

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

1 Purpose of submission

- 1.1 The Standard Re-entry Resubmission requested Section 100 (Efficient Funding of Chemotherapy) Authority Required (STREAMLINED) listing for dostarlimab in combination with carboplatin and paclitaxel for the treatment of primary advanced or first recurrent (A/R) mismatch repair proficient (pMMR) endometrial cancer (EC).
- 1.2 Listing of dostarlimab (DOS) was requested on the basis of a cost-effectiveness analysis versus chemotherapy alone (comprised of carboplatin and paclitaxel (CP)).

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

| Component | Description |
|----------------|--|
| Population | Patients with primary advanced or first recurrent pMMR 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) + platinum-containing chemotherapy (carboplatin and paclitaxel) every 3 weeks Subsequent cycles: Dostarlimab (1,000 mg) monotherapy every 6 weeks for up to 3 years or until disease progression, whichever occurs first. |
| Comparator | Main comparator: Carboplatin and paclitaxel every 3 weeks for six cycles, followed by second-line pembrolizumab + lenvatinib in a proportion of patients. Near market comparator: Durvalumab + chemotherapy ± Olaparib and Pembrolizumab + chemotherapy |
| Outcomes | Overall survival, progression-free survival, objective response rate, duration of response, health-related quality of life, safety. |
| Clinical claim | In patients with primary advanced or first recurrent pMMR 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. |

Abbreviations: AUC = area under curve; pMMR = proficient mismatch repair

Source: Table 2, p21 of the resubmission.

Underlined text indicate change in components compared to what was previously considered by the PBAC at the November 2023 PBAC meeting.

2 Background

Registration status

- 2.1 DOS was TGA registered on 17 April 2025 for the use of DOS in combination with CP in A/R EC regardless of MMR/MSI status, i.e. the dMMR/MSI-H criteria was removed from the existing indication.
- 2.2 The TGA Delegate's overview stated the Delegate considered whether the positive efficacy results in the all-comers population are entirely driven by the efficacy in the

Public Summary Document – May 2025 PBAC Meeting

dMMR/MSI-H population, or if there is activity in the MMRp/MSS group as well. The Delegate concluded there was sufficient evidence to establish efficacy for dostarlimab plus carboplatin-paclitaxel followed by dostarlimab in the treatment of adult patients with primary advanced or recurrent MMRp/MSS EC. The Delegate also considered the persisting and significant unmet clinical need for treatment of primary advanced or recurrent EC (TGA Delegate's Overview, March 2025).

- 2.3 DOS was previously approved by the TGA for the following indications:
- 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; and
 - as monotherapy for the treatment of adult patients with recurrent or advanced mismatch repair deficient (dMMR) endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.
- 2.4 The resubmission was made under the TGA/PBAC Parallel Process. At the time of evaluation for PBAC consideration, the TGA clinical evaluator report was available, and the delegate's overview was provided with the pre-sub-committee response (PSCR) on 28 March 2025.

Previous PBAC consideration

- 2.5 At its November 2023 meeting, the PBAC recommended DOS for use in 1L A/R dMMR EC. The PBAC also considered a request for the all-comers population (i.e. inclusive of both dMMR and pMMR) at the November 2023 meeting but this was not recommended. The PBAC considered that the clinical benefit of DOS in the pMMR population was unclear, noting it was possible that these patients may benefit more from 2L PEM+LEN (paragraph 7.17, dostarlimab public summary document [PSD], November 2023 PBAC meeting).

Public Summary Document – May 2025 PBAC Meeting

Table 2: Summary of key matters of concern

| Component | Matter of concern | How the resubmission addresses it |
|---|---|--|
| TGA indication | The PBAC noted that the sponsor had not yet submitted an application to the TGA for dostarlimab in the broader all-comers population (i.e. inclusive of pMMR). (Paragraph 7.20, dostarlimab PSD, November 2023) | Addressed. The resubmission was submitted under a parallel TGA/PBAC process, with the proposed TGA indication being for use in 1L A/R EC irrespective of MMR status. TGA has approved registration for the new indication (TGA Approval Letter, 11 April 2025). |
| Comparator | The PBAC considered that 1L CP was the appropriate comparator in the all-comers population, but 1L CP followed by 2L PEM+LEN was also a relevant comparator, and there were several near market comparators which were likely to be particularly relevant for patients with pMMR and any resubmission should include consideration of the near market comparators (Paragraph 7.19 and 7.22, dostarlimab PSD, November 2023) | Partially addressed. Main comparator remains 1L CP (based on the RUBY trial), but it was argued that a substantial proportion of patients in RUBY also used subsequent immunotherapy which was representative of 2L PEM+LEN (50.7%). However, the ESC noted characteristics of these patients who used subsequent immunotherapy and the duration of treatment was unknown. The ESC noted approx. 49% of patients would receive 2L PEM+LEN in Australian clinical practice. Naïve indirect comparison presented against near market comparators, PEM and DUR. |
| Clinical benefit | The PBAC considered that in the context of the much smaller demonstrated PFS benefit in the pMMR population compared with the dMMR population, and the uncertain OS benefit, the clinical place for dostarlimab as 1L treatment for pMMR EC was unclear. (Paragraph 7.20, dostarlimab PSD, November 2023) | Partially addressed. Updated OS data from RUBY IA2 presented for dMMR, pMMR and all-comers, and OS was now considered statistically significantly different in favour of DOS in the all-comers population. However, this benefit was likely driven by the efficacy of DOS in the dMMR population. The ESC noted the updated data showed a reduced benefit from the previous submission; 0.79 (IA2) compared to 0.73 (IA1). |
| | The PBAC considered any resubmission for DOS for the pMMR 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. (Paragraph 7.22, dostarlimab PSD, November 2023) | Not addressed. Efficacy of 2L PEM+LEN was not specifically considered in the resubmission. The characteristics of patients who were treated with subsequent immunotherapy in RUBY, and the duration of subsequent immunotherapy was unknown and therefore may not be applicable to the PBS population. The comparative efficacy (and safety) of 1L DOS+CP and 1L CP followed by 2L PEM+LEN in pMMR EC should be considered uncertain. |
| Economic evaluation and financial estimates | 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. (Paragraph 7.22, dostarlimab PSD, November 2023) | Partially addressed. The nominal ICER in the resubmission was similar to the November 2023 submission for dMMR however the resubmission's model included adjustments which favoured DOS and the results from the two (re)submissions cannot be compared directly. In the financial estimates, the number of eligible EC patients was reasonably consistent with the November 2023 submission, with the pMMR population (73%) being the complement to the dMMR population (27%). |

1L = first line; 2L = second line; A/R = locally advanced or recurrent; CP = carboplatin + paclitaxel; dMMR = mismatch repair deficient; DOS = dostarlimab; DUR = durvalumab; EC = endometrial cancer; IA = interim analysis; ICER = incremental cost effectiveness ratio; LEN = lenvatinib; OS = overall survival; PEM = pembrolizumab; PFS = progression free survival, pMMR = mismatch repair proficient; PSD = public summary document;

Source: Constructed during the evaluation

Public Summary Document – May 2025 PBAC Meeting

2.6 The PBAC also considered durvalumab (DUR) + CP ± olaparib (OLA) for A/R EC at the November 2024 PBAC meeting. The PBAC recommended DUR+CP for the treatment of dMMR EC on the basis of non-inferior efficacy and safety to DOS+CP. The PBAC deferred making a recommendation for the treatment of pMMR EC due to ongoing TGA considerations¹. The PSD for the November 2024 consideration of DUR was not available at the time of evaluation.

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

| 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 / Treatment of Concept: | | | |
| 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] | | | |
| Administrative Advice: No increase in the maximum number of repeats may be authorised. | | | |
| Administrative Advice: No increase in the maximum amount or number of units may be authorised | | | |
| Administrative Advice: Special Pricing Arrangements apply. | | | |
| Severity: Advanced, metastatic or 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 mismatch repair proficient (pMMR) 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: | | | |

¹ <https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2024-11/pbac-web-outcomes-11-2024.pdf>.

Public Summary Document – May 2025 PBAC Meeting

| | |
|--|--|
| | The condition must be, at treatment initiation with this drug, either: (i) untreated with systemic therapy, (ii) treated with neoadjuvant/adjuvant systemic therapy, but the cancer has recurred or progressed after more than 6 months from the last dose of systemic therapy |
| | AND |
| | Clinical criteria: |
| | Patient must not have received prior treatment with a programmed cell death-1 (PD-1) or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition |
| | AND |
| | Clinical Criteria |
| | Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score no higher than 1 prior to treatment initiation. |

| 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 / Treatment of Concept: | | | |
| 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] | | | |
| | Administrative Advice: No increase in the maximum number of repeats may be authorised. | | |
| | Administrative Advice: No increase in the maximum amount or number of units may be authorised | | |
| | Administrative Advice: Special Pricing Arrangements apply. | | |
| Indication: Advanced, metastatic or recurrent endometrial carcinoma | | | |
| Treatment Phase: Continuing treatment | | | |
| Clinical criteria: | | | |
| Patient must have previously received PBS-subsidised treatment with this drug for this condition | | | |
| AND | | | |
| Clinical criteria: | | | |
| Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this condition, | | | |
| AND | | | |
| Treatment criteria: | | | |
| Patient must not be undergoing continuing PBS-subsidised treatment where this benefit is extending treatment beyond 36 cumulative months from the first administered dose, once in a lifetime. | | | |
| Restriction Summary / Treatment of Concept: | | | |
| 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] | | | |
| Indication: Advanced, metastatic or recurrent endometrial carcinoma | | | |
| Treatment Phase: Transitioning from non-PBS to PBS subsidised treatment – ‘Grandfather’ treatment | | | |

Public Summary Document – May 2025 PBAC Meeting

| | |
|--|---|
| | Clinical criteria: |
| | Patient must have mismatch repair proficient (pMMR) 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, (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 a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score no higher than 1 prior to treatment initiation |
| | 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. |

- 3.2 The requested effective ex-manufacturer price of \$ [REDACTED] per 500 mg vial was [REDACTED] price for DOS in dMMR EC which was listed on the PBS on 1 May 2024 following recommendation by the PBAC at the November 2023 meeting.
- 3.3 The proposed maximum quantity and number of repeats were also consistent with the November 2023 submission for dMMR EC. For the initial treatment phase, the resubmission proposed that the maximum amount (500 mg) and five repeats be allowed, which aligned with the dosage recommendation for the first six doses (every three weeks (Q3W) over 18 weeks). For the continuing treatment phase, the maximum amount (1,000 mg) and three repeats were proposed, which permits

Public Summary Document – May 2025 PBAC Meeting

- approximately six months of therapy (24 weeks) between each prescription, consistent with the PBAC Guidelines.
- 3.4 Except for the requirement for patients to have pMMR EC as determined by an immunohistochemistry test (instead of dMMR EC), the requested initiation, continuing and grandfathering restrictions for DOS in pMMR 1L A/R EC presented in the resubmission were consistent with the current PBS restriction for DOS for dMMR 1L A/R EC.
 - 3.5 The requested restriction requires patients to not have developed disease progression while receiving PBS-subsidised treatment with DOS for pMMR EC, and included a requirement that limited the treatment duration to a maximum of 36 months. However, in the pivotal RUBY trial, patients were able to use DOS even with disease progression if they were clinically stable, at the investigator's discretion after discussion with the Sponsor. Patients could also use DOS for longer than 36 months following discussion between the Sponsor and the Investigator, and in RUBY at interim analysis 2 (IA2), among pMMR patients randomised to DOS+CP, 16/189 (8.5%) received treatment for longer than three years. These differences in DOS treatment duration may reduce the applicability of results from RUBY to the proposed PBS population. The draft product information (PI) also did not restrict treatment to a maximum of 36 months.
 - 3.6 The resubmission argued that biomarker specific listings were consistent with the recent PBS listings of OLA and niraparib as maintenance treatment in 1L ovarian cancer for BRCAm (BRCA mutation) and HRD BRCAwt (homologous recombination deficiency, BRCA wild-type) populations. This may not be appropriate, as patients who are HRD negative and BRCAwt remain ineligible for OLA and niraparib in 1L ovarian cancer. In contrast, if the proposed population of pMMR patients is recommended for listing, then both pMMR and dMMR EC patients would be eligible for DOS+CP, and there would not be any ineligible patients based on MMR/MSI status, therefore it may not be necessary to include both restrictions. The ESC considered a combined PBS listing for DOS+CP for A/R EC (silent on MMR status) may be appropriate.
 - 3.7 A grandfathering restriction was requested for < 500 pMMR patients anticipated to be on the sponsor's patient access program, which the resubmission stated would commence in [redacted]. A maximum amount of 1,000 mg was requested as this will provide sufficient dose (i.e., 1,000 mg every three weeks) for patients who completed the first six cycles of treatment under the access program before transitioning to PBS-subsidised treatment, as well as patients who have yet to complete the first six cycles of treatment (i.e., 500 mg every three weeks). In the resubmission's financial model, grandfathered patients were assumed to have completed the initiating phase (first 6 cycles) of treatment under the access program before transitioning to PBS-subsidised treatment.

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 is the most common type of cancer of the uterus, and accounts for about 95% of all cases of uterine cancer, the most frequently diagnosed gynaecological cancer in Australian women (Cancer Council, 2023). In Australia, the 5-year relative survival rates by stages are not available. However, in the UK, 5-year relative survival rates for Stage I, II, III and IV EC were 92.2%, 74.1%, 47.8%, and 15.1%, respectively for women diagnosed during 2013-2017 (Cancer Research UK 2019).
- 4.2 Endometrial cancers may be classified based on the mismatch repair (MMR) status, as normal/proficient (pMMR) or deficient (dMMR) tumours. The PBAC previously considered that dMMR accounts for 27% of A/R EC (paragraph 4.2, dostarlimab PBAC PSD, November 2023), with the remaining 73% classified as pMMR. dMMR tumours can develop microsatellite instability (MSI), which is a change in the length of repetitive sequences in tumour DNA compared with normal DNA. Therefore, MSI-H is the observable characteristic (phenotype) displayed when errors occur in the DNA MMR system (Luchini, 2019). The complement to this subgroup, pMMR EC, are also referred to as microsatellite stable (MSS).
- 4.3 As noted in the RUBY trial protocol v.4 (p43), benefit associated with DOS was expected to be more profound for patients with dMMR/MSI-H A/R EC tumours compared to pMMR/MSS A/R EC. Previously, the ESC had considered that MMR status was likely to be a treatment effect modifier for the outcome of progression free survival (PFS) in RUBY (Paragraph 6.24, dostarlimab PSD, November 2023 PBAC meeting).
- 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 programmed cell death protein-1 (PD-1), resulting in inhibition of binding to programmed death ligand 1 (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 resubmission claimed that the combination of immune checkpoint inhibitors with chemotherapy synergise to produce an enhanced anti-tumour response.

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

5 Comparator

- 5.1 The resubmission nominated CP as the main comparator. For a proportion of patients, 1L platinum-containing chemotherapy followed by second line (2L) pembrolizumab (PEM) plus lenvatinib (LEN) would be the comparator. The resubmission noted that

Public Summary Document – May 2025 PBAC Meeting

the PBAC previously considered that CP was the appropriate comparator for the all-comers population, but 1L CP followed by 2L PEM+LEN is also a relevant comparator for a proportion of the population (paragraph 7.19, dostarlimab PSD, November 2023 PBAC meeting). The resubmission assumed that 1L CP followed by 2L PEM+LEN would be the comparator in approximately half of the population (assumed to be 50.7% in the economic evaluation based on RUBY IA2 and 49% in financial estimates, based on a 51% reported response rate to 1L platinum-based chemotherapy as reported in Miller 2012 and accepted by the PBAC (Table 20, dostarlimab PSD, November 2023). The ESC considered the nominated comparators were appropriate. However, the clinical evidence presented may not be sufficiently representative of the second comparator (1L CP followed by 2L PEM+LEN) (see paragraph 6.12).

- 5.2 In addition, the resubmission noted that the PBAC previously considered that there should be evaluation of the near market comparators to help inform the clinical place of DOS+CP as 1L treatment of EC (paragraph 7.22, dostarlimab PBAC PSD, November 2023). To address this, the resubmission also nominated DUR+CP with or without OLA (considered by the PBAC at the November 2024 PBAC meeting) and PEM plus chemotherapy (PEM+CP) as near market comparators as both regimens had ongoing trials for 1L A/R EC, and a supplementary clinical comparison was presented as an Appendix. No direct comparative evidence was provided and instead an unanchored indirect comparison was presented (see paragraph 6.23).
- 5.3 At the November 2024 PBAC meeting, the PBAC recommended the listing of DUR+CP for dMMR EC based on non-inferiority to DOS+CP but deferred the recommendation for pMMR EC due to ongoing TGA considerations. The PBAC had not previously considered PEM+CP for 1L A/R EC.

