For public – contains redacted information

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

Technology appraisal committee A [4th February 2025]

Chair: Radha Todd

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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 has a poor prognosis

Causes

- Endometrial cancer 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 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
- Primary advanced endometrial cancer (stages 3 and 4) 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

- Unusual vaginal bleeding, pelvic pain, lump in abdomen or pelvis, unintended weight loss
- 5yr survival rate is 48% for stage 3 cancer, 15% for stage 4, 20% for recurrent disease

Clinical perspectives

Benefits of immunotherapy are clearer in the dMMR population but the unmet need is higher in the pMMR population

Submissions from clinical expert:

- The aim of treatment is generally to improve quality of life and survival where possible, but the introduction of immunotherapy for dMMR disease is potentially improving long term survival to the point of potential cure in a significant proportion of patients (dostarlimab is currently available in the CDF)
- It is more burdensome to add immunotherapy first line to chemotherapy but clinicians should be familiar and comfortable managing patients on immunotherapy and their toxicities
- The pathway of care is not always well defined across the country, guidelines are not always specific or frequently updated
- Unclear if pMMR population will gain substantial benefit due to heterogeneity of the population - there are some pMMR tumours with biomarkers associated with especially poor prognosis - but the unmet need is higher in people with pMMR tumours in general

Abbreviations: dMMR, mismatch repair deficient; pMMR mismatch repair proficient; CDF, cancer drugs fund

Patient perspectives

Patients would welcome more treatment options for endometrial cancer

Submission from Peaches Womb Cancer Trust

- Effective treatment options at this stage are very limited
- People would like a first-line treatment which will further reduce the chance of the cancer recurring compared to chemotherapy
- Chemotherapy is seen as a poor option to many people, the side effects are challenging physically and psychologically
- While pembrolizumab can cause fatigue and thyroid issues, the side effects are less severe and more manageable than chemotherapy side effects

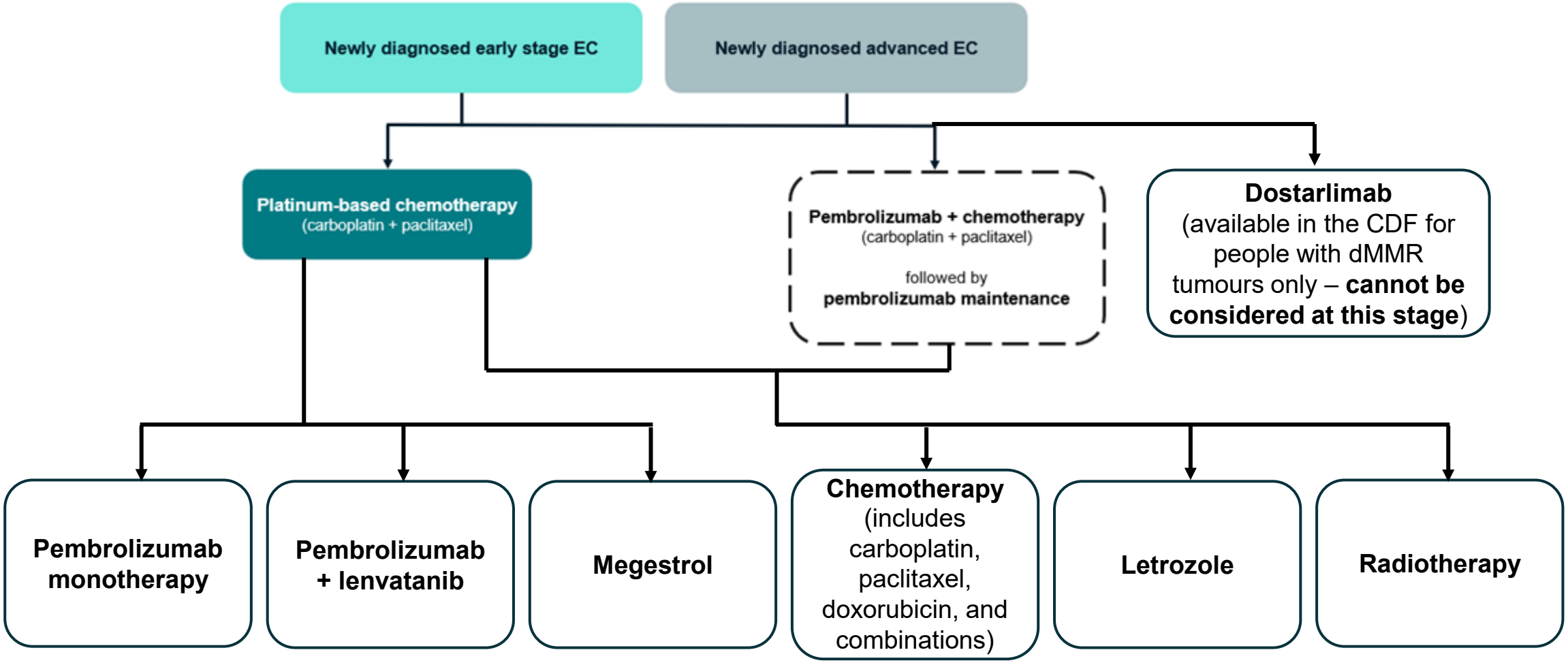
"The current approach is geared towards expecting a recurrence and then adding a more effective second-line treatment"

"my perspective of pembrolizumab has been that it has really improved my quality of life: to the extent that I feel that I was able to thrive whilst on active treatment"

Are the additional side effects associated with adding pembrolizumab to chemotherapy acceptable to patients?

Company treatment pathway

This evaluation



What are the most appropriate comparators for the technology?
Is the company's treatment pathway appropriate?

