Slides for PUBLIC – no ACIC information

NICE National Institute for Health and Care Excellence

Dostarlimab for previously treated advanced and recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID3802]

Lead team presentation

Lead team: Justin Daniels, Ana Duarte, Richard Ballerand

ERG: Warwick Evidence

Technical team: Luke Cowie, Ellie Donegan, Henry Edwards

Company: GSK

2nd November 2021

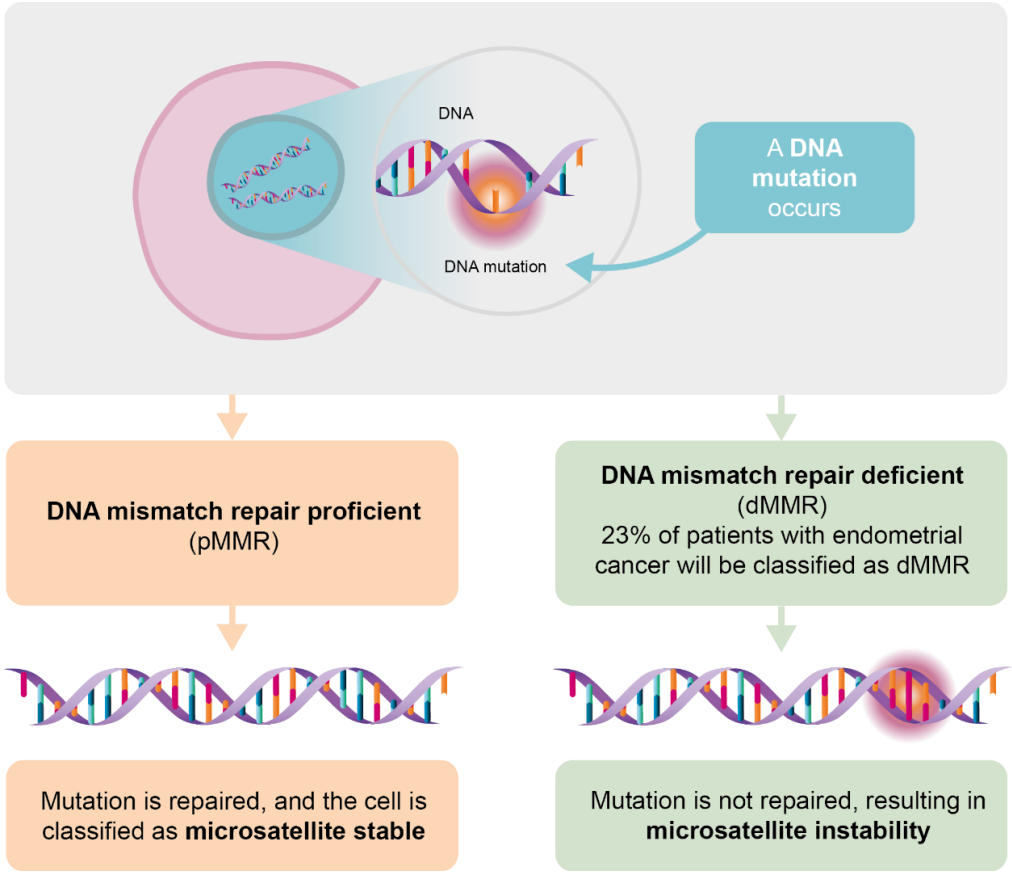
Endometrial cancer (1)

- Endometrial cancer (EC) is a type of uterine cancer originating in the lining of the womb (uterus), the endometrium
- Endometrioid carcinoma is the most common subtype of EC
  - typically diagnosed during the early stages
  - less aggressive than other less common subtypes
- Estimated 2,162 deaths every year in the UK
- For people with recurrent or advanced EC the standard of care is
  - platinum-based chemotherapy (first-line)
  - No standard second-line treatment.
- Disease progression is therefore associated with a very poor prognosis

Endometrial cancer (2)

- DNA mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) EC → subtype of EC comprising ~23% of cases
  - This is a subgroup where PD-1/PD-L1 inhibition is most effective → the focus of this appraisal
- Most people with recurrent or advanced dMMR/MSI-H EC who have progressed on or following treatment with a platinum-containing regimen (approx. 124 patients per year in England) will go on to receive further lines of chemotherapy, either as monotherapy or as a doublet chemotherapy regimen.
- Each subsequent line of chemotherapy results in increased chemoresistance
  - associated with a substantial burden of toxicity.

