

5.04 DOSTARLIMAB, Solution concentrate for I.V. infusion 500 mg in 10 mL, Jemperli[®], GLAXOSMITHKLINE AUSTRALIA PTY LTD.

1 Purpose of submission

- 1.1 The category 2 submission requested a Section 100 Efficient Funding of Chemotherapy Program, Authority Required (streamlined) listing for use in combination with platinum-containing chemotherapy (PBC) for the treatment of primary advanced or first recurrent (A/R) endometrial cancer (EC).
- 1.2 Listing of dostarlimab (DOS) was requested on the basis of a cost-effectiveness analysis versus chemotherapy alone (carboplatin-paclitaxel (CP)).

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

Component	Description
Population	Population 1 (dMMR; proposed TGA indication): Patients with primary advanced or first recurrent dMMR endometrial cancer that has a low potential for cure by radiation therapy or surgery alone or in combination. Population 2 (all-comers; aligned with trial design): Patients with primary advanced or first recurrent endometrial cancer that has a low potential for cure by radiation therapy or surgery alone or in combination.
Intervention	First six cycles: dostarlimab (500 mg) + carboplatin-paclitaxel every 3 weeks Subsequent cycles: dostarlimab (1,000 mg) every 6 weeks for up to 3 years or until disease progression, whichever occurs first.
Comparator	Carboplatin (AUC 5 mg/mL/min) and paclitaxel (175 mg/m ²) every 3 weeks for 6 cycles, followed by second-line pembrolizumab plus lenvatinib in a proportion of patients.
Outcomes	Overall survival, progression-free survival, objective response rate, duration of response, safety.
Clinical claim	Population 1 (dMMR; proposed TGA indication): In patients with primary advanced or first recurrent dMMR endometrial cancer, dostarlimab plus platinum-containing chemotherapy is superior in terms of efficacy compared to platinum-containing chemotherapy alone, with an inferior but manageable safety profile. Population 2 (all-comers; aligned with trial design): In patients with primary advanced or first recurrent endometrial cancer, dostarlimab plus platinum-containing chemotherapy is superior in terms of efficacy compared to platinum-containing chemotherapy alone, with an inferior but manageable safety profile.

Source: Table 2, p20 of the submission.

AUC = area under curve; dMMR = mismatch repair deficient; TGA = Therapeutic Goods Administration

- 1.3 Listing was sought for either of two potential populations:
- Population 1: patients with DNA mismatch repair deficient (dMMR); and
 - Population 2: ‘all-comers’/intention to treat (ITT) population i.e. regardless of mismatch repair (MMR) status.
- 1.4 While the submission listed the intervention as “dostarlimab (500 mg) + platinum-containing chemotherapy followed by dostarlimab (1,000 mg)”, in the pivotal RUBY

trial and in the economic and financial model presented by the submission, only CP was used.

- 1.5 The submission noted for pembrolizumab (PEM) in combination with lenvatinib (LEN; collectively PEM+LEN) for second line (2L) treatment of A/R EC, that while the TGA approved indication restricts utilisation to patients that are not high microsatellite instability (MSI-H) or dMMR, the PBAC recommended the listing PEM+LEN for 2L A/R EC regardless of biomarker status (paragraph 7.1, pembrolizumab Public Summary Document [PSD], March 2022 PBAC meeting). The submission therefore presented both populations for PBAC consideration.
- 1.6 However, the circumstances regarding the recommendation of PEM+LEN are not directly comparable to DOS+CP given:
 - PEM has been TGA approved for both dMMR and pMMR EC that has progressed following prior treatment; PEM monotherapy for non-colorectal tumours (i.e. EC) that are MSI-H or dMMR, and PEM+LEN for EC that is not MSI-H or dMMR, whereas patients with dMMR/MSI-H EC represent the only subgroup for whom TGA approval was sought for DOS; and
 - Tests for interaction around PFS conducted during the evaluation suggested that MMR status was a treatment effect modifier in RUBY, the key clinical trial. In comparison, the PBAC noted that even though the TGA had not specifically registered combination therapy with PEM+LEN in the dMMR EC population, in the key trial (KN755) “superior efficacy of combination therapy was observed in the ITT population comprising both dMMR and pMMR patients with no evidence that biomarker status was a treatment effect modifier” (paragraph 7.5, pembrolizumab PSD, March 2022 PBAC meeting). A comparison of results from DOS+CP (1L) with PEM+LEN (2L) is presented in Table 7.

2 Background

Registration status

- 2.1 The submission was made under the TGA/PBAC Parallel Process. The TGA application is being evaluated via Project Orbis. The TGA Delegate’s Overview was available at the time of PBAC consideration. The Delegate was supportive of approving the registration of dostarlimab for the following indication:

“JEMPERLI is indicated in combination with carboplatin and paclitaxel for the treatment of adult patients with primary advanced or recurrent mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer”.
- 2.2 The all-comers population (Population 2), which included pMMR/MSS and MMR status unknown EC, was broader than the proposed TGA indication which specified the biomarker status of dMMR/MSI-H. The Pre-Sub-Committee Response (PSCR)

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indicated that the sponsor projects that an application for the all-comers population in RUBY Part 1 will be submitted to the FDA |||||.

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

3 Requested listing

MEDICINAL PRODUCT Form	Dispensed Price Max Amt	Max. Amount	No. of Rpts
Dostarlimab (initial)	public published price private published price public effective price^a private effective price^a	500 mg	5
Dostarlimab (continuing)	public published price private published price public effective price^a private effective price^a	1000 mg	3
Available brands			
Jemperli (dostarlimab 500 mg / 10 mL injection, 1 x 10 mL vial)			

^a The effective prices were updated during the evaluation to current values (August 2023).

Requested restriction: dMMR (Population 1)

Category / Program: Section 100 – Efficient Funding of Chemotherapy
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Severity: Primary advanced or first recurrent
Condition: Endometrial cancer
Indication: Primary advanced or first recurrent endometrial cancer
Treatment Phase: Initial
<p>Clinical criteria: The condition must be unsuitable for (i) curative surgical resection, and/or (ii) curative radiotherapy, AND</p> <p>The condition must be, at treatment initiation with this drug, either: (i) untreated with systemic therapy, or (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,</p> <p>AND</p> <p>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,</p> <p>AND</p> <p>Patient must have an ECOG performance status of 0 or 1,</p> <p>AND</p> <p>The treatment must be in combination with platinum-containing chemotherapy, unless contraindicated or not tolerated,</p> <p>AND</p> <p>Patient must have deficient mismatch repair (dMMR) endometrial cancer, as determined by immunohistochemistry test.</p>
<p>Administrative Advice: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>
Treatment Phase: Continuing
<p>Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND</p>

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<p>Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition, AND The treatment must not exceed a maximum total of 36 months in a lifetime for this condition.</p>
<p>Administrative Advice: No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.</p>

Requested restriction: grandfathered patients

<p>Category / Program: Section 100 – Efficient Funding of Chemotherapy</p>
<p>Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners</p>
<p>Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)</p>
<p>Severity: Primary advanced or first recurrent</p>
<p>Condition: Endometrial cancer</p>
<p>Indication: Primary advanced or first recurrent endometrial cancer</p>
<p>Treatment Phase: Transitioning from non-PBS to PBS subsidised treatment – ‘Grandfather’ treatment</p>
<p>Clinical criteria: Patient must have received non-PBS subsidised treatment with this drug for this condition prior to [PBS listing date], AND The condition must be, prior to initiation of non-PBS-subsidised treatment with this drug, unsuitable for (i) curative surgical resection, and/or (ii) curative radiotherapy, AND The condition must be, prior to initiation of non-PBS-subsidised treatment with this drug, either: (i) untreated with systemic therapy, or (ii) treated with neoadjuvant/adjuvant systemic therapy, but the cancer has recurred or progressed after more than 6 months from the last dose of systemic therapy, AND Patient must have an ECOG performance status of 0 or 1 prior to initiation of non-PBS-subsidised treatment with this drug for this condition, AND The treatment must be, at initiation of non-PBS-subsidised treatment with this drug, used in combination with platinum-containing chemotherapy for the first six cycles, unless contraindicated or not tolerated, AND Patient must have deficient mismatch repair (dMMR) endometrial cancer, as determined by immunohistochemistry test, AND Patient must not have developed disease progression while receiving non-PBS-subsidised treatment with this drug for this condition, AND The treatment must not exceed a maximum total of 36 months in a lifetime for this condition.</p>
<p>Administrative Advice: No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply</p>

- 3.1 The submission proposed a special pricing arrangement (SPA) for DOS, with the proposed published and effective ex-manufacturer price (EMP) per 500 mg vial as \$| and \$| respectively. This was reduced to \$| per 500 mg vial in the Pre-PBAC response.
- 3.2 The requested restrictions for the all-comers population were identical to those proposed for the dMMR population, with the exception of the clinical criterion that the “patient must have deficient mismatch repair (dMMR) endometrial cancer, as determined by immunohistochemistry test”.
- 3.3 The submission requested a grandfathering listing for < 500 patients who were anticipated to be treated via an access program. The sponsor stated that all of these patients would have dMMR EC.

- 3.4 The PBAC noted that in the RUBY trial patients were treated with dostarlimab in combination with carboplatin and paclitaxel, and the TGA Delegate’s proposed indication also specified carboplatin and paclitaxel, whereas the proposed restrictions did not specify the platinum-containing chemotherapy regimen. The PBAC considered this difference was reasonable and unlikely to impact on the patient population or clinical outcomes.
- 3.5 The PBAC noted that use of DOS monotherapy where platinum-containing chemotherapy was contraindicated or not tolerated was broader than the proposed TGA indication and treatment in the RUBY trial. The PBAC considered that intolerance/contraindication should be removed and the clinical criterion should be amended to “The treatment must be initiated in combination with platinum-containing chemotherapy”.
- 3.6 The proposed criteria were otherwise consistent with the patient population and treatment interventions in the RUBY trial and the PBAC considered they were appropriate.

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 Endometrial cancers may be classified based on the MMR status, as normal (pMMR) or dMMR tumours. EC is associated with dMMR in up to 33% of cases (Morona 2020; Scarpa 2016), though the PBAC and DUSC previously considered 27% to be an appropriate estimate for the prevalence of dMMR in A/R EC (paragraph 7.11, dostarlimab 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-H is the observable characteristic (phenotype) displayed when errors occur in the DNA MMR system (Luchini, 2019).
- 4.3 The submission noted that immunohistochemistry (IHC) MMR testing is now routine clinical and pathology practice in EC, and so the basis for requiring a co-dependent submission was not met.
- 4.4 DOS+CP is intended for use in patients with A/R EC who have not been previously treated with systemic therapy, or if treated with neoadjuvant/adjunct systemic therapy, the cancer has recurred or progressed after more than 6 months from the last dose of systemic therapy.

- 4.5 DOS is a humanised, monoclonal antibody of the immunoglobulin G4 isotype that binds with high affinity and specificity to PD-1, resulting in inhibition of binding to PD-L1 and PD-L2. This blocks PD-1 pathway-mediated immune inhibition, resulting in immune reactivation, including reactivation of the anti-tumour immune response. The submission claimed that the combination of immune checkpoint inhibitors with chemotherapy can further synergise to enhance the anti-tumour response.

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

5 Comparator

- 5.1 The submission nominated CP as the main comparator. This was reasonable, however CP may not be the only relevant comparator.
- 5.2 At its March 2022 and March 2023 meetings, the PBAC recommended the listing of PEM+LEN for the treatment of 2L A/R EC regardless of biomarker status. Given PEM+LEN was listed on the PBS from 1 June 2023 with a requirement that the condition must be untreated with a PD-(L)1 inhibitor, the submission acknowledged that 1L DOS + CP followed by 2L chemotherapy would replace 1L platinum-containing chemotherapy followed by 2L PEM+LEN in a proportion of patients. 2L immunotherapy was used by patients enrolled in RUBY and was considered in the economic analysis and financial estimates of the submission. A comparison of results from RUBY (1L DOS+CP compared to 1L CP alone) and KN775 (2L PEM+LEN compared to the physician's choice of 2L doxorubicin or paclitaxel alone) is presented in Table 7 below.
- 5.3 A near market comparator, PEM in combination with CP (PEM+CP) was identified during the evaluation, with an ongoing phase 3 trial (NCT03914612) in which patients with advanced-stage, metastatic, or recurrent EC were assigned to receive 1L PEM or placebo (PBO) along with combination therapy with CP. Results from an early interim analysis from NCT03914612 were extracted during the evaluation and are presented in Table 7 below. The PBAC noted that phase 3 trials in 1L treatment of advanced, metastatic or recurrent EC are also underway for atezolizumab ± chemotherapy (ATTEND), durvalumab ± chemotherapy ± olaparib (DUO-E) and PEM + LEN (LEAP), with results recently published for DUO-E.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician noted that there are approximately 7,000 new cases of endometrial cancer per year and incidence and rates of death are continuing to rise. The clinician noted that whilst around 80% of patients with early endometrial cancer are cured, there are higher death rates in disadvantaged populations and in indigenous women, and there remains a high unmet

need for effective treatments. The clinician noted that results of the RUBY trial show that dostarlimab will benefit women with endometrial cancer and rapid access to treatment would be valuable. With a larger benefit in the dMMR arm, but clinically meaningful result in the ITT population, the clinician noted that there is an argument for providing access for both groups.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from Rare Cancers Australia via the Consumer Comments facility on the PBS website. The comments noted that patients living with endometrial cancer currently undergo a range of examinations, medical appointments and fertility treatments, and patients who self-fund treatment experience an added financial burden. The comments noted the high unmet medical need for effective and tolerable treatment options in this setting to provide a clinically relevant improvement in efficacy and a reduction of toxicity over that of chemotherapy and other treatment options.
- 6.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the dostarlimab submission, categorising it as one of the therapies of “highest priority for PBS listing” on the basis of the RUBY trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for dostarlimab in combination with platinum-containing chemotherapy, 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-containing chemotherapy alone.

Clinical trial

- 6.4 The submission was based on one head-to-head trial comparing DOS+CP to CP alone (PBO+CP): RUBY (N=494). A claim of superiority for both the dMMR cohort (Population 1) and all-comers (Population 2) was made on the outcomes of OS and PFS.
- 6.5 Details of the trial presented in the submission are provided in Table 2.

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]

Table 2: Trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
RUBY	A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) plus Carboplatin-paclitaxel versus Placebo plus Carboplatin-paclitaxel in Patients with Recurrent or Primary Advanced Endometrial Cancer (RUBY)	Clinical study report. 7 March 2023
	A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) plus Carboplatin-paclitaxel versus Placebo plus Carboplatin-paclitaxel in Patients with Recurrent or Primary Advanced Endometrial Cancer (RUBY)	Clinical study protocol v4.0. 31 March 2022
	Mirza, M. R., Chase, D. M., Slomovitz, B. M. et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer https://doi.org/10.1056/NEJMoa2216334	<i>N Engl J Med</i> 2023; 388: 2145-2158
	Hanker, L., Mirza, M. R., Coleman, R. L. et al. ENGOT-EN6/GOG-3031/NSGO-RUBY: A phase 3, randomized, double-blind, multicenter study of dostarlimab + carboplatin-paclitaxel versus placebo + carboplatin-paclitaxel in recurrent or primary advanced endometrial cancer (EC).	Conference abstract <i>Oncology Research and Treatment</i> 2020, 43:122
	Mirza, M. R., Coleman, R. L., Hanker, L. C. et al. ENGOT-EN6/NSGO-RUBY: A phase III, randomized, double-blind, multicenter study of dostarlimab + carboplatin-paclitaxel versus placebo + carboplatin-paclitaxel in recurrent or primary advanced endometrial cancer (EC).	Conference abstract <i>Journal of Clinical Oncology</i> 2020, 38(15).
	Mirza, M. R., Coleman, R. L., Hanker, L. et al. ENGOT-EN6/GOG-3031/nsgo-ruby: A phase 3, randomised, double-blind, multicenter study of dostarlimab + carboplatin-paclitaxel versus placebo + carboplatin-paclitaxel in recurrent or primary advanced endometrial cancer (EC).	Conference abstract <i>International Journal of Gynecological Cancer</i> 2020, 30:A112-A113.
	NCT03981796. A Study of Dostarlimab (TSR-042) Plus Carboplatin-paclitaxel Versus Placebo Plus Carboplatin-paclitaxel in Patients With Recurrent or Primary Advanced Endometrial Cancer.	NCT record 2019
	EUCTR2019-001576-11-FI. A study to determine whether the addition of Dostarlimab (TSR-042) delays recurrence of advanced endometrial cancer.	EUCTR record 2019
EUCTR2019-001576-11-HU. A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) plus Carboplatin-paclitaxel versus Placebo Plus Carboplatin-paclitaxel in Patients with Recurrent or Primary Advanced Endometrial Cancer (RUBY)—RUBY.	EUCTR record 2019	

Source: Table 14, p43 of the submission.

6.6 RUBY is an ongoing phase 3 trial consisting of two parts. Part 1 aimed to evaluate the efficacy and safety of treatment with DOS+CP and PBO+CP in patients with A/R EC. In part 1, eligible patients were randomised in a 1:1 ratio to the following treatment arms:

- Arm 1: DOS intravenous (IV) in combination with CP every 3 weeks (Q3W) for 6 cycles; followed by DOS IV every 6 weeks (Q6W), referred to as the DOS+CP arm; or
- Arm 2: PBO IV in combination with CP Q3W for 6 cycles; followed by PBO IV Q6W, referred to as the PBO+CP arm.

