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

PART 1 FOR PROJECTOR – contains no confidential information

Technology appraisal committee A [2nd meeting: 2 September 2025]

Chair: Radha Todd

External assessment group: BMJ TAG

Technical team: Sharlene Ting, Yelan Guo, Lizzie Walker, Ian Watson

Company: GlaxoSmithKline

Draft guidance consultation

Preliminary recommendation

Dostarlimab plus platinum-containing chemotherapy should not be used to treat primary advanced or recurrent endometrial cancer with microsatellite stability (MSS) or mismatch repair proficiency (MMRp) in adults when systemic treatment is suitable

DG consultation responses

- **Company:** new evidence and analyses

Dostarlimab (JEMPERLI)

- **Marketing authorisation:** with PCC for treatment of primary advanced or recurrent EC in adults who are candidates for systemic therapy (label extension to expand use in MMRp/MSS EC)
- **Company positioning:** first-line add-on to PCC
- **Comparator:** carboplatin + paclitaxel (PCC)

*Link to Appendix – Background

RECAP

Abbreviations: DG, draft guidance; EC, endometrial cancer; PCC, platinum-containing chemotherapy

Draft guidance – committee considerations

ACM1 key issues	Committee considerations / preferences	Company response
RUBY-1 generalisability	Subsequent treatment use (proportion and type) not reflective of NHS practice	Additional justification provided
Clinical effectiveness of dostarlimab uncertain	PFS: statistically significant at IA1 but not IA2 OS: not statistically significant at IA2, data immature, heavy censoring	Additional justification provided
Extrapolating PFS	Use more recent IA2 data cut than IA1	Updated to IA2
Extrapolating OS – modelling uncertain	Use IA2 data cut in analyses for OS adjusting for benefits and costs of subsequent treatments	Treatment switching analyses provided but not included in model
Treatment-effect waning	More justification for modelling approach Analyses that explore interplay of subsequent treatments on OS and waning	Additional justification and scenario analyses provided
TP53mut and p53abn subgroups	Explore cost-effectiveness analyses	Not provided

***Link to Appendix – Company model**

Abbreviations: ACM, appraisal committee meeting; IA1/2, interim analysis 1/2; OS, overall survival; p53abn, p53-abnormal; PFS, progression-free survival; TP53mut, TP53-mutated

Key issues

Issue	ICER impact	Slide
Generalisability of RUBY-1 results – subsequent treatments	Unknown	6 – 8
Subsequent treatments – impact on PFS	Small	9 – 10
Subsequent treatments – impact on OS	Unknown	11
Treatment-effect waning	Large	12 – 13
TP53mut and p53abn subgroups	Unknown	14

Small: <£3,000/QALY; Large: >£3,000/QALY

Company updated and EAG base case are largely aligned with minor differences (see slide 15)

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; p53abn, p53-abnormal; PFS, progression-free survival; TP53mut, TP53-mutated

Clinical evidence: RUBY-1 trial

RECAP

Ongoing, phase 3, multinational, double-blind, randomised (stratified by MMR status)

- **376** adults with MMRp/MSS EC (primary Stage 3 or 4 or first recurrent), ECOG PS 0 or 1
  - 64% had subsequent treatments: 55% in dostarlimab vs 73% in placebo
- 2 planned interim data cuts used in economic model:
  - **IA1** (28 September 2022) for PFS, HRQoL and TTD
  - **IA2** (22 September 2023) for adverse events and OS (54.8% data maturity)
- Results (median in months):
  - **PFS**: 9.9 in dostarlimab vs 7.9 in placebo; statistically significant at IA1, not IA2
  - **PFS2** (time to progression on first subsequent treatment or death) **at IA2**: 24.6 in dostarlimab vs 15.9 in placebo; statistically significant
  - **OS at IA2**: 34 in dostarlimab vs 27 in placebo; not statistically significant

ACM1 committee considerations

- Dostarlimab's clinical effectiveness and generalisability of RUBY-1 results to NHS uncertain
  - Subsequent treatment:
    - more people had subsequent treatment in RUBY-1 than expected in NHS
    - bevacizumab and 2L immunotherapy after 1L immunotherapy not used in NHS
    - impact on survival outcomes and treatment-effect waning uncertain
- TP53mut subgroup: better PFS benefit than overall population; exploratory analyses in p53abn and TP53mut subgroups useful

