Dostarlimab with carboplatin and paclitaxel for treating primary advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID3968]

For zoom – contains no confidential data

Technology appraisal committee A [5 December 2023]

Chair: Radha Todd

Lead team: G.J. Melendez-Torres, Ravi Ramessur, Richard Ballerand

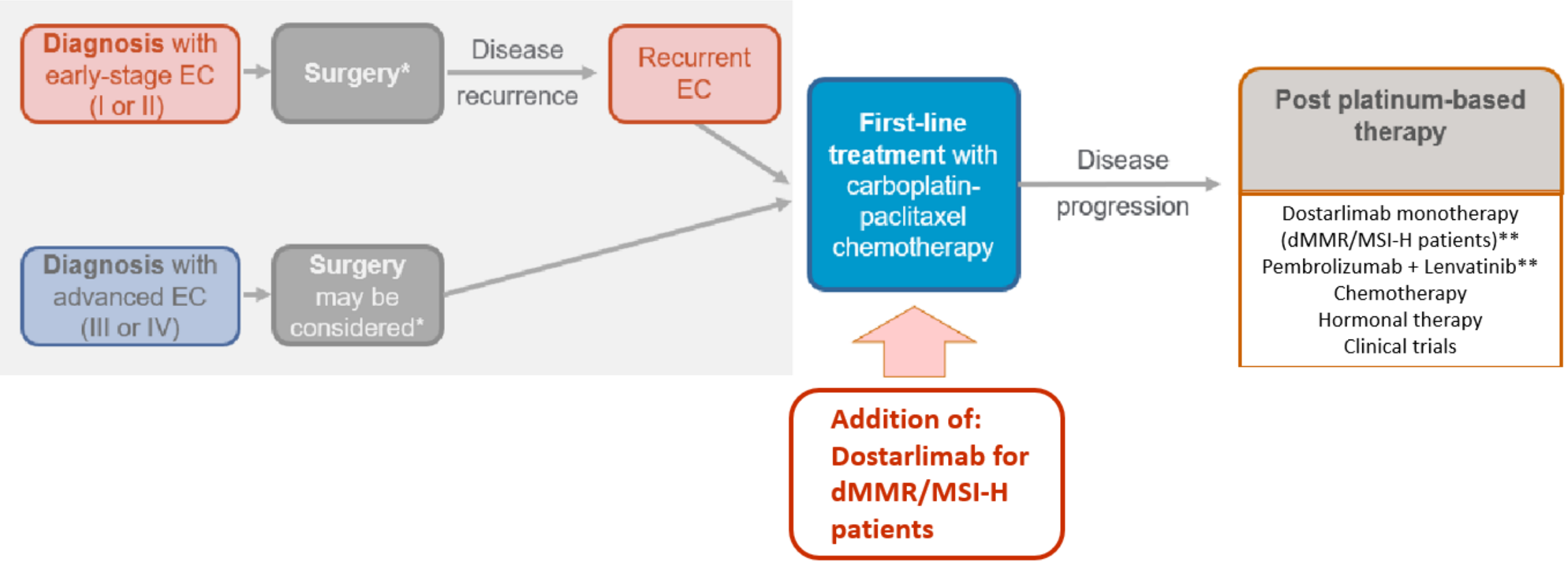
External assessment group: Warwick Evidence

Technical team: Alex Sampson, Caron Jones, Janet Robertson

Company: GSK

Treatment pathway

Dostarlimab currently only available for progressed disease. Aiming to bring forward to earlier line



*At any stage, patients may also receive neoadjuvant or adjuvant radiotherapy, chemotherapy, or hormone therapy, in addition to surgery.
**As per pivotal trial inclusion/exclusion criteria, anti-PD-L1 not used in post platinum setting if treated with anti-PDL-1 in the first-line

NICE

dMMR/MSI-H = mismatch repair deficient or high microsatellite instability; EC = Endometrial cancer;

Patient perspectives

Patients welcome a targetted treatment option at earlier stage in the pathway

Submissions from Peaches Womb Cancer Trust

- Effective treatment options at this stage are limited, leaving people feeling frustrated, hopeless and abandoned
- Women want treatment options that will increase life expectancy and give them hope of living a meaningful life for longer
- People should have equal access to the potential survival benefits of newer cancer treatments, regardless of their cancer type
- The impact of current treatments differs between individuals, but many would accept some increase in treatment side effects for improved long-term survival

"Current approach is geared towards expecting a recurrence and then adding a more effective second line treatment. It is paramount to offer patients a first line treatment which will further reduce the chance of the cancer recurring."

Clinical perspectives

Adding dostarlimab to 1st line treatment would deliver durable and meaningful clinical benefits

Submissions from clinical experts:

- Urgent need to improve survival in this patient group (median OS typically <2yrs)
- Data shows durable benefit from dostarlimab when compared to chemotherapy alone - reported benefits likely to continue with additional follow-up
- Some additional resource/capacity implications if recommended (longer chair time, additional dostarlimab monotherapy maintenance cycles and monitoring for IO-related AEs)
- Data on other checkpoint inhibitors in similar population (pembro, atezo and durva) has shown large, significant improvements in PFS, indicating robustness of benefit

'Durable responses seen with first line dostarlimab are a step-change in the treatment of dMMR/MSI-H disease*, offering potential for long-lasting disease control and extended survival'*

AE = adverse events; dMMR/MSI-H = mismatch repair deficient or high microsatellite instability; IO = immuno-oncology; OS = overall survival; PFS = progression free survival;

Equality considerations

Widespread access to more effective treatment could help address inequalities

- Black ethnic groups have substantially higher mortality rates for endometrial cancer mortality than other ethnic groups in the UK
- Access to innovative treatment on the NHS for late-stage disease can help address severe inequalities in survival outcomes by ethnicity or socio-economic deprivation

Key issues

OS benefit has the largest impact on cost effectiveness estimates

Issue	Resolved?	ICER impact	ICER impact
No comparison provided with pembrolizumab + lenvatinib	For discussion	Unknown	?
RUBY-1 doesn't provide reliable estimate of the benefit in dMMR/MSI-H subgroup	For discussion	Unknown	?
Lack of efficacy in people with stage III disease	Unable to resolve	Unknown	?
Uncertain degree of PFS benefit	For discussion	Small	↑
Uncertain degree of OS benefit	For discussion	Large	↑↑↑
Underrepresentation of adverse events	For discussion	Small	↑
Unknown use, costs & effects of subsequent therapies	For discussion	Small	↑

dMMR/MSI-H = mismatch repair deficient or high microsatellite instability; OS = overall survival; PFS = progression free survival;

Decision problem

A comparator could not be considered due to small sample size

	Final scope	Company	EAG comments
Population	Adult patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer	Adult patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer **and who are candidates for systemic therapy** (*matches MA*).	No specific criteria for 'candidate for systemic therapy.' Submission based on low potential for cure by radiotherapy or chemo.
Intervention	Dostarlimab with platinum-containing chemotherapy	As per scope	Appropriate
Comparators	• Platinum-based doublet For people who had neoadjuvant or adjuvant platinum-based doublet chemotherapy: • Pembrolizumab + lenvatinib	• Platinum-based doublet – Carboplatin and paclitaxel Very low numbers of people received prior platinum containing doublet chemotherapy (n=10). No relevant published evidence from KEYNOTE-775.	Agree insufficient evidence to consider people who had neoadj/adj. platinum-based doublet chemotherapy.

