Durvalumab with platinum-based chemotherapy, then with or without olaparib, for treating newly diagnosed advanced or recurrent endometrial cancer [ID6317]

Confidential information **redacted**

Technology appraisal committee A [04 March 2025]

Chair: James Fotheringham

Lead team: Richard Ballerand, Mario Ganau, Becky Pennington

External assessment group: BMJ

Technical team: Emma McCarthy, Jo Richardson, Emily Crowe

Company: AstraZeneca

Durvalumab with platinum-based chemotherapy, then with or without olaparib, for treating newly diagnosed advanced or recurrent endometrial cancer [ID6317]

- ✓ **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

Diagnosis and classification

- Mismatch repair helps cells 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

Patient perspectives

Patients would welcome more treatment options for endometrial cancer

Submissions from Peaches Womb Cancer Trust and patient expert

- Physical symptoms can be debilitating and have a significant impact on quality of life
- Effective treatment options at this stage are very limited and the possibility of recurrence causes stress
- Chemotherapy is seen as a poor option to many people, and side effects are challenging physically and psychologically
    - Immunotherapy has fewer and less severe side effects
- People would like a first-line treatment which will further reduce the chance of the cancer recurring compared to chemotherapy
    - Unmet need particularly in pMMR population in whom immunotherapy is less effective

"Access to an immunotherapy has been life changing for me in terms of quality of life and impact on my survival."

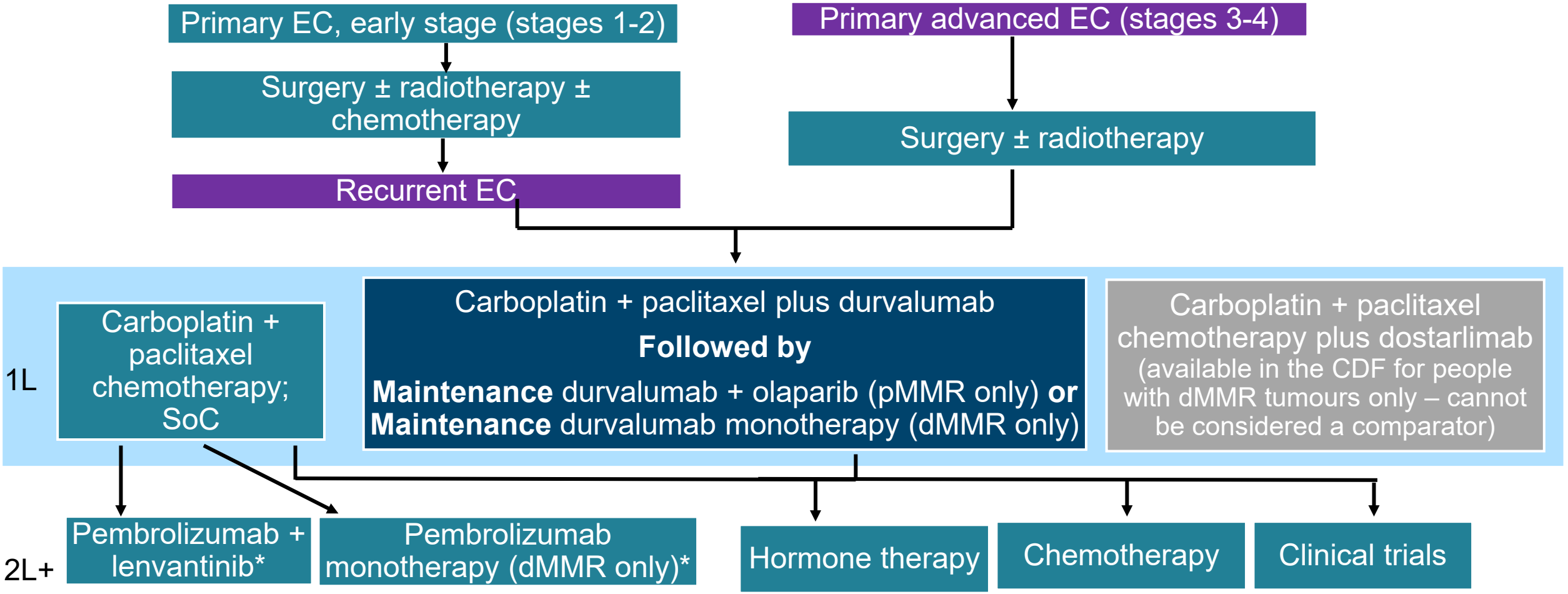
"With [immunotherapy], I feel much more relaxed and able to live a normal life…I am grateful every day that I am able to live my life fully and without many of the side effects of previous treatments."

pMMR; mismatch repair proficient

Treatment pathway

= Intervention

EAG – treatment pathway in line with current clinical practice



* Treatments available after SoC only - Blueteq criteria does **not** allow 2 lines of immunotherapy

Is the treatment pathway correct?
Is platinum-based chemotherapy followed by standard care the appropriate comparator for both pMMR and dMMR subgroups?

EC, endometrial cancer; pMMR, mismatch repair proficient; dMMR, mismatch repair deficient; CDF, Cancer Drugs Fund

Equality considerations

Equality issue raised by company and clinical expert regarding EC incidence across ethnic groups

- Incidence rates and mortality for uterine cancer are higher in Black ethnic group compared with White ethnic group
- The incidence of different molecular subtypes of EC (including MMR status) varies across ethnic groups
    - Company considered this an equality issue since patients with pMMR EC have fewer first line treatment options in clinical practice and worse prognosis
    - Clinical expert noted that patients in Black ethnic group may have more aggressive histology and may be more likely to have molecular subtypes with a poorer prognosis
- There is some data suggesting differential responses to immunotherapy across ethnic groups

Are there any other equalities issues to consider in this appraisal?

MMR, mismatch repair; pMMR; mismatch repair proficient; EC, endometrial cancer

Durvalumab (Imfinzi) and olaparib (Lynparza) (AstraZeneca)

Marketing authorisations – granted Dec 2024	**Durvalumab** Durvalumab in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with: • Durvalumab as monotherapy in endometrial cancer that is mismatch repair deficient (dMMR) • Durvalumab in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR). **Olaparib** Maintenance treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair proficient (pMMR) whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel.
Administration	**Durvalumab** • Induction: durvalumab 1,120 mg administered intravenously with platinum-based chemotherapy (carboplatin + paclitaxel) every 21 days for 4-6 cycles • Maintenance: 1,500 mg every 4 weeks as either monotherapy or in combination with olaparib. **Olaparib:** 300 mg (2 x 150 mg tablets) orally administered twice daily (equivalent to a daily dose of 600 mg)
Price	Confidential commercial access agreements in place for durvalumab and olaparib

Key issues

Key issue	ICER impact
Immaturity of data from DUO-E clinical trial	Unknown
Subsequent treatment usage	Unknown
Cap on treatment duration	Large
Proportion initiating olaparib maintenance treatment (pMMR subgroup only)	Large
Estimation of newly progressed patients per model cycle	Moderate

