Single Technology Appraisal

Dostarlimab with platinum-based chemotherapy for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6415]

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Dostarlimab with platinum-based chemotherapy for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6415]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from GlaxoSmithKline**
   a. Company's Draft Guidance Response Technical Appendix

2. **Comments on the Draft Guidance from experts:**
   a. Patient expert, nominated by Peaches Womb Cancer Trust

3. **External Assessment Group critique of company comments on the Draft Guidance**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Dostarlimab with platinum-based chemotherapy for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6415]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Wednesday 20 August 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology. • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank):	GlaxoSmithKline Ltd

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Not applicable
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	GSK does not receive funding from the tobacco industry
Name of commentator person completing form:	[redacted]
Comment number	**Comments**
Overview	GSK appreciates the opportunity to comment on the draft guidance document and to address the committee's concerns and uncertainties in re this appraisal. The draft guidance recommendation not to recommend dostarlimab in combination with platinum containing chemotherapy (PCC) is disappointing as it restricts access to a clinically effective treatment option for patients with primary advanced or recurrent endometrial cancer (EC) characterised by mismatch repair proficient/microsatellite stable (MMRp/MSS) disease. As recognised within the draft guidance, and as stated during the first committee meeting, patients affected by this indication have an extremely poor prognosis and high burden of disease which not only affects those directly impacted by the disease but their families and carers as well. Notwithstanding this, GSK welcomes the opportunity to respond to the draft guidance and hopes that the following response will aid the committee in reaching a conclusion regarding the clinical and cost-effectiveness of dostarlimab within this indication. GSK

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	understands that the committee were unable to reach agreement on the clinical and cost-effectiveness of dostarlimab primarily due to the following areas of uncertainty: 1. The generalisability of subsequent treatments used in Part 1 of the RUBY trial (RUBY-1) to clinical practice in the United Kingdom (UK) (3.5) 2. The impact of subsequent treatments, especially immunotherapies, on post-progression outcomes such as progression-free survival 2 (PFS2) and overall survival (OS) (3.6, 3.10, 3.11) 3. OS extrapolation and the impact of treatment waning (3.12) 4. Clinical and cost-effectiveness in subgroups, such as tumours with tp53 mutations (3.19) 5. Maturity of the progression free survival (PFS) data informing cost-effectiveness modelling (3.9) GSK hopes that the following draft guidance response will address these areas of concern. Specifically, it is hoped that the evidence included below will support the case that: • Treatments received at later lines of therapy in RUBY-1 are largely consistent with what is expected in UK clinical practice. Any divergences from UK clinical practice do not bias the OS results of the RUBY-1 trial • Due to the synergistic mechanism of action of dostarlimab in combination with a platinum-based taxane chemotherapy doublet, the benefits of treatment extend beyond the first progression event resulting in greater improvements to OS • Immunotherapies used in later lines of treatment have only modest benefits, and have negligible impact on the OS benefits observed in the RUBY-1 trial • Treatment effect waning has been captured within the submitted base-case resulting in survival extrapolations which are consistent with clinical expectation • The clinical effectiveness of dostarlimab supports its reimbursements for all patients with mismatch repair proficiency, within the indication.
Comments and area's needing clarification	
(1).	**Comments on draft guidance** **The subsequent treatments used in RUBY-1 are appropriate for decision-making (3.2, 3.5)** GSK would like to clarify that the treatments used at later lines of therapy in RUBY-1 are largely reflective of what is utilised in UK clinical practice. As shown in Table 1, the most used treatment type was conventional chemotherapy ([redacted]) followed by immunotherapy. As noted by clinical experts during the committee meeting, not all patients are suitable for systemic anticancer therapy at subsequent lines of treatment due to tolerability or fitness concerns and therefore may be treated with palliative or non-cytotoxic methods such as radiation therapy or hormone therapy. These treatment modalities are reflective of what is available in UK clinical practice. As

identified by the external assessment group (EAG) and as described in the draft guidance, one exception to this is the use of bevacizumab which was used by a small number of patients in the RUBY-1 trial ([redacted]). There is limited evidence supporting the efficacy of bevacizumab in this setting; however, this is also true for most treatments used in this context. Prognosis, especially following relapse, is particularly poor. The exception to this is the immunotherapy-based regimen, pembrolizumab with lenvatinib, which has demonstrated superiority over chemotherapy singlet treatments in a Phase 3 controlled trial (1). However, as further described below (Comment (3), the benefit of this treatment in practice remains modest. In summary, the proportion of patients being treated at subsequent lines of therapy, as well as the types of treatment regimens used, remain consistent with what is expected in clinical practice.

Table 1: Subsequent treatment recorded in the RUBY-1 trial (MMRp/MSS)

	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)	Total (N=376)
Any follow-up anticancer therapy, n (%)	105 (54.7)	134 (72.8)	239 (63.6%)
[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy	34 (17.7%)	68 (37.0%)	102 (27.1%)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CP, carboplatin and paclitaxel.

Notably, of patients initially treated with carboplatin and paclitaxel (CP) alone who went on to receive a follow-up anti-cancer treatment (FUACT), approximately 50.7% (N=68/134) received an immunotherapy treatment (Table 1). This mirrors expected use of immunotherapy at second line as advised by the Cancer Drugs Fund (CDF) lead to the EAG. Furthermore, analysis of the time-to-first-subsequent treatment (TFST) confirms most of these patients required a second line of treatment within 12 months of initiating their first line, indicating that the impact of such treatments on post-progression outcomes would be well-captured within the available RUBY-1 follow-up (median: 37.5 months) (2).

Divergence in subsequent treatment use versus UK clinical practice, notably immunotherapy retreatment, did not result in improved efficacy in the dostarlimab arm of the RUBY-1 trial

GSK understand that retreatment with immunotherapy following progression on or after dostarlimab treatment in first line would not be permitted in UK clinical practice, despite this occurring in 17.7% of patients in the dostarlimab arm of the RUBY-1 trial. As a result, it has been suggested that there is uncertainty over whether the dostarlimab arm outcomes are reflective of UK clinical practice, or whether they are overestimated because of immunotherapy retreatment. It should be noted that advice by clinical experts given to both GSK and as part of the committee meeting is that retreatment with immunotherapy is not expected to improve post-progression outcomes. As such, this phenomenon has not been identified as a significant area of concern in previous technology appraisals in this therapy area (3-5).

However, to address committee concerns, a post hoc analysis is presented below (

Table 2), exploring survival outcomes based on initial trial-assigned treatments, and subsequent treatments among MMRp/MSS patients enrolled in the RUBY-1 trial (6).

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

Table 2: Post-hoc analyses: OS in patients receiving FUACT of pembrolizumab with lenvatinib versus chemotherapy in each arm (ITT analysis set, MMRp/MSS subgroup)

	MMRp/MSS		MMRp/MSS Pem/Len after progression		MMRp/MSS Chemotherapy after progression	
	D+CP	P+CP	D+CP	P+CP	D+CP	P+CP
Median OS (95% CI), months	[redacted]					
24-month probability of OS (95% CI). %	[redacted]					

[redacted]

Abbreviations: D+CP, dostarlimab and carboplatin and paclitaxel; MMRp, mismatch repair proficient; MSS, microsatellite stable; NR, not reached; OS, overall survival; P+CP, placebo + carboplatin and paclitaxel; Pem/Len, pembrolizumab with lenvatinib.

With more than three years of follow-up data, these analyses reinforce the efficacy of dostarlimab in combination with CP as a first-line treatment for patients with primary advanced or recurrent MMRp/MSS EC. The evidence supports that treatments

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	administered at later lines of therapy in the RUBY-1 trial are consistent with what is expected in UK clinical practice. Any deviations observed are not expected to introduce bias into the OS results within the trial.
(2).	**Comments on draft guidance** **Treatment with dostarlimab in combination with CP is associated with durable post-progression benefits (3.6, 3.10, 3.11)** GSK acknowledges the uncertainties identified by the committee regarding the post progression- benefits of dostarlimab, how this may be impacted by subsequent treatments, and the related plausibility of the cost-effectiveness -base-case. GSK appreciates this opportunity to present additional evidence from the RUBY-1 trial, which supports a robust post-progression benefit from the upfront use of dostarlimab in combination with CP in this setting. This reinforces the utility of making dostarlimab available for use in the first line setting rather than delaying treatment with other innovative therapies at later lines. To address these concerns, the following response will cover the key points outlined below: • Significant post-progression benefits were observed in the RUBY-1 as a result of the first-line use of dostarlimab in combination with CP. These benefits are not attributable to immunotherapy retreatment. • The post-progression benefits of the RUBY-1 trial are consistent with the mechanism of action of immunotherapy agents and are observed in many other therapy areas. This frequently results in a greater OS treatment effect compared with the PFS. **First line use of dostarlimab in combination with CP was associated with PFS2 post-progression benefits** Treatment with dostarlimab in the RUBY-1 trial resulted not just in an improvement in PFS outcomes but also an improvement in PFS2, an endpoint reflecting the time-to-second-progression event (specifically defined as time to progression on the first follow-up anticancer therapy). This improvement in PFS2, a median improvement of 8.7 months (hazard ratio [HR]: 0.74; 95% confidence interval [CI]: 0.57-0.97), is notably greater than the median improvement of [redacted] months for PFS ([redacted]). It is recognised that, due to their mechanism of action implicating the immune system, immunotherapy treatments such as dostarlimab can result in significant post-progression benefits. This is observed in the RUBY-1 trial within the PFS2 outcomes and further supported by analysis of the time between first and second progression event (PFS2-PFS1). The analysis, described in Table 3 shows that upfront use of dostarlimab in combination with CP increases the time between first and second progression events, despite the significant use of immunotherapies following progression with CP alone. The median time between first and second progression events in the dostarlimab arm was [redacted] months, compared with [redacted] months in the CP arm, corresponding to a HR of [redacted]).

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Draft guidance comments form

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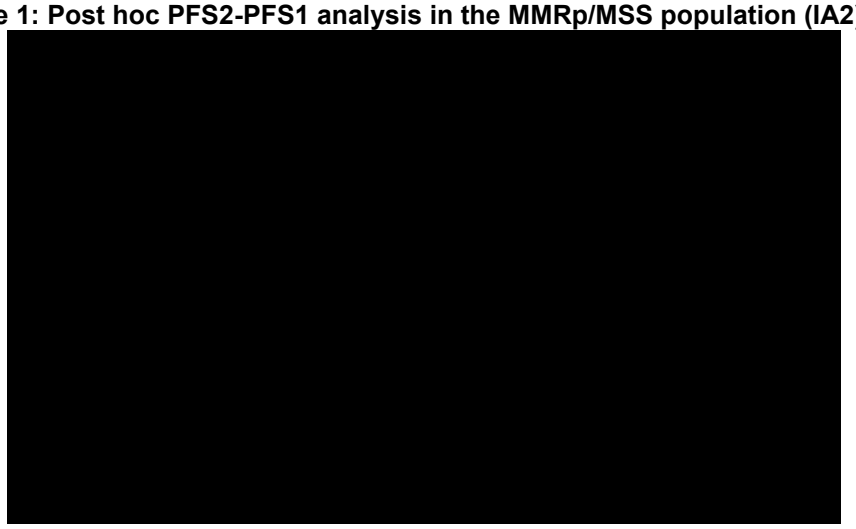
Table 3: Post hoc PFS2-PFS1 analysis in the MMRp/MSS population (IA2)

	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)
Median PFS2-PFS1 (months)	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]	
p-value	[redacted]	

Source: Data on file, PFS2-PFS1 analysis (7).
Abbreviations: CI, confidence interval; CP, carboplatin and paclitaxel; IA2, second interim analysis; MMRp, mismatch repair proficient; MSS, microsatellite stable; PFS1, progression-free survival 1; PFS2, progression-free survival 2.

Figure 1: Post hoc PFS2-PFS1 analysis in the MMRp/MSS population (IA2)



Source: Data on file, PFS2-PFS1 analysis (7).
Note: PFS1 is defined as the time from randomization to the date of first documentation of investigator assessed disease progression per RECIST v1.1 or death by any cause, whichever is earlier.
PFS2 is defined as the time from randomization to date of assessment of progression on the first subsequent anticancer therapy following study treatment or death by any cause, whichever is earlier.
PFS2-PFS1 is defined as the time from investigator assessed disease progression to the date of assessment of progression on the first subsequent anticancer therapy following study treatment or death by any cause, whichever is earlier.
Abbreviations: CI, confidence interval; CP, carboplatin and paclitaxel; IA2, second interim analysis; MMRp, mismatch repair proficient; MSS, microsatellite stable; PFS1, progression-free survival 1; PFS2, progression-free survival 2.

Notably, of those patients who received subsequent treatment in the CP arm (N=134), approximately 51% received an immunotherapy treatment (N=68). As previously noted, some patients in the dostarlimab arm also received an immunotherapy-based regimen. However, there is no evidence that would support an additive effect of immunotherapy-retreatment over any other subsequent treatment in this setting. Furthermore, in an additional PFS2 landmark analysis of the RUBY-1 trial, the outcomes of patients receiving retreatment with immunotherapy in the dostarlimab arm are similar compared to all patients receiving any follow-up anticancer therapy after dostarlimab (Table 4). These PFS2 results are consistent with the trends seen in OS, as outlined in Comment (2), and indicate that outcomes in the dostarlimab arm are not positively biased as a result of immunotherapy retreatment, in line with expert expectation.

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Draft guidance comments form

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Table 4: KM analysis of IA2 PFS2 in patients who received FUACT with IO, and those who received any FUACT (MMRp/MSS population)

Category subcategory	Patients who received FUACT with IO		Patients who received *any* FUACT	
	Dostarlimab in combination with CP (N=34)	Placebo in combination with CP (N=68)	Dostarlimab in combination with CP (N=105)	Placebo in combination with CP (N=134)
Number of patients who have FUACT				
n (%)	34 (17.7)	68 (37.0)	105 (54.7)	134 (72.8)
Median PFS2, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
PFS2				
Status, n (%)				
Events observed	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]
Estimates for PFS2 (months)				
Quartile (95% CI)				
25%	[redacted]	[redacted]	[redacted]	[redacted]
50%	[redacted]	[redacted]	[redacted]	[redacted]
75%	[redacted]	[redacted]	[redacted]	[redacted]
PFS2 probability (95% CI)				
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]
Month 30	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence intervals; CP, carboplatin and paclitaxel; FUACT, follow-up anti-cancer therapy; IO, immunotherapy; n, number; PFS2, progression free survival 2

The post progression benefits of immunotherapies are well recognised and have frequently been shown to improve OS by a greater magnitude compared with PFS

As outlined above, in the MMRp/MSS population, dostarlimab in combination with CP demonstrated prolonged PFS benefits beyond first progression, delaying time to second progression or death. Importantly, these post-progression benefits are consistent with findings from other immunotherapy trials, which frequently show greater OS benefits relative to PFS improvements. The post-progression benefits observed across immunotherapy trials, such as RUBY-1, are likely driven by two clinical mechanisms.

I. **Extended PFS:** Longer PFS increases recovery time from cytotoxic chemotherapy (8, 9).
II. **T-cell presence:** Enhanced T-cell activity post-immunotherapy discontinuation may improve tumour elimination upon exposure to chemotherapy-induced immunogenic cell death (10, 11).