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 presented a general overview of the population and disease in Australia. The clinician outlined the current treatment options and the limited effective treatments for advanced and recurrent endometrial cancers. The clinician noted the importance of early immunotherapy, noting approximately two thirds of women do not receive second line therapy. The clinician noted the RUBY trial showed a trend in reduced risk of death by 21% and a 7 month improvement in median overall survival in the pMMR subgroup, although it was noted this was not statistically significant. The PBAC noted the clinician suggested the OS curves remain separated, however, this was not the case for the pMMR subgroup, as the curves were converging beyond 24 months.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (3), medical

Public Summary Document – May 2025 PBAC Meeting

organisation (1), the Medical Oncology Group of Australia (MOGA) and consumer organisations (2), Inherited Cancers Australia and Rare Cancers Australia, via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with dostarlimab including improvement in quality of life to spend additional time with loved ones. The side-effects of DOS were noted but it was considered to be well-tolerated. The comments expressed high unmet need within the pMMR population and noted a trend to improved OS.

- 6.3 Inherited Cancers Australia described the need for new treatments due to increasing incidence of endometrial cancer over the past 20 years. Further it noted that chemotherapy and its side effects are difficult for patients to manage. The PBAC noted that the input by Inherited Cancers incorrectly suggested data established improved overall survival in the pMMR subgroup.
- 6.4 Rare Cancers Australia described how patients are often diagnosed at a later stage which worsens their prognosis and noted that many patients report experiencing physical, emotional, social and financial strain from the disease. It was also noted that surgical treatment heavily affects quality of life and is associated with extensive recovery time.
- 6.5 The MOGA expressed its strong support for the dostarlimab submission, categorising it as one of the therapies of “high priority for PBS listing” on the basis of the RUBY trial. The PBAC noted that the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for dostarlimab, which was 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement), based on a comparison with CP.² However, the PBAC noted that the ESMO-MCBS score refers to the all-populations rather specifically the sub-population, pMMR. MOGA also noted DOS was associated with higher rates of toxicity leading to treatment discontinuations.

Clinical trials

- 6.6 The resubmission was based on one head-to-head trial comparing DOS+CP to placebo + CP (n=494): RUBY. This was the same trial as previously considered by the PBAC at the November 2023 meeting. However, a new data cut from RUBY at IA2 (compared to IA1 in the November 2023 submission) was presented in the resubmission. RUBY IA2 reported updated results for overall survival (OS), time to disease progression on first subsequent anticancer therapy following study treatment or death (PFS2) and safety outcomes. No new PFS results (i.e. the dual primary endpoint) were available in RUBY at IA2.
- 6.7 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 placebo + CP in patients with A/R

² Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

Public Summary Document – May 2025 PBAC Meeting

EC. In part 1, eligible patients were randomised in a 1:1 ratio to the following treatment arms:

- Arm 1: DOS intravenous (IV) 500 mg in combination with CP every 3 weeks (Q3W) for 6 cycles; followed by DOS 1000 mg IV every 6 weeks (Q6W), referred to as the DOS+CP arm; or
- Arm 2: placebo IV in combination with CP Q3W for 6 cycles; followed by placebo IV Q6W, referred to as the placebo + CP arm.

6.8 Details of the trial presented in the resubmission are provided in Table 3.

Table 3: Trials 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) (IA1 data-cut) | 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) (IA2 data-cut) | Clinical study report. 19 January 2024 |
| | 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 |
| | 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., Chase, D. M., Slomovitz, B. M. et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer https://doi.org/10.1056/NEJMoa2216334 | <i>New England Journal of Medicine</i> 2023; 388: 2145-2158 |
| | Mirza, M. R., Ghamande, S., Hanker, L. C., Black, D. et al.. 38MO Progression-free survival (PFS) in primary advanced or recurrent endometrial cancer (pA/rEC) in the overall and mismatch repair proficient (MMR/MSS) populations and in histological and molecular subgroups: results from part 2 of the RUBY trial. https://doi.org/10.1016/j.esmoop.2024.103538 | <i>ESMO open</i> 2024, 9 (5), 103538 |
| | 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. |
| | Powell, M. A., Auranen, A., Willmott, L. J., Gilbert, L. et al 37MO Dostarlimab plus chemotherapy in primary advanced or recurrent endometrial cancer (pA/rEC) in the RUBY trial: overall survival (OS) by MMR status and molecular subgroups. https://doi.org/10.1016/j.esmoop.2024.103537 | <i>ESMO open</i> 2024, 9 (5), 103527 |
| Powell, M. A., Bjørge, L., Willmott, L., Novák, Z. et al . Overall survival in patients with endometrial cancer treated with dostarlimab plus carboplatin-paclitaxel in the randomized ENGOT-EN6/GOG-3031/RUBY trial.. https://doi.org/10.1016/j.annonc.2024.05.546 | <i>Annals of Oncology</i> 2024; 35(8): 728-738 | |

Source: Table 14, p43 of the resubmission.

Blue shaded cells indicate publications previously considered by the PBAC

6.9 The key features of the direct randomised trial are summarised in Table 4.

Public Summary Document – May 2025 PBAC Meeting

Table 4: 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 37.2 mths ^a | Low | 1L A/R EC | PFS by IA, OS ^b | Proportion progression free, overall survival, utilities. |
| RUBY (dMMR/MSI-H) | 118 | R, DB, MC 36.6 mths | Low ^c | | PFS by IA ^c , OS ^d | |
| RUBY (pMMR/MSS) | 376 | R, DB, MC 37.5 mths | High | | PFS by IA, OS ^d | |

Source: Constructed during the evaluation using information sourced from Table 14.1.1.34, pp752-754 RUBY IA2 CSR

DB = double blind; dMMR = mismatch repair deficient; IA = Investigator assessment; MC = multi-centre; MMS = microsatellite stable; MSI-H = high microsatellite instability mths = months; OS = overall survival; PFS = progression-free survival; pMMR = mismatch repair proficient; R = randomised.

a Inconsistently reported as both 37.2 months and 47.2 months in the RUBY IA2 CSR

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

c 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.

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

- 6.10 The risk of bias in the pMMR subgroup in RUBY was considered high as none of the outcomes were included in the statistical analysis plan, and as such, no formal statistical testing was conducted in the pMMR subgroup. The terms all-comers population and intention to treat (ITT) population are used interchangeably in relation to RUBY, and both refer to the full randomised population regardless of MMR status.
- 6.11 The resubmission argued that the interpretation of pMMR subgroup results should also consider that randomisation was stratified by MMR/MSI status, the pMMR subgroup included a notable sample size (N=376), and substantial OS follow-up was available as of the IA2 data-cut (37.5 months; >50% maturity). It was unclear whether this sample size was sufficient or reflective of a 'notable sample size'. For comparison, the NRG-GY018 trial which compared PEM+CP to CP alone (used to inform the unanchored indirect comparison with the near market comparator of PEM+CP) enrolled 590 pMMR patients. This was based on sufficient sample to provide 90% power to detect a relative reduction of 30% in the pMMR subgroup after 394 PFS events, which was more events required than pMMR patients enrolled in RUBY. Overall, the risk of bias in the pMMR subgroup of RUBY was considered to be high.
- 6.12 In the pMMR population in RUBY at IA2, 34/105 (32.4%) and 68/134 (50.7%) of patients who received any follow-up anti-cancer therapy were treated with subsequent immunotherapy in the DOS+CP and placebo + CP arms, respectively. The resubmission implied that the subsequent use of immunotherapy in the placebo + CP arm of RUBY was representative of 2L PEM+LEN use in the current Australian clinical setting, as no adjustments were made in the economic model to account for additional benefits associated from 2L PEM+LEN in the CP arm of the model (see paragraph 6.50). This was not appropriate as the characteristics of patients who received subsequent immunotherapy and the duration of subsequent treatment in RUBY was unknown.

Comparative effectiveness

- 6.13 As discussed in paragraph 6.6, RUBY IA2 reported updated results for OS, PFS2 and safety outcomes only. As such, the information below will focus on the updated results.
- 6.14 Table 5 summarises the OS results from RUBY, with OS results from IA1 extracted during the evaluation for comparison. Figure 1 to Figure 3 shows the Kaplan-Meier (KM) results for OS in the ITT, pMMR and dMMR populations in RUBY at IA2, respectively. The OS results for the pMMR subgroup from RUBY at IA2 were used to inform the economic evaluation.

Public Summary Document – May 2025 PBAC Meeting

Table 5: KM analysis of overall survival in RUBY

| OS | All-comers | | pMMR/MSS | | dMMR/MSI-H | |
|--|---|----------------------|-----------------------------------|----------------------|-----------------------------------|----------------------|
| | DOS+CP (N=245) | PBO+CP (N=249) | DOS+CP (N=192) | PBO+CP (N=184) | DOS+CP (N=53) | PBO+CP (N=65) |
| IA2 OS based on source verified MMR status | | | | | | |
| Median FU, months | 37.3 | 37.1 | 37.6 | 37.2 | 36.4 | 36.9 |
| Events, n (%) | 109 (44.5) | 144 (57.8) | 97 (50.5) | 109 (59.2) | 12 (22.6) | 35 (53.8) |
| Censored, n (%) | 136 (55.5) | 105 (42.2) | 95 (49.5) | 75 (40.8) | 41 (77.4) | 30 (46.2) |
| Median OS, months (95% CI) | 44.6 (32.6, NR) | 28.2 (22.1, 35.6) | 34.0 (28.6, NR) | 27.0 (21.5, 35.6) | NR (NR, NR) | 31.4 (20.3, NR) |
| Hazard Ratio (95% CI) ^a | 0.69 (0.54, 0.89) ^b | | 0.79 (0.60, 1.04) ^c | | 0.32 (0.17, 0.63) ^c | |
| p-value (1 sided) | 0.0020 ^b | | Nominal 0.0493 ^c | | Nominal 0.0002 ^c | |
| Landmark survival estimates, probability (95% CI) | | | | | | |
| 12 months | 83.3 (77.9, 87.4) | 80.9 (75.4, 85.3) | 82.3 (76.0, 87.1) | 81.2 (74.7, 86.2) | 86.8 (74.2, 93.5) | 79.9 (67.9, 87.8) |
| 18 months | 77.3 (71.4, 82.1) | 65.6 (59.3, 71.2) | 74.7 (67.8, 80.3) | 65.1 (57.6, 71.5) | 86.8 (74.2, 93.5) | 67.3 (54.4, 77.3) |
| 24 months | 70.1 (63.8, 75.5) | 54.3 (47.8, 60.3) | 66.5 (59.2, 72.8) | 53.2 (45.6, 60.2) | 82.8 (69.5, 90.7) | 57.5 (44.4, 68.6) |
| 30 months | 60.5 (54.0, 66.5) | 49.1 (42.6, 55.3) | 54.4 (46.9, 61.3) | 47.4 (39.9, 54.5) | 82.8 (69.5, 90.7) | 54.1 (41.0, 65.5) |
| IA1 | | | | | | |
| Median FU, months | 25.5 | 25.3 | 25.8 | 25.4 | 24.6 | 25.1 |
| Events, n (%) | 65 (26.5) | 100 (40.2) | 58 (30.2) | 76 (41.3) | 7 (13.2) | 24 (36.9) |
| Censored, n (%) | 180 (73.5) | 149 (59.8) | 134 (69.8) | 108 (58.7) | 46 (86.8) | 41 (63.1) |
| Median OS, months (95% CI) | NR (NR, NR) | NR (23.2, NR) | NR (29.8, NR) | 29.8 (21.9, NR) | NR (NR, NR) | NR (23.2, NR) |
| Hazard Ratio (95% CI) ^a | 0.64 (0.46, 0.87) ^d | | 0.73 (0.52, 1.02) ^c | | 0.30 (0.13, 0.70) ^c | |
| p-value(1 sided) | 0.0021 ^d | | Nominal 0.0333 ^c | | Nominal 0.0016 ^c | |

Source: Table 32, p73 of the resubmission.

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

Text in bold indicate statistically significant differences

Text in italics indicate values extracted during the evaluation

Blue shaded cells indicate values previously considered by the PBAC at the November 2023 meeting

a Stratified Cox regression

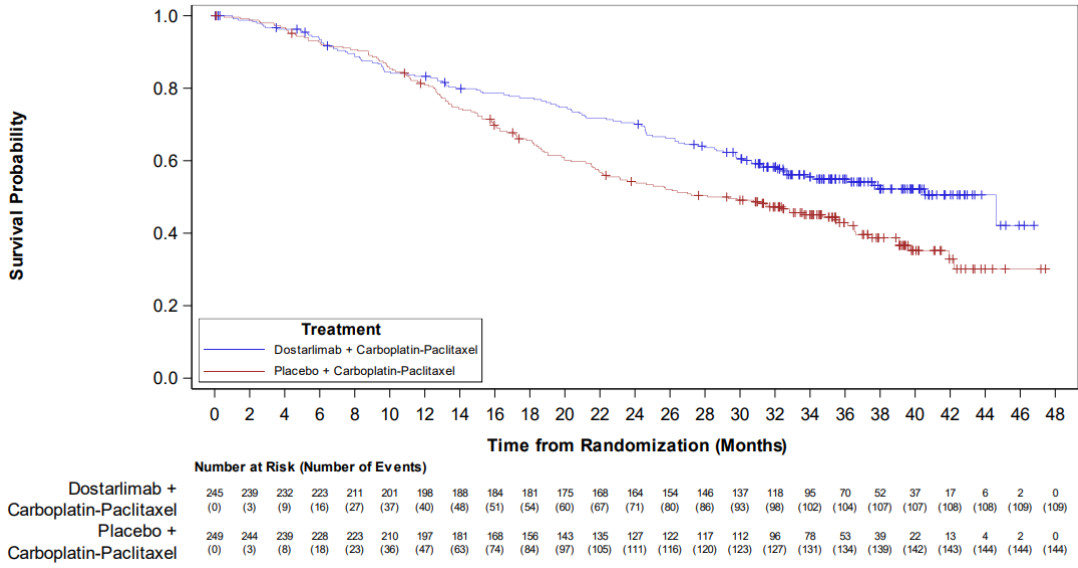
b Prespecified p-value stopping boundary for OS in IA2 was 0.01101, and was met at IA2.

c OS in the dMMR and pMMR subpopulations were not planned analyses and no statistical significance could be claimed. For a 1-sided test in RUBY, a p-value of 0.025 is required for the 95% confidence interval to exclude the null.

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

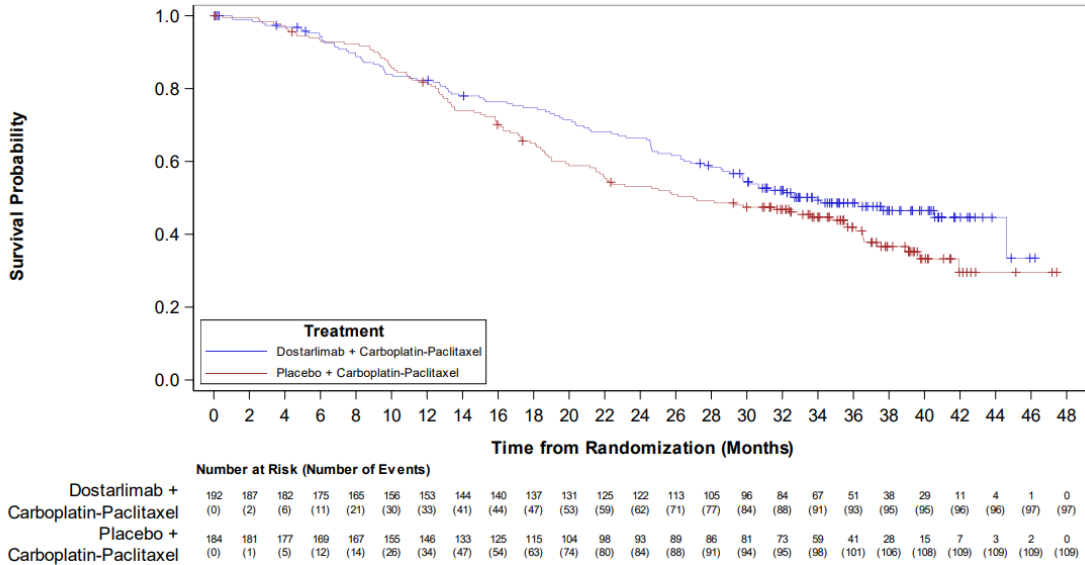
Public Summary Document – May 2025 PBAC Meeting

Figure 1: KM plot for overall survival in all-comers population (IA2 data-cut)