Other issues (addressed in appendix slides)	ICER impact
Treatment waning (linked to cap on treatment duration)	Unknown
Wastage	Small

pMMR, mismatch repair proficient

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Key clinical trial – DUO-E

Clinical trial designs and outcomes

	DUO-E (NCT04269200)
Design	Phase 3 randomised, double-blind, placebo-controlled trial
Population	Adults (n=718) with newly diagnosed advanced (stage 3 or 4) EC or recurrent epithelial EC with low cure potential from surgery (excluding sarcomas)
Interventions	• Durvalumab in combination with first line carboplatin-paclitaxel, then maintenance durvalumab plus olaparib (SoC+D+O) (n=239, n=191 pMMR) • Durvalumab in combination with first line carboplatin-paclitaxel, then maintenance durvalumab plus placebo (SoC+D) (n=238, n=46 dMMR)
Comparator	First line carboplatin-paclitaxel with placebo, then placebo maintenance (SoC) (n=192 pMMR, n=49 dMMR)
Duration	Median follow up SoC: 12.6 months Median follow up SoC+D+O and SoC+D: 15.4 months
Key outcomes	PFS (primary), OS, ORR, DoR, TTD, QoL
Locations	22 countries across Europe, Asia, North America, South America, Australia (no UK patients)
Key subgroups	Mismatch repair status (dMMR or pMMR) - pre-specified for PFS only

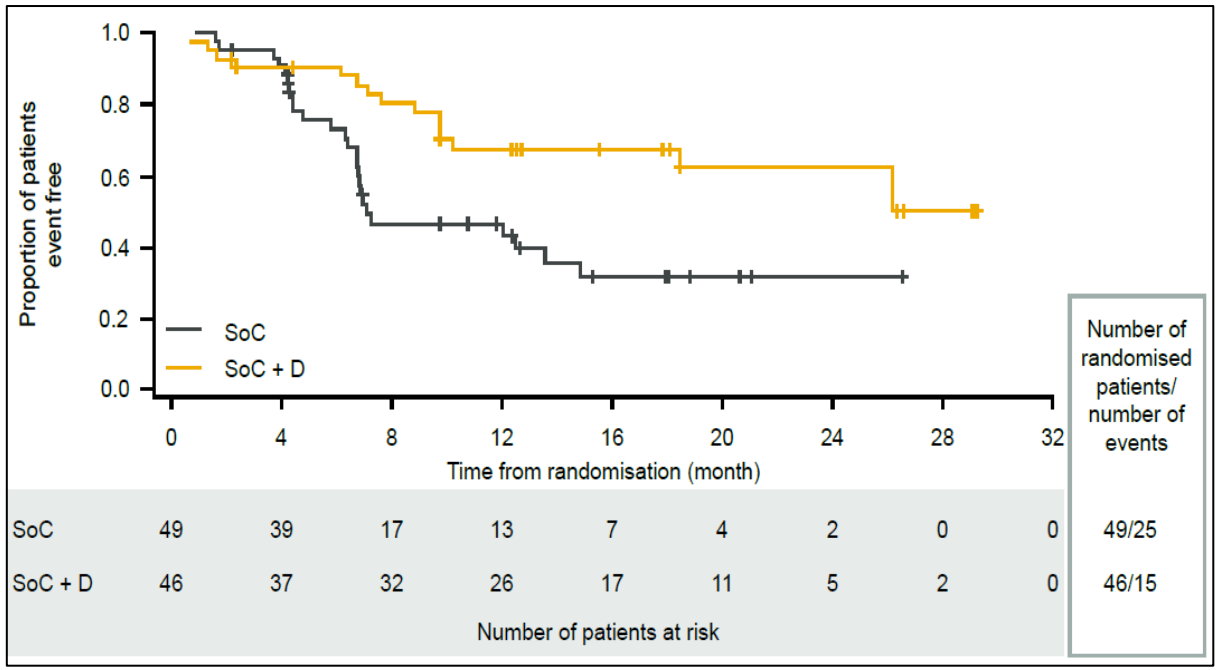
EAG - Randomisation stratified by MMR status, but trial did not exclusively randomise dMMR patients to receive SoC+D or pMMR patients to receive SoC+D+O to match marketing authorisation

EC; endometrial cancer; SoC+D+O, standard of care plus durvalumab plus olaparib; ; SoC+D, standard of care plus durvalumab; SoC, standard of care; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; DoR, duration of response; TTD, time to treatment discontinuation; dMMR, mismatch repair deficient; pMMR, mismatch repair proficient

DUO-E – dMMR progression-free survival and overall survival

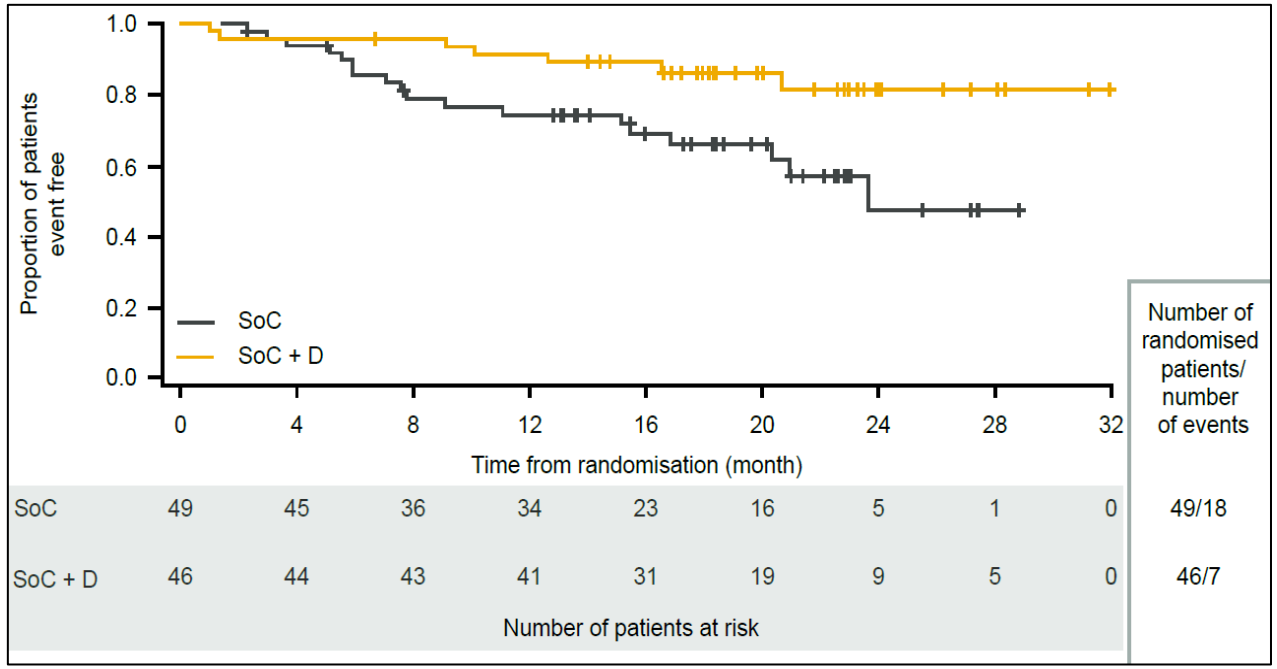
Durvalumab in combination with platinum-based chemotherapy followed by maintenance durvalumab monotherapy improves PFS and OS vs SoC alone in dMMR subgroup

Investigator-assessed PFS in dMMR subgroup (SoC (n=49) compared with SoC+D (n=46))



HR (95% CI)	0.42 (0.22 to 0.80)

OS in dMMR subgroup (SoC (n=49) compared with SoC+D (n=46))



HR (95% CI)	0.34 (0.13 to 0.79)