dMMR/MSI-H = mismatch repair deficient or high microsatellite instability; MA = marketing authorisation;

Decision problem

Subgroups could not be considered due to small sample size

	Final scope	Company	EAG comments
Subgroups	• Local vs metastatic recurrence • People who had primary debulking surgery vs people who have not	• Not provided due to small sample size	Subgroups may correlate with treatment efficacy or prognostic outcomes.
Outcomes	• Progression-free survival • Overall survival • Response rates • Duration of response • Adverse effects of treatment • Health-related quality-of-life	As per scope, plus: • disease control rate • time to second objective disease progression	Appropriate

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Clinical trial 1 baseline characteristics (dMMR/MSI-H)

EAG noted people in placebo arm were older, had higher BMI but better ECOG performance status

	Dostarlimab plus CP (N=53)	Placebo plus CP (N=65)
Median Age	61.0	66.0
Age >=65	23 (43.4)	35 (53.8)
Median BMI	30.55	35.50
ECOG Performance Status, n (%) • **0** • **1**	 28 (53.8) 24 (46.2)	 39 (60.0) 26 (40.0)
Disease status		
Primary stage III	10 (18.9)	14 (21.5)
Primary stage IV	16 (30.2)	19 (29.2)
Recurrent	27 (50.9)	32 (49.2)

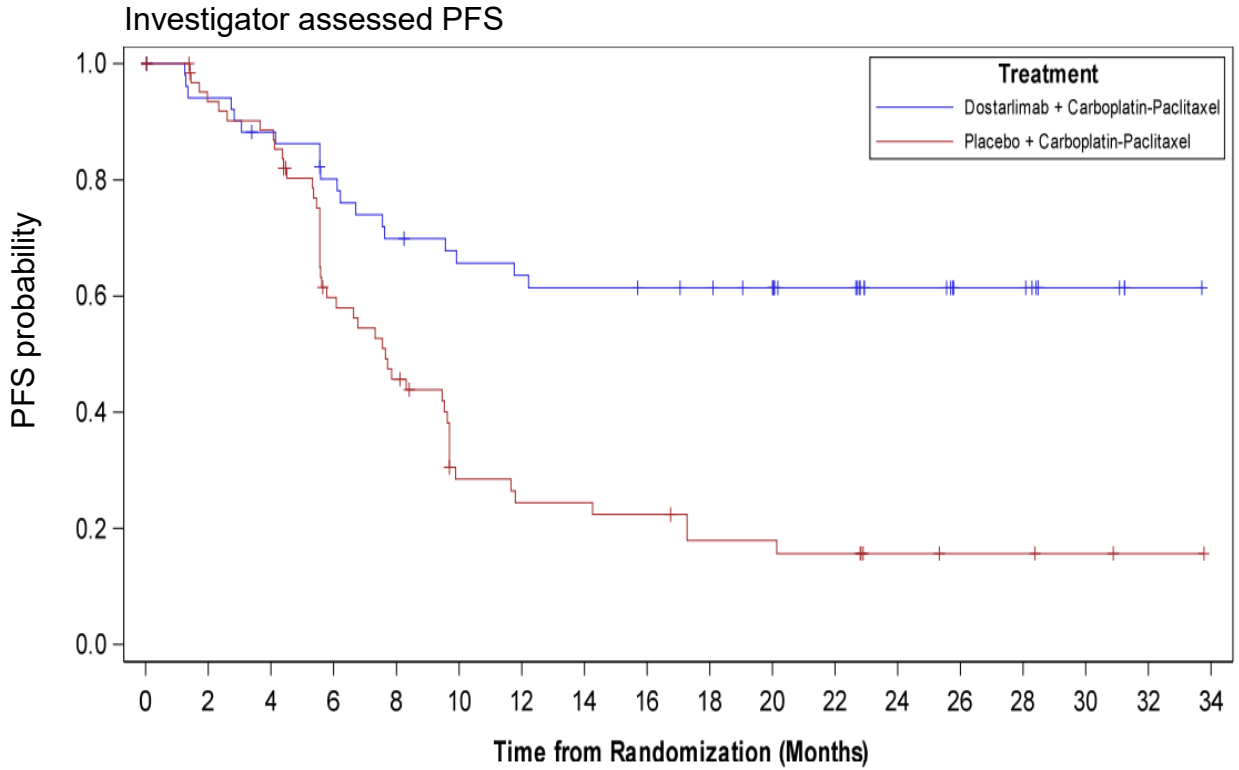
EAG comments:

- Unclear if randomisation was appropriate for dMMR/MSI-H subgroup
- Differences between arms in some potential prognostic factors
  - BMI higher in placebo arm
  - Proportion aged ≥65yrs higher in the placebo arm
  - Proportion with ECOG PS 1 is higher in the dostarlimab arm
  - Imbalance in number of participants in each arm - some moved into/out of dMMR/MSI-H group post-randomisation. Characteristics unknown.
- Impact of these differences on estimate is unclear
- PFS and OS hazard ratios were stable when adjusted for weight/age differences
- Differences in age and ECOG score make generalisability uncertain

BMI = body mass index; dMMR/MSI-H = mismatch repair deficient or high microsatellite instability; ECOG = Eastern Cooperative Oncology Group; OS = overall survival; PFS = progression free survival;

Clinical trial results: PFS (dMMR/MSI-H)

Dostarlimab extends PFS compared to placebo



Numbers at Risk

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

- Dostarlimab reduced risk of progression or death by 72% vs placebo
- PFS plateaued at ~12mths in the dostarlimab arm
- Median PFS not reached in dostarlimab arm