*Link to Appendix – RUBY-1 results

Key issue: Generalisability of RUBY-1 – subsequent treatment use

Company: RUBY-1's subsequent treatment use largely reflect UK clinical practice

Company

- Reiterates proportion having subsequent treatment, lines and types of regimens are largely consistent with what is expected in clinical practice except bevacizumab
  - Conventional chemotherapy most common, then immunotherapy
- Among those who had any subsequent anti-cancer therapy in placebo arm:
  - **50.7%** (68/134) had subsequent immunotherapy, many within 12 months of starting 1L → impact on post-progression outcomes captured

EAG comments

- Few people have subsequent bevacizumab and are similar between arms; unlikely to have large impact on RUBY-1 outcomes
- Subsequent immunotherapies used in both arms: proportion in placebo arm similar to UK clinical practice but not for dostarlimab arm → treatment effect of dostarlimab may be overestimated

*Link to Appendix – Subsequent treatment use in RUBY-1

Abbreviations: 1L, first line

Key issue: Generalisability of RUBY-1 – impact of subsequent treatment on clinical outcomes (1)

Company: post hoc analysis showed subsequent immunotherapies used in RUBY-1 did not improve OS in dostarlimab arm

Company: immunotherapy after 1L dostarlimab progression not permitted in NHS

- Clinical advice to company and at ACM1: immunotherapy retreatment unlikely to improve post-progression outcomes; not a concern in previous NICE appraisals
- Provided post hoc OS analysis by most common subsequent treatment used post progression (immunotherapy vs chemotherapy)

Post-hoc analysis: OS in people having subsequent treatments (PEM + LEN vs chemotherapy) at 24 months

	Overall		PEM+LEN		Chemotherapy	
	D+CP	P+CP	D+CP	P+CP	D+CP	P+CP
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: 1L, first line; ACM, appraisal committee meeting; CI, confidence interval; CP, carboplatin + paclitaxel; D, dostarlimab; LEN, lenvatinib; NR, not reported; OS, overall survival; PEM, pembrolizumab

Key issue: Generalisability of RUBY-1 – impact of subsequent treatment on clinical outcomes (2)

EAG: impact of subsequent treatment use on RUBY-1 outcomes remains uncertain

EAG comments

- 17.7% on dostarlimab had subsequent immunotherapy, potential to overestimate treatment effect than would be expected in NHS
  - Company did not provide evidence from previous trials to support its statement that retreatment with immunotherapy is not expected to improve post-progression outcomes
- Post hoc OS analysis: median OS and 24-month probability of OS [redacted] between people on [redacted]
  - Limitations: small numbers (not all subsequent immunotherapies included, only PEM+LEN), randomisation broken, no baseline characteristics of subgroups reported, unclear if disease severity, other prognostic factors or treatment effect modifiers differed

- Does the company's post hoc analysis on OS by most common subsequent treatment used post progression (immunotherapy vs chemotherapy) resolve the uncertainty in the generalisability of RUBY-1?

Abbreviations: LEN, lenvatinib; OS, overall survival; PEM, pembrolizumab

Key issue: Subsequent treatment – impact on PFS (1)

Company: PFS in dostarlimab arm not biased in favour of those having subsequent immunotherapies

Company

- Dostarlimab increased time between PFS and PFS2 despite greater use of subsequent immunotherapy in placebo arm
  - Dostarlimab + CP median [redacted] months vs Placebo + CP [redacted] months; HR [redacted], 95% CI [redacted], p=[redacted]
- Action of immunotherapies on immune system can improve post-progression
- Reiterated PFS2 was longer than PFS at IA2 (see slide 5)
- Post-hoc subgroup analysis showed shorter PFS2 in people having subsequent immunotherapy than any subsequent anti-cancer treatment in dostarlimab arm

Post hoc subgroup analysis: PFS2 at IA2 in people who had subsequent anti-cancer treatments

	Subsequent immunotherapy		Any subsequent treatment	
	D+CP (n=34)	P+CP (n=68)	D+CP (n=105)	P+CP (n=134)
Median PFS2, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
PFS2 events observed, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
PFS2 events censored	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CP, carboplatin + paclitaxel; D, dostarlimab; HR, hazard ratio; IA2, interim analysis 2; P, placebo; PFS, progression-free survival

Key issue: Subsequent treatment – impact on PFS (2)

EAG: PFS is likely more reliable estimate of dostarlimab treatment effect than PFS2