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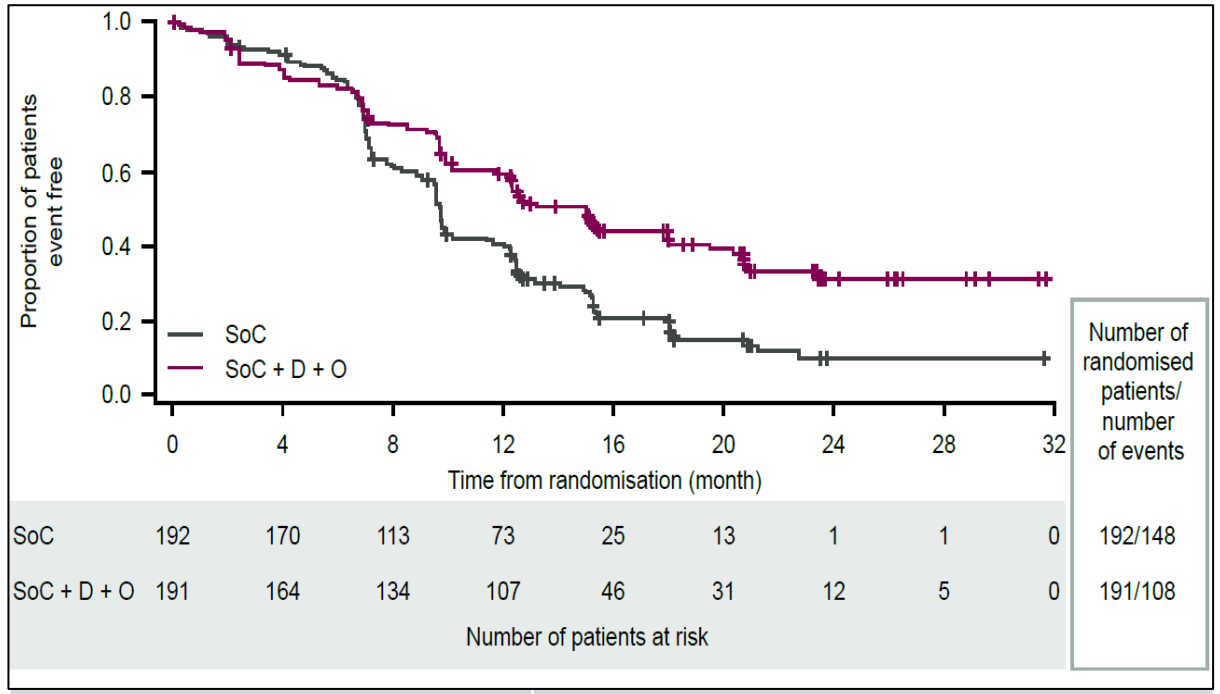
dMMR, mismatch repair deficient; SoC, standard of care; SoC+D. standard of care plus durvalumab; MA, marketing authorisation; PFS, progression-free survival; OS, overall survival; CI. Confidence interval

DUO-E – pMMR progression-free survival and overall survival

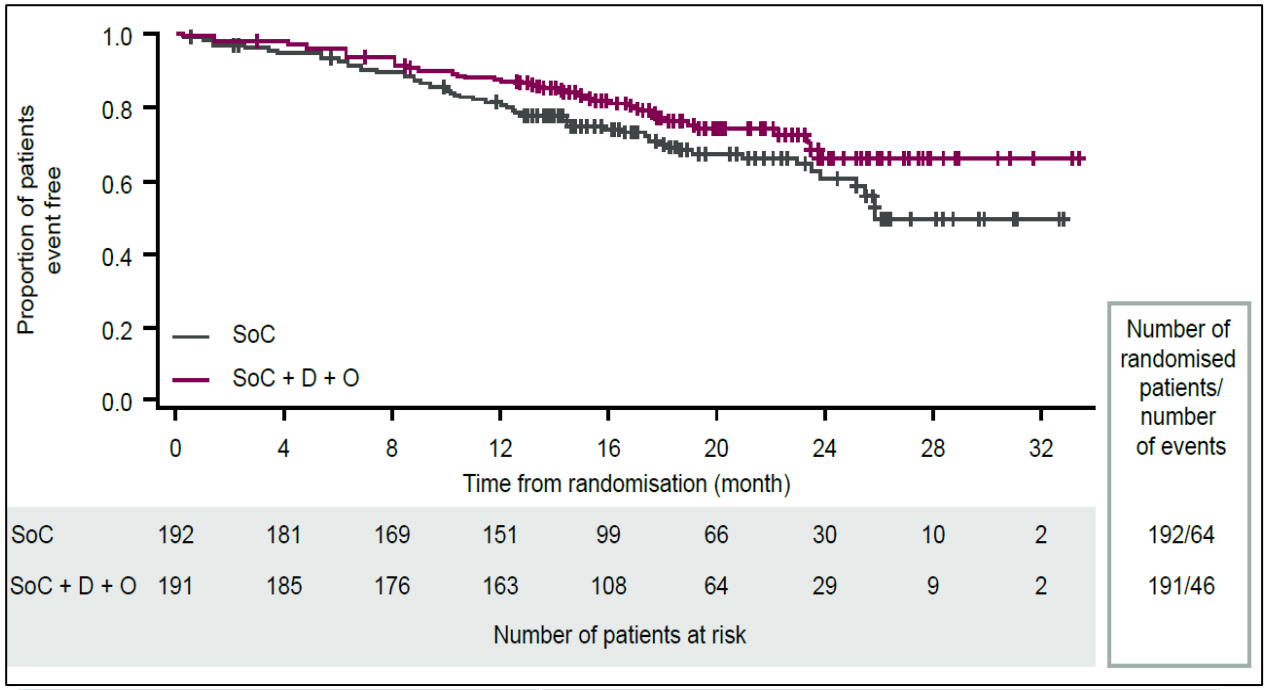
Durvalumab in combination with platinum-based chemotherapy followed by maintenance durvalumab with olaparib improves PFS vs SoC alone in pMMR subgroup, but HR for OS includes 1

Investigator-assessed PFS in pMMR subgroup (SoC (n=192) compared with SoC+D+O (n=191))



HR (95% CI)	0.57 (0.44 to 0.73)

OS in pMMR subgroup (SoC (n=192) compared with SoC+D+O (n=191))



HR (95% CI)	0.69 (0.47 to 1.00)

NICE

pMMR, mismatch repair proficient; SoC+D+O. standard of care plus durvalumab plus olaparib; MA, marketing authorisation; PFS, progression-free survival; OS, overall survival; CI. Confidence interval

Key issue: Immaturity of DUO-E data

EAG – outcome data is very immature (particularly for OS) – uncertainty is significant

Maturity of outcomes as of primary DCO (April 2023):

Outcomes	Maturity (n/N) - dMMR subgroup		Maturity (n/N) - pMMR subgroup	
	SoC	SoC+D	SoC	SoC+D+O
PFS	51.0% (25/49)	32.6% (15/46)	77.1% (148/192)	56.5% (108/191)
OS	36.7% (18/49)	15.2% (7/46)	33.3% (64/192)	24.1% (46/191)
TTD	-	[redacted]	-	[redacted]

Company

- Validated long term survival using committee discussion from appraisal of dostarlimab in dMMR endometrial cancer (TA963)
- Further analysis expected in Q4 2025 (expected 87% of target OS events), final DCO predicted for 2026

EAG

- Immaturity of data makes extrapolations (particularly for OS) highly uncertain – further data needed
- Company's use of TA963 for validation problematic as committee considered there was uncertainty in these clinical results (and the preferred approach for OS was undecided)

