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Pembrolizumab with platinum-based chemotherapy then pembrolizumab maintenance for treating advanced or recurrent endometrial cancer

Technology appraisal committee A [6th May 2025]

Chair: Radha Todd

External assessment group: Birmingham Centre for Evidence and Implementation Science (BCEIS)

Technical team: George Millington, Albany Chandler, Emily Crowe

Company: Merck Sharp & Dohme

Pembrolizumab with platinum-based chemotherapy then pembrolizumab maintenance for treating advanced or recurrent endometrial cancer

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on Endometrial cancer

Primary advanced or recurrent endometrial cancer can be either mismatch repair deficient or proficient

Epidemiology

- ~9,700 new endometrial cancer cases in the England every year. 2,300 of those have primary advanced or recurrent endometrial disease

Diagnosis and classification

- Mismatch repair is a system the body uses to correct mutations in DNA which can cause cancer – endometrial cancer can be mismatch repair deficient (dMMR) or proficient (pMMR)
- dMMR tumours are more likely to have high levels of mutation, and typically respond better to immunotherapy than pMMR tumours

ACM 1 – draft guidance recommendation

Pembrolizumab with carboplatin and paclitaxel should not be used for untreated primary advanced or recurrent endometrial cancer in adults.

Committee concluded that it was not possible to establish a plausible cost-effectiveness estimate – analysis and critique of the model by MMR subgroup was required

Response to draft guidance consultation

- Company
- Clinical expert

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Key issues from ACM1 and company's response

Committee

- The committee requested separate analyses for the dMMR and pMMR subgroups. It requested further analysis of the following key issues by MMR subgroup:
  - overall survival extrapolation
  - starting age in the model
  - health state utility values
  - treatment effect waning
  - subsequent treatment mix
- The committee noted its preference for the resource use estimates from the EAG's clinical expert. But it also welcomed an analysis assuming greater resource use for the pembro with chemo arm