EAG comments

- PFS2 reflects time to person's second progression event, rather than length of time from controlled disease to a second progression
- Caution in interpretating post-progression benefit because of longer PFS2 vs PFS:
  - PFS2 does not isolate treatment effect of dostarlimab; includes additional effects of different subsequent treatments
  - Populations between arms not balanced: PFS2 includes everyone, not only those experienced a first progression event. Dostarlimab arm largely reflects disease that had an early failure on initial treatment. Placebo arm likely included more people whose condition progressed
- Limitations in post hoc subgroup analysis on PFS2: no explanation on choice of subsequent treatment given to people at disease progression → unclear if difference in median PFS2 is because of type of subsequent treatment or differences in patient characteristics

- Does the company's post hoc analysis on PFS2 by subsequent treatment use (immunotherapy vs any subsequent anti-cancer treatment) resolve the uncertainty in dostarlimab's treatment effect on clinical outcomes?

Abbreviations: PFS, progression-free survival

Key issue: Subsequent treatment – impact on OS

EAG: methods used for adjusted OS analysis are uncertain

Company provided:

- RWE of subsequent PEM+LEN use that showed no incremental efficacy vs chemotherapy regimens commonly used in NHS at 2L
- Treatment-switching analyses using rank-preserving structural failure time models (RPSTMs) that adjusted for 2L immunotherapy treatment: provided base case, scenario and sensitivity analyses that relaxed the common treatment effect assumption

EAG comments

- RWE: difficult to assess relative effects of subsequent immunotherapy and chemotherapy because analysis likely includes selection bias
- Inverse Probability of Censoring Weights (IPCW) models may be more appropriate than RPSTMs if immunotherapy effects vary and if it is started at different times → IPCW analysis not presented by company

- Are the OS analyses provided by the company appropriate for decision-making?

*Link to Appendix – Treatment-switching analysis

Abbreviations: 2L, second line; LEN, lenvatinib; OS, overall survival; PEM, pembrolizumab; RWE, real world evidence

Key issue: Treatment-effect waning (1)

Company maintains treatment-effect waning implicitly captured in OS curves

Background

- Company and EAG agree that treatment-effect waning captured in OS curves
- Committee: treatment-effect waning not implicitly captured in model. Additional evidence and analyses useful

Company

- Reiterated fitting independent OS curves implicitly captured treatment-effect waning as evidenced by HR for OS over time, OS estimates consistent with clinical expectation and RUBY-1 data, company's approach is consistent with previous NICE appraisals in this therapy area with less mature OS data
- Provided scenarios of gradual treatment waning with effect reduced to same level as CP arm after 3 years at 3 and 5 years after dostarlimab's stopping rule (i.e. 6-8 years and 8-10 years after starting dostarlimab) with additional waning applied to:
  - all patients
  - those without complete response (74.2% in dostarlimab arm)

NICE

Abbreviations: CP, carboplatin + paclitaxel; HR, hazard rate; OS, overall survival

Key issue: Treatment-effect waning (2)

EAG: treatment-effect waning is captured in data for observed period of RUBY-1 that informs PFS and OS extrapolation

EAG comments

- Company explained treatment-effect waning scenarios captured additional treatment-effect waning. Curves based on artificial adjustment that overrides the modelled dostarlimab + CP hazard to converge with the modelled hazards for CP at specified timepoints
- Main dostarlimab effect is to reduce risk of progression. Hazard rate plot for PFS shows treatment effect peaks at about 1 year (within observed period of RUBY-1) and then diminishes after until it is equal to CP arm. Follow-up for RUBY-1 is about 4 years and most people on dostarlimab + CP stop treatment before maximum duration of 3 years.
- Observed RUBY-1 data informing PFS and OS extrapolation capture treatment-effect waning

- Is treatment-effect waning captured in PFS and OS extrapolations? If not, how should treatment-effect waning be modelled?

Abbreviations: CP, carboplatin + paclitaxel; HR, hazard rate; OS, overall survival; PFS, progression-free survival

Key issue: TP53mut and p53abn subgroups

Company does not consider it informative to explore cost-effectiveness scenarios in p53abn or any other subgroup

Background

- Stakeholders highlighted higher incidence of p53abn subtype of MMRp EC in women of Black African or Caribbean background (more aggressive p53abn subtype associated with poorer outcomes)
- Committee noted subgroup analyses in TP53mut population showed better PFS benefit compared with overall population at IA1 – exploratory analyses in subgroups would be useful

Company

- Potential for dostarlimab to disproportionately benefit a single subgroup in MMRp/MSS population is not supported by RUBY-1 evidence, external expert opinion, underlying clinical rationale, or external evidence on this issue

EAG comments

- Unmet need for all MMRp EC does not prevent subgroup analysis (regardless of breaking of randomisation and small p53abn subgroup numbers leading to uncertainties)

- Is committee able to make a recommendation for the full population?