DCO; data cut off; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation; pMMR, mismatch repair proficient; dMMR, mismatch repair deficient

PFS extrapolations for dMMR subgroup

Company prefers 2 knot spline for SoC+D , EAG prefers 1-knot spline

small impact on ICER

PFS KM curves, 1 knot-spline extrapolations and 2-knot spline extrapolations of SoC and SoC+D:

Year	SoC+D (%)		
	KM	2 knot spline	1 knot spline
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	-	[redacted]	[redacted]
5	-	[redacted]	[redacted]
10	-	[redacted]	[redacted]

Company

- Standard parametric models not clinically plausible when comparing with clinical expert estimates of PFS – spline models more appropriate
- Use of spline models aligns with preferred approach in dostarlimab appraisal (TA963)

EAG

- 1-knot spline preferred for SoC+D – better statistical fit and better captures tail end of KM curve (but subject to uncertainty)
- EAG considers 1 knot spline appropriate for SoC arm (in line with company approach)
- Choice of extrapolation has small impact on cost effectiveness

Which PFS extrapolation for SoC+D is more plausible for the dMMR subgroup?

SoC, standard of care; SoC+D. standard of care plus durvalumab; PFS; progression-free survival, OS; overall survival; dMMR, mismatch repair deficient; KM, Kaplan-Meier; pMMR, mismatch repair proficien

See appendix for pMMR PFS extrapolations

OS extrapolations for dMMR subgroup

small impact on ICER

For both SoC and SoC+D, company prefers log-normal, EAG prefers log-logistic

OS KM curves, lognormal extrapolations and log logistic extrapolations for SoC and SoC+D:

Year	SoC (%)		
	KM	Log-normal	Log-logistic
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	-	[redacted]	[redacted]
5	-	[redacted]	[redacted]
10	-	[redacted]	[redacted]

Year	SoC+D (%)		
	KM	Log-normal	Log-logistic
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	-	[redacted]	[redacted]
5	-	[redacted]	[redacted]
10	-	[redacted]	[redacted]

EAG

- Results for SoC arm using log-logistic similar to company base case using the lognormal distribution.
- Log-logistic OS estimates for SoC+D closer to estimates shown in dostarlimab appraisal (TA963)

Which OS extrapolation is more plausible for the dMMR subgroup?

SoC, standard of care; SoC+D. standard of care plus durvalumab; OS, overall survival; dMMR, mismatch repair deficient; KM, Kaplan-Meier

See appendix for pMMR OS extrapolations

Key issue: Subsequent treatment usage

Background

- In DUO-E, [redacted]% of dMMR patients on SoC+D and [redacted]% of pMMR patients on SoC+D+O receiving subsequent treatments had immunotherapies - but 2nd immunotherapy use not part of UK practice
- Subsequent immunotherapy use in SoC arms [redacted] than expected in UK practice [redacted]

Company

- Re-challenge with immunotherapy not permitted in UK clinical practice according to Blueteq criteria
- Dostarlimab excluded from dMMR subsequent treatments in SoC arm of model (only in CDF) - proportions updated to assume increased usage of pembrolizumab monotherapy (in line with clinical expert opinion)

EAG comments

- Clinical efficacy may be [redacted]
- EAG's clinical experts [redacted]
- Company's adjustment of subsequent treatment proportions to capture costs of SoC without dostarlimab is reasonable, but no real-world data to validate this

How does the difference in subsequent immunotherapy use in UK practice affect the generalisability of the data?

pMMR, mismatch repair proficient; dMMR, mismatch repair deficient; SoC+D+O; standard of care plus durvalumab plus olaparib; SoC+D. standard of care plus durvalumab;; OS, overall survival; SoC, standard of care; CDF, Cancer Drugs Fund

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Key issue: Cap on treatment duration

Background

- Company model assumes treatment with olaparib and durvalumab continues until disease progression or up to a maximum treatment duration of 3 years
  - DUO-E treatment regimen – continue until disease progression or unacceptable toxicity

Company

- Assumption of treatment duration cap aligns with other EC immunotherapies
- Discontinuation prior to progression or toxicity may occur in clinical practice
  - Company clinical experts – patients expected to discontinue immunotherapy within five years (due to remission), with discussions at 1-3 years depending on response

EAG comments

- Cap on treatment duration artificially limits intervention acquisition costs
- Uncertainty in long-term efficacy estimates with a hard cap on treatment duration due to immaturity of data
- Company has not explored treatment waning assumptions after artificial treatment duration cap
- SPC says treatment should continue until disease progression or unacceptable toxicity – EAG prefers no cap on treatment duration with TTD extrapolations tending to 0 (see appendix):
  - dMMR = gamma distribution preferred (in line with company approach to TTD)
  - pMMR = exponential distribution preferred

Should there be a cap on treatment duration in the model?
If yes, does committee need to consider a stopping rule?
If no cap is preferred, what is the appropriate extrapolation of TTD in pMMR and dMMR?

EC, endometrial cancer; SPC, summary of product characteristics; pMMR, mismatch repair proficient; dMMR, mismatch repair deficient; TTD; time to treatment discontinuation

Key issue: Cap on treatment duration

Stopping rules in other immunotherapies for EC:

Immunotherapy	Stopping rule in SPC	Stopping rule in clinical trials	Additional stopping rule in NICE recommendation
Dostarlimab (TA779*, TA963*) (dMMR/high MSI EC only)	Until disease progression or unacceptable toxicity, or for a duration of up to 3 years	GARNET (key trial for TA779) - none RUBY (key trial for TA963) – 3 years	N/A – stopping rule in SPC
Pembrolizumab monotherapy (TA914)	None for EC	KEYNOTE-158 (key trial for EC in TA914) - 2 years	2 years of uninterrupted treatment, or earlier if the cancer progresses
Pembrolizumab with lenvatinib (TA904)	None for EC	KEYNOTE-775 - 2 years for pembrolizumab, lenvatinib until clinical progression	None

* Recommendations in CDF only

Should there be a cap on treatment duration in the model?
If yes, does committee need to consider a stopping rule?
If no cap is preferred, what is the appropriate extrapolation of TTD in pMMR and dMMR?

EC, endometrial cancer; SPC, summary of product characteristics; pMMR, mismatch repair proficient; dMMR, mismatch repair deficient; TTD; time to treatment discontinuation

Key issue: Olaparib maintenance treatment (pMMR only)

Background

- In the model, [redacted]% of pMMR patients start treatment with olaparib based on DUO-E data
  - DUO-E median time from randomisation to first treatment with olaparib = 19.6 weeks
- MA indicates that pMMR population should receive durvalumab and olaparib in combination (no MA for durvalumab alone in this subgroup)

Company

- Not all patients started treatment with olaparib in SoC+D+O arm due to disease progression, ineligibility for treatment (i.e. adverse events) or patient choice ([redacted]% received maintenance durvalumab monotherapy)
- In DUO-E, if AEs prevent further dosing, patients can discontinue the treatment causing AEs and continue with the other – anticipating this use in UK clinical practice

EAG comments

- Company's proportion is based on proportion at time of randomisation and underestimates costs –
  - EAG prefers [redacted]% based on proportion of SoC+D+O patients receiving maintenance treatment
- Olaparib acquisition costs in model only applied to patients alive and progression-free after week 18
- Scenario analysis with all progression-free patients in SoC+D+O arm of the model receiving olaparib (but may underestimate treatment effectiveness)
- Using maintenance durvalumab monotherapy in pMMR does not align with MA (see appendix)

How would olaparib be used in combination with durvalumab in clinical practice? What circumstances would make someone ineligible for olaparib at maintenance stage?