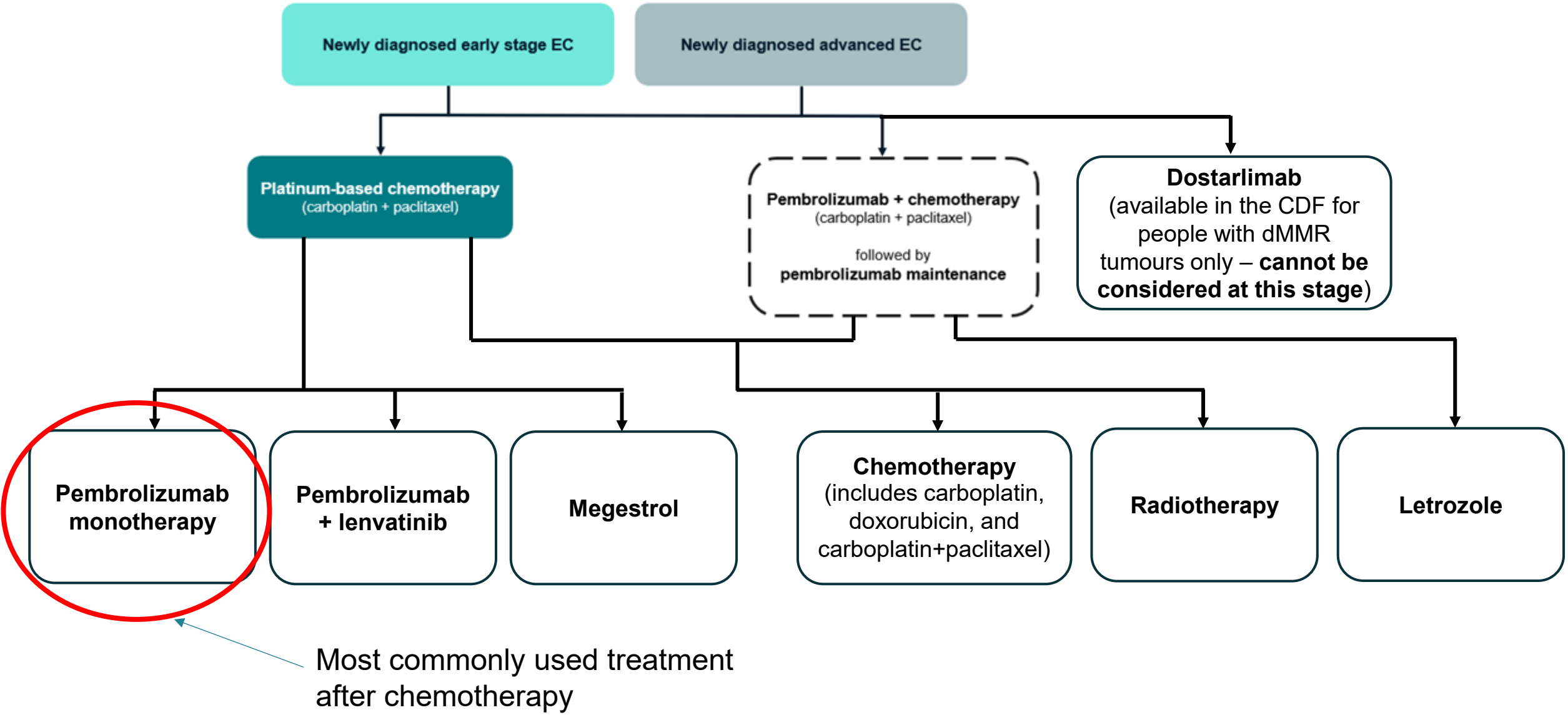
Company

- Updated base case analysis for the dMMR and pMMR cohorts including:
  - updated baseline mean age to reflect NHS England data
  - updated utility value for PFS, based on KEYNOTE-B21 for patients with pMMR endometrial cancer
  - updated subsequent treatment distributions to reflect clinical opinion from a wider range of experts
  - correction to resource use implementation to align with committee preferences
- Maintained OS and PFS extrapolations presented in original submission for the subgroups
- Maintained no treatment effect waning in its base case – provided more justification for exclusion and provided updated scenarios including applying waning to all treated and those without complete response

Abbreviations: dMMR, mismatch repair deficient; MMR, mismatch repair; OS, overall survival; PFS, progression-free survival; pMMR mismatch repair proficient

Company treatment pathway - dMMR

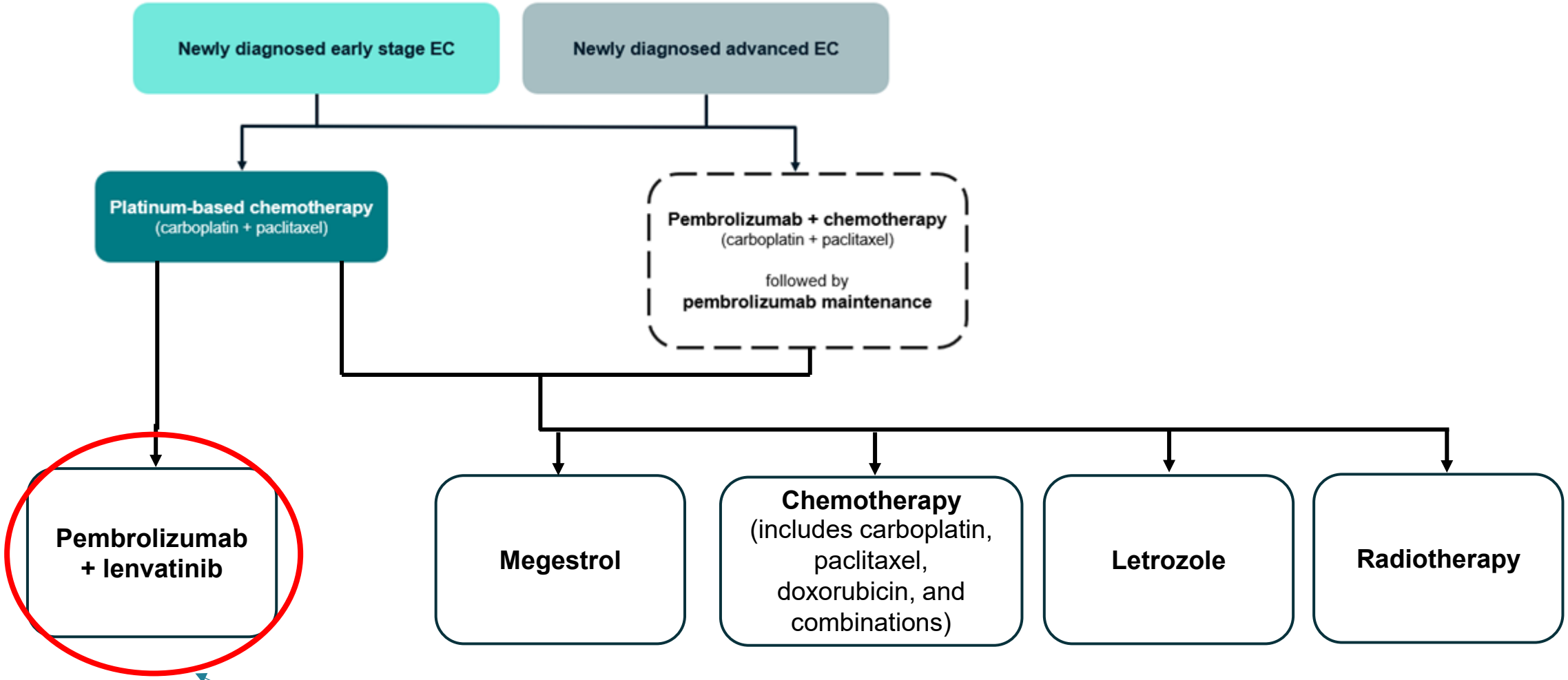
This evaluation



Abbreviations: CDF, Cancer Drug Fund; dMMR, mismatch repair deficient; EC, endometrial cancer