Mechanism of dMMR/MSI-H



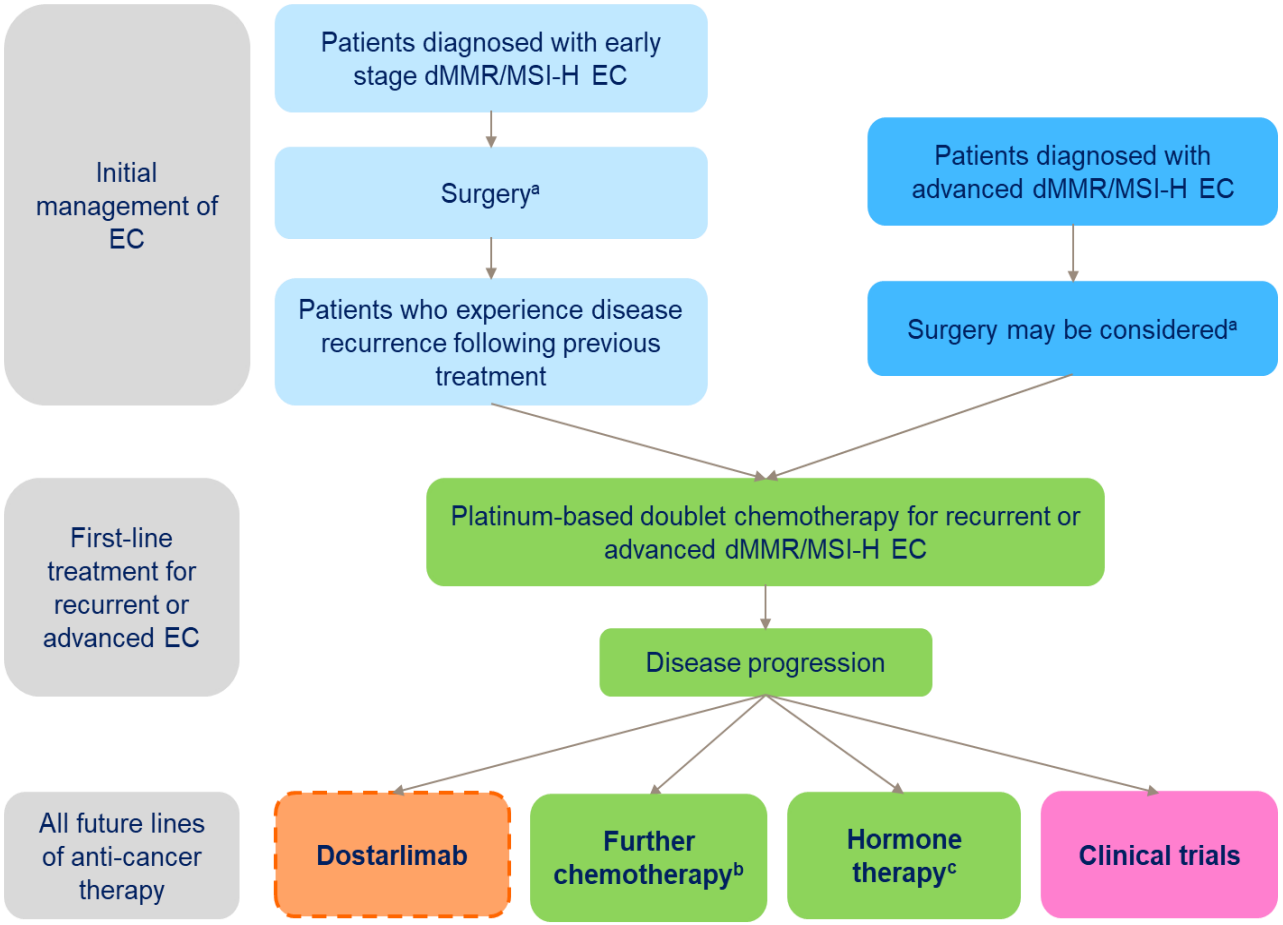
- dMMR/MSI-H is a molecular biomarker indicating a defective DNA repair process.
- Is highly immunogenic compared to other subtypes, with increased levels of circulating tumour infiltrating lymphocytes and high expression of immune checkpoint molecules.
- dMMR/MSI-H tumours are therefore more likely to respond to immuno-oncology treatment.