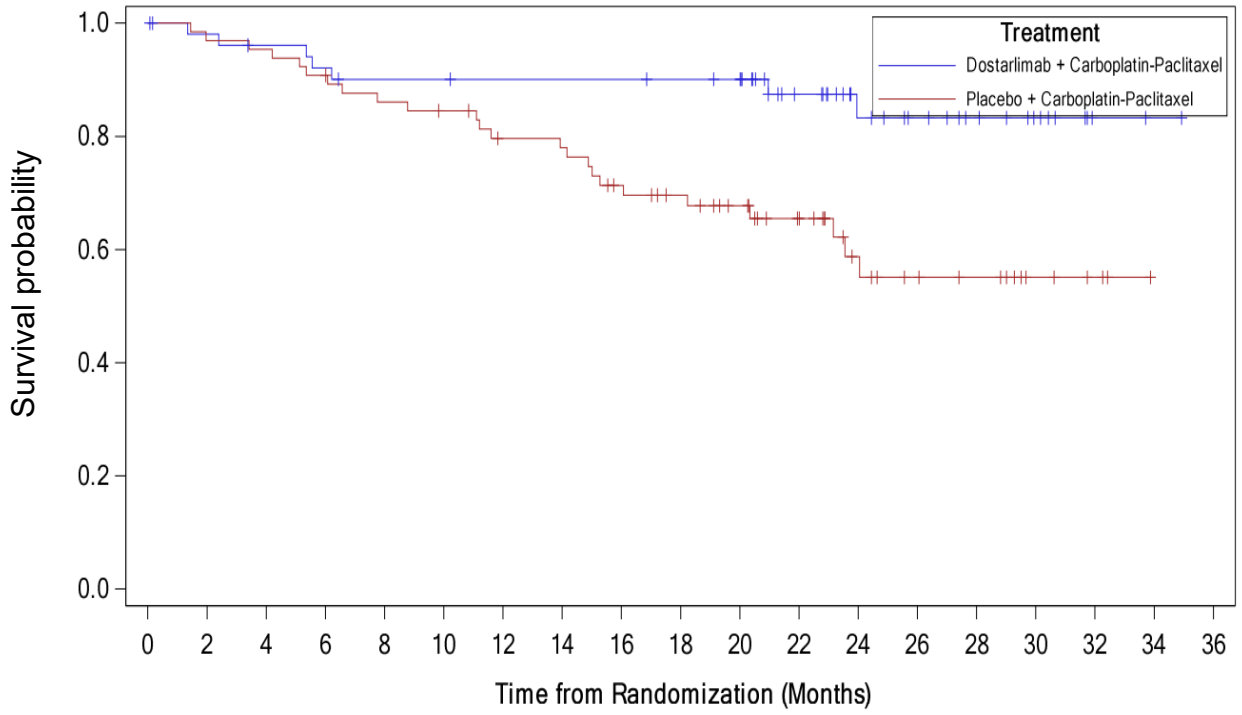
	Dostarlimab plus CP (N=53)	Placebo plus CP (N=65)
Events observed (progression or death)	19 (35.8%)	47 (72.3%)
PFS; Month 12 (95% CI)	[redacted]	[redacted]
Hazard ratio (95% CI)	0.28 (0.16, 0.50) p-value <0.0001	

NICE

CI = confidence interval; CP = carboplatin plus paclitaxel; dMMR/MSI-H = mismatch repair deficient or high microsatellite instability; PFS = progression free survival;

Clinical trial results: OS (dMMR/MSI-H)

Dostarlimab extends OS vs. placebo but confidence intervals wider than PFS



Numbers at Risk

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

- Dostarlimab reduced risk of death by 70% vs placebo
- Separation of the survival curves began around 6 months (due to plateau in dostarlimab arm)
- OS data 26% mature, with wide confident intervals

	Dostarlimab plus CP (N=53)	Placebo plus CP (N=65)
Events observed	7 (13.2%)	24 (36.9%)
OS; Month 12 (95% CI)	[redacted]	[redacted]
Hazard ratio (95% CI)	0.30 (0.13, 0.70) p-value [redacted]	

Additional outcomes covered in backup slide

NICE

CI = confidence interval; CP = carboplatin plus paclitaxel; dMMR/MSI-H = mismatch repair deficient or high microsatellite instability; OS = overall survival; PFS = progression free survival;

Cost effectiveness

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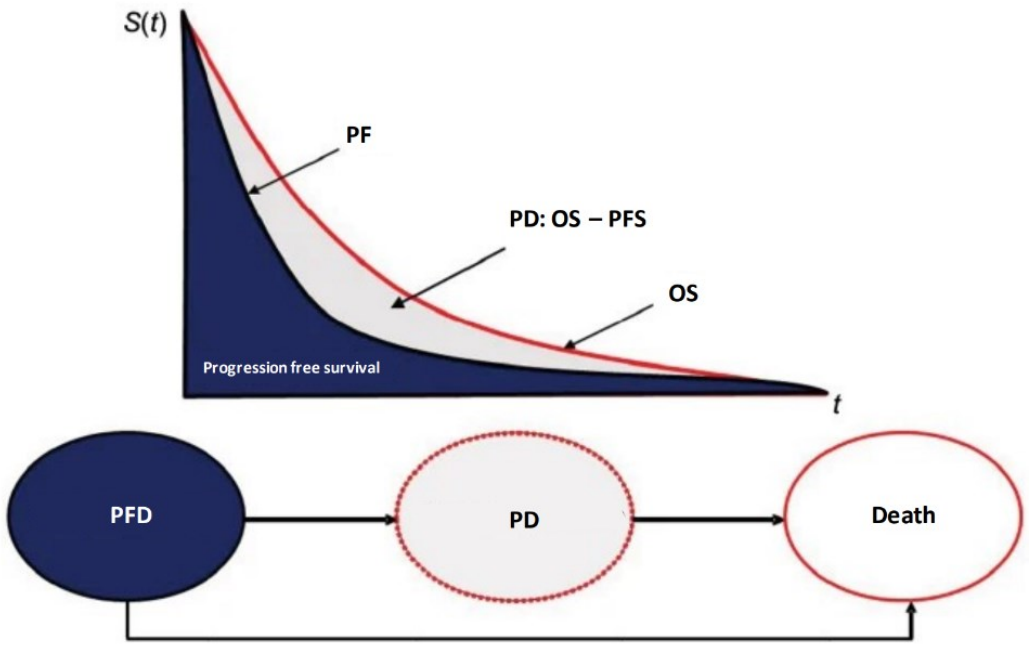
Company's model overview: Partitioned Survival model

EAG says model structure is appropriate

- 3 health states (progression-free survival, post-progression survival, and death)



Area	Company assumptions/sources
Time horizon	Lifetime [redacted]
Source of clinical effectiveness data	RUBY-1 (dMMR/MSI-H)
Source of AEs	RUBY-1 (ITT)
Source of utilities	RUBY-1 (ITT)
Source of resource use	Clinical opinion and RUBY-1
Source of costs	BNF, NHS reference costs, PSSRU
Severity Modifier	No
Treatment waning	No
Stopping rule	3 years

BNF = British National Formulary; dMMR/MSI-H = mismatch repair deficient or high microsatellite instability; EAG = External Assessment Group; ITT = Intention-to-treat; OS = overall survival; PD = progressed disease; PFD = progression-free disease; PFS = progression-free survival; PSSRU = Personal Social Services Research Unit

Key issue: Suitability of trial data for estimating treatment effect

EAG questions whether trial data reflects true benefit of intervention

Background

- Population for this appraisal is dMMR/MSI-H; a pre-specified subgroup of the full RUBY-1 population

EAG comments

- Small sample size of dMMR/MSI-H population (n=118), limited follow-up, randomisation issues, lower average age at recruitment and lack of data for subgroups result in 'very high' uncertainty
- True benefit gained from dostarlimab+CP may be very different to what has been observed
- No other data sources identified
- Further follow-up from RUBY-1 combined with novel data generation would reduce the uncertainty
- Prefer to use 67.1 years as starting age (taken from UKCTOCS) as more representative of population

Company

- RUBY-1 is a direct head-to-head RCT aligned with decision problem - most robust source of evidence
- Trial met its primary endpoint - prolonging PFS for patients with dMMR/MSI-H

Is RUBY-1 trial data suitable for decision making?