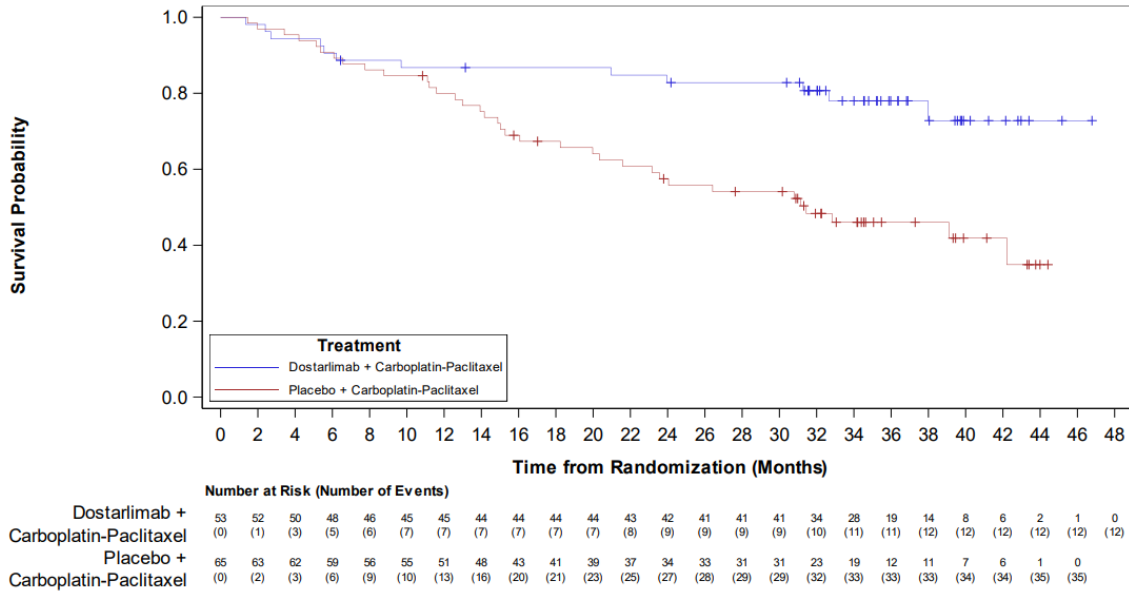
Source: Figure 7, p74 of the resubmission

Figure 2: KM plot for overall survival in pMMR/MSS cohort (IA2 data-cut)



Source: Figure 8, p75 of the resubmission

Figure 3: KM plot for overall survival in dMMR/MSI-H cohort (IA2 data-cut)



Source: Figure 9, p75 of the resubmission

- 6.15 The resubmission stated that, at the IA2 data cut with 37.2 months of median follow-up and 51.2% OS maturity in the ITT population, there was a statistically significant benefit in OS in RUBY (OS hazard ratio (HR) = 0.69, 95% CI 0.54, 0.89, stratified 1-sided log rank test p-value = 0.002) as the pre-specified p-value stopping boundary at IA2 (0.01101) was crossed. Multiplicity in RUBY was controlled for using a graphical method. To control for Type I error at the interim analysis, the statistical design of the trial incorporated an alpha-spending function where the stopping boundaries were adjusted based on the actual information fraction observed at the time of analysis (Lan-DeMets approach with O’Brien- Fleming type). Statistical significance for OS in the ITT population could not be concluded at IA1 as the stratified 1-sided log-rank test p-value (p=0.0021) was outside the stopping boundary for declaring statistical significance (p≤0.00177) at the first interim analysis. This was associated with a 16.4 month improvement in median OS (DOS+CP: 44.6 months vs placebo + CP: 28.2 months), with the separation in KM survival curves observed from 10 months in the IA1 data-cut sustained out to the IA2 data-cut (see Figure 1). The resubmission also noted that ESMO categorised DOS+CP as a therapy with substantial benefit for 1L A/R EC (ESMO-MCBS score of 4) in the ITT population of RUBY.
- 6.16 In the pMMR population, the resubmission claimed that at the IA2 data cut with 37.5 months of median follow-up and 54.8% OS maturity, there was a 21% reduction in the risk of death in DOS+CP compared to placebo + CP (HR = 0.79; 95% CI 0.60, 1.04; nominal stratified 1-sided log-rank test p-value = 0.0493) and a clinically meaningful improvement of 7.0 months in median OS (DOS+CP: 34.0 months vs placebo + CP: 27.0 months). The resubmission acknowledged that RUBY was not powered to detect differences in the pMMR population and neither OS or PFS in the pMMR population was included in the preplanned statistical analysis and multiplicity control.

Public Summary Document – May 2025 PBAC Meeting

- 6.17 The evaluator considered the claim of ‘clinically meaningful’ improvement in OS in pMMR patients in RUBY may not be reasonable and may not be applicable to the proposed PBS population for the following reasons:
- The 95% confidence interval around the OS HR includes 1.0, and RUBY was not powered to detect differences in the pMMR population as it was not part of the formal statistical analysis plan. There was also no clear separation in the OS KM curve, unlike in the dMMR subgroup;
 - No MCID was proposed to determine clinical significance for difference in absolute OS in the pMMR population. To provide some context, the RUBY trial was designed with the hypothesis of demonstrating an absolute difference of 13 months gain in OS in the ITT population, which may be used as a proxy for an MCID. In this case, the benefit of 7.0 months was substantially lower and would not be considered clinically meaningful. The MCID proposed for PEM+LEN at the March 2022 PBAC meeting for OS HR was 0.75, which if applied to the OS HR in the pMMR population of RUBY at IA2 (OS HR = 0.79), would also lead to a conclusion that the benefit may not be clinically meaningful;
 - The usage of DOS beyond disease progression and beyond three years in some patients were not aligned with the proposed restriction and likely favoured DOS+CP. Moreover, in the pMMR population, 32.4% (34/105) patients in the DOS+CP arm who progressed received subsequent immunotherapy, whereas these patients would not be eligible to receive PBS subsidised immunotherapy after progression. This suggests that the OS results in RUBY in the DOS+CP arm would be more favourable than in the proposed PBS population;
 - As noted in paragraph 6.12, while the proportion of pMMR patients using subsequent immunotherapy in the placebo + CP arm in RUBY at IA2 (50.7%) was similar to current Australian clinical practice (49%), the characteristics of patients using subsequent immunotherapy in RUBY and the duration of subsequent therapy was unknown and may not be reflective of Australian clinical practice, and the OS in the placebo + CP arm of RUBY may not be representative of the Australian population.
- 6.18 In RUBY at IA2, the OS benefit in the dMMR subgroup was substantially higher than in the pMMR subgroup, which suggests that for OS, MMR may be a treatment effect modifier, just as the ESC and the PBAC had previously considered that MMR was a treatment effect modifier for PFS (paragraph 6.24 and 7.21, dostarlimab PSD, November 2023 PBAC meeting). Tests for interaction conducted during the evaluation for OS at IA2 (assuming HR as an odds ratio, see Table 6) reported a p value of 0.0140, which suggested that MMR was likely a treatment effect modifier for OS benefit associated with DOS in RUBY at IA2. As such, it may be reasonable to conclude that the statistically significant OS benefit observed in the ITT population at IA2 was driven by the benefit in the dMMR subgroup.

Public Summary Document – May 2025 PBAC Meeting

Table 6: Test for interaction between the dMMR/MSI-H and pMMR/MSS subgroups in RUBY

| Outcome | dMMR/MSI-H | | | pMMR/MSS | | | Test for p-value ^a |
|-------------------------|--------------|--------------|-------------------|--------------|--------------|-------------------|-------------------------------|
| | DOS+CP (n/N) | PBO+CP (n/N) | HR (95% CI) | DOS+CP (n/N) | PBO+CP (n/N) | HR (95% CI) | |
| IA1 ^b | | | | | | | |
| OS | 7/53 | 24/65 | 0.32 (0.14, 0.74) | 58/192 | 76/184 | 0.73 (0.52, 1.03) | <i>0.0760</i> |
| 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 |
| IA2 | | | | | | | |
| OS | 12/53 | 35/65 | 0.32 (0.17, 0.63) | 97/192 | 109/184 | 0.79 (0.60, 1.04) | 0.0140 |

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 likely to be significant (<0.05)

Blue shaded cells indicate values previously considered by the PBAC

Text in italics indicate values calculated during the evaluation

^a 95% confidence interval with three decimal places used for testing

^b OS HR at IA1 differed to Table 5 as these are based on the unstratified cox model

Note that the results for the test of interaction presented 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.

- 6.19 Moreover, the point estimates for OS HR in the ITT, dMMR and pMMR subgroups were all marginally lower (i.e. less favourable for DOS) at IA2 than at IA1. This relative difference is important when interpreting the economic evaluation results relative to the November 2023 submission.
- 6.20 The resubmission noted that IA2 did not include any updated results for PFS and as such, all PFS results from RUBY have been previously considered by the PBAC (Table 7). PFS in pMMR (PFS HR = 0.76, 95% CI 0.59, 0.98) was not part of the statistical analysis plan, no formal statistical testing was conducted, and no claim of statistical significance could be made.
- 6.21 The PBAC had previously considered that the PFS benefit in the pMMR population was much smaller when compared to the dMMR population, and combined with the uncertain OS benefit, the clinical place for DOS in 1L treatment for pMMR EC was unclear (paragraph 7.20, dostarlimab PSD, November 2023). Given the OS benefit in the pMMR population remains uncertain (see paragraph 6.17), it may be reasonable for the same conclusion to be reached based on the IA2 results. The PFS results for the pMMR subgroup from RUBY at IA1 (see Table 7) were used to inform the economic evaluation.

Public Summary Document – May 2025 PBAC Meeting

Table 7: KM analysis of progression-free survival per investigator assessment in RUBY

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

Source: Table 33, pp75 of the resubmission.

CI=confidence interval

Values in bold indicate statistically significant differences.

Blue shaded cells indicate values previously considered by the PBAC at the November 2023 PBAC meeting

- 6.22 The resubmission stated that at the time of the IA2 data-cut, compared to placebo + CP, DOS+CP reduced the risk of progression following first subsequent anticancer therapy or death in the ITT, pMMR/MSS and dMMR/MSI-H cohorts, by demonstrating an HR of 0.66, 0.74 and 0.33, respectively. PFS2 was not used by the resubmission in the economic model. The biological mechanism by which DOS+CP improves PFS2 was not discussed by the resubmission. The results were possibly confounded by use of DOS beyond primary disease progression which was allowed in RUBY but would not be allowed under the proposed restriction.
- 6.23 As discussed in paragraph 5.2, the resubmission nominated DUR+CP with or without OLA and PEM+CP as near market comparators. In the appendix to the resubmission, an unanchored indirect comparison between DOS+CP with the near market comparators was presented. The identified trials included in the comparisons were:
- RUBY: DOS+CP followed by maintenance DOS as monotherapy versus placebo + CP followed by placebo in patients with A/R EC;
 - NRG-GY018: PEM+CP followed by maintenance PEM as monotherapy versus placebo + CP followed by placebo in patients with A/R EC; and
 - DUO-E: DUR+CP followed by maintenance DUR as monotherapy or in combination with OLA versus placebo +CP followed by placebo in patients with A/R EC.
- 6.24 The resubmission claimed that an assessment of the external and internal validity of the pivotal trials indicated that a formal quantitative indirect treatment comparison was not appropriate due to a high degree of heterogeneity observed. Key sources of heterogeneity in baseline characteristics identified included:
- Race: majority of patients in all three trials were white but the proportion was higher in RUBY (74.1%) and NRG-GY018 (72.1%) than in DUO-E (56%). 30.1% of

Public Summary Document – May 2025 PBAC Meeting

patients enrolled in DUO-E were Asian, compared to 3.5% in RUBY and 5.3% in NRG-GY018.

- Difference in proportion of disease status: RUBY enrolled a lower proportion of patients with recurrent disease (47.1% vs 52.5% in DUO-E and 56.3% in NRG-GY018) and higher proportion of primary Stage III patients (18.1% in RUBY vs 5.2% in DUO-E), and DUO-E had higher proportion of newly diagnosed Stage IV patients.
- Carcinosarcoma patients excluded from NRG-GY018 but included in RUBY (10.4%) and DUO-E (8.0%).
- More patients in NRG-GY018 had received prior anticancer radiotherapy (39.6%) than either DUO-E (30.6%) or RUBY (26.3%). Patients with an ECOG PS of 2 were able to enrol in NRG-GY018, but not RUBY or DUO-E.

The evaluation considered it was unclear whether these differences in baseline characteristics would have precluded an indirect comparison as no evidence was provided that each of these were treatment effect modifiers.

6.25 The resubmission also claimed that there were differences in tumour scan frequencies, duration of follow-up and statistical analyses between the three trials:

- Radiographic tumour assessment for disease progression was performed more frequently in RUBY than NRG-GY018 or DUO-E. In RUBY, scans were performed every six weeks until week 25, followed by every nine weeks for the remainder of the first year on the study. Thereafter scans were completed every 12 weeks until radiographic PD was confirmed. In contrast, NRG-GY018 required scans to be performed every nine weeks for the first nine months, then every 12 weeks until radiographic PD was confirmed. In DUO-E, scans were performed every nine weeks for the duration of the chemotherapy treatment period (six cycles, 18 weeks), then every 12 weeks while patients remained on the study. More frequent scans may increase the likelihood of finding evidence of progression at an earlier time point but it was unclear how this may have affected an indirect comparison in which the comparative results against a common comparator would be assessed. That is, even if RUBY reported a shorter PFS due to the more frequent scans compared to NRG-GY018 and DUO-E, the PFS HR within the trial should not be affected as the more frequent scan frequency would apply to both the DOS+CP and CP arm; and
- The median duration of follow-up was longest in RUBY (ITT: 37.2 months; pMMR: 37.5 months; dMMR: 36.6 months), compared to NRG-GY018 (pMMR: 8.4-8.8 months; dMMR: 13.3-13.7 months) and DUO-E (ITT: 16.4-17.5 months).

6.26 The resubmission further claimed that there were differences in ‘statistical analyses’ which may preclude an indirect comparison. It was unclear what differences in ‘statistical analyses’ were identified, but may be related to the fact that OS was not part of the formal statistical analysis plan in NRG-GY018. Further, outcomes in the pMMR subgroup were not part of the formal statistical analysis plan in either RUBY or DUO-E.

Public Summary Document – May 2025 PBAC Meeting

- 6.27 Overall, though the issues of heterogeneity are acknowledged, it was unclear whether these differences were of a sufficient magnitude to preclude a formal indirect comparison, as the resubmission has not clearly outlined the impact of these differences.
- 6.28 It was difficult to draw a meaningful conclusion for the comparative treatment efficacy of DOS+CP, PEM+CP or DUR+CP (with or without OLA) in 1L A/R pMMR EC from the unanchored indirect comparison. OS results from NRG-GY018 and DUO-E were too immature to be meaningful. Nominally, DUR+OLA+CP had the longer median PFS (15 months) and the best reduction in risk of progression or death when compared to CP (PFS HR = 0.57, 95% CI 0.44, 0.73) and DOS+CP had the shortest median PFS (tied with DUR+CP) among immunotherapies (9.9 months) and a PFS HR (0.76, 95% CI 0.59, 0.98) compared to CP which was worse than PEM+CP (PFS HR = 0.60, 95% CI 0.46, 0.78) in NRG-GY018 and DUR+OLA+CP (PFS HR = 0.57, 95% CI 0.44, 0.73) in DUO-E.
- 6.29 Separate to the unanchored indirect comparison, the resubmission also identified Zhu 2024a as part of the literature search on published economic evaluations. Zhu 2024a presented a network meta-analysis (NMA) which included RUBY, NRG-GY018 and DUO-E and therefore was considered potentially informative for the near-market comparators of DOS+CP. From among 211 initially identified articles, four phase III randomised clinical trials enrolling 2577 patients were incorporated into the NMA. These trials were RUBY (at IA1), NRG-GY018, DUO-E and AtTEnd (NCT03603184), which was a phase III double-blind RCT of atezolizumab in combination with CP in women with A/R EC. Atezolizumab was not considered a near-market comparator in the resubmission as there had been no TGA application at the time of the resubmission.
- 6.30 Zhu 2024a reported the HRs for PFS and OS, as well as the relative risk (RR) values for AEs, calculated through a Bayesian network meta-analysis approach along with 95% CIs. Different treatments were ranked according to their likelihood of showing the best and worst outcomes, using P-scores for each outcome, where a higher P-score represented better efficacies.
- 6.31 Based on the NMA from Zhu 2024a³, in the pMMR population:
- Only DUR+CP+OLA was associated with greater OS benefits over CP alone (HR=0.59; 95% CI 0.39 to 0.89) and it also had the highest P-score (0.94) of all the included therapies. For DOS+CP, DUR+CP and PEM+CP versus CP the 95% CIs for each respective hazard ratio crossed the null, suggesting that these treatments may have no OS benefit over CP; and

³ Note that the results of the NMA presented are derived from post-hoc analyses identified 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, NRG-GY018 or DUO-E. 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.

Public Summary Document – May 2025 PBAC Meeting

- All the immunotherapy regimens were associated with greater PFS benefits compared to CP alone with hazard ratio point estimates ranging from 0.54 (PEM+CP) to 0.76 (DOS+CP). Neither DUR+CP, DUR+CP+OLA nor PEM+CP were shown to have a PFS which was statistically significantly different to that of DOS+CP, though the P-score for DOS+CP (0.49) was lower than for DUR+CP+OLA (P-score = 0.86) and PEM+CP (P-score = 0.92) suggesting that DOS+CP may be the least effective therapy out of the three options among pMMR patients.