Clinical issues

- How would these patents currently be treated in the NHS?
- What is the prognosis for this advanced disease?
- Given the single arm trial, what is the best comparator data?
- Which factors are most important in relation to prognosis? The company states the most important are number of lines of prior anti-cancer treatment, histology and ECOG PS. Is this reasonable?
- Is the subgroup of patients identified as GARNET-like from RWE as suitable comparator arm to represent current care?
- How robust is the OS MAIC analyses for efficacy of dostarlimab compared with current treatment (UK RWE study)?

Clinical effectiveness

Proposed treatment pathway



- Does this represent the current treatment pathway in the NHS?
- What is the likely prognosis of people receiving 2nd line treatment for endometrial cancer?

[a] At any stage, patients may also receive neoadjuvant or adjuvant radiotherapy, chemotherapy or hormone therapy, in addition to surgery. [b] Further chemotherapy may consist of carboplatin plus paclitaxel, doxorubicin or gemcitabine, carboplatin monotherapy, paclitaxel monotherapy, doxorubicin monotherapy, among others. [c] Although not licensed, hormone therapy would consist of either letrozole or medroxyprogesterone acetate.

Patient and carer perspective

Unmet need

- Currently no alternatives to chemotherapy
- Considerable unmet need for women with advanced endometrial cancer
    - conventional chemotherapy provides very limited effect
- Affects an older population, but many are still of working age
- The outlook is currently bleak – no effective treatment to extend life

Potential benefits of dostarlimab

- 30 minute infusion vs whole day to chemotherapy transfusions
    - Saving patient and clinical time and money
- Improve quality of life
    - Able to resume and maintain normal activities in day-to-day life
- Treatment would allow continued working and contribution to the economy
    - Whole societal benefits, as well as enabling women to retain their identity

Clinical and professional submissions

Submission from National Cancer Research Institute, Association for Cancer Physicians, Royal College of Physicians, Royal College of Radiologists

Aim of treatment

- Improve progression free survival and control symptoms by reducing tumour bulk

Clinical need

- Current survival rates with 1st line carboplatin-paclitaxel is disappointing
- Women with relapsed /advanced endometrial cancer have limited efficacious treatment options
  - Significant need for novel therapeutic options

Dostarlimab

- Substantial step-change
- Expected it to improve progression free survival compared to current care
- Will improve quality of life due to less toxicity than some chemotherapy agents, and by delaying progression events and therefore disease-related complications.

Dostarlimab (Jemperli, GSK)

Description of technology	Dostarlimab is a humanised, monoclonal antibody which binds to programmed cell death protein 1 (PD-1), a cell surface receptor expressed on activated T-cells. It blocks the PD-1 signalling resulting in an increased anti-tumour immune response and cancer cell death.
Marketing authorisation (granted June 2021)	Dostarlimab is indicated as monotherapy for the treatment of adult patients with mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.
Administration	• Dostarlimab 500 mg is administered via a 30-minute IV infusion every 3 weeks (Q3W) (Day 1 of each 21-day cycle) for the first 4 cycles. • Followed by dostarlimab 1,000 mg administered via IV infusion every 6 weeks (Q6W) (Day 1 of each 42-day cycle) for subsequent cycles.
Price (list price)	The list price of dostarlimab is £5,887.33 per 500 mg vial. Based on the time on treatment in the base case cost-effectiveness analysis, the average discounted cost per course of treatment with dostarlimab (including drug acquisition and administration costs) is £126,652 at list price. There is a simple discount PAS for dostarlimab.