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Draft guidance comments form

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Table 5 illustrates examples of immunotherapies delivering significant OS benefits despite modest PFS outcomes across various indications.

Table 5: Immunotherapies have driven greater OS benefits than PFS benefits

Trial (Indication)	Therapy	Median PFS (mo)	Median OS (mo)	HR (PFS & OS)	P-value (PFS & OS)	Median PFS vs OS benefit, months
CheckMate 067 (Melanoma) (12)	Nivolumab + Ipilimumab vs Nivolumab vs Ipilimumab	11.5 vs 6.9 vs 2.9	71.9 vs 36.9 vs 19.9	NS	NS	+4.6 vs +35†
CheckMate 057 (NSCLC) (13)	Nivolumab vs Docetaxel	2.3 vs 4.2	12.2 vs 9.4	PFS: 0.92 OS: 0.73	PFS: 0.39 OS: 0.002	-1.9 vs +2.8
IMpower133 (SCLC) (14)	Atezolizumab + Chemo vs Chemo	5.2 vs 4.3	12.3 vs 10.3	PFS: 0.77 OS: 0.76	PFS: NS OS: 0.0154	+0.9 vs +2
CheckMate 017 (SQ SCLC) (15)	Nivolumab vs Docetaxel	3.5 vs 2.8	9.2 vs 6.0	PFS: 0.62 OS: 0.59	<0.001	+0.7 vs +3.2
CheckMate 141 (RCC) (16)	Nivolumab vs Docetaxel	2.0 vs 2.3	7.5 vs 5.1	PFS: 0.89 OS: 0.70	PFS: 0.32 OS: 0.01	-0.3 vs +2.4
KEYNOTE-006 (Melanoma) (17)	Pembrolizumab vs. Ipilimumab	8.4 vs 3.4	32.7 vs 15.9	PFS: 0.57 OS: 0.73	PFS: <0.0001 OS: 0·00049	+5 vs +16.8
KEYNOTE-189 (NSCLC) (18)	Pembrolizumab + Chemo vs Chemo	9 vs 4.9	22.0 vs 10.6	PFS: 0.50 OS: 0.60	NS	+4.1 vs +11.4
CheckMate 214 (RCC) (19)	Nivolumab + Ipilimumab vs Sunitinib	12.2 vs 12.3	NR vs 38.4	PFS: 0.89 OS: 0.69	NS	OS benefit despite no PFS benefit
CheckMate 025 (RCC) (20)	Nivolumab vs Everolimus	4.2 vs 4.5	25.8 vs 19.7	PFS: 0.84 OS: 0.73	PFS: 0.0331 OS: <0.001	-0.3 vs +6.1
KEYNOTE-040 (HNSCC) (21)	Pembrolizumab vs. Chemo	2.1 vs 2.3	8.4 vs 6.9	PFS: 0.98 OS: 0.80	PFS: 0.3250 OS: 0.016	-0.2 vs +1.5

† Compared with Nivolumab alone.

Abbreviations: Chemo, chemotherapy; HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio; MSS, microsatellite stable; NR, not reached; NS, not stated; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; SCLC, small cell lung cancer; SQ, squamous.

Evidence from the RUBY-1 trial highlights the sustained clinical benefits provided by dostarlimab in combination with CP, which extend beyond first progression and into subsequent lines of therapy. Post-progression benefits are supported by PFS2 outcomes, which are endorsed by the European Medicines Agency (EMA) as a

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	surrogate marker for OS, and consistent with broader immunotherapy trial findings that demonstrate greater OS benefits relative to PFS improvements (22). These findings support the durable efficacy of dostarlimab in combination with CP for patients with primary advanced/recurrent EC.
(3).	**Comments on draft guidance** **Immunotherapies used in later lines of treatment have only modest benefits and have negligible impact on the OS outcomes observed in the RUBY-1 trial (3.5, 3.6, 3.12, 3.18, 3.19)** GSK acknowledges the committee's concerns regarding the influence of subsequent treatments, including immunotherapies, on PFS2 and OS outcomes. GSK appreciates the opportunity to address the concerns by outlining the following: • The pembrolizumab with lenvatinib regimen demonstrated efficacy against chemotherapy *singlet* agents only in the KN-775 trial. More recent evidence suggests no incremental efficacy versus more effective chemotherapy *doublet* regimens, which had been more commonly used in the National Health Service (NHS) at second line. • Consistent with clinical expectation, treatment switching analyses demonstrate trial OS results are robust, regardless of the use of subsequent immunotherapies. **Immunotherapies in the relapsed setting have shown modest efficacy benefits** Pembrolizumab with lenvatinib was the most frequently used second-line immunotherapy in the RUBY-1 trial and remains the only approved second-line immunotherapy for patients with MMRp/MSS EC within the UK, supported by a survival benefit demonstrated in the KN-775 trial (23). However, despite the availability of this innovative treatment, outcomes for patients with MMRp/MSS EC remain poor. While pembrolizumab with lenvatinib exhibited superior efficacy compared with chemotherapy *singlet* regimens in the KN-775 trial, its effectiveness in UK clinical practice warrants further consideration (23). Firstly, the KN-775 trial compared pembrolizumab with lenvatinib against chemotherapy singlet regimens, either paclitaxel or doxorubicin. However, real-world evidence (RWE) from numerous UK studies (Table 6) demonstrates that chemotherapy doublets (e.g., carboplatin-paclitaxel, carboplatin-liposomal doxorubicin, and cisplatin-doxorubicin) had been the most commonly used second-line treatments prior to the availability of the pembrolizumab with lenvatinib regimen in the NHS (24-27). Therefore, whilst the efficacy of pembrolizumab with lenvatinib as a chemotherapy-sparing regimen was demonstrated in the KN-775 trial, it has not demonstrated efficacy against the pre-existing SoC in the UK. As described further below, more recent evidence does not indicate that it improves outcomes compared with these more effective chemotherapy regimens.

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Table 6: UK RWE studies on second-line treatment use

Publication	Previously treated recurrent or advanced endometrial cancer in England: A real-world observational analysis (25)	Real-world patient characteristics and survival outcomes in patients with advanced or recurrent endometrial cancer in England: a retrospective, population-based study (24)	A real-world retrospective observational study of patients with advanced/recurrent endometrial cancer across England (27)
Publication year	2022	2024	2025
Setting	England	England	England
Study description	Non-interventional, retrospective, observational study using NCRAS	Non-interventional, retrospective, observational study using NCRAS	Non-interventional, retrospective, observational study, using EHRs from seven NHS trusts
Time period	Jan 2013 to Sept 2020	Jan 2013 to Aug 2021	2000 to 2023
First most common 2L treatment	Carboplatin + Paclitaxel	Carboplatin + Paclitaxel	Cisplatin + doxorubicin
Second most common 2L treatment	Carboplatin + Paclitaxel	Paclitaxel	Carboplatin + paclitaxel
Third most common 2L treatment	Liposomal doxorubicin	Liposomal doxorubicin	Paclitaxel

Abbreviations: 2L, second line; EHR, electronic health records; NCRAS, National cancer registry data; NHS, National health service; RWE, real world evidence; UK, United Kingdom.

Since the availability of the pembrolizumab with lenvatinib regimen in the NHS, two more recent publications have reported on the effectiveness of this regimen versus chemotherapy doublet regimens:

1. **Wang et al 2025**, A retrospective observational study using propensity score matching to compare pembrolizumab with lenvatinib to carboplatin-paclitaxel in pretreated, recurrent or advanced EC (28)

2. **LEAP-001,** A phase 3, randomised head-to-head trial in the first line setting comparing pembrolizumab with lenvatinib to carboplatin-paclitaxel (29)

Wang et al. (2025) (28)
Wang et al. (2025) compared pembrolizumab with lenvatinib against the chemotherapy doublet, CP, in platinum-pretreated EC patients (28). This retrospective, observational study used propensity score matching to compare real-world outcomes between cohorts treated with pembrolizumab with lenvatinib and those treated with carboplatin-paclitaxel. The study found that pembrolizumab with lenvatinib did not improve survival over CP (Median OS: 19.1 vs. 18.5 months; HR: 1.08 [95% CI: 0.81, 1.46]; p=0.60). The study was consistent with previous evidence in this disease area showing survival improvements against doxorubicin monotherapy alone. A limitation of this study is that the results are not reported by mismatch repair (MMR) status which can be a predictive marker for immunotherapy agents.

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	LEAP-001 The LEAP-001 trial was a phase 3, head-to-head comparison of pembrolizumab with lenvatinib against carboplatin-paclitaxel in a first line, 'RUBY-like' cohort of patients with primary advanced or recurrent EC. The dual primary endpoints of the trial were PFS and OS in patients with MMRp/MSS EC and in the overall population. This trial failed to meet the primary endpoints, showing no improvement in PFS or OS compared with CP alone in the MMRp/MSS population (median PFS : 9.6 vs. 10.2 months; HR: 0.99 and median OS: 30.9 vs. 29.4 months; HR: 1.02), revealing no significant survival advantage (29). Whilst immunotherapies have been shown to improve outcomes in primary MMRp/MSS EC, outcomes in the relapsed setting remain extremely poor regardless of whether patients are treated with chemotherapy or chemotherapy-sparing options such as pembrolizumab with lenvatinib. As shown in the LEAP-001 trial, immunotherapy alone has limited efficacy in MMRp/MSS tumours, with co-administration alongside chemotherapy required to meaningfully improve outcomes (30, 31). This combination with chemotherapy can result in increased tumour sensitivity to immunological anti-cancer effects. Overall, the evidence above shows that, despite the availability of innovative options such as pembrolizumab with lenvatinib, outcomes differ little compared to chemotherapy doublet. The modest survival benefits observed in clinical trials and RWE highlight the limited efficacy of these treatments which would therefore not meaningfully impact the long-term OS analyses observed within the RUBY-1 trial. **<u>Treatment switch analysis demonstrates the durability of results, regardless of treatment with subsequent immunotherapy</u>** To further investigate the impact of subsequent immunotherapy, use on OS within the RUBY-1 trial, treatment switching analyses were conducted using rank-preserving structural failure time models (RPSFTM). These analyses adjusted for second-line treatment with immunotherapies, including pembrolizumab with lenvatinib, in the MMRp/MSS population. Figure 2 illustrates KM curves comparing the base-case- scenario, adjusted for subsequent immunotherapy use, and the scenario adjusted specifically for second-line use of pembrolizumab with lenvatinib. Table 7 presents the KM analysis results with RPSFTM adjustments for OS. The results demonstrate that OS benefits derived from dostarlimab in combination with CP were sustained regardless of the type of subsequent treatment, whether immunotherapy or not, with adjusted HRs similar to unadjusted HRs, confirming the survival advantage of dostarlimab in combination with CP. Consistent with clinical expectation, the treatment effect of dostarlimab on OS compared with CP alone nominally improves slightly when adjustments are made to exclude the use of immunotherapy following progression with CP (HR: 0.76, 95% CI: 0.542, 1.061). However, it should be noted that immunotherapy is now an established part of the UK treatment pathway in the relapsed setting.

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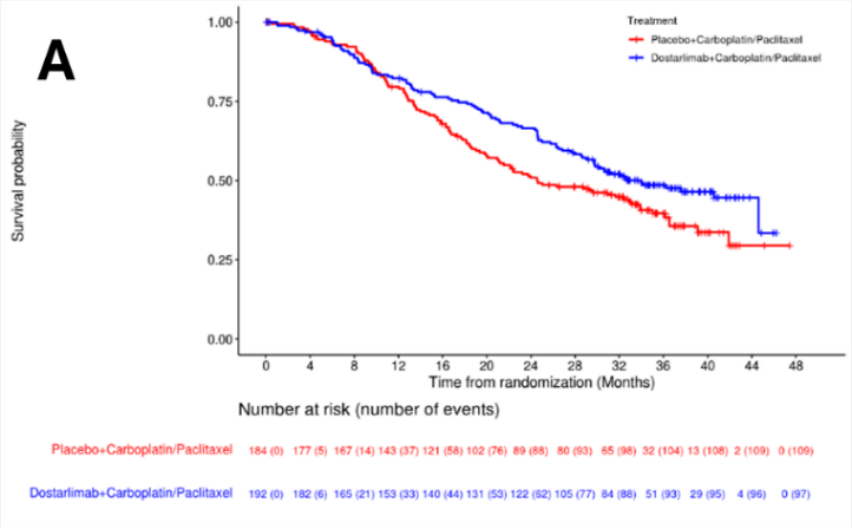
Consultation on the draft guidance document – deadline for comments 5pm on Wednesday 20 August 2025. Please submit via NICE Docs.

Figure 2: KM curves with RPSFTM adjustment of OS (ITT analysis set, MMRp/MSS subgroup) (A) -Base-case scenario (All IO's) and (B) Scenario analysis (pembrolizumab with lenvatinib)



[redacted]

A) -Base-case scenario - adjust for switching to any immunotherapy or combination of immunotherapy as a FUACT for all comers. MMRp/MSS and dMMR/MSI-H selected based on stratification factors from clinical database (verified source). (B) Scenario analysis - adjust for switching to pembrolizumab with lenvatinib combination therapy as a FUACT in MMRp/MSS subjects. MMRp/MSS and dMMR/MSI-H selected based on stratification factors from clinical database (verified source).
Abbreviations: dMMR, mismatch repair deficient; FUACT, follow-up anticancer treatment; IO, immunotherapy; ITT, intention-to-treat; KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable; OS, overall survival; RPSFTM, rank-preserving structural failure time models.

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Draft guidance comments form

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Table 7: Summary of KM Analysis with RPSFTM adjustment for OS (ITT analysis set, MMRp/MSS subgroup)

	Psi (95% CI)	Adjusted HR (95% CI)	AF	p-value	Unadjusted HR (95% CI)
-Base-case scenario (adjustment for all subsequent IO's)	[redacted]	0.76 (0.542, 1.061)	1.28	[redacted]	0.79 (0.602, 1.044)
Scenario analysis† (adjustment for Pem/Len)	[redacted]	0.77 (0.564, 1.057)	1.25	[redacted]	

†For scenario analysis, [redacted] of source-verified MMRp/MSS patients switched to an anti-PD-1/anti-PD-L1 FUACT, including [redacted] patients in the dostarlimab + CP arm and [redacted] of patients in the CP arm. Overall, [redacted] of the MMRp/MSS patients were administratively censored.
Abbreviations: AF, acceleration factor; CI, confidence interval; FUACT, follow-up anticancer treatment; HR, hazard ratio; IO, immunotherapy; ITT, intention-to-treat; KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; OS, overall survival; Pen/len, pembrolizumab with lenvatinib; RPSFTM, rank preserving structural failure time model.

The modest OS impact observed in clinical trials with innovative second-line immunotherapy treatments, coupled with treatment switching analyses demonstrating the negligible influence of subsequent therapies on survival, suggest that second-line treatments are unlikely to meaningfully impact long-term OS outcomes. These findings provide additional support for the durability and efficacy of dostarlimab in combination with CP in the first line treatment of patients with MMRp/MSS primary advanced or recurrent EC, consistent with other post-hoc analyses (

Table 2)

(4).