Comparative harms

- 6.32 Updated safety information from RUBY at IA2 was presented in the resubmission. The resubmission stated that no differences were observed in the DOS+CP and placebo + CP safety profiles between the IA1 and IA2 data cuts or between dMMR or pMMR patients, and there were no new treatment emergent adverse events (TEAEs) leading to death at IA2. The resubmission further stated that the adverse event profiles were similar across the ITT, pMMR and dMMR populations, and therefore the resubmission presented safety data for the ITT population. While there were slight increases in most adverse event (AE) categories, the differences were small and were consistent with longer follow-up and treatment. However, it appears that there was one fewer TEAE leading to treatment discontinuation in the placebo + CP arm in the pMMR population (and consequently the ITT population) at IA2 compared to IA1, and the reason for this was unclear⁴. Serious AEs (SAEs) occurring in at least 2% of patients with a difference of at least 1% between treatment arms from RUBY IA2 (sepsis, pyrexia, dyspnoea, muscular weakness, anaemia, asthenia and pulmonary embolism) were included in the economic evaluation.
- 6.33 The resubmission further stated that the DOS+CP safety profile was generally consistent with the known safety profiles of the individual agents in the ITT, pMMR and dMMR populations.
- 6.34 During the reporting period of the most recent Periodic Benefit Risk Evaluation Report (PBRER) from 21 October 2023 to 20 April 2024, Guillain-Barré Syndrome was newly identified as a validated signal, and the assessment was ongoing as of the data lock point of the PBRER. Sarcoidosis was also newly identified as a validated signal during the reporting period of this report and the assessment was also ongoing following the data lock point of the PBRER. The lack of long-term safety was identified as ‘missing information’ in the PBRER.
- 6.35 The resubmission claimed that DOS+CP had an inferior but manageable safety profile compared to CP. Given that in RUBY, DOS+CP was associated with more grade≥3 TEAEs, serious AEs, immune related AEs, a claim of inferior safety was likely

⁴ Note that the PSCR clarified this discrepancy was due to two cases of TEAE leading to treatment discontinuation in the PBO+CP arm being reclassified between IA1 and IA2. For one patient, the trial site reconfirmed that the discontinuation was due to a non-AE reason. The second patient was recorded in the IA2 database, indicating that they had continued to receive treatment and were not a true discontinuation. One new TEAE leading to treatment discontinuation occurred during the IA2 follow-up, resulting in a net decrease of 1 patient.

Public Summary Document – May 2025 PBAC Meeting

reasonable. However, DOS+CP was also associated with more TEAEs resulting in death (five events compared to no events in placebo + CP, RR = 11.23, RD = 0.02, in the all-comers population) and adverse events in these patients would not be considered ‘manageable’⁵. The PBAC had previously considered that the claim of inferior comparative safety was reasonable. (Paragraph 6.43, dostarlimab PSD, November 2023 PBAC meeting).

6.36 The ESC noted that DOS+CP was associated with more TEAEs resulting in death (five events compared to no events in placebo+CP, RR = 11.23, RD = 0.02), suggesting the TEAEs are not necessarily manageable⁵.

Benefits/harms

6.37 Given the lack of significant differences in OS and PFS in pMMR patients in RUBY and the uncertainty of the OS benefit in the pMMR population, no comparative benefits were presented. A summary of the comparative harms for DOS+CP versus placebo + CP in RUBY at IA2 is presented in Table 8 (note this is for all-comers, not the pMMR subgroup).

Table 8: Summary of comparative benefits for DOS+CP and PBO+CP

| 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) | | | | | |
| 174/241 | 148/246 | 1.20 (1.06, 1.37) | 72.2 | 60.2 | 0.12 (0.04, 0.20) |
| Any SAEs (all-comers) | | | | | |
| 96/241 | 69/246 | 1.42 (1.10, 1.83) | 39.8 | 28.0 | 0.12 (0.03, 0.20) |
| Any treatment related SAEs (all-comers) | | | | | |
| 47/241 | 30/246 | 1.60 (1.05, 2.44) | 19.5 | 12.2 | 0.07 (0.01, 0.14) |
| Any TEAE leading to treatment discontinuation (all-comers) | | | | | |
| 60/241 | 40/246 | 1.53 (1.07, 2.19) | 24.9 | 16.3 | 0.09 (0.02, 0.16) |
| Any immune-related TEAEs (all-comers) | | | | | |
| 141/241 | 91/246 | 1.58 (1.31, 1.93) | 58.5 | 37.0 | 0.22 (0.13, 0.30) |
| Any DOS- or PBO-related immune-related TEAEs (all-comers) | | | | | |
| 98/241 | 40/246 | 2.50 (1.82, 3.46) | 40.7 | 16.3 | 0.24 (0.17, 0.32) |
| 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) |

Source: Constructed during the evaluation using information sourced from Table 37, pp84-85 of the resubmission.

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

Grey shaded cells indicate safety signals which were also included in the benefit/harms table in the November 2023 submission (note that the numbers may have changed due to longer follow up)

*Note that the results for relative risk (RR) and risk difference (RD) presented in Table 8 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.

⁵ Note that none of the TEAEs leading to death in the pMMR/MSS population (general physical health deterioration, COVID-19, opiate overdose) in RUBY were considered related to study treatment. Two TEAEs leading to death were experienced in the dMMR group of the RUBY trial (myelosuppression and hypovolemic shock). No additional TEAEs leading to death occurred between the IA1 and IA2 analyses.

Public Summary Document – May 2025 PBAC Meeting

- 6.38 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 12 additional patients will experience any TEAE (grade ≥ 3).
 - Approximately 12 additional patients will experience any SAE.
 - Approximately 7 additional patients will experience any treatment related SAE.
 - Approximately 9 additional patients will experience TEAE leading to treatment discontinuation.
 - Approximately 22 additional patients will experience any immune-related TEAE.
 - Approximately 24 additional patients will experience any DOS-or PBO-related TEAE.
 - Approximately 2 additional patients will experience any TEAE with the outcome of death.

Clinical claim

- 6.39 The resubmission described that, in patients with primary advanced or first recurrent pMMR EC, DOS+CP was superior in terms of effectiveness compared with CP alone, based on the pMMR subgroup results of RUBY. The resubmission claimed that DOS+CP was inferior to CP alone but had a manageable safety profile based on the all-comer results of RUBY.
- 6.40 The therapeutic conclusion of superior effectiveness was not adequately supported by the evidence presented the resubmission and may not be applicable to the Australian population because:
- Neither OS nor PFS in the pMMR subgroup were included in the original statistical analysis plan which included multiplicity controls, and as such, no formal statistical testing was conducted in the pMMR subgroup. In RUBY, the 95% confidence interval around the OS HR in pMMR patients (OS HR = 0.79, 95% CI 0.60, 1.04, nominal p-value = 0.0493) at IA2 included 1.0, and RUBY was not powered to detect differences in the pMMR population as it was not part of the formal statistical analysis plan. It was likely that the statistically significant OS benefit in the ITT population was driven by the efficacy of DOS in the dMMR population. Tests for interaction conducted during the evaluation also suggest that MMR status was a treatment effect modifier for OS in RUBY. No MCID was proposed to determine clinical significance for difference in absolute OS in the pMMR population;
 - The usage of DOS beyond disease progression and beyond three years in some patients were not aligned with the proposed restriction and likely favoured DOS+CP. Moreover, in the pMMR population, 32.4% (34/105) patients who progressed received subsequent immunotherapy, whereas these patients would

Public Summary Document – May 2025 PBAC Meeting

not be eligible to receive PBS subsidised immunotherapy after progression. This suggests that the OS results in RUBY in the DOS+CP arm would be more favourable than in the proposed PBS population;

- While the proportion of pMMR patients using subsequent immunotherapy in the placebo + CP arm in RUBY at IA2 (50.7%) was similar to current Australian clinical practice (49%), the characteristics of patients using subsequent immunotherapy in RUBY and the duration of subsequent therapy was unknown and may not be reflective of Australian clinical practice, and the OS in the placebo + CP arm of RUBY may not be representative of the Australian population; and
- The PBAC had previously considered that the PFS benefit in the pMMR population (PFS HR = 0.76, 95% CI 0.59, 0.98) was much smaller than in the dMMR population (PFS HR = 0.28, 95% CI 0.16, 0.50) and that combined with the uncertain OS benefit, the clinical place for dostarlimab as 1L treatment for pMMR EC was unclear (paragraph 7.20, dostarlimab PSD, November 2023 PBAC meeting). Given no new PFS data was presented in RUBY at IA2 and the OS benefit remains uncertain; the same conclusion was likely reasonable.

6.41 Whilst the resubmission provided more mature data, it did not confirm a statistically significant OS benefit in the pMMR subgroup, and the ESC considered results in this group are likely to be mixed. The ESC did not consider the comparative clinical effectiveness claim in the population was well supported.

6.42 The ESC considered the claim of inferior safety was reasonable as in RUBY at IA2, DOS+CP was associated with more grade \geq 3 TEAEs, serious AEs and immune related AEs. Though it should be acknowledged that DOS+CP was also associated with more TEAEs resulting in death (five events compared to no events in placebo + CP, RR = 11.23, RD = 0.02) and in these patients the adverse events would not be considered 'manageable'⁶. The PBAC had previously considered that the claim of inferior comparative safety was reasonable (Paragraph 6.43, dostarlimab PSD, November 2023 PBAC meeting).

6.43 The PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data.

6.44 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.45 The resubmission presented a stepped economic evaluation based on the RUBY trial. The type of economic evaluation presented was a cost-utility analysis (CUA). The ESC considered a CUA would be reasonable, if the clinical claim was supported by PBAC.

⁶ Note that none of the TEAEs leading to death in the pMMR/MSS population (general physical health deterioration, COVID-19, opiate overdose) in RUBY were considered related to study treatment. Two TEAEs leading to death were experienced in the dMMR group of the RUBY trial (myelosuppression and hypovolemic shock). No additional TEAEs leading to death occurred between the IA1 and IA2 analyses.

Public Summary Document – May 2025 PBAC Meeting

- 6.46 The structure of the economic model was similar to the November 2023 submission. OS was informed by the pMMR population data from RUBY at IA2, with PFS, time to treatment discontinuation (TTD) and utilities informed by the pMMR population data from RUBY at IA1. Selected safety data from the all-comers population was used (see paragraph 6.32). A summary of the key components of the economic evaluation as well as a comparison with economic model in the November 2023 submission is presented in Table 9.

Public Summary Document – May 2025 PBAC Meeting

Table 9: Key components of the economic evaluation

| Component | May 2025 (pMMR model) | Nov 2023 (dMMR model) | Justification/comments |
|---|--|---|---|
| Type of analysis | Cost-utility analysis | | Reasonable |
| Outcomes | Life years gained, quality-adjusted life years | | Reasonable |
| Time horizon | 7.5 years in model base case vs 37.5 months follow up in RUBY at IA2 in pMMR patients | 10 years in model base case based on median follow up of 24.8 months in RUBY at IA1 for dMMR patients. 7.5 years proposed in PSCR and considered appropriate (paragraph 7.8, dostarlimab PSD, November 2023) | Median OS in pMMR patients (DOS+CP: 34 months, CP: 27 months) was lower than in dMMR patients (DOS+CP: Not reached at 36.4 months median follow-up, CP: 31.4 months), therefore using the same time horizon may not be appropriate and a shorter time horizon for pMMR may be more reasonable. |
| Methods used to generate results | Partitioned survival model | | Reasonable |
| Health states | Progression-free; progressed disease; dead | | Reasonable |
| Cycle length | 7 days | | Reasonable |
| Transition probabilities | <p>Until median follow-up DOS+CP and CP arm: PFS from RUBY IA1 and OS KM from RUBY IA2</p> <p>After median follow-up DOS+CP: OS/PFS extrapolated with loglogistic^a CP: OS/PFS extrapolated with loglogistic</p> <p>At three years; forced linear convergence of DOS+CP arm PFS and OS to CP arm from three years to 7.5 years</p> | <p>Until median follow-up CP arm: PFS and OS KM from RUBY IA1 DOS+CP arm: PFS and OS KM from RUBY IA1</p> <p>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 (7.5 years after PSCR)</p> | <p>May 2025 model updated to reflect the pMMR population of the RUBY trial and OS data from the IA2 data-cut of RUBY.</p> <p>The ESC previously considered that compared to relying on Miller 2020, parametric extrapolations appear more clinically plausible for the proposed PBS population (paragraph 6.60, dostarlimab PSD, November 2023 PBAC meeting). The use of parametric extrapolations in the resubmission were reasonable. However, the linear convergence applied in the resubmission's model was not reasonable.</p> |
| Health-related quality of life ^b | Based on EQ-5D-5L scores from RUBY IA1 (using Norman 2023 scoring algorithm) pMMR: PFS utility: 0.8760 for both arms; PD utility: 0.8285 for both arms | Based on EQ-5D-5L scores from RUBY IA1 (using Viney 2011 scoring algorithm) dMMR: PFS utility: 0.7747 for both arms; PD utility: 0.7402 for both arms | Updated to use Norman 2023 based on ESC advice (paragraph 6.47, dostarlimab PSD, November 2023 PBAC meeting). However, this introduced an issue of consistency between the November 2023 and May 2025 model. |
| Software package | Microsoft Excel | | Reasonable |

Source: Table 54, p111 and table 55, p113 of the resubmission,

CP = carboplatin + paclitaxel; DOS = dostarlimab; dMMR = mismatch repair deficient; EQ-5D-5L = European Quality of Life 5 Dimensions 5 Level; ESC = economic sub-committee; HR = hazard ratio; IA = interim analysis; KM = Kaplan-Meier; OS = overall survival; PFS = progression free survival; pMMR = mismatch repair proficient; PSCR = pre-subcommittee response; PSD = public summary document; a Note: in the base case the parametric function applied for the extrapolation of OS in the DOS arm does not impact the model results as curve convergence is applied immediately following KM data.

b 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.

Public Summary Document – May 2025 PBAC Meeting

- 6.47 The use of parametric extrapolations based on RUBY data to inform the model was a key difference compared to the November 2023 submission. In the November 2023 submission, after the median follow-up, OS and PFS in the CP arm were instead informed by Miller 2020, which reported outcomes from the GOG0209 study, a phase III, randomised, noninferiority, open-label study of CP versus paclitaxel-doxorubicin-cisplatin (TAP) in 1L A/R EC, which enrolled patients between 2003 and 2009. However, the ESC considered that the long-term survival outcomes in Miller 2020 were implausibly high for the proposed PBS population due to enrolling patients with less severe disease compared to RUBY, and the use of parametric extrapolations for PFS and OS curves were more clinically plausible (paragraph 6.60, dostarlimab PSD, November 2023 PBAC meeting). It was unclear if there was a preference for any specific parametric function for any extrapolation for DOS+CP in dMMR or the all-comers population at the November 2023 PBAC meeting. The ESC noted there were still relatively large numbers alive at the median follow up cut point and it would be informative to see the GebSKI criterion used as an alternative approach to determine the extrapolation point for the KM curves.
- 6.48 In the base case of the economic model, the loglogistic parametric function was used to extrapolate the PFS curve beyond the median follow-up duration at RUBY IA1 for both the DOS+CP arm (25.82 months) and the CP arm (25.36 months). It was unclear why the loglogistic function was chosen for the DOS+CP arm PFS extrapolation as the lognormal function had the best statistical fit by both Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Nonetheless, the choice of parametric extrapolation for PFS in the DOS+CP arm had only a small impact (using the lognormal function for the PFS extrapolation in DOS+CP decreased the ICER by 1%). This was likely due to the assumption of convergence starting at three years (such that the extrapolation impacted the model directly only between the end of follow-up at 25.8 months till 36 months, after which the linear extrapolation was applied and the extrapolation became irrelevant) as well as the relatively small difference between PD and PF utilities. Loglogistic was the best fit by AIC and BIC for the CP arm for PFS.
- 6.49 In the base case of the economic model, the loglogistic parametric function was used to extrapolate the OS curve beyond the median follow-up duration at RUBY IA2 for both the DOS+CP arm (37.62 months) and the CP arm (37.16 months). However, as linear convergence was assumed to start from 36 months, the extrapolation function for OS in the DOS+CP arm had a minor impact on the model in the base case.
- 6.50 The loglogistic function was used in the base case for OS in the CP arm, as it had the lowest AIC and BIC. However, all parametric functions had similar AIC and BIC values and good visual fit, suggesting any of them may be reasonable. The best fitting OS extrapolation function of the CP arm should be considered uncertain, as the resubmission posits that the subsequent use of immunotherapy in RUBY was reflective of 2L immunotherapy use in current Australian clinical practice and was sufficient to capture the OS benefits of 2L PEM+LEN without any further adjustments. However, this was uncertain as the characteristics of patients who were treated with