Abbreviations: CDF, Cancer Drug Fund; dMMR, dMMR, mismatch repair deficient; 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)

Anticipated 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 expected 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	• 200 mg every 3 weeks or 400 mg every 6 weeks administered as an IV infusion
Price	• The list price of pembrolizumab is £2,630 per 100 mg vial • Pembrolizumab is subject to a commercial access agreement

Key issues

Key issue	ICER impact
Representativeness of the all-comer post-hoc analyses	Unknown
Uncertain degree of overall survival benefit	Large
Representativeness of health state utilities for the all-comer population of KEYNOTE-868	Unknown
Resource use levels for pembrolizumab + CT arm underestimated in the model	Large
Uncertainty around subsequent treatment mix for CT arm	Small

Other issues (addressed in appendix slides)	
Limitations of sub-groups examined	Unknown
Starting age at baseline in the economic model	Small
Adverse events selected for costing in the model	Small
HRQoL assessed in pMMR cohort only	Unknown
Treatment waning	Small

Abbreviations: CT, chemotherapy; HRQoL, health-related quality of life; pMMR mismatch repair proficient

Key issues: Representativeness of the all-comer post-hoc analyses

EAG not convinced of suitability of post-hoc combination of pMMR and dMMR cohorts for analyses

Background

- The population in KEYNOTE-868 was pre-specified into 2 separate cohorts based on MMR status
- The company conducted post-hoc analysis which combined the pMMR and dMMR cohorts to produce an 'all-comer' ITT population
- The all-comer ITT population is used for all analysis except for AEs (which used a combined population but not ITT) and HRQoL data (pMMR cohort only in KEYNOTE-868, dMMR only included in the model)

Company

- The combined all-comer population is appropriate to reflect the decision problem, aligning with the anticipated marketing authorisation

EAG comments

- Post-hoc analyses are unplanned and retrospective, so may introduce bias or overgeneralise results
- Subgroup analyses focusing on the dMMR and pMMR cohorts separately were conducted but would prefer stratified analyses maintaining both the combination and preserving the separate cohorts
- However, clinical evidence in the KEYNOTE-868 trial is still relevant to the decision problem

Are the combined, post-hoc 'all-comer' population analyses suitable for decision-making?
Are the separate MMR subgroups more appropriate for decision-making?

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Abbreviations: dMMR, mismatch repair deficient; ITT, intention to treat; MMR, mismatch repair; pMMR mismatch repair proficient

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Key clinical trials

Clinical trial designs and outcomes

For a diagram of the study design, see appendix slide 33

	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. For more information, see appendix slide 32

Should a 2-year stopping rule be included in any recommendation?
Could the results in the missing subgroups be significantly different than the overall population?
Could significantly different results in these groups impact decision making?
Does the lack of UK patients in the trial affect generalisability of the results to the NHS?

Key clinical trial results – KEYNOTE-868

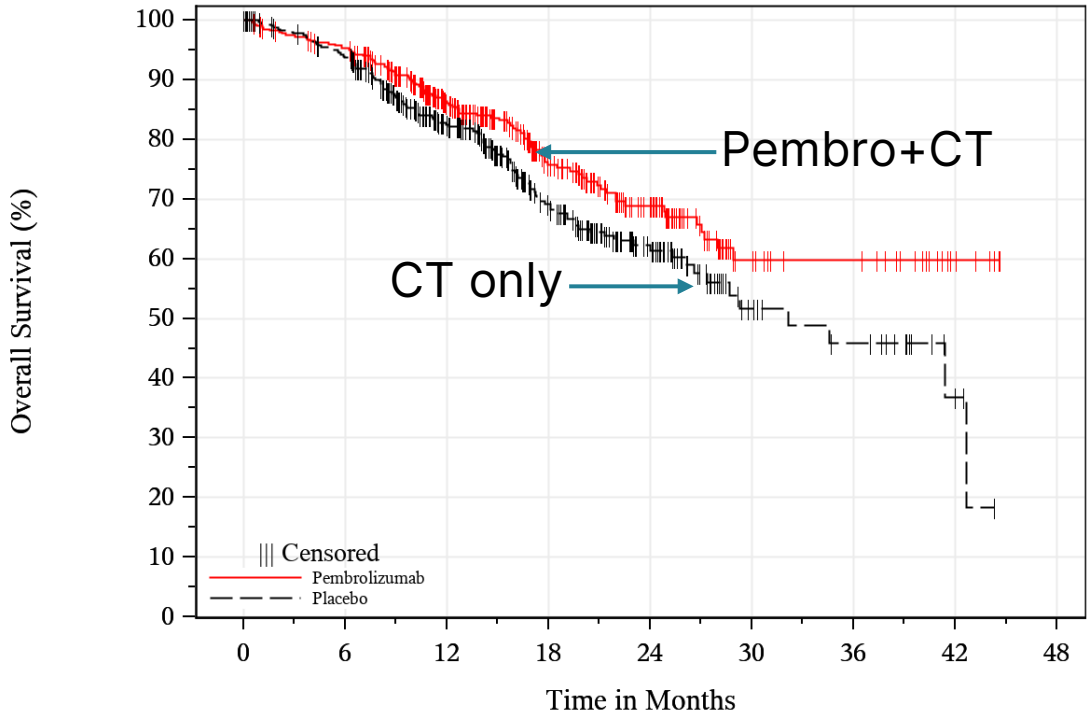
Pembro plus chemo (n=408) improves PFS and OS compared to chemo alone (n=411)

Figure: Pembro plus chemo vs chemo only – PFS

[redacted]

HR (95% CI; p-value)	[redacted]

