olaparib (N=239)
Deaths (%)	82 (34.0)	65 (27.3)	52.0 (21.8)
Median, months (95% CI)	25.9 (23.9, NR)	NR (NR, NR)	NR (NR, NR)
HR versus PC (95% CI)	-	0.77 (0.56, 1.07)	0.59 (0.42, 0.83)
P value versus PC	-	0.120	0.003
HR versus durvalumab + PC (95% CI)	-	-	0.77 (0.53, 1.10)
P value versus durvalumab + PC	-	-	NR
Percentage of patients alive at:			
6 months (95% CI)	91.2 (86.8, 94.2)	93.7 (89.7, 96.1)	95.8 (92.3, 97.7)
12 months (95% CI)	79.7 (74.0, 84.3)	84.2 (78.9, 88.3)	87.7 (82.7, 91.3)
18 months (95% CI)	69 (62.3, 74.8)	74.6 (68, 80.1)	79.4 (73.2, 84.3)
Median range of follow-up in censored patients, months	18.6	18.4	18.7

Source: Table 2.15, p80 of the submission.
CI = confidence interval; D = durvalumab; FAS = full analysis set; HR = hazard ratio; NR = not reached; O = olaparib; OS = overall survival; PC = paclitaxel + carboplatin

Figure 5: Kaplan Meier Curve for OS (FAS)



Source: Figure 2.9, p79 of the submission.
CI = confidence interval; Durva = durvalumab; FAS = full analysis set; NR = not reached; Olap = olaparib; OS = overall survival; SoC = standard of care

[5] The redacted information relates to the TGA assessment of durvalumab and olaparib for the treatment of endometrial cancer. Details about the TGA assessment will be available in the TGA Australian Public Assessment Report for this assessment once it is published at www.tga.gov.au/resources/auspar.

6.33 While the OS hazard ratio point estimate showed a numerical improvement for both the comparisons of the durvalumab + PC arm compared with the PC arm (HR = 0.77; 95% CI: 0.56, 1.07; p = 0.120) and the durvalumab + PC + olaparib arm compared with the PC arm (HR = 0.59; 95% CI: 0.42, 0.83; p = 0.003), the results did not reach statistical significance as defined in the DUO-E CSR (2-sided significance level p-value stopping boundary of p < 0.0011 and P< 0.0006 for the comparisons, respectively).

6.34 Table 10 summarises the DUO-E OS results analysed by MMR subgroup.

Table 10: Results for OS by MMR subgroup

dMMR	**PC (N=49)**	**durvalumab + PC (N=46)**	**durvalumab + PC + olaparib (N=48)**
Deaths (%)	18 (36.7)	7 (15.2)	6 (12.5)
Censored patients (%)	31 (63.3)	39 (84.8)	42 (87.5)
Median, months (95% CI)	23.7 (16.9, NR)	NR (NR, NR)	NR (NR, NR)
Survival rate 6 months	85.3% (71.5, 92.7)	95.7% (83.7, 98.9)	95.7% (84.0, 98.9)
Survival rate 12 months	74.4 (59.4, 84.6)	91.2 (78.2, 96.6)	89.2 (7.06, 95.4)
Survival rate 18 months	65.8 (49.4, 78)	86.1 (71.5, 93.6)	89.2 (76.0, 95.4)
HR vs PC	-	0.34 (0.13, 0.79)	0.28 (0.10, 0.68)
HR vs durvalumab + PC	-	-	0.84 (0.27, 2.52)
Median duration of follow-up, months	18.4	19.1	19.9
pMMR	**PC (N=192)**	**durvalumab + PC (N=192)**	**durvalumab + PC + olaparib (N=191)**
Deaths (%)	64 (33.3)	58 (30.2)	46 (24.1)
Censored patients (%)	128 (66.7)	134 (69.8)	145 (75.9)
Median, months (95% CI)	25.9 (25.1, NR)	NR (NR, NR)	NR (NR, NR)
Survival rate 6 months	92.7 (87.9, 95.6)	93.2 (88.6, 96.0)	95.8 (91.8, 97.9)
Survival rate 12 months	81.0 (74.6, 85.9)	82.5 (76.3, 87.2)	87.3 (81.7, 91.3)
Survival rate 18 months	69.9 (62.3, 76.2)	71.7 (64.0, 78.1)	76.9 (69.5, 82.7)
HR vs PC	-	0.91 (0.64, 1.30)	0.69 (0.47, 1.00)
HR vs durvalumab + PC	-	-	0.75 (0.51, 1.11)
Median duration of follow-up, months	18.6	18.2	18.4

Source: Table 2.25, p100 of the submission.
dMMR = deficient mismatch repair; HR = hazard ratio; MMR = mismatch repair; NR = not reached; OS = overall survival; PC = paclitaxel + carboplatin; pMMR = proficient mismatch repair

6.35 The submission claimed that the hazard ratios for the comparisons of durvalumab + PC and durvalumab + PC + olaparib versus PC were consistent with the results for PFS, with the patients with pMMR EC deriving benefit from the addition of olaparib in the maintenance phase of therapy; however, none of these differences were assessed for statistical significance. In dMMR EC patients, both comparisons for each of the durvalumab-containing arms compared to PC had a 95% CI upper limit of less than 1.0, but these results were not considered to be of statistical significance as they were subsets of the OS ITT analysis for which the results did not reach statistical significance. Moreover, the number of patients and events in the dMMR EC subgroup were small and therefore the analyses were associated with higher uncertainty.

6.36 The submission did not present subgroup analyses for OS by *BRCAm* status. However, the TGA CER (round 2) noted that based on the dMMR subgroup of the FAS, for non-

tumour *BRCAm* patients, and patients in the FAS for whom the tumour *BRCAm* status was unknown, | | | | | | | | | | | | | | | | | | | | | | | | | | | | [6]

6.37 At the DCO, for the outcome second disease progression or death (PFS2):

- 245 PFS2 events were reported in the FAS (34.1% maturity);
- PFS2 events has occurred in 35.7% of patients in the durvalumab + PC arm compared with 39.8% of patients in the PC arm (HR = 0.80, 95% CI: 0.59, 1.07) and 26.8% of patients in the durvalumab + PC + olaparib arm (HR = 0.55, 95% CI: 0.40, 0.76 versus PC); and
- The median PFS2 for patients in the PC arm was 19.1 months versus 22.2 months in durvalumab + PC arm and not yet reached in the durvalumab + PC + olaparib arm.

<u>Other outcomes – DUO-E</u>

6.38 The submission also presented other outcomes from DUO-E. Briefly:

- Time to second progression (PFS2) was generally longer in durvalumab + PC and durvalumab + PC + olaparib compared to PC in both dMMR and pMMR subgroups;
- Objective response rate (ORR) was assessed in the 81.3% of patients (584/718) with measurable disease at baseline. ORR favoured durvalumab + PC and durvalumab + PC + olaparib compared to PC but the 95% for the estimated odds ratios all included the null;
- In the FAS, median duration of response was 7.7 months in the PC arm, 13.1 months in the durvalumab + PC arm and 21.3 months in the durvalumab + PC + olaparib arm, with the same median time to onset of response across all treatment arms (2.1 months). Median duration of response appeared to be longer in all treatment arms in dMMR compared to pMMR.

6.39 Results for the DUO-E patient reported outcomes (PROs) were not available by MMR status. In the economic model, which included only pMMR EC patients, utilities were applied based on the different health states.

<u>Indirect treatment comparison</u>

6.40 As discussed in paragraph 6.6, to support the comparison of durvalumab + PC and dostarlimab + PC in patients with dMMR EC, the submission presented three ITCs, using data from DUO-E for durvalumab and RUBY for dostarlimab using PC as the common comparator:

[6] The redacted information relates to the TGA assessment of durvalumab and olaparib for the treatment of endometrial cancer. Details about the TGA assessment will be available in the TGA Australian Public Assessment Report for this assessment once it is published at www.tga.gov.au/resources/auspar.

- ITC 1: Unadjusted ITC using data for dMMR EC patients from DUO-E and dMMR and/or MSI-H data from RUBY (OS and PFS assessed).
- ITC 2: Unadjusted ITC including patients with dMMR and/or MSI-H in both DUO-E and RUBY (OS and PFS assessed). Whilst the PBS restriction for dostarlimab is specifically for dMMR patients, RUBY recruited patients using either MSI status or IHC for MMR status. To address this difference, DUO-E samples were retrospectively retested for MSI status, and MSI-H patients without dMMR were identified (n=12), thereby increasing the DUO-E sample size from 95 to 107 patients. While this method resulted in identifying both dMMR and MSI-H patients for DUO-E in line with RUBY, these patient populations were inconsistent with the dostarlimab PBS restriction and the proposed durvalumab restriction due to the inclusion of MSI-H patients. It was also unadjusted for differences in the trial patient populations.
- ITC 3: Matching-adjusted indirect comparison (MAIC) was conducted as for ITC 2 but further adjusted for differences found across DUO-E and RUBY baseline characteristics with respect to patients from the Asian region and with Stage III versus Stage IV newly diagnosed advanced or metastatic disease (only PFS assessed).