CP = carboplatin plus paclitaxel; dMMR/MSI-H = mismatch repair deficient or high microsatellite instability; EAG = External Assessment Group; PFS = progression free survival; RCT = randomised control trial; UKCTOCS = United Kingdom Collaborative Trial of Ovarian Cancer Screening;

Key issue: Degree of PFS benefit

EAG assumes equal hazards when curves cross, company says treatment benefit continues

Background

Placebo arm	Agree on Odds K=2
Dosta arm	Company: Odds k=1 EAG: Weibull plus equal hazards when curves cross (placebo HR from ~5yrs)

- In company model the PFS benefit for dostarlimab is sustained for the duration of the model

EAG comments

- Sustained PFS benefit is implausible - no rationale why, among people with good responses, the long term PFS hazard rates would differ between treatment arms
- Company expert predictions for dostarlimab are much more optimistic than EAG expert predictions

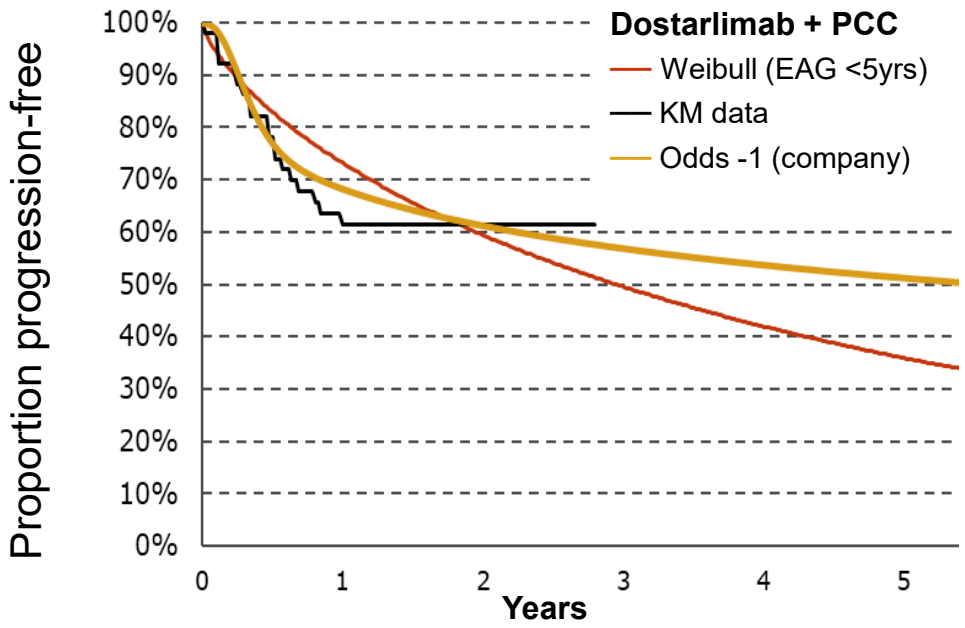
Company

- Odds k=1 has better statistical and visual fit with data than Weibull, and is aligned with adviser estimates
- Hazard rate for dostarlimab is non-monotonic, so Weibull (EAG preferred) isn't appropriate
- RUBY-1 demonstrates clear difference between progression rates and response rates for patients treated with dostarlimab vs placebo - application of equal hazards is not supported
- Log-logistic (EAG alternative) isn't suitable due to poor fit to observed data and implausible hazards in yr1

EAG = External Assessment Group; HR = hazard rate; PFS = progression free survival;

Key issue: Degree of PFS benefit

Company and EAG disagree on extrapolation approach for dostarlimab arm



Estimates of PFS for people receiving dostarlimab

Yrs	Company Advisers (mean)	EAG Adviser	Company Preferred (spline odds 1 knot)	EAG preferred (Weibull/ equal)
2	60%	60%	61%	59%
5	46%	20%	51%	36%
20	30%	10%	36%	12%

- EAG selected Weibull as most consistent with clinical expert predictions
- Company says Weibull does not fit observed data from ~18mths (applied until ~5yrs in EAG model)
- EAG model expects 12% of people to be progression-free at 20yrs, vs 36% in company model
- Expert estimates range from 10-30% progression free at 20yrs

Is it appropriate to assume equal PFS hazard rates from when curves cross (~5yrs onwards?)
Which approach to extrapolating PFS does committee prefer?

EAG = External Assessment Group; KM = Kaplan-Meier; PFS = progression free survival; PCC = platinum containing chemotherapy;

Key issue: Degree of OS benefit

Company and EAG disagree on extrapolation and waning approaches

Background

- Uncertain degree of OS benefit comprised of 3 elements:
  - Large variation in clinical adviser survival estimates
  - Disagreement on if/when to include treatment waning, given observed hazard rates
  - Different extrapolation approaches for both arms:

Placebo arm	Company: KM+log-logistic.	EAG: log-logistic
Dosta arm	Company: KM + HR applied to placebo	EAG: exponential + waning from 80wks

EAG comments

- Exponential selected due to HR observed in RUBY-1. Prefer not to use KM as tail based on very few people
- Treatment waning included as no justification of why long term HR would differ for people who respond well to either treatment
- Company OS extrapolation is inconsistent with RUBY-1 and EAG's clinical expert says its implausible

Company

- EAG's choice of curve and the applied waning approach is overly pessimistic; Isn't evidence driven, conflicts with the observed data from RUBY-1, and doesn't align with clinical opinion or NICE Methods
- Long term difference in HRs between arms is justified; RUBY-1 shows clear benefit for dostarlimab in PFS and response rates, and long-term studies show immunotherapy has durable impact

EAG = External Assessment Group; HR = hazard rates; OS = overall survival; PFS = progression free survival;

Degree of OS benefit: Adviser estimates

Company says EAG clinical expert underestimates survival in both arms

Estimates of OS for people receiving placebo+CP

	Adviser estimates		Model estimates	
Yrs	Company Advisers' mean	EAG Adviser	Company Preferred (KM + log-logistic)	EAG preferred (log-logistic)
2	58%	60%	55%	61%
3	46%	30%	53%	47%
5	30%	10%	34%	31%
10	17%	5%	16%	14%
20	13%	3%	7%	6%

Estimates of OS for people receiving dostarlimab+CP

	Adviser estimates		Model estimates	
Yrs	Company Advisers' mean	EAG Adviser	Company Preferred (KM + HR)	EAG preferred (exponential with convergence)
2	82%	80%	83%	85%
3	76%	50%	83%	75%
5	67%	20%	72%	51%
10	53%	10%	57%	24%
20	44%	8%	39%	10%