What proportion of people starting maintenance treatment with olaparib in the pMMR subgroup should be used?

pMMR, mismatch repair proficient;; SoC+D+O; standard of care plus durvalumab plus olaparib; MA, marketing authorisation; AE, adverse events

Key issue: Estimation of newly progressed patients per model cycle

Background

- Estimation of newly progressed disease patients in the model is based on a constant proportion of [redacted] from DUO-E (with one off cost applied on disease progression)

Company

- DUO-E: percentage of non-fatal progression events (for ITT population) remains constant over time for duration of follow up so far (18 months)
- Estimated at 30 months (duration of DUO-E study) that 36-44% of progression events are fatal
  - Scenario provided reducing constant proportion of non-fatal events to 75% after 60 months
- Low number of progression events were fatal – modelling time to progression would be similar to PFS

EAG comments

- Use of a constant proportion likely overestimates new progression – there may be cycles with death but not new progression
- Company's approach likely leads to an overestimation in costs of subsequent treatment
- EAG prefers to calculate newly progressed patients per cycle directly from the model (see appendix for method) – but not part of EAG base case due to limitations in method

How should the proportion of newly progressed patients per cycle be modelled?

ITT; intention to treat

Summary of differences in company and EAG base case

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Survival extrapolation for PFS in SoC + D (dMMR)	2-knot spline	1 knot spline
OS distribution in dMMR subgroup	Log-normal	Log-logistic
Treatment duration cap	3 years	None
TTD extrapolation	dMMR: Gamma with 3-year treatment cap pMMR: Log-logistic with 3-year treatment cap	dMMR: Gamma pMMR: Exponential
Proportion of patients initiating olaparib (pMMR)	[redacted]	[redacted]
Drug wastage (see appendix)	Excluded	Included
Subsequent treatment administration cost	SB15Z from NHS reference costs 2021/22 (£399.92)	SB15Z – from NHS reference costs 2022/23 (£393.16)

pMMR, mismatch repair proficient; dMMR, mismatch repair deficient;; SoC+D. standard of care plus durvalumab;; PFS, progression-free survival; OS, overall survival; TTD, time to treatment discontinuation

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential discounts

dMMR subgroup:

- Company base case ICERs < £20,000 per QALY gained
- EAG deterministic base case ICERs are between £20,000 and £30,000 per QALY while probabilistic ICERs are above £30,000 per QALY gained

pMMR subgroup:

- Company and EAG base case ICERs are both above £30,000 per QALY gained

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Managed access

Company has not submitted a managed access proposal

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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Summary of issues

Key issue	ICER impact	Slide
Immaturity of data from DUO-E clinical trial	Unknown	13
Subsequent treatment usage	Unknown	16
Cap on treatment duration	Large	18
Proportion initiating olaparib maintenance treatment (pMMR subgroup only)	Large	20
Estimation of newly progressed patients per model cycle	Moderate	21

Other issues (addressed in appendix slides)	ICER impact	Appendix slide
Treatment waning (linked to cap on treatment duration)	Unknown	39
Wastage	Small	46

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

Summary of key questions for committee

- Which PFS extrapolation for SoC+D is more plausible for the dMMR subgroup? (slide 14)
- Which OS extrapolation is more plausible for the dMMR subgroup? (slide 15)
- How does the difference in availability of subsequent immunotherapy use in UK practice affect the generalisability of the DUO-E data? (slide 16)
- Should there be a cap on treatment duration in the model? (slides 18-19)
    - If yes, does committee need to consider a stopping rule?
    - If no cap is preferred, what is the appropriate extrapolation of TTD in pMMR and dMMR?
- How would olaparib be used in combination with durvalumab in clinical practice? What circumstances would make someone ineligible for olaparib at maintenance stage? (slide 20)
    - What proportion of people starting maintenance treatment with olaparib in the pMMR subgroup should be used?
- How should the proportion of newly progressed patients per cycle be modelled? (slide 21)

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Thank you.

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Supplementary appendix

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Clinical perspectives

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

Submission from clinical expert:

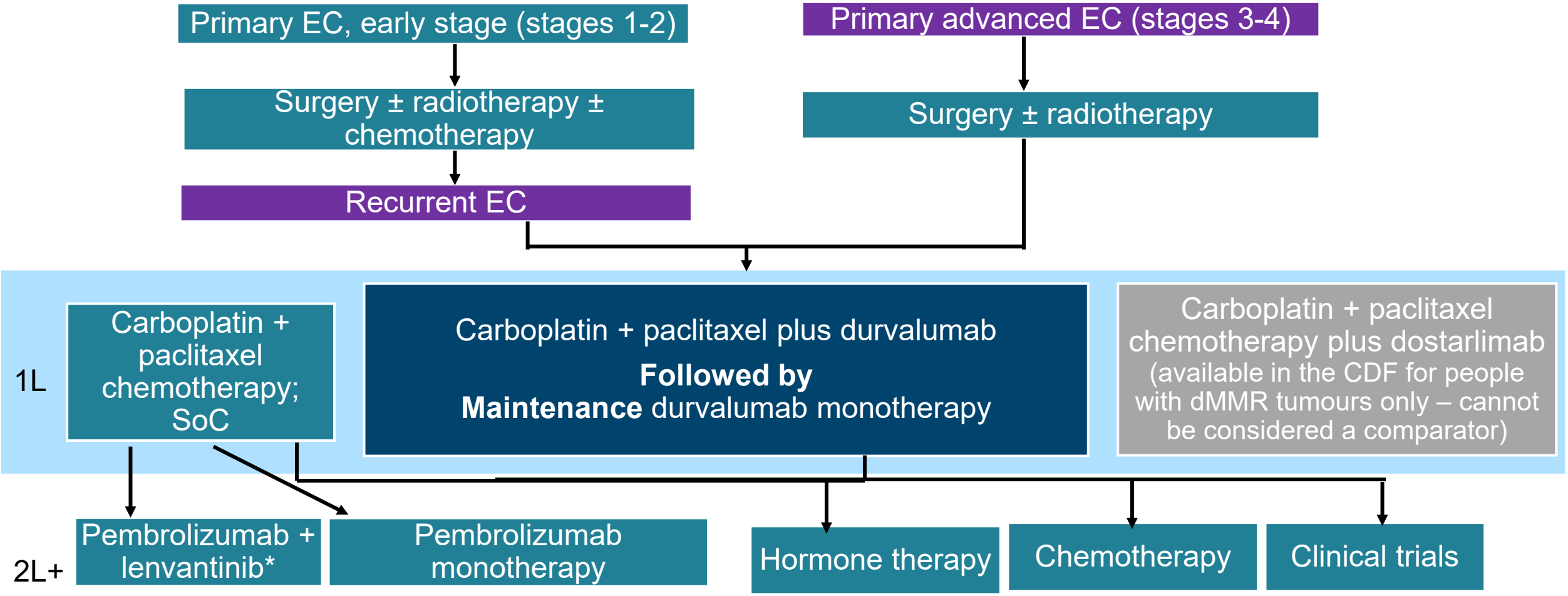
- Treatment aims to improve quality of life and survival where possible – but introduction of immunotherapy potentially improves long-term survival to the point of cure in a significant proportion of the dMMR population
- Data shows carboplatin + paclitaxel plus durvalumab followed by maintenance durvalumab + olaparib is beneficial in people with pMMR disease where unmet need is higher (and the addition of olaparib is particularly beneficial in pMMR tumours with biomarkers associated with especially poor prognosis).
    - Heterogeneity in pMMR population means it is unclear whether full pMMR population will gain substantial benefit
- 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
- Monitoring of treatment response on maintenance therapy would be done with cross-sectional imaging every 9-12 weeks (not currently part of routine surveillance)
- Care pathway not always well defined across the country - guidelines not always specific or frequently updated

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

Treatment pathway - dMMR

= Intervention

EAG – treatment pathway in line with current clinical practice



* Treatments available after SoC only - Blueteq criteria does **not** allow 2 lines of immunotherapy

Is the treatment pathway correct?
Is platinum-based chemotherapy followed by standard care the appropriate comparator for both pMMR and dMMR subgroups?