Part 2 aimed to evaluate the efficacy and safety of treatment with DOS+CP followed by DOS plus niraparib (Arm 3) versus treatment with PBO+CP followed by double PBO (Arm 4) in patients with A/R EC. Only part 1 of RUBY was included in the submission, as part 2 included treatment with niraparib, it was not considered relevant.

- 6.7 The key features of the direct randomised trial are summarised in Table 3. RUBY trial data presented in the submission were from the first interim analysis (data cut off 28 September 2022).

Table 3: Key features of the included evidence

Trial (population)	N	Design/ median follow up	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
DOS+CP vs PBO+CP						
RUBY (all-comers)	494	R, DB, MC 25.4 mths	Low	1L A/R EC	PFS by IA, OS ^b	Proportion progression free, overall survival, utilities.
RUBY (dMMR/MSI-H)	118	R, DB, MC 24.8 mths	Low ^a		PFS by IA ^a , OS ^c	
RUBY (pMMR/MSS)	376	R, DB, MC 25.7 mths	High		PFS by IA, OS ^c	

Source: Constructed during the evaluation using information sourced from Table 19&24, pp52,59-60 of the submission,

DB = double blind; dMMR = mismatch repair deficient; IA = Investigator assessment; MC = multi-centre; OS = overall survival; PFS = progression-free survival; pMMR = mismatch repair proficient; R = randomised.

^a PFS in dMMR was part of the statistical analysis plan as hypothesis 1 therefore being a subgroup, risk of bias was lower than in pMMR but higher than in all-comers.

^b PFS and OS in all-comers were part of the statistical analysis plan as hypotheses 2 and 3

^c OS in dMMR, PFS and OS in pMMR were not part of the statistical analysis plan and not formally tested

- 6.8 While it was reasonable to conclude a low risk of bias for the all-comers population, the requested dMMR population (Population 1) 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.
- 6.9 Randomisation in RUBY was stratified by three stratification factors: MMR/MSI status, prior external radiotherapy (yes or no) and disease status (recurrent, primary stage III or primary stage IV). However, some patients were incorrectly stratified at randomisation, with discrepancies between the values used to randomise patients with the source verified values in the electronic case report form (eCRF). In the base case, patients were analysed and presented according to the stratum assigned at randomisation for prior external radiotherapy and disease status, but actual MMR/MSI status from the source verified values in the eCRF was used.
- 6.10 Therefore, there was an imbalance in the number of patients between the two treatment arms with respect to MMR/MSI status in the subsets (n=22; 9 and 13 patients were miscategorised as pMMR/MSS and dMMR/MSI-H at randomisation, respectively). Paired sensitivity analyses using population classification based on the value entered at randomisation compared to population classification based on source verified value was performed. Results based on MMR/MSI status classification by value entered at randomisation were numerically less favourable for the DOS+CP arm (except for OS in the dMMR/MSI-H subgroup), compared to results based on classification by source verified value, however the differences were small and not expected to be meaningfully different.
- 6.11 The PBAC noted that just under half of the patients included in the RUBY trial had recurrent disease, a third had primary stage IV disease and the remainder had primary

stage III disease. Just over half of the patients in RUBY had endometrioid histologic type, though the trial included patients with a range of histologic types.

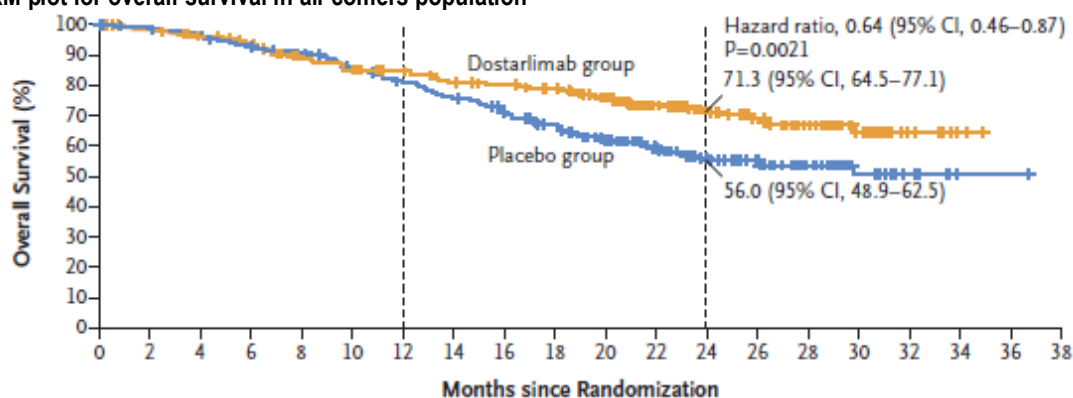
- 6.12 A substantial number of patients in RUBY received subsequent immunotherapy following progression. In the all-comers population, 38/115 (33%) and 86/163 (53%) of patients who received any follow-up anti-cancer therapy were treated with subsequent immunotherapy in the DOS+CP and PBO+CP arms, respectively. In the dMMR subgroup, of patients who received any follow up anticancer therapy, the number of patients who used subsequent immunotherapy was 8/15 (53%) and 25/38 (66%) in the DOS+CP and PBO+CP arms, respectively.
- 6.13 In RUBY, the graphical method was used for multiplicity control of multiple hypotheses (H1, H2 and H3) of primary end points, and family-wise one-sided type I error (alpha) was controlled at 0.025. An alpha level of 0.02 was initially allocated to hypotheses regarding PFS by investigator assessment (IA) and an alpha level of 0.005 was initially allocated to hypotheses regarding OS. Scheduling of the interim analysis data cut-off was driven by time from the commencement of the trial (~36 months), with the efficacy stopping boundaries adjusted to account for the actual number of events. For PFS, hypotheses were hierarchically tested in the dMMR/MSI-H population and then in the all-comers population; OS was tested only in the all-comers population. Based on the rejection of the null hypothesis for both H1 (PFS in dMMR/MSI-H) and H2 (PFS in all-comers) at the first interim analysis, the next interim analysis for H3 (OS in all-comers) is expected to occur ~48 months from the commencement of the trial or at ~69% information fraction (221 events). The sponsor did not provide any further information regarding when the next interim analysis is likely to be available.

Comparative effectiveness

Primary outcomes

- 6.14 Figure 1, Figure 2 and Figure 3 show the OS Kaplan-Meier (KM) results for the all-comers population, dMMR/MSI-H and pMMR/MSS cohorts respectively. Table 4 summarises the OS statistics across the all-comers population, and the dMMR/MSI-H and pMMR/MSS cohorts.

Figure 1: KM plot for overall survival in all-comers population



No. at Risk

Dostarlimab group	245	235	224	214	198	190	183	174	169	162	145	110	83	64	45	25	7	2	0	
Placebo group	249	242	237	226	219	203	189	177	162	147	125	88	65	48	33	15	6	1	1	0

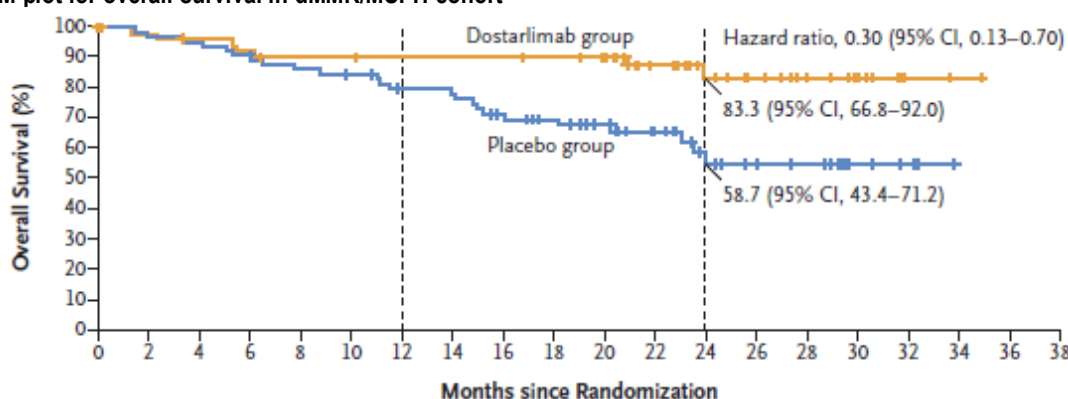
No. of Events

Dostarlimab group	0	3	8	15	25	33	35	42	44	47	53	57	60	62	64	65	65	65	65	
Placebo group	0	3	7	17	22	35	45	57	68	78	88	93	97	98	99	100	100	100	100	100

Source: Figure 7, p68 of the submission.

CI = confidence interval

Figure 2: KM plot for overall survival in dMMR/MSI-H cohort



No. at Risk

Dostarlimab group	53	50	48	46	44	44	43	43	43	42	41	29	20	16	12	8	2	1	0
Placebo group	65	63	62	59	55	53	48	47	41	37	32	25	16	12	10	5	3	0	

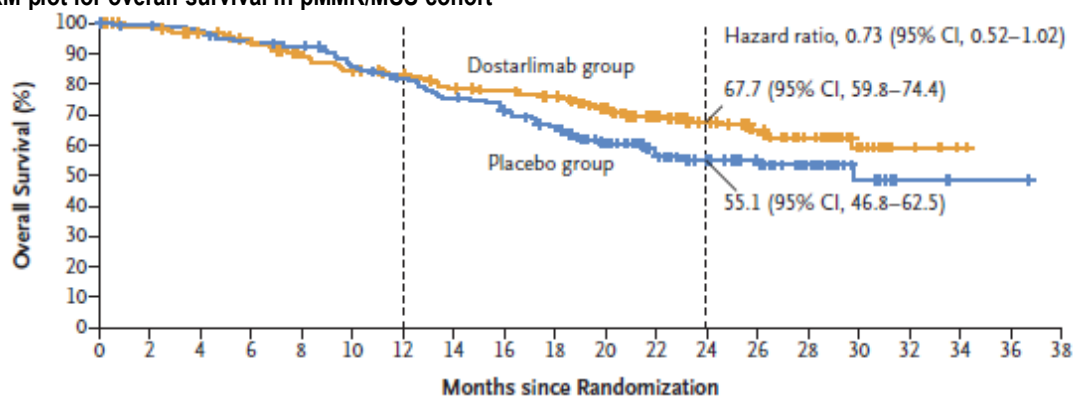
No. of Events

Dostarlimab group	0	1	2	4	5	5	5	5	5	5	5	6	7	7	7	7	7	7	7
Placebo group	0	2	3	6	9	10	13	14	18	19	20	21	23	24	24	24	24	24	24

Source: Figure 8, p68 of the submission.

CI = confidence interval

Figure 3: KM plot for overall survival in pMMR/MSS cohort



No. at Risk

Dostarlimab group	192	185	176	168	154	146	140	131	126	120	104	81	63	48	33	17	5	1	0	
Placebo group	184	179	175	167	164	150	141	130	121	110	93	63	49	36	23	10	3	1	1	0

No. of Events

Dostarlimab group	0	2	6	11	20	28	30	37	39	42	48	51	53	55	57	58	58	58	58	
Placebo group	0	1	4	11	13	25	32	43	50	59	68	72	74	74	75	76	76	76	76	76

Source: Figure 9, p69 of the submission.

CI = confidence interval

Table 4: KM analysis of overall survival in RUBY

OS	All-comers		dMMR/MSI-H		pMMR/MSS	
	DOS+CP (N=245)	PBO+CP (N=249)	DOS+CP (N=53)	PBO+CP (N=65)	DOS+CP (N=192)	PBO+CP (N=184)
Median FU, months	25.5	25.3	24.6	25.1	25.8	25.4
Events, n (%)	65 (26.5)	100 (40.2)	7 (13.2)	24 (36.9)	58 (30.2)	76 (41.3)
Censored, n (%)	180 (73.5)	149 (59.8)	46 (86.8)	41 (63.1)	134 (69.8)	108 (58.7)
Median OS, months (95% CI)	NR (NR, NR)	NR (23.2, NR)	NR (NR, NR)	NR (23.2, NR)	NR (29.8, NR)	29.8 (21.9, NR)
Hazard Ratio (95% CI)	0.64 (0.46, 0.87)		0.30 (0.13, 0.70)		0.73 (0.52, 1.02)	
p-value	0.0021		0.0016		0.0333	
Landmark survival estimates, probability (95% CI)						
12 months	84.6 (79.2, 88.7)	81.3 (75.7, 85.7)	90.1 (77.8, 95.7)	79.6 (67.5, 87.6)	83.1 (76.7, 87.9)	81.8 (75.3, 86.8)
18 months	79.0 (73.0, 83.8)	66.9 (60.4, 72.5)	90.1 (77.8, 95.7)	69.6 (56.5, 79.4)	75.8 (68.7, 81.5)	66.0 (58.4, 72.5)
24 months	71.3 (64.5, 77.1)	56.0 (48.9, 62.5)	83.3 (66.8, 92.0)	58.7 (43.4, 71.2)	67.7 (59.8, 74.4)	55.1 (46.8, 62.5)
30 months	64.7 (55.6, 72.3)	50.6 (41.0, 59.4)	83.3 (66.8, 92.0)	55.1 (39.1, 68.4)	59.1 (48.2, 68.4)	48.7 (36.5, 59.7)

Source: Table 30, p67 of the submission.

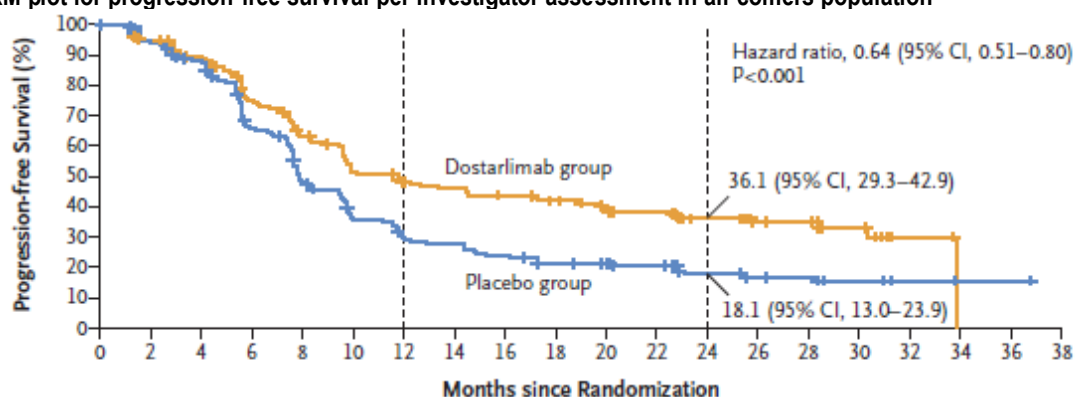
CI=confidence interval; CP=carboplatin-paclitaxel; dMMR=mismatch repair deficient; DOS=dostarlimab; FU=follow-up; pMMR=mismatch repair proficient; MSI-H=high microsatellite instability; MSS=microsatellite stable; NR=not reached; PBO=placebo; OS=overall survival

6.15 In the all-comers population (33% overall OS maturity), there was a trend in favour of the DOS+CP arm with a 36% reduction in deaths compared to the PBO+CP arm (HR=0.64; 95% CI 0.46, 0.87; median OS not reached for either arm). A separation of the KM survival curves from approximately 10 months was observed. However, the submission noted that the stratified log-rank test p-value (p=0.0021) was outside the

stopping boundary for declaring statistical significance ($p \leq 0.00177$) at the first interim analysis therefore statistically significant differences could not be claimed.

- 6.16 With an overall 26% OS maturity in the dMMR/MSI-H cohort, a 70% reduction in deaths was observed for patients enrolled in the DOS+CP arm of RUBY compared to patients enrolled in the PBO+CP arm (HR=0.30; 95% CI 0.13, 0.70; median OS not reached for either arm). OS in the dMMR/MSI-H population was not a pre-specified primary endpoint and no formal statistical test was performed; therefore, these results should be interpreted with caution. A separation of the KM survival curves from approximately 6 months was observed, driven by mortality in the control arm and a relative plateau in the DOS+CP arm.
- 6.17 In the pMMR/MSS cohort (36% overall OS maturity), there was a trend in favour of the DOS+CP arm, with a 27% reduction in deaths compared to PBO+CP (HR=0.73; 95% CI 0.52, 1.02; median OS was not reached for the DOS+CP arm versus 29.8 months for the PBO+CP arm). However, the upper bound of the 95% CI was greater than one, suggesting there may be no difference between the two treatment arms, and no formal statistical testing was performed for OS in the pMMR/MSS cohort. A separation of the KM survival curves from approximately 12 months was observed.
- 6.18 Figure 4, Figure 5 and Figure 6 show the PFS by IA KM results for the all-comers population, and the dMMR/MSI-H and pMMR/MSS cohorts respectively. Table 5 summarises the PFS statistics for the all-comers population, and the dMMR/MSI-H and pMMR/MSS cohorts.