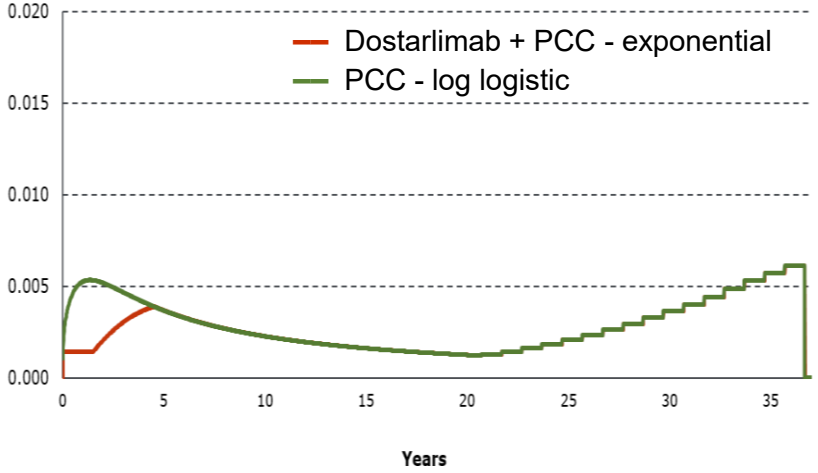
- Company says clinical estimates provided by one EAG adviser for long-term OS are highly conservative and more aligned with relapsed setting by year 5
- Large differences between EAG adviser estimates, and company adviser estimates (mean of 5 advisers)
- EAG and company base cases fall between these estimates, but with large differences (EAG models 10% of dostarlimab arm to be alive at 20 years, Company models 39%)

CP = carboplatin plus paclitaxel; EAG = External Assessment Group; HR = hazard ratio; KM = Kaplan-Meier; OS = overall survival;

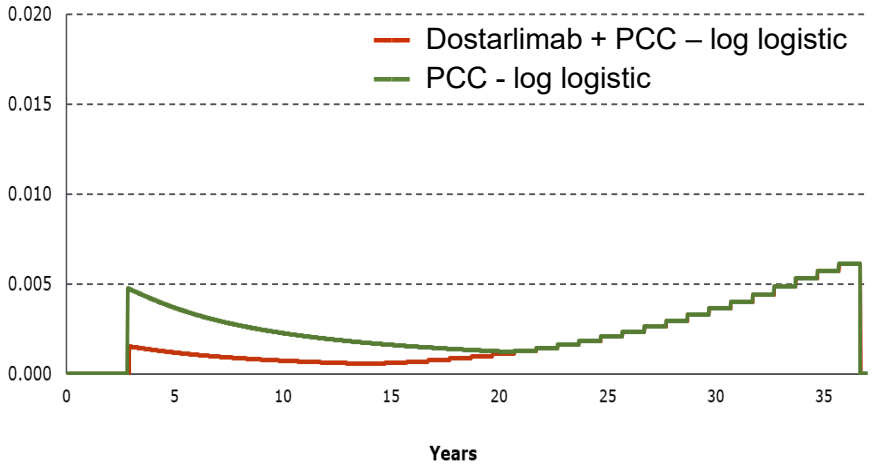
Degree of OS benefit: OS Hazard rates

Company assumes sustained treatment effect, EAG assumes waning

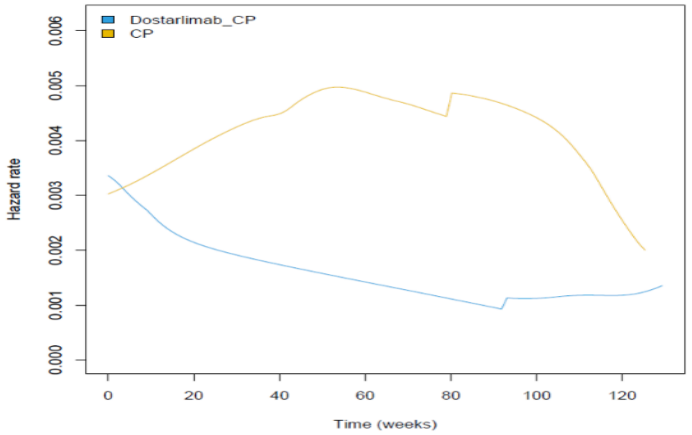
OS hazard rates (EAG preferred):



OS hazard rates (company preferred):



OS hazard rate RUBY 1 (<2.5yrs)



- In EAG base case treatment effect wanes (from 80 weeks over 3yrs) due to 'observed convergence of hazard rates in RUBY-1' - company prefers no waning
- Company says applied waning approach lacks justification and:
  - Produces a clinically implausible modelled hazard rate for dostarlimab (constant hazard <80 weeks, followed by sharp linear increase over 3yrs, before sustained decline)
  - Doesn't align with RUBY-1, which shows early and sustained response and a decline in risk over time
  - Doesn't align with previous appraisals (TA914/TA779), where waning applies after treatment has stopped

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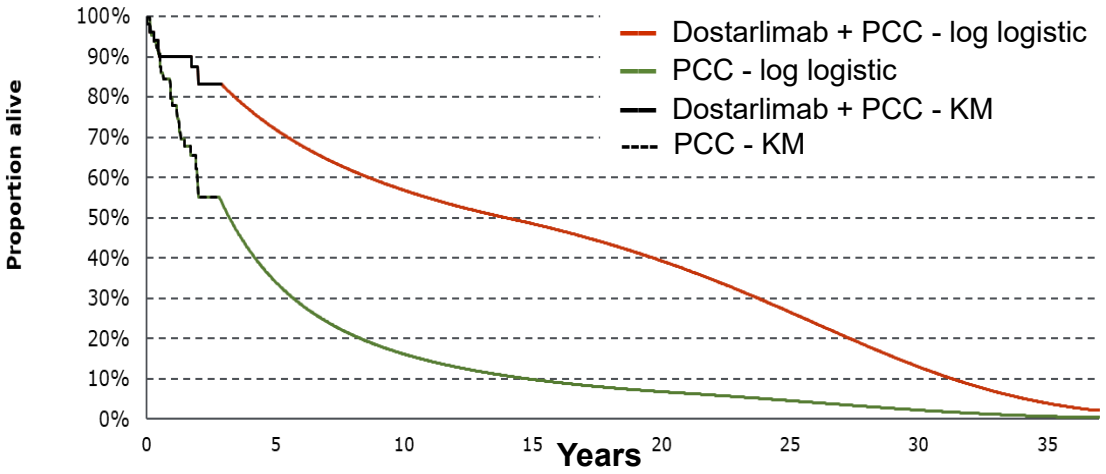
CP = carboplatin plus paclitaxel; EAG = External Assessment Group; OS = overall survival; PCC = platinum containing chemotherapy;