Figure: Pembro plus chemo vs chemo only – OS



Number of Participants at Risk

Pembrolizumab	408	377	262	147	84	28	21	7	0
Placebo	411	368	241	139	71	21	15	4	0

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

 For OS extrapolation graphs - see appendix

Key issues: Uncertain degree of overall survival benefit

EAG believe company choice of OS model in pembro plus CT arm is too optimistic, EAG agree with company choice of model in CT only arm

Background

KEYNOTE-868 had a median follow-up time of [redacted]

- Median OS was not reached in the pembrolizumab arm over the study period

Further data from KEYNOTE-868 will only be available after final analysis, currently planned for [redacted]

Company

- Standard parametric curves had good visual and statistical fit for OS data and clinical plausibility in the CT arm

Pembro plus CT arm

- 2-piece log-logistic and log-normal, and 2 and 3-knot odds and normal curves provided suitable visual and statistical fits for OS KM data
- Lower bound of OS was constructed by taking a weighted average of OS landmarks from TA963 expert opinion. Estimates of OS with a PD-L1 inhibitor plus CT for dMMR population and OS for CT only treatment in the pMMR population were used to produce the lower bound of OS – believes this is highly conservative – pembro expected to increase OS regardless of MMR status
- From 90 weeks, both 2-knot splines and the 2-piece log-logistic deviate from observed HR, representing a potentially unrealistic conservative scenario – may underestimate true HR
- 3-knot odds spline provides marginally better fit to 5 to 50 week observed HR and less overly optimistic long-term hazard than the remaining 2 plausible models, so it was chosen as the base case

Abbreviations: CT, chemotherapy; dMMR, mismatch repair deficient; HR, Hazard ratio; KM, Kaplan-Meier; OS, overall survival; pMMR, mismatch repair proficient

Key issues: Uncertain degree of overall survival benefit

EAG believe company choice of OS model in pembro plus CT arm is too optimistic, EAG agree with company choice of model in CT only arm

EAG comments

- Relatively short follow-up period limits robustness of long-term effectiveness conclusions
- Agrees with company choice of OS model in CT only arm, but concerns with pembro plus CT arm:
- Near the end of the study period, all models appear to underestimate OS – may be due to plateau at 30 months
- 3-knot odds spline provides second closest match to clinical expert estimates of OS for 1L dMMR EC patients receiving a PD-1 inhibitor + CT from TA963 – sixth best match to lower bound set estimate
- EAG preferred model for the pembro plus CT arm is the 2-piece log-logistic model with a 9.4-week data cut – the same model as the CT only arm – and most plausible 20-year OS estimate judged by the EAG's clinical experts
- 9.4 week cut log-logistic matches closest with the lower bound set estimations of survival

Survival estimates (pembro plus CT)	Years			
	2	5	10	20
NICE TA963 company and EAG advisors' mean estimates for 1L dMMR EC patients receiving PD-1 Inhibitor + CT	82%	59%	46%	38%
Weighted average of dMMR with PD-1 inhibitor + CT (from TA963) and pMMR with CT only (from clinical experts) – lower bound set	59%	27%	16%	10%
3-knot odds spline (company base case)	69%	43%	25%	13%
9.4 week cut 2-piece log-logistic (EAG base case)	71%	40%	21%	9%

Table: Estimates of OS at landmark time points from clinical experts and from EAG and company base cases for pembro+CT arm

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

Key issues: Uncertain degree of overall survival benefit

EAG believe company choice of OS model in pembro plus CT arm is too optimistic, EAG agree with company choice of model in CT only arm