Company treatment pathway - pMMR

This evaluation



Abbreviations: CDF, Cancer Drug Fund; pMMR, mismatch repair proficient; EC, endometrial cancer

Equality considerations

The company highlighted a number of potential equalities issues:

- Endometrial cancer only affects people with female reproductive organs
- Incidence rates for endometrial cancer are higher in the Black ethnic group compared with the White ethnic group
- Black women are more likely to be diagnosed with the higher-risk, non-endometrioid endometrial cancer subtypes (38% of Black women with endometrial cancer were diagnosed with non-endometrioid cancer, compared to 20% of women of other ethnic groups).
- Black women are more likely to receive a late-stage diagnosis of endometrial cancer compared to women from other ethnic groups
- The diagnostic method for endometrial cancer, transvaginal ultrasound, is less reliable when fibroids are present and for high-risk, non-endometrioid endometrial cancer tumours, both of which are more common in Black women

Pembrolizumab (Keytruda, Merck Sharp & Dohme)

Marketing authorisation	• Pembrolizumab, in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of primary advanced or recurrent endometrial carcinoma in adults • MHRA MA granted in March 2025
Mechanism of action	• Pembrolizumab is a checkpoint inhibitor targeting and blocking PD-1 which is responsible for dampening T-lymphocyte immune responses in the tumour microenvironment
Administration	• For first-line treatment of primary advanced or recurrent endometrial carcinoma, the recommended dose of pembrolizumab is 200 mg every 3 weeks for 6 cycles in combination with chemotherapy, followed by pembrolizumab 400 mg every 6 weeks for up to 14 cycles as monotherapy (total of 2 years on treatment)
Price	• The list price of pembrolizumab is £2,630 per 100 mg vial • Pembrolizumab is subject to a commercial access agreement

Key issues

Extrapolation key issues	ICER impact
Choice of survival extrapolations – dMMR subgroup - PFS	Small
Choice of survival extrapolations – pMMR subgroup - PFS	Moderate
Choice of survival extrapolations – pMMR subgroup - OS	Large
Other key issues	
Treatment effect waning	Large
Health state utility values	Small

Resolved issues (company and EAG aligned)
Subsequent treatment mix
Resource use estimates
Starting age in model

Abbreviations: dMMR, mismatch repair deficient; OS, overall survival; PFS, progression-free survival; pMMR mismatch repair proficient

Pembrolizumab with platinum-based chemotherapy then pembrolizumab maintenance for treating advanced or recurrent endometrial cancer

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Key issues: Choice of survival extrapolations

EAG and company disagree on several survival extrapolations

Background

- At ACM1, the committee requested analysis of survival by MMR subgroup
- The company had already provided survival extrapolations by subgroup in its initial submission, the EAG provided their preferred extrapolations by subgroup after ACM1
- In its response to consultation, the company maintained its preferred extrapolations
- The company and EAG agree on OS extrapolations for the dMMR subgroup but disagree on other extrapolations

Subgroup	Treatment	Outcome	Company	EAG
dMMR	CT only	PFS	Two-piece gamma with 27-week cut	Generalised gamma
		OS	Exponential	Exponential
	Pembrolizumab + CT	PFS	Generalised gamma	Log-logistic
		OS	Log-logistic	Log-logistic
pMMR	CT only	PFS	1-knot odds spline	2-knot hazard spline
		OS	Gamma	1-knot hazard spline
	Pembrolizumab + CT	PFS	37-week two-piece generalised gamma	1-knot hazard spline
		OS	Log-logistic	1-knot normal spline

Abbreviations: dMMR, mismatch repair deficient; MMR, mismatch repair; OS, overall survival; PFS, progression-free survival; pMMR mismatch repair proficient

Key issues: Choice of survival extrapolations – dMMR subgroup

EAG and company disagree on choice of PFS extrapolations for the dMMR subgroup

Company

Pembro+CT arm – PFS - generalised gamma

- Both the company and EAG selections were considered plausible by company experts
- But, experts' expectation of an earlier and flatter plateau align with company's choice of generalised gamma
- EAG preferred extrapolation is too pessimistic, believes generalised gamma is more consistent with PFS assumptions raised by clinical experts in TA963 - after PFS for 5 years, risk of progression is very low

CT only arm – PFS - two-piece gamma with 27-week cut

- All standard parametric curves had very poor fits to the trial PFS data – preferred 2-piece gamma
- 2-piece gamma has better visual fit and was preferred by experts at company's advisory board