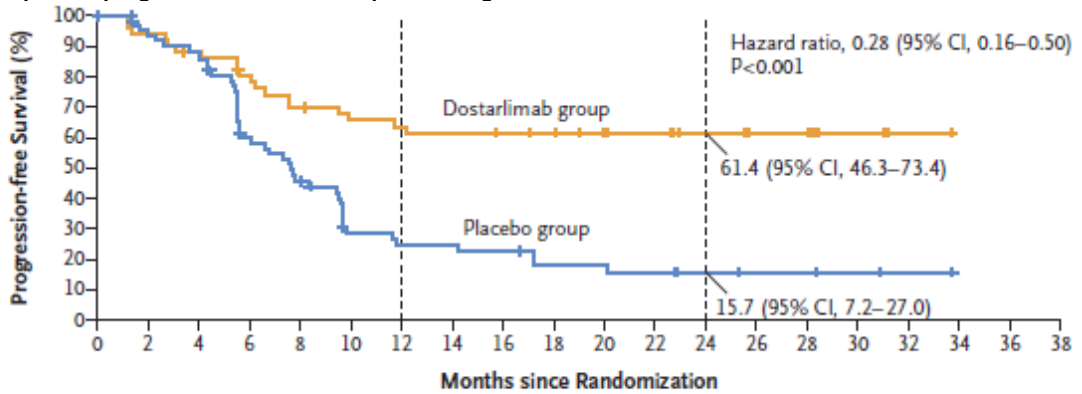
Figure 4: KM plot for progression-free survival per investigator assessment in all-comers population



No. at Risk	
Dostarlimab group	245 220 197 157 130 105 94 90 84 78 66 52 34 23 22 12 2 0
Placebo group	249 219 200 144 103 74 59 57 48 42 39 32 20 14 13 5 2 1 1 0
No. of Events	
Dostarlimab group	0 12 25 55 80 103 110 113 118 122 127 128 131 132 132 133 134 135
Placebo group	0 14 29 77 115 141 155 157 166 170 170 172 175 176 176 177 177 177 177

Source: Figure 10, p70 of the submission.
CI=confidence interval

Figure 5: KM plot for progression-free survival per investigator assessment in dMMR/MSI-H cohort



No. at Risk

Dostarlimab group	53	48	44	39	34	31	30	29	28	27	25	19	13	9	9	4	1	0
Placebo group	65	57	54	34	26	14	12	12	11	8	8	7	4	3	3	2	1	0

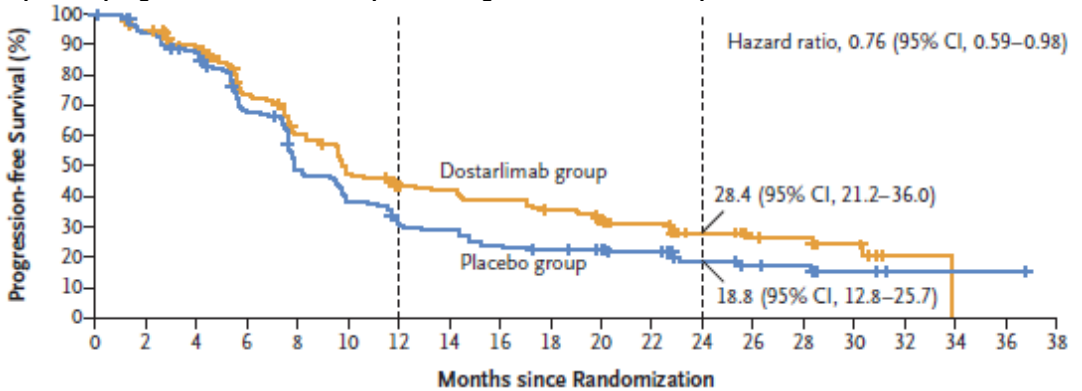
No. of Events

Dostarlimab group	0	3	6	10	15	17	18	19	19	19	19	19	19	19	19	19	19	19	
Placebo group	0	4	7	24	32	41	43	43	44	46	46	47	47	47	47	47	47	47	47

Source: Figure 11, p71 of the submission.

CI=confidence interval

Figure 6: KM plot for progression-free survival per investigator assessment in pMMR/MSS cohort



No. at Risk

Dostarlimab group	192	172	153	118	96	74	64	61	56	51	41	33	21	14	13	8	1	0		
Placebo group	184	162	146	110	77	60	47	45	37	34	31	25	16	11	10	3	1	1	1	0

No. of Events

Dostarlimab group	0	9	19	45	65	86	92	94	99	103	108	109	112	113	113	114	115	116	
Placebo group	0	10	22	53	83	100	112	114	122	124	124	125	128	129	129	130	130	130	130

Source: Figure 12, p71 of the submission.

CI=confidence interval

Table 5: KM analysis of progression-free survival per investigator assessment in RUBY

PFS	All-comers		dMMR/MSI-H		pMMR/MSS	
	DOS+CP (N=245)	PBO+CP (N=249)	DOS+CP (N=53)	PBO+CP (N=65)	DOS+CP (N=192)	PBO+CP (N=184)
Median FU, months	25.5	25.3	24.6	25.1	25.8	25.4
Events, n (%)	135 (55.1)	177 (71.1)	19 (35.8)	47 (72.3)	116 (60.4)	130 (70.7)
Disease progression	125 (51.0)	169 (67.9)	16 (30.2)	44 (67.7)	109 (56.8)	125 (67.9)
Death	10 (4.1)	8 (3.2)	3 (5.7)	3 (4.6)	7 (3.6)	5 (2.7)
Censored, n (%)	110 (44.9)	72 (28.9)	34 (64.2)	18 (27.7)	76 (39.6)	54 (29.3)
Median PFS, months (95% CI)	11.8 (9.6, 7.1)	7.9 (7.6, 9.5)	NR (11.8, NR)	7.7 (5.6, 9.7)	9.9 (9.0, 13.3)	7.9 (7.6, 9.8)
Hazard Ratio (95% CI)	0.64 (0.51, 0.80)		0.28 (0.16, 0.50)		0.76 (0.59, 0.98)	
p-value	<0.0001		<0.0001		0.0177	

Source: Table 31, pp69-70 of the submission.

CI=confidence interval

Values in bold indicate statistically significant differences.

- 6.19 With 63% PFS maturity in the all-comers population, DOS+CP was associated with a 36% lower risk of progression or death compared to the PBO+CP arm (HR=0.64; 95% CI 0.51, 0.80, stratified log-rank test p-value <0.0001; median PFS 11.8 months versus 7.9 months). A separation of the KM curves occurring from approximately 5 months was observed. The stopping boundary (p=0.02) for claiming superiority of DOS+CP over PBO+CP in prolonging PFS in the all-comers population was crossed, and a statistically significant PFS benefit could be concluded.
- 6.20 With 56% PFS maturity in the dMMR/MSI-H cohort, patients enrolled in the DOS+CP arm were observed to have a 72% lower risk of progression or death than patients enrolled in the PBO+CP arm (HR=0.28; 95% CI 0.16, 0.50, stratified log-rank test p-value < 0.0001; median PFS not reached versus 7.7 months, respectively). The KM plot showed similar PFS between the two treatment arms over the first 4 months, after which there is a notable divergence as the curve for DOS+CP plateaued and the curve for PBO+CP continued to decline. The stopping boundary (p=0.00630) for claiming superiority of DOS+CP over PBO+CP in prolonging PFS in the dMMR/MSI-H population at the interim analysis was crossed, and a statistically significant PFS benefit could be concluded.
- 6.21 With 65% PFS maturity in the pMMR/MSS population, DOS+CP was associated with a 24% lower risk of progression or death compared to the PBO+CP arm based on the point estimate (HR=0.76; 95% CI 0.59, 0.98; median PFS 9.9 months versus 7.9 months). No formal statistical testing was conducted for PFS in the pMMR/MSS population, and the upper bound of the 95% CI was close to one. A separation of KM curves was observed from around 8 months, however the curves did not continue to diverge.
- 6.22 Only three hypotheses were formally tested in RUBY (PFS in the dMMR/MSI-H cohort; PFS and OS in the all-comers population). Therefore, analyses performed outside of these hypotheses, which the trial was neither powered nor designed for, should be

interpreted with caution. Statistical significance was achieved for PFS by IA for the dMMR/MSI-H cohort and the all-comers population, but not OS.

- 6.23 In the pMMR/MSS cohort, OS results in RUBY suggested that there may be no difference between treatments (upper 95% CI exceeded one) and while PFS by IA results favoured DOS+CP, the upper 95% CI was close to one. Notably, the pMMR/MSS cohort made up the majority of both RUBY (76.1% of all enrolled) and the proposed PBS population (73% expected), and while a beneficial result was observed for PFS by IA in the all-comers population, this was likely driven by the high benefit observed in the dMMR/MSI-H subgroup (PFS HR=0.28; 95% CI 0.16, 0.50).
- 6.24 A test for interaction for the outcomes of OS and PFS by IA, between the two subgroups was performed during the evaluation² (Table 6). The results suggested that MMR status (based on the eCRF) may be a treatment effect modifier for DOS in A/R EC when considering the outcome of PFS by IA. The PSCR argued that while these tests for interaction indicated MMR/MSI status may act as a treatment effect modifier for PFS (nominal p=0.0061), no treatment modification effect was demonstrated for OS (nominal p=0.076). The PSCR claimed that as such, there was no conclusive evidence to suggest that MMR status was a treatment effect modifier in RUBY. However, given the immaturity of OS, it was unreasonable to make any claims regarding treatment effect modification based on OS. 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.

Table 6: Outcomes for the dMMR/MSI-H subgroup and the complement (pMMR/MSS)

Outcome	dMMR/MSI-H			pMMR/MSS			Test for p-value
	DOS+CP (n/N)	PBO+CP (n/N)	HR (95% CI)	DOS+CP (n/N)	PBO+CP (n/N)	HR (95% CI)	
OS	7/53	24/65	0.32 (0.14, 0.74)	58/192	76/184	0.73 (0.52, 1.03)	0.0760*
PFS by IA	19/53	47/65	0.33 (0.19, 0.57)	116/192	130/184	0.76 (0.60, 0.98)	0.0061*

Source: Constructed during evaluation, extracted from figures 15.2.1 and 15.2.2 of the RUBY CSR (all-comers, categorised by MMR/MSI status, HR based on unstratified cox model).

CI = confidence interval; CP=carboplatin-paclitaxel; DOS=dostarlimab; HR = hazard ratio; IA = Investigator assessment; n = number of participants reporting data; N = total participants in group; OS = overall survival; PFS = progression-free survival; PBO=placebo

Bold indicates values that are statistically significant

*Note that the results for the test of interaction presented in Table 6 are derived from ad-hoc/ post-hoc analyses conducted during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for RUBY. 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.

² Note that the results for the test of interaction are derived from ad-hoc/ post-hoc analyses conducted during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for RUBY. 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.

- 6.25 As discussed in paragraph 5.2, 1L DOS+PBC followed by 2L chemotherapy would replace 1L PBC followed by 2L PEM+LEN in a proportion of patients. Further, as discussed in paragraph 5.3, PEM+CP was identified as a near market comparator, with some early interim results available. As such, results for these interventions were extracted during the evaluation and are presented alongside results from RUBY (Table 7).

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Table 7: Summary of OS and PFS outcomes for DOS+CP, PEM+LEN and PEM+CP

Outcome		All-comers		dMMR/MSI-H		pMMR/MSS	
		Tx	Chemo	Tx	Chemo	Tx	Chemo
DOS+CP (RUBY) – 1L, median follow up 24.8 months (dMMR/MSI-H) and 25.7 months (pMMR/MSS)							
N		245	249	53	65	192	184
OS	Median, months (95%CI)	NR (NR, NR)	NR (23.2, NR)	NR (NR, NR)	NR (23.2, NR)	NR (29.8, NR)	29.8 (21.9, NR)
	HR (95% CI)	0.64 ^a (0.46, 0.87)		0.30 ^b (0.13, 0.70)		0.73 ^c (0.52, 1.02)	
PFS	Median, months (95%CI)	11.8 (9.6, 17.1)	7.9 (7.6, 9.5)	NR (11.8, NR)	7.7 (5.6, 9.7)	9.9 (9.0, 13.3)	7.9 (7.6, 9.8)
	HR (95% CI)	0.64 ^d (0.51, 0.80)		0.28 ^d (0.16, 0.50)		0.76 ^e (0.59, 0.98)	
PEM+LEN (KN775) – 2L, median follow-up 11.4 months overall							
N		411	416	65	65	346	351
OS	Median, months (95%CI)	18.3 (15.2, 20.5)	11.4 (10.5, 12.9)	NR (NR, NR)	8.6 (5.5, 12.9)	17.4 (14.2, 19.9)	12.0 (10.8, 13.3)
	HR (95% CI)	0.62 ^d (0.51, 0.75)		0.37 ^f (0.22, 0.62)		0.68 ^d (0.56, 0.84)	
PFS	Median, months (95%CI)	7.2 (5.7, 7.6)	3.8 (3.6, 4.2)	10.7 (5.6, NR)	3.7 (3.1, 4.4)	6.6 (5.6, 7.4)	3.8 (3.6, 5.0)
	HR (95% CI)	0.56 ^d (0.47, 0.66)		0.36 ^f (0.23, 0.57)		0.60 ^d (0.50, 0.72)	
PEM+LEN (KN775) – 2L, median follow-up 14.7 months overall ^g							
N		411	416	65	65	346	351
OS	Median, months (95%CI)	18.7 (15.6, 21.3)	11.9 (10.7, 13.3)	31.9 (15.6, NR)	8.6 (5.5, 13.4)	18 (14.9, 20.5)	12.2 (11.0, 14.1)
	HR (95% CI)	0.65 (0.55, 0.77)		0.43 (0.28, 0.68)		0.70 (0.58, 0.83)	
PFS	Median, months (95%CI)	7.3 (5.7, 7.6)	3.8 (3.6, 4.2)	10.7 (5.6, 20.3)	3.7 (3.1, 4.4)	6.7 (5.6, 7.4)	3.8 (3.6, 5.0)
	HR (95% CI)	0.56 (0.48, 0.66)		0.39 (0.25, 0.60)		0.60 (0.50, 0.72)	
PEM+CP (NCT03914612) – 1L, median follow-up 12 months (dMMR) and 7.9 months (pMMR)							
N		405	408	112	113	293	295
OS	Median, months (95%CI)	NA	NA	NA	NA	NA	NA
	HR (95% CI)	NA		NA		NA	
PFS	Median, months (95%CI)	18.8 (NA, NA)	8.5 (NA, NA)	NR (30.6, NR)	7.6 (6.4, 9.9)	13.1 (10.5, 18.8)	8.7 (8.4, 10.7)
	HR (95% CI)	NA		0.30 (0.19, 0.48) ^h		0.54 (0.41, 0.71) ^h	

Source: Constructed during the evaluation using data sourced from Table 4, p15 of the pembrolizumab PSD, March 2022 PBAC meeting, and Tables 30&31, p67&69 of the submission.

Blue shaded cells indicate values previously considered by the PBAC

1L = first line; 2L = second line; Chemo = chemotherapy; CI = confidence interval; CP = carboplatin-paclitaxel; dMMR = deficient mismatch repair; DOS = dostarlimab; HR = hazard ratio; LEN = lenvatinib; MSI-H = high microsatellite instability; MSS = microsatellite stable; N = total participants in group; NR = not reached; OS = overall survival; PEM = pembrolizumab; PFS = progression free survival; pMMR = proficient mismatch repair; Tx = treatment.

a Stratified log-rank test p-value (0.0021) was marginally outside the stopping boundary for claiming statistical significance (p=0.00177).

b p=0.0016. Not primary endpoint and should be interpreted with caution

c p=0.0333. Not primary endpoint and should be interpreted with caution

d p<0.001

e p=0.00177. Not primary endpoint and should be interpreted with caution

f nominally p<0.0001 as per submission, but not part of formal statistical analysis plan and should be considered exploratory

g As reported in Makker 2023³, with median follow up of 18.7 months in PEM + LEN and 12.2 months in chemo arm. As this was not a planned analysis, none of the results were formally tested for statistical significance and p values not reported.

h p<0.001

Note that the alpha value for PFS in KN775 was 0.0005 due to multiplicity adjustments, therefore a 95% confidence interval may not be informative

Text in bold indicate statistically significant results

- 6.26 Interim results from NCT03914612 indicate that the addition of PEM to standard 1L chemotherapy resulted in significantly longer PFS than with chemotherapy alone, regardless of MMR status.
- 6.27 Based on the results of RUBY, in patients with pMMR EC, it was unclear whether 1L DOS+CP was superior to 1L CP (see paragraph 6.23). Comparatively, the PBAC (at the March 2022 PBAC meeting) accepted that 1L PBC followed by 2L PEM+LEN was superior to 1L PBC followed by 2L chemotherapy (based on results of KN775). Under the current PBS restriction for PEM+LEN, if a patient received 1L treatment with DOS+CP, they would not be eligible for 2L treatment with PEN+LEN with PBS subsidy. As such, patients with pMMR EC treated with 1L DOS+CP (with uncertain incremental benefit compared to CP based on RUBY) would be unable to access PBS-subsidised 2L PEM+LEN (with accepted incremental benefit compared to 2L chemotherapy based on KN775), and this may result in a worse outcome for patients with pMMR EC.
- 6.28 The PBAC also noted the results of the DUO-E trial, published in October 2023⁴, which compared 3 treatment arms: (1) chemotherapy, (2) durvalumab + chemotherapy, followed by durvalumab and (3) durvalumab + chemotherapy, followed by durvalumab + olaparib. In the ITT population the PFS HR was 0.71 (95%CI, 0.57, 0.89; p=0.003) for the durvalumab arm (arm 2) compared with chemotherapy (arm 1). The PBAC noted that there appeared to be additional benefit from the addition of olaparib for the pMMR population (PFS HR 0.77 for durvalumab vs 0.57 for durvalumab + olaparib) whereas there was no additional benefit for the dMMR group (PFS HR 0.42 for durvalumab vs 0.41 for durvalumab + olaparib).

Secondary outcomes

- 6.29 RUBY also reported objective response rate (ORR), disease control rate (DCR), duration of response (DOR) and progression-free survival 2 (PFS2), defined as time from randomisation until the date of disease progression on first subsequent anticancer therapy following study treatment or death by any cause. The results of these key secondary outcomes are presented in Table 8. Results generally suggest more favourable outcomes in the DOS+CP arm compared to the PBO+CP arm, though no statistical testing could be conducted based on the statistical analysis plan.