6.41 In ITC 3, to determine whether matching had minimised differences, the baseline characteristics of the durvalumab + PC and PC arms before and after matching were summarised and compared against the published baseline data for RUBY (Table 11). The weights estimated in the MAIC were summarised using summary statistics and histogram plots. The histogram of weights was inspected to identify the presence of extreme weights (indicating that the MAIC is influenced by the outcomes of a small number of patients). The effective sample size (ESS) was calculated to approximate the sample size required to obtain a similar level of precision as the weighted data. (A low ESS may indicate a lack of overlap in the matching populations and/or the overmatching of characteristics across studies.) The submission stated that ITC 3 included adjustment for the main differences in baseline characteristics identified between DUO-E and RUBY, which were the proportion of patients in the Asian region and EC disease stage. The PSCR outlined that this adjustment resulted in different post-weighting values for non-matched characteristics (i.e. for age group, ECOG status, histological type and race), with some characteristics where the value was more closely matched to RUBY and others where the value was not. An example of the latter was histologic subtype where serous histology in DUO-E increased from 3.7% to 4.1% compared with RUBY 1.7%.

Table 11: DUO-E (pre and post weighting) and RUBY baseline characteristics for dMMR/MSI-H populations in ITC 3

Variable	Subgroups	DUO-E		RUBY
		Pre-weighting	Post-weighting	-
Age group (years)	<65	55.1%	47.9%	50.8%
	>=65	44.9%	52.1%	49.2%
Disease status	Primary stage III	9.3%	20.3%	20.3%
	Primary stage IV	40.2%	29.7%	29.7%
	Recurrent	50.5%	50.0%	50.0%
ECOG performance status	(0) Normal activity	57.0%	58.3%	56.8%
	(1) Restricted activity	43.0%	41.7%	42.4%
Histologic type	Endometrioid	78.5%	82.1%	84.7%
	Serous	3.7%	4.1%	1.7%
	Other	17.8%	13.8%	13.6%
Race	American Indian or Alaska Native	0.9%	2.9%	0.8%
	Asian	27.1%	1.2%	1.7%
	Black or African American	1.9%	4.1%	8.5%
	Not reported	3.7%	4.1%	3.4%
	Other	2.8%	5.1%	0.0%
	White	63.6%	82.6%	84.7%

Source: Table 2.35, p110 of the submission
dMMR = deficient mismatch repair; ECOG = Eastern Cooperative Oncology Group; MSI-H = microsatellite instability high
a Data for DUO-E was listed as 'data on file' in the submission and therefore could not be independently verified.
Data for RUBY could not be found in the source listed in the submission (Mirza 2023, Table 1) and therefore this data could not be independently verified.

6.42 In the base case analysis, the ESS for both trial arms was 67.4 (63.0%), compared to the original sample size for the two relevant trial arms (n=107), indicating a reasonable loss of information from matching, due to the differences in the trials. These reduced sample sizes further increased the uncertainty of results. The most notable differences were that the proportion of Asian patients had decreased from 27.1% to 1.2% and the proportion of white patients had increased from 63.7% to 82.6%. The submission claimed that after matching, there was minimal difference in the baseline characteristics of patients between DUO-E and RUBY. The evaluation considered that matching based on region may not be appropriate as this implies that, like durvalumab + PC in DUO-E, the treatment effect for dostarlimab + PC also differed by region in RUBY; an assumption which was not supported by any evidence presented in the submission. By assigning a zero weight to all Asian patients in DUO-E, the benefits for durvalumab + PC may be overestimated and the MAIC may be biased in favour of durvalumab + PC. The PSCR stated that the Asian region was matched in the MAIC because 27.1% of patients in DUO-E were recruited from the Asian region versus 1.7% in RUBY, and that the treatment effect of durvalumab + PC in dMMR patients in DUO-E was slightly better in patients from the Asian region versus patients in rest of world. The PSCR stated that this information was unknown for dostarlimab + PC, but that adjusting for Asian region patients in the dMMR population could potentially bias against durvalumab + PC.

6.43 The PSCR stated that disease stage was matched because 9.3% of patients in DUO-E had Stage III EC versus 20.3% in RUBY. The PSCR stated that the treatment effect of dostarlimab + PC in the RUBY trial was lower in patients with stage III versus stage IV

disease. Therefore, by adjusting for disease stage in the MAIC, the results could theoretically be biased towards dostarlimab + PC if the same treatment effect difference was not observed for durvalumab + PC in stage III versus stage IV disease. The PSCR noted that results by stage III versus stage IV from DUO-E were not analysed due to the very small number of patients in DUO-E with stage III disease. The submission also noted that the PFS results in the investigational arms were very similar but the curves for the common comparator (PC) demonstrated that the control arm of RUBY performed worse than the control arm in DUO−E. The ESC noted that this was a key transitivity issue between the trials and further increased the uncertainty with the ITCs. It was unclear whether the adjustments in the MAIC improved or exacerbated this transitivity issue.

6.44 Table 12 presents results for ITC 1, ITC 2 and ITC 3.

Table 12: Summary of results for ITC1, ITC 2 and ITC 3

	DUO-E		RUBY	
	durvalumab + PC	**PC**	**dostarlimab + PC**	**PC**
ITC 1 (Unadjusted ITC)				
Number of patients, n	46	49	53	65
OS				
Events, n (%)	7 (15.2)	18 (36.7)	7 (13.2)	24 (36.9)
HR (95% CI)	0.34 (0.13, 0.79)		0.30 (0.13, 0.70)	
ITC of durvalumab + PC vs dostarlimab + PC, HR (95% CI), p-value	1.13 (0.33, 3.89); p=0.8424			
PFS				
Events, n (%)	15 (32.6)	25 (51.0)	19 (35.8)	47 (72.3)
HR (95% CI); p-value	0.42 (0.22, 0.80); NR		0.28 (0.16, 0.50); p<0.001	
ITC of durvalumab + PC vs dostarlimab + PC, HR (95% CI), p-value	1.50 (0.634, 3.548); p=0.3560*			
ITC 2 (ITC results in the dMMR/MSI-H population)				
Number of patients, n [a]	55	52	53	65
OS				
Events, n (%)	8 (14.5%)	21 (40.4%)	7 (13.2%)	24 (36.9%)
HR (95% CI)	0.30 (0.12, 0.65)		0.30 (0.13, 0.70)	
ITC of durvalumab + PC vs dostarlimab + PC, HR (95% CI), p-value	1.00 (0.31-3.23); p=1.0000*			
PFS				
Events, n (%)	17 (30.9%)	28 (53.8%)	19 (35.8%)	47 (72.3%)
HR (95% CI); p-value	0.37 (0.20, 0.67)		0.28 (0.16, 0.50)	
ITC of durvalumab + PC vs dostarlimab + PC, HR (95% CI), p-value	1.32 (0.57, 3.04) p=0.5108*			
ITC 3 (MAIC results for PFS in the dMMR/MSI-H population) [b]				
ITC of durvalumab + PC vs dostarlimab + PC, HR (95% CI), p-value	1.05 (0.41, 2.68); NR*			

Source: Tables 2.32 and 2.33, Figures 2.19, 2.21 and 2.23, p113-117 of the submission.

CI = confidence interval; dMMR = deficient mismatch repair; FU = follow up; HR = hazard ratio; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparisons; MSI-H = microsatellite instability high; MSS-H = microsatellite stable high; NR = not reported; OS = overall survival; PC = paclitaxel + carboplatin; PFS = progression free survival

a ITC 2 included both dMMR and MSI-H patients which increased the DUO-E sample size from 95 to 107 (95 patients were dMMR and an additional 12 were MSI-H). Patient numbers could not be independently verified as these details were not provided in 'Attachment 2.10_ITC' to the submission.

b The number of patients included in the MAIC was not provided in the submission and ITC 3 results were referenced as 'data on file'. The submission (p116) claimed that in the base case analysis, the effective sample size (ESS) for both trial arms was 67.4 (63.0%), compared to the original sample size for the two relevant trial arms (n=107), indicating a reasonable loss of information from matching, due to the differences in the trials. The submission (p112) claimed that OS was not tested in the MAIC given it would be subject to a high degree of uncertainty due to the immaturity of the OS data in both trials and the small number of events observed in both investigational treatment arms (n=7 in DUO-E).

Note that results denoted by (*) are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.45 The submission claimed that the results from each of the ITCs demonstrate that durvalumab is non-inferior to dostarlimab in terms of efficacy for patients with dMMR and/or MSI-H EC and that the HR for the differences in PFS and OS shifted closer to 1 as the populations were more closely matched. The ESC noted that this was uncertain as:

- No non-inferiority margin was nominated. The PBAC guidelines (v5.0) (p39) specified that a lack of a statistically significant difference between the proposed

medicine and the comparator does not adequately establish non-inferiority. This is especially true in an ITC in which confidence intervals are likely wide and biased towards the null;

- As noted by the submission, PFS in the common comparator arm differed between the trials and was a key transitivity issue. The submission did not present the PFS results of the common comparator in the MAIC to demonstrate whether the matching improved or exacerbated this transitivity issue;
- When the RUBY trial was considered by the PBAC during the most recent evaluation of dostarlimab, the PBAC found the results from the dMMR population were prone to a higher risk of bias given the smaller sample size (23.9% of the all-comers population, n=118) and RUBY was not powered for the outcome of OS in this subgroup (paragraphs 6.7 and 6.8, dostarlimab PSD, November 2023 PBAC meeting). Consequently, the ITC conducted using the dMMR/MSI-H subpopulations from DUO-E and RUBY would be associated with a high risk of bias; and
- The results of the MAIC were highly uncertain as the already small sample size in dMMR/MSI-H patients was further reduced from the matching due to the exclusion of Asian patients from DUO-E. Further, matching based on region may not be appropriate as it was unknown whether dostarlimab would have different PFS in Asian and non-Asian patients. If there was no difference in dostarlimab response between Asian and non-Asian patients (unlike durvalumab + PC in which response was worse in Asians), then by assigning a zero weight to all Asian patients in DUO-E, the benefits for durvalumab + PC may be overestimated and the MAIC may be biased in favour of durvalumab + PC.