EAG comments

Pembro+CT arm – PFS - log-logistic

- Hazard shape of the log-logistic is more appropriate than gen gamma and aligned with observed data maturity
- Both options plausible – but considering lack of mature data, prefers to be cautious with extrapolations

CT only arm – PFS - generalised gamma

- Company's two-piece approach introduces additional model complexity without sufficient justification
- Given long-term uncertainty, gen gamma provides a more stable and interpretable long-term extrapolation

Abbreviations: CT, chemotherapy; dMMR, mismatch repair deficient; PFS, progression-free survival

Key issues: Choice of survival extrapolations – dMMR subgroup

EAG and company disagree on choice of PFS extrapolations for the dMMR subgroup

Company 5-year PFS = [redacted]%

EAG 5-year PFS = [redacted]%

Figure - Company and EAG PFS curve selections: dMMR subgroup

Are the company's or the EAG's choices of extrapolation most suitable?

Abbreviations: CT, chemotherapy; dMMR, mismatch repair deficient; PFS, progression-free survival

Key issues: Choice of survival extrapolations – pMMR subgroup - PFS

EAG and company disagree on choice of PFS and OS extrapolations for the pMMR subgroup

Company

- EAG's selection in both arms lack face validity. CT arm has higher PFS after 5.5 years, higher response rate and observed treatment effect for pembro+CT means this is implausible

Pembro+CT arm – PFS - 37-week two-piece generalised gamma*

- EAG highlight that 2-knot splines provided best visual fit but selected 1-knot hazard, that has poor visual fit to the observed data, especially in the tail
- Company's preferred extrapolation sits in a middle ground between the 1-knot and 2-knot splines

CT only arm – PFS - 1-knot odds spline

- 1-knot odds spline has excellent visual fit and concordance with clinical experts' predictions
- Clinical experts estimated PFS at 5 years would be 2-3%, EAG estimates >10% which is overly optimistic

EAG comments

- The curve crossing is an artefact of uncertain long-term projections - does not undermine the validity of model in the observed trial data

Pembro+CT arm – PFS - 1-knot hazard spline

- Spline models show best fit to KM and hazards, with 2-knot models having best visual fit
- 1-knot hazard spline chosen because of good visual fit and more cautious interpretation of uncertain evidence

CT only arm – PFS - 2-knot hazard spline

- Spline models strong visual fit, 2-knot models best fitting with reasonable hazard function
- Company estimates based on advisory board input rather than empirical data – long-term PFS assumptions remain speculative

*company DG response states 2-piece log-logistic; model uses generalised gamma

Key issues: Choice of survival extrapolations – pMMR subgroup - PFS

EAG and company disagree on choice of PFS and OS extrapolations for the pMMR subgroup

Figure - Company and EAG PFS curve selections: pMMR subgroup

Are the company's or the EAG's choices of extrapolation most suitable?

Abbreviations: CT, chemotherapy; PFS, progression-free survival; pMMR mismatch repair proficient

Key issues: Choice of survival extrapolations – pMMR subgroup - OS

EAG and company disagree on choice of PFS and OS extrapolations for the pMMR subgroup

Company

Pembro+CT arm – OS - log-logistic

- Log-logistic has good statistical fit, best overall visual fit to hazards, and concordance with clinician opinion
- Some pMMR patients are expected to have a very good, long-term response to pembro+CT. This is better captured using the log-logistic than the 1-knot normal

CT only arm – OS - gamma

- Gamma has best statistical and visual fit, matches clinical input - experts felt the gamma curve best represented the expected shape of the OS curve for the pMMR CT arm
- EAG's extrapolation very similar - long-term estimates deviating by approximately 1% at 2, 5, 10 and 20 years

EAG comments

Pembro+CT arm – OS - 1-knot normal

- Log-logistic plausible, but 1-knot normal spline better fit to KM data and stable hazard
- Complete response in trial is not evidence of long tail in OS without long-term follow up – log-logistic implies flatter hazard than observed in trial and may overestimate survival in later years

CT only arm – OS - 1-knot hazard spline

- 1-knot hazard has good visual fit, is consistent across outcomes, and has a stable hazard function
- Gamma also good fit and plausible option (choice has limited impact on CE estimates)

Abbreviations: CE, cost-effectiveness; CT, chemotherapy; KM, Kaplan-Meier; OS, overall survival; pMMR mismatch repair proficient

Key issues: Choice of survival extrapolations – pMMR subgroup - OS

EAG and company disagree on choice of PFS and OS extrapolations for the pMMR subgroup

Figure - Company and EAG OS curve selections: pMMR subgroup

Are the company's or the EAG's choices of extrapolation most suitable?