Abbreviations: EC, endometrial cancer; IA1, interim analysis 1; MMRp, mismatch repair proficiency; MSS, microsatellite stability; p53abn, p53-abnormal; PFS, progression-free survival; TP53mut, TP53-mutated

Summary of company and EAG base case assumptions

Company updated base case includes:

- PFS extrapolations using more mature PFS data from IA2
- Subsequent treatment proportions from IA2 data-cut
- Committee's preference from ACM1 of EAG's approach to modelling TTD, health-state resource use for dostarlimab arm and cost for oral administration of lenvatinib (excluded)

EAG comments

- Company's updated base case PFS curves based on IA2 KM data are appropriate
- Company's use of subsequent treatment proportions from IA2 and removal of bevacizumab use from calculation of subsequent treatment proportions are appropriate

EAG preferred base case

- Includes all assumptions from company's updated base case
- And corrections as in ACM1:
  - Use of 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 450mg used for subsequent treatment cost

Abbreviations: ACM, appraisal committee meeting; IA2, interim analysis 2; KM, Kaplan-Meier; PFS, progression free survival; TTD, time to treatment discontinuation

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

- Company and EAG base case ICERs: >£30,000 per QALY
- All scenarios >£30,000 per QALY

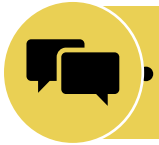
NICE

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year

Other considerations

- **Severity modifier:** QALY shortfall calculations did not meet severity modifier threshold

- **Managed access:** company has not submitted a managed access proposal. Committee can make a recommendation with managed access if:
  - technology cannot be recommended for use because evidence is too uncertain
  - technology has **plausible potential** to be cost effective at **currently agreed price**
  - new evidence that could **sufficiently support case for recommendation** is expected from clinical trials, or could be collected from people having it in clinical practice
  - data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**



- Are there any additional equality issues or uncaptured benefits to consider?

 Abbreviations: QALY, quality-adjusted life year

Summary of key issues

Issue	Slide
Does the company's post hoc analysis on OS by most common subsequent treatment used post progression (immunotherapy vs chemotherapy) resolve the uncertainty in the generalisability of RUBY-1?	8
Does the company's post hoc analysis on PFS2 by subsequent treatment use (immunotherapy vs any subsequent anti-cancer treatment) resolve the uncertainty in dostarlimab's treatment effect on clinical outcomes?	10
Are the OS analyses provided by the company appropriate for decision-making?	11
Is treatment-effect waning captured in PFS and OS extrapolations? If not, how should treatment-effect waning be modelled?	13
Is committee able to make a recommendation for the full population?	14
Are there any additional equality issues or uncaptured benefits to consider?	17