Comparative harms

6.46 The DUO-E safety analysis set (SAS) included all randomised patients who received at least one dose of study drug. Table 13 provides an overall summary of DUO-E adverse events (AEs) by treatment arm. A notable difference between the investigational arms and PC arm was the increased incidence of immune-related AEs (28.1% and 23.5% in the durvalumab + PC and durvalumab + PC + olaparib arms, respectively versus 6.8% in the PC arm).

Table 13: Overall Summary of Adverse Events in DUO-E

	PC (N=236), n (%)	durva + PC (N=235), n (%)	durva + PC vs PC RR (95% CI)	durva + PC vs PC RD (95% CI)	durva + PC + ola (N=238), n (%)	durva + PC + ola vs PC RR (95% CI)	durva + PC + ola vs PC RD (95% CI)
Any AE	236 (100)	232 (98.7)	0.99 (0.97, 1.00)	-1.3 (-2.7, 0.2)	237 (99.6)	1.00 (0.99, 1.00)	-0.4 (-1.2, 0.4)
Any AE Grade ≥ 3	133 (56.4)	129 (54.9)	0.97 (0.83, 1.14)	-0.01 (-0.10, 0.08)	160 (67.2)	**1.19 (1.03, 1.38)**	**0.11 (0.02, 0.20)**
Any serious AE (SAE)	73 (30.9)	73 (31.1)	1.00 (0.77, 1.31)	0.0 (-0.08, 0.09)	85 (35.7)	1.15 (0.89, 1.49)	0.05 (-0.04, 0.13)
Any AE with outcome = death	8 (3.4)	4 (1.7)	0.50 (0.15, 1.64)	-0.02 (-0.05, 0.01)	5 (2.1)	0.62 (0.21, 1.87)	-0.01 (-0.04, 0.02)
Any AE leading to discontinuation of durvalumab/ placebo	19 (8.1)	26 (11.1)	1.37 (0.78, 2.41)	0.03 (-0.01, 0.06)	22 (9.2)	1.15 (0.64, 2.06)	-0.01 (-0.04, 0.06)
Any AE leading to discontinuation of olaparib/placebo	5 (2.1)	11 (4.7)	2.21 (0.78, 6.26)	0.03 (-0.01, 0.06)	21 (8.8)	**4.16 (1.60, 10.86)**	0.07 (0.03, 0.11)
Any AE leading to discontinuation of PC	32 (13.6)	31 (13.2)	0.97 (0.78, 6.26)	0.0 (-0.07, 0.06)	31 (13)	0.96 (0.61, 1.52)	-0.01 (-0.07, 0.06)
Any immune-related AEs	16 (6.8)	66 (28.1)	**4.14 (2.47, 6.94)**	0.21 (0.15, 0.28)	56 (23.5)	**3.47 (2.05, 5.87)**	0.17 (0.11, 0.23)
Any infusion reaction AEs	38 (16.1)	35 (14.9)	0.92 (0.61, 1.41)	-0.01 (-0.08, 0.05)	40 (16.8)	1.04 (0.70, 1.57)	0.01 (-0.06, 0.07)

Source: Table 2.19, p87 of the submission

AE = adverse event; CI = confidence interval; durva = durvalumab; ola = olaparib; PC = paclitaxel + carboplatin; RD = risk difference; RR = relative risk; SAE = serious adverse event

Bold indicates values where the 95% CI for the relative risk did not include '1'.

6.47 AEs occurring in ≥ 20% of patients in any treatment arm are summarised in Table 14.

Table 14: Adverse Events Occurring in > 20% of patients in Any Treatment Arm in DUO-E

System organ class	PC (N=236), n (%)	durva + PC (N=235), n (%)	durva + PC vs PC RR (95% CI)	durva + PC vs PC RD (95% CI)	durva + PC + ola (N=238), n (%)	durva + PC + ola vs PC RR (95% CI)	durva + PC + ola vs PC RD (95% CI)
Gastrointestinal							
Nausea	105 (44.5)	96 (40.9)	0.92 (0.74, 1.13)	-0.04 (-0.13, 0.05)	130 (54.6)	**1.23 (1.02, 1.48)**	**0.10 (0.01, 0.19)**
Constipation	81 (34.3)	64 (27.2)	0.79 (0.60, 1.04)	-0.07 (-0.15, 0.01)	78 (32.8)	0.95 (0.74, 1.23)	-0.02 (-0.10, 0.07)
Diarrhoea	66 (28.0)	74 (31.5)	1.13 (0.85-1.49)	0.04 (-0.05, 0.12)	67 (28.2)	1.01 (0.75, 1.34)	0.0 (-0.08, 0.08)
Vomiting	43 (18.2)	49 (20.9)	1.14 (0.79, 1.65)	0.03 (-0.05, 0.10)	61 (25.6)	1.41 (0.99, 1.99)	0.07 (0.0, 0.15)
Nervous System							
Neuropathy peripheral	66 (28.0)	61 (26.0)	0.93 (0.69, 1.25)	-0.02 (-0.10, 0.06)	60 (25.2)	0.90 (0.67, 1.22)	-0.03 (-0.11, 0.05)
Peripheral sensory neuropathy	66 (28.0)	60 (25.5)	0.91 (0.68, 1.23)	--0.02 (-0.10, 0.06)	60 (25.2)	0.90 (0.67, 1.22)	-0.03 (-0.11, 0.05)
Skin and subcutaneous tissue disorder							
Alopecia	118 (50.0)	118 (50.2)	1.0 (0.84, 1.20)	0.00 (-0.09, 0.09)	121 (50.8)	1.01 (0.85, 1.22)	0.01 (-0.08, 0.10)
General disorders and administration site							
Fatigue	87 (36.9)	82 (34.9)	0.95 (0.74, 1.21)	-0.02 (-0.11, 0.07)	93 (39.1)	1.06 (0.84, 1.33)	0.02 (-0.07, 0.11)
Blood and lymphatic system disorders							
Anaemia	128 (54.2)	111 (47.2)	0.87 (0.73, 1.04)	-0.07 (-0.16, 0.02)	147 (61.8)	1.14 (0.98, 1.33)	0.08 (-0.01, 0.16)
Neutropenia	31 (13.1)	36 (15.3)	1.17 (0.75, 1.82)	0.02 (-0.04, 0.09)	49 (20.6)	**1.57 (1.04, 2.37)**	**0.07 (0.01, 0.14)**
Investigations							
Neutrophil count decreased	63 (26.7)	44 (18.7)	**0.70 (0.50, 0.99)**	-0.08 (-0.16, 0.00)	50 (21)	0.79 (0.57, 1.09)	-0.06 (-0.13, 0.02)
Musculoskeletal							
Arthralgia	58 (24.6)	71 (30.2)	1.23 (0.91, 1.65)	0.06 (-0.02, 0.14)	58 (24.4)	0.99 (0.72, 1.36)	0.0 (-0.08, 0.08)
Infections							
COVID-19	32 (13.6)	36 (15.3)	1.13 (0.73, 1.76)	0.02 (-0.05, 0.08)	48 (20.2)	1.49 (0.99-2.24)	0.07 (0.0, 0.13)
UTI	50 (21.2)	33 (14.0)	**0.66 (0.44, 0.99)**	-0.07 (0.14, 0.00)	48 (20.2)	0.95 (0.67, 1.35)	-0.01 (-0.08, 0.06)
Metabolism and nutrition							
Decreased appetite	46 (19.5)	42 (17.9)	0.92 (0.63, 1.34)	-0.02 (-0.09, 0.05)	55 (23.1)	1.19 (0.84, 1.68)	0.04 (-0.04, 0.11)

Source: Table 2.20, p87 of the submission

durva = durvalumab; ola = olaparib; PC = paclitaxel + carboplatin; RD = risk difference; RR = relative risk; UTI = urinary tract infection

Bold indicates values where the 95% CI for the relative risk did not include '1'.

6.48 Treatment emergent AEs (TEAEs) classified as > grade 3 reported in > 2% of patients were also reported in the submission. Relative risks calculated during the evaluation did not identify any events which may be different between treatment arms, though

the number of some events were very low (less than 10 instances) and the follow-up of DUO-E may not be long enough for some events to develop.

6.49 Serious AEs (SAEs) occurring in > 1% of patients in DUO-E were also reported. Notably, there were more cases of anaemia reported in the PC arm (10/36, 4.2%) than in the durvalumab + PC arm (1/235, 0.4%) but not compared to the durvalumab + PC + olaparib arm (16/238, 6.7%). This could not be explained and, as all three treatment arms received PC, there was no biological reason why the PC arm would have more anaemia events than durvalumab + PC.

6.50 In the DUO-E overall population, immune-mediated AEs were similar in the durvalumab + PC and durvalumab + PC + olaparib arms, but were higher than in the PC arm. In the PC arm, the most frequent immune-mediated AE was dermatitis/rash (3.4%). In both the durvalumab + PC and durvalumab + PC + olaparib arms, the most frequent immune-mediated AE was hypothyroid events (14.5% and 11.8%, respectively), followed by dermatitis/rash (6.4% and 6.3%, respectively) and hepatic events (2.6% and 2.1%, respectively). Hyperthyroidism is a known durvalumab-related AE. The durvalumab PI reports that durvalumab as monotherapy is associated with a 10.1% rate of hyperthyroidism based on pooled data across multiple tumour types.

6.51 The submission claimed that, unlike efficacy, safety was not likely to differ between dMMR and pMMR patient populations, which the evaluation considered was likely reasonable.