³ Makker et al. Lenvatinib Plus Pembrolizumab in Previously Treated Advanced Endometrial Cancer: Updated Efficacy and Safety From the Randomized Phase III Study 309/KEYNOTE-775. *Clinical Oncology* 41, no. 16 (June 01, 2023) 2904-2910.

⁴ Westin and Moore 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* Published online October 21, 2023.

Table 8: Key secondary outcomes in RUBY

	All-comers		dMMR/MSI-H		pMMR/MSS	
	DOS+CP	PBO+CP	DOS+CP	PBO+CP	DOS+CP	PBO+CP
Patients with evaluable disease at baseline, n	212	219	49	58	163	161
Objective response rate (ORR) ^a						
ORR, n (%)	149 (70.3)	142 (64.8)	38 (77.6)	40 (69.0)	111 (68.1)	102 (63.4)
95% CI	63.6, 76.3	58.1, 71.2	63.4, 88.2	55.5, 80.5	60.4, 75.2	55.4, 70.8
Disease control rate (DCR) ^{a, b}						
DCR, n (%)	191 (90.1)	192 (87.7)	44 (89.8)	51 (87.9)	147 (90.2)	141 (87.6)
95% CI	85.3, 93.8	82.6, 91.7	77.8, 96.6	76.7, 95.0	84.5, 94.3	81.5, 92.2
Duration of response (DOR)						
Number of responders, n	149	142	38	40	111	102
Events, n (%)	82 (55.0)	115 (81.0)	14 (36.8)	33 (82.5)	68 (61.3)	82 (80.4)
Disease progression, n (%)	79 (53.0)	112 (78.9)	13 (34.2)	33 (82.5)	66 (59.5)	79 (77.5)
Death, n (%)	3 (2.0)	3 (2.1)	1 (2.6)	0	2 (1.8)	3 (2.9)
Censored, n (%)	67 (45.0)	27 (19.0)	24 (63.2)	7 (17.5)	43 (38.7)	20 (19.6)
Median DOR, months (95% CI)	10.6 (8.2, 17.6)	6.2 (4.4, 6.7)	NR (10.1, NR)	5.4 (3.9, 8.1)	8.6 (6.9, 13.1)	6.3 (4.4, 6.9)
Progression free survival 2 (PFS2)						
Number of patients	245	249	53	65	192	184
Median PFS2, months (95% CI)	NR (25.0, NR) ^c	18.5 (14.9, 22.6)	NR (NR, NR) ^c	22.0 (13.4, NR)	26.2 (19.6, NR)	15.9 (13.7, 22.1)
Hazard Ratio (95% CI)	0.65 (0.50, 0.84)		0.37 (0.19, 0.73)		0.71 (0.54, 0.95)	

Source: Table 32, p72, Table 33, p73 and Table 34, p75 of the submission.

CI=confidence interval; CP=carboplatin-paclitaxel; dMMR=mismatch repair deficient; DOS=dostarlimab; pMMR=mismatch repair proficient; MSI-H=high microsatellite instability; MSS=microsatellite stable; NR = not reached; PBO=placebo

^a Denominator is number of patients with target lesion at baseline.

^b DCR is defined as the percentage of patients with a RECIST v1.1 CR, PR, SD, Non-CR/Non-PD, No disease.

^c Added during evaluation as 95%CI was omitted by the submission.

6.30 Patient reported outcomes in RUBY included results from the European Quality of Life scale, 5-Dimensions, 5-Levels (EQ-5D-5L). The EQ-5D-5L data from RUBY were translated to EQ-5D utility values for application in the submission's economic model. Utility values were generally similar between the two arms. This is discussed further in Table 13.

Comparative harms

6.31 A summary of safety outcomes reported in RUBY is presented in Table 9 (all-comers) and Table 10 (dMMR/MSI-H). All patients (100%) experienced at least one treatment-emergent adverse event (TEAE). The relative risk and risk difference was calculated for each group during the evaluation.

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Table 9: Summary of adverse events in all-comers in RUBY (safety analysis set)

Adverse Events, n (%)	DOS+CP (N=241)	PBO+CP (N=246)	RR* (95% CI)	RD* (95% CI)
Any TEAE	241 (100)	246 (100)	-	0.00 (-0.02, 0.02)
Treatment-related TEAEs	236 (97.9)	243 (98.8)	0.99 (0.96, 1.02)	-0.01 (-0.04, 0.02)
Any Grade ≥3 TEAEs	170 (70.5)	147 (59.8)	1.18 (1.04, 1.35)	0.11 (0.02, 0.19)
Treatment-related Grade ≥3 TEAEs	122 (50.6)	114 (46.3)	1.09 (0.91, 1.31)	0.04 (-0.05, 0.13)
Any SAEs	91 (37.8)	68 (27.6)	1.37 (1.06, 1.77)	0.10 (0.02, 0.18)
Treatment-related SAEs	44 (18.3)	30 (12.2)	1.50 (0.98, 2.30)	0.06 (-0.00, 0.13)
Any TEAE leading to treatment discontinuation	57 (23.7)	41 (16.7)	1.42 (0.99, 2.03)	0.07 (-0.00, 0.14)
Any TEAE leading to infusion interruption	49 (20.3)	49 (19.9)	1.02 (0.72, 1.45)	0.00 (-0.07, 0.08)
Any TEAE leading to infusion delay	109 (45.2)	97 (39.4)	1.15 (0.93, 1.41)	0.06 (-0.03, 0.15)
Any TEAE leading to dose reduction	68 (28.2)	68 (27.6)	1.02 (0.77, 1.36)	0.01 (-0.07, 0.09)
Any immune-related TEAEs	137 (56.8)	88 (35.8)	1.59 (1.30, 1.95)	0.21 (0.12, 0.30)
Any DOS- or PBO-related immune-related TEAEs	92 (38.2)	38 (15.4)	2.47 (1.78, 3.46)	0.23 (0.15, 0.30)
Any infusion-related reactions	44 (18.3)	49 (19.9)	0.92 (0.64, 1.32)	-0.02, (-0.09, 0.05)
Any TEAE with outcome of death	5 (2.1)	0	11.23 (1.34, ∞)	0.02 (0.01, 0.05)
Treatment-related TEAE leading to death	2 (0.8)	0	5.10 (0.53, ∞)	0.01 (-0.01, 0.03)

Source: Table 35, pp78-79 of the submission.

RR and RD calculated during evaluation using StatsDirect (version 3.3.3), using the random effects model.

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

CP=carboplatin-paclitaxel; DOS=dostarlimab; PBO = placebo; RD = risk difference; RR = relative risk; SAE=serious adverse event; TEAE=treatment-emergent adverse event

*Note that the results for relative risk (RR) and risk difference (RD) presented in Table 9 are derived from ad-hoc / post-hoc analyses conducted during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for RUBY. 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.

Table 10: Summary of adverse events in dMMR/MSI-H cohort in RUBY (safety analysis set)

Adverse Events, n (%)	DOS+CP (N=52)	PBO+CP (N=65)	RR* (95% CI)	RD* (95% CI)
Any TEAE	52 (100)	65 (100)	-	0.00 (-0.07, 0.06)
Treatment-related TEAEs	52 (100)	65 (100)	-	0.00 (-0.07, 0.06)
Any Grade ≥3 TEAEs	37 (71.2)	42 (64.6)	1.10 (0.85, 1.42)	0.07 (-0.11, 0.23)
Treatment-related Grade ≥3 TEAEs	30 (57.7)	32 (49.2)	1.17 (0.83, 1.65)	0.09 (-0.10, 0.26)
Any SAEs	14 (26.9)	20 (30.8)	0.88 (0.49, 1.54)	-0.04 (-0.20, 0.13)
Treatment-related SAEs	9 (17.3)	9 (13.8)	1.25 (0.55, 2.85)	0.04 (-0.10, 0.18)
Any TEAE leading to treatment discontinuation	9 (17.3)	11 (16.9)	1.02 (0.46, 2.23)	0.00 (-0.13, 0.15)
Any TEAE leading to infusion interruption	16 (30.8)	14 (21.5)	1.43 (0.78, 2.63)	0.09 (-0.07, 0.26)
Any TEAE leading to infusion delay	24 (46.2)	28 (43.1)	1.07 (0.71, 1.60)	0.03 (-0.15, 0.21)
Any TEAE leading to dose reduction	11 (21.2)	18 (27.7)	0.76 (0.40, 1.44)	-0.07 (-0.22, 0.10)
Any immune-related TEAEs	38 (73.1)	24 (36.9)	1.98 (1.40, 2.87)	0.36 (0.18, 0.52)
Any DOS- or PBO-related immune-related TEAEs	25 (48.1)	8 (12.3)	3.91 (1.99, 7.93)	0.36 (0.20, 0.51)
Any infusion-related reactions	12 (23.1)	13 (20.0)	1.15 (0.58, 2.28)	0.03 (-0.12, 0.19)
Any TEAE with outcome of death	2 (3.8)	0	6.23 (0.66, ∞)	0.04 (-0.02, 0.13)
Treatment-related TEAE leading to death	2 (3.8)	0	6.23 (0.66, ∞)	0.04 (-0.02, 0.13)

Source: Table 35, pp78-79 of the submission.

RR and RD calculated during evaluation using StatsDirect (version 3.3.3), using the random effects model.

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

CP=carboplatin-paclitaxel; dMMR=mismatch repair deficient; DOS=dostarlimab; MSI-H=high microsatellite instability; PBO=placebo; RD=risk difference; RR = relative risk; SAE=serious adverse event; TEAE=treatment-emergent adverse event

*Note that the results for relative risk (RR) and risk difference (RD) presented in Table 10 are derived from ad-hoc / post-hoc analyses conducted during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for RUBY. 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.

- 6.32 The most frequently reported serious adverse events (SAEs) (≥2% of patients) in the DOS+CP arm were sepsis, pulmonary embolism, pyrexia, dyspnoea and muscular weakness, while those in the PBO+CP arm were asthenia, anaemia, urinary tract infection and pulmonary embolism. SAEs which occurred in ≥2% of patients and also had a ≥1% difference between treatment arms (sepsis, pyrexia, dyspnoea, muscular weakness, anaemia and asthenia) were included in the submission's economic model.
- 6.33 Immune-related adverse events (irAEs) were identified as any ≥Grade 2 AEs based on a prespecified search list of preferred terms and MedDRA Version 25.0. Patients in the DOS+CP arm had a higher risk of experiencing irAEs compared to patients in the PBO+CP arm, and this was consistent across the dMMR/MSI-H and pMMR/MSS cohorts and the all-comers population. Overall, patients in the DOS+CP arm of RUBY were more likely to experience the following irAEs: infusion-related reaction; hypothyroidism; rash; rash maculo-papular; alanine aminotransferase increased; aspartate aminotransferase increased; and hyperthyroidism. The higher incidence of irAEs in the dMMR/MSI-H population compared to the pMMR/MSS population (DOS+CP: 73.1% and 52.4% respectively; PBO+CP: 36.9% and 35.4% respectively) was likely due to difference in duration of treatment with DOS between the two populations. The submission claimed that the nature and types of irAEs in the safety profile were consistent with the mechanism of action of DOS and were similar to those reported for other PD-(L)1 inhibitors. Most irAEs were not serious in nature and did not lead to treatment discontinuation or death.

Table 11: Summary of immune-related adverse events in all-comers

Immune-related TEAEs, n (%)	DOS+CP (N=241)		PBO+CP (N=246)		Relative Risk* (95% CI)	Risk Difference* (95% CI)
	All events	DOS-related	All events	PBO-related	DOS/PBO-related	DOS/PBO-related
Any immune-related TEAE	137 (56.8)	92 (38.2)	88 (35.8)	38 (15.4)	2.47 (1.78, 3.46)	0.227 (0.150, 0.303)
Arthralgia	32 (13.3)	14 (5.8)	31 (12.6)	16 (6.5)	0.89 (0.45, 1.77)	-0.007 (-0.052, 0.038)
Infusion-related reaction	31 (12.9)	4 (1.7)	30 (12.2)	0	9.19 (1.07, ∞)	0.017 (0.001, 0.042)
Hypothyroidism	27 (11.2)	27 (11.2)	8 (3.3)	7 (2.8)	3.94 (1.79, 8.72)	0.084 (0.040, 0.133)
Hypersensitivity	6 (2.5)	0	4 (1.6)	1 (0.4)	0.34 (0.00, 3.91)	-0.004 (-0.023, 0.012)
Drug Hypersensitivity	7 (2.9)	0	11 (4.5)	1 (0.4)	0.34 (0.00, 3.91)	-0.004 (-0.023, 0.012)
Rash	21 (8.7)	16 (6.6)	6 (2.4)	5 (2.0)	3.27 (1.27, 8.49)	0.046 (0.011, 0.087)
Rash maculo-papular	16 (6.6)	11 (4.6)	0	0	23.48 (2.95, ∞)	0.046 (0.026, 0.080)
Pruritus	15 (6.2)	8 (3.3)	4 (1.6)	3 (1.2)	2.72 (0.79, 9.38)	0.021 (-0.006, 0.053)
ALT increased	15 (6.2)	14 (5.8)	2 (0.8)	2 (0.8)	7.15 (1.84, 28.00)	0.050 (0.021, 0.088)
AST increased	12 (5.0)	10 (4.1)	1 (0.4)	1 (0.4)	10.21 (1.71, 61.65)	0.037 (0.014, 0.071)
Hyperthyroidism	8 (3.3)	8 (3.3)	1 (0.4)	1 (0.4)	8.17 (1.34, 50.13)	0.029 (0.007, 0.061)

Source: Table 43, p85 of the submission. The relative risk and risk difference were analysed during the evaluation. This was performed via StatsDirect (version 3.3.3), using the random effects model.

Bold indicates values where the 95% CI did not include '1' for relative risk, or '0' for risk difference

ALT=alanine aminotransferase; AST aspartate aminotransferase; CP=carboplatin-paclitaxel; DOS=dostarlimab; PBO=placebo TEAE=treatment-emergent adverse event

*Note that the results for relative risk (RR) and risk difference (RD) presented in Table 11 are derived from ad-hoc / post-hoc analyses conducted during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for RUBY. 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.

6.34 The most recent Periodic Benefit Risk Evaluation Report (PBRER) for DOS, from 21 October 2022 to 20 April 2023, found that, at present, no significant efficacy or safety issues were highlighted from long-term follow-up of patients in clinical trials assessing DOS.

Benefits/harms

6.35 A summary of the comparative benefits and harms for DOS+CP versus PBO+CP is presented in Table 12.

Table 12: Summary of comparative benefits for DOS+CP and PBO+CP

Benefits					
Survival (median duration of follow up 25.5 months for DOS+CP and 25.3 months for PBO+CP, at first interim analysis); all-comers					
Event	DOS+CP		PBO+CP		HR (95% CI)
PFS ^a Events, n/N (%)	135/245 (55.1)		177/249 (71.1)		0.64 (0.51, 0.80); p<0.0001
OS Events, n/N (%)	65/245 (26.5)		100/249 (40.2)		0.64 (0.46, 0.87); p=0.0021
Landmark PFS estimates, probability (95% CI)					
6 months	75.0 (68.7, 80.2)		65.9 (59.3, 71.7)		
12 months	48.2 (41.3, 54.8)		29.0 (23.0, 35.2)		
18 months	41.9 (35.1, 48.6)		21.6 (16.3, 27.4)		
24 months	36.1 (29.3, 42.9)		18.1 (13.0, 23.9)		
Survival (median duration of follow up 24.6 months for DOS+CP and 25.1 months for PBO+CP, at first interim analysis); dMMR					
PFS ^a Events, n/N (%)	19/53 (35.8)		47/65 (72.3)		0.28 (0.16, 0.50); p<0.0001
OS Events, n/N (%)	7/53 (13.2)		24/65 (36.9)		0.30 (0.13, 0.70); p=0.0016
Landmark PFS estimates, probability (95% CI)					
6 months	80.2 (66.3, 88.8)		59.7 (46.2, 70.9)		
12 months	63.5 (48.5, 75.3)		24.4 (13.9, 36.4)		
18 months	61.4 (46.3, 73.4)		17.9 (8.9, 29.5)		
24 months	61.4 (46.3, 73.4)		15.7 (7.2, 27.0)		
Harms					
DOS+CP, n/N	PBO+CP, n/N	RR* (95% CI)	Event rate/100 patients		RD* (95% CI)
			DOS+CP	PBO+CP	
Any Grade ≥3 TEAEs (all-comers)					
170/241	147/246	1.18 (1.04, 1.35)	70.5	59.8	0.11 (0.02, 0.19)
Any SAEs (all-comers)					
91/241	68/246	1.37 (1.06, 1.77)	37.8	27.6	0.10 (0.02, 0.18)
Any immune-related TEAEs (all-comers)					
137/241	88/246	1.59 (1.30, 1.95)	56.8	35.8	0.21 (0.12, 0.30)
Any DOS- or PBO-related immune-related TEAEs (all-comers)					
92/241	38/246	2.47 (1.78, 3.46)	38.2	15.4	0.23 (0.15, 0.30)
Any TEAE with outcome of death (all-comers)					
5/241	0/246	11.23 (1.34, ∞)	2.1	0.0	0.02 (0.01, 0.05)
Any immune-related TEAEs (dMMR/MSI-H)					
38/52	24/65	1.98 (1.40, 2.87)	73.1	36.9	0.36 (0.18, 0.52)
Any DOS- or PBO-related immune-related TEAEs (dMMR/MSI-H)					
25/52	8/65	3.91 (1.99, 7.93)	48.1	12.3	0.36 (0.20, 0.51)

Source: Constructed during the evaluation using information sourced from Table 31&35, pp69-70&78-79 of the submission.