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Treatment pathway - pMMR

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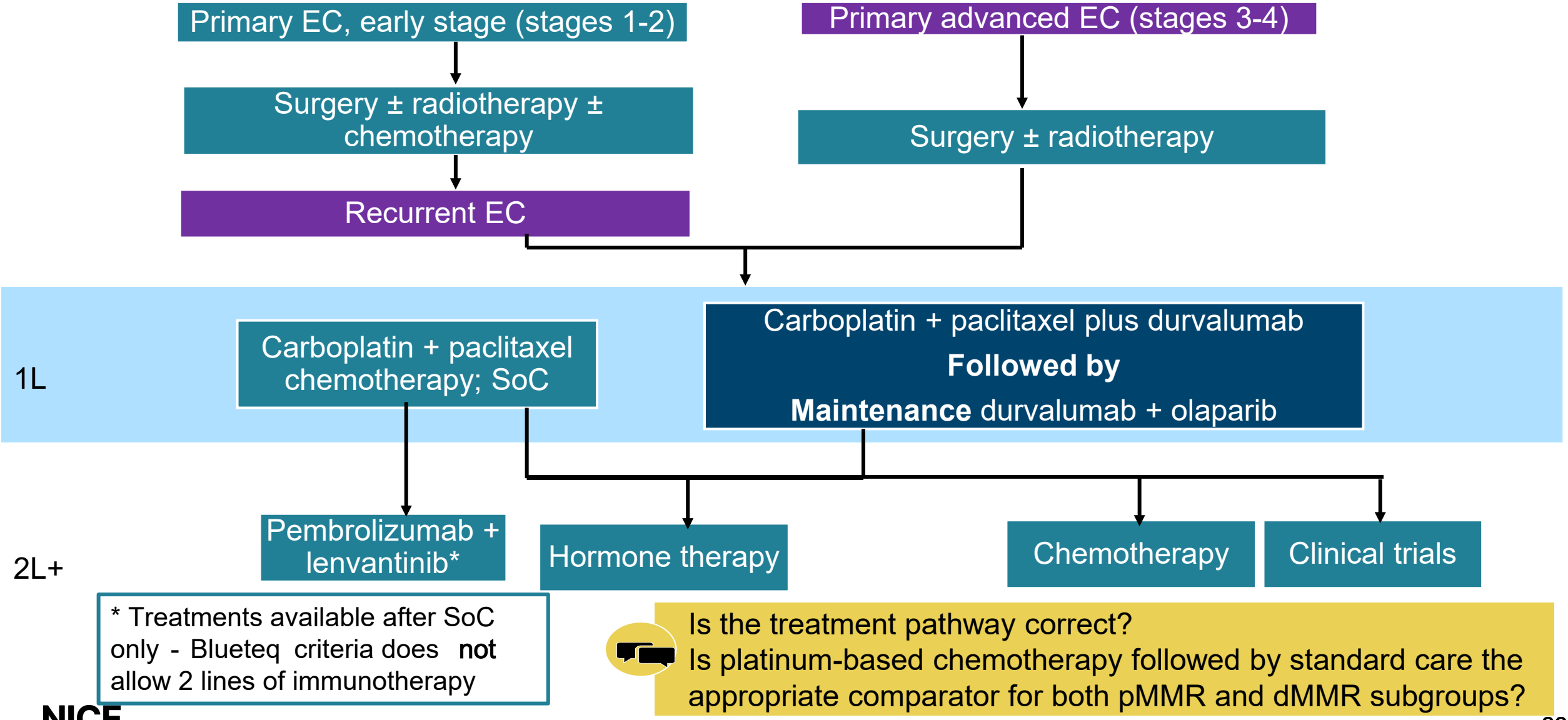
EAG – treatment pathway in line with current clinical practice



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EC, endometrial cancer; pMMR, mismatch repair proficient; dMMR, mismatch repair deficient; CDF, Cancer Drugs Fund