6.52 Regarding safety, the TGA CER (round 1) reported:

- [redacted][7]
- [redacted][7]

6.53 A summary of TEAEs and the corresponding ITC results for durvalumab + PC vs dostarlimab + PC are presented in Table 15 for DUO-E and RUBY (using data from the safety analysis populations in both trials). The evaluation noted that as with the ITC results for comparative effectiveness, it was difficult to interpret the comparative safety from the ITC due to small sample sizes and wide confidence intervals. However, there may be some biological plausibility in dostarlimab and durvalumab having a similar safety profile given the similarities in mechanism of action.

[7] The redacted information relates to the TGA assessment of durvalumab and olaparib for the treatment of endometrial cancer. Details about the TGA assessment will be available in the TGA Australian Public Assessment Report for this assessment once it is published at www.tga.gov.au/resources/auspar.

Table 15: Summary of adverse events DUO-E and RUBY

Summary of TEAEs	DUO-E			RUBY			ITC of DUO-E vs RUBY RR (95% CI) <1 favours durva + PC	durva + PC vs dostar + PC RD (95% CI)[a]
	durva + PC (N=44), n (%)	PC (N=46), n (%)	Within trial RR (95% CI)	dostar + PC (N=52), n (%)	PC (N=65), n (%)	Within trial RR (95% CI)		
Any TEAE	44 (100)	46 (100)	1.00 (0.96, 1.04)	52 (100)	65 (100)	1.00 (0.97, 1.03)	1.00 (0.95, 1.05)	0.0 (0.0, 0.0)
Drug-related TEAE	42 (95.5)	44 (95.7)	1.00 (0.91, 1.09)	52 (100)	65 (100)	1.00 (0.97, 1.03)	1.00 (0.91, 1.1)	-0.05 (-0.11, 0.02)
Any Grade ≥3 TEAE	23 (52.3)	29 (63.0)	0.83 (0.58, 1.19)	37 (71.2)	42 (64.6)	1.10 (0.86, 1.41)	0.76 (0.49, 1.17)	-0.19 (-0.38, 0.00)
Drug-related Grade ≥3 TEAE	18 (40.9)	23 (50.0)	0.82 (0.52, 1.29)	30 (57.7)	32 (49.2)	1.17 (0.83, 1.65)	0.70 (0.40, 1.24)	-0.17 (-0.37, 0.03)
Any SAE	13 (29.5)	15 (32.6)	0.91 (0.49, 1.68)	14 (26.9)	20 (30.8)	0.88 (0.49, 1.56)	1.03 (0.44, 2.41)	0.03 (-0.16, 0.21)
Drug-related SAE	5 (11.4)	10 (21.7)	0.52 (0.19, 1.41)	9 (17.3)	9 (13.8)	1.25 (0.53, 2.92)	0.42 (0.11, 1.55)	-0.06 (-0.20, 0.08)
Any immune-related TEAE	19 (43.2)	10 (21.7)	**1.99 (1.04, 3.78)**	38 (73.1)	24 (36.9)	**1.98 (1.38, 2.83)**	1.01 (0.48, 2.10)	-0.30 (-0.49, 0.11)
Any infusion-related TEAE	3 (6.8)	7 (15.2)	0.45 (0.12, 1.62)	12 (23.1)	13 (20.0)	1.15 (0.58, 2.31)	0.39 (0.09, 1.71)	-0.16 (-0.30, -0.03)
Any TEAE leading to treatment discontinuation	9 (20.5)	7 (15.2)	1.34 (0.55, 3.30)	9 (17.3)	9 (13.8)	1.25 (0.53, 2.92)	1.07 (0.31, 3.69)	0.03 (-0.13, 0.19)
TEAEs leading to death	0 (0.0)	1 (2.2)	0.35 (0.01, 8.33)	2 (3.8)	0 (0.0)	6.23 (0.31, 126.9)	0.06 (0.00, 5.11)	-0.19 (-0.38, 0.00)

Source: Table 2.36, p118 of the submission.

CI = confidence interval; dostar = dostarlimab; durva = durvalumab; ITC= indirect treatment comparison; PC = paclitaxel + carboplatin; RR = relative risk; SAE= serious adverse event; TEAE= treatment emergent adverse event.

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

a Naïve unanchored comparison of risk of AEs for treatment with durvalumab + PC (DUO-E) versus dostarlimab + PC.

Benefits/harms

6.54 Benefits and harms were not presented for the comparison of durvalumab + PC and dostarlimab + PC as the submission made a claim of non-inferiority.

6.55 On the basis of direct comparison evidence presented by the submission in the pMMR population, for every 100 patients treated with durvalumab + PC + olaparib in comparison with PC:

- Approximately 20 additional patients will remain progression-free at 12 months (see Table 5); and
- Approximately 17 additional patients will experience any immune-related TEAEs (see Table 13).

Clinical claim

6.56 The submission provided the following clinical claims:

- durvalumab + PC is non-inferior in terms of efficacy and safety to dostarlimab + PC in patients with dMMR EC;

- durvalumab + PC is superior in terms of efficacy and non-inferior in terms of safety compared to PC in patients with dMMR EC. However, this was considered to be a supplementary comparison during evaluation as dostarlimab is PBS-listed in this group; and
- durvalumab + PC + olaparib is superior in terms of efficacy and inferior in terms of safety compared to PC in patients with pMMR EC.

6.57 The ESC considered that the claims of superior efficacy versus PC alone (for both populations) were likely reasonable based on the subgroup analyses of PFS from DUO-E. However, the ESC considered that the following issues regarding DUO-E may limit the applicability and/or increase the uncertainty of the results:

- MMR subgroup analyses in DUO-E were not predefined and hypotheses for these subgroups were not tested, and as such, these subgroup analyses are likely to be associated with a higher risk of bias and should be interpreted with caution;
- The results comparing durvalumab + PC + olaparib vs durvalumab + PC in DUO-E were used to justify the proposed use of durvalumab + PC for the treatment of dMMR EC and durvalumab + PC + olaparib for the treatment of pMMR. Although this comparison was a pre-specified exploratory analysis, it was not included as a treatment comparison of interest for DUO-E. Consequently, hypotheses for this comparison were not predefined and these analyses may be associated with a higher risk of bias. Moreover, DUO-E did not inform the efficacy of PC + olaparib to justify the addition of durvalumab in pMMR patients;
- The DUO-E OS results presented in the submission did not meet the pre-defined statistical thresholds for superiority, and as such a statically significant improvement in OS could not be concluded for the ITT, much less the subgroups based on MMR status;
- The DUO-E PFS results indicated BRCAm and PD-L1 status may be treatment effect modifiers, and the relative proportion of A/R EC patients in Australia with BRCAm and their PD-L1 status was unknown. The requested restriction was also agnostic to BRCAm and PD-L1 status. Importantly, any patient treated with 1L durvalumab + PC (with or without olaparib) would not be eligible to receive PBS subsidised 2L pembrolizumab + lenvatinib. Therefore, if 1L durvalumab was used in a subgroup of patients for whom it was not effective, these patients may be worse off compared to the current treatment landscape in which they may be eligible for 2L pembrolizumab + lenvatinib.

6.58 The submission described durvalumab + PC + olaparib as inferior in terms of safety compared with PC alone in patients with pMMR EC, which the submission claimed was largely due to the increased incidence of immune-related AEs. The ESC considered that this was reasonable and consistent with the safety results in both the whole trial population (safety analysis set) and by MMR status in DUO-E.

dMMR population

6.59 The submission claimed that based on the ITCs conducted for the dMMR EC population, durvalumab + PC is non-inferior to dostarlimab + PC in terms of efficacy and safety. The ESC considered that this claim was likely reasonable, but noted the issues outlined in paragraph 6.45.

6.60 The PBAC considered that the claim that durvalumab + PC was non-inferior compared to dostarlimab + PC in terms of both comparative effectiveness and safety in patients with dMMR EC was reasonable.

pMMR population

6.61 The PBAC did not comment on the effectiveness or safety of durvalumab + olaparib + PC compared to PC in the pMMR EC population.

Economic analysis

6.62 The submission presented both a CMA (durvalumab + PC compared to dostarlimab + PC in dMMR EC) and a cost effectiveness analysis (durvalumab + PC + olaparib compared to PC in pMMR EC).

CMA versus dostarlimab (dMMR)

6.63 Based on the results of the ITC, the submission concluded that durvalumab + PC is non-inferior in terms of efficacy and safety compared with dostarlimab + PC in dMMR EC patients. On this basis, the submission presented a CMA comparing durvalumab + PC with dostarlimab + PC in patients with dMMR EC, as outlined in Table 16.