GARNET trial design

An open-label, single-arm, multicentre, non-randomised Phase I trial

Population	• Patients with recurrent or advanced dMMR/MSI-H EC who have progressed on or after platinum-based chemotherapy. • ECOG PS of ≤1 • At least one prior anti-cancer treatment, with most ([redacted]%) receiving exactly one prior line of anti-cancer therapy. • ERG notes GARNET population is broadly representative of UK patients.
Locations	International trial with centres in nine countries: United Kingdom (nine sites), Poland, Canada, Denmark, France, Italy, Spain, United States
Intervention	Dostarlimab
Comparator	N/A (single arm trial)
Follow up	Median follow-up in the company submission was [redacted] months
Primary outcomes	Objective response rate (ORR) and duration of response (DOR)
Secondary outcomes	Immune-related disease control rate (irDCR), immune-related disease control rate (irDOR), immune-related progression-free survival (irPFS), and immune-related objective response rate (irORR)

GARNET ITT– Key results

An open-label, single-arm, multicentre, non-randomised Phase I trial

Efficacy outcomes	Efficacy evaluable set, (n=[redacted]); ITT population (n=[redacted])
ORR (95% CI)	[redacted]
Complete response	[redacted]
Partial response	[redacted]
DOR, median (95% CI) months Median follow-up [redacted] months	[redacted]
PFS, median (95% CI) months Median follow-up [redacted] months	[redacted]
OS, median (95%) CI months Median follow-up [redacted] months	[redacted]

The primary endpoints in GARNET were ORR and DOR.

ORR – objective response rate; DOR – duration of response; PFS – progression-free survival; OS – overall survival; CI – confidence interval; ITT – intention to treat

PFS & OS KM curves from GARNET (efficacy population and ITT population)

- Efficacy population (n=[redacted]): only patients who had measurable disease at baseline and at least 24 weeks follow-up to allow analysis of response-related endpoints in GARNET.
- Intention-to-treat population (ITT, n=129): all patients that received at least one dose of dostarlimab, informs the base case cost-effectiveness analysis.

UK Real World Evidence (RWE) study

- Patients identified from a total of 45,494 diagnosed with EC between 2013 and 2018.
- 3,415 had advanced or recurrent EC and similar baseline characteristics to GARNET cohort.
- [redacted] of these had received exactly one prior platinum doublet therapy.

[redacted]

Population n=[redacted]	• Recurrent or advanced EC that are treated with their subsequent line of therapy following their first line of platinum-based doublet chemotherapy. • No information on dMMR/MSI-H status. No ECOG PS for [redacted]% of cohort.
Registry data	National Cancer Registry Analysis System (NCRAS): combines linked data from the Hospital Episode Statistics (HES), systemic anti-cancer therapy (SACT), National Radiotherapy Dataset (RTDS), Cancer Outcomes and Services Dataset (COSD), Office for National Statistics (ONS) mortality data.
Interventions	A range of the most commonly utilised EC chemotherapy regimens in UK clinical practice, based on NCRAS data.
Outcomes (all from 2nd line)	Overall survival (OS), time to next therapy (TTNT, used as a proxy for PFS), and time to treatment discontinuation (TTD).