CI=confidence interval; HR = hazard ratio; NR = not reported; PBO = placebo; RD = risk difference; RR = risk ratio

^a Investigator assessed

*Note that the results for relative risk (RR) and risk difference (RD) presented in Table 12 are derived from ad-hoc / post-hoc analyses conducted during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for RUBY. 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.

6.36 On the basis of direct comparison evidence presented by the submission, in the all-comers population, for every 100 patients treated with DOS+CP in comparison with PBO+CP:

- Approximately 16 additional patients will remain progression-free after a median of 25.4 months

- Although uncertain as not statistically significant, approximately 14 additional patients will remain alive, after a median of 25.4 months.
 - Approximately 11 additional patients will experience any TEAE (grade ≥ 3).
 - Approximately 10 additional patients will experience any SAE.
 - Approximately 21 additional patients will experience any immune-related TEAE.
 - Approximately 23 additional patients will experience any DOS- or PBO-related TEAE.
 - Approximately 2 additional patients will experience any TEAE with the outcome of death.
- 6.37 On the basis of direct comparison evidence presented by the submission, in the dMMR population, for every 100 patients treated with DOS+CP in comparison with PBO+CP:
- Approximately 37 additional patients will remain progression-free after a median of 24.8 months.
 - Although uncertain as not formally tested for statistical significance, approximately 24 additional patients will remain alive after a median of 24.8 months.
 - Approximately 36 additional patients will experience any immune-related TEAEs.
 - Approximately 36 additional patients will experience any DOS- or PBO-related immune-related TEAEs.

Clinical claim

- 6.38 The submission described DOS+CP as superior in terms of effectiveness compared with CP alone in patients with A/R dMMR EC (Population 1). This was largely supported by the results of the RUBY trial (Part 1; first interim analysis) which reported a statistically significant PFS benefit in favour of DOS+CP (HR=0.28; 95%CI 0.16, 0.50). While an OS benefit in favour of the DOS+CP arm was also observed (HR=0.30; 95% CI 0.13, 0.70), the trial was not powered to detect this treatment difference, and as such, should be interpreted with caution. The ESC agreed with the commentary that the claim of superior effectiveness was supported for the dMMR population.
- 6.39 The PBAC considered that the claim of superior comparative effectiveness was reasonable for the dMMR population, based on a statistically significant PFS benefit. The PBAC considered that it appeared likely there would be an overall survival benefit, however this was not tested for statistical significance and was based on a small number of events.
- 6.40 The submission described DOS+CP as superior in terms of effectiveness compared with CP alone in patients with A/R EC (all-comers; Population 2). Although a statistically significant PFS benefit in favour of DOS+CP was observed in the RUBY trial (HR=0.64; 95%CI 0.51, 0.80), the OS benefit in favour of DOS+CP (HR=0.64; 95%CI 0.46,

0.87) did not achieve statistical significance. The ESC noted that in the pMMR subgroup, DOS+CP had uncertain efficacy, suggesting that the benefit in the all-comers population was largely driven by the benefit in patients with dMMR EC.

- 6.41 The PBAC considered that the claim of superior comparative effectiveness was not sufficiently supported for the all-comers population. Although there was a statistically significant PFS benefit, this appeared to be largely driven by the dMMR cohort and as the data are immature, it is unclear whether patients with pMMR EC would have the same benefit from first line dostarlimab as for first line PBC followed by second line combination treatment with PEM+LEN (where an OS benefit was demonstrated). The PBAC noted that there are a number of trials underway for near-market comparators, with different combinations of treatment that are likely to provide additional data regarding the best course of treatment for patients with pMMR EC.
- 6.42 The submission described DOS+CP as inferior (but with a manageable safety profile) in terms of safety compared to CP alone. This claim was adequately supported. The ESC noted that the rate of irAEs was higher in the dMMR subgroup but that this was consistent with the longer duration of treatment for dMMR patients.
- 6.43 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

- 6.44 The submission presented a stepped economic evaluation based on the RUBY trial. The type of economic evaluation presented was a cost-utility analysis. The submission included economic evaluations for the two proposed populations for PBAC consideration: dMMR (Population 1) and all-comers (Population 2). The same economic model was employed across both populations, with population specific inputs from the RUBY trial (Part 1) applied to the relevant population (e.g., PFS, OS, time to treatment discontinuation (TTD)). The ESC considered that the all-comers model was of limited value as the benefit was driven by the clinical effect in dMMR patients.
- 6.45 The cost-effectiveness of DOS in the pMMR/MSS population was also considered by the submission in the same model to illustrate the relative value of DOS by MMR status, however, this was not assessed during the evaluation given the submission was not requesting listing of DOS specifically for the patients with pMMR EC (though they are captured in the all-comers population).
- 6.46 The PBAC considered that, as the clinical claim of superior clinical efficacy was not accepted for the all-comers population, the relevant economic model was the model specific to the dMMR population.

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Table 13: Summary of model structure, key inputs and rationale

Component	Description	Justification/comments
Treatment comparison	Intervention: DOS+CP Comparator: CP	Reasonable.
Type of analysis	Cost-utility analysis	Consistent with the submission's clinical claim of superior efficacy of DOS+CP compared to CP alone. This was appropriate for dMMR patients (Population 1) but was more uncertain for all-comers (Population 2) – see paragraphs 6.38
Patient population	dMMR (Population 1) all-comers (Population 2)	
Outcomes	Life years gained; quality-adjusted life years	Appropriate.
Time horizon	10 years in the model base case vs. median follow-up of 25.4 months in RUBY (all-comers) and 24.8 months (dMMR)	The PBAC considered this was optimistic for patients with advanced/recurrent EC and uncertain given the length of study follow-up.
Methods used to generate results	Partitioned survival model	Appropriate.
Health states	Progression-free; progressed disease; dead	Appropriate.
Cycle length	7 days	May be overly granular given the RUBY schedule of events where one cycle of treatment was 3 or 6 weeks during the treatment period.
Transition probabilities	Until median follow-up CP arm: PFS and OS KM from RUBY DOS+CP arm: PFS and OS KM from RUBY After median follow-up CP arm: PFS and OS from Miller 2020 DOS+CP arm: HR applied to CP arm (OS HR=0.30 and PFS HR=0.28 for dMMR cohort; OS HR=0.64 and PFS HR=0.64 for all-comers) until three years; forced linear convergence to CP arm from three years to 10 years	The PBAC considered the modelled OS was uncertain due to the immaturity of the trial data. Use of data from Miller (2020) was uncertain given transitivity issues associated with the use of a long-term survival study and it was unclear whether the convergence applied was sufficient to compensate for subsequent immunotherapy in Australian practice.
Health-related quality of life	Based on EQ5D scores from RUBY (using Australian scoring algorithm) dMMR: PFS utility: 0.7747* for both arms; PD utility: 0.7402* for both arms all-comers: PFS utility: 0.7779* for both arms; PD utility: 0.7339* for both arms	For the dMMR cohort, it was unclear if it was reasonable that both the PD utility (0.7747*) and PF utility (0.7402*) were higher than the reported baseline utility (0.73*) for dMMR patients in RUBY.
Software package	Microsoft Excel	Reasonable.

Source: Table 52, p102 of the submission.

CP = carboplatin-paclitaxel; DOS = dostarlimab; EQ-5D = European quality of life scale, 5-Dimensions; OS = overall survival; PD = progressive disease; PFS = progression-free survival.

**Note that the utility values were provided 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.*

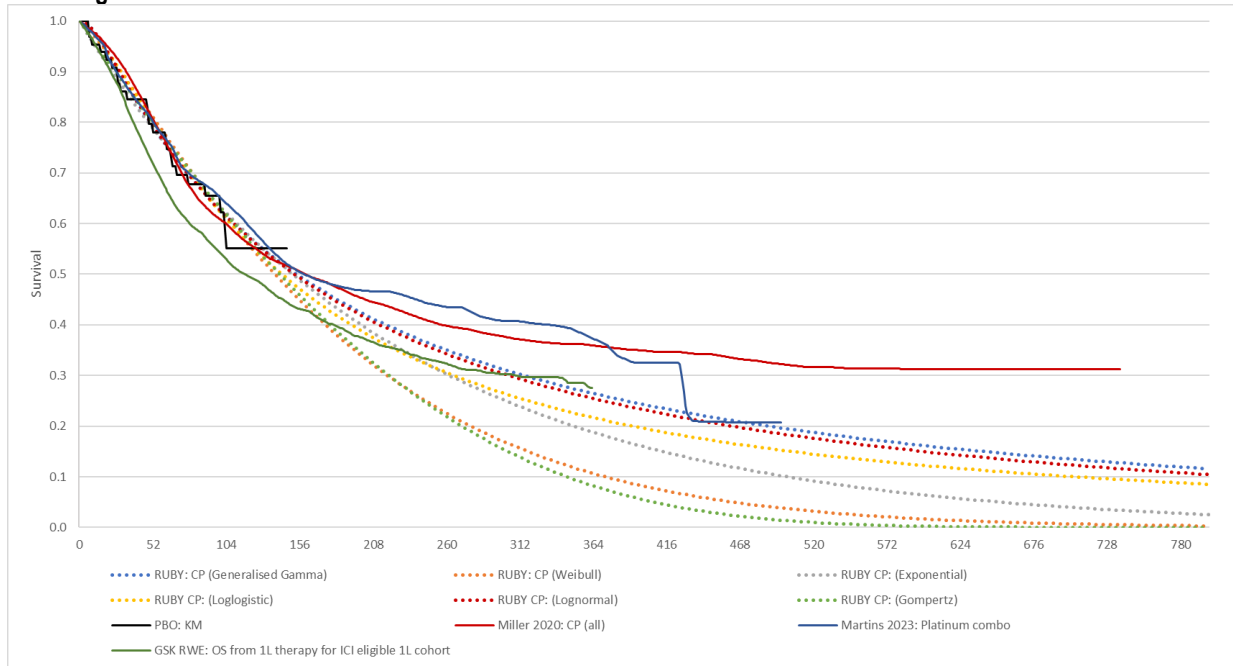
6.47 The ESC noted that EQ-5D-5L data were mapped to the EQ-5D-3L value set using Viney 2011 and considered that these should have been updated to reflect the Australian EQ-5D-5L value set based on Norman et al (2023).

6.48 In order to inform the longer-term transition probabilities beyond RUBY, the submission presented extrapolations using fitted parametric functions to KM curves from RUBY or from long-term survival studies (Miller 2020, Martins 2023 or GSK RWE study). The submission considered fitted parametric functions were not suitable for the extrapolation of OS and PFS in the CP arm of the model. Among the long-term

survival studies, Miller 2020 was the preferred data source for the submission as follow-up was available out to 10-years. For the base case, instead of using extrapolation from parametric functions as is the standard method (PBAC guidelines v5.0, p75), extrapolation was applied in which conditional probabilities derived from the CP arm of the ITT cohort in Miller 2020 were applied directly in estimating survival in the CP arm beyond the median follow-up of the trial.

- 6.49 Miller 2020 reported outcomes from the GOG0209 study, a phase III, randomised, noninferiority, open-label study of CP versus paclitaxel-doxorubicin-cisplatin in 1L A/R EC. Patients enrolled in the CP arm reported in Miller 2020 appeared to have less severe disease compared to patients enrolled in the CP arm of RUBY. For example, 41.7% (280/672) of patients in the CP arm of Miller 2020 had stage III disease compared to 18.9% (47/249) in RUBY, and 47.8% (119/249) of patients in RUBY had recurrent/progressed disease compared to 28.3% (190/672) in the CP arm of Miller 2020. Patients enrolled in Miller 2020 (median age 61 years) were also on average younger than those enrolled in the CP arm of RUBY (median age 65 years). The MMR status of patients enrolled in Miller 2020 was not reported and this represented a potential transitivity issue. The ESC agreed with the commentary that patients enrolled in the CP arm reported in Miller 2020 appeared to have less severe disease compared to patients enrolled in the CP arm of RUBY.
- 6.50 Martins 2023 conducted an observational, population-based, retrospective cohort study among adults (≥ 18 years) in Alberta, Canada, newly diagnosed with A/R EC between 2010-2018, with follow-up to December 2019. It was unclear if patients reported in Martins 2023 were comparable to patients enrolled in RUBY as patient demographic and clinical characteristics were not individually reported.
- 6.51 The GSK RWE Study (identified as Ingles 2023 during the submission's literature search) was a descriptive, non-interventional retrospective cohort study of EC patients diagnosed between 2013-2019 (with follow-up to August 2021) in England. A cohort of A/R patients was constructed to match as closely as possible the patients selected into the RUBY trial, who received a 1L systemic anticancer treatment ($n=2,376$; referred to as the immune checkpoint inhibitors (ICI) eligible 1L cohort), along with a second cohort which was a subgroup of the first but received CP as the treatment ($n=902$; referred to as the ICI eligible 1L CP cohort). Despite the matching, patients in RUBY may potentially be healthier than in the GSK RWE study with a higher proportion of patients with Stage I/II disease at diagnosis (33.7% vs 16.9% and 20.2%, in RUBY, the ICI eligible 1L, and the ICI eligible 1L CP cohorts respectively). The MMR status of patients involved in the GSK RWE study was not reported and no comparison could be made.
- 6.52 Figure 7 presents an overlay of parametric functions fitted to OS data from the CP arm of RUBY (dMMR), and OS curves from the long-term survival studies. Figure 8 presents the overlay of parametric functions fitted to PFS data from the CP arm of RUBY (dMMR) and PFS curves from Miller 2020.

Figure 7: Overlay of parametric functions fitted to OS data from the CP arm of RUBY (dMMR cohort) and OS curves from long-term survival studies

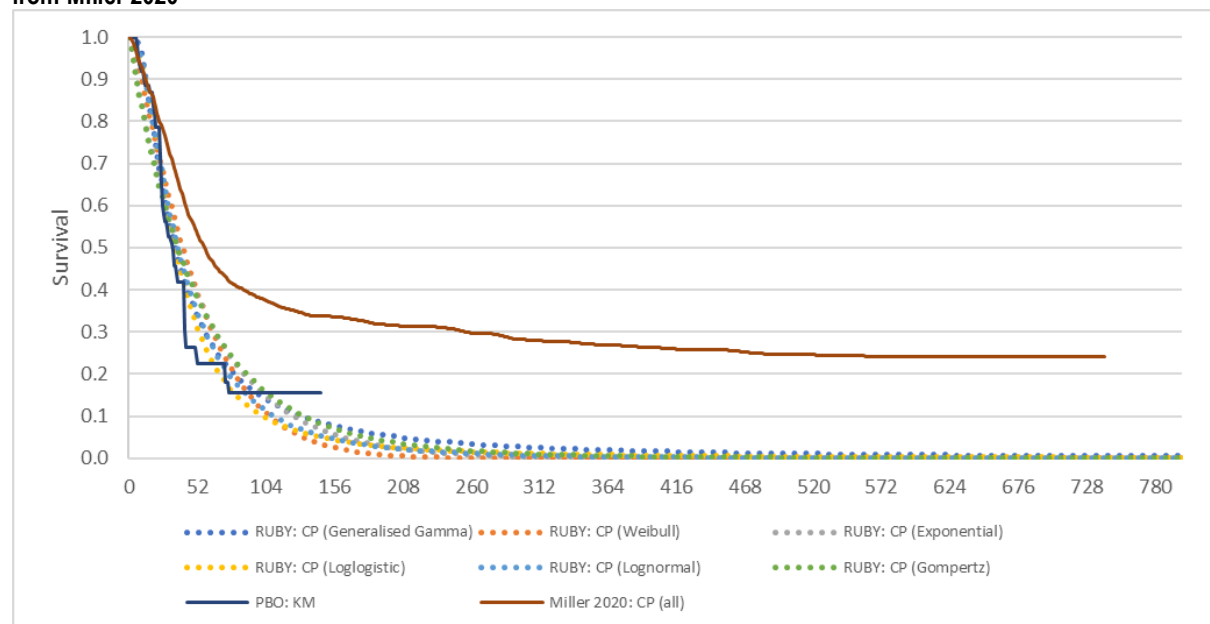


Source: Figure 50, p142 of the submission, and constructed during the evaluation using information from the submission’s economic model (Excel workbook ‘Jemperli (dostarlimab) 1L EC CUA_July 2023’)

1L = first-line; CP = carboplatin-paclitaxel; ICI = immune checkpoint inhibitors; KM = Kaplan-Meier; PBO = placebo; RWE = real world evidence

Note that the Kaplan Meier plots and fitted curves depicted in Figure 7 are presented specifically for the purposes of informing the PBAC consideration. Their interpretation and application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Figure 8: Overlay of parametric functions fitted to PFS data from the CP arm of RUBY (dMMR cohort) and PFS curves from Miller 2020



Source: Constructed during the evaluation using information from the submission's economic model (Excel workbook 'Jemperli (dostarlimab) 1L EC CUA_July 2023')

CP = carboplatin-paclitaxel; KM = Kaplan-Meier; PBO = placebo

Note that the Kaplan Meier plots and fitted curves depicted in Figure 8 are presented specifically for the purposes of informing the PBAC consideration. Their interpretation and application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

- 6.53 Survival curves from both the fitted parametric functions and the long-term survival studies generally aligned with the OS KM data from the CP arm of RUBY. However, the submission noted that the fitted parametric functions predict significantly lower long-term survival compared to that observed across the long-term survival studies. The submission considered that Miller 2020 demonstrated that long-term PFS was expected to plateau, which aligned with the relative plateauing observed in OS across the long-term survival studies while fitted parametric functions did not predict a plateauing of PFS, and therefore were likely to also underestimate long-term PFS in the CP arm. Miller 2020 was the only long-term survival study identified that reported on PFS.
- 6.54 Given Miller 2020 enrolled patients between 2003 and 2009, transition probabilities based on Miller 2020 would not have accounted for 2L immunotherapy (PEM+LEN), which would be available to patients in the Australian setting. The PBAC have accepted that 2L PEM+LEN would deliver significant improvement in efficacy compared to chemotherapy (paragraph 7.1, pembrolizumab PSD, March 2022 PBAC meeting), and therefore, although OS in Miller 2020 was conservative in comparison to the fitted parametric functions explored by the submission, the OS in the CP arm in the model would be expected to be underestimated compared to Australian practice. Based on updated efficacy data from the KN775 trial (Makker 2023, median follow-up of 18.7 months) approximately 30% of patients in the PEM+LEN arm (2L) were alive at

3 years (Fig 1B of Makker 2023) and approximately 15% were progression free at 3 years (Fig 1D of Makker 2023).