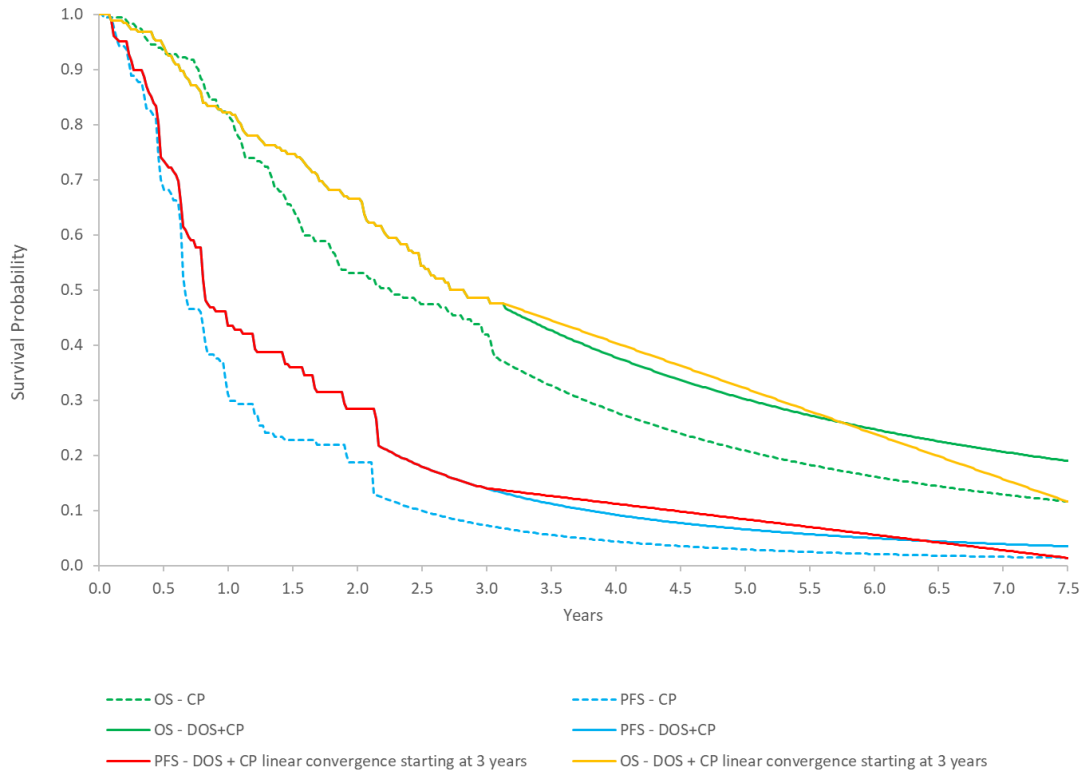
Public Summary Document – May 2025 PBAC Meeting

subsequent immunotherapy in RUBY was unclear, and they may not be representative of the patients who would be treated with 2L PEM+LEN under the current PBS restrictions. Moreover, the duration of subsequent therapy used by these patients was unknown.

- 6.51 Of all the extrapolation functions around OS and PFS, the choice of OS extrapolation had the largest impact on the ICER as it affected not only the CP arm, but also the DOS+CP arm due to the linear convergence assumed. The loglogistic function chosen in the base case resulted in an ICER which was roughly in the middle of all six possible parametric functions, with the Gompertz function resulting in the lowest ICER (-1% compared to loglogistic) and the exponential function resulting in the highest ICER (+1% compared to loglogistic).
- 6.52 Similar to the November 2023 submission, in the base case of the model the resubmission applied a linear convergence in the economic model from three years onwards for PFS and from the median follow-up of 37.62 months in OS, such that after this time point, a constant (linear) rate of decline was applied so that at the end of the time horizon (7.5 years), the proportion remaining alive and alive in the progression free (PF) health state was the same in the DOS+CP and CP arm of the model. This can be seen in Figure 4 below, as the DOS+CP arm OS and PFS with linear convergence (solid yellow and solid red lines, respectively) were forced to intersect at 7.5 years with the CP arm OS and PFS curves (dotted green and dotted blue lines, respectively), respectively. Comparatively, both the OS and PFS traces for DOS+CP without convergence (solid green and solid blue lines, respectively) remained above the CP arm at 7.5 years. The convergence applied in the November 2023 model was intended to address the following issues (paragraph 7.8, dostarlimab PSD, November 2023 PBAC meeting):
- 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 in the long-term follow-up data, and
 - The potential overestimate of DOS+CP OS due to 2L immunotherapy use in the DOS+CP arm in RUBY.
- 6.53 It may be reasonable to assume that the linear convergence applied in the resubmission would address the same issues. However, it needs to be considered that the November 2023 advice was in the context of a different population (dMMR) for which the benefit for DOS+CP was considerably more favourable than in the pMMR population, and the extrapolation methods in the two models were also different. As such, what was reasonable for convergence in the dMMR model may not be reasonable for the pMMR economic model. Figure 4 shows a model trace of the economic evaluation with and without linear convergence starting at three years (36 months).

Public Summary Document – May 2025 PBAC Meeting

Figure 4: Model trace showing no convergence and linear convergence starting at 36 months (i.e. the base case)



Source: constructed during evaluation using the resubmission’s economic model spreadsheet

Note that the Kaplan Meier plots and fitted curves depicted in Figure 4 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.

6.54 Given the stated purpose of the convergence, it would be expected that application of convergence would result in substantially more conservative estimates for OS and PFS of DOS+CP. However, the linear OS and PFS curves from the convergence actually sat above the OS and PFS curves without convergence until crossing over at 5.77 years for OS and 6.40 years for PFS. This could also be seen when looking the results, as the incremental difference for (discounted) life years gained (LYG) without convergence (0.4654) was only 1% higher than with linear convergence (0.4621), and the discounted time of survival in PF state for the DOS+CP arm (which was a function of the PFS curve) was actually 7% higher with convergence (1.5436 years) than without convergence (1.5132 years).

6.55 While the base case model with convergence estimated an ICER which was [REDACTED]% higher than the model without convergence, this was due entirely to differences in the terminal care costs estimated. There was almost no difference in QALY (+0.0013) with and without convergence, but the model without convergence had an incremental cost (\$) which was \$[REDACTED] lower than the base case (\$[REDACTED]). Of this difference of \$[REDACTED], \$[REDACTED] was attributable to lower terminal care costs and explained the majority of the difference in ICER between the two models. This raised serious concerns as to the

Public Summary Document – May 2025 PBAC Meeting

- validity of the linear convergence applied in the resubmission and whether it was fit for purpose as it does not appear to be particularly conservative with regards to OS or PFS.
- 6.56 Moreover, starting convergence earlier (e.g. at two years) actually increased the proportion of patients remaining in the PF health state in the DOS+CP arm. This was unexpected as convergence should result in the difference between treatment arms being smaller than what was observed, and starting convergence earlier should, in theory, result in smaller incremental differences. This was also reflected in the results as starting convergence at two years (accompanied with the truncation point changing from median follow up to 24 months) decreased the ICER by $\frac{1}{2}$ % compared to the base case of beginning convergence at three years.
- 6.57 As such, alternative methods to account for the uncertainties in the model (as outlined in paragraph 6.52) may be appropriate. An alternative convergence method which assumed the same rate of change in PFS and OS in both the DOS+CP arm and the CP arm after three years was tested during the evaluation and increased the ICER by $\frac{1}{2}$ %, which was driven by a decrease of 22% in LYG and QALY, as would be expected from an application of convergence. Alternatively, removing convergence and adopting a more conservative parametric extrapolation for OS and PFS in the DOS+CP arm (to address the uncertainties relating to long term incremental benefits of DOS+CP and the potential overestimate of OS in the DOS+CP arm due to the model not assuming any 2L immunotherapy use) and more optimistic OS extrapolation for the CP arm (to address potential underestimates of OS due to 2L immunotherapy use) may also be considered. The ESC considered the use of the more conservative extrapolation approach, where the same rate of change in PFS and OS is assumed in both treatment arms, was a more reasonable approach. The PSCR accepted this alternative approach, which increased the base case ICER by $\frac{1}{2}$ %. ESC further considered a shorter 5-year time horizon would be more appropriate in this setting given poorer overall survival outcomes in the pMMR population, relative to dMMR patients
- 6.58 The resubmission stated that the TTD curve from the pMMR subgroup in RUBY at IA1 was used to model time on treatment with DOS in the economic model. The results from the TTD KM curve used in the economic model do not appear to be aligned with the reported usage in RUBY at IA2. For example, the median duration of treatment in the TTD KM curve used in the economic model was 33.14 weeks, whereas the reported median duration of DOS+CP treatment in RUBY IA2 was 39 weeks. This may indicate that the economic model may have underestimated the usage of DOS which would favour DOS+CP. The economic model estimated a mean treatment duration of 54.48 weeks, which was reduced to 52.64 weeks after relative dose intensities (RDI) were included. This was lower than the mean duration of 57.15 weeks reported in the RUBY IA2 CSR (though it was also noted that the mean duration of treatment in RUBY IA2 CSR was reported inconsistently). It was likely that the duration of DOS in the economic model was underestimated and favoured the DOS+CP arm. Assuming a mean treatment duration of 57.15 weeks for DOS by adding an additional 2.67 weeks

Public Summary Document – May 2025 PBAC Meeting

of treatment in the maintenance phase (discounted by 5% for three years and then applying a 97.7% RDI) increased the ICER by 1%.

6.59 Another key difference between the resubmission and the November 2023 submission was the utility values. Health state utilities were derived from the pMMR population in RUBY at the IA1 data-cut, as patient reported outcomes were not re-evaluated at the IA2 data-cut. European Quality of Life scale, 5-Dimensions, 5-Levels (EQ-5D-5L) data from RUBY were translated to Australian utilities via the Norman 2023 validated value set, in line with ESC advice (paragraph 6.47, dostarlimab PSD, November 2023 PBAC meeting). In the November 2023 submission, EQ-5D-5L data was mapped to EQ-5D-3L using Viney 2011, as the resubmission claimed that Norman 2023 was not published at the time of submission. A comparison of the utility values from RUBY using the different value sets is presented in Table 10.

Table 10: Utility values derived from EQ-5D-5L results in RUBY at IA1

| | ITT | | pMMR | | dMMR | |
|------------|-------------|------------|-------------|------------|-------------|------------|
| | Norman 2023 | Viney 2011 | Norman 2023 | Viney 2011 | Norman 2023 | Viney 2011 |
| PF | 0.8715 | 0.7779 | 0.8760 | 0.7802 | 0.8635 | 0.7747 |
| PD | 0.8194 | 0.7339 | 0.8285 | 0.7350 | 0.8033 | 0.7402 |
| Difference | 0.0521 | 0.0440 | 0.0475 | 0.0452 | 0.0602 | 0.0345 |

Source: Table 81, p152 of the resubmission and the resubmission’s economic model spreadsheet

Abbreviations: dMMR = mismatch repair deficient ITT = intention to treat; PD = progressed disease; PF = progression free; pMMR = mismatch repair proficient

Text in italics indicate values extracted or calculated during the evaluation

Grey shaded cells indicate values used in the base case of the model of the resubmission

Blue shaded cells indicate values used in the base case of the dMMR model from the November 2023 submission

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.

6.60 In the pMMR subgroup, the difference between the PF and the progressed disease (PD) states were similar when using either Norman 2023 or Viney 2011 to convert EQ-5D-5L from RUBY to utilities. However, the magnitudes of the utilities were substantially higher when using Norman 2023. Of the two sources, the utilities based on Norman 2023 were less aligned with the published literature, as the utility value for PD (0.8285) was higher than most of the PF values (mostly between 0.8 to 0.817) in published economic analyses in EC. The PF utility in pMMR using Norman 2023 may also be overly optimistic given it was almost equal to the health state utility for the Australian population norm of 0.88 for women aged 55–64 years based on McCaffrey 2016⁷, despite the patients in the model all being diagnosed with A/R EC. Moreover, the utilities in the pMMR subgroup were also higher than for the dMMR subgroup (PF = 0.8635, PD = 0.8033) using the Norman 2023 value set.

6.61 The change from using Viney 2011 to Norman 2023 value set for utilities had a sizeable impact on the ICER. Using the utilities from Viney 2011 in the resubmission’s model increased the ICER by 1%. This was due to the model assuming that patients in the

⁷ McCaffrey N, Kaambwa B, Currow DC, Ratcliffe J. Health-related quality of life measured using the EQ-5D-5L: South Australian population norms. Health Qual Life Outcomes. 2016 Sep 20;14(1):133. doi: 10.1186/s12955-016-0537-0. PMID: 27644755; PMCID: PMC5028927.

Public Summary Document – May 2025 PBAC Meeting

DOS+CP arm remained in both the PF and PD health states longer than patients in the CP arm and as such, a lower utility in both the PF and PD health state led to a lower incremental QALY gain in the model.

- 6.62 As such, while it may have been more appropriate to have used the Norman 2023 value set to provide Australian utilities based on the RUBY EQ-5D-5L results, the resultant utilities appear to be inconsistent with published literature and may be overestimated. Moreover, the results in the resubmission, based on the Norman 2023 utilities, cannot be compared to the November 2023 dMMR model results which were based on the Viney 2011 utilities and presents a comparability issue with previous submissions which affects the interpretation of the results in the resubmission. This is discussed further in paragraph 6.72. The ESC noted the previous advice that the Norman 2023 utilities should have been used and considered it appropriate for the resubmission to include them. However, when comparing the ICER to the previous submission, the dMMR ICER would need to be updated to reflect these values. The revised dMMR ICER would be \$45,000 to < \$55,000/QALY using the Norman 2023 utilities (as opposed to \$55,000 to < \$75,000/QALY accepted by PBAC in November 2023).
- 6.63 Similar to the November 2023 model, it was assumed that no patients in the DOS+CP arm would receive 2L PEM+LEN, which would be consistent with the current PBS restriction for 2L PEM+LEN which excludes patients who have previously had PD-(L)1 inhibitor treatment. This was inconsistent with the results from RUBY at IA2, in which 32.4% of patients who reported any subsequent anti-cancer therapy use had immunotherapy. The resubmission argued that ‘there is no evidence that subsequent immunotherapy is effective in patients treated with prior dostarlimab’. This was not reasonable, as it would not be logical for patients to be receiving treatment if it was not deemed to have clinical benefit. Moreover, in the November 2023 submission, both the ESC and the PBAC considered that there was potential overestimate of DOS+CP OS due to 2L immunotherapy use in the DOS+CP arm in RUBY (paragraph 6.77 and 7.8, dostarlimab PSD, November 2023). In the November 2023 submission, this was partially accounted for by the convergence, but as discussed in paragraph 6.54, the convergence applied in the resubmission may not be fit for purpose, and as such, would favour DOS+CP.
- 6.64 The resubmission assumed that 50.3% of patients who progress in the CP arm will be treated with 2L PEM+LEN in the model, based on results from RUBY at IA2. No adjustments to the OS curve from the CP arm in RUBY at IA2 were made to account for 2L PEM+LEN use by the resubmission, which may not be reasonable as 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). As discussed in paragraph 6.17, the characteristics of patients who used subsequent immunotherapy and the duration of subsequent immunotherapy in RUBY at IA2 was unknown and may not be applicable to the Australian population. Moreover, in RUBY at IA2, not all patients who received subsequent immunotherapy

Public Summary Document – May 2025 PBAC Meeting

used 2L PEM+LEN, as 32% (20/63) of patients who used PEM used it as monotherapy. Reducing the cost of LEN in the model by 32% increased the ICER by 1%.

- 6.65 The resubmission stated that a unit cost of \$51,413 (derived from Goldsbury 2018) was used to inform the terminal care costs as this was the value used for PEM+LEN in 2L A/R EC (paragraph 6.72, Pembrolizumab PSD, March 2022 PBAC meeting) and dostarlimab in 1L A/R dMMR EC (paragraph 7.8, Dostarlimab PSD, November 2023 PBAC meeting) and was 'accepted' by the PBAC. This may not be entirely appropriate, as the ESC had previously noted that these costs were averages of several kinds of cancers, of which none were endometrial. It was unclear whether this average would be representative of endometrial cancer costs. Further, the ESC noted that the terminal care cost was based on the 12 months prior to death and considered this may result in double counting as some of these costs would have accrued in the progressed health state (paragraph 6.72, pembrolizumab PSD, March 2022 PBAC meeting). As such, the inclusion of both terminal care costs and subsequent therapy costs in the resubmission's model likely included an element of double counting and favoured DOS, as removal of terminal care costs increased the ICER by 1% in the base case.
- 6.66 The key drivers of the model are presented in Table 11. These differed to the November 2023 submission in which the rate of convergence was listed as the most impactful key driver. This was due to the change in patient population resulting in differences in incremental benefit, and changes in the extrapolation of OS from being based on Miller 2020 to parametric extrapolations as well as changes in the utility values, meaning the resubmission model behaves somewhat differently to the November 2023 submission.