Comments on draft guidance

Treatment effect waning has been captured within the submitted base-case resulting in survival extrapolations which are consistent with clinical expectation (3.12, 3,18)

Within the draft guidance, the committee has requested further evidence to justify the inclusion or exclusion of treatment effect waning (3.12, 3.18, 3.19) related to the extrapolation of longer-term OS in the dostarlimab arm (32). GSK welcomes the opportunity to:

1. Sufficiently justify why it is inappropriate to add additional treatment effect waning
2. Explore the impact of treatment effect waning on the base-case cost-effectiveness estimates.

In further support of the submitted base-case with respect of treatment effect waning, GSK would like to outline the following points:

1. Treatment effect waning is already accounted for within the base-case survival curve
2. Base-case survival estimates, as well as pre- and post-progression survival benefits are consistent with clinical expectation and the RUBY-1 clinical trial data

3. The approach followed is consistent with previous appraisals in this therapy area, with the RUBY-1 trial having markedly more mature OS data.

Treatment effect waning is already accounted for within the base-case survival curve

Firstly, GSK would like to address a potential misunderstanding regarding the implicit capturing of treatment effect waning within the submitted model. The committee previously stated, *"The committee did not think that treatment-effect waning was implicitly captured in the model, as the company's extrapolated OS curves with and without incorporated treatment waning were different."*

The economic model used independent parametric distributions to estimate OS for both treatment arms, as the proportional hazards assumption did not hold. By using independent curves, implicit treatment effect waning is inherently captured through the modelling approach, as demonstrated in Figure 3, where the implied HR between the two arms peaks at approximately 3 years and gradually trends toward 1 (i.e. no treatment effect) thereafter. This reflects the methods utilised as part of the durvalumab with platinum-based chemotherapy with or without olaparib appraisal in primary advanced or recurrent EC and was accepted by the committee in this instance (4). Functionality exists in the cost-effectiveness model to override the modelled hazard in the dostarlimab arm to artificially converge the dostarlimab arm hazard with that of the comparator at user specifiable time points. Therefore, the treatment-effect waning scenarios which had been presented in the original company submission and again in the following section reflect *additional* waning compared with what is considered within the company base-case.

Figure 3: Implied HR over time in company submission

Abbreviations: HR, hazard ratio, OS, overall survival.

Base-case survival estimates, as well as pre- and post-progression survival benefits are consistent with clinical expectation and the RUBY-1 clinical trial data

As reported in Table 8 below, the majority of the life years gained (LYG) in the -base-case are accrued in the progression-free (PF) health state with a similar but slightly smaller LYG in the progressed-disease (PD) state. These results are consistent with

clinical expectation and the RUBY-1 trial results, which demonstrate not only a direct treatment effect in delaying the initial disease progression, but also efficacy in delaying subsequent progression events as illustrated by the PFS2-PFS1 analysis as part of Comment (2). This shows that dostarlimab's efficacy extends into post-progression benefits, with the magnitude of benefit in delaying subsequent progression events (HR: [redacted]) closely aligning with PFS efficacy ([redacted]). This is consistent with the mechanism of action of immunotherapy treatments such as dostarlimab as has observed in other disease areas (See Comment (2)).

Based on the clinical evidence supporting dostarlimab, the expected benefit of delaying subsequent progression events appears comparable to the efficacy of dostarlimab in delaying initial disease progression. The -base-case results which estimate a LYG of [redacted] in the PD state, lower than the [redacted] in the PF health state, is in line with expectation.

Table 8: Base-case LYG by health state

Health state	LY Dostarlimab +CP	LY CP	Incremental LYG
PF	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; LY, life years; LYG, life years gained; PD, progressed disease; PF, progression-free

The approach followed is consistent with previous appraisals in this therapy area, with the RUBY-1 trial having markedly more mature OS data

Clinical rationale
GSK are aware that in other disease areas, where a substantial proportion of patients are forced to discontinue treatment at a predefined stopping rule, uncertainty can arise regarding the suitability of extrapolating into the 'off-treatment' period. However, most patients in the RUBY-1 trial had discontinued dostarlimab treatment prior to the 3-year stopping rule indicating that the observed RUBY-1 OS data available out to almost 4 years are suitable for extrapolation without requirement for additional arbitrary waning of the treatment effect.

Previous technology appraisals
The approach of not including explicit treatment waning aligns with recent appraisals, such as durvalumab with platinum-based chemotherapy (NICE ID6317), where sustained treatment benefits of immunotherapies were recognised, and waning was not raised as a key issue (4). Despite the negative outcome for the MMRp/MSS population, this technology appraisal guidance also implemented a 3-year stopping rule, similar to that in place for dostarlimab.

Other appraisals such as dostarlimab for the analogous mismatch repair deficient/ microsatellite instability-high (dMMR/MSI-H) subgroup of the RUBY-1 trial was similarly recommended by NICE without requirement for additional treatment waning in the base-case despite this being considered by the committee (5).

The most recent technology appraisal of pembrolizumab in combination with CP (ID6381) is the exception to recent recommendations by NICE in first line primary

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Wednesday 20 August 2025. Please submit via NICE Docs.

	advanced or recurrent EC, where additional treatment waning was preferred by the committee and applied only to a proportion of patients who had not achieved a complete response to treatment (3). However, it should be noted that this evidence package was associated with significant uncertainty given the very short follow-up and minimal improvements in OS observed in the trial's final analysis. At the final analysis, median follow-up in the intervention and CP arms, was 15.7 and 15 months, respectively, and median improvement in OS was <1 month in both the interim and final analysis datasets (32). This is in contrast to the median follow-up of 37.5 months in the MMRp/MSS subgroup of the RUBY-1 trial which showed a 7-month improvement in median OS. **<u>Exploring the impact of explicit treatment waning on modelling outcomes and post-progression benefits</u>** For the reasons outlined above, treatment waning is not included within the -base-case, however, conservative waning scenarios have been presented for completeness, reflective of the most recent pembrolizumab in combination with CP appraisal (ID6381) (3). The following scenarios were explored: • Gradual treatment waning applied three years after the stopping rule and reducing to the same level as the comparator arm after two years (i.e. 6-8 years after initiating treatment) and five years after the stopping rule (i.e. 8-10 years after initiating treatment). Scenario are explored whereby: o Additional waning is applied to all patients o Additional waning is applied to those without a complete response (74.2% of patients in the dostarlimab arm, which is the proportion of patients whose disease was at least controlled with dostarlimab but didn't achieve a complete response) Please see Appendix for the results of these scenarios. --- As demonstrated above, treatment effect waning is implicitly captured within the submitted base-case model through independent parametric survival distributions. The base-case survival estimates, including both pre- and post-progression benefits, demonstrate consistency with the trial data and the mechanism of action for immunotherapy treatments such as dostarlimab, resulting in outcomes that are both clinically plausible and conservative. Additionally, the approach followed aligns with precedents set in recent NICE technology appraisals, reinforcing the robustness of the submitted evidence package and the appropriateness of excluding additional arbitrary treatment effect waning.
(5).	**Comments on draft guidance** **Dostarlimab in combination with CP improves outcomes across the entire MMRp/MSS population of the RUBY-1 trial, with no subgroup appearing to benefit disproportionately (3.19)** GSK appreciates the committee's desire to identify a subgroup within the MMRp/MSS population within which dostarlimab in combination with CP is a particularly clinically and/or cost-effective treatment option, specifically highlighting patients with p53 abnormal (abn) tumours. However, this does not appear to be clinically appropriate for the following reasons:

Dostarlimab with platinum-based chemotherapy for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6415]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Wednesday 20 August 2025. Please submit via NICE Docs.

	I. Evidence from the RUBY-1 trial does not indicate any robust incremental treatment effect within this sub-population II. The broader body of evidence relating to programmed cell death protein 1 (PD-1) treatments in p53abn tumours is contradictory, more so than the evidence for programmed death-ligand 1 (PD-L1) inhibitor plus poly (ADP-ribose) polymerase inhibitor (PARPi) regimens such as durvalumab + olaparib in this sub-population III. Clinical experts, both at the first committee meeting and in consultation with GSK, have confirmed that the benefits of the RUBY-1 regimen are seen across biomarker subgroups IV. A significant and high unmet need exists across all patients with MMRp/MSS EC, not just those with p53abn tumours As has been recognised by the EAG and cited in Slides 3 and 4 of the committee meeting presentation, a significant unmet need exists for effective, innovative treatments which can delay or stop progression for patients with MMRp/MSS EC. Expert statements from clinicians have confirmed that whilst MMRp/MSS constitutes a heterogenous population, there is currently no identifiable subpopulation which is most likely to derive benefit from dostarlimab in combination with CP. Furthermore, it has been emphasised that routinely performed tests for molecular subtypes cannot reliably identify patients who may achieve better outcomes. As highlighted by one of the clinical experts as part of their expert statement, *"Benefit from dostarlimab was consistent across histological subtypes and a trend in favour of dostarlimab was seen in both the 22% of participants with TP53 mutated cancer (HR 0.55) and the 54% with NSMP cancer (HR 0.77) indicating that utilising these routinely performed tests cannot be used to select patients with MMR-proficient cancers more likely to benefit from dostarlimab."* Subgroup analyses based on molecular classification were submitted in the original company submission, including PFS and OS outcome data for p53abn and no specific molecular profile (NSMP) populations. The estimated HRs for both PFS and OS remain <1 across both subgroups and both endpoints. It should be noted however that, unlike the MMRp/MSS subgroup of the RUBY-1 trial, there was no stratification for these molecular subgroups as part of the trial design meaning that randomisation was not maintained for these analyses. As a result, these populations constitute subgroups of a subgroup of the RUBY-1 population and so outcome data should not be considered suitably robust to confidently guide clinical decision making. Of note, the p53abn MMRp/MSS population consisted of small sample sizes with 47 and 41 patients in the dostarlimab and placebo arms, respectively. Other limitations of these analyses include the different testing method used in the RUBY-1 trial (whole exome sequencing [WES]) compared with what would be used in UK practice (Immunohistochemistry [IHC]), and the substantial proportion of patients (~20%) who lacked any molecular classification data and who were excluded from the analysis. As such, whilst the molecular classification analysis of the RUBY-1 trial is of clinical interest, it should not be considered sufficiently robust to guide clinical decision making. Additionally, a 2025 network meta-analysis by Villacampa et al. summarised the effectiveness of immunotherapies and poly-(ADP-Ribose) polymerase (PARP)

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Wednesday 20 August 2025. Please submit via NICE Docs.

	inhibitors as treatments for primary advanced or recurrent EC, including in patients with p53abn and p53 wildtype tumours (33). Their findings do not support the supposition that p53abn tumours are particularly responsive to immunotherapy-based regimens such as dostarlimab in combination with CP within the MMRp/MSS population. Instead, they conclude that addition of a PARPi is required to further improve efficacy within this cohort. This is also supported by the underlying mechanism of action of PARPis and TP53's role in homologous recombination repair deficiency, a mechanism that underpins synthetic lethality and drives cytotoxicity in PARPi-treated cells (3). Interestingly, despite trends observed in the RUBY-1 trial, Villacampa et al. also suggests that the greatest benefit from immunotherapy may lie in TP53 wildtype tumours, further challenging the rationale for restricting immunotherapy access based on TP53 mutation status using current evidence (33). --- In summary, the potential for dostarlimab to disproportionately benefit a single subgroup of patients within the MMRp/MSS population is not supported by either RUBY-1 trial evidence, external expert opinion, underlying clinical rationale, or by external evidence on this subject matter. As such, GSK do not consider it informative to explore cost-effectiveness scenarios within the p53abn or any other subgroup currently.

Committee's preferred assumptions

In response to the Committee's requests (see *Comments and area's needing clarification*) and preferred assumptions (see *Committee's preferred assumptions*), we provide an updated -base-case analysis that supports access to dostarlimab for patients living with MMRp/MSS primary advanced or recurrent EC.

In response to the draft guidance, GSK presents an updated -base-case analysis, incorporating the following changes based on the findings and evidence discussed:

- Updated PFS extrapolations utilising the more mature PFS data from the second interim analysis (IA2)
- Updated subsequent treatment proportions utilising the more mature IA2 data-cut.

In addition, the committee's preferred assumptions have been adopted in the company -base-case in the following scenarios:

- Implementation of TTD
- Health state resource use for the dostarlimab arm
- Exclusion of the cost of oral administration for lenvatinib.

Table 9 reports the updated Company -base-case, including the revised patient access scheme (PAS) of [redacted]%. In the updated Company -base-case, dostarlimab is associated with incremental costs of £[redacted] and incremental quality-adjusted life years (QALYs) of 0.753 vs CP, resulting in an incremental cost-effectiveness ratio (ICER) of £[redacted] per QALY. A full breakdown of results based on the updated base-case- is found in the Appendix.

Dostarlimab with platinum-based chemotherapy for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6415]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Wednesday 20 August 2025. Please submit via NICE Docs.

Table 9: Base-case results (deterministic)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Dostarlimab in combination with CP	[redacted]	[redacted]	[redacted]	[redacted]	-	-
CP	[redacted]	[redacted]	[redacted]	[redacted]	0.753	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; LY, life years; QALY, quality-adjusted life year

To test specific alternative inputs for the assessment of structural and parametric uncertainty, scenario analyses were also conducted. Specifically, to address the committees' concerns, scenario analyses were conducted on treatment effect waning, PFS extrapolations and subsequent treatments. A summary of the results of the scenario analyses can be found in the Appendix, with an increase in the proportion of patients receiving pembrolizumab and lenvatinib following discontinuation from CP having the biggest impact, resulting in a [redacted] for dostarlimab vs CP. Updated one-way sensitivity analysis (OWSA) and probabilistic sensitivity analysis (PSA) results are also presented in the appendix and are shown to be highly congruent with the results of the deterministic analysis.

(6).	**The Committee's preferred assumptions-** **PFS data from the more mature IA2 data cut has been incorporated into the model (3.9, 3.19)** The company acknowledges the committee's concerns regarding the initial PFS data from first interim analysis (IA1) and the preference for modelling based on longer follow-up data, which is considered more informative and reliable. In response to these concerns, the company has incorporated PFS data from the longer-followed IA2 data cut into the economic model, as requested by the committee, to ensure that the model reflects the longer follow-up period and provides a more robust basis for decision-making. As illustrated in Figure 4 PFS outcomes from the more mature IA2 data cut are consistent with the IA1 PFS analysis presented in the original company submission. As in the original company base-case, extrapolations were required since the follow-up period remains shorter than the model's lifetime horizon.

Dostarlimab with platinum-based chemotherapy for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6415]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Wednesday 20 August 2025. Please submit via NICE Docs.

Figure 4: PFS outcomes from IA1 and IA2 of the RUBY-1 trial

Similarly to IA1 PFS, flexible curves were considered most appropriate to extrapolate IA2 PFS given the poor fit of the standard parametric models to the observed data (see Appendix). In line with the approach outlined in the company submission, 9 flexible spline models were fit to the PFS data from RUBY-1 (Hazards, knots (k)=1,2,3; Odds, k=1,2,3 and Normal, k=1,2,3). The choice of curve for the dostarlimab and CP arms was selected by considering visual fit, goodness-of-fit statistics such as Akaike information criterion (AIC) and clinical plausibility.