Table 16: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Durvalumab added to PC was assumed to be non-inferior in terms of efficacy compared with dostarlimab added to PC.
Therapeutic claim: safety	Durvalumab added to PC was assumed to be non-inferior in terms of safety compared with dostarlimab added to PC.
Evidence base	Indirect comparison of outcomes for durvalumab and dostarlimab using DUO-E (placebo-controlled RCT investigating addition of durvalumab to PC) and RUBY (placebo-controlled RCT investigating addition of dostarlimab to PC) in dMMR patients with EC, with PC as the common reference in the analysis.
Equi-effective doses	In DUO-E, durvalumab was administered as 1,120mg every three weeks by IV infusion for a maximum of 6 cycles (with carboplatin + paclitaxel), followed by 1500mg every four weeks by IV infusion as maintenance. In RUBY, dostarlimab was administered as 500mg every three weeks by IV infusion for a maximum of 6 cycles (with carboplatin + paclitaxel), followed by 1000mg every six weeks by IV infusion as maintenance.
Direct medicine costs	The submission calculated the equi-effective doses based on the total number of milligrams administered over the maximum 36-month treatment duration assumed for all patients, based on the treatment duration estimated in the November 2023 dostarlimab model (the submission assumed the same average treatment duration for each arm). On this basis, patients were assumed to receive 5.1 initiation doses for both durvalumab and dostarlimab, and the number of maintenance doses was calculated based on the respective dosage regimens for dostarlimab (administered 4 weekly, resulting in 18 maintenance doses) and dostarlimab (administered 6 weekly resulting in 12 maintenance doses). Given that IV chemotherapy drugs in Australia are costed through the Efficient Funding of Chemotherapy scheme, the equi-effective doses used in the CMA are based on the most efficient combination of vials required to provide the number of milligrams needed each infusion.
Other costs or cost offsets	Given that durvalumab in dMMR will join the risk-share arrangement in place for dostarlimab, and given the advice from clinicians that, given the treatment paradigm in this setting, few patients will remain on treatment for longer than three years, the CMA assumed that all dMMR patients treated with durvalumab will cease therapy at month 36.

Source: Table 3.38, p175 of the submission.
CMA = cost-minimisation approach; dMMR = deficient mismatch repair; PC = paclitaxel + carboplatin; RCT = randomised controlled trial

6.64 For both durvalumab and dostarlimab, the equi-effective dose was based on the number of doses of dostarlimab as reported in the dostarlimab November 2023 public summary document, i.e. 5.1 initiation and 12.0 maintenance doses. This was based on a mean duration of therapy of 88.9 weeks (20.5 months) (Table 18, dostarlimab PSD, November 2023 PBAC meeting), accounting for differences in maintenance dosing schedules (per paragraph 6.67). The ESC noted that this mean duration of therapy was based on the economic model provided in the dostarlimab submission, and did not account for the revisions to the economic model recommended by the PBAC (per paragraph 7.8, dostarlimab PSD, November 2023 PBAC meeting).

6.65 The submission assumed the same average duration of therapy for dostarlimab and durvalumab. The submission did not test the reasonableness of this assumption (e.g. by extrapolating the duration of therapy observed in the trials – noting extrapolation would be required given the differences in duration of follow-up in the trials), and as such it was unclear if this was reasonable. The ESC noted that if durvalumab were used for a longer duration than dostarlimab in clinical practice, this assumption would not be conservative. The PBAC considered that it was difficult to estimate any potential differences in the mean (extrapolated) duration of treatment between durvalumab and dostarlimab in the dMMR population given the: dMMR population comprised a

relatively small subgroup of each of the trials; and differences in baseline characteristics between the trials (as shown in Table 11).

6.66 The ESC considered that an additional uncertainty in the calculation of equi−effective doses was that the doses applied in the November 2023 dostarlimab economic evaluation included assumptions around dosage reduction and discontinuation rates which may be unique to dostarlimab and may not be applicable to durvalumab. For dostarlimab, the model incorporated dose intensities of 94.7% and 97.3% for initiation and maintenance doses, respectively (Table 18, dostarlimab PSD, November 2023 PBAC meeting), whereas dose intensity was not incorporated in the durvalumab CMA.

6.67 Table 17 provides an overview of the establishment of the equi-effective doses. The CMA base case for dMMR EC assumed patients receiving either durvalumab or dostarlimab will have received 5.1 induction doses. The number of maintenance doses was based on a treatment duration in the maintenance phase of 72 weeks and was assumed to differ based on the different maintenance regimens between the drugs, with durvalumab maintenance administered four-weekly (18 maintenance doses) and dostarlimab maintenance administered six-weekly (12 maintenance doses). The equi-effective doses, based on a maximum treatment duration of 36 months, were estimated as:

durvalumab 32,712 mg = dostarlimab 14,550 mg.

Table 17: Equi-effective dose over 36-month treatment duration

	Durvalumab			Dostarlimab		
	Milligrams administered per infusion	Number of infusions	Total milligrams administered per course	Milligrams administered per infusion	Number of infusions	Total milligrams administered per course
Induction	1,120	5.1	5,712	500	5.1	2,550
Maintenance	1,500	18.0	27,000	1000	12.0	12,000
Total		**23.1**	**32,712**		**17.1**	**14,550**

Source: Table 3.40, p178 of the submission

6.68 The CMA incorporated IV administration costs due to the different frequency of dosing between durvalumab and dostarlimab. The results of the CMA using the published price of dostarlimab are presented in Table 18.

Table 18: Cost per course over the maximum 36-month total treatment duration for durvalumab and dostarlimab (base case)

Assumed price of dostarlimab	Treatment	Total drug acquisition cost (DPMQ)	IV administration costs	Total cost per course
Published price of dostarlimab	Durvalumab	$	$2,842.46	$
	Dostarlimab	$133,629.19	$2,104.16	$135,733.34
	Incremental	-$	$738	-$

Source: Table 3.41, p179 of the submission.

CUA versus PC alone (pMMR)

6.69 The submission presented a stepped economic evaluation for patients with advanced, metastatic or recurrent pMMR EC to compare durvalumab + PC + olaparib vs PC based

on the DUO-E trial. The type of economic evaluation presented was a cost-utility analysis (CUA). [redacted]. [8]

[redacted][8]

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6.71 [redacted] [8]

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6.72 [redacted]. [8]

[8] This information has been redacted at the sponsor's request, as it was not part of the PBAC's decision making for this submission.

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6.73 [redacted].[9]

6.74 [redacted][9]

6.75 [redacted][9]

6.76 [redacted]

[9] This information has been redacted at the sponsor's request, as it was not part of the PBAC's decision making for this submission.

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6.77 [redacted][10]

6.78 [redacted][10]

6.79 [redacted][10]

6.80 [redacted][10]

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6.81 [redacted][10]

6.82 [redacted][10]

6.83 [redacted][10]

[10] This information has been redacted at the sponsor's request, as it was not part of the PBAC's decision making for this submission.

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6.86 [redacted]

[11] This information has been redacted at the sponsor's request, as it was not part of the PBAC's decision making for this submission.

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6.87 [redacted][12]

(i) [redacted][12]

(ii) [redacted][12]

(iii) [redacted][12]

(iv) [redacted][12]

6.88 [redacted][12]

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[12] This information has been redacted at the sponsor's request, as it was not part of the PBAC's decision making for this submission.

Durvalumab cost/patient/course

dMMR population

6.89 Table 26 shows the doses of durvalumab used in DUO-E in dMMR A/R EC patients, the CMA and the financial estimates presented in the submission and the resulting drug cost per patient for a course of durvalumab for the treatment of dMMR EC. The durations of treatment for durvalumab and olaparib were not consistent between the trial, the CMA and the financial estimates. Differences were due to different assumptions around duration of initiation and treatment between the trial, model and the financial estimates (see paragraph 6.92). The PSCR provided revised financial estimates in which the number of doses per patient was more consistent with the CMA.

Table 26: Drug cost per patient for durvalumab treatment for dMMR EC (as per submission proposed price)

	Trial dose and duration	CMA	Financial estimates
Durvalumab, mean number of initiation doses	5.8 [a]	5.1 [f]	7.2 [c]
Durvalumab, mean initiation actual exposure	17.4 weeks [b]	15.3 weeks [b]	5 months [g]
Cost/patient, durvalumab initiation [e]	$	$	$
Durvalumab, mean number of maintenance doses	8.3 [c]	18 [f]	19.5 [c]
Durvalumab, duration of maintenance treatment	33.0 weeks [d]	72 weeks [b]	18 months [g]
Cost/patient, durvalumab maintenance [e]	$	$	$
Total cost/patient/course	**$**	**$**	**$**

Source: Estimated during the evaluation using the submission's model 'Attachment 3.6_CMA' and DUO-E CSR.
DPMA = dispensed price maximum amount; NR = not reported; PC = paclitaxel + carboplatin
a Sourced from DUO-E data provided in Attachment 3.3 to the submission.
b Calculated based on mean number of durvalumab initiation doses.
c Calculated based on treatment duration.
d Mean maintenance actual exposure for durvalumab + PC arm, sourced from DUO-E CSR Table 14.3.1.1.2A.
d Sourced from DUO-E CSR Table 14.3.1.1.3A.
e Calculated using the mean number of durvalumab initiation and maintenance doses and multiplying by the proposed DPMQ. DPMQ calculated based on a 51%:49% split of private: public hospital use.
f Assumption made in CMA.
g Assumption made in financial estimates.

pMMR population

6.90 [13]

[13] This information has been redacted at the sponsor's request, as it was not part of the PBAC's decision making for this submission.

|||||||||||||||[14]

Estimated PBS usage & financial implications

6.91 This submission was not considered by DUSC.

6.92 The financial estimates incorporated the impact of listing: (a) durvalumab + PC in patients with dMMR EC; and (b) durvalumab + PC + olaparib in patients with pMMR EC. However, the evaluation noted that there were significant errors and omissions in the financial estimates presented in the submission, and considered that the estimates presented were not informative as:

- A significant proportion of patients were not included in the usage estimates although they were calculated as eligible patients, leading to a gross underestimation of the utilisation and cost associated with durvalumab and olaparib. These following patient groups were not included in the financial estimates:
    - dMMR patients with stage III/IV unresectable EC, treated with durvalumab + PC (duration of treatment group [DTG] 2);
    - pMMR patients with stage III/IV unresectable EC, treated with durvalumab + PC + olaparib (DTG 4);

[14] This information has been redacted at the sponsor's request, as it was not part of the PBAC's decision making for this submission.