- 6.55 Overall, the ESC considered that it appeared that underlying differences between Miller 2020 and the CP arm of RUBY (difference in age, disease severity, MMR status at baseline and subsequent treatments used) were likely to have led to a different conditional probability of survival in RUBY compared to Miller 2020. The ESC considered that extrapolation of the trial data is a key source of uncertainty in the model.
- 6.56 For the DOS+CP arm of the model, the submission deemed that it was inappropriate to apply fitted parametric functions given they were considered to be inappropriate for the extrapolation of CP survival outcomes in the 1L A/R EC setting. In the base case, KM data from RUBY was used until the median follow-up in RUBY (dMMR: 24.6-25.1 months). After the median follow up of RUBY, OS and PFS HRs from RUBY were applied to the CP arm to generate results for DOS+CP until three years. Between three years and the modelled 10-year time horizon, linear convergence of DOS+CP survival curves to CP survival curves was applied such that at 10 years, the proportion remaining progression free (based on PFS) and alive (based on OS) was the same in both treatment arms. A summary of the approach to survival (OS and PFS) applied in the base case is provided in Table 14.

Table 14: Summary of survival curves applied in the model base case

Time period	CP	DOS+CP
dMMR		
0 – median FU	KM data (RUBY) (Baseline to 25.1 months)	KM data (RUBY) (Baseline to 24.6 months)
Median FU – 36 months	Per cycle risks derived from Miller 2020 (incorporating life tables adjustment)	Trial-based HR relative to CP survival (incorporating life tables adjustment)
36 – 120 months		Linear convergence (incorporating life tables adjustment)

Source: Table 75, p144 of the submission.

CP = carboplatin-paclitaxel; dMMR = mismatch repair deficient; DOS = dostarlimab; FU = follow-up; HR = hazard ratio; ITT = intention to treat; KM = Kaplan-Meier; MSI-H = microsatellite instability-high.

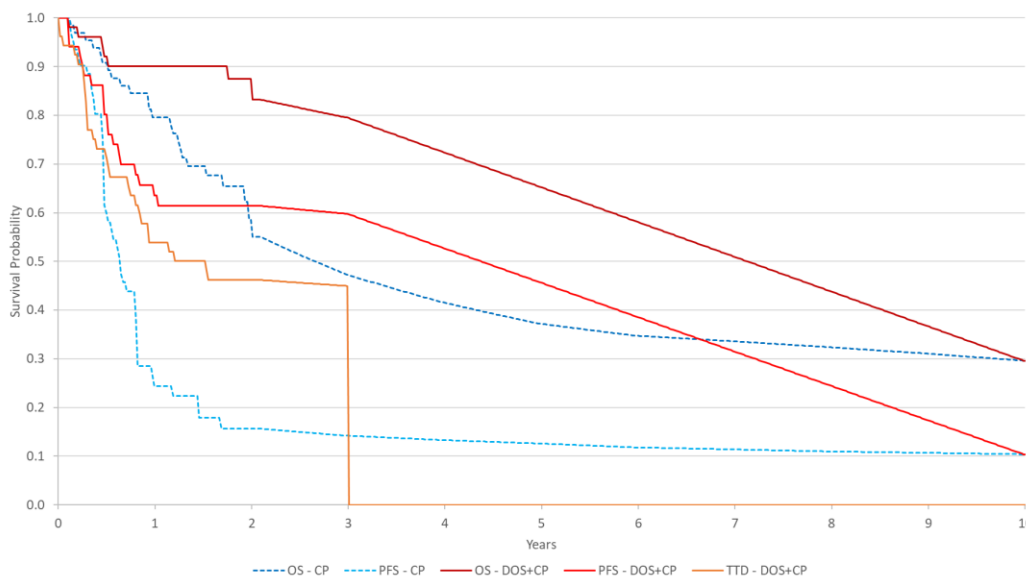
- 6.57 The submission argued that the potential impact of 2L immunotherapy on the incremental benefit of DOS+CP over CP was appropriately and adequately captured by the forced convergence of the OS curves. The evaluation considered this may not be an appropriate use of convergence, which affected only the results of the DOS+CP arm. The results from the CP alone arm would remain underestimated relative to the proposed PBS population and the estimate for the CP alone arm in the model cannot be interpreted alone nor validated externally.
- 6.58 In addition, convergence would also need to account for the fact that of dMMR patients randomised to the DOS+CP arm in RUBY, 53% of patients who received any follow-up anti-cancer therapy were treated with subsequent immunotherapy after progression (see paragraph 6.12) whereas they would not be able to access PBS subsidised 2L immunotherapy under the proposed listing in the event of progression or recurrence following treatment with DOS+CP.

- 6.59 Overall, the ESC and the PBAC agreed with the evaluation that the assumption of convergence was appropriate. However, it was uncertain whether the rate of convergence was sufficient to have addressed the combined issues of uncertainty associated with long term incremental benefit with DOS+CP relative to CP, the underestimated OS in the CP arm due to omission of 2L immunotherapy and the potential overestimate of DOS+CP OS due to 2L immunotherapy use in the DOS+CP arm in RUBY.
- 6.60 The ESC considered that differences in trial populations and 2L treatment contexts, including a relatively younger and healthier population in Miller compared with the CP arm in RUBY, with no available data on dMMR status, meant that clinical outcomes were not directly comparable. The ESC considered that the long-term survival outcomes in Miller 2020 were implausibly high for the proposed PBS population, and the approach to extrapolation of outcomes was not well-justified. The ESC considered that extrapolated PFS and OS curves using parametric extrapolations appeared more clinically plausible for the relevant population, however, particularly for the dMMR population, OS curves were based on relatively few events (7 deaths in the DOS+CP arm and 24 in the CP arm), resulting in a high level of uncertainty for the extrapolated PFS and OS curves.
- 6.61 The ESC noted that regardless of the extrapolation approach (base case or parametric extrapolations), for the dMMR population, survival in the CP arm showed a sharp drop between 22 and 24 months. At 22 months 65.5% of patients were alive, at 24.1 months 55.1% were alive, so survival was reduced by 10.4% in 2.1 months. Further, the survival at 23.5 months was 62.2% and so in <3 weeks (0.6 month) the survival was reduced by 7.1%. Based on Figure 2 these reductions in survival reflect 2 events i.e. 21 deaths at 22 months and 23 at 24 months, and a reduction in the number at risk from 25 at 22 months to 16 at 24 months. Changing the cut point for use of KM curves for the CP arm from 24.61 months (median follow-up) to 22 months increased the ICER from \$75,000 to < \$95,000 to \$75,000 to < \$95,000 for the base case extrapolation method and from \$55,000 to < \$75,000 to \$75,000 to < \$95,000 using parametric extrapolations. The PBAC considered that the immaturity of the trial data and the small number of patients in the dMMR subgroup resulted in a high level of uncertainty in the modelled OS and PFS benefit.
- 6.62 The ESC considered convergence of extrapolated curves should be applied to account for uncertainty in long term outcomes and potential differences in 2L treatments compared with Australian clinical practice. A more rapid rate of convergence would provide more certainty and may be more appropriate given the high number of sources of uncertainty.
- 6.63 In the base case, CP costs were applied as a lump sum in the first cycle based on the mean number of cycles and doses in RUBY across the treatment arms for the respective dMMR and all-comers populations. Treatment duration for DOS was informed by the TTD KM for DOS+CP in RUBY until the median follow-up, after which it was informed by the PFS curve for the DOS+CP arm in RUBY until three years at

which point all patients will discontinue. This was based on the assumption that patients will discontinue at progression, or until the maximum duration of three years, which was consistent with the maximum treatment duration of 36 months in the requested restriction.

- 6.64 The median treatment durations extracted from the TTD KMs applied in the submission’s economic model for DOS were not consistent with the reported median duration on treatment in RUBY and appeared to underestimate the duration on treatment based on the reported median duration of treatment in RUBY (dMMR: ~61 weeks in model vs. 76.5 weeks reported in RUBY). The PSCR identified there was an error in the model in that decrements in the KM plot were inadvertently applied one cycle early. The median treatment duration for dMMR patients increased to 79.14 weeks when this was corrected. The PSCR stated the remaining difference was due to a difference in the definition of TTD in the model and duration of treatment/exposure in the RUBY CSR.
- 6.65 Model traces illustrating the PFS, OS and TTD curves applied in the economic model for the dMMR cohort using the base case and parametric extrapolations are shown below.

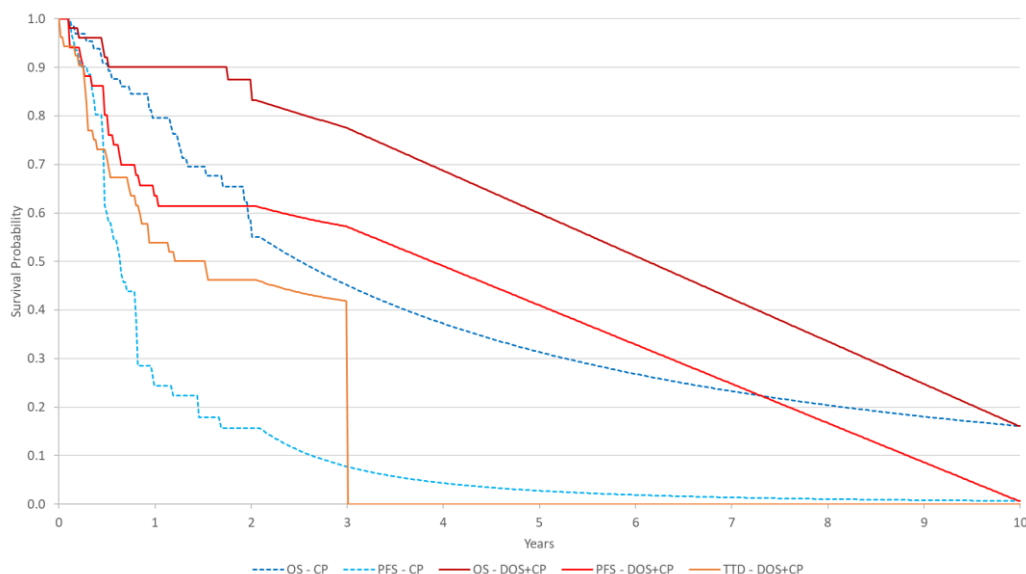
Figure 9: PFS, OS and TTD curves applied in the model base case (dMMR) – Base case



Source: Constructed using the corrected model (PSCR, base case).

Note that the Kaplan Meier plots and fitted curves depicted in Figure 9 are presented specifically for the purposes of informing the PBAC consideration. Their interpretation and application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Figure 10: PFS, OS and TTD curves applied in the model base case (dMMR) – Parametric extrapolations



Source: Constructed using the corrected model (PSCR) with application of parametric extrapolations with best fit (AIC) DOS+CP arm parametric function (OS, PFS, TTD): Exponential, generalised Gamma, Gompertz; CP arm parametric function (OS, PFS): Lognormal, log-logistic, with convergence applied.

Note that the Kaplan Meier plots and fitted curves depicted in Figure 10 are presented specifically for the purposes of informing the PBAC consideration. Their interpretation and application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.66 A summary of the key drivers of the model are presented in Table 15.

Table 15: Key drivers of the model

Description	Method/Value	Impact Base case: \$█ ¹ /QALY gained (dMMR)
Rate of Convergence	In the base case, convergence starts at three years in the model with a linear decline such that at 10 years the proportion who are progression free and alive are equal between arms. While the assumption of convergence may be considered appropriate, the rate of convergence may not sufficiently address the uncertainty associated the omission of 2L subsequent therapy use and uncertainty associated with the application of transition probabilities based on a long-term survival study (Miller 2020).	High, favours DOS+CP. The application of convergence between 3 and 7.5 years increased the ICER by 31% (dMMR).
Time horizon	Base case time horizon was 10 years. Given the length of study follow-up (around 25 months) and uncertainty associated with extrapolation methods used by the submission, this could be considered optimistic. However time horizon as a key driver was tied to the assumptions around rate of convergence.	High, favours DOS+CP. A time horizon of 5 years increased the ICER by 28% (dMMR). A time horizon of 7.5 years increased the ICER by only 1-2%. However this assumed that convergence remained at 10 years rather than at the end of the time horizon.

Source: Table 113&114, pp170-172 of the submission.

2L = second-line; CP = carboplatin=paclitaxel; dMMR = mismatch repair-deficient; DOS = dostarlimab; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year.

Note: PSCR corrected base case ICERs are \$75,000 to < \$95,000/QALY (dMMR) and \$75,000 to < \$95,000/QALY (all-comers)

The redacted values correspond to the following ranges:

¹ \$75,000 to < \$95,000

6.67 The ESC noted that the impact of the time horizon was tied to the assumptions around rate of convergence. The ESC considered that the time horizon of 10 years was

clinically reasonable for the 1L dMMR population as some patients may have an extended response to 1L treatment with immunotherapy. The PBAC recalled that a time horizon of 5 years was considered appropriate for PEM+LEN in second line treatment of advanced EC. The PBAC considered that a time horizon of 7.5 years was appropriate given the length of follow up available for the RUBY trial and uncertainty in the extrapolation of outcomes.

- 6.68 The applied efficacy values based on OS and PFS HR were not considered key drivers of the model because of the assumptions of convergence. Changing the OS and PFS HR only directly affected results between the end of median follow up (around 25 months) till the start of convergence at three years.
- 6.69 As discussed in paragraph 6.32, several AEs were included in the economic model. However these were not considered drivers in the economic model due to the small contribution to the overall incremental cost (0-1% of total incremental cost).
- 6.70 The ESC noted that the application of health care resource use had a substantial impact on the ICER, driven by the cost of 2L treatments in patients with disease progression.
- 6.71 Results of the stepped economic evaluation for the dMMR population are presented in Table 16. These results were based on an assumed price for 2L subsequent immunotherapy with PEM+LEN of \$60,000 (10 administrations, based on median cycles of KN775) per treatment course per patient.

Table 16: Results of the stepped economic evaluation (dMMR)

Step and component	DOS+CP	CP	Increment
Step 1: trial-based costs and outcomes (30 months) ^a			
Costs ^b	\$	\$2,630	\$
LY	2.1642	1.8146	0.3496
PLYG	1.6531	0.8805	0.7726
Incremental cost/extra LYG gained			\$ ¹
Incremental cost/extra PLYG gained			\$ ²
Step 2: Extrapolation to 10 years			
Costs ^b	\$	\$2,630	\$
LY	6.3595	3.9134	2.4461
PLYG	4.9082	1.5722	3.3360
Incremental cost/extra LYG gained			\$ ³
Incremental cost/extra PLYG gained			\$ ⁴
Step 3: Translation of outcomes to QALYs			
Costs ^b	\$	\$2,630	\$
QALY	4.8761	2.9506	1.9254
Incremental cost/extra QALY gained			\$ ⁵
Step 4: Curve convergence			
Costs ^b	\$	\$2,630	\$
LYG	5.4529	3.9134	1.5395
QALY	4.1678	2.9506	1.2171
Incremental cost/extra LYG gained			\$ ⁶
Incremental cost/extra QALY gained			\$ ⁷
Step 5 (base case): Inclusion of health care resource use			
Costs ^b	\$	\$77,910	\$
LYG	5.4529	3.9134	1.5395
QALY	4.1678	2.9506	1.2171
Incremental cost/extra LYG gained			\$ ⁵
Incremental cost/extra QALY gained (base case)			\$ ⁶
Step 5 (base case): Inclusion of health care resource use (corrected model)			
Costs ^b	\$	\$77,935	\$
LYG	5.4625	3.9301	1.5324
QALY	4.1757	2.9640	1.2116
Incremental cost/extra LYG gained			\$ ⁵
Incremental cost/extra QALY gained (base case - corrected)			\$ ⁶

Source: Table 105, p164 of the submission. and corrected using revised worksheet provided with the PSCR

CP = carboplatin-paclitaxel; dMMR = mismatch repair deficient; DOS = dostarlimab; ICER = incremental cost-effectiveness ratio; LY= life year; PLYG = progression-free life year; QALY = quality adjusted life year.

a Observed trial data used over the 30-month time horizon, compared to a median follow-up in RUBY of 24.8 months overall for dMMR.

b Costs were updated to reflect MBS and PBS items as of 22 August 2023

The redacted values correspond to the following ranges:

¹ \$255,000 to < \$355,000

² \$115,000 to < \$135,000

³ \$45,000 to < \$55,000

⁴ \$35,000 to < \$45,000

⁵ \$55,000 to < \$75,000

⁶ \$75,000 to < \$95,000

⁷ \$95,000 to < \$115,000

6.72 The corrected incremental cost and incremental QALYs for the all-comers cohort were \$| and 0.6702 respectively, resulting in an ICER of \$75,000 to < \$95,000. The corrected incremental cost and incremental QALYs for the pMMR cohort were \$| and 0.5189 respectively, resulting in an ICER of \$95,000 to < \$115,000. However, given that the

PFS and OS results for the pMMR cohort were not statistically significantly different in RUBY, the incremental benefit and ICER should be interpreted with caution.