Public Summary Document – May 2025 PBAC Meeting

Table 11: Key drivers of the model

| Description | Method/Value | Impact Base case: \$ ██████ ¹ /QALY gained. |
|--------------------|--|---|
| Convergence method | The base case applied a linear convergence method, which was likely unfit for purpose as it does not appear to be particularly conservative with regards to OS or PFS. An alternative convergence method e.g. assuming the same rate of change in PFS and OS in both the DOS+CP arm and the CP arm after three years may be more appropriate. Alternatively, using more conservative extrapolations for DOS+CP (e.g. generalised gamma) and more optimistic extrapolations for the CP arm (e.g. exponential) in lieu of extrapolation may also be appropriate. | High. Using the alternate convergence method based on rate of change increased the ICER by ██████%. Using Generalised Gamma for DOS+CP OS (most conservative without crossover) and exponential for CP OS (least conservative function) increased the ICER by ██████%. |
| Time horizon | The base case time horizon (7.5 years) was the same as in the dMMR population from the November 2023 submission. However, evidence from RUBY indicate that survival outcomes in dMMR were better than in pMMR and a shorter time horizon in the resubmission may be appropriate. | Moderate. Favours DOS+CP. Using a 5-year time horizon increased the ICER by ██████% |
| Utilities | High values for model health states based on Norman 2023 value set compared to Viney 2011 value set as used in the November 2023 submission. | Moderate. Favours DOS+CP. Using utilities from the Viney 2011 value set increased the ICER by ██████%. |

Source: Constructed during the evaluation based on results of sensitivity analyses.

CP = carboplatin + paclitaxel; dMMR = mismatch repair deficient; DOS = dostarlimab; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression free survival; pMMR = mismatch repair proficient; QALY = quality adjusted life years

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

6.67 The results of the stepped economic evaluation are presented in Table 12.

Public Summary Document – May 2025 PBAC Meeting

Table 12: Results of the stepped economic evaluation

| Step and component | DOS+CP | CP | Increment |
|---|--------|----------|------------------|
| Step 1a: trial-based costs and outcomes (PFS) ^a | | | |
| Costs ^b | \$█ | \$2,662 | \$█ |
| Progression-free LYs | 1.2560 | 1.0339 | 0.2221 |
| Incremental cost/extra PFLY gained | | | \$█ ¹ |
| Step 1b: trial-based costs and outcomes (OS) ^c | | | |
| Costs ^b | \$█ | \$2,662 | \$█ |
| LY | 2.4512 | 2.2317 | 0.2196 |
| Incremental cost/extra LY gained | | | \$█ ¹ |
| Step 2: Extrapolation to 7.5 years | | | |
| Costs | \$█ | \$2,662 | \$█ |
| LY | 3.2330 | 2.7676 | 0.4654 |
| Progression-free LYs | 1.5132 | 1.1348 | 0.3784 |
| Incremental cost/extra LY gained | | | \$█ ² |
| Incremental cost/extra PFLY gained | | | \$█ ³ |
| Step 3: Translation of outcomes to QALYs | | | |
| Costs | \$█ | \$2,662 | \$█ |
| QALY | 2.7498 | 2.3465 | 0.4033 |
| Incremental cost/extra QALY gained | | | \$█ ³ |
| Step 4: Curve convergence | | | |
| Costs | \$█ | \$2,662 | \$█ |
| Progression-free LYs | 1.5436 | 1.1348 | 0.4088 |
| LY | 3.2296 | 2.7676 | 0.4621 |
| QALY | 2.7484 | 2.3465 | 0.4019 |
| Incremental cost/extra progression-free LY gained | | | \$█ ² |
| Incremental cost/extra LY gained | | | \$█ ² |
| Incremental cost/extra QALY gained | | | \$█ ³ |
| Step 5: Inclusion of health care resource use | | | |
| Costs | \$█ | \$70,281 | \$█ |
| LY | 3.2296 | 2.7676 | 0.4621 |
| Progression-free LYs | 1.5436 | 1.1348 | 0.4088 |
| Progressed disease LYs | 1.6860 | 1.6327 | 0.0533 |
| QALY | 2.7484 | 2.3465 | 0.4019 |
| Progression-free QALYs | 1.3522 | 0.9941 | 0.3581 |
| Progressed disease QALYs | 1.3968 | 1.3527 | 0.0441 |
| Incremental cost/extra LY gained | | | \$█ ⁴ |
| Incremental cost/extra QALY gained (base case) | | | \$█ ⁴ |

Source: Table 106, pp 168 and Table 108, p169 of the resubmission and resubmission's economic model spreadsheet

CP = carboplatin-paclitaxel; dMMR = mismatch repair deficient; DOS = dostarlimab; ICER = incremental cost-effectiveness ratio; LY= life year; QALY = quality adjusted life year; TTD = time to treatment discontinuation.

Text in italics indicate values updated during the evaluation.

a time horizon of 46 months assumed based on maximum duration of OS KM data for RUBY at IA2

b KM data for TTD for DOS used until 33 months compared to 25.82 months from step 2 onwards

c time horizon of 33 months assumed based on maximum duration of PFSS KM data for RUBY at IA1

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000

² \$95,000 to < \$115,000

³ \$115,000 to < \$135,000

⁴ \$55,000 to < \$75,000

6.68 The PSCR acknowledged uncertainty regarding the magnitude of benefit, and that a more conservative approach beyond the trial-based period was required. The most conservative scenario suggested by the evaluation (Δ LYG: 0.3608), which assumes the

Public Summary Document – May 2025 PBAC Meeting

same rate of change in PFS and OS in both treatment arms (i.e., apply PFS and OS from CP for DOS+CP) after three years was accepted as a reasonable basis for consideration as an alternative base case for the economic model. The resulting ICER was \$75,000 to < \$95,000/QALY (see underlined sensitivity analysis in Table 14). The ESC agreed with revised based, but further considered a shorter 5-year time horizon would be more appropriate in this setting given poorer overall survival outcomes in the pMMR population, relative to dMMR patients.

- 6.69 The extrapolation to 7.5 years (Steps 2 and 3) and the inclusion of health care resource use (Step 5) had the largest impact on the ICER. The extrapolation from 46 months to 90 months (7.5 years) resulted in a 70% increase in progression free LYG and 138% increase in LY gained, and the inclusion of health care resources increased the cost of CP arm substantially compared to the DOS+CP arm due to the inclusion of 2L immunotherapy only in the CP arm and the terminal care costs favouring DOS+CP primarily due to discounting (as the convergence applied in the base case assumed the same number of deaths in both arms by the end of the time horizon).
- 6.70 The model assumed that patients treated with DOS+CP would have a longer survival in both PF and PD health states compared to the CP arm. This may not be reasonable as 50.7% of patients who progressed from 1L treatment in the CP arm were assumed to be treated with 2L PEM+LEN whereas all patients who progressed in the DOS+CP arm were assumed to be treated only with chemotherapy in the cost calculations. The PBAC had previously accepted that 2L PEM+LEN provided additional benefit for some patients with A/R EC who have progressed on previous treatment (Paragraph 7.1, pembrolizumab PSD, March 2022 PBAC meeting). For comparison, the November 2023 model for DOS+CP in dMMR EC estimated, the CP arm had a 43% longer undiscounted survival time (47% when discounted) in PD compared to the DOS+CP arm, which would be more consistent with the efficacy of 2L PEM+LEN, which is only available to patients in the CP arm. This indicated that the resubmission's model was likely biased in favour of DOS+CP.
- 6.71 In the November 2023 consideration of DOS+CP, the PBAC considered that for any resubmission in the pMMR population, the economic evaluation (and financial estimates) should be revised to be consistent with those accepted for the dMMR population. (Paragraph 7.22, dostarlimab PSD, November 2023). While the resubmission claimed that the ICER in the resubmission for pMMR patients (\$55,000 to < \$75,000/QALY in the base case) was comparable to the November 2023 model accepted by the PBAC for dMMR patients (\$55,000 to < \$75,000/QALY), this was not a fair comparison, or a reasonable conclusion, due to the different utility values applied. A comparison of the results in the pMMR and dMMR subgroups using the resubmission's model and different utility sources and the November 2023 model in dMMR patients previously considered by the PBAC is summarised in Table 13. Additional inconsistencies between the resubmission and the November 2023 are discussed in paragraph 6.72.

Public Summary Document – May 2025 PBAC Meeting

Table 13: Comparison of economic evaluation results in May 2025 resubmission and November 2023 submission using different utility values

| | pMMR (May 2025 resubmission model) | | dMMR | | |
|---|---------------------------------------|------------------------|---------------------------------------|--------------------------------------|--------------------------------------|
| | Norman 2023 utilities (base case) | Viney 2011 utilities | Norman 2023 utilities, May 2025 model | Viney 2011 utilities, May 2025 model | Viney 2011 utilities, Nov 2023 model |
| Incremental cost | \$█ | \$█ | \$█ | \$█ | \$█ |
| Incremental LYG | 0.4621 | 0.4621 | 1.2078 | 1.2078 | 1.0820 |
| Incremental QALY | 0.4019 | 0.3578 | 1.0799 | 0.9567 | 0.8631 |
| ICER | \$█ ¹ /QALY | \$█ ² /QALY | \$█ ³ /QALY | \$█ ¹ /QALY | \$█ ¹ /QALY |
| % difference from pMMR base case | - | +█% | -█% | -█% | +█% |
| % difference from Nov 2023 (dMMR) results | -█% | -█% | -█% | -█% | - |

Source: Table 54, p111-112 and Table 111, p171 of the resubmission, and calculated during the evaluation using the resubmission's economic model spreadsheet

dMMR = mismatch repair deficient; ICER = incremental cost effectiveness ratio; LYG = life years gained; pMMR = mismatch repair proficient; QALY = quality adjusted life year.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$75,000 to < \$95,000

³ \$45,000 to < \$55,000

6.72 There were significant issues with the consistency of the economic model results between the resubmission and the November 2023 submission which suggest that the resubmission model is more favourable towards DOS+CP, and a comparison of the nominal ICER across the two (re)submissions may not be appropriate. Specifically:

- The May 2025 resubmission model estimated a higher incremental LYG in the dMMR subgroup than the November 2023 model. This higher LYG was unexpected given the OS HR in dMMR patients at IA2 (OS HR = 0.32, 95% CI 0.17, 0.63) as used in the May 2025 model was less favourable than at IA1 (OS HR = 0.30, 95% CI 0.13, 0.70) as used in the November 2023 model (see Table 5) and may be related to the change in extrapolation methods (see paragraph 6.47). Compared to the November 2023 dMMR model results, the ICER in the dMMR subgroup was lower by █% (when using utilities based on Viney 2011) or █% (when using utilities based on Norman 2023) when using the May 2025 model; and
- As discussed in paragraph 6.59, the resubmission used a different source for calculating utility values (Norman 2023) compared to the November 2023 resubmission (Viney 2011). Using the same set of utility values for both subgroups in the same May 2025 model, the ICER for the pMMR subgroup was around █% higher than the dMMR subgroup. This would be consistent with the results of RUBY and previous PBAC considerations that DOS+CP appears to be more effective in dMMR than pMMR patients and MMR was a treatment effect modifier. Comparatively, the nominal ICER in the May 2025 base case for pMMR was █% lower than the ICER in the November 2023 dMMR model;

6.73 Overall, it was likely the results from the two models cannot be compared directly as the resubmission's model was more favourable towards DOS+CP. Instead, it may be

Public Summary Document – May 2025 PBAC Meeting

more reasonable to compare the results of the pMMR subgroup in the May 2025 model against the ICER of the dMMR subgroup using the same model and utility values for consistency. During the evaluation, it was estimated that in order for the pMMR subgroup to achieve an ICER of \$45,000 to < \$55,000/QALY (i.e. same as the dMMR subgroup results using the Norman 2023 utilities in the May 2025 model), the price per 500 mg vial of DOS will need to be decreased to \$|, or a |% price reduction from the requested price of \$|. However, this estimate was based on a model using linear convergence which may be invalid for the pMMR population (but appears to be reasonable for the dMMR population).

- 6.74 The results of key univariate and multivariate sensitivity analyses are summarised in Table 14.

Public Summary Document – May 2025 PBAC Meeting

Table 14: Univariate and multivariate sensitivity analysis around the economic evaluation

| | Incr. cost | Incr. QALYs | ICER | % Difference |
|--|------------|-------------|------------------|--------------|
| Base case | \$█ | 0.4019 | \$█ ¹ | - |
| Time horizon (BC: 7.5 years) | | | | |
| 5 years (convergence assumptions unchanged i.e. does not fully converge at 5 years) | \$█ | 0.2991 | \$█ ² | █% |
| 10 years | \$█ | 0.4019 | \$█ ¹ | -█% |
| Discount rate (BC: 5%) | | | | |
| 0% | \$█ | 0.4745 | \$█ ¹ | -█% |
| 3.5% | \$█ | 0.4219 | \$█ ¹ | -█% |
| Utility values (BC: PF=0.8760; PD=0.8285) | | | | |
| PF=0.7802; PD=0.7350 (RUBY via Viney 2011) | \$█ | 0.3578 | \$█ ² | █% |
| PF=0.736; PD=0.70 (KN-775, as used in March 2022 2L PEM+LEN submission) | \$█ | 0.3379 | \$█ ² | █% |
| Terminal care costs excluded (BC: \$51,413 based on Goldsbury 2018) | \$█ | 0.4019 | \$█ ¹ | █% |
| % immunotherapy use among subsequent treatment (BC: CP arm = 50.7% [RUBY IA2 DC ^a], DOS+CP arm = 0% [PEM+LEN restriction ^b]) | | | | |
| CP arm = 48.8% (RUBY IA1 DC ^a), DOS+CP arm = 0% | \$█ | 0.4019 | \$█ ¹ | █% |
| Convergence of survival curves (BC: between 3 d to 7.5 years) | | | | |
| No convergence | \$█ | 0.4033 | \$█ ¹ | -█% |
| Convergence assuming same rate of change (i.e. apply PFS and OS from CP for DOS+CP) after 3 years till 7.5 years ^c | \$█ | 0.3152 | \$█ ² | +█% |
| Parametric Extrapolations: DOS+CP PFS (BC: Loglogistic) | | | | |
| Best fitting curve by AIC and BIC: Lognormal | \$█ | 0.4032 | \$█ ¹ | -█% |
| Parametric Extrapolations: CP OS (BC: Loglogistic) | | | | |
| Least conservative for ICER: Weibull | \$█ | 0.4479 | \$█ ¹ | -█% |
| Most conservative for ICER: Exponential | \$█ | 0.3426 | \$█ ² | +█% |
| Parametric Extrapolation: DOS TTD (BC: Gompertz) | | | | |
| Least conservative for ICER: Exponential | \$█ | 0.4019 | \$█ ¹ | -█% |
| Most conservative for ICER: Lognormal | \$█ | 0.4019 | \$█ ¹ | +█% |
| Convergence start at 2 years (BC start at 3 years) ^d | \$█ | 0.5914 | \$█ ³ | -█% |
| Assuming mean 57.15 weeks of DOS treatment (BC: 54.48 weeks without RDI adjustment; 52.64 with RDI adjustment) ^e | \$█ | 0.4019 | \$█ ¹ | +█% |
| Accounting for 32% of patients using 2L immunotherapy in CP arm used PEM monotherapy (BC: 0% PEM monotherapy) ^f | \$█ | 0.4019 | \$█ ¹ | +█% |
| Multivariate sensitivity analysis | | | | |
| Gen Gamma for DOS+CP OS (most conservative without crossover) ^g and exponential for CP OS (least conservative function) | \$█ | 0.3120 | \$█ ² | +█% |

Abbreviations: BC = base case; CP = carboplatin-paclitaxel; DC = data-cut; DOS = dostarlimab; HR = hazard ratio; ICER = incremental cost effectiveness ratio; PD = progressed disease; PF = progression free; pMMR = mismatch repair-proficient; QALY = quality adjusted life year.

Source: Table 111, p171 of the resubmission

^a Data from the pMMR/MSS population in RUBY.

^b Patients receiving 1L dostarlimab will not be eligible for 2L PEM+LEN as the PEM+LEN restriction requires patients to be untreated with PD-1/PD-L1 inhibitor therapy and tyrosine kinase inhibitor therapy.