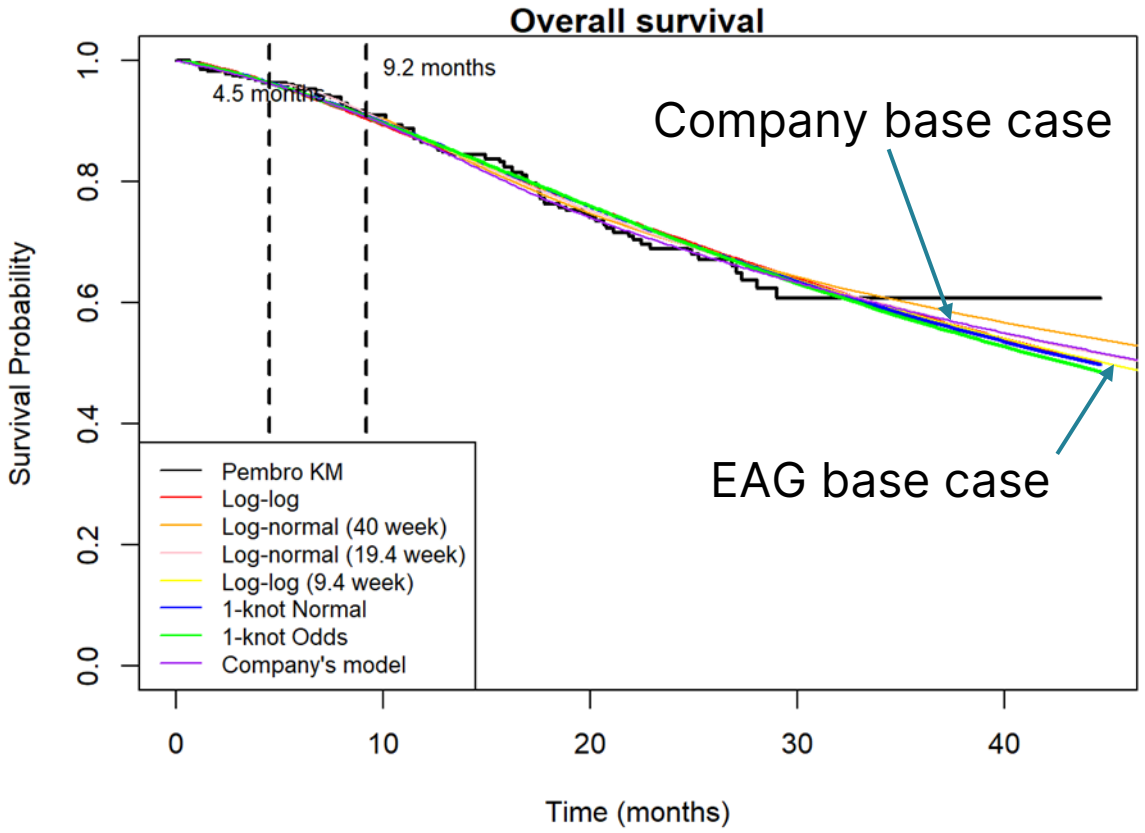


Figure: Pembro plus chemo OS KM data and 6 most plausible extrapolations – trial period

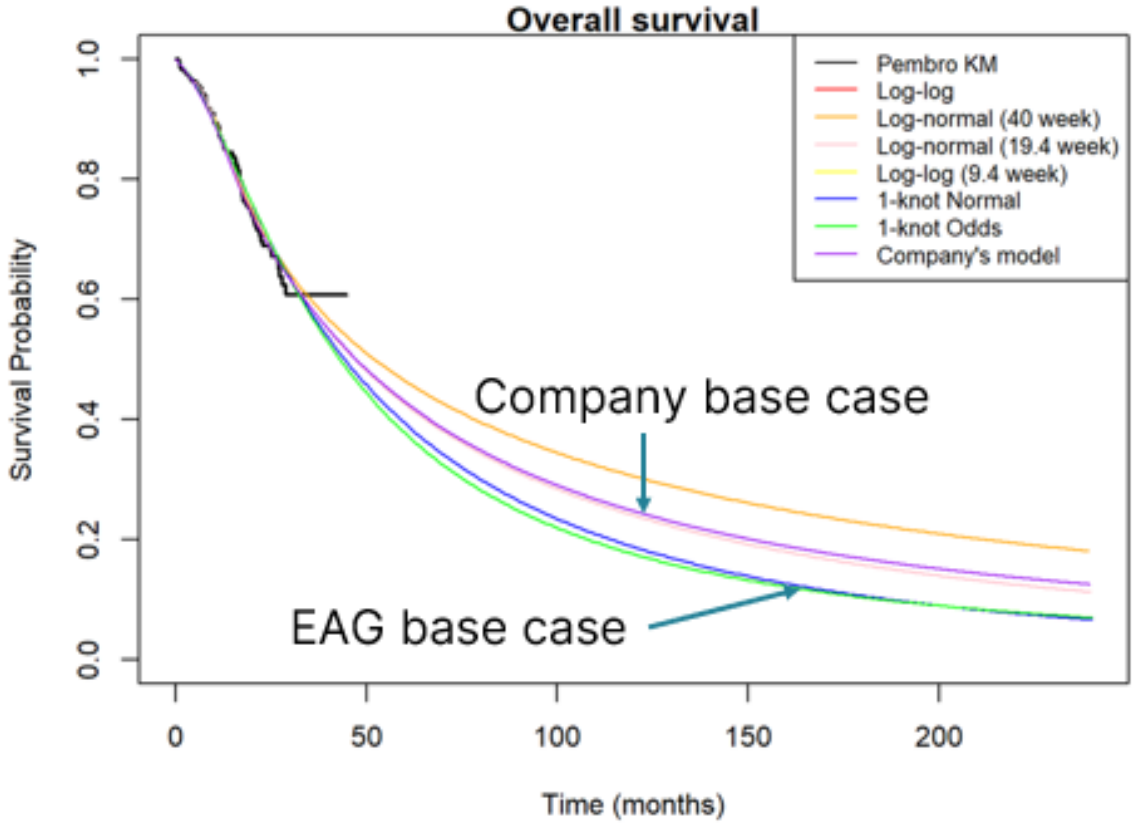


Figure: Pembro plus chemo OS KM data and 6 most plausible extrapolations – 240-month time horizon

Abbreviations; CT, chemotherapy; KM, Kaplan-Meier; OS, overall survival

Key issues: Uncertain degree of overall survival benefit

EAG believe company choice of OS model in pembro plus CT arm is too optimistic, EAG agree with company choice of model in CT only arm

Figure: Time dependant hazard ratio of pembro plus chemo compared to chemo only in trial

Figure: Company base case pembro plus chemo OS hazard function

Figure: EAG base case pembro plus chemo OS hazard function

Which OS extrapolation is most plausible?

Abbreviations: CT, chemotherapy; OS, overall survival

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Key issues: Representativeness of health state utilities for the all-comer population of KEYNOTE-868

EAG concerned with size of sample used to derive health state utilities

For more information on this issue see appendix slides 35 and 36

Background

- EQ-5D data was not collected in KEYNOTE-868 – other HRQoL data was collected
- Utility values in the model were based on [redacted] patients in the endometrial cancer subgroup in KEYNOTE-158

Company

- Several sources of health state utilities were considered for use in the appraisal (see appendix slide 36)
- Health state utilities from KEYNOTE-158 (2L+, dMMR only) were determined to be most suitable for base case analysis because it included a subgroup of patients with endometrial cancer who were treated with pembrolizumab, which aligns reasonably well with the inclusion criteria for KEYNOTE-868
- Utility values from KEYNOTE-158 may underestimate that of the 1L population

EAG comments

- Sample size used to derive utilities is small, so the data has limited generalisability, is statistically unstable with wide confidence intervals, and may under- or overestimate utility values, affecting model accuracy
- dMMR accounts for 27% of KEYNOTE-868; clinical opinion that utilities likely to differ between dMMR and pMMR population as worse response in pMMR
- Company could have used statistical methods to make utility value estimates more robust
- Overall satisfied with how progression-based utilities, AE and age-related disutilities were applied in model

NICE Are the health state utilities used in the model suitable for decision making?