  - pMMR patients with stage I, II or III EC with recurrence, treated with durvalumab + PC (DTG 5); and
  - pMMR patients with stage III/IV unresectable EC, treated with durvalumab + PC (DTG 6).

  The PSCR acknowledged that the above subgroups were omitted and corrected the errors in a revised workbook.

- Cost offsets were not applied:
  - dMMR: While a reduction in the number of scripts of dostarlimab in dMMR EC patients was estimated, this was not estimated accurately, and the costs were not calculated nor included as offsets. The PSCR stated that the submission did not present the treatment cost-offsets (only the MBS offsets to account for the difference in administration) because the PBS listing of durvalumab would be cost neutral to Government if the PBAC accepts the CMA in the dMMR population. The cost-offsets for dostarlimab were included in the PSCR's revised financial estimates; and
  - pMMR: The submission appeared to have estimated the cost offsets associated with potential reduction in 2L pembrolizumab and lenvatinib use. However, the assumptions and inputs behind the estimation were not fully described (e.g. it was unclear what dosage assumptions were used) so could not be independently verified, and these offsets were not included by the submission in the overall financial estimates. The PSCR confirmed that these cost offsets were estimated based on a reduction in utilisation of pembrolizumab and lenvatinib in 2L pMMR EC should durvalumab and olaparib be PBS listed in the proposed pMMR population. The revised estimates provided with the PSCR incorporated cost offsets associated with reduced 2L pembrolizumab and lenvatinib use.
- [redacted] [15]
- [redacted]; [15]
- The duration of treatment for durvalumab was not consistent with the CMA (for dMMR) or the CUA (for pMMR):
  - dMMR: The submission's financial estimates assumed a treatment duration of 5 months for initiation and 18 months in the maintenance phase for dMMR patients. This corresponds to 7.22 doses for initiation (compared to 5.1 doses assumed in the CMA and a maximum of 6 cycles in the draft PI) and 19.5 doses for maintenance (compared to 18 doses assumed in the CMA), leading to an

[15] This information has been redacted at the sponsor's request, as it was not part of the PBAC's decision making for this submission.

overestimate of durvalumab usage in the dMMR population. This was amended in the PSCR to be consistent with the assumptions applied in the submission's CMA; and

- [redacted][16]

- Resource costs (distribution fee, diluent fee, preparation fee and dispensing fees) in the initiation phases of durvalumab were double counted, overestimating the financial impact; and
- MBS items were not accurately estimated:
  - In dMMR patients, an incremental difference of six injections compared to dostarlimab was assumed, which appeared to be based on the CMA rather than the treatment duration estimates in the submission's financial estimates. The PSCR acknowledged the differences in the treatment duration of durvalumab and dostarlimab in the dMMR population between the CMA and the financial estimates, due to the financial estimates applying a mean duration of 88.94 weeks to align with those accepted for dostarlimab (Table 18, dostarlimab PSD, November 2023 PBAC meeting);
  - pMMR: The administration costs for grandfathered patients were not included.

6.93 The submission adopted an epidemiological approach for both dMMR and pMMR. The data sources, parameters and assumptions used to estimate the financial impact of listing durvalumab and olaparib for 1L A/R EC are summarised in Table 28.

[16] This information has been redacted at the sponsor's request, as it was not part of the PBAC's decision making for this submission.

Table 28: Key inputs for financial estimates

Data	Value in the submission	Source	Comment (including revisions made in the PSCR)
Eligible population - dMMR + pMMR			
Incident EC patients	Yr 1: 3,464 Yr 2: 3,568 Yr 3: 3,675 Yr 4: 3,785 Yr 5: 3,898 Yr 6: 4,015	AIHW 2023 Cancer Data in Australia was used to obtain all age-specific rates of uterine cancer [a]. This rate was then multiplied by the Australian female population (ABS population – 3222.0 Series B) to calculate annual incidence until 2023, after which a 3% annual growth rate was applied. Then the application of 95% (proportion of uterine cancer reported as EC) to derive the projected incidence of EC (as reported by Cancer Australia).	The estimated EC incidence was consistent with the figures presented for dostarlimab. The average growth rate of 3% and 95% proportion of EC were consistent with the dostarlimab submission (Table 20, dostarlimab PSD, November 2023 PBAC meeting). The ABS dataset could not be independently verified during the evaluation. [b]
Distribution of disease	Proportion with Stage I-II disease: 82.0% Proportion with Stage III disease with curative intent: 8.0% Proportion with Stage III/IV unresectable disease: 10.0%	Table 20, dostarlimab PSD, November 2023 PBAC meeting Original source referenced: Surveillance, Epidemiology, and End Results (SEER) database and clinician feedback, accepted by PBAC in the PEM submission (Table 15, pembrolizumab PSD, March 2022 meeting).	The submission's financial estimates did not include the following: DTG 2: dMMR patients with Stage III/IV EC DTG 4: pMMR patients with stage III/IV EC, treated with durvalumab + olaparib DTG 5: pMMR patients with stage I, II or III recurrence treated with durvalumab DTG 6: pMMR patients with stage III/IV EC, treated with durvalumab These patients were included in the evaluation's corrected estimates and the PSCR revised estimates.
Proportion with first recurrence Stage I/II	13%	Table 20, dostarlimab PSD, November 2023 PBAC meeting	DUSC previously considered the 13% estimate of recurrence in Stage I/II EC may be reasonable (p5, dostarlimab DUSC advice, March 2022 meeting).
Proportion with first recurrence Stage III curative	30%	Table 20, dostarlimab PSD, November 2023 PBAC meeting	The PBAC considered a 30% recurrence rate for stage III patients would be appropriate, based on the 5 year failure-free survival in PORTEC3 of 70.9% (Table 20, dostarlimab PSD, November 2023 PBAC meeting).
Proportion with ECOG 0-1	80%	Table 20, dostarlimab PSD, November 2023 PBAC meeting	DUSC previously considered that 80% was overestimated and 70% may be a more reasonable estimate. (p6, dostarlimab DUSC advice, March 2022 meeting).
Proportion with dMMR / pMMR	27% / 73%	Table 20, dostarlimab PSD, November 2023 PBAC meeting	DUSC previously considered this proportion to be appropriate (p7, dostarlimab DUSC advice, March 2022 meeting). However, this was higher than the proportion of dMMR (20%) in DUO-E.

Data	Value in the submission	Source	Comment (including revisions made in the PSCR)
Treatment utilisation			
Grandfathered patients (pMMR)	[redacted] [1c]	Sponsor estimate.	The submission stated that this included [redacted] [1] pMMR patients from a patient access program but did not provide any further details.
Durvalumab market share of dMMR	50%	Sponsor Estimate.	The submission claimed that this was validated by Australian Clinical Advisory Board but provided no further details. The PBAC considered that this was overestimated in Years 1-3 (see paragraph 6.97).
Uptake rate of 1L immuno-therapy (dMMR and pMMR)	95%	Sponsor Estimate. The submission reported that this was validated by Australian Clinical Advisory Board.	The PBAC previously accepted an uptake rate of 95% for 2L immunotherapy in A/R EC (Table 15, pembrolizumab PSD, March 2022 meeting).
Durvalumab treatment duration - dMMR	Initial phase: 5.0 months (21.7 weeks, 7.2 doses Q3W)[d]; maintenance phase: 18 months (78 weeks, 19.5 doses Q4W) [e] Total 99.7 weeks	The submission claimed that treatment duration was consistent with the CMA	The duration of treatment in the financial estimates provided in the submission was longer than assumed in the CMA presented (87.3 weeks; 5.1 doses initiation and 18 doses maintenance). The PSCR stated that, in the revised estimates, dMMR patients were assumed to receive 3.5 months of induction and 16.6 months of maintenance durvalumab, consistent with the CMA.
Durvalumab treatment duration – pMMR	Initial phase: 5.0 months (21.7 weeks, 7.2 doses Q3W)[d]; maintenance phase 14.7 months (63.7 weeks, 15.9 doses Q4W) [e] Total 85.4 weeks	The submission claimed that treatment duration was consistent with the economic model	Despite the submission claiming that there were six doses in initial phase, the inputs into the submission's spreadsheet implied a treatment duration of 5 months, which the model converted to 7.2 doses. The source of maintenance treatment duration was unclear. In the economic evaluation presented by the submission, the average treatment durations (based on cost of durvalumab) was 4.5 months for initiation and 15.2 months for maintenance. The PSCR stated that pMMR patients were assumed to receive 4.5 months of induction and 15.2 months of maintenance durvalumab in the revised estimates.
Olaparib treatment duration (pMMR)	Initial phase: 5.0 months, maintenance phase 14.7 months [f]	The submission claimed that treatment duration was consistent with the economic model	As per the proposed regimen and as used in DUO-E, olaparib should only be used in the maintenance phase. This was amended during the evaluation. The PSCR stated that pMMR patients were assumed to receive 15.2 months of maintenance olaparib in the revised estimates.
[redacted] [17]	[redacted] [17]	[redacted] [17]	[redacted] [17]

[17] This information has been redacted at the sponsor's request, as it was not part of the PBAC's decision making for this submission.