^c Rate of change in OS and PFS from CP arm calculated by dividing proportion remaining alive (Column N, sheet 'CP') and proportion remaining progression free (Column S, sheet 'CP') at any given cycle by the proportion in the previous cycle (e.g. rate of change for OS at cycle 4 would be estimated by dividing OS at cycle 4 by OS in cycle 3). In DOS+CP arm, OS and PFS with convergence adjustment (Column P and V, respectively, sheet 'DOS+CP') has convergence adjustment formula changed from OS/PFS in previous cycle minus the linear gradient (e.g. For OS in cycle 158/3.01 years, convergence formula is OS in cycle 157 minus 0.002, the gradient of the linear convergence curve) to OS/PFS multiplied by rate of change for CP arm as detailed above (e.g. For OS in cycle 158/3.01 years, convergence formula is OS in cycle 157*rate of change in OS for CP in cycle 157, which was estimated by dividing OS in cycle 157 by OS in cycle 156)

^d Truncation point for both OS and PFS in both DOS+CP and CP arm changed to 24 months

^e Calculated by assuming an additional 2.67 weeks of DOS maintenance at the end of treatment. A cost of \$█ (calculated as 2.67/61.05^3*.977*\$█) was added to the discounted cost for DOS+CP arm (BG9, sheet 'DOS+CP'). Cost was calculated as 2.67 weeks

Public Summary Document – May 2025 PBAC Meeting

extra from a six weekly dosing cycle in the 4th year of treatment (therefore three instances of annual discounting of 5%) adjusted by the RDI for maintenance therapy of 97.7%.

f Lenvatinib drug costs (Cell D68, sheet 'Subsequent Tx') multiplied by 0.68

g Weibull and Gompertz functions were more conservative for DOS+CP, but not used as these resulted in the OS curves crossing over.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$75,000 to < \$95,000

³ \$45,000 to < \$55,000

6.75 Overall, the resubmission's ICER in the base case was likely underestimated and favoured DOS+CP as:

- The assumption of linear convergence in the resubmission had validity issues as it did not provide particularly conservative estimates for OS and was in fact more favourable for DOS+CP for PFS compared to the model without convergence (see paragraph 6.54). The convergence applied in the model was unlikely to have addressed uncertainty regarding long term incremental benefit of DOS+CP and differences in subsequent immunotherapy use between the model and in RUBY;
- The incremental OS and PFS benefit associated with DOS+CP compared to CP in pMMR patients used to inform the model was uncertain, given that RUBY did not report statistically significant benefits for OS or PFS in the pMMR subgroup as it was not part of the statistical analysis plan. In RUBY, the 95% confidence interval around the OS HR in pMMR patients (OS HR = 0.79, 95% CI 0.60, 1.04, nominal p-value = 0.0493) at IA2 includes 1.0. RUBY was not powered to detect differences in the pMMR population as it was not part of the formal statistical plan and it may not have been reasonable to model any difference in OS between the DOS+CP arm and the CP arm;
- It was likely unreasonable that the model predicted that DOS+CP patients would also survive longer in the PD health states compared to CP patients, as a proportion of patients in the CP arm were able to have 2L PEM+LEN whereas patients in the DOS+CP arm would only be treated with 2L chemotherapy under the current PBS restrictions for 2L PEM+LEN. The PBAC has previously considered that 2L PEM+LEN provides, for some patients, a significant improvement in efficacy including an improvement in OS compared with chemotherapy (Paragraph 7.1, pembrolizumab PSD, March 2022 PBAC meeting) and as such, the inverse (longer survival in PD for CP only arm compared to DOS+CP arm) would be expected;
- Even though Norman 2023, which allowed mapping of EQ-5D-5L results from RUBY into Australian utilities, was a reasonable value set for the utility mapping, the resultant utilities were generally higher than utilities used in published literature and previous PBAC considerations for DOS in 1L A/R dMMR EC. Using higher utility values based on Norman 2023 favoured DOS+CP as the model predicted that patients in the DOS+CP arm survived longer in both PF and PD health states compared to patients in the CP arm and introduced consistencies with previous PBAC considerations for DOS in 1L A/R dMMR EC;

Public Summary Document – May 2025 PBAC Meeting

- The treatment duration of DOS may have been underestimated compared to the duration of treatment reported in RUBY at IA2 (see paragraph 6.58);
 - Assuming all 2L immunotherapy to be PEM+LEN when 32% of pMMR patients in the CP arm used 2L PEM monotherapy led to an overestimate of cost in the CP arm; and
 - The time horizon may be optimistic given that pMMR patients appear to have worse outcomes than dMMR patients and a shorter time horizon may be more appropriate.
- 6.76 The ESC considered the most conservative scenario suggested by the evaluation and accepted in the PSCR, which assumes the same rate of change in PFS and OS in both treatment arms, was a reasonable alternative base case for the economic model.
- 6.77 The ESC noted that the KM truncation points applied in the model, based on median follow-up time, occurred when a relatively large proportion of patients remained alive. ESC advised that the use of the Gebski criterion to determine the KM truncation points would be more appropriate.
- 6.78 The ESC noted the PSCR considered the revised base case ICER of \$75,000 to < \$95,000/QALY was within the range previously recommended for PEM+LEN in 2L A/R EC (\$75,000 to < \$95,000/QALY). The ESC considered comparability of the revised base case to the November 2023 dMMR model was more relevant. This would require the dMMR cohort data being applied to the current pMMR model given the model changes in this resubmission; the dMMR ICER reduced from \$55,000 to < \$75,000 to \$45,000 to < \$55,000/QALY in this scenario.
- 6.79 The ESC considered additional sensitivity analyses using the revised base case may be informative (see Table 15):

Public Summary Document – May 2025 PBAC Meeting

Table 15: Univariate and multivariate sensitivity analysis around the economic evaluation

| Univariate sensitivity analyses | Incr. cost | Incr. QALYs | ICER | % Difference |
|---|------------|-------------|------------------|--------------|
| PSCR Base case - Convergence assuming same rate of change (i.e. apply PFS and OS from CP for DOS+CP) after 3 years | \$█ | 0.3152 | \$█ ¹ | - |
| 5 years (BC: 7.5 years) | \$█ | 0.2438 | \$█ ² | +█% |
| Terminal care costs excluded (BC: \$51,413 based on Goldsbury 2018) | \$█ | 0.3152 | \$█ ¹ | +█% |
| Assuming mean 57.15 weeks of DOS treatment (BC: 54.48 weeks without RDI adjustment; 52.64 with RDI adjustment) ^a | \$█ | 0.3152 | \$█ ¹ | +█% |
| Accounting for 32% of patients using 2L immunotherapy in CP arm used PEM monotherapy (BC: 0% PEM monotherapy) ^b | \$█ | 0.3152 | \$█ ¹ | +█% |
| Cost per 500mg DOS = \$█ (BC: \$█) | \$█ | 0.3152 | \$█ ³ | -█% |

Abbreviations: BC = base case; CP = carboplatin-paclitaxel; DOS = dostarlimab; HR = hazard ratio; ICER = incremental cost effectiveness ratio; Incr. = incremental; OS = overall survival; PD = progressed disease; PEM = pembrolizumab; PF = progression free; PFS = progression free survival; pMMR = mismatch repair-proficient; QALY = quality adjusted life year; RDI = relative dose intensity

^a Calculated by assuming an additional 2.67 weeks of DOS maintenance at the end of treatment. A cost of \$█ (calculated as 2.67/6/1.05³*.977*\$█) was added to the discounted cost for DOS+CP arm (BG9, sheet 'DOS+CP'). Cost was calculated as 2.67 weeks extra from a six weekly dosing cycle in the 4th year of treatment (therefore three instances of annual discounting of 5%) adjusted by the RDI for maintenance therapy of 97.7%.

^b Lenvatinib drug costs (Cell D68, sheet 'Subsequent Tx') multiplied by 0.68

The redacted values correspond to the following ranges:

¹ \$75,000 to < \$95,000

² \$95,000 to < \$115,000

³ \$45,000 to < \$55,000

6.80 As discussed above, the clinical benefit of DOS+CP in pMMR patients was uncertain and it was unclear whether the differences, particularly for OS, should have been modelled with the results being in favour of DOS+CP. The ESC noted the relatively weak evidence for clinical efficacy meant that it was uncertain if a cost-utility analysis was justified in this setting.

Drug cost/patient/course

6.81 Drug acquisition costs for DOS in pMMR patients as proposed in the resubmission are summarised in Table 16.

Public Summary Document – May 2025 PBAC Meeting

Table 16: Drug cost per patient for DOS (pMMR) (as per submission proposed price)

| | Trial dose (RUBY at IA2) and duration | Model | Financial estimates |
|---|---------------------------------------|--------------------------|----------------------------|
| Mean number of initiation doses | 6 ^c | 5.15 | 6 ^e |
| Mean number of maintenance doses | 6.525 | 6.20 | 5.77 ^e |
| Mean duration ^a | 56.9 weeks | 52.64 weeks ^d | 52.64 weeks ^d |
| Alternative mean duration ^a | 57.15 weeks | - | - |
| Cost/patient/course (undiscounted) ^b | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] ^f |

Source: Estimated during the evaluation information from Table 23, pp60-61 of the resubmission using the resubmission’s economic model and financial estimate spreadsheets

Text in italics indicate values calculated during the evaluation

pMMR = proficient mismatch repair; DOS = dostarlimab; Q3W = every three weeks; Q6W = every six weeks; RDI = relative dose intensity
 a In table 23 of the resubmission, the mean duration of DOS was reported to be 56.9 weeks. However, in table 14.1.1.24 of RUBY IA2 CSR, mean (SD) of 57.15 (49.6) weeks for DOS+CP and 54.29 (49.1) weeks for placebo + CP was reported. Table 14.1.1.24 estimates the mean duration of overall study treatment (e.g., 57.15 weeks for DOS+CP), while Table 14.1.1.25 estimates the mean duration of each component of study treatment (e.g., 56.88 weeks for DOS). The marginal difference is due to a small proportion of patients discontinuing dostarlimab prior to carboplatin and paclitaxel, resulting in a slightly higher mean duration of overall study treatment compared to the dostarlimab component only.

b Price based on \$ [REDACTED]/500mg/dose for initiation and \$ [REDACTED]/100mg/dose for maintenance doses, based on the requested AEMP of \$ [REDACTED] weighted by a 67% private and 33% public split, as used by the resubmission in their estimates.

c Assumption based on recommended dosage of 6 doses (Q3W) for initiation, totalling 18 weeks and remainder given every six weeks (Q6W) as maintenance, assuming 57.15 weeks of treatment

d Includes RDI adjustments of 94% for initiation doses and 97.7% for maintenance doses. Assuming 100% RDI, the duration of treatment was 54.48 weeks in the economic model

e Assumption based on recommended dosage of 6 doses (Q3W) for initiation, totalling 18 weeks and remainder given every six weeks (Q6W) as maintenance, assuming 52.64 weeks of treatment

f Assuming longer initiation relative to maintenance (as in the financial estimates) leads to a slight increase in cost of DOS as, after accounting for dispensing fees, the cost per 1000 mg DOS Q6W is less than double that of 500 mg DOS Q3W. The number of doses in the financial estimates (11.77) was also higher than in the economic model (11.35) even though the duration was the same.

* 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.

Estimated PBS usage & financial implications

6.82 This resubmission was not considered by DUSC.

6.83 An epidemiological approach was employed to estimate the financial impact of listing DOS (for use in combination with platinum-containing chemotherapy) on the PBS for the treatment of 1L A/R pMMR EC. The same approach to estimating financials as the November 2023 submission was used with the following adjustments compared with the November 2023 submission:

- Analysis period updated to 2025-2030 compared with 2024-2029;
- Incidence of uterine cancer over analysis period updated to reflect the newly available AIHW long-term incidence projections for uterine cancer;
- Proportion with pMMR of 73%, representing the complement of 27% accepted for proportion with dMMR;
- Mean duration of treatment for dostarlimab updated to 52.64 weeks, informed by the economic model compared with 86.84 weeks;
- Grandfather patient estimates updated (< 500 patients in Year 1 compared to < 500 patients in Year 1);

Public Summary Document – May 2025 PBAC Meeting

- AHI, Dispensing fees and EFC fees updated (July 2024 fees); and
- MBS fee updated (Item 13950: \$123.05)

6.84 As in the November 2023 submission, the resubmission 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 resubmission 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.

6.85 Key data sources used for estimating the financial estimates are presented Table 17.

Table 17: Key inputs for financial estimates

| Data | Value and Source | Comment |
|---------------------------------|---|---|
| Eligible population | | |
| Incidence of endometrial cancer | Yr 1 (2025): 3,443 Yr 2 (2026): 3,542 Yr 3 (2027): 3,639 Yr 4 (2028): 3,734 Yr 5 (2029): 3,828 Yr 6 (2030): 3,921 Source: Total incidence of uterine cancer as projected by the AIHW. 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). | Reasonable. Updated source was appropriate. DUSC has previously considered that the estimate for the proportion of uterine cancer reported as EC (95%) was reasonable (Table 14, dostarlimab PSD, March 2022 PBAC meeting). The estimates in the resubmission were slightly lower than estimated in the November 2023 resubmission between 2025 (3,467) and 2029 (3,898). |
| 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 feedback, as used in the PEM submission (Table 15, pembrolizumab PSD, March 2022 meeting). | Unchanged from November 2023 submission. 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 resubmission) (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: 30% Source: Fung-Kee-Fung 2006; De Boer 2019 | The November 2023 submission originally used a 36% rate for Stage III curative. The PBAC considered a 30% recurrence rate for Stage III patients would be appropriate, based on the 5 year failure-free survival in PORTEC3 of 70.9%. (Table 20, dostarlimab PSD, November 2023 PBAC meeting), and the resubmission appropriately used the 30% input. DUSC previously considered the 13% estimate of recurrence in Stage I/II EC may be reasonable (p5, dostarlimab DUSC advice, March 2022 meeting). |

Public Summary Document – May 2025 PBAC Meeting

| Data | Value and Source | Comment |
|---|---|--|
| | <p>Timing of first recurrence Yr 1: 34.6% in Stage I/II, 17.3% in Stage III Yr 2: 50.0% Yr 3: 7.7% Yr 4: 3.85% Yr 5+: 3.85% Note: The Yr 1 recurrence rate was adjusted (x 0.5) for the Stage III curative population. In this setting, the majority of patients are treated with adjuvant chemoradiotherapy. Based on the proposed restriction criteria and RUBY, only patients who experience first recurrence 6 months after the last dose of systemic therapy would be eligible for DOS. Source: Huijgens 2013</p> | <p>Resubmission claimed that this was unchanged, but this was not accurate. In the November 2023 submission, the year 4 rate was 0% and the year 5+ rate was 7.7% as per Huijgens 2013, but in the resubmission, this 7.7% was split between year 4 and 5. This change did not lead to any tangible differences in the financial estimates. DUSC has previously considered this estimate reasonable (p5, dostarlimab DUSC advice, March 2022 meeting).</p> <p>For Stage III curative patients recurring within the first year, the resubmission assumed that half (17.43%) would recur within 6 months of systemic therapy (and therefore would not be eligible for DOS under the proposed restriction). However, it was unclear whether this adjustment of 0.5 would be accurate in practice.</p> |
| <p>Proportion expected to receive 1L PBC</p> | <p>90% Source: Assumption and considered to already incorporate ECOG 0-1 status given patients expected to receive 1L CP would have to be suitable for or well enough to tolerate treatment. Resubmission cited paragraphs 6.85 and 7.10, Dostarlimab PBAC PSD, November 2023, which indicated “The PBAC considered that the changes applied in the PSCR (removal of adjustment for ECOG 0-1 for DOS+CP) were appropriate and had corrected errors identified in the evaluation.”</p> | <p>This was not appropriate and may be overestimated. The discussion in paragraph 7.10 (as cited by the resubmission) appears to be related to ECOG in the 2L usage and not 1L. In the 1L setting, the PBAC had instead stated that “(t)he PBAC considered that the proportion of patients with ECOG 0-1 and expected to receive 1L PBC of 72% (90%x80%) was reasonable.” (Table 20, dostarlimab PSD, November 2023 PBAC meeting). Tested in sensitivity analysis</p> |
| <p>Proportion with pMMR</p> | <p>73% Source: Gupta 2021</p> | <p>DUSC considered a 27% for dMMR to be reasonable (Table 14, dostarlimab PSD, March 2022 PBAC meeting), therefore a 73% for pMMR as the complement was reasonable.</p> |
| <p>Proportion of patients treated with 1L PBC who are eligible for 2L PEM+LEN</p> | <p>49% Source: Based on 51% response rate in Miller 2012 RCT, as used in the PEM submission (Table 15, pembrolizumab PSD, March 2022 meeting).</p> | <p>DUSC considered this estimate may be reasonable (Table 15, pembrolizumab PSD, March 2022 PBAC meeting). 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. (Paragraph 7.10, dostarlimab PSD, November 2023 PBAC meeting)</p> |
| <p>Prevalent patients (Stage I/II patients and Stage III curative patients who experience recurrence in 2023)</p> | <p>Probability of survival from diagnosis: Yr 1: 84.0% Source: AIHW 5-year relative cancer survival data 2016-2020 (C54.1)</p> | <p>Decreased from 85.1% in the November 2023 submission. This was similar to the estimate (83.5%) applied in the PEM submission and in line with DUSC consideration that as the prevalent pool were not all diagnosed in the last year, it was not reasonable to apply the one-year survival rate to all prevalent patients (Table 15, pembrolizumab PSD, March 2022 meeting). Unlike the November 2023 submission, half-cycle correction was not applied to the prevalent population.</p> |