Abbreviations: CT, chemotherapy; OS, overall survival; pMMR mismatch repair proficient

Key issues: Treatment effect waning

Company believe treatment waning shouldn't apply, EAG believe treatment waning should apply from year 5

Background

- The company did not include TEW in its base case but included a scenario
- At ACM1, the committee requested a rationale for why TEW was smaller than expected and requested a scenario in the dMMR and pMMR subgroups where TEW applies to everyone
- TEW refers to relative efficacy between arms, not an absolute loss of pembrolizumab treatment effect

Company

- Still disagrees that TEW should be applied, more discussion of rationale in appendix
- Mechanism of action means treatment effect is maintained after stopping treatment – immune system will continue to recognise cancer cells
- Other pembro trials show continued treatment effect after stopping; KEYNOTE-868 shows no evidence of TEW
- Precedent in other endometrial cancer appraisals for no TEW (ID6317 [1L], ID6426 [1L], and TA914 [2L])
- In its previous TEW analysis, effect was small because it only applied to people without an objective response
- Conducted scenario analysis around TEW for all patients and those who did not have a complete response
- TEW in scenarios applied 7 years after stopping pembro and hazard equalled chemo only arm at 9 years to reflect committee opinion in TA914 and TA997
- Suggests alternative OS curves, with flatter tail in CT arm so hazards in both arms converge, better represent TEW (scenarios presented)

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Abbreviations: 1L, first line; 2L second line; CT, chemotherapy; dMMR, mismatch repair deficient; OS, overall survival; pMMR mismatch repair proficient; TEW, treatment effect waning

Key issues: Treatment effect waning

Company believe treatment waning shouldn't apply, EAG believe treatment waning should apply from year 5

EAG comments

- Limited follow up in KEYNOTE-868, so insufficient evidence to support sustained treatment effect
- Plausible that treatment effect continues for some time after stopping treatment, however, clinical advice in TA779 suggested patients without CR may lose response after stopping treatment
- Studies cited not strong evidence for excluding TEW: longest follow-up is in melanoma, but unknown number at risk and differences in patient characteristics, disease mechanisms and treatment efficacy
- KEYNOTE-158 (dMMR endometrial cancer) has small number at risk, with max follow-up of 5 years, so sustained treatment effect uncertain; unclear if duration of effect can be generalised to pMMR; single arm study doesn't inform relative efficacy
- Company's scenarios including waning with alternative OS curves increase ICER by 25% and 28% in dMMR and pMMR subgroups, highlighting that TEW is important driver of uncertainty, not included in base case
- Broad committee consensus for assuming gradual treatment waning effect in endometrial cancer, usually between 5-7 years and 7-9 years after starting treatment
- EAG's clinical experts suggest loss of relative treatment benefit after stopping – but one expert suggested treatment effect would stop immediately after 5 years
- Appropriate to include TEW to all patients between years 5-7 after starting pembro, as in TA904 and TA737

Should treatment effect waning be applied?
If so, should it apply to all or only non-complete responders and when should it apply?

Abbreviations: CR, complete response; CT, chemotherapy; dMMR, mismatch repair deficient; IO, immunotherapy; OS, overall survival; pMMR mismatch repair proficient; TEW, treatment effect waning

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Key issues: Health state utility values

Company present new approach to utilities, EAG prefer using the original approach

Background

- Company used endometrial cancer HRQoL data from KEYNOTE-158 (2L+, dMMR) in original base case
- ACM1 conclusion: KEYNOTE-158 data suitable for dMMR population, but may not represent pMMR population. Requested exploration of other pMMR HRQoL data sources or justifying use of KEYNOTE-158 for pMMR HRQoL

Company

- KEYNOTE-B21 most suitable source for utility values (previously untreated post-surgical patients with endometrial cancer)
  - The disease recurrence heath state from KEYNOTE-B21 is largely aligned with the model's PFS health state
  - In the pMMR group, utility for disease recurrence health state in KEYNOTE-B21 is based on >100 patients
  - Utilities for PD not available from KEYNOTE-B21, so PD utility from KEYNOTE-158 continues to be used
- It is reasonable to use the same utilities for the dMMR and pMMR subgroups, for justification, see appendix

EAG comments

- dMMR results from KEYNOTE-B21 lack face validity – may question the reliability of the pMMR values
- KEYNOTE-B21 population may have received different previous treatment and have different current treatment
- Prefers not to mix utility source without good justification - one value from pMMR population, one from dMMR
- Expert stated population alignment with KEYNOTE-158 was better – EAG prefer to maintain original utilities
- Data supports utilities for pMMR are higher than dMMR, so maybe conservative to use dMMR for both subgroups
- Differences in utilities likely to be small and have little impact on CE estimates

NICE Should the original utilities or the company's updated utilities be used?