Data	Value in the submission	Source	Comment (including revisions made in the PSCR)
Dostarlimab treatment duration (dMMR)	Initiation phase: 20.0 weeks (5.66 scripts) Maintenance phase: 68.94 weeks (11.16 scripts)	Table 18, dostarlimab PSD, November 2023 PBAC meeting	This treatment duration differed to the CMA (5.1 doses initiation and 12 doses continuing), which appeared to have been inappropriate and did not appear to have been corrected in the PSCR's revised estimates.
Costs			
Dostarlimab	For dMMR EC, a PBS listing for durvalumab (+ PC) would result in substitution of dostarlimab (+ PC). However, the submission did not include dostarlimab costs in the financial estimates.		Inappropriate. Offsets were not included in the financial estimates provided in the submission but were included in the PSCR's revised estimates.
Pembrolizumab and lenvatinib	The submission presented the estimated cost offsets from avoided 2L pembrolizumab + lenvatinib due to the use of 1L durvalumab.		These were not incorporated into the financial estimates and could not be verified. Cost offsets for pembrolizumab and lenvatinib were included in the PSCR revised estimates.
Infusion costs	$123.05	MBS item 13950	Consistent with the economic model and CMA.

Source: Tables 4.1, 4.2, 4.3,4.4,4.5, 4.6, 4.7, 4.8,4.10, 4.11, 4.12, 4.13, 4.14, 4.15, 4.16, 4.17, 4.21, 4.22 pp184- 196, 200 of the submission.
ABS = Australian Bureau of Statistics; AIHW = Australian Institute of Health and Welfare; dMMR = deficient mismatch repair; EC = endometrial cancer; EC = endometrial cancer; ECOG = Eastern Conference Oncology Group; PC = paclitaxel + carboplatin; pMMR = proficient mismatch repair; Q3W = every three weeks; Q4W = every four weeks
a Rates for 2024 to 2030 were set to equal 25.1, which was equal to the rate calculated from AIHW data for 2023.
b The submission's data corresponded to the ABS data for years 2012-2016 but was different from 2017 onwards.)
c All grandfathered patients were assumed to receive durvalumab and olaparib for 14.7 months (maintenance).
d Durvalumab initial dose of 1,120 mg (2 x 500 mg + 1 x 120 mg) given every 3 weeks for 6 cycles. Dose intensity assumed to be 100%.
e Durvalumab maintenance dose of 1,500 mg (3 x 500 mg) given every 4 weeks. Dose intensity assumed to be 100%.
f Olaparib dose of 600mg per day (4 tablets per day). Dose intensity assumed to be 100%.
The redacted values correspond to the following ranges:
1 <500

dMMR population

6.94 Table 29 presents the revised estimates for the dMMR population that were presented in the PSCR. These estimates include changes to the duration of therapy for durvalumab, and cost offsets associated with reduced dostarlimab use. These estimates have not been evaluated.

Table 29: Estimated use and financial implications for the dMMR population, as presented in the PSCR

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of initiating patients treated, dMMR	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Number of scripts (PBS + RPBS)						
Durvalumab dMMR, initial	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Durvalumab dMMR, maintenance	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2	[redacted]2
Estimated financial implications of durvalumab						
dMMR durvalumab (effective)	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
dMMR durvalumab (published)	[redacted]4	[redacted]5	[redacted]5	[redacted]5	[redacted]5	[redacted]5
Estimated cost offsets (published)						
Dostarlimab scripts	-[redacted]2	-[redacted]2	-[redacted]2	-[redacted]2	-[redacted]2	-[redacted]2
Cost to PBS/RPBS less copayments (published)	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6
Net costs (published)						
Net cost to PBS/RPBS	[redacted]3	[redacted]6	[redacted]6	[redacted]6	[redacted]6	[redacted]6
Net MBS impact	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3
Net cost to PBS/RPBS/MBS	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3	[redacted]3

Source: Attachment 4_revised UCM_dMMR and pMMR durvalumab and financial estimates_inc Pem_Len and updated DoT.xlsx provided with the PSCR

dMMR = deficient mismatch repair; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS= Repatriation Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

1 <5,000

2 500 to < 5,000

3 $0 to < $10 million

4 $10 million to < $20 million

5 $20 million to < $30 million

6 net cost saving

6.95 The PSCR estimated that the cost to the PBS/RPBS for the proposed listing of durvalumab at the proposed effective price was $0 to < $10 million in Year 1, increasing to $0 to < $10 million in Year 6, for a total cost over six years of $30 million to < $40 million. Including cost offsets for reduced use of dostarlimab, the PSCR estimated a net cost to the PBS/RPBS of $0 to < $10 million over the first 6 years of listing (noting the PSCR did not appear to have corrected the dostarlimab treatment duration, as outlined in Table 28).

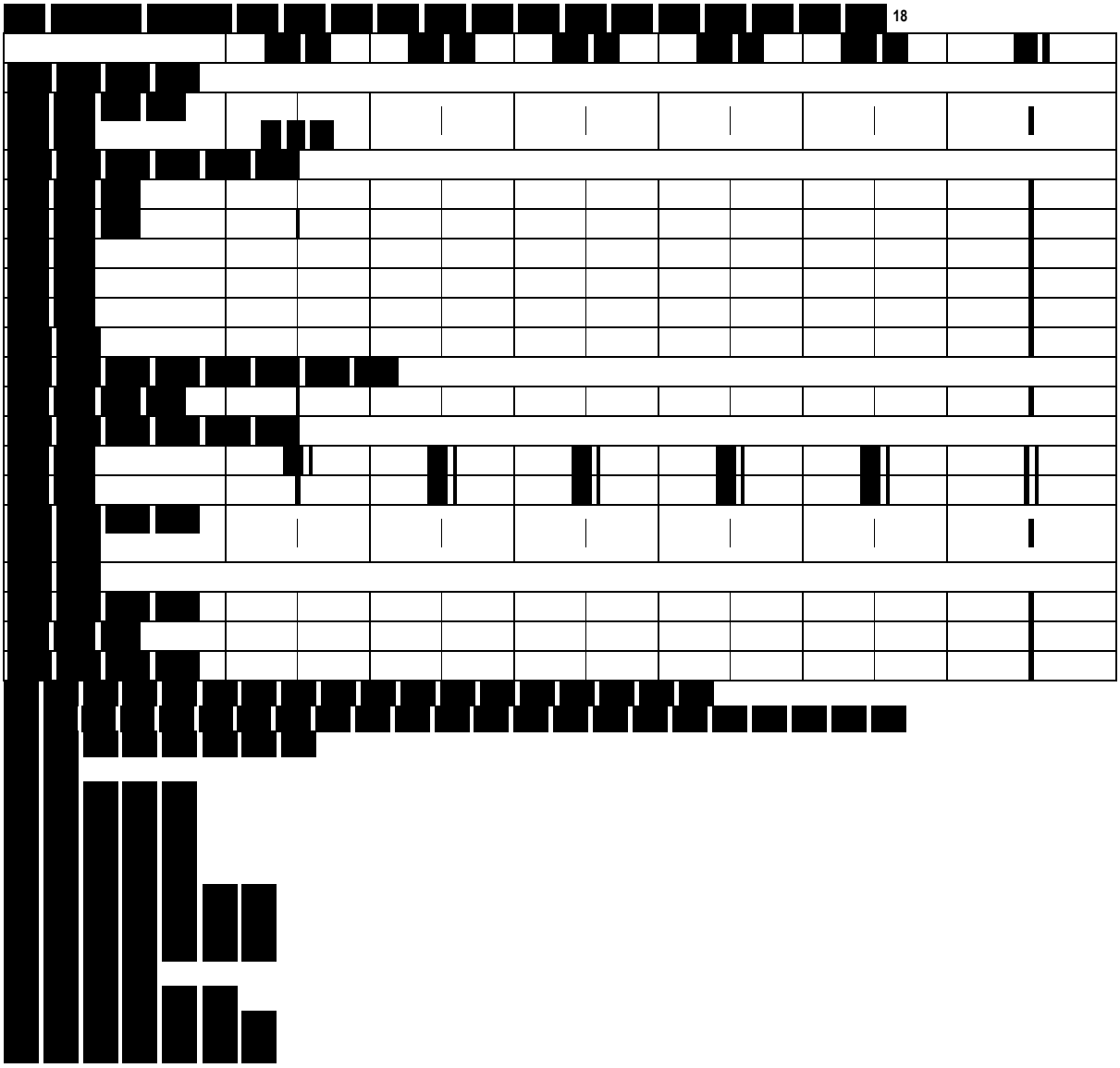
6.96 The pre-PBAC response stated that the only difference in cost between durvalumab and dostarlimab in the dMMR population would be due to the differences in the frequency of infusions between the two therapies.

6.97 The PBAC considered the durvalumab dosing assumptions applied in the financial estimates should be consistent with the assumptions included in the cost-minimisation approach accepted by the PBAC. The PBAC considered that the durvalumab market share in dMMR of 50% each year was overestimated in the first

three years. The PBAC considered a market share of 30% in Year 1, 40% in Year 2 and 50% in Year 3 and beyond would be more appropriate.

pMMR population

6.98 [redacted]. [18]



6.99 [redacted]. [18]

[18] This information has been redacted at the sponsor's request, as it was not part of the PBAC's decision making for this submission.

Quality Use of Medicines

6.100 The submission stated that the sponsor is planning education activities through their medical science liaisons to ensure appropriate and best practice with respect to prescribing. Additionally, the sponsor will work collaboratively with healthcare professionals to ensure that durvalumab and olaparib are used appropriately and in line with the available clinical evidence and TGA restriction.

Financial Management – Risk Sharing Arrangements

6.101 The submission stated that the sponsor is aware there is an existing RSA which includes the 1L dMMR population for whom dostarlimab is currently PBS listed and also the 2L population who are eligible to receive pembrolizumab plus lenvatinib. With respect to the pMMR population, there is currently no RSA in place that includes utilisation in the 1L treatment setting.