 Abbreviations: PFS, progression-free survival; OS, overall survival

NICE National Institute for Health and Care Excellence

Thank you
End of Part 1

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

Supplementary appendix

NICE National Institute for Health and Care Excellence

Background

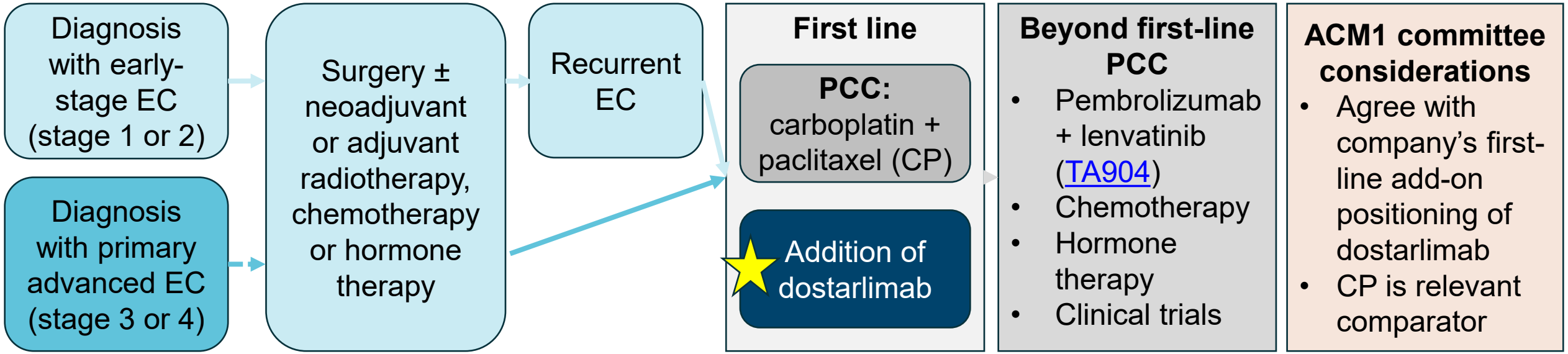
RECAP

Endometrial cancer: most common (96%) uterine cancer, starts in endometrium or uterus (lining of womb)

- 20% of new EC are primary advanced and 13% of initially treated are recurrent EC
- 75% of EC are MMR proficient (DNA repair mechanisms remain intact so mutations are corrected) or microsatellite stable (short, repeating sequences of DNA remain stable and do not change in length)
- Often incurable and associated with high symptom burden, aggressive progression, low life expectancy

Treatment pathway, company positioning and marketing authorisation of dostarlimab (JEMPERLI)

Marketing authorisation: dostarlimab in combination with PCC for treatment of primary advanced or recurrent EC in adults who are candidates for systemic therapy (label extension to expand use in MMRp/MSS EC)

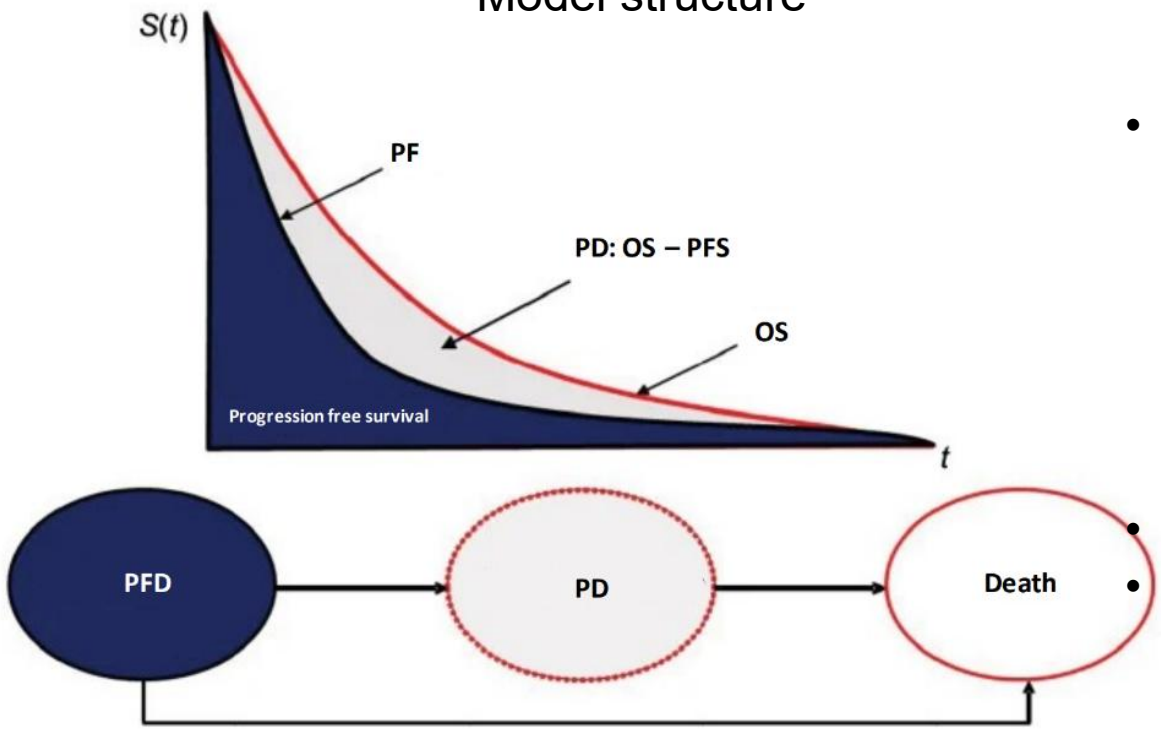


*Link to Draft guidance consultation

NICE Abbreviations: ACM, appraisal committee meeting; DNA, deoxyribonucleic acid; EC, endometrial cancer; MMR, mismatch repair; PCC, platinum-containing chemotherapy