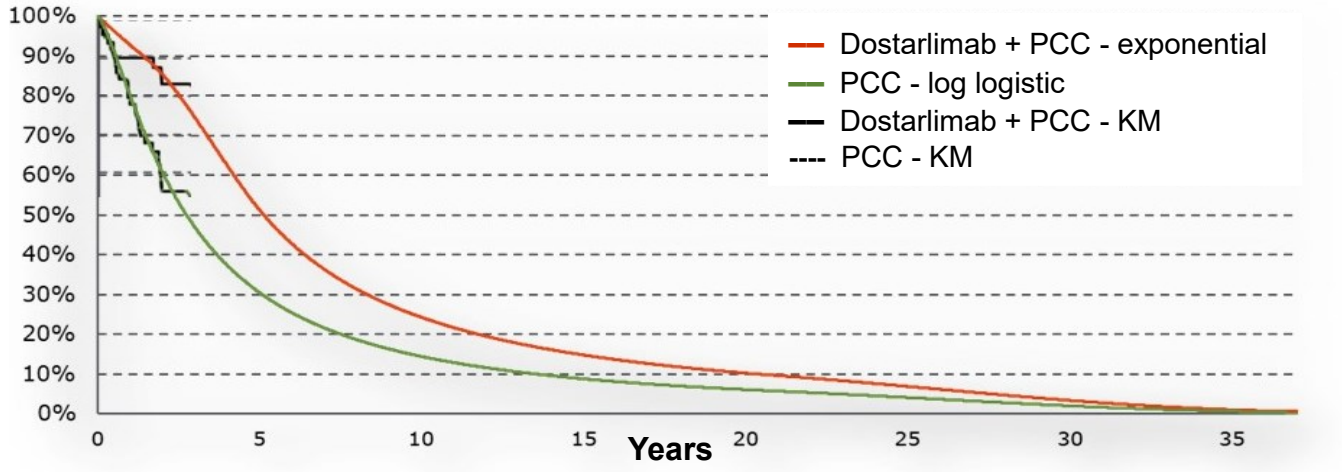
Degree of OS benefit: OS extrapolations

Preferred extrapolation curves have large impact on expected survival

Company preferred



EAG preferred



- Company prefers KM data followed by log logistic (placebo) and HR applied to placebo arm for dostarlimab
- EAG prefers log-logistic without KM data (placebo) and exponential without KM data (dostarlimab), plus treatment waning starting 80 weeks from baseline
- EAG says exponential is preferred for dostarlimab as hazard rate in RUBY-1 is constant, company says it isn't suitable as hazard rate is non-monotonic
- Company says EAG curves are too pessimistic (based on company expert opinion) and lack justification

Is it appropriate to assume treatment effect waning? If so, when and over what period?
Which approach to extrapolating OS does committee prefer?

CP = carboplatin + paclitaxel; EAG = External Assessment Group; KM = Kaplan-Meier; OS = overall survival; PCC = platinum containing chemotherapy;

Key issue: Impact of Adverse Events

EAG says AEs are under-reported and impact underestimated

Background

- Disutilities and treatment costs for AEs grade 3+ were included in company model (ITT population)
- AEs only included if ≥ 5% of the ITT population affected
- Severe and serious TEAEs were ~10% higher in dMMR/MSI-H patients receiving dostarlimab vs placebo

EAG comments

- Limited follow-up and sample size mean it is likely that AEs are under-reported and impact underestimated
- Immune related AEs were common, but were only included in company model if grade 3+ and affected ≥5% participants (EAG prefers 2% threshold)
- Ongoing monitoring costs associated with immune related AEs for those continuing with dostarlimab monotherapy have been significantly underestimated in the CEM (EAG prefers 0.23 outpatient visits per week from cycle 19+, vs 0.13 company base case)

Company

- UK clinical experts said dostarlimab was well-tolerated and there appeared to be no meaningful additional toxicity from the addition of dostarlimab to CP

Which approach for modelling AEs does committee prefer?

AE = adverse events; CE = cost-effectiveness model; CP = carboplatin plus paclitaxel; EAG = External Assessment Group; ITT = Intention-to-treat; PD = progressed disease; TEAE = Treatment emergent adverse events

Key issue: Use, costs & effects of subsequent therapies

EAG says subsequent treatment costs highly uncertain

Background

- Subsequent treatment use informed by RUBY-1 data (for lenvatinib plus pembrolizumab) and expert advice
- More use of subsequent treatment in CP arm given more patients had progressed

EAG comments

- Robust information on subsequent treatment use is not available. Data from RUBY-1 is immature and may not be generalisable to England.
- No established standard 2nd line treatment and expert opinion varies significantly
- EAG unable to validate duration of subsequent treatment use, and therefore cost - lack of detail given
- Subsequent treatments could substantially influence the cost-effectiveness (although sensitivity analyses suggests small effect on ICER)

Company

- Subsequent treatments in RUBY-1 trial not all available on NHS, so was necessary to use expert opinion
- Uncertainty is explored in scenario analyses which base subsequent use on RUBY-1 only

Is committee satisfied with company approach?

Subsequent treatment use figures

CP = carboplatin plus paclitaxel; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio;

Further key issues that can't be resolved with current data

Lack of comparison to pembrolizumab+lenvatinib

- Small number of patients may have already been treated with platinum-based chemo (before/after surgery)
- These patients would be eligible for pembrolizumab + lenvatinib (which is recommended post-platinum chemo in TA904), as an alternative to dostarlimab.
- EAG accepts that no comparison can be provided for this small group, due to a lack of available data
- It is therefore unknown whether dostarlimab is cost effective against pemb + lenv for this group
- Treatment pathway slide

Lack of efficacy in people with stage III disease

- Data shows lack of efficacy in people with stage III disease (~20% of dMMR/MSI-H population). This persists across the dMMR/MSI-H and MMRp subgroups – unclear if robust finding (or due to chance). EAG unable to exclude from analyses.

How can lack of comparison with pembrolizumab + lenvatinib, and apparent lack of efficacy in people with Stage III disease, be addressed by committee?

CP = carboplatin plus paclitaxel; dMMR/MSI-H = mismatch repair deficient or high microsatellite instability; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio;

Summary of company and EAG base case assumptions

EAG and company differ on survival curves, AEs and baseline age

Assumption	Company base case	EAG base case
Extrapolation of PFS	Dosta: flexible Odds K=1 Placebo: flexible Odds K=2	Dosta: Weibull with equal hazard from when curves cross Placebo: flexible Odds K=2
Extrapolation of OS	Dosta: KM, followed by extrapolated CP with HR applied CP: KM, followed by Log-logistic	Dosta: exponential with converging hazards over 3yrs from 80 weeks (treatment waning) CP: Log-logistic (no KM)
Disutilities and costs included for AEs	Grade 3+, with incidence of ≥5% in either arm	Grade 3+, with incidence of ≥2% in either arm
AE monitoring resource use	0.13 outpatient visits per week from cycle 19+	0.23 outpatient visits per week from cycle 19+
Baseline age	([redacted]) (RUBY-1 dMMR/MSI-H)	67.1 (from UKCTOCS)

AE = adverse events; CP = carboplatin plus paclitaxel; dMMR/MSI-H = mismatch repair deficient or high microsatellite instability; EAG = External Assessment Group; KM = Kaplan-Meier; UKCTOCS = United Kingdom Collaborative Trial of Ovarian Cancer Screening;

Cost-effectiveness results and scenarios

OS extrapolations and treatment waning have the biggest impact on cost effectiveness

All ICERs are reported in PART 2 slides due to confidential discounts

Company base-case

- AE disutilities excluded ←→
- Completion rates switched off ↑
- Utility score dMMR/MSI-H (not ITT) ↑
- Treatment wastage off ←→
- Subsequent treatment source:
  - Without lenvatinib + pembrolizumab ↑
  - with lenvatinib + pembrolizumab and dostarlimab ↑
- PFS BICR ↑
- Use full extrapolated Weibull for TTD (no KM) ↑
- Administration cost:
  - Dosta cycle 19+ admin. cost; SB12Z ↓
  - Dosta cycle 19+ admin. cost; IV biologics ↓