For the CP arm, all flexible spline models provided a similar visual fit. The Hazards, k=2,3; Odds, k=2,3 and Normal, k=2,3 curves provided the best statistical fit to the data and were within 3 AIC points of each other. However, each of these models do not appear to be clinically plausible, resulting in an overestimation of PFS from approximately year 5 onwards, likely due to overfitting in the 'tail' of the PFS Kaplan-Maier curve. Each of these models result in a relative plateau beginning after approximately 3 years which is not supported by clinical input to this appraisal or others in this therapy area (Table 10). These are also inconsistent with committee preferences for CP PFS in TA1064, which was also used RUBY-1 data to estimate PFS for the corresponding dMMR/MSI-H subgroup of the RUBY-1 trial. As outlined in Appendix L.1.2 of the Company Submission, there is not expected to be any meaningful difference in outcomes for MMR deficient and proficient populations being treated with CP. Lastly, within the CP arm, the 2- and 3-knot models result in the CP PFS being higher at 15 years (range: 8-9%) than all dostarlimab arm PFS models (range: 0-7%) which clinical experts have advised as not being clinically plausible given the observed reduction in risk of progression or death for dostarlimab in combination with CP vs CP alone.

Of the remaining distributions, the Odds, k=1 model results in landmark PFS estimates that align closely with expert advice received as part of this evidence submission and with expert input into similar appraisals in this therapy area. The Normal, k=1 model is also tested in scenario analysis, aligning more closely with

expert advice received as part of appraisal ID6381. Further detail on the PFS curve selection for CP has been included in the appendix.

Table 10: PFS landmark survival estimates

	Year 2	Year 3	Year 5	Year 10	Year 15	Year 20
Expert advice - RUBY-1 MMRp	-	-	18%	5%	-	2%
Expert advice (ID6381 - MMRp)	10%	-	2-3%	1-2%	-	NR
Expert advice (TA963 - dMMR)	23%	15%	9%	7%	-	6%
Expert advice (ID6381 - dMMR)	15%	-	5-10%	3-5%	-	-
Committee preference TA1064 (dMMR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Original company base-case (MMRp IA1)	20%	15%	10%	5%	3%	2%
PFS IA2 KM	[redacted]	[redacted]	NA	NA	NA	NA
Hazards - k=0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazards - k=1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazards - k=2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazards - k=3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds - k=0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds - k=1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds - k=2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds - k=3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Normal - k=0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Normal - k=1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Normal - k=2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Normal - k=3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; IA2, interim analysis 2; k, knots; KM, Kaplan-Meier; PFS, progression-free survival

For the dostarlimab arm, all flexible spline models provided a similar visual fit to the observed data. All models other than the Normal, k=1 model were within 3 AIC points of each other indicating that none of these models could be considered statistically superior. The Odds, k=1 model has been selected in the base-case, as this provides the most conservative estimates of PFS at 3- and 5-years and has a good statistical and visual fit to the observed data. Alternative conservative (Hazards, k=3) and optimistic (Normal, k=3) curve choices have been tested in scenario analysis. Further detail on the PFS curve selection for dostarlimab has been included in the Appendix.

Dostarlimab with platinum-based chemotherapy for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6415]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Wednesday 20 August 2025. Please submit via NICE Docs.

Table 11: Dostarlimab in combination with CP PFS landmark survival estimates

	Year 2	Year 3	Year 5	Year 10	Year 15	Year 20
Selected CP PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS IA2 KM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazards - k=1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazards - k=2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazards - k=3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds - k=1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds - k=2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds - k=3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Normal - k=1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Normal - k=2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Normal - k=3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; k, knots; KM, Kaplan-Meier; NA, not applicable; PFS, progression-free survival

The selected PFS curves for dostarlimab and CP are presented in Figure 5. The PFS IA2 curves have been included in the updated company base-case. Scenario analyses are presented in the appendix which use the following PFS curves:

- Dostarlimab: Hazards, k=3 and CP: Odds, k=1 flexible spline models
- Dostarlimab: Normal, k=3 and CP: Normal, k=1 flexible spline models

Figure 5: Selected IA2 PFS extrapolations

Abbreviations: CP, carboplatin and paclitaxel; IA2, second interim analysis; KM, Kaplan-Meier; PFS, progression-free survival.

(7).

The committee's preferred assumption –

Subsequent treatment proportions have been updated based on the more mature IA2 datacut

In the pre-existing company base-case, the distribution of subsequent treatments was based on the IA1 data cut. To ensure alignment between costs and outcomes,

which are derived based on the IA2 data cut, GSK has updated the distribution of subsequent treatment being applied in the model to reflect this.

Subsequent treatment proportions incorporated into the economic model were derived from RUBY-1 trial data and adapted to reflect UK clinical practice. These proportions were calculated by expressing the number of patients receiving each subsequent treatment regimen as a proportion of the total that received a subsequent treatment in each arm. As within the original company submission, given the large number of chemotherapy regimens recorded in the trial, many of which are utilised by a single patient, only the six most common chemotherapy regimens which are also available in UK practice were included.

The proportions in the dostarlimab arm are adapted to account for patients who were retreated with immunotherapy in the RUBY-1 trial which would not occur in UK practice. The proportion of patients receiving immunotherapy in the dostarlimab arm is distributed proportionately across the other treatments. As outlined in Comment (1) and (2), this is not expected to impact OS outcomes.

As highlighted previously, a small number of patients in the RUBY-1 trial were treated with bevacizumab (N=14). For simplicity, and to ensure the distributional proportions of other subsequent treatments remain consistent with what is expected in clinical practice, bevacizumab use is *not* also redistributed across other treatment regimens.

Table 12: Subsequent treatment mix derived from IA2*

	RUBY-1 trial (adjusted)	
	Dostarlimab in combination with CP (N=192)	**CP (N=184)**
Patients receiving FUACT	105	134
Carboplatin and doxorubicin	[redacted]	[redacted]
Carboplatin and paclitaxel	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]
Immunotherapy	[redacted]	[redacted]
Hormone therapy	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; FUACT, follow-up anti-cancer therapy.
*Percentages expressed as a proportion of patients receiving any FUACT

The updated proportions of patients receiving subsequent treatments (see Table 12 above) remain largely consistent with those presented in the IA1 analysis. This alignment is further supported by the EAG report, which states, *"the EAG acknowledges that the proportion of immunotherapy use in the CP arm of the company's original base-case (48.8%) was deemed reflective of UK clinical practice, based on advice received by the EAG from the NHS England CDF lead".* Additionally, these values align with those in similar appraisals, such as NICE ID6381 (pembrolizumab with carboplatin and paclitaxel for untreated advanced or recurrent EC), where company experts estimated that around 50% of people with MMRp/MSS

Dostarlimab with platinum-based chemotherapy for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6415]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Wednesday 20 August 2025. Please submit via NICE Docs.

	EC would have immunotherapy if their cancer progressed, which was supported by both the company and EAG, and accepted by the appraisal committee (3).

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Dostarlimab with platinum-based chemotherapy for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6415]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Wednesday 20 August 2025. Please submit via NICE Docs.

Factual inaccuracies

The company wish to clarify factual inaccuracies made in the draft guidance.

Description of problem	Description of proposed amendment	Justification for amendment
N/A		

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Use this comment form and submit it as a Word document (not a PDF).
Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
Do not paste other tables into this table – type directly into the table.
In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as ''depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
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If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.
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Draft Guidance Response

Technical Appendix

1. IA2 PFS

To address the committee's concerns on uncertainty, the economic model has been updated to include the more mature and most recent second interim analysis (IA2) data cut to extrapolate progression-free survival (PFS).

The PFS from this more mature data cut is consistent with the first interim analysis (IA1) of PFS, [redacted], reflecting the relatively stable PFS within each arm with the extended follow-up (please see clarification questions response for more detail).

1.1. CP PFS

In keeping with the approach to modelling IA1 PFS flexible modelling approaches are considered more appropriate for the extrapolation of PFS for the carboplatin and paclitaxel (CP) arm of the RUBY-1 trial. This also aligns with the approach used to model the PFS placebo arm in TA963 (2). Standard parametric models provided a poor visual fit, but for completeness, are presented in Figure 1. Table 1 provides a summary of the goodness-of-fit data for the IA2 PFS of CP. The flexible models considered are presented in Figure 2, with the corresponding landmark estimates of PFS presented in Table 2.

Figure 1: Independent survival curves – CP PFS IA2

Abbreviations: CP, carboplatin and paclitaxel; IA2, second interim analysis; PFS, progression-free survival.

Table 1: Summary of goodness-of-fit data for the IA2 PFS of CP (flexible models)

PFS	CP	
Distribution	**AIC**	**Ranking**
Hazards, k=1	[redacted]	[redacted]
Hazards, k=2	[redacted]	[redacted]
Hazards, k=3	[redacted]	[redacted]
Odds, k=1	[redacted]	[redacted]
Odds, k=2	[redacted]	[redacted]
Odds, k=3	[redacted]	[redacted]
Normal, k=1	[redacted]	[redacted]
Normal, k=2	[redacted]	[redacted]
Normal, k=3	[redacted]	[redacted]

Note: A small AIC value represents a better goodness of fit.
Abbreviations: AIC, Akaike information criterion; CP, carboplatin and paclitaxel; IA2, second interim analysis; PFS, progression-free survival.

Figure 2: Flexible models for PFS compared with KM data, CP

Abbreviations: CP, carboplatin and paclitaxel; KM, Kaplan-Meier; PFS, progression-free survival.

Table 2: Flexible model estimates of the proportion of patients who would be progression-free at landmark time points treated with CP

Months (years)	CP								
	Hazards, k=1	Hazards, k=2	Hazards, k=3	Odds, k=1	Odds, k=2	Odds, k=3	Normal, k=1	Normal, k=2	Normal, k=3
24 (2)	[redacted]								
36 (3)	[redacted]								
60 (5)	[redacted]								
120 (10)	[redacted]								
240 (20)	[redacted]								

Abbreviations: CP, carboplatin and paclitaxel.

1.2. Dostarlimab in combination with CP progression-free survival

Table 3 provides a summary of the goodness-of-fit data for the IA2 PFS of dostarlimab + CP. The flexible models considered are presented in Figure 3, with the corresponding landmark estimates of PFS presented in Table 4, which is compared with the selected CP PFS curve.

Table 3: Summary of goodness-of-fit data for dostarlimab in combination with CP for PFS (flexible models)

PFS	Dostarlimab in combination with CP	
Distribution	AIC	Ranking
Hazards, k=1	[redacted]	[redacted]
Hazards, k=2	[redacted]	[redacted]
Hazards, k=3	[redacted]	[redacted]

PFS	Dostarlimab in combination with CP	
Distribution	**AIC**	**Ranking**
Odds, k=1	[redacted]	[redacted]
Odds, k=2	[redacted]	[redacted]
Odds, k=3	[redacted]	[redacted]
Normal, k=1	[redacted]	[redacted]
Normal, k=2	[redacted]	[redacted]
Normal, k=3	[redacted]	[redacted]

Note: A small AIC value represents a better goodness of fit.
Abbreviations: AIC, Akaike information criterion; CP, carboplatin and paclitaxel; PFS, progression-free survival

Figure 3: Flexible models for PFS compared with KM data, dostarlimab in combination with CP

Abbreviations: CP, carboplatin and paclitaxel; KM, Kaplan-Meier; PFS, progression-free survival.

Table 4: Flexible model estimates of the proportion of patients who would be progression-free at landmark time points treated with dostarlimab in combination with CP

Months (years)	CP curve	Dostarlimab + CP								
		Hazards			Odds			Normal		
		k=1	k=2	k=3	k=1	k=2	k=3	K=1	k=2	k=3
24 (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 (3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 (5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
120 (10)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
240 (20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CP, carboplatin and paclitaxel.

2. Treatment switching analysis

Treatment switching analyses have been conducted on the MMRp/MSS population. The aim of this analysis being to evaluate the impact of dostarlimab plus CP versus CP on OS in the MMRp/MSS population, adjusting for treatment switching to follow-up anticancer therapies (FUACTs), including immunotherapy. This analysis has been conducted to address concerns on the impact of FUACT on survival outcomes from the RUBY-1 trial.

The RUBY-1 study evaluated the efficacy of dostarlimab plus CP compared to CP in the MMRp/MSS population, with OS as a key endpoint. Treatment switching to FUACTs, such as pembrolizumab plus lenvatinib, is common in clinical practice and can confound survival outcomes in randomized trials. To address these concerns, treatment switching analyses were conducted using robust statistical methods to estimate OS outcomes as if FUACT switching had not occurred.

2.1. Methods

Two established statistical methods were employed to adjust for treatment switching: Rank Preserving Structural Failure Time Model (RPSFTM) and Inverse Probability of Censoring Weights (IPCW).

- **RPSFTM:** Where counterfactual survival times were considered. This results in OS measures that would have been observed if patients had not switched to FUACT.
- **IPCW:** Where patients were artificially censored at the time they switched to a FUACT. IPCW considers a hypothetical world where no patients would switch to alternative therapy.

Analyses were conducted for the intention-to-treat (ITT) MMRp/MSS population and biomarker status verified post-randomization. Adjustments were made for baseline covariates, including body mass index (BMI) and Eastern Cooperative Oncology Group (ECOG) performance status, and stratification factors such as prior external pelvic radiotherapy and disease status.

Treatment switching analyses have been conducted for (1) all IO's and (2) pembrolizumab with lenvatinib alone.

- **Base case:** Adjust for any FUACT switching to any IO or IO combination as a follow-up anti-cancer treatment for all comers.

- The FUACT IO treatments seen in the secondary interim analysis were as below; also, the MK7694A and investigational product (flagged as IO in the dataset) were also included: Atezolizumab/Ipatasertib, Avelumab/Axitinib, Bevacizumab/Atezolizumab, Dostarlimab, Durvalumab/Cediranib, Durvalumab/Olaparib, Nivolumab/BMS-986207/COM701, Nivolumab/Lucitanib, Pembrolizumab, Pembrolizumab/Lenvatinib, Pembrolizumab/Tamoxifen, Retifanlimab/Epacadostat

- **Scenario analysis:** Pembrolizumab with lenvatinib combination for MMRp/MSS (MMRp/MSS subgroup only).

2.2. Results

For the MMRp/MSS population, RPSFTM adjustments demonstrated modest reductions in HRs for OS with dostarlimab plus CP compared to CP. Results are shown below for both the base case and sensitivity analysis for both scenarios. The sensitivity analysis relaxes the common treatment effect assumption by retaining the full treatment effect for patients randomized to the dostarlimab plus CP arm but retaining only 75% of the treatment effect for those who switch treatment.

Table 5: Summary of Kaplan-Meier Analysis with RPSFTM Adjustment for OS (Base Case)

	Psi (95% CI)	Adjusted HR (95% CI)	AF	p-value	Unadjusted HR (95% CI)
Base case scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Base case (Sensitivity Analysis) *	[redacted]	[redacted]	[redacted]	[redacted]	
Scenario analysis (adjustment for pem/len)	[redacted]	[redacted]	[redacted]	[redacted]	
Scenario analysis (adjustment for pem/len) (Sensitivity Analysis) *	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: AF, acceleration factor; CI, confidence interval; dMMR, deficient mismatch repair; HR, hazard ratio; ITT, intention-to-treat; MMR, mismatch repair; MMRp, mismatch repair proficient; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSS, microsatellite stable; N/A, not applicable; OS, overall survival; RM, at randomization; RPSFTM, rank preserving structural failure time model; SE, standard error
* The sensitivity analysis results, mirrors the results for the Kaplan-Meier analysis with RPSFTM. This sensitivity analysis relaxes the common treatment effect assumption by retaining the full treatment effect for patients randomized to the D+CP arm but retaining only 75% of the treatment effect for those who switch treatment.
¥For Scenario analysis, 65 (17%) of source-verified MMRp/MSS patients switched to an anti-PD-1/anti-PD-L1 FUACT, including 22 D+CP patients (11% of D+CP arm) and 43 PBO+CP patients (23% of the PBO+CP arm). Overall, 170 (45%) of the MMRp/MSS patients were administratively censored.