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

PAS discounts

For dMMR, when using confidential prices, the company base case ICER is below £20,000 per QALY, the EAG base case ICER is above £30,000 per QALY

For pMMR when using confidential prices, the company base case ICER is between £20,000 and £30,000 per QALY, the EAG base case ICER is above £30,000 per QALY

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Abbreviations: dMMR, mismatch repair deficient; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; pMMR mismatch repair proficient; QALY, quality-adjusted life year

Pembrolizumab with platinum-based chemotherapy then pembrolizumab maintenance for treating advanced or recurrent endometrial cancer

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Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- 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
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

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- ✓ **Summary**

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Key issues

Extrapolation key issues	ICER impact	Slide
Choice of survival extrapolations – dMMR subgroup - PFS	Small	14
Choice of survival extrapolations – pMMR subgroup - PFS	Moderate	16
Choice of survival extrapolations – pMMR subgroup - OS	Large	18
Other key issues		
Treatment effect waning	Large	20
Health state utility values	Small	23

Resolved issues (company and EAG aligned)	Appendix slide
Subsequent treatment mix	35
Resource use estimates	37
Starting age in model	39

Abbreviations: dMMR, mismatch repair deficient; OS, overall survival; PFS, progression-free survival; pMMR mismatch repair proficient

Pembrolizumab with platinum-based chemotherapy then pembrolizumab maintenance for treating advanced or recurrent endometrial cancer

Supplementary appendix

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Key clinical trials

Clinical trial designs and outcomes

	KEYNOTE-868
Design	Phase 3 Randomised, Placebo-controlled
Population	People with advanced or recurrent endometrial cancer
Intervention	Pembrolizumab plus paclitaxel and carboplatin then pembrolizumab maintenance
Comparator	Paclitaxel and carboplatin, then placebo maintenance
Duration	18 weeks on initial treatment, then up to 84 weeks maintenance (2 years total)
Key outcomes	PFS (primary), ORR, DOR, OS
Locations	US, Canada, Japan and South Korea
Subgroups	MMR status (dMMR or pMMR)

Information concerning site of recurrence or previous primary debulking surgery was not systematically collected in KEYNOTE-868. EAG note that the NICE scope included local versus metastatic recurrence, and previous primary debulking surgery as subgroups to be considered if evidence allowed. As data was not collected, subgroup analysis was unable to be performed.

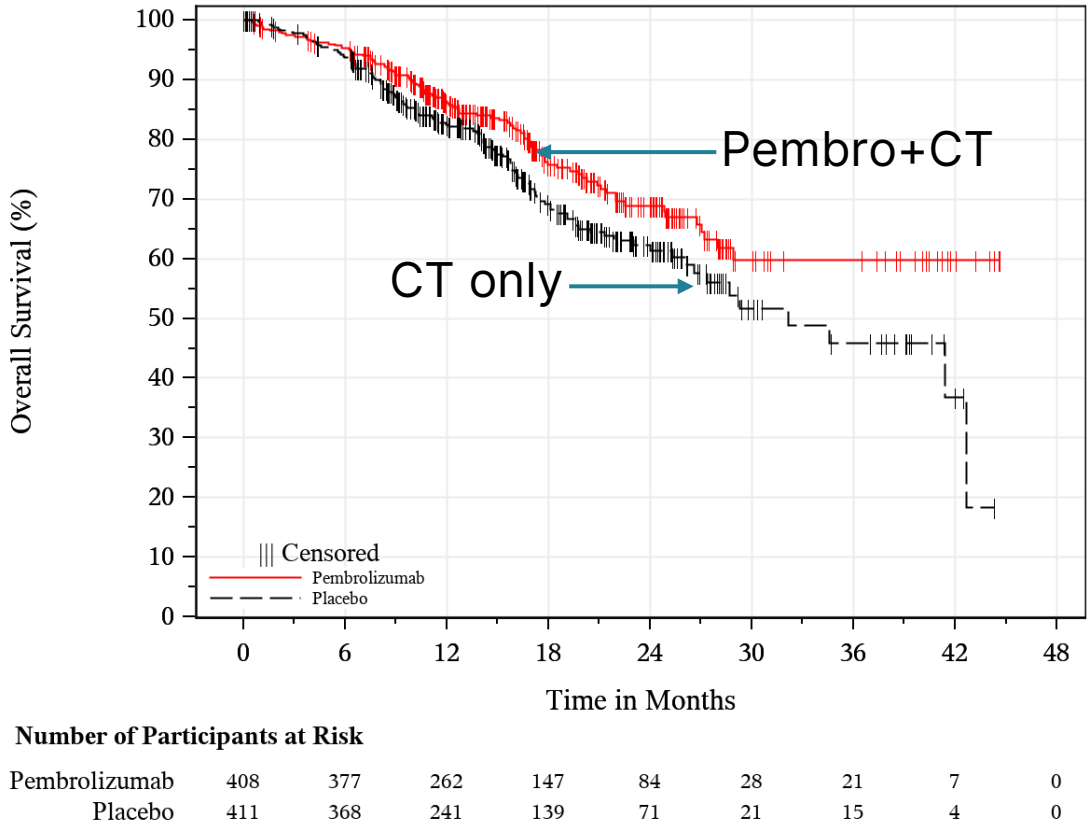
Key clinical trial results – KEYNOTE-868 – all comer population