Key issues: Resource use levels for pembrolizumab + CT arm underestimated in the model

Company

- Resource use in the model was determined by consulting clinical experts, an advisory board, and conducting a manual search of HTAs in similar cancers – same for both MMR subgroups (applied to all-comers)

EAG comments

- Clinical expert advised that people receiving immunotherapy have regular thyroid function and glucose levels tests to identify and treat toxicity; company not accounted for additional tests - blood tests lower in pembro+CT arm (every 6 weeks) than CT arm (3.5 weeks)
- Provided 2 updated resource use scenarios, 1 sourced from EAG clinical experts, 1 sourced from TA963

Table: Company base case and EAG scenarios for average time between resource use in the pembro+CT arm of the model

Health state	Resource	Frequency	Frequency	Source	Frequency	Source
		Company BC	EAG scenario 1		EAG scenario 2	
PFS (on treatment)	Blood tests	6 weeks	3 weeks (cycle 1-17) 6 weeks (cycle 18+)	EAG expert	3 weeks (cycle 1-18) 1 month (cycle 19+)	TA963
	Outpatient visits	6 weeks	3 weeks (cycle 1-17) 6 weeks (cycle 18+)	EAG expert	<3 weeks† (cycle 1-18) 2 months (cycle 19+)	TA963
PFS (off treatment)	Blood tests	6 weeks	12 weeks	EAG expert	6 weeks	Company BC
	Outpatient visits	16 weeks	12 weeks	EAG expert	16 weeks	Company BC

NICE

What is the most appropriate resource use scenario for decision making?

Key issues: Uncertainty around subsequent treatment mix for CT arm

Background

- Subsequent treatments in the model are calculated as a one-off cost on entry into the PD state
- One-off entry cost is estimated by using a weighted average of subsequent treatment costs

Company

- Proportion of patients receiving each subsequent treatment was derived from KEYNOTE-868, then adjusted and validated by UK clinicians

EAG comments

- Clinical experts advised that giving pembrolizumab monotherapy as subsequent treatment after chemotherapy is not standard UK practice - pembrolizumab plus lenvatinib is now typically used
- Conducted a scenario analysis replacing pembrolizumab monotherapy with pembrolizumab plus lenvatinib – resulted in [redacted] in ICER
- Additional UK evidence on subsequent therapy mix for patients with advanced or recurrent endometrial cancer who have progressed disease might help resolve the uncertainty

How should uncertainty in the subsequent treatment mix be accounted for?

Abbreviations: CT, chemotherapy; PD, progressed disease

Key issues: Uncertainty around subsequent treatment mix for CT arm

Table: Company base case duration and distribution of subsequent treatments used to derive one-off cost

	Pembrolizumab + chemotherapy		Chemotherapy only	
Subsequent treatment	% share	Mean duration in weeks	% share	Mean duration in weeks
Carboplatin	1.65%	[redacted]	1.84%	[redacted]
Carboplatin + paclitaxel	14.31%	[redacted]	11.34%	[redacted]
Doxorubicin	13.69%	[redacted]	1.22%	[redacted]
Letrozole	7.31%	[redacted]	4.60%	[redacted]
Megestrol	0.00%	[redacted]	1.84%	[redacted]
Paclitaxel	8.27%	[redacted]	8.98%	[redacted]
Pembrolizumab	0.00%	[redacted]	16.76%	[redacted]
Pembrolizumab + Lenvatinib	0.00%	[redacted]	23.95%	[redacted]
Radiotherapy	23.06%	[redacted]	11.68%	[redacted]
No treatment	31.72%	[redacted]	17.78%	[redacted]

How should uncertainty in the subsequent treatment mix be accounted for?

Abbreviations: CT, chemotherapy

Summary of company and EAG base case assumption differences

EAG base case includes 2 changes to company base case:

- OS extrapolation in pembro plus CT arm
- Starting age (minimal impact on ICER)

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Pembro+CT OS extrapolation	3-knot odds spline	9.4 week cut 2-piece log-logistic
Starting age	65.4 years	67.1 years

Abbreviations: CT, chemotherapy; OS, overall survival

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

PAS discounts

When the company and EAG base case ICERs are calculated using confidential prices, both are between £20,000 and £30,000 per QALY

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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

Key issue	ICER impact	Slide
Representativeness of the all-comer post-hoc analyses	Unknown	10
Uncertain degree of overall survival benefit	Large	15
Representativeness of health state utilities for the all-comer population of KEYNOTE-868	Unknown	20
Resource use levels for pembrolizumab + CT arm underestimated in the model	Large	21
Uncertainty around subsequent treatment mix for CT arm	Small	22

Other issues (addressed in appendix slides)	ICER impact	Appendix slide
Limitations of sub-groups examined	Unknown	32
Starting age at baseline in the economic model	Small	38
Adverse events selected for costing in the model	Small	39
HRQoL assessed in pMMR cohort only	Unknown	40
Treatment waning	Small	41

Abbreviations: CT, chemotherapy; HRQoL, health-related quality of life; pMMR mismatch repair proficient