Company's model

Model structure



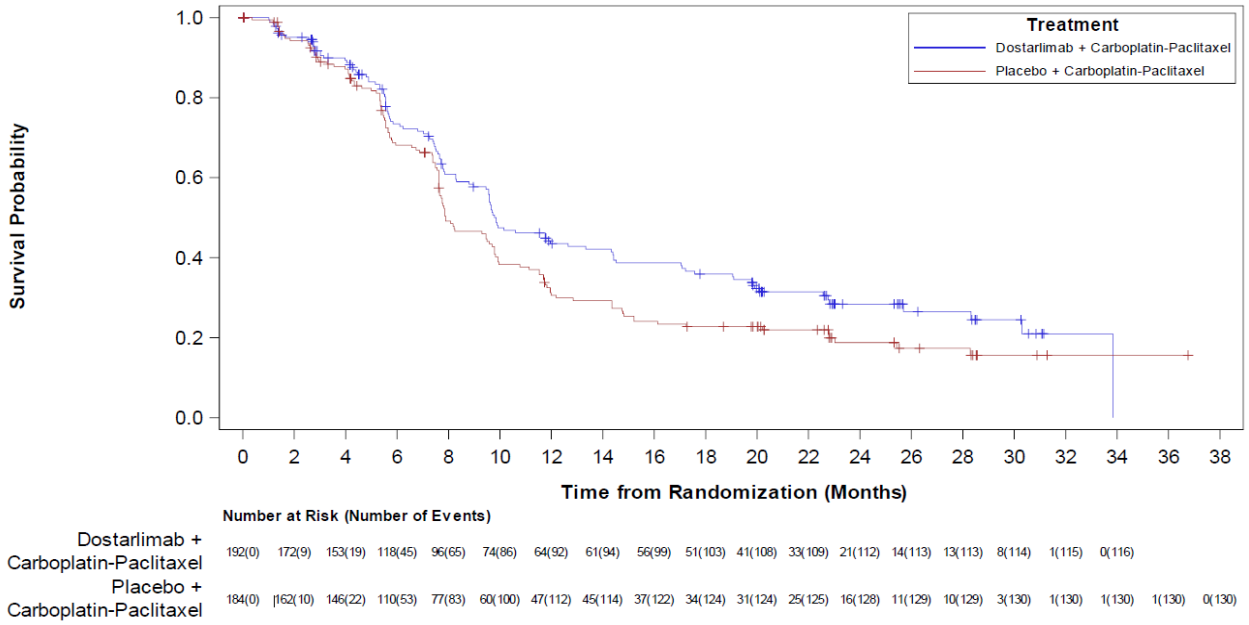
- Assumption with **greatest effect on ICER:** how costs of subsequent treatments for CP arm are estimated

- 3-state PSM: PF, PD, death
  - % based on parametric survival curves extrapolated from RUBY-1 PFS and OS data
- Constraints applied:
  - Risk of progression or mortality risk per cycle > age-matched general population mortality
  - PFS capped to OS (PFS ≤ OS)
  - TTD ≤ PFS
  - 18-week duration cap for CP arm
  - 3-year duration cap for TTD KM dostarlimab curve
- First 18 cycles: start in PF in either arm
- After 18 cycles:
  - Dostarlimab + CP have dostarlimab up to 3 years
  - Placebo + CP have routine surveillance only
- Lifetime horizon (36 years); 1-week cycle; NHS/PSS perspective, 3.5% discounting
- Baseline characteristics (RUBY-1): [redacted] years, [redacted] kg, [redacted] BSA, GFR [redacted] ml/min

*Link to DG committee considerations

RUBY-1 PFS results at IA1 and IA2 for MMRp/MSS EC

PFS KM at IA1 (Sep 2022; median follow up [redacted])



PFS KM at IA2 (Sep 2023; median follow up 37.5 months)

[redacted]

Outcome	IA1		IA2	
	Dostarlimab + CP (n=192)	Placebo + CP (n=184)	Dostarlimab + CP (n=192)	Placebo + CP (n=184)
Median PFS, months (95% CI)	9.9 (9.0 to 13.3)	7.9 (7.6 to 9.8)	[redacted]	[redacted]
Hazard ratio (95% CI)	0.76 (0.59 to 0.98)		[redacted]	
Log rank test, p value	0.02		not reported	