- 6.73 Of the 1.851 life years gained in the model (undiscounted), 0.635 (34%) were accumulated during the 30-month “trial-based” period of the model (step 1) and the remaining 1.216 (66%) were accumulated during the extrapolated period of the model. The ESC considered that the modelled life years gained (1.532, discounted) was high compared with other immunotherapies (e.g. 0.70 LY gained for 2L PEM+LEN, Table 11 Pembrolizumab PSD, March 2022 PBAC meeting) and likely to be optimistic for the advanced/recurrent setting.
- 6.74 The results of key univariate and multivariate sensitivity analyses for the dMMR population are summarised in Table 17.

Table 17: Results of key sensitivity analyses (dMMR)

	Incr. cost	Incr. QALYs	ICER	% Difference
Base case	\$█	1.2171	\$█ ¹	-
Base case (corrected)	\$█	1.2116	\$█ ¹	
Time horizon (10 years)				
5 years	\$█	0.8030	\$█ ²	█%
7.5 years	\$█	1.1234	\$█ ¹	█%
Discount rate (5%)				
3.5%	\$█	1.2845	\$█ ³	█%
0%	\$█	1.4666	\$█ ³	█%
Proportion using subsequent immunotherapy (56.8% (25/44) of progressed patients or 65.8% (25/38) of subsequent treatments)				
Change proportion using subsequent immunotherapy to 51.3% of progressed patients (equal to 37.2% of all patients)	\$█	1.2171	\$█ ¹	█%
Terminal care costs (\$63,048; Goldsbury 2018)				
\$0 (excluded)	\$█	1.2171	\$█ ¹	█%
PFS and OS HR (point estimate from RUBY, OS = 0.3, PFS = 0.28)				
Upper 95% CI (OS = 0.70, PFS = 0.50)	\$█	1.1048	\$█ ¹	█%
Lower 95% CI (OS = 0.13, PFS = 0.16)	\$█	1.2670	\$█ ³	█%
Convergence of survival curves (between 3 to 10 years)				
Between 3 and 7.5 years	\$█	0.9276	\$█ ²	█%
No convergence	\$█	1.9254	\$█ ⁴	█%
Method of extrapolation for OS and PFS (LT real-world data plus HRs [Miller 2020 ITT – CP arm])^a				
OS KM data up to 22 months for CP arm (base case 25.07 months)	\$█	1.1383	\$█ ¹	
DOS+CP arm parametric function ^b (OS, PFS): Exponential, generalised Gamma CP arm parametric function ^b (OS, PFS): Lognormal, log-logistic (includes convergence between 3-10 years)	\$█	1.2642	\$█ ³	█%
As above + corrected	\$█	1.2587	\$█ ³	
As above + OS KM data up to 22 months for CP arm (base case 25.07 months)	\$█	1.1298	\$█ ¹	
DOS+CP arm parametric function ^c (OS, PFS): Exponential, Gompertz CP arm parametric function ^c (OS, PFS): Exponential, log-logistic (includes convergence between 3-10 years)	\$█	1.3228	\$█ ³	█%
As above + corrected	\$█	1.3173	\$█ ³	
As above + OS KM data up to 22 months for CP arm (base case 25.07 months)	\$█	1.1951	\$█ ¹	
Multivariate sensitivity analyses				
Time horizon of 5 years and survival convergence between 3 and 5 years	\$█	0.6173	\$█ ⁵	█%
Time horizon of 7.5 years and convergence of survival curves between 3 and 7.5 years	\$█	0.9276	\$█ ²	█%

Source: Table 113, pp170-171 of the submission. Values in italics added based on PSCR corrected model

CP = carboplatin-paclitaxel; DOS = dostarlimab; dMMR = mismatch repair-deficient; HR = hazard ratio; ICER = incremental cost effectiveness ratio; Incr. = incremental; ITT = intention to treat; LT, long term; OS = overall survival; PFS = progression free survival; QALY = quality adjusted life year; TTD = time to treatment discontinuation.

a When parametric functions were applied, extrapolated TTD was based on a fitted Gompertz parametric curve.

b Best fitting per AIC

c Best fitting per BIC

The redacted values correspond to the following ranges:

¹ \$75,000 to < \$95,000

² \$95,000 to < \$115,000

³ \$55,000 to < \$75,000

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⁴ \$35,000 to < \$45,000

⁵ \$135,000 to < \$155,000

- 6.75 In the model's base case for the dMMR cohort 47.66% of all CP patients were estimated to receive subsequent immunotherapy (2L PEM+LEN) and 42.74% for all-comers⁵. This was higher than observed in RUBY (38.5% for dMMR and 34.5% for all-comers) and the assumed usage of 2L PEM in the March 2022 PEM submission considered by the PBAC (37.2%; see Table 19). Adjusting the proportion of 2L immunotherapy use to 37.2% overall, increased the ICER by 6-7%. The PSCR noted the marginally higher estimate of 2L immunotherapy use in the economic model compared to RUBY was expected given this accounts for patients progressing beyond the trial period, who would then become eligible for subsequent treatment.
- 6.76 Given the assumption of convergence such that the number of deaths was equal at 10 years, differences in terminal care costs (\$63,048 per death, based on Goldsbury 2018) were wholly a function of discounting. Removal of terminal care costs increased the ICER by 5%. The PBAC noted that the terminal care costs were relatively high; terminal care costs of \$51,413 were applied in the PEM+LEN submission (Table 13, Pembrolizumab PSD, March 2022/2023 PBAC meetings). The alternative sources presented in the submission were also lower: \$42,946 (Reeve 2018) and \$32,950 (AIHW). The PBAC noted that use of the highest terminal care cost favoured dostarlimab.
- 6.77 Overall, the ESC considered that the modelled outcomes were highly uncertain due to the immature overall survival and likely to be optimistic for patients with advanced/recurrent EC. Further, the PBAC noted that the small number of patients in the dMMR cohort also increased uncertainty in the modelled outcomes. The ESC considered that the multivariate sensitivity analyses applying both earlier convergence and a shorter time horizon (Table 17) were potentially informative, given the combined issues of uncertainty associated with long term incremental benefit with DOS+CP relative to CP, the underestimated OS in the CP arm due to omission of 2L immunotherapy and the potential overestimate of DOS+CP OS due to 2L immunotherapy use in the DOS+CP arm in RUBY.
- 6.78 The PBAC noted that the pre-PBAC response provided a revised base case applying convergence between 3 and 7.5 years, with a time horizon of 7.5 years and a lower effective price of \$| per vial (reduced from \$| per vial). This maintained the ICER at \$75,000 to < \$95,000 per QALY for the dMMR population. The Pre-PBAC response noted that using parametric extrapolations reduced this ICER to less than \$75,000 to < \$95,000 per QALY. The PBAC considered this was an appropriate model

⁵ Note that the modelled subsequent immunotherapy proportions were provided 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.

scenario given uncertainty in the modelled outcomes and uncertainty regarding their applicability to Australian clinical practice in terms of 2L immunotherapy.

Drug cost/patient/course

6.79 Drug acquisition costs for DOS as proposed in the submission are summarised in Table 18 for the dMMR population. The Pre-PBAC response proposed a reduction in the price for dostarlimab from \$| to \$| EMP per 500 mg vial, which would reduce the costs shown in Table 18. Costs for CP were not included in Table 18 as they were expected to remain relatively unchanged.

Table 18: Drug cost per patient for DOS (dMMR) (as per submission proposed price)

	Trial dose and duration	Model	Financial estimates
Mean number of initiation doses	6 ^a	5.10 ^c	5.66 ^f
Mean number of maintenance doses	8.4 ^a	12.0 ^d	11.16 ^g
Mean duration	71.3 weeks	87.32 weeks ^e	86.84 weeks ^e
Mean duration - corrected		88.94 weeks*	88.94 weeks*
Cost/patient/course - corrected	\$ ^b	\$	\$

Source: Estimated during the evaluation using table 21, p54-55 of the submission, economic model and financial estimate spreadsheets, corrected values from PSCR financial estimates and economic model

dMMR = mismatch repair-deficient; DOS = dostarlimab; Q3W = every three weeks; Q6W = every six weeks

a RUBY reported a total of 14.4 doses, assume 6 doses (Q3W) for initiation and remainder as maintenance.

b Price based on \$| x first 6 doses + \$| x subsequent 8.4 doses, weighted by a 67% private and 33% public split, as used by the submission in their estimates.

c Estimated during evaluation by dividing total cost of DOS for first six administrations for initiation (which accounted for a relative dose intensity of 94.37%) by the unit cost of DOS given Q3W.

d Estimated during evaluation by dividing total cost of DOS after the first six cycles (which accounted for a relative dose intensity of 97.27%) by the unit cost of DOS given Q6W.

e The treatment duration from the model was calculated during the evaluation and differed to the values reported by the submission (used in the financial estimates). The submission's duration of treatment estimate (86.84 weeks*) was based on the sum of the proportion of patients on treatment at each cycle, but included periods for when patients would not have been receiving treatment, which was not accurate. For example, the estimate assumed 94.3% of patients were on treatment in cycles 2 and 3 even though patients received no treatment at these time points as they were dosed at the first cycle and every 3 or 6 cycles thereafter.

f Estimated by multiplying a relative dose intensity of 94.37% for the first 6 cycles (Q3W for 18 weeks).

g Estimated by multiplying a relative dose intensity of 97.27% for 68.84 weeks*, using Q6W dosing.

* Note that the modelled dose and duration of treatment were provided 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.

6.80 A table comparing total subsequent 2L immunotherapy usage in RUBY, the economic model and the financial estimates was constructed during the evaluation (Table 19). Estimates from the submission's economic model and financial estimates were higher than reported in RUBY and the assumptions in the March 2022 pembrolizumab submission (37.2%), which may be reasonable as it accounts for patients who progress beyond the trial period. No usage for 2L immunotherapy in the DOS+CP arm was assumed in the economic model or financial estimates in the submission.

Table 19: Total subsequent immunotherapy usage (2L PEM+LEN) presented by the submission

	RUBY (n/N)		Economic model		Financial estimates	
	dMMR	All-comers	dMMR	All-comers	dMMR	All-comers
DOS+CP arm	15.1% (8/53)	15.5% (38/245)	Assumed to be 0%*		Assumed to be 0%*	
CP arm	38.5% (25/65)	34.5% (86/249)	47.7% ^{a*}	42.7% ^{a*}	46.6% ^{b*}	

Source: Constructed during the evaluation using information sourced from outputs from the submission's economic model (Excel workbook 'Jemperli (dostarlimab) 1L EC CUA_July 2023') and Table 15, pembrolizumab PSD, March 2022 PBAC meeting.

1L = first-line; 2L = second-line; CP = carboplatin-paclitaxel; DOS = dostarlimab; dMMR = mismatch repair deficient; ECOG = Eastern Cooperative Oncology Group; PBC = platinum-based chemotherapy; PEM+LEN = Pembrolizumab + Lenvatinib; PSD = public summary document

a Calculated during the evaluation. Reported by the submission as 43.8%* but could not be verified during the evaluation.

b The submission claimed that 46.6%* of 1L patients would be treated with 2L PEM+LEN (49%* x 95%*) in the CP arm in the financial estimates but this did not account for only the proportion of patients with ECOG PS of 0-1 (80%*).

* Note that the modelled subsequent immunotherapy proportions were provided 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.

Estimated PBS usage & financial implications

6.81 This submission was not considered by DUSC.

6.82 The submission used an epidemiological approach to estimate the financial impact of listing DOS (for use in combination with PBC) for dMMR patients (Population 1) and all-comers (Population 2) on the PBS for the treatment of 1L A/R EC. The submission estimated the eligible population from the following patient populations: Stage I/II EC patients who experience first recurrence; Stage III patients who were treated with curative intent and experience first recurrence; primary advanced (Stage III and Stage IV) patients; prevalent patients with first recurrent Stage I-III disease; and grandfathered patients. The submission considered the use of subsequent immunotherapy as an offset only (i.e. the proportion of patients who would have otherwise been treated with 2L PEM+LEN) in their financial estimates.

6.83 Key data sources used for estimating the financial estimates are presented in Table 20.

Table 20: Key inputs for financial estimates

Data	Value and Source	Comment
Eligible population		
Incident EC patients	Calculated by applying the average growth rate (3%) based on the AIHW uterine cancer incidence projections for 2019-2022 to the incidence of uterine cancer in 2022 (AIHW ICD-10: C54 and C55). Then the application of 95% (proportion of uterine cancer reported as EC) to derive the projected incidence of EC (as reported by Cancer Council, and as used in PEM (Table 15, pembrolizumab PSD, March 2022).	Sources and approach were consistent with PEM estimates.
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% Source: Surveillance, Epidemiology, and End Results (SEER) database and clinician	These values were previously used in the submission for PEM (2L EC) (Table 15, pembrolizumab PSD, March 2022 meeting). In a separate submission for DOS (2L EC), the proportion of patients with Stage III-IV disease was estimated to be 21% (vs 18% used by this

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Data	Value and Source	Comment
	feedback, as used in the PEM submission (Table 15, pembrolizumab PSD, March 2022 meeting).	submission) (Table 23, dostarlimab PSD, November 2022 meeting). The separation of Stage III disease with curative intent was in line with previous DUSC advice that “a proportion of Stage III patients would be treated with curative intent” (Table 14, dostarlimab PSD, March 2022 PBAC meeting).
First recurrence	Proportion with first recurrence Stage I/II: 13% Stage III curative: 36% Source: Fung-Kee-Fung 2006; De Boer 2019	DUSC previously considered the 13% estimate of recurrence in Stage I/II EC may be reasonable (p5, dostarlimab DUSC advice, March 2022 meeting). The evaluation noted the recurrence rate of 36% for Stage III patients may be overestimated given this was based on patients with high-risk EC (PORTEC3, De Boer 2019). The PBAC considered 30% recurrence rate for stage III patients would be appropriate, based on the 5 year failure-free survival in PORTEC3 of 70.9% . .
Proportion expected to receive 1L PBC	90% Source: Assumption	The application of the proportion expected to receive 1L PBC and the proportion with ECOG 0-1 may result in potential double counting given patients expected to receive 1L PBC would have to be suitable for or well enough to tolerate treatment. The ESC noted that in consideration of PEM, the PBAC considered that the submission’s increase from 70% to 75% of patients receiving 1L PBC was not reasonable. The PBAC considered that the proportion of patients with ECOG 0-1 and expected to receive 1L PBC of 72% (90% \times 80%) was reasonable.
Proportion with ECOG 0-1 (DOS+CP)	80% Source: Table 15, pembrolizumab PSD, March 2022 PBAC meeting	
Proportion with dMMR	27% Source: Gupta 2021	DUSC previously considered this may be reasonable (Table 14, dostarlimab PSD, March 2022 PBAC meeting).
Proportion of patients treated with 1L PBC who are eligible for 2L PEM+LEN	49% Source: Based on 51% response rate in Miller 2012 RCT, as used in the PEM submission (Table 15, pembrolizumab PSD, March 2022 meeting).	DUSC previously considered this estimate may be reasonable and it was accepted by the PBAC (Table 15, pembrolizumab PSD, March 2022 PBAC meeting).
Proportion with ECOG 0-1 (2L PEM+LEN)	Assumed to be 100% by the submission.	The submission did not adjust for the proportion with an ECOG performance score of 0-1 for 2L PEM+LEN. Patients’ ECOG status may have changed between 1L and 2L therapies are considered. This omission may lead to an overestimate of the offset costs of PEM+LEN. The proportion of patients with ECOG 0-1 for 2L PEM+LEN was estimated to be 80% in the submission for PEM. DUSC and PBAC previously considered this was reasonable in the 2L setting (Table 15, pembrolizumab PSD, March 2022 meeting). The overall proportion of 1L patients treated with 2L PEM would therefore be 49% \times 80% \times 95% uptake = 37%. The PBAC considered that the

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Pre-PBAC revised estimates which apply a lower price for dostarlimab. The financial estimates below assume a cost of \$60,000 per course per patient for 2L PEM+LEN. Current script use of CP was expected to be the same as the script use of CP (in combination with DOS) in the proposed listing scenario, therefore there was no financial impact due to changes in CP utilisation.

- 6.85 The PSCR presented revised base case financial estimates that addressed the issues raised above, specifically: the removal of adjustment for ECOG 0-1 for DOS+CP, removal of half-cycle correction in the derivation of the prevalent population, adjusting for ECOG 0-1 for 2L PEM+LEN (80%), and a revised mean duration of DOS treatment. The ESC noted these revisions resulted in a substantial increase in the patient numbers and financial impact for dostarlimab.

Table 21: Estimated use and financial implications (dMMR) revised PSCR

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimation of use and financial impact of the proposed medicine (PBS and RPBS)						
Pts treated with DOS+CP (█%) ^a	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Grandfathered patients	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts						
Total DOS scripts	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
PBS/RPBS cost less co-pay						
DOS total (eff)	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³
Estimation of changes in use and financial impact of other medicines (PBS and RPBS)						
PEM+LEN PBS/RPBS cost less co-pay	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴
Net cost to PBS/RPBS (eff)	\$█ ⁵	\$█ ³	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ³
Net MBS costs	\$█ ⁶	\$█ ⁶	\$█ ⁶	\$█ ⁶	\$█ ⁶	\$█ ⁶
Net cost to Govt health budget (eff)	\$█ ⁵	\$█ ³	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ³
Pre-PBAC revised (effective price \$█ per vial)						
Dostarlimab cost to PBS/RPBS (effective)	\$█ ⁵	\$█ ³	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁵
Cost offsets (PEM+LEN) to PBS/RPBS ^a	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴
Net costs to PBS/RPBS	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁵

Source: Tables 125, 128, 130, 133, 135, 137, 139, 145&147, pp189-194, 196-199, 203 & 204 of the submission.