Public Summary Document – May 2025 PBAC Meeting

| Data | Value and Source | Comment |
|---|--|--|
| Treatment utilisation | | |
| Grandfathered patients (1L A/R dMMR EC) | █ ¹ in Yr 1 Source: Sponsor estimate | A patient access program was anticipated to commence in █ for the treatment of patients with 1L A/R pMMR EC by the resubmission. This was consistent with resubmission's (p37) grandfathering clause which requested for █ ¹ patients. |
| Uptake rate of 1L DOS (plus platinum containing chemotherapy) | █% Source: Assumption | PBAC previously accepted an uptake rate of 95% for 2L immunotherapy in A/R EC (Table 15, pembrolizumab PSD, March 2022 meeting). |
| Mean duration of DOS treatment | pMMR: 52.64 weeks (18 weeks initiation and 34.64 week continuation), equivalent to 11.77 doses Note: grandfathered patients were assumed to have receive 50% of mean duration of treatment (26.32 weeks) Note that this builds in the RDI for DOS Dosage of 500 mg Q3W for six cycles and then 1000 mg Q6W thereafter assumed. Grandfathered patients assumed to only use 1000 mg Q6W regimen. Source: economic model | Economic model estimated mean of 15.46 weeks on initiation and 37.18 week continuation. Assuming longer initiation relative to maintenance (as in the financial estimates) leads to a slight increase in cost of DOS as, after accounting for dispensing fees, the cost per 1000 mg DOS Q6W is less than double that of 500 mg DOS Q3W. The number of doses in the financial estimates (11.77) was also higher than in the economic model (11.35) which led to slightly higher MBS estimates for administration. As discussed in paragraph 6.58, the economic model appears to have underestimated the duration of treatment compared to what was reported in RUBY at IA2. This may have carried over to the financial estimates. |
| Mean duration of PEM+LEN | PEM: █ weeks LEN: █ weeks Source: estimated based on pricing information provided by the Department Dosage of PEM 200 mg Q3W and LEN 10 mg two tabs daily assumed | As discussed in paragraph 6.64, not all pMMR patients who used subsequent immunotherapy in the CP arm of RUBY used PEM+LEN, and 32% used only PEM monotherapy. As such, the cost offsets assuming the full course of LEN may be overestimated. |
| Mean duration of CP | Not included in the resubmission | Was previously considered in the November 2023 submission. However, given the low cost of CP relative to immunotherapies, and the likelihood that CP use will remain relatively unchanged, likely reasonable to exclude. |

Source: Table 113, pp174-176 of the resubmission, resubmission's financial estimates spreadsheet

1L = first-line; 2L = second-line; AEMP = approved ex-manufacturer price; AIHW = Australian Institute of Health and Welfare; A/R = advanced or recurrent; CP = carboplatin-paclitaxel; dMMR = mismatch repair deficient; DOS = dostarlimab; DUSC = drug utilisation sub-committee; EC = endometrial cancer; ECOG = Eastern Cooperative Oncology Group; ICD-10 = International Classification of Diseases version 10; MBS = Medicare Benefits Schedule; PBC = platinum-based chemotherapy; PBS = Pharmaceutical Benefits Scheme; PEM+LEN = pembrolizumab + lenvatinib; RDI = relative dose intensity; RPBS = Repatriation Pharmaceutical Benefits Scheme; Yr = year.

Blue shading indicates data previously seen by the PBAC.

The redacted values correspond to the following ranges:

¹ < 500

6.86 The estimated financial impact of PBS listing DOS for pMMR is summarised in Table 18.

Public Summary Document – May 2025 PBAC Meeting

Table 18: Estimated use and financial implications of the proposed DOS listing (pMMR)

| | 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) | | | | | | |
| Incident Pts treated with DOS+CP (█%) | █ 1 | █ 1 | █ 2 | █ 2 | █ 2 | █ 2 |
| Prevalent patients ^a | █ 1 | █ 1 | █ 1 | █ 1 | █ 1 | █ 1 |
| Grandfathered patients | █ 1 | █ 1 | █ 1 | █ 1 | █ 1 | █ 1 |
| Total pMMR treated with DOS | █ 2 | █ 1 | █ 2 | █ 2 | █ 2 | █ 2 |
| PBS/RPBS cost less co-pay | | | | | | |
| DOS total (pub) | \$ █ 3 | \$ █ 4 | \$ █ 4 | \$ █ 5 | \$ █ 5 | \$ █ 5 |
| DOS total (eff) | \$ █ 6 | \$ █ 7 | \$ █ 7 | \$ █ 7 | \$ █ 7 | \$ █ 7 |
| Estimation of changes in use and financial impact of other medicines (PBS and RPBS) | | | | | | |
| Patients no longer treated with 2L PEM+LEN (49%) ^b | █ 1 | █ 1 | █ 1 | █ 1 | █ 1 | █ 1 |
| PBS/RPBS cost less co-pay | | | | | | |
| 2L PEM+LEN offset (pub) | -\$ █ 8 | -\$ █ 8 | -\$ █ 8 | -\$ █ 8 | -\$ █ 8 | -\$ █ 8 |
| 2L PEM+LEN offset (eff) | -\$ █ 8 | -\$ █ 8 | -\$ █ 8 | -\$ █ 8 | -\$ █ 8 | -\$ █ 8 |
| Estimated financial implications for the PBS/RPBS | | | | | | |
| Net cost to PBS/RPBS (pub) | \$ █ 9 | \$ █ 6 | \$ █ 6 | \$ █ 6 | \$ █ 6 | \$ █ 6 |
| Net cost to PBS/RPBS (eff) | \$ █ 7 | \$ █ 10 | \$ █ 10 | \$ █ 10 | \$ █ 10 | \$ █ 10 |
| Estimated financial implications for the health budget | | | | | | |
| Net change in prescriptions | █ 2 | █ 1 | █ 1 | █ 1 | █ 2 | █ 2 |
| Net change in MBS services ^c | █ 2 | █ 2 | █ 2 | █ 2 | █ 2 | █ 2 |
| Net MBS costs ^d | \$ █ 11 | \$ █ 11 | \$ █ 11 | \$ █ 11 | \$ █ 11 | \$ █ 11 |
| Net cost to Govt health budget (eff) | \$ █ 7 | \$ █ 10 | \$ █ 10 | \$ █ 10 | \$ █ 10 | \$ █ 10 |

Source: Tables 114 to 121, p178-182, Table 124 to 127 p184-186, Table 130 p187, Table 132 to 135 p189-190 of the resubmission

Text in italics indicates values calculated and extracted during the evaluation.

2L = second-line; CP = carboplatin-paclitaxel; DOS = dostarlimab; EC = endometrial cancer; eff = effective; Govt = government; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; PEM+LEN = pembrolizumab + lenvatinib; pMMR = mismatch repair proficient; pts = patients; pub = published; RPBS = Repatriation Pharmaceutical Benefits Scheme.

a < 500 prevalent patients estimated to be treated with dostarlimab, of which < 500 was assumed to be treated under grandfathered restriction and removed to avoid double counting

b Excludes grandfathered patients, 500 to < 5,000 patients treated with DOS In year 1 considered for offsets

c Calculated as differences between number of DOS+CP administrations (11.77 for each incident and prevalent patient and 4.39 for each grandfathered patient) and number of 2L PEM+LEN administrations offset █ for each patient, based on PEM duration of █ weeks given every three weeks)

d based on 80% rebate on MBS item 13950 (\$123.05 per administration)

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$100 million to < \$200 million

⁴ \$60 million to < \$70 million

⁵ \$70 million to < \$80 million

⁶ \$30 million to < \$40 million

⁷ \$20 million to < \$30 million

⁸ net cost saving

⁹ \$50 million to < \$60 million

¹⁰ \$10 million to < \$20 million

¹¹ \$0 to < \$10 million

6.87 The estimated net cost to the government budget of listing DOS on the PBS/RPBS at the proposed effective price was \$20 million to < \$30 million (\$20 million to < \$30 million to PBS/RPBS) in Year 1, \$10 million to < \$20 million (\$10 million to < \$20 million to PBS/RPBS) in Year 2 and increasing to \$10 million to < \$20 million (\$10 million to < \$20 million to PBS/RPBS) in Year 6 for pMMR patients. The total cost

Public Summary Document – May 2025 PBAC Meeting

- over the six-year period was \$90 million to < \$100 million (\$90 million to < \$100 million to PBS/RPBS, \$0 to < \$10 million to MBS).
- 6.88 The resubmission's financial estimates included < 500 grandfathered patients. The resubmission stated that a patient access program is anticipated to commence in [] for the treatment of patients with 1L A/R pMMR EC, and that the eligibility for the access program will be aligned with the proposed PBS restriction criteria for 1L A/R pMMR EC. The resubmission assumed that only < 500 of the < 500 grandfathered patients will be prevalent patients though no justification was provided. Presumably, the remaining < 500 grandfathered patients would have been incident patients diagnosed between when the access program begins and the PBS listing of DOS for pMMR. However, this timeframe was uncertain, and as the resubmission has not provided any basis for their estimation of grandfathered patients, this number should be considered uncertain.
- 6.89 The resubmission's estimated number of 1L A/R EC patients treated with DOS were reasonably aligned with the November 2023 resubmission's PSCR revised base case financial estimates. For example, using the November 2023's estimates of < 500 dMMR patients treated with DOS in Year 3, or 2026, (corresponding to Year 2 in the current resubmission due to difference in time of resubmission, and not including any prevalent patients), and the prevalence of 27% dMMR and 73% pMMR, the November 2023 submission would have estimated 500 to < 5,000 ($< 500 \div 27\% \times 73\%$) pMMR patients treated with DOS 2026, which was similar to the 500 to < 5,000 patients estimated in the resubmission.
- 6.90 It was unclear however whether the November 2023 resubmission's revised base case financial estimates assumed 90% 1L platinum chemotherapy use (i.e. 90% uptake of chemotherapy and 100% ECOG 0-1) or 72% (i.e. 90% uptake of chemotherapy and 80% ECOG 0-1). In the resubmission, the proportion of patients treated with 1L platinum-based chemotherapy (90%) may be overestimated as the PBAC considered that the proportion of patients with ECOG 0-1 (80%) and expected to receive 1L PBC (90%) of 72% ($90\% \times 80\%$) was reasonable (Table 20, dostarlimab PSD, November 2023 PBAC meeting). Consequently, the number of pMMR patients treated with DOS and the financial impact may be overestimated.
- 6.91 In the resubmission's financial estimates, there were uncertainties around the duration of DOS treatment assumed, as the mean 52.64 weeks of treatment assumed, which was 54.48 weeks before adjusting for RDI, may be underestimated compared to the mean duration of 57.15 weeks reported in RUBY IA2. The duration of treatment in Grandfathered patients (50% of non-grandfathered patients) should also be considered uncertain as it was not supported by any evidence.

Quality Use of Medicines

- 6.92 The resubmission stated that the Sponsor intends to implement medical education activities, including 1:1, small group meetings and large meetings, and a Patient Card (additional TGA risk minimisation measure) to promote safe and effective use of dostarlimab in clinical practice. The patient card is intended to inform patients about

Public Summary Document – May 2025 PBAC Meeting

signs and symptoms of the most common immune-related events with dostarlimab, 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 resubmission did not propose any risk sharing arrangement (RSA) but stated that the sponsor was willing to consider an RSA according to the base case financial estimates to facilitate the listing of DOS for 1L A/R pMMR EC.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of dostarlimab (DOS) in combination with carboplatin and paclitaxel (CP) for the treatment of primary advanced or first recurrent (A/R) mismatch repair proficient (pMMR) endometrial cancer (EC). The PBAC recalled it had previously considered there was a high clinical need for 1L treatments for endometrial cancer but 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 (pembrolizumab + lenvatinib) (dostarlimab PSD, November 2023 PBAC meeting, paragraph 7.17). Based on the updated evidence presented in the resubmission, the PBAC considered the evidence did not establish a clear clinical benefit in pMMR, with the more mature overall survival (OS) data not showing a significant improvement in the pMMR subgroup of the key trial and overall safety was inferior to current therapy.
- 7.2 The PBAC noted there was support from clinicians and consumer groups for dostarlimab to be used in the pMMR population, with MOGA providing strong support for its PBS listing, considering it high priority. The PBAC noted the TGA Delegate had concluded there was sufficient evidence to establish efficacy for dostarlimab plus carboplatin-paclitaxel followed by dostarlimab in the treatment of adult patients with primary advanced or recurrent pMMR EC. Whilst the PBAC acknowledged there may be efficacy in a small subset of the pMMR population, it was unclear which patients this may be. It was noted 73% of EC patients have pMMR and microsatellite stability (MSS), with predicted reduced responses to immunotherapy. The PBAC considered there was a risk that, if PBS listed, many patients with pMMR/MSS EC not benefiting from first-line therapy with DOS would be ineligible for effective second-line therapy with PEM+LEN.
- 7.3 The PBAC recalled it had previously stated that carboplatin and paclitaxel (CP) was the appropriate comparator for the all-comers population, but 1L CP followed by 2L PEM+LEN is also a relevant comparator for a proportion of the population (dostarlimab PSD, November 2023 PBAC meeting, paragraph 7.19). The PBAC noted the resubmission stated that 1L CP followed by 2L PEM+LEN would be the comparator in approximately half of the population. The PBAC considered it remained unclear if

Public Summary Document – May 2025 PBAC Meeting

the comparator arm in the RUBY trial was representative of this half of the population as the characteristics of patients who received subsequent immunotherapy and the duration of subsequent treatment in the RUBY trial was unknown.

- 7.4 The PBAC noted the resubmission included a new data cut (the second interim analysis (IA2)), from the RUBY trial, a head-to-head trial comparing DOS+CP to placebo+CP (n=494). The IA2 data reported updated results for OS, time to disease progression on first subsequent anticancer therapy following study treatment or death (PFS2) and safety outcomes. No new PFS results (i.e. the dual primary endpoint) were available in RUBY at IA2. The pMMR subgroup included a notable sample size (N=376), and substantial OS follow-up was available as of the IA2 data-cut (37.5 months; >50% maturity), however it was noted that outcomes in the pMMR subgroup were not included in statistical analysis plan for RUBY and the risk of bias in the pMMR subgroup was high (see paragraph 6.11).
- 7.5 The PBAC noted IA2 data showed a significant OS benefit for the all-comers population (HR = 0.69, 95% CI 0.54, 0.89), but this outcome was driven by the mismatch repair deficient (dMMR) subgroup (HR = 0.32, 95% CI 0.17, 0.63). The IA2 data for the pMMR subgroup was not convincing, with the point estimates for OS HR slightly worse than in the first IA and 95% confidence intervals crossing the null (HR = 0.79, 95% CI 0.60, 1.04 (IA2) compared to HR = 0.73, 95% CI 0.52, 1.02 (IA1)). The PBAC also noted that the median 7 months improvement in OS may not be meaningful given issues raised with interpreting the minimum clinically important difference (MCID) (see paragraph 6.17). The PBAC noted no updated PFS data were available and as such its overall interpretation of the evidence remained unchanged from November 2023 when it considered that the PFS benefit in the pMMR population was much smaller when compared to the dMMR population, and combined with the uncertain OS benefit, the clinical place for DOS in 1L treatment for pMMR EC was unclear (paragraph 7.20, dostarlimab PSD, November 2023). The PBAC considered the claim of superior comparative efficacy was not adequately supported in the resubmission due to the uncertainty in OS benefit for pMMR population remaining unchanged with the updated data.
- 7.6 The PBAC reaffirmed that the claim of inferior comparative safety of DOS+CP versus CP alone was reasonable in this resubmission. The PBAC recalled it had previously accepted this claim in its submission for dostarlimab at its November 2023 meeting (dostarlimab PSD, November 2023 PBAC meeting). The PBAC noted the resubmission interpretation of treatment emergent adverse events (TEAEs) as ‘manageable’ was unreasonable given DOS+CP was also associated with more TEAEs resulting in death (five events compared to no events in placebo + CP, RR = 11.23, RD = 0.02)⁸.

⁸ Note that none of the TEAEs leading to death in the pMMR/MSS population (general physical health deterioration, COVID-19, opiate overdose) in RUBY were considered related to study treatment. Two TEAEs leading to death were experienced in the dMMR group of the RUBY trial (myelosuppression and hypovolemic shock). No additional TEAEs leading to death occurred between the IA1 and IA2 analyses.

Public Summary Document – May 2025 PBAC Meeting

7.7 The PBAC considered that the model and financial estimates for pMMR were not relevant as the clinical claim was not accepted.

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

Outcome:

Not recommended

8 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.

9 Sponsor's Comment

GSK is disappointed by the PBAC's decision not to recommend dostarlimab (Jemperli) for pMMR patients. GSK considers that subsequent follow-up from the RUBY trial has established the overall survival (OS) benefit for Jemperli plus CP in the overall primary advanced / first recurrent EC population (Powell et al., 2024). GSK considers that at least half of the women treated in the first-line setting would not be eligible for immunotherapy in the second-line setting (paragraph 7.10, Dostarlimab PSD, November 2023).