EAG base-case

- **Treatment waning**
  - Starts at 208 weeks, over 3yrs ↓↓
  - Starts at 260 weeks, over 3yrs ↓↓
  - Starts at 80 weeks, over 1yr ↑ ↑
  - Starts at 80 weeks, over 5yrs ↓
  - Starts at 80 weeks, over 7yrs ↓ ↓
- **PFS IA distributions**: ←→
  Dostarlimab + CP = Log-logistic
- **OS distributions:** ↑ ↑
  Dostarlimab + CP = Exponential
  CP = Exponential
- **Starting age at baseline 66.0 years** ↓
- **Outpatient visit frequency 0.13 p/wk for dostarlimab** ↓

AE = adverse events; BICR = Blinded independent central review; CP = carboplatin plus paclitaxel; EAG = External Assessment Group; ITT = Intention-to-treat; KM = Kaplan-Meier; OS = overall survival; PFS = progression free survival; TTD = time to treatment discontinuation;

Managed access

Company provided a managed access proposal – NICE says CDF is appropriate

- **Company preference is routine commissioning, but has provided managed access proposal**
- **Feasibility assessment from NICE Managed Access team concluded:**
  - Yes, managed access is appropriate
  - Additional data collection could help resolve uncertainties in long term data
  - Current OS estimates are immature but maturity is expected in 1-2 years (data cuts are event driven)
  - Further data may help inform effectiveness in relevant subgroups
  - SACT could be used to validate some outcomes, such as adverse events, or provide more data on usage, costs and effects of subsequent therapies within UK practice

Managed access checklist for committee:

The technology cannot be recommended for use because the evidence is too uncertain	**To discuss**
The technology has the **plausible potential** to be cost effective at **currently agreed price**	**To discuss**
New evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice	**Confirmed ✓**
Data could be collected within reasonable timeframe (**<5 years**) without **undue burden**	**Confirmed ✓**

If entering the CDF, how long would data collection need to be to sufficiently resolve uncertainties?

CDF = Cancer Drugs Fund; OS = overall survival; SACT = Systemic Anti-Cancer Therapy Dataset;

Summary of key issues for discussion

- Is RUBY-1 trial data suitable for decision making?
- Is it appropriate to assume equal PFS hazard rates from when hazards cross (~5yrs onwards)?
- Which approach to extrapolating PFS does committee prefer?
- Is it appropriate to assume treatment effect waning? If so, when and over what period?
- Which approach to extrapolating OS does committee prefer?
- Which approach for modelling AEs does committee prefer?
- Is committee satisfied with company approach for modelling subsequent therapies?
- How can lack of comparison with pembrolizumab + lenvatinib, and apparent lack of efficacy in people with Stage III disease, be addressed by committee?

AE = adverse events; OS = overall survival; PFS = progression free survival;

NICE National Institute for Health and Care Excellence

Thank you.

Background on Endometrial cancer

Primary advanced or recurrent endometrial cancer has a poor prognosis

Causes

- Endometrial cancer (EC) is a type of uterine cancer that starts in the lining of the uterus
- Risk factors include age, excessive oestrogen, obesity, family history, diabetes and polycystic ovary syndrome

Epidemiology

- ~9,700 new EC cases in the England every year.
    - 2,300 of those have primary advanced or recurrent endometrial disease
    - 500 of these have dMMR/MSI-H disease; a subtype of EC

Diagnosis and classification

- EC is assessed according to tumour location, volume and spread, histological and molecular subtype
- Primary advanced endometrial cancer (stages III and IV) is cancer which started in the uterus but has spread to other parts of the body. Approx 20% of cases diagnosed at this stage.

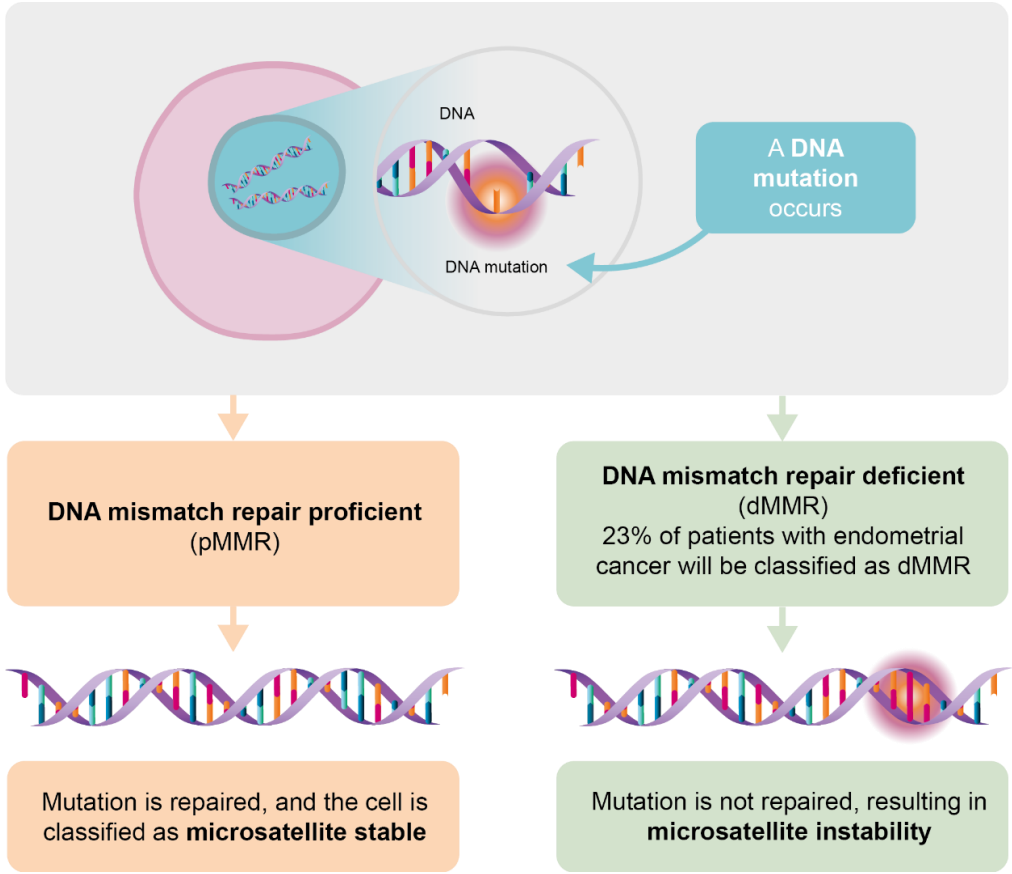
Symptoms and prognosis

- Symptoms include unusual vaginal bleeding, pelvic pain, lump in abdomen or pelvis, unintended weight loss
- 5yr survival rate is 48% for stage III cancer, 15% for stage IV, 20% for recurrent disease

dMMR/MSI-H = mismatch repair deficient or high microsatellite instability; EC = Endometrial cancer;

Mechanism of dMMR/MSI-H

dMMR/MSI-H tumours more likely to respond to immunotherapy



- dMMR/MSI-H is a molecular biomarker indicating a defective DNA repair process
- Diagnostic testing for dMMR/MSI-H is now routine [NICE diagnostics guidance DG42]
- dMMR/MSI-H cancer causes a strong immune response, with increased levels of circulating tumour infiltrating lymphocytes and high expression of immune checkpoint molecules
- dMMR/MSI-H tumours are therefore more likely to respond to immuno-oncology treatment