In the base-case scenario, RPSFTM estimated an AF of [redacted] for OS, indicating that survival time was extended by 28% for patients who remained on dostarlimab +CP versus CP alone. The adjusted HR for OS was [redacted]). Scenario-specific analyses, focusing on MMRp/MSS patients treated with pembrolizumab plus lenvatinib, showed consistent trends, with an adjusted HR of [redacted]. However, the magnitude of improvement in OS outcomes remained modest, and FUACT adjustments did not significantly alter the overall survival benefit observed in the trial.

2.3. Conclusions

Among the methods employed, RPSFTM was considered more reliable due to its robustness in scenarios with low switching proportions (<30%), high treatment effect, small sample sizes, and high censoring rates observed in the RUBY trial. The key findings indicate that FUACT switching had a minimal impact on OS outcomes. The RPSFTM-adjusted HRs for OS in the MMRp/MSS population remained consistent with unadjusted estimates, suggesting that the survival benefit of dostarlimab plus CP was not significantly influenced by subsequent immunotherapies. Adjusted and unadjusted analyses consistently demonstrated that dostarlimab plus CP provided robust OS outcomes, independent of FUACT receipt. These findings support the efficacy of dostarlimab plus CP as a frontline treatment in the MMRp/MSS population.

Several factors contribute to the modest influence of FUACT switching on OS outcomes. Less than one-third of RUBY trial participants switched to FUACTs, limiting their overall impact on survival estimates. The RUBY trial demonstrated a significant survival benefit for dostarlimab+CP, which reduces the relative impact of adjustments for FUACT switching. The RPSFTM methodology reliably accounts for treatment switching in scenarios with strong primary treatment effects and low switching proportions. Subgroup analyses, such as those for the MMRp/MSS population, were limited by small sample sizes, reducing the reliability of adjustments like IPCW.

These findings confirm the robustness of the RUBY trial's conclusions, demonstrating a clinically meaningful improvement in OS with dostarlimab plus CP compared to CP. Adjusted HRs further validate this benefit, reinforcing the role of dostarlimab plus CP as a frontline treatment for the MMRp/MSS population.

Although both, RPSFTM and IPCW were explored, RPSFTM is considered more reliable due to several reasons. Firstly, there are lower switching proportions (<30%), smaller sample sizes, high censoring proportions and with a higher treatment effect within the

RUBY-1 trial. Secondly, RPSFTM assumes common treatment effect, but even if assumption is moderately violated, results tend to be robust.

For a full description of the RPSFTM methods, please see Table 6, which outlines the RPSFTM methods, in line with NICE reporting requirements.

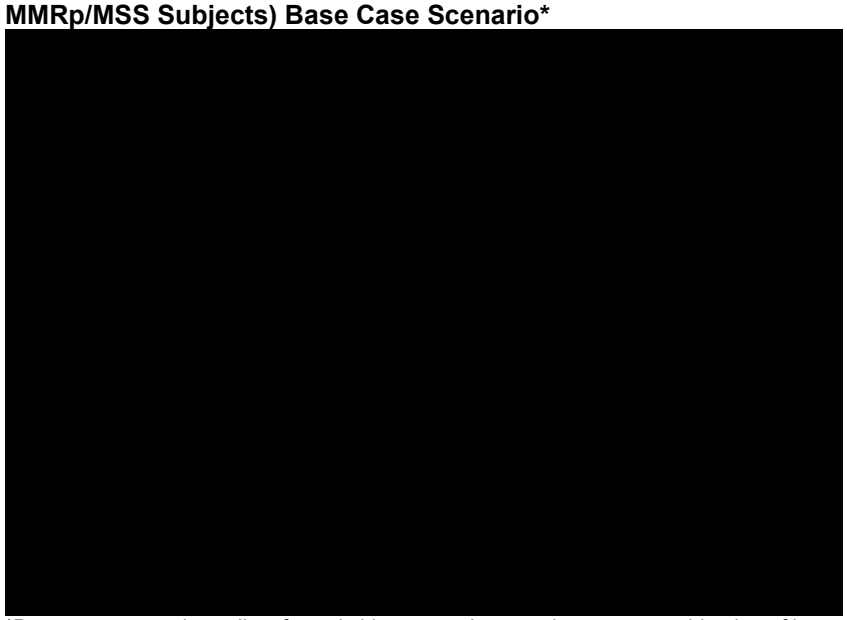
Table 6: Reporting guidelines for treatment switching adjustment analyses

<table>
<tr><th colspan="2">Description of the data and unadjusted results</th></tr>
<tr><td>Provide unadjusted results from an ITT analysis for comparison.</td><td>For the MMRp/MSS source-verified population, the unadjusted ITT analysis showed a HR for OS of [redacted] (95% CI: 0.602, 1.044) for Dostarlimab + CP versus CP alone</td></tr>
<tr><td>Describe the treatment switching mechanism - who can switch and when.</td><td>Patients could switch to FUACT after discontinuing study treatment due to progression of disease, clinical progression, AEs, or other reasons such as investigator decision or withdrawal of consent.</td></tr>
<tr><td>Detail the number of patients who switched, the number eligible to switch, and when switching occurred.</td><td>In the base case, 33 patients (17%) in the Dostarlimab + CP arm and 68 patients (37%) in the CP alone arm switched to FUACT.
In the scenario analysis (adjustment for pem/len), 22 patients (11%) in the Dostarlimab + CP arm and 43 patients (23%) in the CP alone arm switched to FUACT.
Switching typically occurred after PD or clinical progression.</td></tr>
<tr><td>Give an overview of the data available for adjustment - what predictors were collected and how frequently were they measured.</td><td>Predictors included baseline covariates such as age, BMI, ECOG performance status, histology, disease grade, hormone receptor status, prior external pelvic radiotherapy, and disease status. Time-varying covariates such as progression status and adverse events were also collected.
Measurements were taken at baseline, during treatment, and at follow-up visits.</td></tr>
<tr><td>Include a summary of subsequent treatments received in both/all arms of the trial, including which subsequent treatments were received, the number and proportion of patients that received subsequent treatments, and when subsequent treatments were received.*</td><td>In the base case, pembrolizumab/lenvatinib was the most common FUACT, received by [redacted]% of Dostarlimab + CP patients and [redacted]% of CP alone patients. Other FUACTs included pembrolizumab monotherapy ([redacted]% Dostarlimab + CP; [redacted]% CP alone) and durvalumab/cediranib ([redacted]% CP alone).

<table>
<tr><th>Treatment</th><th>Dosta + CP N=34</th><th>CP alone N=68</th><th>Total N=102</th></tr>
<tr><td>Atezolizumab/ipatasertib</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Avelumab/axitinib</td><td></td><td></td><td></td></tr>
<tr><td>Bevacizumab/atezolizumab</td><td></td><td></td><td></td></tr>
<tr><td>Durvalumab/cediranib</td><td></td><td></td><td></td></tr>
<tr><td>Durvalumab/olaparib</td><td></td><td></td><td></td></tr>
<tr><td>Nivolumab/BMS-986207/COM701</td><td></td><td></td><td></td></tr>
<tr><td>Nivolumab/lucitanib</td><td></td><td></td><td></td></tr>
<tr><td>Pembrolizumab</td><td></td><td></td><td></td></tr>
<tr><td>Pembrolizumab/lenvatinib</td><td></td><td></td><td></td></tr>
<tr><td>Retifanlimab/epacadostat</td><td></td><td></td><td></td></tr>
<tr><td>Investigational product</td><td></td><td></td><td></td></tr>
</table>

Switching typically occurred after discontinuation of study treatment, which was associated with discontinuation due to progression or AEs.</td></tr>
<tr><td>Describe which switches do not represent standard treatment pathways in the NHS in</td><td>This analysis aims to understand the impact that subsequent IO usage has on OS. Differences compared to the standard NHS treatment pathway are twofold:
(1) IO re-treatment is not permitted- therefore, following on from initial first-line treatment with dostarlimab, treatment with subsequent IO would not be permitted</td></tr>
</table>

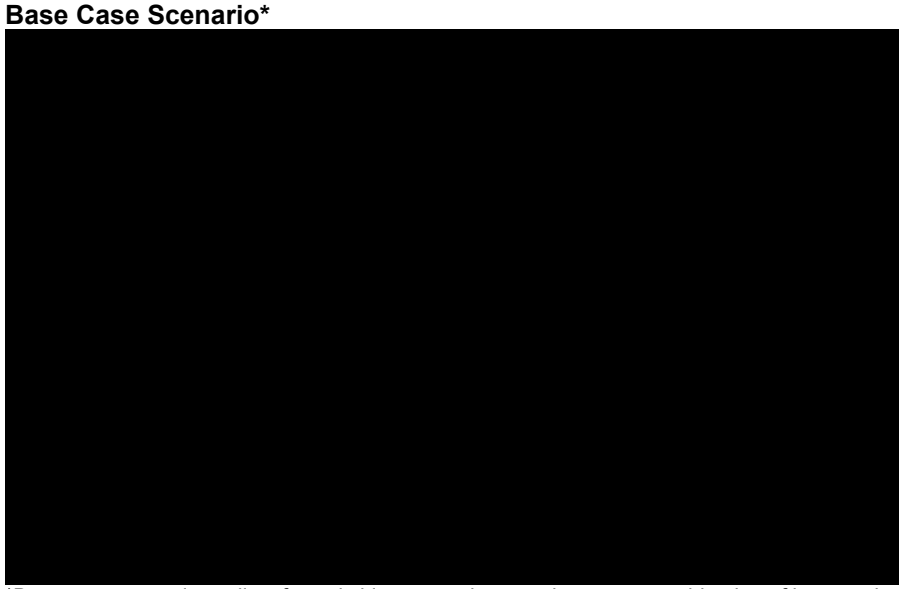
England and Wales.*	(2) Although pembrolizumab/ lenvatinib is the primary subsequent IO utilised, other IO's were permitted as part of the RUBY trial. These IO's are not routinely commissioned and therefore, not representative of the NHS pathway.
Describe and justify the type of switches that adjustments have been made for.*	Adjustments were made for switches to FUACTs involving immunotherapy (anti-PD-1/PD-L1 therapies) as IO re-treatment is not allowed as part of the NHS clinical pathway. Adjustments were justified to isolate the survival benefit of the first-line treatment (Dostarlimab + CP vs. CP alone).
Method selection	
State whether the chosen adjustment approach, including all model fitting steps, was prespecified; if not, explain how the final method and model were selected.	The adjustment methods (RPSFTM and IPCW) were not prespecified but were selected based on feasibility and robustness. RPSFTM and IPCW were considered the most appropriate methods for adjusting survival estimates in the presence of treatment switching. RPSFTM was preferred as it retains randomization, is robust in scenarios with low switching proportions (<30%), high treatment effects, and high censoring rates, and directly adjusts survival times using counterfactual estimates. Unlike IPCW, which relies on large sample sizes and accurate covariate estimation, RPSFTM is less sensitive to convergence issues and violations of the common treatment effect assumption. TSE was also initially considered but deemed inappropriate as it requires switching to occur immediately after a common secondary baseline, such as PD. In the RUBY study, switching occurred for various reasons beyond PD, with over 20% of patients initiating FUACT late, violating TSE assumptions. Additionally, TSE struggles with convergence in small sample sizes, making it unsuitable for this analysis. As such, RPSFTM was chosen as the primary method due to its reliability in scenarios with low switching proportions and high treatment effects. IPCW was used as a secondary method. All methods are aligned with those outlined in NICE DSU 16 and 24 (3, 4)
RPSFTM (Rank Preserving Structural Failure Time Model)	
Provide a statement around the plausibility of the common treatment effect assumption.*	The common treatment effect assumption was considered plausible based on prior studies showing a ~25% decrement in treatment effect for switchers compared to patients randomized to Dostarlimab + CP. Sensitivity analyses were conducted to test robustness to violations of this assumption. The sensitivity analysis was conducted to assess the impact of relaxing the common treatment effect assumption in the RPSFTM model. This analysis retained the full treatment effect for patients randomized to the dostarlimab plus carboplatin-paclitaxel arm but assumed that patients who switched to FUACT experienced only 75% of the treatment effect.
State and justify the structural model assumed (e.g. as treated, ever treated).	The structural model assumed was "as treated," where survival times were adjusted based on time spent on the experimental treatment (Dostarlimab + CP). This approach retains the randomization property of the trial.
State the metric used for g-estimation (e.g. log-rank test), including baseline variables for adjustment where applicable.	G-estimation was performed using the log-rank test. Baseline variables included MMR/MSI status, prior external pelvic radiotherapy, and disease status.
State the grid-search or interval bisection algorithm used for g-estimation.	The AF is estimated using G-estimation, through a grid search estimation procedure, which balances counter-factual event times across randomized groups, i.e., by assuming treatment switchers from the comparator arm remained on randomized treatment, and all patients on the experimental arm were entirely untreated (off experimental treatment) the whole time.

	A grid-search algorithm was used to estimate the causal parameter ψ, minimizing the test statistic or Z-score to identify the true value of ψ.
Present the estimated time ratio (or acceleration factor) and its confidence interval.	In the base case, the AF was [redacted] for the MMRp/MSS source-verified population. In the scenario analysis (adjustment for pem/len), the AF was [redacted] These values indicate extended survival for patients on Dostarlimab + CP compared to CP alone.
Compare counterfactual survival times between randomised groups in a Kaplan-Meier plot.	KM plots comparing counterfactual survival times are presented below, showing improved survival for Dostarlimab + CP versus CP alone after adjustment. **Figure 4: Graph of Kaplan Meier Analysis for Counterfactual Survival Times Between Randomized Treatment Arms of Overall Survival (ITT Analysis Set - MMRp/MSS Subjects) Base Case Scenario***  *Base case scenario - adjust for switching to any immunotherapy or combination of immunotherapy as a follow-up anti-cancer treatment (FUACT) for all comers. MMRp/MSS and dMMR/MSI-H selected based on stratification factors from clinical database (verified source). RPSFTM model has been derived with adjustment for strata including prior external pelvic radiotherapy (strat2v) and disease status (strat3v). This figure shows counterfactual survival times (treatment-free time) on both arms, such that patients in the Dostarlimab + Carboplatin/Paclitaxel (C/P) experimental arm would only have received C/P, and none of the patients in the comparator arm Placebo + C/P arm would have switched to any subsequent base-case therapy. Given patients are randomized, then if both arms were treatment free, then their survival distributions should be similar if causal parameter psi (ψ) has been estimated as expected. RPSFTM rank preserving structural failure time model.
Detail the model fitted to the adjusted dataset, including the method used to calculate confidence intervals around the estimated treatment effect and/or survival extrapolation (e.g. retain ITT p-value, bootstrapping) and baseline variables adjusted for.	Adjusted confidence intervals were calculated using inflated standard errors based on the Wald test statistic from the ITT comparison. Baseline variables adjusted for included MMR/MSI status, prior external pelvic radiotherapy, and disease status.