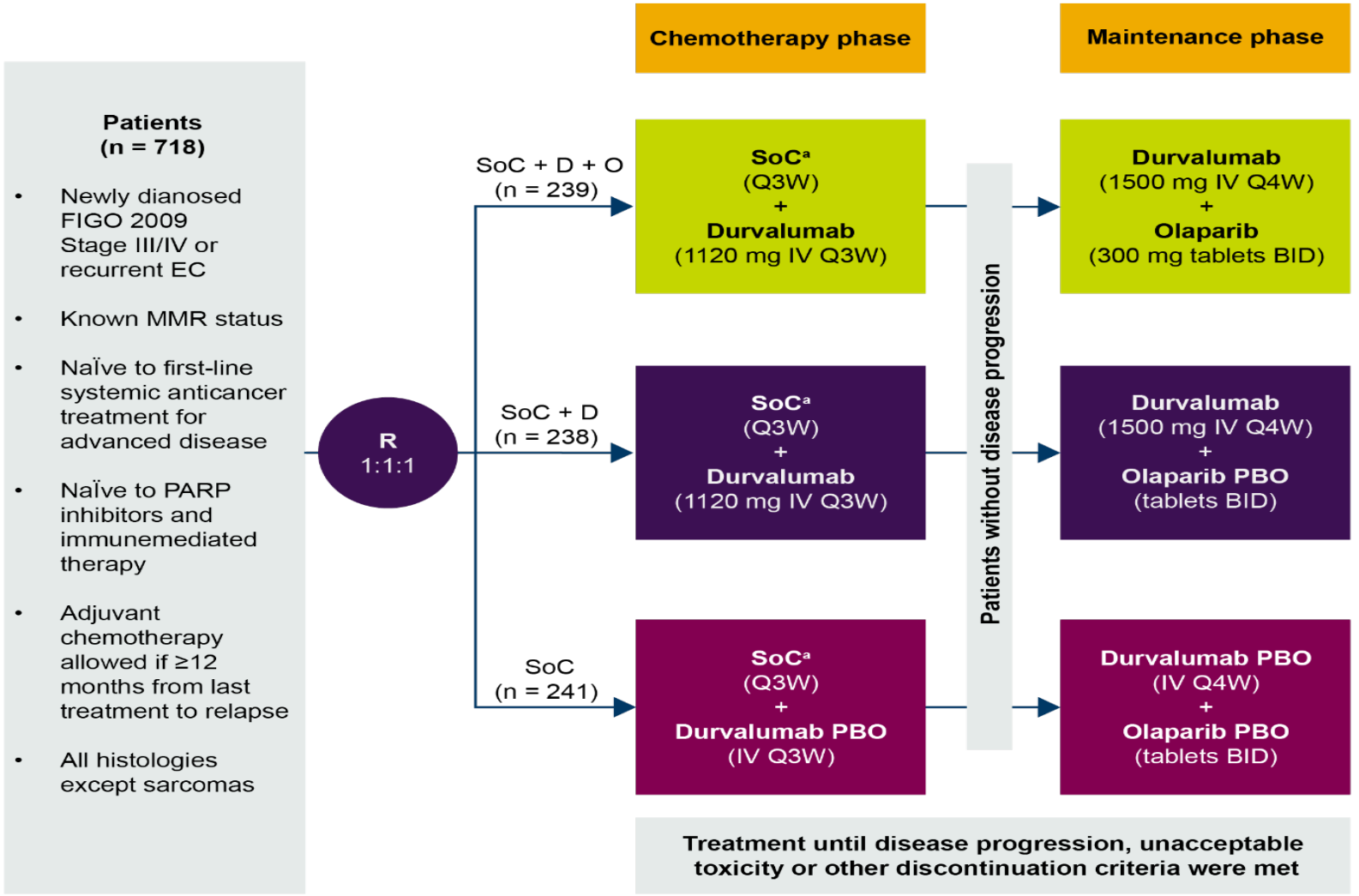
Decision problem

	Final scope	Company	EAG comments
Population	People with newly diagnosed advanced or recurrent EC	People with newly diagnosed advanced or recurrent EC. CS focuses on analysis of pMMR and dMMR subgroups.	Population split by MMR status aligns with MAs for durvalumab and olaparib – appropriate.
Interventions	Durvalumab with platinum-based chemotherapy, followed by maintenance durvalumab with or without olaparib.	**pMMR**: Induction durvalumab with platinum-based chemotherapy, followed by maintenance durvalumab with olaparib (SoC+D+O) **dMMR**: Induction durvalumab with platinum-based chemotherapy, followed by maintenance durvalumab (SoC+D)	Appropriate - aligns with MAs for durvalumab and olaparib.
Comparators	Platinum-based chemotherapy, hormone therapy (both followed by routine surveillance)	Platinum-based chemotherapy (paclitaxel + carboplatin) followed by routine surveillance	Hormone therapy used in small proportion of patients not suited for chemotherapy – reasonable to exclude as comparator
Outcomes	OS, PFS, response rate, duration of response, AEs, HRQoL	As per scope	Data on HRQoL and AEs based on ITT population instead of MMR subgroups – but not unreasonable

NICE

EC, endometrial cancer; pMMR, mismatch repair proficient; dMMR, mismatch repair deficient; SoC+D+O; standard of care plus durvalumab plus olaparib; SoC+D. standard of care plus durvalumab; MA, marketing authorisation; PFS, progression-free survival; OS, overall survival; AEs, adverse events; HRQoL, health related quality of life; MMR, mismatch repair; ITT, intention to treat; CS, company submission

DUO-E study design



[a] Six cycles of carboplatin at AUC of 5 or 6 mg per mL/min and paclitaxel 175 mg/m2

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PFS extrapolations for pMMR subgroup

For both SoC and SoC+D+O, EAG considers company's log-logistic extrapolation appropriate

PFS KM curves, and log-logistic extrapolations for SoC and SoC+D+O in the PMMR subgroup:

Year	SoC (%)		SoC+D+O (%)	
	KM	Log-logistic	KM	Log-logistic
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	-	[redacted]	-	[redacted]
5	-	[redacted]	-	[redacted]
10	-	[redacted]	-	[redacted]

EAG

- Company explored flexible spline models – but analysis demonstrated these did not offer meaningful advantages over standard parametric models
- Changes in chosen PFS extrapolation are not a key driver of cost effectiveness

NICE

SoC, standard of care; SoC+D. standard of care plus durvalumab; OS, overall survival; pMMR, mismatch repair proficient; KM, Kaplan-Meier

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OS extrapolations for pMMR subgroup

EAG – company's extrapolations reasonable but more mature OS data still needed

OS KM curves, lognormal extrapolations and log-logistic extrapolations for SoC and SoC+D+O:

Year	SoC (%)		SoC+D+O (%)	
	KM	Log-logistic	KM	Log-logistic
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	-	[redacted]	-	[redacted]
5	-	[redacted]	-	[redacted]
10	-	[redacted]	-	[redacted]

EAG

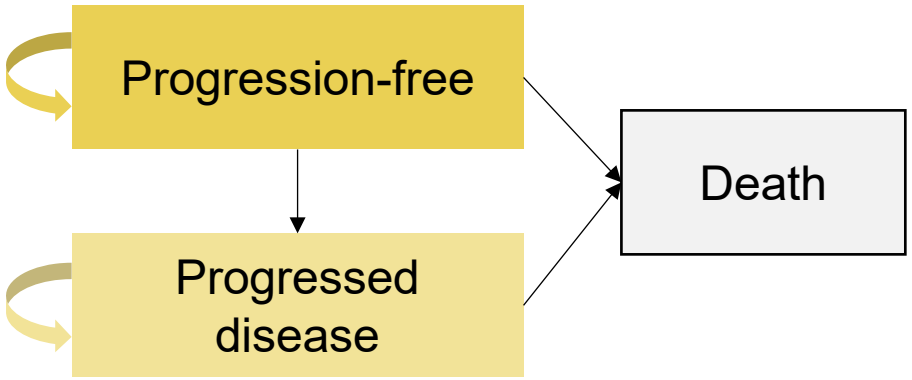
- Company has validated OS estimates for SoC against published data and long-term OS estimates not unreasonable. If using the same type of distribution for treatment arms of a model, then not unreasonable to apply to SoC+D+O in absence of more long-term data
- Significant uncertainty in OS data due to immaturity – benefits of subsequent immunotherapy may not be fully captured in extrapolations

SoC, standard of care; SoC+D. standard care plus durvalumab; OS, overall survival; pMMR, mismatch repair proficient; KM, Kaplan-Meier

Company's model overview

Three state partitioned survival model with dMMR and pMMR modelled separately

Model structure



EAG

- Model structure is appropriate
- Acquisition costs based on TTD with shorter cycle (1 week) than OS/PFS cycles (1 month) – but no significant inconsistencies

- Technology affects **costs** by:
  - Increasing drug acquisition costs
- Technology affects **QALYs** by:
  - Increasing survival
- Assumptions with greatest ICER effect:
  - Method for estimating long-term survival for dMMR patients
  - Duration of treatment with durvalumab and olaparib
  - Proportion of progression-free pMMR patients starting maintenance treatment with olaparib in addition to durvalumab.

pMMR, mismatch repair proficient; dMMR, mismatch repair deficient;; OS, overall survival; PFS, progression-free survival ; ICER, incremental cost-effectiveness ratio; TTD; time to treatment discontinuation; QALY, quality-adjusted life year.