Decision making framework – key issues

What are committee's preferred assumptions?	
Combined all-comer population	Is it reasonable to combine the dMMR and pMMR subgroups for analysis? Are the combined, post-hoc 'all-comer' analyses suitable for decision-making?
OS data and extrapolation	Is the [redacted] median follow-up time long enough for reliable analysis of OS? Which OS extrapolation is most plausible? 3-knot odds spline **(company base case),** 9.4 week 2-piece log-logistic **(EAG base case)** or another extrapolation?
Representativeness of health state utilities for the all-comer population of KEYNOTE-868	Are the utility values used in the model based on [redacted] patients in the endometrial cancer subgroup in KEYNOTE-158 suitable for decision-making? Are any of the other utility data sources more suitable (see appendix slide)?
Resource use levels for pembrolizumab + CT arm	What is the most appropriate resource use scenario for decision making (see appendix slide)?
Subsequent treatments for CT arm	Is the subsequent treatment mix for the CT arm suitable for decision-making (see appendix slide)?
What is the committee's preferred ICER?	What is the committee's preferred ICER threshold - and why? What is the committee's preferred ICER (is this a range)?

Decision making framework – other issues

What are committee's preferred assumptions?	
Subgroups	Does not having local versus metastatic recurrence, and previous primary debulking surgery as subgroups affect decision making?
Starting age in the model	What is the most appropriate starting age for the model? 65.4 years **(company base case),** 67.1 years **(EAG base case)** or another starting age?
Adverse events selected for costing in the model	Grade 3+ AEs occurring in more than 2% (EAG preference but not base case) or 5% (base case assumption) of patients in either arm
HRQoL assessed in pMMR cohort only	Does HRQoL data being collected in the pMMR cohort only in the trial (but not used in the model) affect decision making
Treatment waning	Should treatment waning be included as an assumption in the model?
What is the committee's preferred ICER?	What is the committee's preferred ICER threshold - and why? What is the committee's preferred ICER (is this a range)?

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Supplementary appendix

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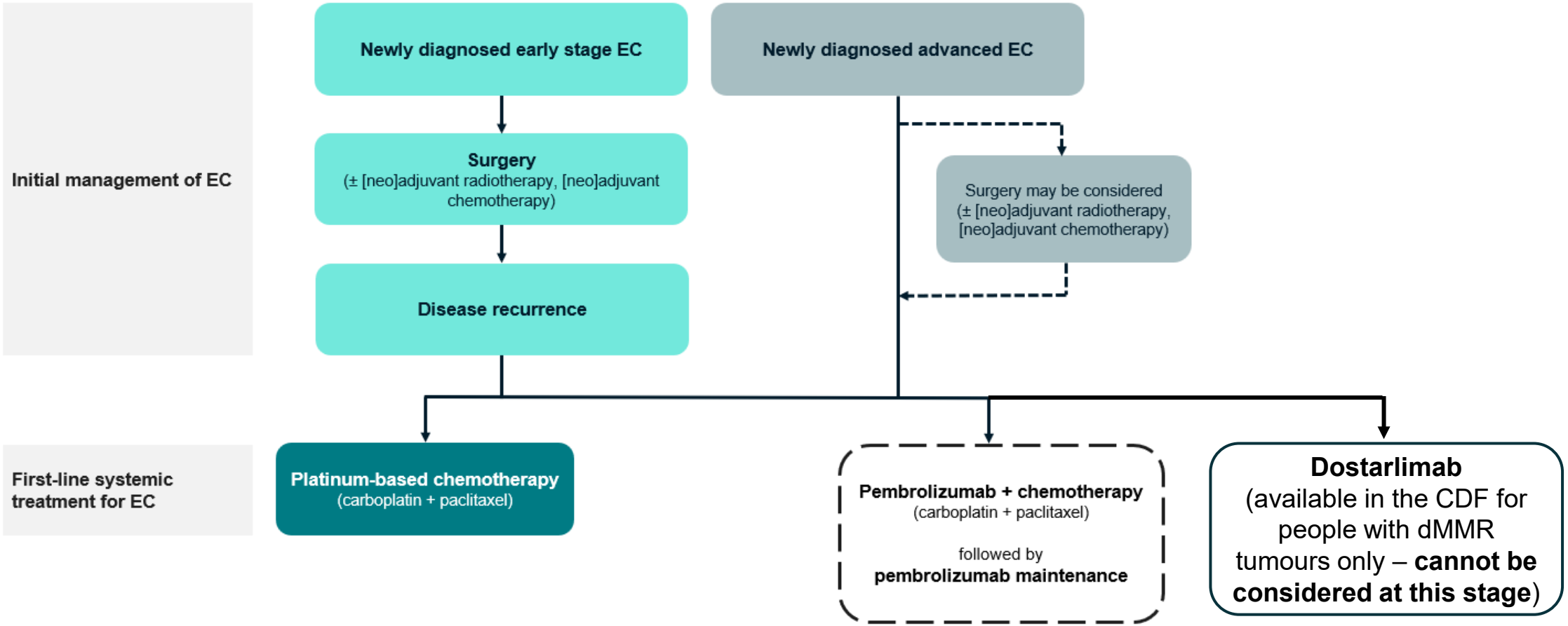
1L Treatment pathway



What are the most appropriate comparators for the technology?