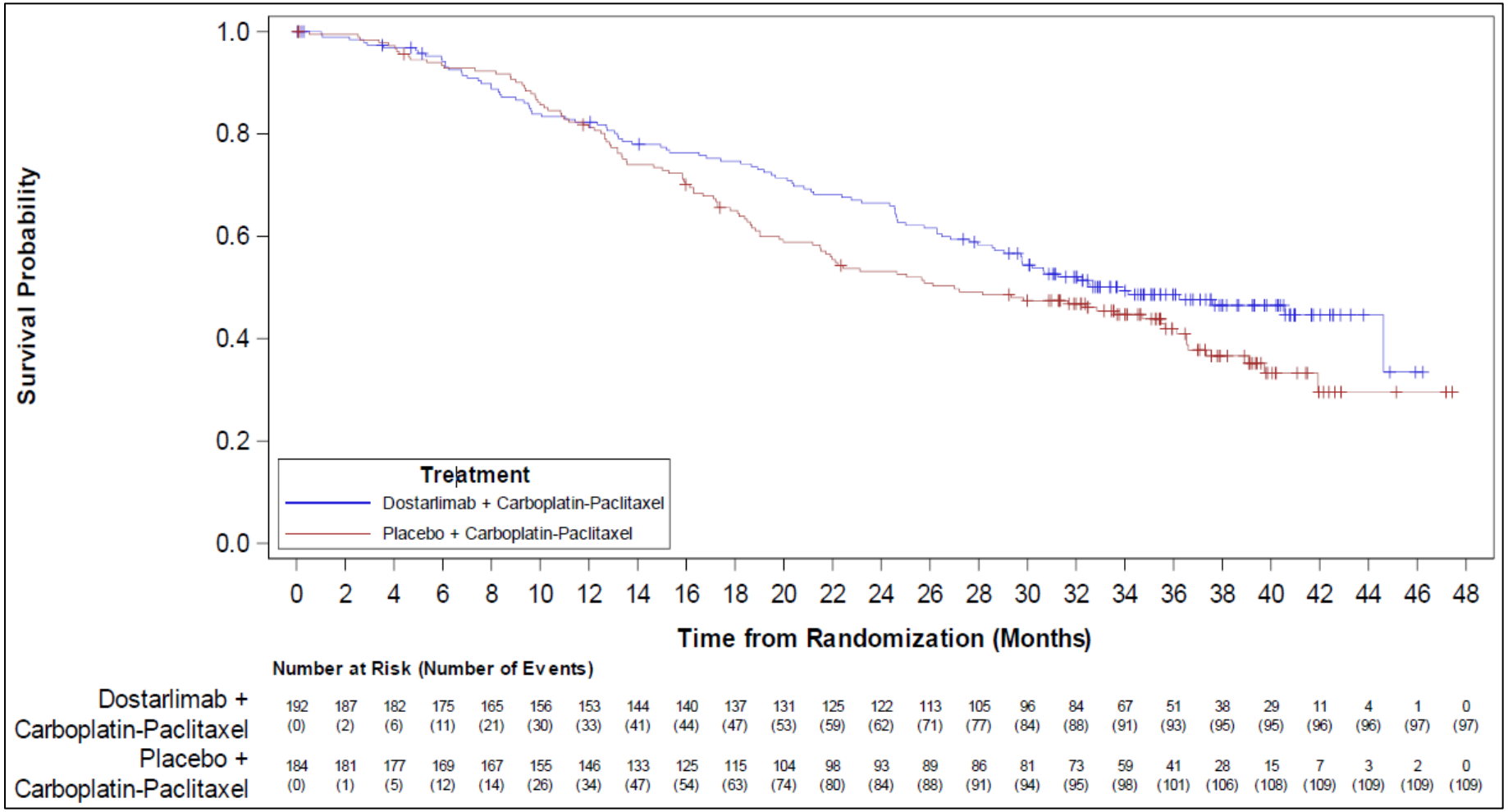
*Link to RUBY-1

NICE Abbreviations: CI, confidence interval; CP, carboplatin plus paclitaxel; HR, hazard ratio; IA1/2, interim analysis 1/2; KM, Kaplan-Meier; MMRp, mismatch repair proficient; MSS, microsatellite stable; OS, overall survival; PFS, progression-free survival