6.102 For context, paragraph 7.11 of the dostarlimab Public Summary Document, November 2023 PBAC meeting states: "The PBAC considered that shared financial caps with 2L PEM+LEN would be appropriate, given the substantial overlap in patient populations and because the cost-effectiveness for dostarlimab relies on cost offsets for 2L PEM+LEN. The PBAC considered that the caps should be increased to account for additional patients treated 1L dostarlimab, with offsets for 2L PEM+LEN."

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

7 PBAC Outcome

Deficient mismatch repair (dMMR) endometrial cancer

7.1 The PBAC recommended the listing of durvalumab, in combination with platinum-based chemotherapy (paclitaxel + carboplatin, PC), for the treatment of deficient mismatch repair (dMMR) endometrial cancer (EC), on the basis that it should be available only under special arrangements under Section 100 (Efficient Funding of Chemotherapy). The PBAC accepted that durvalumab was non-inferior in terms of efficacy and safety compared with dostarlimab + PC. The PBAC considered that the cost minimisation approach (CMA) and financial impact estimates presented were generally reasonable and advised that durvalumab should join the existing risk sharing arrangement (RSA) for this condition.

7.2 The PBAC noted the comments from Rare Cancers Australia and Medical Oncology Group of Australia (MOGA) expressing their support for the submission.

7.3 The PBAC noted that the TGA Delegate in their preliminary view, was inclined to approve the registration of durvalumab for use in combination with PC as a first-line treatment for adult patients with advanced or recurrent dMMR endometrial cancer.

7.4 The PBAC considered that the proposed place in therapy, as an alternative to dostarlimab + PC, was appropriate. The PBAC considered that dostarlimab + PC was the appropriate comparator.

7.5 The PBAC noted that the submission was based on the dMMR subgroup of the DUO-E trial, which compared durvalumab + PC to PC alone and indirect treatment comparisons with dostarlimab + PC (data was presented from the RUBY trial).

7.6 Compared to PC alone, the PBAC noted that durvalumab + PC in dMMR EC patients was associated with a statistically significant benefit in terms of progression free survival (PFS; HR = 0.42; 95% CI: 0.22, 0.80). The PBAC noted that the data for overall survival (OS) were immature in this population, but that the OS benefit appeared to support the use of durvalumab + PC over PC alone (OS; HR = 0.34; 95% CI: 0.13, 0.79). The PBAC considered that durvalumab + PC was superior to PC alone in terms of effectiveness and inferior in terms of safety.

7.7 The PBAC noted that the submission presented three ITCs using data from the DUO-E and RUBY trials, with PC as the common comparator: (i) unadjusted ITC including dMMR EC patients from DUO-E and dMMR and/or MSI-H patients from RUBY; (ii) unadjusted ITC including dMMR and/or MSI-H patients from both DUO-E and RUBY; and (iii) matching-adjusted indirect comparison (MAIC) adjusted for differences in baseline characteristics. The PBAC noted that none of the ITCs demonstrated a significant difference between durvalumab + PC and dostarlimab + PC in terms of PFS or OS (see Table 12).

7.8 The PBAC noted that there were issues with the ITCs, including differences in PFS response in the common comparator arm and small sample sizes in the subgroups

which increased the risk of bias, particularly in the MAIC. However, overall, the PBAC considered that the claim that durvalumab + PC was non-inferior in terms of efficacy compared to dostarlimab + PC in patients with dMMR EC was acceptable, noting the limitations of the ITCs.

7.9 In terms of safety, the PBAC considered that although the data were difficult to interpret due to the small sample sizes and wide confidence intervals, durvalumab + PC was likely to be non-inferior to dostarlimab + PC, particularly given the similar mechanism of action of durvalumab and dostarlimab.

7.10 The PBAC noted that the submission presented a CMA which assumed the same average duration of therapy for durvalumab and dostarlimab. The PBAC considered that this was reasonable in this particular case given the claim of non-inferior efficacy and safety, the similar results across the ITCs and the same maximum duration of therapy for the two therapies. The PBAC considered that the equi-effective doses were:

Durvalumab: 5.1 infusions of induction (1,120 mg per infusion) + 18.0 infusions of maintenance (1,500 mg per infusion), i.e. 32,712 mg =

Dostarlimab: 5.1 infusions of induction (500 mg per infusion) + 12.0 infusions of maintenance (1,000 mg per infusion), i.e. 14,550 mg

7.11 The PBAC noted that intravenous administration costs were incorporated into the CMA due to different frequency of dosing of durvalumab and dostarlimab and considered that this was reasonable.

7.12 The PBAC considered that the PSCR's proposed utilisation estimates for durvalumab in dMMR patients were generally reasonable, noting that the assumed 50% market share of durvalumab was overestimated in the first years of listing (see paragraph 6.97). The PBAC noted that when the effective cost minimised prices of durvalumab and dostarlimab were used, the listing of durvalumab resulted in a small cost saving to the PBS/RPBS due to the inclusion of MBS administration costs in the CMA.

7.13 The PBAC advised that it was appropriate for durvalumab to be added to the existing RSA for dostarlimab, pembrolizumab and lenvatinib for EC with no increase to the expenditure caps.

7.14 The PBAC considered that the restriction for durvalumab should align with the current listing for dostarlimab. The PBAC advised that a criterion stating that 'Patient must not be undergoing continuing PBS-subsidised treatment where this benefit is extending treatment beyond 36 cumulative months from the first administered dose, once in a lifetime' should be included in the durvalumab continuing restriction.

7.15 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because durvalumab is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over dostarlimab, or not expected to address a high and urgent unmet clinical need given the presence of alternative therapies, the criteria prescribed by the *National Health*

(Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022 for Pricing Pathway A were not met.

7.16 The PBAC advised that durvalumab for dMMR EC is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended for dMMR endometrial cancer

Proficient mismatch repair (pMMR) endometrial cancer

7.17 The PBAC deferred making a recommendation for durvalumab, in combination with olaparib plus platinum-based chemotherapy, for the treatment of proficient mismatch repair (pMMR) endometrial cancer (EC).

7.18 The PBAC noted that 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.

7.19 The PBAC, noting that durvalumab and olaparib would be considered at a future Advisory Committee on Medicines meeting, advised that consideration of durvalumab + olaparib + PC for pMMR EC would be deferred until TGA registration for the indication was confirmed.

Outcome:
Deferred

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT **Form**	**PBS item code**	**Max. Amount**	**№. of Rpts**
DURVALUMAB Injection	NEW (Public) NEW (Private)	1120 mg	5
Available brands			
Imfinzi (durvalumab 120 mg/2.4 mL injection, 2.4 mL vial)			
Imfinzi (durvalumab 500 mg/10 mL injection, 10 mL vial)			
Restriction Summary [new] / Treatment of Concept: [new]			
	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals		
	Prescriber type: ☒Medical Practitioners		
	Restriction type: ☒Authority Required (STREAMLINED) [new code]		
	Administrative Advice: No increase in the maximum amount or number of units may be authorised.		
	Administrative Advice: No increase in the maximum number of repeats may be authorised.		
	Administrative Advice: Special Pricing Arrangements apply.		
	Episodicity: Not Applicable		
	Severity: Advanced, metastatic or recurrent		
	Condition: Endometrial carcinoma		

	Indication: Advanced, metastatic or recurrent endometrial carcinoma
	Treatment Phase: Initial treatment covering the first 6 treatment cycles
	Clinical criteria:
	Patient must have deficient mismatch repair (dMMR) endometrial cancer, as determined by immunohistochemistry test
	AND
	Clinical criteria:
	The condition must be unsuitable for at least one of the following: (i) curative surgical resection, (ii) curative radiotherapy
	AND
	Clinical criteria:
	The treatment must be initiated in combination with platinum-containing chemotherapy
	AND
	Clinical criteria:
	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
	Clinical criteria:
	Patient must not have received prior treatment with a programmed cell death-1 (PD-1) or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition
	AND
	Clinical criteria:
	Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status no higher than 1 prior to treatment initiation
	Prescribing Instructions: Retain all pathology imaging and investigative test results in the patient's medical records.

MEDICINAL PRODUCT **Form**	**PBS item code**	**Max. Amount**	**№. of Rpts**
DURVALUMAB	NEW (Public) NEW (Private)	1500 mg	5
Available brands			
Imfinzi durvalumab 120 mg/2.4 mL injection, 2.4 mL vial			
Imfinzi durvalumab 500 mg/10 mL injection, 10 mL vial			
Restriction Summary [new] / Treatment of Concept: [new]			
	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals		
	Prescriber type: ☒Medical Practitioners		
	Restriction type: ☒Authority Required (STREAMLINED) [new code]		
	Administrative Advice: No increase in the maximum amount or number of units may be authorised		
	Administrative Advice: No increase in the maximum number of repeats may be authorised.		
	Administrative Advice: Special Pricing Arrangements apply.		
	Indication: Advanced, metastatic or recurrent endometrial carcinoma		
	Treatment Phase: Continuing Treatment		
	Clinical criteria:		

	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition
	AND
	Treatment criteria:
	Patient must not be undergoing continuing PBS-subsidised treatment where this benefit is extending treatment beyond 36 cumulative months from the first administered dose, once in a lifetime.
	Prescribing Instructions: Retain all pathology imaging and investigative test results in the patient's medical records.
	Prescribing Instruction: Patients with a body weight of 30 kg or less during continuing treatment must receive weight-based dosing, equivalent to durvalumab 20 mg/kg, until weight is greater than 30 kg

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

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

The sponsor had no comment.