Present results both with and without re-censoring applied.	Results were presented with and without re-censoring. Re-censoring was applied to reduce bias from informative censoring, but non-re-censored results were also provided for comparison **Figure 5: Graph of KM Curves with RPSFTM Adjustment of Overall Survival (ITT Analysis set - MMRp/MSS Subjects) Base Case Scenario***  *Base case scenario - adjust for switching to any immunotherapy or combination of immunotherapy as a follow-up anti-cancer treatment (FUACT) for all comers. MMRp/MSS and dMMR/MSI-H selected based on stratification factors from clinical database (verified source). RPSFTM-adjusted counterfactual survival times for overall survival have been derived with adjustment for strata including prior external pelvic radiotherapy (strat2v) and disease status (strat3v). RPSFTM rank preserving structural failure time model. **Table 7: Summary of KM Analysis with RPSFTM Adjustment for OS (Base Case)** | | **Psi (95% CI)** | **Adjusted HR (95% CI)** | **AF** | **p-value** | **Unadjusted HR (95% CI)** | | **Base case scenario** | | | | | | | **Scenario analysis* (adjustment for pem/len)** | | | | | | *For Scenario analysis (adjustment for pem/len), 65 (17%) of source-verified MMRp/MSS patients switched to an anti-PD-1/anti-PD-L1 FUACT, including 22 D+CP patients (11% of D+CP arm) and 43 PBO+CP patients (23% of the PBO+CP arm). Overall, 170 (45%) of the MMRp/MSS patients were administratively censored. Abbreviations: AF, acceleration factor; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; RM, at randomization; SE, standard error
Report on sensitivity analyses showing the robustness of treatment effect estimates and survival extrapolations to violations of key assumptions. Sensitivity analysis around the	Sensitivity analyses relaxed the common treatment effect assumption by retaining only 75% of the treatment effect for switchers. Results showed consistent reductions in HRs for OS across all populations, confirming robustness to violations of key assumptions

common treatment effect assumption should be included.

Figure 6: Sensitivity Analysis: Graph of KM Curves with RPSFTM Adjustment of Overall Survival (ITT Analysis Set - MMRp/MSS Subjects) Base Case Scenario*



*Base case scenario - adjust for switching to any immunotherapy or combination of immunotherapy as a follow-up anti-cancer treatment (FUACT) for all comers. MMRp/MSS and dMMR/MSI-H selected based on stratification factors from clinical database (verified source). RPSFTM-adjusted counterfactual survival times for overall survival have been derived with adjustment for strata including prior external pelvic radiotherapy (strat2v) and disease status (strat3v).
This sensitivity analysis only retains 75% of the treatment effect for treatment switchers. RPSFTM rank preserving structural failure time model.
The sensitivity analysis results, mirrors the results for the Kaplan-Meier analysis with RPSFTM. This sensitivity analysis relaxes the common treatment effect assumption by retaining the full treatment effect for patients randomized to the D+CP arm but retaining only 75% of the treatment effect for those who switch treatment.

Table 8: Summary of KM Analysis with RPSFTM Adjustment for OS (Base Case)

	Psi (95% CI)	Adjusted HR (95% CI)	AF	p-value	Unadjusted HR (95% CI)
Base case (Sensitivity Analysis) *					
Scenario analysis# (adjustment for pem/len) (Sensitivity analysis)					

* The sensitivity analysis results, mirrors the results for the Kaplan-Meier analysis with RPSFTM. This sensitivity analysis relaxes the common treatment effect assumption by retaining the full treatment effect for patients randomized to the D+CP arm but retaining only 75% of the treatment effect for those who switch treatment.
#For Scenario analysis (adjustment for pem/len), 65 (17%) of source-verified MMRp/MSS patients switched to an anti-PD-1/anti-PD-L1 FUACT, including 22 D+CP patients (11% of D+CP arm) and 43 PBO+CP patients (23% of the PBO+CP arm). Overall, 170 (45%) of the MMRp/MSS patients were administratively censored.
Abbreviations: AF, acceleration factor; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; MMRp, mismatch repair proficient; MSI, microsatellite instability; MSS, microsatellite stable; N/A, not applicable; OS, overall survival; RM, at randomization; RPSFTM, rank preserving structural failure time model; SE, standard error.

3. Updated economic results

3.1. Updated company base case incremental cost-effectiveness analysis results

3.1.1. Base case

Following the draft guidance, the updated model base case has been updated to address some of the Committee's concerns.

The updated base case includes the following:

1. Using the more mature data from the IA2 data cut to inform:
    - PFS data
    - Distribution of subsequent treatments
2. Using the EAG's approach to model health-state resource use for the dostarlimab arm
3. The Committee's preferred approach for each of the following assumptions:
    - Excluding the cost of oral administration for lenvatinib
    - Using the EAG's preferred approach to modelling TTD

Table 9 reports cost-effectiveness results for the updated Company base case, [redacted]. In the updated Company base case, dostarlimab is associated with incremental costs of £[redacted] and incremental quality-adjusted life years (QALYs) of 0.753 vs CP, resulting in an incremental cost-effectiveness ratio (ICER) of £[redacted] per QALY.

Table 9: Base case results (deterministic)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Dostarlimab in combination with CP	[redacted]	[redacted]	[redacted]	[redacted]	-	-
CP	[redacted]	[redacted]	[redacted]	[redacted]	0.753	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; EAG, Evidence assessment group; LY, Life years; PAS, Patient access scheme; PFS, progression-free survival; QALY, Quality adjusted life-years; TTD, time to treatment discontinuation.

3.1.2. Probabilistic sensitivity analysis

Table 10 includes the probabilistic results based on the updated base case using the updated simple PAS discount of [redacted] Figure 7 and Figure 8 show the incremental cost-

effectiveness plane scatterplot and CEAC associated with the probabilistic analysis of the companies updated base case.

Table 10: Updated company base case results (probabilistic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
Dostarlimab in combination with CP	[redacted]	[redacted]	[redacted]	[redacted]	-	-
CP	[redacted]	[redacted]	[redacted]	[redacted]	0.750	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 7: Incremental cost-effectiveness plane scatterplot

Abbreviations: CP, carboplatin and paclitaxel; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.

Figure 8: Cost-effectiveness acceptability curve

Abbreviations: CP, carboplatin and paclitaxel.

3.1.3. Deterministic sensitivity analysis

Deterministic sensitivity analysis was undertaken on the updated company base case using the updated PAS discount of [redacted] The one-way sensitivity analysis (OWSA) varied one parameter at a time, assessing the impact on the incremental QALYs and incremental costs, and subsequently the ICER. A lower and upper bound was assigned to suitable parameters.

Results of the OWSA are presented in Table 11 and show the top 10 model drivers of the ICER for dostarlimab with CP versus CP. As shown in Table 11, there are two parameters that result in a dominating ICER, and as such, these parameters are not included within the tornado diagram.

- Total cost for average total treatment duration (£) Pembrolizumab and lenvatinib
- Proportion receiving pembrolizumab and lenvatinib following discontinuation from CP

The results of the OWSA are also presented in a tornado diagram in Figure 9.

Table 11: Tabulated OWSA results (deterministic)

Parameter	Lower bound ICER (£/QALY)	Upper bound ICER (£/QALY)	Difference (£/QALY)
Updated company base case	[redacted]		
Outpatient visit Dostarlimab+CP in PD state from cycle 19+	[redacted]	[redacted]	[redacted]
Outpatient visit CP in PD state from cycle 19+	[redacted]	[redacted]	[redacted]
Outpatient visit unit cost	[redacted]	[redacted]	[redacted]
Outpatient visit Dostarlimab+CP in PF state from cycle 19+	[redacted]	[redacted]	[redacted]
Admin cost up to cycle 18 (£) Dostarlimab+CP	[redacted]	[redacted]	[redacted]
Admin cost (£) CP	[redacted]	[redacted]	[redacted]
Outpatient visit Dostarlimab+CP in PF state up to cycle 18	[redacted]	[redacted]	[redacted]
Admin cost cycle 19+ (£) Dostarlimab	[redacted]	[redacted]	[redacted]
Outpatient visit CP in PF state up to cycle 18	[redacted]	[redacted]	[redacted]
CT scan Dostarlimab+CP in PD state from cycle 19+	[redacted]	[redacted]	[redacted]
Total cost for average total treatment duration (£) Pembrolizumab and lenvatinib	[redacted]	[redacted]	[redacted]
Proportion receiving Pembrolizumab and lenvatinib following discontinuation from CP	[redacted]	[redacted]	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; ICER, Incremental cost-effectiveness ratio; OS, overall survival; OWSA, one-way sensitivity analysis; PD, progressed disease; PF, progression free; PFS, progression-free survival; RDI, relative dose intensity.

Figure 9: Tornado diagram

Abbreviations: CP, carboplatin and paclitaxel; ICER, incremental cost-effectiveness ratio.

3.1.4. Scenario analysis

Scenario analyses were conducted on the updated company base case using the updated PAS discount of [redacted], to test specific alternative inputs for the assessment of structural and parametric uncertainty. Table 12 includes the results of scenario analyses.

Generally, the cost-effectiveness results remained robust across the scenario analyses, with the ICER remaining below [redacted] per QALY in all tested scenarios. The scenario analyses with the biggest impact on the ICER were those that tested the assumptions associated with subsequent therapy. Increasing the proportion of patients in the placebo arm being treated with pembrolizumab with lenvatinib upon progression to 75% to account for the projected market uptake of pembrolizumab with lenvatinib at second line in 2025, [redacted].

Table 12: Scenario analyses (deterministic)

No	Category	Base-case value	Scenario value	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/ QALY)
1	Updated company base case	-	-	[redacted]	[redacted]	0.753	[redacted]
2	PFS Curve selection	Dostarlimab: Odds, k=1 flexible spline model CP: Odds, k=1 flexible spline model	Dostarlimab: Hazards, k=3 flexible spline model CP: Odds, k=1 flexible spline model	[redacted]	[redacted]	0.750	[redacted]
3			Dostarlimab: Normal, k=3 flexible spline model CP: Normal, k=1 flexible spline model	[redacted]	[redacted]	0.776	[redacted]
4	Treatment effect waning: OS	No waning	Waning from 6-8 years- applied to all patients	[redacted]	[redacted]	0.660	[redacted]
5			Waning from 6-8 years- applied to those without a complete response	[redacted]	[redacted]	0.684	[redacted]
6		No waning	Waning from 8-10 years- applied to all patients	[redacted]	[redacted]	0.711	[redacted]
7			Waning from 8-10 years- applied to those without a complete response	[redacted]	[redacted]	0.722	[redacted]
8	Subsequent treatments	RUBY-1 IA2 data used, with no IO retreatment	75% market share assumed for PEM+LEN in CP proportions	[redacted]	[redacted]	0.753	[redacted]

Abbreviations: AE, adverse event; CP, carboplatin and paclitaxel; ICER, incremental cost-effectiveness ratio; IO, immunotherapy; LEN, lenvatinib; LY, life years; OS, overall survival; PEM, pembrolizumab; PFS, progression-free survival; QALYs, quality-adjusted life years

References

1. GSK Dostarlimab (Jemperli). A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) plus Carboplatin-paclitaxel versus Placebo plus Carboplatin-paclitaxel in Patients with Recurrent or Primary Advanced Endometrial Cancer (RUBY). Clinical Study Report 19-Janurary-2024 (data cut off: 22-SEP-2023).

2. National institute for Health and Care Excellence. Committee Papers | Single Technology Appraisal | Dostarlimab with platinum-based chemotherapy for treating advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID3986]. Available on: https://www.nice.org.uk/guidance/ta963/evidence/committee-papers-pdf-13366765117. 2024.

3. Latimer NR AK. NICE DSU Technical Support Document 16: Adjusting Survival Time Estimates in the Presence of Treatment Switching. PMID: 27466662. 2014.

4. Bell Gorrod H LN, Abrams KR. NICE DSU Technical Support Document 24: Adjusting Survival Time Estimates in the Presence of Treatment Switching – An Update to TSD 16. 2024.

NICE National Institute for Health and Care Excellence

Dostarlimab with platinum-based chemotherapy for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6415]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on **Wednesday 20 August 2025**. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Patient Rep Peaches Womb Cancer Trust

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NICE National Institute for Health and Care Excellence

Dostarlimab with platinum-based chemotherapy for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6415]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on **Wednesday 20 August 2025**. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	No disclosures.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No disclosures
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I have no comments to make and feel it encapsulates the discussion had at Committee whilst I was in attendance.

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NICE National Institute for Health and Care Excellence

Dostarlimab with platinum-based chemotherapy for advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6415]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on **Wednesday 20 August 2025**. Please submit via NICE Docs.

2	
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Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer with microsatellite stability or mismatch repair proficiency [ID6145]

EAG response to company draft guidance comments

August 2025

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 172882.

1 Introduction

This document provides the External Assessment Group's (EAG's) critique of the company's response to the draft guidance (DG) document produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of dostarlimab with carboplatin and paclitaxel (hereafter known as dostarlimab + CP) for treating primary advanced or recurrent endometrial cancer (EC) with microsatellite stability (MSS) or mismatch repair proficiency (MMRp).

In the DG, the committee outlined several areas that needed clarification and further analyses from the company, including:

- Using the interim analysis 2 (IA2) data cut for progression-free survival (PFS) from RUBY-1 in the model.
- Analyses for overall survival (OS) adjusted for the benefits and costs of subsequent treatments, particularly subsequent immunotherapies.
- Use progression-free survival 2 (PFS2) to address pre- and post-progression survival.
- Presentation of Kaplan–Meier (KM) curves for PFS and OS with and without subsequent immunotherapies to assess the potential impact of subsequent immunotherapies on the treatment effect.
- Presentation of KM curves for PFS and OS that account for the potential differences in the timing of subsequent immunotherapy started across the 2 treatment arms (for example, using treatment switching methods).
- Further justification for the exclusion of treatment waning in the model, with discussion around the potential interplay between the impact of subsequent treatments on OS and treatment-effect waning is explored.
- p53-abnormal or TP53mut subgroups, including cost-effectiveness estimates, that include relevant diagnostic testing costs.

In their response to the DG, the company attempted to address the committee's concerns by providing more data, justification and scenario analysis. A summary of the company's comments on the DG are as follows:

1. Subsequent treatments used in RUBY-1 are appropriate for decision making.
2. Treatment with dostarlimab + CP is associated with durable post-progression benefits.

3. In RUBY-1, immunotherapies used in later lines of treatment have only modest benefits and have a negligible impact on OS.
4. Treatment-effect waning is implicitly captured in the company's base case and survival extrapolations are consistent with clinical expectations.
5. Dostarlimab + CP improves outcomes across the entire MMRp/MSS population of the RUBY-1 trial.
6. PFS based on the IA2 data cut from RUBY-1 has been included in the company's revised base case analyses.
7. The company's model has been updated to include subsequent treatment data based on the IA2 data cut from RUBY-1.

The company has also included the following assumptions preferred by committee and the EAG as part of their revised base case:

- Use of time-to-treatment discontinuation (TTD) KM data for both treatment arms and dostarlimab relative dose intensity (RDI) applied from cycle one.
- Health-state resource use for the dostarlimab + CP after three years is equal to the progression-free week 18+ health-state resource use for the CP arm of the model.
- Removal of oral administration cost for lenvatinib.