NICE

dMMR/MSI-H = mismatch repair deficient or high microsatellite instability;

Dostarlimab (Jemperli, GSK))

Marketing authorisation	MHRA approval granted Oct 2023: 'Dostarlimab is indicated in combination with platinum containing chemotherapy for the treatment of adult patients with mismatch repair deficient/microsatellite instability-high primary advanced or recurrent endometrial cancer and who are candidates for systemic therapy.' Treatment should 'continue until disease progression or unacceptable toxicity, or for a duration of **up to 3 years**'.
Mechanism of action	• Dostarlimab is a humanised, monoclonal antibody which binds to PD-1, a cell surface receptor expressed on activated T-cells. It blocks the PD-1 signalling resulting in an increased anti-tumour immune response and cancer cell death.
Administration	• Dostarlimab 500 mg is administered via IV infusion every 3 weeks for the first 6 cycles, followed by dostarlimab 1,000 mg administered via IV infusion every 6 weeks for subsequent cycles.
Price	The list price of dostarlimab is £5,887.33 per 500 mg vial. There is a simple discount PAS for dostarlimab.

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IV = intravenous; PAS = patient access scheme; PD-1 = programmed cell death protein 1;

Key clinical evidence comes from RUBY-1 trial

NCT03981796

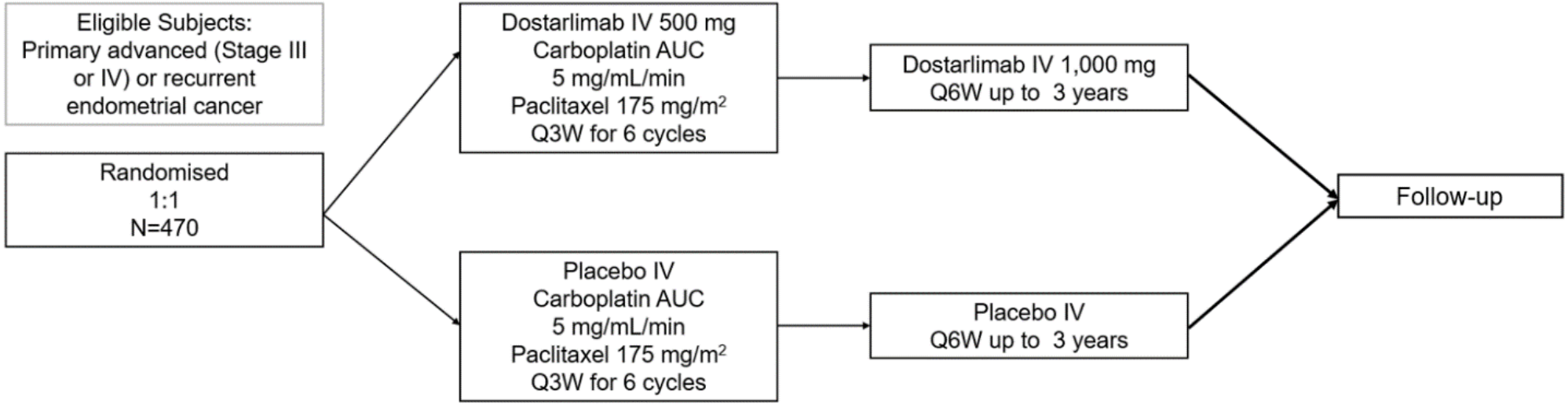
Design	Phase 3, randomised, double-blind, multicentre, placebo-controlled study
Population	People with primary stage III or stage IV endometrial cancer or first recurrent endometrial cancer, with a low potential for cure by radiation therapy or surgery alone or in combination
Pre-specified subgroup	dMMR/MSI-H (n=118)
Intervention	Dostarlimab in combination with carboplatin plus paclitaxel (CP)
Comparator(s)	Placebo in combination with CP
Median follow-up	24.79 months
Primary outcome	PFS (*investigator assessment per RECIST v1.1), OS**
Key secondary outcomes	ORR, PFS (BICR) DOR, DCR, PROs, PFS2 and safety.
Locations	US, Canada, Israel, Europe (including UK)
Used in model?	Yes

* OS is not a primary endpoint for the dMMR/MSI-H population (prespecified subgroup analysis)

BICR = Blinded independent central review; CP = carboplatin plus paclitaxel; DCR = disease control rate; dMMR/MSI-H = mismatch repair deficient or high microsatellite instability; DOR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression free survival; PFS2 = second objective disease progression; PROs = Patient reported outcomes;

Clinical trial 1 study design

Dostarlimab was added to CP, followed by dostarlimab monotherapy



- Dostarlimab treatment continued for up to 3 years, or until progressive disease/unacceptable toxicity
- Treatment beyond 3 years could be considered at investigator/sponsor discretion
- Patients with PD who were clinically stable could continue treatment until the it was no longer having clinical benefit/tolerated

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AUC = area under the curve dosing; CP = carboplatin plus paclitaxel; IV = intravenous; PD = progressed disease; Q3W = every 3 weeks; Q6W = every 6 weeks;

Other outcomes

ORR was slightly higher with dostarlimab, DCR and HRQoL were similar

	Dostarlimab in combination with CP (N=53)	Placebo in combination with CP (N=65)
Objective response rate		
n (%) (95% CI)	38 (77.6%) (63.4%, 88.2%)	40 (69.0%) (55.5%, 80.5%)
Disease control rate		
n/N (%) (95% CI)	44 (89.8%) (77.8%, 96.6%)	51 (87.9%) (76.7%, 95.0%)
Probability of DoR		
Month 12	62.1% (44.4%, 75.5%)	19.2% (8.6%, 33.1%)
Second disease progression		
PFS2	HR of 0.37 (95% CI: 0.19, 0.73)	
EQ-5D-5L Visual Analogue Scores		
Mean (SD) change from baseline to end of treatment	[redacted]	[redacted]

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CP = carboplatin plus paclitaxel; DCR = disease control rate; DoR = duration of response; HR = hazard ratio; HRQoL = health-related quality of life; ORR = objective response rate; PFS2 = second objective disease progression; SD = standard deviation;

Subsequent therapy use

Use of subsequent therapy in cost effectiveness model, by treatment arm

- Same percentages are used in company and EAG base cases
- All percentages are based on company advisory boards, except pemb+lenv which comes from RUBY-1
- Scenario analyses provided to explore impact of different figures

	Second-line treatment							
	Carboplatin and paclitaxel	Doxorubicin	Pembrolizumab and lenvatinib	Letrozole	Medroxyprogesterone acetate	Radiotherapy	Other	No treatment
Dostarlimab arm	46.9%	19.4%	0.0%	5.1%	5.1%	4.1%	0.0%	19.4%
PCC arm	43.8%	15.1%	[redacted]	4.5%	4.5%	7.6%	0.0%	[redacted]

EAG = External Assessment Group; PCC = platinum containing chemotherapy;