Other issues: Limitations of sub-groups examined

EAG concerned that data on recurrence location and surgical history was not captured

Background

- The NICE scope included MMR status, local versus metastatic recurrence, and previous primary debulking surgery as subgroups to be considered if evidence allowed
- The company only included MMR status in its subgroup analysis

Company

- Information concerning site of recurrence or previous primary debulking surgery was not systematically collected in the KEYNOTE-868, so subgroup analysis could not be presented

EAG comments

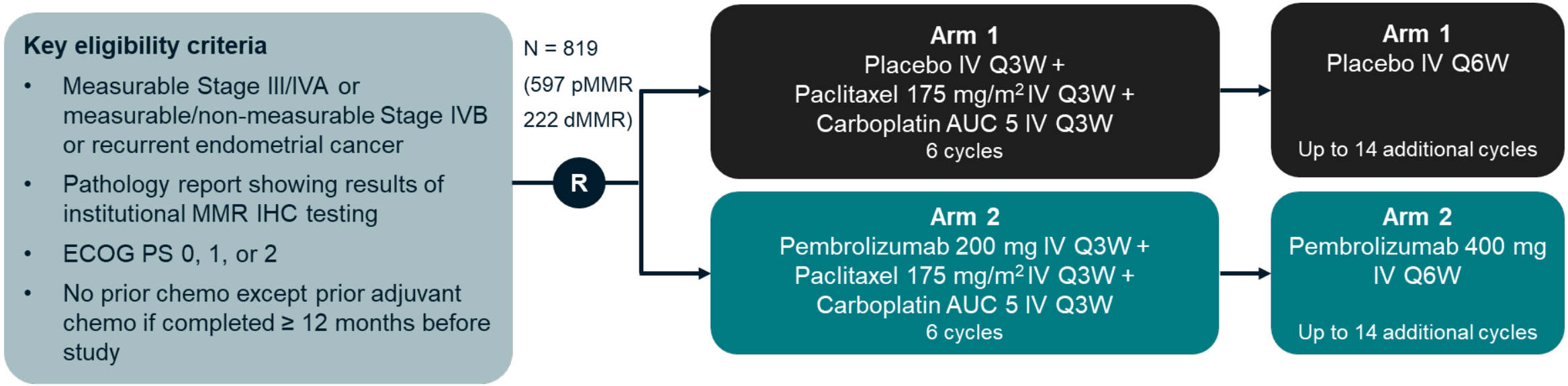
- While molecular subgroups like MMR status can still be evaluated, absence of recurrence site and surgical history data reduces understanding of pembrolizumab's effectiveness in these contexts
- Clinical advice emphasised that systemic treatment in the UK is typically reserved for multisite or extra-abdominal recurrence
- Without the surgical history and recurrence data, the treatment indications for pembrolizumab could be broadly defined (i.e., enrolled trial participants may have been those unsuitable for other therapies)

Could the results in the missing subgroups be significantly different than the overall population? Could significantly different results in these groups impact decision making?

Abbreviations: MMR, mismatch repair

Key clinical trials

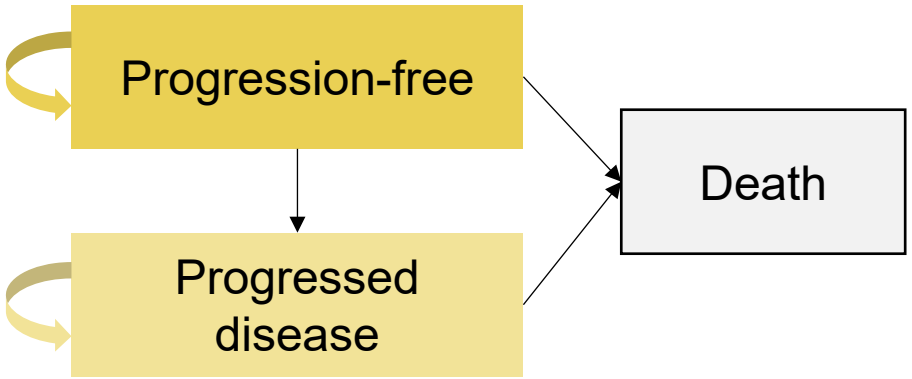
Clinical trial designs and outcomes



Company's model overview

Company developed a three-state partitioned survival model

Model structure



- Technology affects **costs** by:
  - Having higher initial treatment acquisition and administration costs
  - Having a lower subsequent treatment cost
- Technology affects **QALYs** by:
  - Increasing time until progressed disease
  - Increasing OS
- Assumptions with greatest ICER effect:
  - OS extrapolation
  - 2L treatment option
  - Time horizon

EAG comments

- Ample evidence was provided to justify model choice, including its widespread use in oncology modelling and application in previous technology appraisals
- 1-week cycle length and 35-year time horizon are both appropriate for modelling

Key issues: Representativeness of health state utilities for the all-comer population of KEYNOTE-868

Table: Progression-based health state utility values used in the company base case

Health state	Mean utility value (SE)	95% CI	Source
Progression-free	[redacted]	[redacted]	KEYNOTE-158
Progressed	[redacted]	[redacted]	KEYNOTE-158

Table: One time utility decrements applied at the start of the model to account for AEs occurring after starting treatment

Treatment arm	One-time starting utility decrement
Pembro+CT	[redacted]
CT only	[redacted]

Table: AE utility decrements used to calculate starting decrements

Adverse Event	Disutility	Source (disutility)
Neutrophil count decreased	0.00	NICE TA963
White blood cell count decreased	0.00	NICE TA963
Lymphocyte count decreased	0.00	NICE TA963
Hypertension	-0.02	NICE TA963
Anaemia	-0.119	NICE TA963

Are the health state utilities used in the model suitable for decision making?