RUBY-1 OS results at IA2 for MMRp/MSS EC

RECAP

OS KM at IA2 (Sep 2023; median follow up 37.5 months)



*Link to RUBY-1

Outcome	Dostarlimab + CP (n=192)	Placebo + CP (n=184)
Median OS, months (95% CI)	34.0 (28.6 to NE)	27.0 (21.5 to 35.6)
Hazard ratio (95% CI)	0.79 (0.60 to 1.04)	
Log rank test, p value	0.049	

mismatch repair proficient; MSS, microsatellite stable; OS, overall survival

Subsequent treatment use in RUBY-1 at IA2 for MMRp/MSS EC

Subsequent treatment use in RUBY-1 for MMRp/MSS EC at IA2

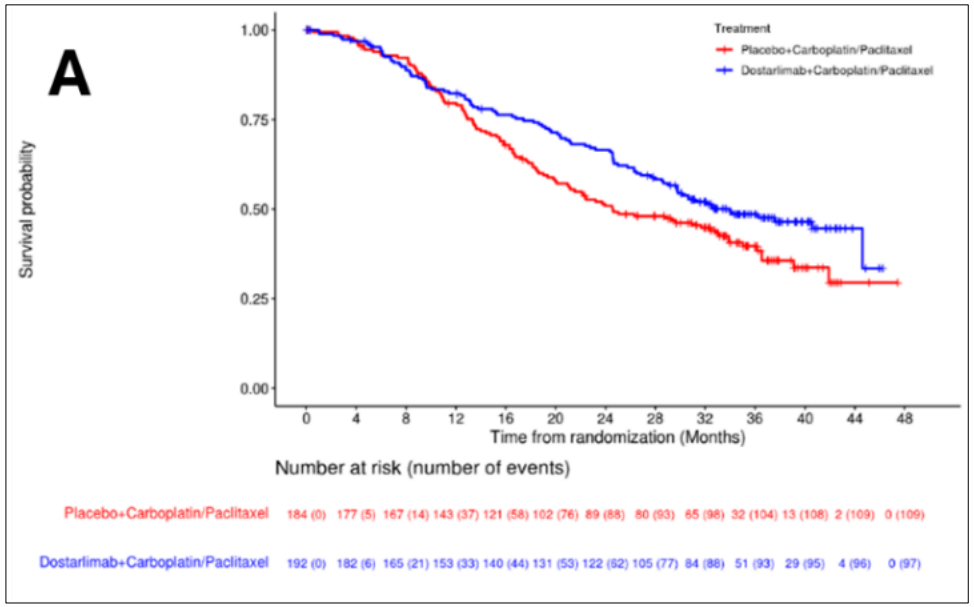
	Dostarlimab + CP (n=192)	Placebo + CP (n=184)	Total (n=376)
Any subsequent anti-cancer treatment, n (%)	105 (54.7)	134 (72.8)	239 (63.6%)
[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy	34 (17.7%)	68 (37.0%)	102 (27.1%)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

*Link to generalisability of RUBY-1 – subsequent treatments

Abbreviations: OS, overall survival;

Treatment-switching analysis – impact on OS (1)

KM curves with RPSFTM adjustment of OS for base-case (A) and scenario (B)



	Psi (95% CI)	Adjusted HR (95% CI)	AF	p-value	Unadjusted HR (95% CI)
Base-case (all subsequent immunotherapies adjusted)	[redacted]	0.76 (0.542, 1.061)	1.28	[redacted]	0.79 (0.602, 1.044)
Scenario (PEM+LEN adjusted)	[redacted]	0.77 (0.564, 1.057)	1.25	[redacted]	

Abbreviations: OS, overall survival;

*Link to Appendix – Subsequent treatment: impact on OS

Treatment-switching analysis – impact on OS (2)

	Adjusted HR (95% CI)	p-value	Unadjusted HR (95% CI)
Base case scenario	0.76 (0.542, 1.061)	[redacted]	0.79 (0.602,1.044)
Base case (Sensitivity Analysis)	[redacted]	[redacted]	
Scenario analysis (adjustment for PEM+LEN)	0.77 (0.564, 1.057)	[redacted]	
Scenario analysis (adjustment for PEM+LEN) (Sensitivity Analysis)	[redacted]	[redacted]	

NICE Abbreviations: CI, confidence interval; HR, hazard ratio; LEN, lenvatinib; PEM, pembrolizumab

*Link to Appendix – Subsequent treatment: impact on OS