Pembro plus chemo (n=408) improves PFS and OS compared to chemo alone (n=411)

Figure: Pembro plus chemo vs chemo only – PFS

[redacted]

Figure: Pembro plus chemo vs chemo only – OS



HR (95% CI; p-value)	[redacted]
HR (95% CI; nominal p-value), unadjusted	0.74 (0.57 to 0.97), p = 0.0153

Clinical trial results and extrapolations – by MMR subgroup

Figure - OS and PFS extrapolation for CT and pembrolizumab + CT – dMMR subgroup

HR PFS (95% CI)	[redacted]
HR OS (95% CI)	[redacted]

Table – HR of OS and PFS trial data for pembrolizumab + CT vs. CT only – dMMR subgroup

Figure - OS and PFS extrapolation for CT and pembrolizumab + CT – pMMR subgroup

HR PFS (95% CI)	[redacted]
HR OS (95% CI)	[redacted]

Table – HR of OS and PFS trial data for pembrolizumab + CT vs. CT only – pMMR subgroup

Key issues: Treatment effect waning

Company believe treatment waning shouldn't apply, EAG believe treatment waning should apply from year 5

Company

Justification for not applying TEW falls under five key points:

- The mechanism of action of pembrolizumab supports a sustained treatment effect
  - IO acts on the immune system, will continue to recognise cancer cells after treatment is stopped
- Longer term data from trials of IOs have shown a continued treatment effect post-discontinuation of treatment
  - KEYNOTE-024, KEYNOTE-158, and KEYNOTE-006 show plateauing of survival with 5, 6, and 10 years of follow-up respectively
- Observed data from the trial support a sustained treatment effect
  - KEYNOTE-868 shows no evidence of TEW, KM for OS and PFS curves separated early and remained separated in favour of pembro+CT in both MMR subgroups
- Certain survival models may already predict some degree of TEW
  - If analysis uses independently fitted models which result in hazards converging over time, then treatment effect waning over time is implicitly assumed, without any TEW explicitly being applied. Scenarios to explore this approach to TEW, with OS curves including converging hazards have been provided
- Precedent in previous appraisals of treatments for endometrial cancer
  - In the DG for ID6317, and FDG for ID6426, for other immunotherapies in 1L dMMR endometrial cancer, the committee's assumptions did not include applying TEW despite applying a treatment cap at 3 years
  - Committee for TA914 (in 2L) said TEW was potentially conservative – applying to 1L is more conservative
  - Clinical opinion in TA914 suggested a functionally cured group – contradicted by applying TEW

Abbreviations: 1L, first line; 2L, second line; CT, chemotherapy; DG, draft guidance; FDG, final draft guidance; IO, immunotherapy; dMMR, mismatch repair deficient; OS, overall survival; PFS, progression-free survival; pMMR mismatch repair proficient; TEW, treatment effect waning

Key issues: Health state utility values

Company present new approach to utilities, EAG prefer using the original approach

Company

The justification for using the same utility values for the dMMR and pMMR subgroups includes:

- The PD health state has a lower utility value than the PFS health state. Therefore, the impact of lower response rate in the pMMR subgroup is already accounted for in the model
- There were higher response rates in KEYNOTE-868 pMMR than KEYNOTE-158 dMMR, likely due to KEYNOTE-158 being conducted in the 2L (and later) setting vs. KEYNOTE-868 in the 1L setting. This indicates response rates to immunotherapy (in combination with CT) are higher when it is used 1L, regardless of MMR status. So, dMMR utilities from KEYNOTE-158 may in fact be conservative for pMMR patients in KEYNOTE-868
- HRQoL was similar for the dMMR and pMMR subgroups in KEYNOTE-775. This indicates that response rate may not be a key determinant of HRQoL at a cohort level
- Similar utilities were derived for the dMMR and pMMR subgroups in RUBY and KEYNOTE-B21 indicating there are no underlying differences in HRQoL between the MMR cohorts
- In the long-term, the PFS health state will be mostly comprised of responders. Even if dMMR have a better response to pembrolizumab, dMMR utilities should still be reflective of pMMR patients who remain progression-free in the long-term as these are also patients who had a good response

Is the company's updated approach to utilities the most suitable approach?