Abbreviations:

Key issues: Representativeness of health state utilities for the all-comer population of KEYNOTE-868

Table: Options for utilities explored by company

Potential utilities source	Used in model?	Rationale
KEYNOTE-868	No	No studies identified which provided suitable mapping algorithm from HRQoL instruments used in KN-868 to EQ-5D
KEYNOTE-158	Yes – base case	EQ-5D from people with 2L+ pembro treatment for dMMR cancer (2L endometrial cancer subgroup): aligns well with population in KN-868, although different line of treatment and dMMR population only
KEYNOTE-826	Yes – scenarios based on progression status and time-to-death	EQ-5D from people with 1L pembro treatment for persistent, recurrent or metastatic cervical cancer: same line of treatment as KN-868 and larger sample size than KN-158, but limited generalisability as different gynaecological cancer
KEYNOTE-775	Yes – scenarios using Australian and Swedish EQ-5D-5L set	EQ-5D from people with 2L+ pembro + lenvatinib for advanced endometrial cancer: utility values from KN-775 unpublished and not available due to contractual 3rd party obligations
Published literature	No	6 studies identified: none reported HRQoL in 1L advanced or recurrent endometrial cancer; none reported HRQoL in any line based on UK value set

Key issues: Representativeness of health state utilities for the all-comer population of KEYNOTE-868

Table: EQ-5D-3L values from KEYNOTE-158 and KEYNOTE-826 based on progression status

Progression status	KEYNOTE-158 (N=[redacted]) Mean (SE)	KEYNOTE-826 (N=545) Mean (SE)
Progression-free	[redacted]	[redacted]
Progressed	[redacted]	[redacted]

Table: Time-to-death utilities from KEYNOTE-826

Time to death	KEYNOTE-826 (N=545) Mean (SE)
≥360 days	[redacted]
180-359 days	[redacted]
90-179 days	[redacted]
30-89 days	[redacted]
<30 days	[redacted]

Company

- Mapping utility data from the HRQoL instruments used in KEYNOTE-868 (FACT-En-TOI, FACT/Gynecologic Oncology Group-Neurotoxicity (GOG-NTX), and PROMIS-Physical Function Scale (short form)) to EQ-5D-3L was also explored.
- Six studies were identified developing a mapping algorithm from the FACT-G to the EQ-5D-5L/3L. There were no studies that described an algorithm from FACT-En-TOI to EQ-5D
- Identified studies used mismatching scales, and did not include people with endometrial cancer
- So, the HRQoL data from KEYNOTE-868 was not used in the model

Other issues: Starting age at baseline in the economic model

EAG believe the starting age in the model to more closely represent clinical practice

Background

- Baseline characteristics in the model were derived from KEYNOTE-868
- The mean age in the trial and model was 65.40 years

Company

- UK clinicians indicated that the KEYNOTE-868 trial population was broadly similar to real-world clinical practice

EAG comments

- Clinical expert advised that a mean starting age of 70 would be more representative of this population
- Apart from 1 source, all alternate sources examined reported mean ages of over 66
- EAG preference is for a starting age of 67.1, as was chosen for TA963 (based on people with stage 3 and 4 endometrial cancer in UK study)

What is the most appropriate starting age for the model?

Other issues: Adverse events selected for costing in the model

Company

- Costs associated with Grade 3+ AEs occurring in more than 5% of patients in either arm are considered in the model which were neutrophil count decreased, white blood cell counts decreased, lymphocyte count decreased, anaemia, and hypertension
- Costs of adverse event management are applied as a one-off in the first model cycle and are the product of rate of AE per subject, number of AE episodes per subject, and the cost of each AE episode

EAG comments

- Accepts the methodology, and the assumptions used to derive the AE cost per episode
- However, would prefer to use Grade 3+ AEs occurring in more than 2% of patients to include pulmonary embolism, hypokalaemia, diarrhoea, and neutropenia as AEs in the model
- Costs may be underestimated if these events are excluded

Should Grade 3+ AEs occurring in more than 2% of patients be included in the model?

Other issues: HRQoL assessed in pMMR cohort only

Background

- HRQoL data was collected on patients in the pMMR cohort only in KEYNOTE-868
- However this data is not used in the company's base case

Company

- Due to the lack of sufficient statistical power in the dMMR group resulting from the smaller sample size, the analyses for HRQoL were prespecified to be conducted only in the pMMR cohort
- Because they were not used in modelling, the impact of not collecting HRQoL in the dMMR subgroup is likely to have minimal effect on the cost effectiveness results presented in the company submission

EAG comments

- The study may have struggled to detect statistically significant HRQoL changes, especially in the dMMR group at the interim analysis stage - indicates a higher risk of type II errors (failing to detect a true effect)
- Uncertainty remains as to whether additional efforts to improve power or conduct exploratory analyses in the dMMR group would have provided valuable insights
- HRQOL in the dMMR population could still have been collected with caveats around limited interpretation of results

Other issues: Treatment waning

Background

- Treatment waning has been considered as an issue in other appraisals of immunotherapies and has been included as an assumption in other pembrolizumab appraisals, for example TA661 and TA914

Company

- The mechanism of action of pembrolizumab supports a sustained treatment effect
- Observed trial data supports a sustained treatment effect
- No concrete and substantial evidence of treatment waning effect for immunotherapies including pembrolizumab
- Long-term data from historic pembrolizumab trials in other indications support a sustained treatment effect
- For completeness, scenario including treatment waning in OS 7 years from starting pembrolizumab treatment (5 years after stopping pembrolizumab) is included

EAG comments

- Clinical advice suggests that "the discussion regarding treatment waning is relevant to all immunotherapy" and given trial's limited follow-up, there is no evidence to suggest that treatment waning does not occur
- Previous appraisals considered it plausible for treatment waning to start 3 to 5 years after stopping immunotherapy so included scenarios with treatment waning in OS 5 and 6 years from starting of pembrolizumab
- Acknowledges that there is no evidence to support treatment waning so not included in base case

Should treatment waning be included as an assumption in the model?