The EAG's critique of each of the company's comments is presented in Section 2, and the company's revised cost-effectiveness results are presented in Section 3. Results presented in this document are inclusive of the patient access scheme (PAS) discount for dostarlimab, which is [redacted], and equates to [redacted] per vial.

Confidential PAS discounts are available for pembrolizumab and lenvatinib, which are included in the model as subsequent treatments. As such, the EAG has produced a confidential appendix to this document. Analyses in the confidential appendix include the company base case results, scenario analyses and EAG scenario analyses.

2 EAG response to company comments

2.1 The generalisability of subsequent treatments used in Part 1 of the RUBY trial (RUBY-1) to clinical practice in the United Kingdom (UK)

The committee were uncertain about the generalisability of the findings of RUBY-1 to patients in the NHS, particularly as the proportion of patients who had subsequent immunotherapy in RUBY-1 was higher than expected in the NHS. The company reported that they considered the treatments used as subsequent later lines of therapy in RUBY-1 to be, "largely reflective of what is utilised in UK clinical practice" (Table 1). They highlighted that conventional chemotherapy was the most common subsequent treatment in the trial (received by [redacted] of all patients), which is one of the treatment options available following disease progression in the NHS.

Table 1. Subsequent treatment recorded in the RUBY-1 trial in the MMRp/MSS population. Reproduced from Table 1 of the company's response.

	Dostarlimab in combination with CP (N=192)	Placebo in combination with CP (N=184)	Total (N=376)
Any follow-up anticancer therapy, n (%)	105 (54.7)	134 (72.8)	239 (63.6%)
[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy	34 (17.7%)	68 (37.0%)	102 (27.1%)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CP, carboplatin and paclitaxel

The EAG notes that [redacted] of patients in the dostarlimab arm and [redacted] of patients in the placebo arm were given bevacizumab as subsequent treatment, which does not reflect current practice in the NHS. However, as the percentage of patients who received bevacizumab was low, and similar between trial arms, the EAG considers it unlikely to have had a major impact on trial outcomes.

The most common subsequent treatment in the placebo arm was immunotherapy, which was received by 37.0% of all patients in RUBY-1 and [redacted] of those patients who received a subsequent treatment. This is marginally higher than the proportion of patients who received subsequent immunotherapy in the IA1 data cut (48.8%) but remains similar to the proportions expected in UK clinical practice, based on advice provided to the EAG from the Cancer Drugs Fund (CDF) lead. Fewer

patients in the dostarlimab arm received immunotherapy (17.7% of all patients in RUBY-1 and [redacted] of those who received a subsequent treatment), but there are concerns about the relevance of this group to NHS clinical practice. Current NHS funding restrictions for immunotherapies mean that any patients who receive dostarlimab will not be eligible for subsequent immunotherapy if they experience disease progression.[1, 2] It is therefore possible that the inclusion of dostarlimab patients who received subsequent immunotherapy in the trial could have led to an overestimation in treatment effect in comparison to what would be expected in NHS clinical practice.

Despite the above concerns, the company stated that retreatment with immunotherapy is not expected to improve post-progression outcomes more than any other subsequent treatment in this setting. Although no evidence from previous trials was provided to support this statement, the company performed a *post-hoc* analysis of the RUBY-1 trial to compare survival outcomes between the ITT population, and patients who received either [redacted]

Table 2. *Post-hoc* analysis of OS in patients receiving immunotherapy or chemotherapy as subsequent treatment following progression (ITT analysis set, MMRp/MSS subgroup). Reproduced from Table 2 of the company's response.

	MMRp/MSS		MMRp/MSS Pem/Len after progression		MMRp/MSS Chemotherapy after progression	
	Dostarlimab + CP [redacted]	Placebo + CP [redacted]	Dostarlimab + CP [redacted]	Placebo + CP [redacted]	Dostarlimab + CP [redacted]	Placebo + CP [redacted]
Median OS (95% CI), months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24-month probability of OS (95% CI), %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence intervals; CP, carboplatin and paclitaxel; MMRp, mismatch repair proficient; MSS, Microsatellite stable; NR, not reached; OS, overall survival

[redacted]

[redacted]

A further limitation of the company's comparison is the use of *post-hoc* analysis methods, which resulted in a breaking of randomisation. Baseline characteristics of the subgroups were not reported and so it is unclear whether patients had comparable levels of disease severity, or if prognostic factors and treatment effect modifiers differed between groups. Without this information, it is not possible to determine [redacted] With the limitations outlined above, uncertainty remains about the impact of subsequent therapies on outcomes in RUBY-1.

2.2 Treatment with dostarlimab in combination with CP results for PFS2 from the RUBY-1 trial

The committee raised concerns about the impact of subsequent immunotherapies on PFS2 results for IA2. In response, the company provided additional analyses of PFS2, which included the time between first and second progression events, and comparisons between patients who received follow-up immunotherapy and those who received any type of follow-up anti-cancer therapy (FUACT). The EAG notes that the definition of PFS2 provided in the RUBY-1 CSR was, "the time from treatment randomisation to the date of assessment of progression on the first subsequent anticancer therapy following study intervention or death by any cause, whichever is earlier". As such, this reflects the time to a patient's second progression event, rather than the length of time from controlled disease to a second progression.

The company reported that immunotherapies can result in significant post-progression benefits, supporting their conclusions with a median PFS2 improvement for dostarlimab over placebo of 8.7 months compared to [redacted] for PFS. Comparisons were also provided for the median time between first and second progression events for each treatment arm:

- Dostarlimab: [redacted]
- Placebo: [redacted]

However, the EAG has some concerns over the interpretation of these results. Firstly, the PFS2 analysis includes all patients, not just those who have experienced a first progression event. As a result, the dostarlimab arm predominantly reflects patients who have had an early failure on initial

treatment, while the placebo arm is likely to include a greater number of patients who have progressed. Consequently, the populations are not balanced in the trial arms when considering PFS2. In addition, PFS2 does not isolate the treatment effect of dostarlimab and instead considers the additional effects of different subsequent treatments, the impact of which has already been highlighted as an area of concern for the committee. As such, these results should be interpreted with caution.

To address concerns about the effects of subsequent treatments on PFS2 the company provided comparisons of the KM analysis for patients who received immunotherapy as a subsequent treatment, and those who received any type of subsequent treatment. In the dostarlimab arm, median PFS2 was [redacted] than those who received any FUACT (Table 3). The company reported that these results demonstrated that results were not biased in favour of retreatment with immunotherapy. However, the EAG considers there to be limitations to this interpretation as no information is provided to explain the choice of FUACT provided to patients at the point of disease progression. Without this information, it is not possible to determine if the difference in median PFS2 is a result of the type of subsequent treatment received, or instead reflects differences in patient characteristics which could have influenced the choice of FUACT. Given the concerns outlined above, the EAG considers PFS to be a more reliable estimate of the effectiveness of treatment with dostarlimab.

Table 3. Results of the KM analysis for patients who received FUACT based on type of treatment received. Reproduced from Table 4 of the company's response.

Category subcategory	Patients who received FUACT with IO		Patients who received *any* FUACT	
	Dostarlimab in combination with CP (N=34)	Placebo in combination with CP (N=68)	Dostarlimab in combination with CP (N=105)	Placebo in combination with CP (N=134)
Number of patients who have FUACT				
n (%)	34 (17.7)	68 (37.0)	105 (54.7)	134 (72.8)
Median PFS2, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence intervals; CP, carboplatin and paclitaxel; FUACT, follow-up anti-cancer therapy; IO, immunotherapy; n, number; PFS2, progression free survival 2

In response to the committee's uncertainties about the treatment effect in RUBY-1, the company provided evidence of previous immunotherapy trials, which have shown significant OS benefits despite modest PFS benefits. The company also reported that PFS2 is often considered a surrogate marker for OS by the European Medicines Agency (EMA). This was used to suggest that the findings

of RUBY-1 demonstrate the effectiveness of dostarlimab for patients with primary advanced/recurrent EC. While the EAG agrees that some of the previous studies highlighted by the company demonstrate significant improvements in OS with immunotherapies, despite non-significant results for PFS, it also notes that effect estimates and statistical significance were not reported for all comparisons. The EAG also notes that the trials are unlikely to have been prospectively designed (or appropriately powered) to detect differences in subsequent treatments and, as such, uncertainties remain about the benefits of dostarlimab for primary advanced/recurrent EC.

2.3 Impact of immunotherapies used in later lines of treatment on outcomes in the RUBY-1 trial

The committee were concerned about the effects of subsequent treatments, in particular the differences in the timing of subsequent immunotherapy between the trial arms, which could impact the treatment effect reported in RUBY-1. In response, the company cited previous trials which have compared the effectiveness of pembrolizumab with lenvatinib (the most frequently used second-line immunotherapy in the RUBY-1 trial) against chemotherapy doublets, suggesting that they indicate only a modest benefit of pembrolizumab with lenvatinib over chemotherapy doublets. Results of the Wang *et al.* 2025 and LEAP-001 trials appear to demonstrate similar levels of effectiveness of pembrolizumab with lenvatinib when compared to carboplatin-paclitaxel in a relevant population.[3, 4] However, the EAG notes that selection bias is likely to be present in these analyses, as the choice of subsequent therapy is likely to be based on both prior therapies and patient characteristics. For instance, a patient who receives immunotherapy after placebo might have more severe disease than those given immunotherapy following a prior immunotherapy. It is therefore difficult to assess the relative effects of subsequent immunotherapy and chemotherapy.

The company also presented a treatment switching analysis to assess the impact of patients switching to subsequent immunotherapies. Rank-preserving structural failure time models (RPSFTM) were used to adjust for second-line treatment with immunotherapy. Four analyses were presented, including: (i) adjustment for all subsequent immunotherapies (base case analysis); (ii) adjustment for only subsequent pembrolizumab with lenvatinib (scenario analysis); and (iii) sensitivity analyses for both the base case and scenario analyses, which relaxed. the common treatment effect assumption, using the full treatment effect for patients in the dostarlimab arm, but retaining only 75% of that effect for any patients who switched treatment (Table 4).

Table 4. Summary of the KM analysis of OS with RPSFTM adjustment for treatment switching. Reproduced from Table 5 of the company's technical appendix.

	Adjusted HR (95% CI)	p-value	Unadjusted HR (95% CI)
Base case scenario	[redacted]	[redacted]	[redacted]
Base case (Sensitivity Analysis) *	[redacted]	[redacted]	
Scenario analysis (adjustment for pem/len)	[redacted]	[redacted]	
Scenario analysis (adjustment for pem/len) (Sensitivity Analysis) *	[redacted]	[redacted]	

Abbreviations: CI, confidence interval; HR, hazard ratio; pem/len, pemrbrolizumab-lenvatinib;

Results of the adjusted analyses were similar to those of the unadjusted analyses, numerically favouring dostarlimab over placebo (Table 4). Sensitivity analyses also produced similar results to the base case and scenario analyses. The company indicated that the results demonstrate a numerical OS benefit associated with dostarlimab over placebo, irrespective of whether subsequent immunotherapy was received.

The company's response states that both RPSFTM and Inverse Probability of Censoring Weights (IPCW) were considered when deciding on the most appropriate analysis method, with the methodological considerations outlined in Section 2.3 of the Technical Appendix, as recommended by NICE DSU TSD 16.[5] The company reports that RPFSTM was chosen over IPCW due to its ability to retain randomisation and perform well in trials with low switching rates and high censoring rates. It was also reported that the results of RPSFTM tend to be robust to moderate violations of the "common treatment effect" assumption.

While much of this justification appears appropriate, the EAG notes that the NICE DSU TSD 16 states that the RPSFTM method relies on the "common treatment effect assumption", while IPCW relies on the "no unmeasured confounders assumption", requiring data to be available on all prognostic variables and treatment effect modifiers. As such, the RPSFTM method may in fact be less robust than IPCW if the effects of immunotherapy are expected to vary depending on when it is received during the trial. This appears to be particularly relevant, given that the committee was concerned that patients in each arm may have started immunotherapies at different times, thereby impacting on the treatment effect of dostarlimab. Instead, assuming that there is sufficient data to meet the no unmeasured confounders assumption, the IPCW method may have been a more appropriate

method of adjustment. However, IPCW results were not reported and so comparisons cannot be made between the results of the two adjustment methods.

The company did not implement the treatment-switching analysis as a scenario in the economic model. However, as explained above, the EAG considers that any ICERs based on the adjusted OS analysis are likely to be similar to the company's base case, given the minimal differences between the estimated HRs. The company's base case ICER could be considered conservative, as numerically, the adjusted OS HRs (base case, sensitivity and scenario analyses) are more favourable for dostarlimab + CP. However, the EAG considers that there is uncertainty in the methods used for the adjusted OS analysis and the use of the adjusted OS data in the model would result in ICERs that are likely to be more uncertain than the company's base case.

2.4 Treatment effect waning

In the DG, the committee requested further clarification from the company to justify their approach to treatment-effect. Specifically, the committee considered treatment-effect waning was not implicitly captured in the model because, "*the company's extrapolated OS curves with and without incorporated treatment waning were different*". In their comments on the DG, the company explained that the treatment-effect waning scenarios captured additional treatment-effect waning and noted that the curves were based on an artificial adjustment in the model, which overrides the modelled dostarlimab + CP hazard to converge with the modelled hazards for CP at specified timepoints. Additionally, the EAG considers that the OS curves would be different based on the company's scenarios forcing the OS hazards for dostarlimab + CP to converge with the hazards for CP alone.

Reducing the risk of disease progression is considered to be the main treatment effect for dostarlimab + CP. As discussed in Section 2.6, the EAG considers that the hazard rate plot for PFS (Figure 2) demonstrates that this treatment effect peaks at around one year (within the observed period of RUBY-1) and then diminishes thereafter until it is equal to the CP arm. The company explained that follow-up for RUBY-1 is around four years and that most people on dostarlimab + CP discontinue treatment before the maximum treatment duration of three years, meaning that the observed data captures treatment-effect waning and this informs the extrapolations of both PFS and OS.

Nonetheless, the company explored three treatment-effect waning scenarios, including waning occurring three and five years after the maximum treatment stopping rule, and waning only being applied to 74.2% of patients in RUBY-1 who did not achieve a complete response. The results of the scenarios are presented in Section 3.2.2 and have minimal impact on the incremental cost-effectiveness ratio (ICER). The EAG notes that in the original submission, the company explored a treatment-effect waning two years after stopping treatment, rather than three years. The EAG ran the original scenario of two years and found it did not have a substantial impact on the ICER.

Overall, the EAG considers that the cost-effectiveness results using list prices for subsequent treatments are robust to gradual treatment-effect waning assumptions. However, please refer to the confidential appendix to this report for cost-effectiveness results inclusive of patient access scheme (PAS) discounts for pembrolizumab and lenvatinib.

2.5 Clinical-effectiveness of dostarlimab in RUBY-1 in subgroups, such as tumours with tp53 mutations

The company did not provide the exploratory analyses for the p53abn and TP53mut subgroups that were requested by the committee. Subgroup analyses were not considered clinically appropriate for the following reasons:

- The RUBY-1 trial did not provide robust evidence of a greater treatment effect for the tp53 mutation subgroups than the wider population;
- The broader body of evidence relating to programmed cell death protein 1 (PD-1) treatments in p53abn tumours is contradictory;
- The company and committee's clinical experts considered that the benefits of the treatment regimen in RUBY-1 were consistent across biomarker subgroups;
- The company considers there to be a significant and unmet need for treatment for all patients with MMRp and MSS EC, not just those with tp53abn tumours.