Abbreviations: 1L, first line; 2L, second line; CT, chemotherapy; dMMR, mismatch repair deficient; HRQoL, health-related quality of life; MMR, mismatch repair; PD, progressed disease; PFS; progression-free survival; pMMR mismatch repair proficient

Key issues: Subsequent treatment mix

EAG agrees with company's new approach to subsequent treatment mix

Background

- At ACM1, the committee concluded that subsequent treatments should be based on MMR subgroups and requested the EAG consider the company's subsequent treatment mix for the pMMR and dMMR subgroups

Company

- Sought further evidence from clinical experts to inform the subsequent treatment assumptions in UK practice
- Experts estimated 62−66% of all dMMR patients who progressed on 1L CT get IO – no changes to BC ([redacted])
- As pembro mono is not available for pMMR disease, three scenarios explored distributing the share assigned to pembro mono in the pMMR subgroups to other treatments – redistributing to all other subsequent treatments equally provided the closest match to experts' estimations for pembro + lenvatinib use (47-51%), so was used in base case
- Other treatments in the mix have been amended based on the further expert input

EAG comments

- EAG considers evidence presented and share allocation method to be appropriate
- Subsequent treatment mix now aligned with the committee's and EAG clinical expert's advice
- EAG includes company treatment mix in its base case

Is the company's updated approach to subsequent treatment mix the most suitable approach?

Abbreviations: 1L, first line; BC, base case; CT, chemotherapy; dMMR, mismatch repair deficient; IO, immunotherapy; MMR, mismatch repair; pMMR mismatch repair proficient

Key issues: Subsequent treatment mix

EAG agrees with company's new approach to subsequent treatment mix

Table: Company base case distribution of subsequent treatments

	dMMR		pMMR	
	Pembrolizumab + CT	CT	Pembrolizumab + CT	CT
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Dostarlimab	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]	[redacted]
Megestrol	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab + lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]
No active treatment	[redacted]	[redacted]	[redacted]	[redacted]

Is the company's updated approach to subsequent treatment mix the most suitable approach?

Abbreviations: CT, chemotherapy; dMMR, mismatch repair deficient; pMMR mismatch repair proficient

Key issues: Resource use estimates

EAG agrees with company's new approach to resource use

Background

- At ACM1, the CDF lead noted that, pembro may sometimes be given on a 3-weekly rather than a 6-weekly cycle
- The committee preferred the PFS resource use estimates from the EAG's clinical expert, but welcomed analysis in the pembro+CT arm reflecting a 3-weekly cycle length for pembro treatment

Company

- Consulted experts regarding resource use – while on treatment, both arms would have blood test and outpatient visit with each cycle of treatment (3-weekly [while on chemo], then 6-weekly) and CT scan every 12 weeks
- Approach to applying resource use and costs in the progression-free health state was incorrectly applied in the previously submitted model – corrected in newest model
- Pembro only maintenance phase is 6-weekly explicitly in the dosing schedule (not the case for other pembro indications) – provided scenario with 3-weekly maintenance dosing for completeness

EAG comments

- The EAG's clinical experts considered the updated resource use estimates acceptable and likely reflective of clinical practice. The EAG thus applies the company's new estimates in its revised base case.

Is the company's updated approach to resource use the most suitable approach?

Abbreviations: CDF, cancer drug fund; [pembro+]CT, chemotherapy; CT, computerised tomography; dMMR, mismatch repair deficient; PFS, progression-free survival; pMMR mismatch repair proficient

Key issues: Resource use estimates

EAG agrees with company's new approach to resource use

Table: Company average resource use in the pembro+CT arm of the model

Health state	Resource	Frequency
PFS (on treatment)	CT scan	12 weeks
	Blood tests	3 weeks (cycle 0-17) 6 weeks (cycle 18-104 [post chemotherapy])
	Outpatient visits	
PFS (off treatment)	CT scan	12 weeks (cycle 0-104) 26 weeks (cycle 105+)
	Blood tests	
	Outpatient visits	

Is the company's updated approach to resource use the most suitable approach?

Abbreviations: [pembro+]CT, chemotherapy; CT, computerised tomography; PFS, progression-free survival

Key issues: Starting age in the model

EAG agrees with company's new approach to starting age in the model

Background

- Company's starting age in the all-comer population was based on the mean age in KEYNOTE-868 (65.4 years)
- The EAG preferred the starting age used in TA963 (67.1 years)
- After ACM1 the CDF clinical lead presented the average age of people in the NHS with dMMR endometrial cancer receiving dostarlimab 1L (66 years median, 65.4 years mean) and pMMR endometrial cancer receiving pembro and lenvatinib at 2L (69 years median, 67.54 years mean)

Company

- **dMMR**: mean baseline age of dMMR participants in KEYNOTE-868 (65.7 years) almost identical to NHS data – new base case uses NHS data
- **pMMR**: NHS data relates to 2L, who are expected to be older; prefer to use mean age of pMMR population from KEYNOTE-868 (65.4 years)
- Doesn't appear to be a meaningful difference in average age of people with dMMR and pMMR disease
- Provided scenario using mean age of 67.54 years for pMMR population

EAG comments

- Accepts the company's new approach and applies the same starting ages as the company in the revised EAG base case.

Is the company's updated approach to starting age the most suitable approach?

Abbreviations: 1L, first line; 2L, second line; CDF, cancer drug fund; dMMR, mismatch repair deficient; pMMR mismatch repair proficient