Footnotes shaded in grey indicate values which differed to all-comers population.

2L = second-line; CP = carboplatin-paclitaxel; dMMR = mismatch repair deficient; DOS = dostarlimab; eff = effective; Govt = government; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; PEM+LEN = pembrolizumab + lenvatinib; pts = patients; RPBS = Repatriation Pharmaceutical Benefits Scheme.

^a Including < 500 prevalent patients (< 500 prevalent patients in revised estimates). An adjustment involving a deduction of the first recurrent Stage I, II and Stage III curative grandfather patients (n=< 500) was made by the submission to avoid double counting.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$20 million to < \$30 million

⁴ net cost saving

⁵ \$10 million to < \$20 million

⁶ \$0 to < \$10 million

- 6.86 With the Pre-PBAC revised financial estimates the estimated net cost to the PBS/RPBS of listing DOS at the proposed effective price (\$█ AEMP per vial) was:

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- \$10 million to < \$20 million in Year 1, increasing to \$10 million to < \$20 million in Year 6 for dMMR patients. The total cost over the first six years of listing was \$80 million to < \$90 million.
 - \$30 million to < \$40 million in Year 1 to \$30 million to < \$40 million in Year 6 for all-comers. The total cost over the first six years of listing was \$200 million to < \$300 million .
- 6.87 The evaluation noted the recurrence rate (36%) used for Stage III may be overestimated given this was based on high-risk EC patients. These patients were also treated with specific interventions, and it was unclear whether these would be reflective of the PBS population. The PBAC considered this should be revised to 30% based on the 5-year failure-free survival in PORTEC3 (De Boer 2019) of 70.9%.
- 6.88 The PBAC noted the duration of treatment was amended in the PSCR and pre-PBAC revised estimates to align with the corrected economic model, which was reasonable.
- 6.89 The evaluation noted the costs of AEs were not considered by the submission, which may underestimate the financial impact of DOS. This was inconsistent with the clinical evidence and the economic model presented by the submission, which claimed that DOS+CP had an inferior safety profile compared to CP alone. The PBAC noted this would not have a substantial impact on the financial estimates as AE costs in the economic model were minimal.
- 6.90 Overall, the evaluation considered it was likely that the financial impact may be underestimated in the submission estimates as the number of eligible patients was underestimated (e.g. from inaccurate and inappropriate application of half cycle corrections), the duration of treatment with DOS may have been underestimated and the offset from 2L PEM + LEN may have been overestimated. The ESC noted that these factors were revised in the PSCR and considered that the revisions appeared to be methodologically reasonable, whilst also noting they resulted in substantial increases in patient numbers.
- 6.91 The financial estimates included < 500 grandfathered patients. The submission noted that a patient access program was anticipated to commence in 2023 for the treatment of patients with 1L A/R dMMR EC. The submission subtracted < 500 patients from the prevalent patients as it was assumed that < 500 out of the < 500 patients would be first recurrent Stage I/II and Stage III curative patients who will contribute towards the prevalent pool. The PBAC considered this was reasonable. Grandfathered patients were assumed to only use maintenance doses (reflected as continuing scripts) in the financial estimates.

Quality Use of Medicines

- 6.92 The submission stated that in addition to routine pharmacovigilance and risk minimisation activities, the Sponsor intended to implement medical education activities and a Patient Card (additional TGA risk minimisation measure) to promote safe and effective use of DOS in clinical practice. The purpose of the Patient Card was

to inform patients about signs and symptoms of the most common immune-related events with DOS, and the main required actions to be taken if they experience any signs or symptoms of immune-related adverse reactions.

Financial Management – Risk Sharing Arrangements

- 6.93 The Sponsor indicated it was willing to enter into a RSA to facilitate listing of DOS plus platinum-containing chemotherapy for the treatment of 1L A/R EC. The ESC noted that a combined cap with 2L PEM+LEN may be appropriate given the cost-effectiveness of DOS relies on a reduction in use of 2L PEM+LEN. The Pre-PBAC response requested a separate RSA for 1L dostarlimab given the different patient population (1L, dMMR vs 2L, all-comers). The PBAC considered that a shared cap would be appropriate, given the substantial overlap in patient populations and because the cost-effectiveness for DOS relies on cost offsets for 2L PEM+LEN. The PBAC considered that the caps should be increased to account for additional patients treated 1L DOS, with offsets for 2L PEM+LEN and considered that the financial estimates, with minor changes as described in paragraph 7.10, provided a reasonable basis for the increase.

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

7 PBAC Outcome

dMMR population

- 7.1 The PBAC recommended the listing of dostarlimab in combination with platinum-containing chemotherapy (DOS+CP), for the treatment of primary advanced or first recurrent endometrial cancer that is mismatch repair deficient (dMMR), on the basis that it should be available only under special arrangements under Section 100 (Efficient Funding of Chemotherapy). The PBAC is satisfied that dostarlimab provides, for some patients, a significant improvement in efficacy over platinum-containing chemotherapy alone, noting a clinical benefit from first line treatment for this population. The PBAC considered that, for the dMMR population, dostarlimab would be acceptably cost effective with a price reduction to account for the uncertain longer-term outcomes, including the uncertain gain in overall survival.
- 7.2 The PBAC noted that there is a high clinical need for effective treatment of endometrial cancer and considered that there was a clear clinical benefit for first line treatment with dostarlimab in the dMMR population.
- 7.3 The PBAC considered that the PBS listing should be aligned to the proposed indication and the conditions of use in the RUBY trial, and therefore should specify initiation of dostarlimab must be in combination with platinum-containing chemotherapy, and the clinical criteria which removed the requirement for combination treatment in cases of intolerance or a contraindication should be removed. The proposed criteria were otherwise consistent with the patient population and treatment interventions in the RUBY trial and the PBAC considered they were appropriate.

- 7.4 The PBAC considered that carboplatin and paclitaxel was the appropriate comparator for the dMMR population. The PBAC also noted that 2L PEM+LEN was a relevant comparator for a proportion of the population, as treatment with 1L DOS would exclude PBS-subsidised use of 2L PEM+LEN.
- 7.5 The PBAC noted that the submission was based on one head-to-head trial comparing DOS+CP to CP alone (RUBY). The PBAC noted that the dMMR population was a relatively small proportion of the patients included in RUBY (118/494, 23.9%). The PBAC considered the submission's claim of superior efficacy for DOS+CP compared to CP alone in the dMMR cohort was reasonably supported by the PFS results in the RUBY trial (HR = 0.28, 95% CI 0.16, 0.50). However, although there was separation in the OS KM curves (HR = 0.30, 95% CI 0.13, 0.70), OS was not formally tested for statistical significance and was based on a small number of events. Therefore, the PBAC considered that the magnitude of the OS benefit was uncertain.
- 7.6 The PBAC noted that the submission presented a cost-utility analysis based on outcomes of the RUBY trial. As the data from the RUBY trial were immature, extrapolation of the outcomes beyond the trial median follow-up for the CP arm was based on long-term data from Miller (2020), a phase III, randomised, open-label study of CP versus paclitaxel-doxorubicin-cisplatin in 1L A/R EC. After the median follow up of RUBY, OS and PFS HRs from RUBY were applied to the CP arm to generate results for DOS+CP. The PBAC considered there was a high level of uncertainty for the extrapolated outcomes in the economic model due to the immature OS data and the modelled outcomes were likely to be optimistic for patients with advanced/recurrent EC. The PBAC noted that the small number of patients in the dMMR cohort also increased uncertainty in the outcomes informing the model. The PBAC considered it would be appropriate to use 22 months of KM data before extrapolating OS for the CP arm, given the sharp drop in OS between 22 and 24 months, based on a small number of events.
- 7.7 The PBAC noted that 2L PEM+LEN was represented, to some extent, in the RUBY trial, where 53% of patients in the CP arm who received subsequent treatment were treated with immunotherapy (38.5% overall). However, it was unclear whether the extent of 2L immunotherapy in the RUBY trial would reflect Australian clinical practice and it is unlikely the benefit from 2L immunotherapy would have been fully captured in the outcomes of RUBY due to the immaturity of the OS data. The PBAC noted that 2L immunotherapy was not represented in the long-term survival data from Miller (2020) used in the economic evaluation for extrapolation of the trial data.
- 7.8 Between three years and the modelled 10-year time horizon, linear convergence of DOS+CP survival curves to CP survival curves was applied, with complete convergence at 10 years. The submission noted that convergence was applied to compensate for subsequent immunotherapy in Australian clinical practice. The PBAC considered that the convergence applied in the model base case was unlikely to sufficiently reflect the combined issues of: (1) uncertainty associated with long term incremental benefit with DOS+CP relative to CP, (2) the underestimated OS in the CP arm due to omission

of 2L immunotherapy in the long-term follow-up data, and (3) the potential overestimate of DOS+CP OS due to 2L immunotherapy use in the DOS+CP arm in RUBY. The PBAC considered that applying convergence between 3 and 7.5 years, with a time horizon of 7.5 years, as proposed in the pre-PBAC response, was appropriate given uncertainty in the modelled outcomes and their applicability to Australian clinical practice. The PBAC also noted that the terminal care costs included in the model were high and favoured dostarlimab. The PBAC considered that the terminal care costs should be reduced to \$51,413 to align with those used for 2L PEM+LEN.

- 7.9 The PBAC considered that with application of the approach and inputs described in paragraphs 7.6 and 7.7, dostarlimab would be acceptably cost effective with a reduction in price resulting in an ICER of \$55,000 to < \$75,000/QALY. The PBAC considered that an ICER of \$55,000 to < \$75,000/QALY would reflect the high clinical need and clear PFS benefit demonstrated for dostarlimab, but uncertain magnitude of OS benefit. The PBAC noted that the ICERs presented in the submission used an assumed cost for 2L PEM+LEN of \$60,000 per patient as the effective prices were unknown to the sponsor. The PBAC considered that model, resulting in an ICER of \$55,000 to < \$75,000/QALY, should incorporate the effective price for 2L PEM+LEN to accurately reflect the cost-offset for reduced 2L treatment.
- 7.10 The PBAC noted that the financial estimates used an epidemiological approach that was largely consistent with the approach accepted for PEM+LEN and considered this was appropriate. The PBAC considered that the changes applied in the PSCR were appropriate and had corrected errors identified in the evaluation. The PBAC noted that the recurrence rate (36%) used for Stage III may be overestimated and considered this should be revised to 30% based on the Stage III 5-year failure-free survival in PORTEC3 (De Boer 2019). The PBAC also considered that the proportion of patients treated with 1L PBC who are eligible for 2L PEM+LEN (49%) would already incorporate ECOG status and uptake therefore should not be reduced further to account for these factors. The PBAC noted that application of the revised cost-effective price for dostarlimab would reduce the total financial impact of 1L dostarlimab, and the effective price for PEM+LEN would need to be included in the financial estimates to accurately reflect the cost-offset for reduced 2L treatment. The PBAC considered that with application of these changes the financial estimates were acceptable.
- 7.11 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. and the PBAC considered that the financial estimates, with minor changes as described in paragraph 7.10 would provide a reasonable basis for the increases.
- 7.12 The PBAC recommended that dostarlimab should not be treated as interchangeable with any other drugs.

- 7.13 The PBAC advised that dostarlimab is not suitable for prescribing by nurse practitioners.
- 7.14 The PBAC recommended that the Early Supply Rule should not apply.
- 7.15 The PBAC noted that no flow-on changes to existing listing were identified as the listing for 2L PEM+LEN currently excludes use of prior PD-L1/PD-1 inhibitors.
- 7.16 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation dostarlimab:
- a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy, over alternative therapies as the magnitude of the OS benefit was uncertain;
 - b) The treatment is not expected to address a high and urgent unmet clinical need because 2L PEM+LEN is also available for this population;
 - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

All-comers population

- 7.17 The PBAC did not recommend listing of dostarlimab for the treatment of primary advanced or first recurrent endometrial cancer in the broader all-comers population, which includes mismatch repair proficient (pMMR) endometrial cancer. The PBAC noted that there is a high clinical need for 1L treatments for endometrial cancer but considered that the clinical benefit in the pMMR population was unclear, noting that it was possible that these patients may benefit more from 2L PEM+LEN.
- 7.18 The PBAC considered that the primary reason for this outcome was due to the comparative clinical evidence provided.
- 7.19 The PBAC considered that, as for the dMMR population, carboplatin and paclitaxel was the appropriate comparator for the all-comers population, but 1L carboplatin and paclitaxel followed by 2L PEM+LEN is also a relevant comparator for a proportion of the population. In addition, there are several near market comparators for 1L treatment of advanced or first recurrent EC and the outcomes of the trials are likely to be particularly relevant for patients with pMMR.
- 7.20 Therefore, the PBAC considered that in the context of the much smaller demonstrated PFS benefit in the pMMR population compared with the dMMR population, and the uncertain OS benefit, the clinical place for dostarlimab as 1L treatment for pMMR EC was unclear. Further, the PBAC noted that the sponsor had not yet submitted an application to the TGA for dostarlimab in the broader all-comers population.

- 7.21 The PBAC noted that the clinical evidence for the all-comers population was based on all patients included in the RUBY trial (N=494), including both dMMR and pMMR EC. Although a statistically significant PFS benefit in favour of DOS+CP was observed in the all-comers population (HR=0.64; 95%CI 0.51, 0.80), the OS benefit did not achieve statistical significance (HR=0.64; 95%CI 0.46, 0.87). The PBAC considered that the claim of superior comparative effectiveness was not sufficiently supported for the all-comers population. Although there was a statistically significant PFS benefit, this appeared to be largely driven by the dMMR cohort and as the data are immature, it is unclear whether patients with pMMR EC would have the same benefit from first line dostarlimab as for first line chemotherapy followed by second line combination treatment with PEM+LEN (where an OS benefit was demonstrated).
- 7.22 The PBAC considered that the model and financial estimates for all-comers were not relevant as the clinical claim was not accepted. The PBAC considered any resubmission for dostarlimab for the pMMR population (the remainder of the all-comers population) should address the key issue of comparative clinical evidence by presenting more mature trial data, demonstrating an overall survival benefit that is equivalent or superior to 2L PEM+LEN. The PBAC also considered that there should be consideration of the near market comparators to help inform the clinical place of DOS+CP as 1L treatment of EC. The PBAC considered that for any resubmission the economic evaluation and financial estimates should be revised to be consistent with those accepted for the dMMR population. The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

General

- 7.23 The PBAC noted that this submission is not eligible for an Independent Review as it is a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new item:

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
DOSTARLIMAB Injection	NEW (Public) NEW (Private)	500 mg	5
Available brands			
Jemperli dostarlimab 500 mg/10 mL injection, 10 mL vial			
Restriction Summary [new]			
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners			
Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED) [new/existing code]			

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	Administrative Advice: No increase in the maximum number of repeats may be authorised.		
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.		
	Administrative Advice: Special Pricing Arrangements apply.		
	Severity: Primary advanced or first recurrent		
	Condition: Endometrial cancer		
	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, or (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, at the time of initiating treatment with this drug, a WHO performance status no higher than 1		
MEDICINAL PRODUCT Form			
	PBS item code		
	Max. Amount		
	No. of Rpts		
DOSTARLIMAB injection	NEW (Public) NEW (Private)	1,000 mg	3
Available brands			
Jemperli dostarlimab 500 mg/10 mL injection, 10 mL vial			
Restriction Summary [new]			
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners			
Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED) [new/existing code]			
	Administrative Advice: No increase in the maximum number of repeats may be authorised.		
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.		
	Administrative Advice: Special Pricing Arrangements apply.		
	Treatment Phase: Continuing treatment		

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	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.		
MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
DOSTARLIMAB Injection	NEW (Public) NEW (Private)	1,000 mg	3
Available brands			
Jemperli dostarlimab 500 mg/10 mL injection, 10 mL vial			
Restriction Summary [new]			
	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals		
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners		
	Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED) [new/existing code]		
	Administrative Advice: No increase in the maximum number of repeats may be authorised.		
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.		
	Administrative Advice: Special Pricing Arrangements apply.		
	Treatment Phase: Transitioning from non-PBS to PBS subsidised treatment – ‘Grandfather’ treatment		
	Clinical criteria:		
	Patient must have deficient mismatch repair (dMMR) endometrial cancer, as determined by immunohistochemistry test,		
	AND		
	Clinical criteria:		
	Patient must have received non-PBS subsidised treatment with this drug for this condition prior to [PBS listing date],		
	AND		
	Clinical criteria:		
	The condition must be, prior to initiation of non-PBS-subsidised treatment with this drug, unsuitable for at least one of the following: (i) curative surgical resection, (ii) curative radiotherapy		
	AND		
	Clinical criteria:		
	The condition must be, prior to initiation of non-PBS-subsidised treatment with this drug, either: (i) untreated with systemic therapy, or (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 have, at the time of initiating treatment with this drug, a WHO performance status no higher than 1		
	AND		

	Clinical criteria:
	The treatment must be, at initiation of non-PBS-subsidised treatment with this drug, used in combination with platinum-containing chemotherapy
	AND
	Clinical criteria:
	Patient must not have developed disease progression while receiving non-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.
	Administrative Advice: 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.
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

This restriction 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

GSK welcomes the recommendation of dostarlimab (Jemperli®) in combination with platinum-containing chemotherapy for the treatment of primary advanced or first recurrent endometrial cancer that is mismatch repair deficient (dMMR). GSK will consider advice from the PBAC regarding Jemperli® in the broader all-comers population.