The EAG agrees that the treatment effect presented in the CS was broadly similar between the overall population and the TP53 subgroup. However, while the company have highlighted the unmet treatment need for all patients, this does not prevent the analysis of subgroup data to identify patients who may experience the greatest benefit from treatment with dostarlimab. The company also outlined methodological concerns with the requested subgroup analyses, including:

- The need to break randomisation for the *post-hoc* analysis;

- Small patient numbers in the p53 subgroup (47 and 41 patients in the dostarlimab and placebo arms, respectively); and
- The different testing methods used in the RUBY-1 trial compared to clinical practice in the NHS.

The EAG notes that there would be some limitations to the requested subgroup analyses, as p53 mutations were not stratified for at randomisation. However, while this may introduce some uncertainties when interpreting the results, it does not consider this sufficient justification to prevent the subgroup analyses being performed. Additionally, while patient numbers are small compared to the wider trial, the EAG notes that these are not dissimilar to the number of patients included in the company's *post-hoc* comparisons of immunotherapy and chemotherapy in Section 2.1. Notably, data for molecular subgroups were presented in the CS (Table 16) and used to indicate similar treatment effectiveness between the TP53 mutation subgroup and wider patient population. Although testing methods may differ between RUBY-1 and NHS clinical practice, the EAG's understanding is that testing for p53abn and TP53 mutations is possible in the NHS. As such, it is important to identify whether this group may experience additional PFS or OS benefits in comparison to the wider patient population, particularly as people with these mutations tend to have poorer outcomes.

Overall, while the EAG acknowledges that there would be limitations to the subgroup analyses requested by the committee, it does not consider the company's concerns outlined above to be sufficient to prevent further analyses being performed for these subgroups.

2.6 Use of PFS from interim analysis 2 (IA2) data cut to inform the economic model

In the DG, the committee requested the company to use the more mature and most recent interim analysis 2 (IA2) data cut from RUBY-1 for the MMRp/ MSS population to extrapolate PFS in the economic model.

Consistent with the approach taken in the original company submission, the company used independently fit survival distributions to extrapolate the IA2 PFS data. The company explored using standard parametric survival distributions (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma) to extrapolate the KM PFS data. However, the company found that the standard parametric models were considered a poor fit to the observed data and instead explored nine flexible spline models (hazards, odds and normal, knots 1 – 3). To select an

appropriate distribution for the extrapolation of each outcome, the company assessed the fit of each modelled curve against the KM data using visual inspection of the curves, goodness of fit statistics, including Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics, and clinical plausibility of the extrapolation over the time horizon of the model. An overview of the company's survival analysis for both CP and dostarlimab + CP is provided in the Technical Appendix to the company's comments on the draft guidance.

The company highlights, and the EAG agrees, that the spline curves with the best statistical and visual fit [redacted]. As discussed in the EAG report, the EAG's clinical experts advised that outcomes for MMRp/MSS EC population are poor and so most patients on CP are likely to relapse. Therefore, [redacted]. The EAG does not consider it appropriate to model [redacted]. The company's approach to focus only on the spline curves that [redacted] are considered appropriate by the EAG, but the statistical fits are poor as a result. For the revised base case, the company selected the odds k=1 spline curve for both CP and dostarlimab + CP based on visual fit and clinical validity.

Figure 1 presents the company's preferred PFS curves. The estimated mean discounted life years in the progression-free health state for CP and dostarlimab + CP was [redacted] years and [redacted] years, respectively. This is comparable to the mean discounted life years estimated as part of the company's original base case, which was [redacted] years and [redacted] years for CP and dostarlimab + CP, respectively.

The hazard rate plot based on the company's selected PFS curves are presented in Figure 2. The hazard rate plot indicates that the risk of progression is similar for both the dostarlimab + CP and CP arms of the model after approximately three years. However, in their response to the DG, the company has explored gradual treatment-effect waning over user-defined timepoints and the results have minimal impact on the ICER (see Section 3.2.2). The EAG maintains that issue of treatment effect waning for immunotherapy, based on the modelled PFS hazards, is unlikely to be a key issue.

The EAG considers the company's revised base case PFS curves based on IA2 KM data are appropriate.

Figure 1. Company revised base case PFS curves for CP and dostarlimab + CP

Abbreviations: CP, carboplatin and paclitaxel; PFS, progression-free survival.

Figure 2. Hazard rate plot over time based on company's revised PFS curves

Abbreviations: CP, carboplatin and paclitaxel.

2.7 Updated subsequent treatment proportions based on the IA2 data cut

The company updated the proportion of patients on subsequent treatment to be based on the IA2 data cut (Table 5) to ensure that outcomes and costs in the model are all aligned. Please see the EAG report for the subsequent treatment data from IA1.

For the dostarlimab + CP arm, the company redistributed the proportion of patients in RUBY-1 who received subsequent immunotherapy ( ) across the chemotherapy regimens to ensure subsequent treatment costs are reflective of UK clinical practice. The adjustment factor for each chemotherapy regimen was calculated based on the percentage usage of each chemotherapy regimen out of all the chemotherapy regimens and then this percentage was applied to the

proportion of patients who had immunotherapy. The adjustment factor for each chemotherapy regimen was then applied to the original proportion to estimate the adjusted proportions, presented in Table 5. The EAG considers the company's approach to the redistribution of immunotherapy across the chemotherapy regimens to be reasonable.

The EAG notes that based on the IA2 data cut, the proportion of CP patients receiving an immunotherapy is [redacted] estimated from the IA1 data cut (48.8%). It is this difference in the proportion of CP patients on pembrolizumab with lenvatinib that is causing the difference between the EAG's base case ICER ([redacted]) presented in the main EAG report and the company's revised base case ICER ([redacted]). The EAG notes that, based on advice from the NHS England Cancer Drugs Fund (CDF) lead, it was expected that the estimate of 48.8% of CP patients receiving pembrolizumab with lenvatinib at second line, based on RUBY-1 IA1 data, was not far from what would be expected in the real world. As such, a difference of [redacted], may not be unreasonable.

In their original submission, the company included a proportion of patients who received bevacizumab in RUBY-1 and redistributed this proportion across all subsequent treatments, which the EAG considered was a key issue. However, as part of their revised base case, the company has removed bevacizumab from the calculation of subsequent treatment proportions, as it is not a regimen that would be provided on the NHS for the treatment of advanced or recurrent EC with MMRp/ MSS. The EAG considers the company's amendment to be appropriate.

Table 5. Updated subsequent treatment proportions used in the model based on IA2 data cut

	Dostarlimab + CP (N=192)			CP (N=184)	
	n	%	Adj. %*	n	%
Patients receiving subsequent treatment	105	54.69%	-	134	72.83%
Carboplatin and doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin and paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin (and PLD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab and lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hormone therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CP, carboplatin with paclitaxel; IA2, interim analysis 2; PLD, Pegylated liposomal doxorubicin.

* Adjusted proportion based on the redistribution of pembrolizumab with lenvatinib. These data are used in the economic model

3 Cost-effectiveness results

3.1 Company's revised cost effectiveness results

As part of their response to the draft guidance (DG), the company made the following changes to their post-clarification base case:

- Implementation of extrapolated progression-free survival (PFS) curves based on the latest interim analysis 2 (IA2) data cut from RUBY-1, which was preferred by the committee.
- Use of time-to-treatment discontinuation (TTD) Kaplan-Meier (KM) data for both treatment arms and dostarlimab relative dose intensity (RDI) applied from cycle one (External Assessment Group [EAG] and committee preferred assumption).
- Health-state resource use for the dostarlimab + CP after three years is equal to the progression-free week 18+ health-state resource use for the CP arm of the model (EAG and committee preferred assumption).
- Removal of oral administration cost for lenvatinib (EAG and committee preferred assumption).
- Update of subsequent treatment proportions based on the IA2 data cut from RUBY-1.

Table 6 presents the company's revised base case deterministic and probabilistic cost-effectiveness results. The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around base case results. Incremental results from the company's PSA are based on 5,000 simulations.

In the base case probabilistic analysis, an incremental quality-adjusted life-year (QALY) gain of 0.75 over carboplatin and paclitaxel (CP), along with [redacted] for dostarlimab + CP, generates an incremental cost-effectiveness ratio (ICER) of [redacted]. The net health benefit (NHB) based on the probabilistic results using the £20,000 and £30,000 thresholds is [redacted] and [redacted], respectively. A positive NHB implies that overall population health would be increased because of the new intervention.

Table 6. Company's base case results (post FAC)

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
CP	[redacted]	[redacted]	[redacted]	-	-	-	-

Dostarlimab + CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.75	[redacted]
Probabilistic results							
CP	[redacted]	[redacted]	[redacted]				
Dostarlimab + CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.75	[redacted]

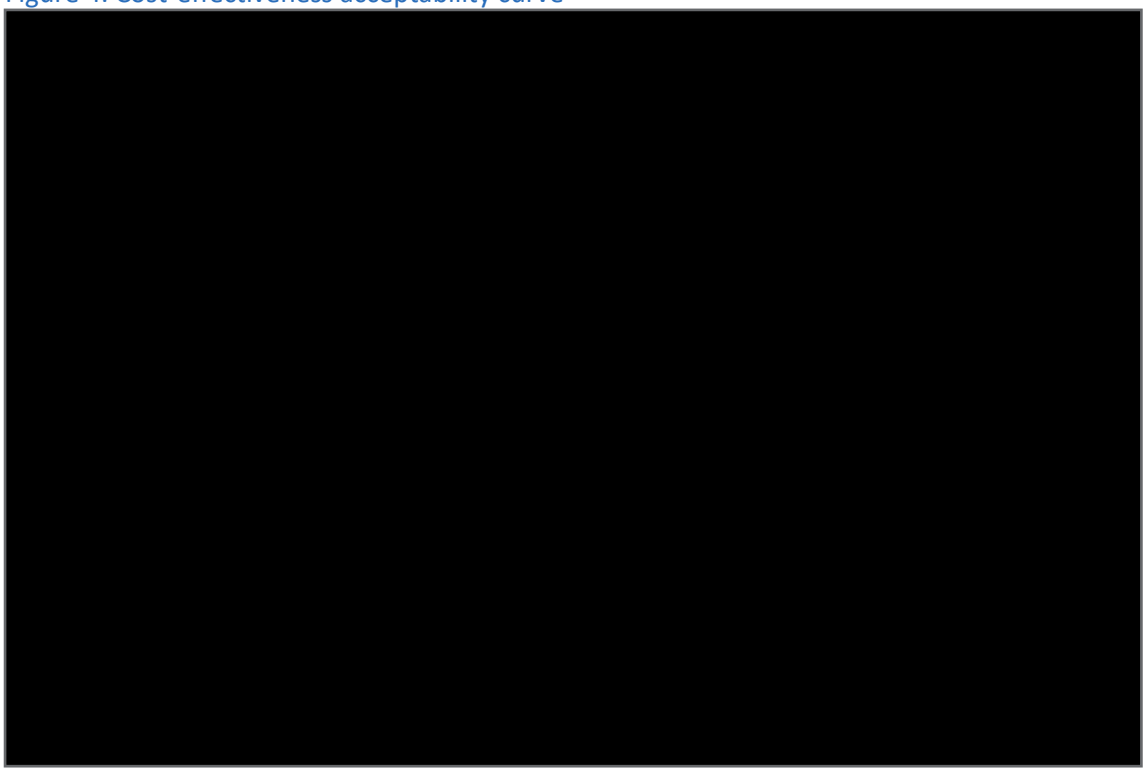
Abbreviations: CP, carboplatin and paclitaxel; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

A PSA scatterplot is presented in Figure 3 and a cost-effectiveness acceptability curve (CEAC) is presented in Figure 4.

Figure 3. Scatterplot of PSA estimates on a cost-effectiveness plane

[redacted]

Figure 4. Cost-effectiveness acceptability curve



3.2 Company's sensitivity analyses

3.2.1 One-way sensitivity analysis

The company conducted one-way sensitivity analyses (OWSAs) to assess the impact on the ICER of varying specific parameters in isolation and to identify the main model drivers. The results are illustrated in the tornado diagram presented in Figure 5.

The ICER was most sensitive to the number of outpatient visits associated with the progression-free (week 19+), outpatient visit unit cost and dostarlimab completion rates per cycle (week 10).

Figure 5. Tornado plot

3.2.2 *Scenario analysis*

The company undertook a series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters, presented in Table 7. In addition, the company conducted several additional scenario analyses requested by the External Assessment Group (EAG), also presented in the tables below.

Table 7. Company deterministic scenario analysis

No.	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
0	**Company base case**	[redacted]	0.753	[redacted]
1	PFS Curve selection: CP - Odds, k=1 flexible spline model Dostarlimab + CP - Hazards, k=3 flexible spline model	[redacted]	0.750	[redacted]
2	PFS Curve selection: CP - Normal, k=1 flexible spline model Dostarlimab + CP - Normal, k=3 flexible spline model	[redacted]	0.776	[redacted]
3	Treatment effect waning: OS - Waning from 6-8 years, all patients	[redacted]	0.660	[redacted]
4	Treatment effect waning: OS - Waning from 6-8 years, 74.2% of patients without a complete response	[redacted]	0.684	[redacted]

5	Treatment effect waning: OS - Waning from 8-10 years, all patients	[redacted]	0.711	[redacted]
6	Treatment effect waning: OS - Waning from 8-10 years, 74.2% of patients without a complete response	[redacted]	0.722	[redacted]
7	Subsequent treatment assumptions - 75% market share assumed for PEM+LEN in CP proportions	[redacted]	0.753	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year.

3.3 Additional analysis undertaken by the EAG

The company incorporated most of the EAG's preferred assumptions as part of their revised base case. However, the following assumptions were not included as part of the company's revised base case or outlined as part of the committee's preferred assumptions:

- Use of the ONS life tables from 2017-2019, as per guidance in the NICE DSU TSD 23.
- Correct nurse and GP costs sourced directly from The Unit Costs of Health and Social Care 2023 Manual.
- Unit cost of carboplatin 450 mg used for subsequent treatment cost.

The EAG has applied the above assumptions to the company's revised base case to provide the committee with cost-effectiveness results with the remainder of the EAG's preferred assumptions, presented in Table 8. The EAG considers that the scenarios had minimal impact on the company's revised base case ICER.

Table 8. Deterministic results of the EAG's scenarios around the company revised base case

	Results per patient	Dostarlimab + CP	CP	Incremental value
0	Company revised base case			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.75
	ICER (£/QALY)	-	-	[redacted]
1	ONS life tables from 2017-2019			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.75
	ICER (£/QALY)	-	-	[redacted]
2	Correct nurse and GP costs from The Unit Costs of Health and Social Care 2023 Manual			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.75
	ICER (£/QALY)	-	-	[redacted]

3	Unit cost of carboplatin 450 mg used for subsequent treatment cost			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.75
	ICER (£/QALY)	-	-	[redacted]
4	Scenario 1+2+3 (akin to EAG's preferred base case)			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.75
	ICER (£/QALY)	-	-	[redacted]

Abbreviations: CP, carboplatin and paclitaxel; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

4 References

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