How company incorporated evidence into model

Input and evidence sources

Input	Assumption and evidence source
Baseline characteristics	Based on final analysis (FAS) of ITT population (mean age 62.6 years)
Intervention and comparator efficacy	DUO-E individual patient level data (split by MMR subgroup)
Time horizon	Lifetime (38 years)
Utilities	EQ-5D-5L data from patients in DUO-E, mapped to EQ-5D-3L
Cycle length	1 month (PFS and OS), 1 week (TTD)
Discount rate	3.5%
Costs	BNF, NHS NCC, PSSRU and eMIT
Resource use	Routine costs informed by TA963 and DUO-E resource use data. One off terminal care cost applied (sourced from PSSRU)
Subsequent treatment	Based on DUO-E trial data and UK clinical expert opinion, [redacted] of progressed patients have subsequent treatment (regardless of MMR status)
Treatment waning	None

ITT; intention to treat; MMR, mismatch repair; OS, overall survival; PFS, progression-free survival; TTD; time to treatment discontinuation; BNF; British National Formulary; NCC, National Cost Collection; PSSRU, Personal Social Services Research Unit; eMIT, electronic market information tool (eMIT);

Other issues: Immunotherapy and treatment waning

EAG considers issue secondary to immaturity of data

Company

- No treatment-waning assumptions included in modelling after treatment duration cap of 3 years
- Company's clinical expert – minimal to no treatment waning effect with immunotherapies in this setting
- Treatment waning effects not included in dostarlimab appraisal (TA963)

EAG comments

- CDF lead in dostarlimab appraisal (TA963) - immunotherapies have showed sustained treatment benefit in other dMMR/MSI-H tumour types, but longer-term data needed
- In EAG's preferred approach to modelling treatment duration, waning effect is less of an issue because patients continue until disease progression or unacceptable toxicity

Previous immunotherapy appraisals in EC

- Appraisals for previously treated EC appraisals (pembrolizumab in TA914, pembrolizumab + lenvatinib in TA904, dostarlimab in dMMR/MSI-H EC in TA779) - committee preferred to apply some waning
- TA963 – uncertainty in whether treatment waning after discontinuation of dostarlimab applies due to immaturity of data – further data requested while in CDF

Does treatment waning need to be considered in the model?

NICE

EC, endometrial cancer; SPC, summary of product characteristics; pMMR, mismatch repair proficient; dMMR, mismatch repair deficient; TTD; time to treatment discontinuation

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TTD extrapolations without treatment duration cap (pMMR subgroup)

Company prefers log-logistic extrapolation with 3-year treatment cap, EAG prefers exponential with no treatment cap

Alternative extrapolations of durvalumab TTD without treatment duration cap – pMMR subgroup

Alternative extrapolations of olaparib TTD without treatment duration cap – pMMR subgroup

	Durvalumab		Olaparib	
	Exponential	Log-logistic	Exponential	Log-logistic
3 years % on treatment	[redacted]	[redacted]	[redacted]	[redacted]
5 years % on treatment	[redacted]	[redacted]	[redacted]	[redacted]
Mean TTD (years)	[redacted]	[redacted]	[redacted]	[redacted]

EAG - Longer time on olaparib with exponential, so estimation for time on combination treatment also longer

What extrapolation is most plausible for TTD for the pMMR subgroup?

pMMR, mismatch repair proficient; TTD; time to treatment discontinuation

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TTD extrapolations without treatment duration cap (dMMR subgroup)

EAG - gamma distribution has best statistical fit but more mature data still needed

Alternative extrapolations of durvalumab TTD without treatment duration cap – dMMR subgroup

	Durvalumab		
	Exponential	Generalised gamma	Gamma (company base case)
3 years % on treatment	[redacted]	[redacted]	[redacted]
5 years % on treatment	[redacted]	[redacted]	[redacted]
Mean TTD	[redacted]	[redacted]	[redacted]

What extrapolation is most plausible for TTD for the dMMR subgroup?

EAG

- Proportion of patients on treatment at 5 years is high based on clinical opinion – more mature data from DUO-E needed to validate assumption
- Mean estimate of TTD at 5 years based on gamma distribution in line with long-term remission assumption of 5 years and reflects EAG clinical expert advice

NICE

pMMR, mismatch repair proficient; TTD; time to treatment discontinuation

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Key issue: Olaparib maintenance treatment (pMMR only)

EAG comments on marketing authorisation

- At time of clarification response, company was seeking a NICE recommendation for the pMMR population aligned to the MA (SoC+D+O), but with flexibility in the recommendation for patients to continue durvalumab monotherapy in the maintenance phase if they are unable to initiate olaparib
- MA indicates that pMMR population should receive durvalumab and olaparib in combination (no MA for durvalumab alone in this subgroup) – flexibility does not align with MA
- Wording of the final SPC and marketing authorisations for durvalumab and olaparib should inform committee and any potential recommendation.

Marketing authorisation for durvalumab and olaparib in pMMR group

- Durvalumab in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with durvalumab in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR).
- Olaparib in combination with durvalumab is indicated for the maintenance treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair proficient (pMMR) whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel.

pMMR, mismatch repair proficient;; SoC+D+O; standard of care plus durvalumab plus olaparib; MA, marketing authorisation;

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Key issue: Estimation of newly progressed patients per model cycle

EAG formula for calculating newly progressed patients per model cycle:

$$PD_{new} = (OS_t - PFS_{t)}) - (OS_{t-1} - PFS_{t-1}) * \left(\frac{OS_t}{OS_{t-1}}\right)$$

PD_{new} – newly progressed patients between times t and t-1;

PFS_t – progression-free survival at time t

PFS_{t-1} – progression-free survival at time t-1

OS_t – overall survival at time t

OS_{t-1} – overall survival at time t-1

EAG

- Formula based approach allows changes in proportion over time
- Limitations to calculation since OS adjustment includes both patients dying from the PF and PD health state, but is equivalent to the company assuming a fixed proportion of deaths will be from the PF health state in model

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How should the proportion of newly progressed patients per cycle be modelled?

pMMR, mismatch repair proficient; dMMR, mismatch repair deficient;; SoC+D. standard of care plus durvalumab; MA, marketing authorisation; PFS, progression-free survival; OS, overall survival;

Key issue: Estimation of newly progressed patients per model cycle

Comparison of company and EAG estimation of newly progressed patients per model cycle for SoC patients – dMMR subgroup

[redacted]

Comparison of company and EAG estimation of newly progressed patients per model cycle for SoC+D patients – dMMR subgroup

[redacted]

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How should the proportion of newly progressed patients per cycle be modelled?

pMMR, mismatch repair proficient; dMMR, mismatch repair deficient;; SoC+D. standard of care plus durvalumab; MA, marketing authorisation; PFS, progression-free survival; OS, overall survival;

Key issue: Estimation of newly progressed patients per model cycle

Comparison of company and EAG estimation of newly progressed patients per model cycle for SoC patients – pMMR subgroup

[redacted]

Comparison of company and EAG estimation of newly progressed patients per model cycle for SoC+D+O patients – pMMR subgroup

[redacted]

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How should the proportion of newly progressed patients per cycle be modelled?

pMMR, mismatch repair proficient; dMMR, mismatch repair deficient;; SoC+D. standard of care plus durvalumab; MA, marketing authorisation; PFS, progression-free survival; OS, overall survival;

Other issues: Wastage

Company excludes drug wastage in base case, EAG prefers to include

Company

- Base case excludes drug wastage for IV drugs – assumes perfect vial sharing
  - Modelled scenario that includes wastage
- Vial sharing for high-cost oncology drugs is expected to be common in clinical practice to minimise wastage

EAG comments

- EAG clinical expert – vial sharing does not happen consistently in UK clinical practice
- EAG prefers to include drug wastage, but this has minimal impact on cost-effectiveness results

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Should drug wastage be included in the model?

EC, endometrial cancer; SPC, summary of product characteristics; pMMR, mismatch repair proficient; dMMR, mismatch repair deficient; TTD; time to treatment discontinuation