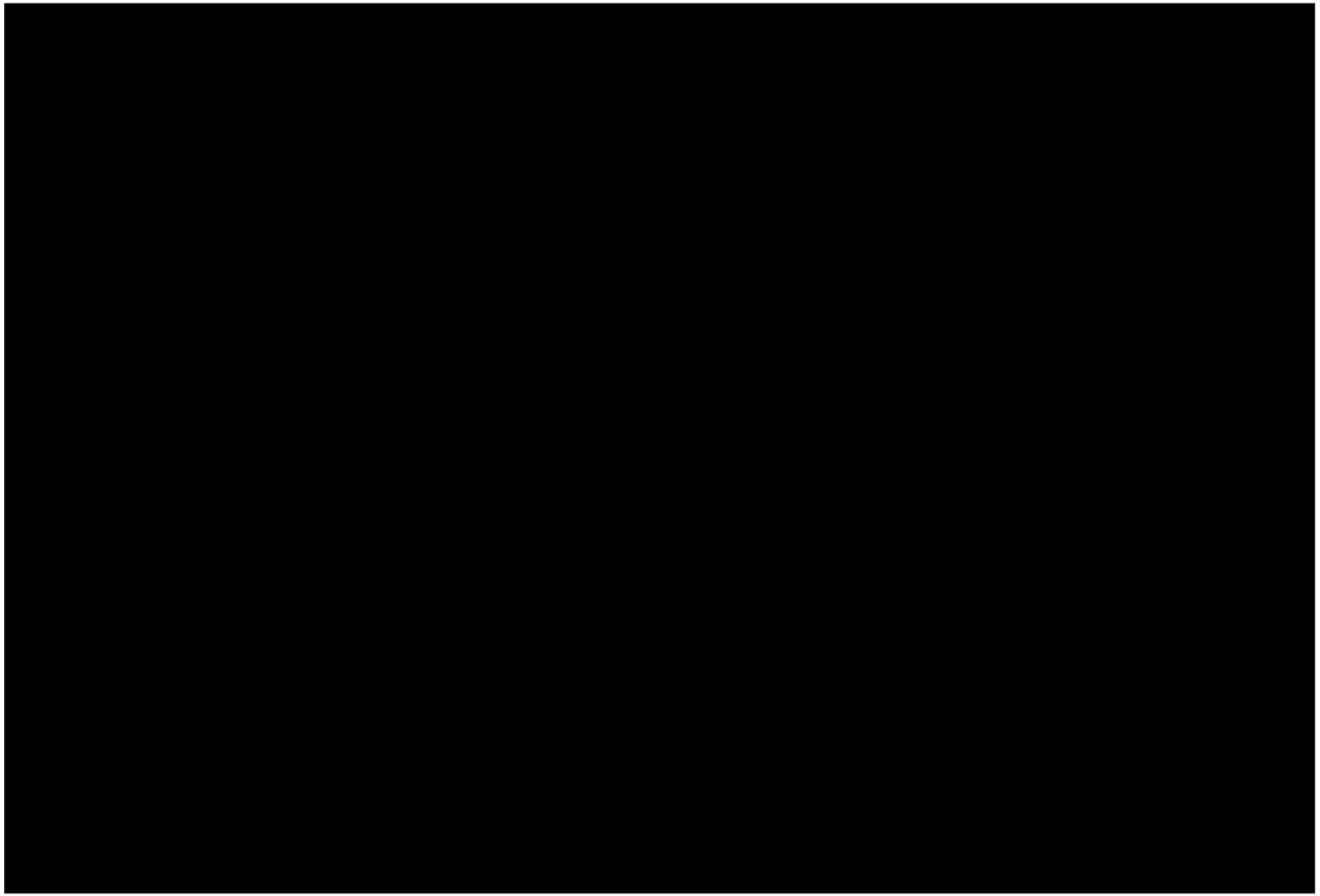
Baseline differences – GARNET and RWE

Characteristic	GARNET-like UK RWE ECOG PS ≤1 cohort (N=[redacted])	GARNET-like UK RWE cohort (N=[redacted])	GARNET ITT population (N=[redacted])
Mean age, years (STD)	[redacted]	[redacted]	[redacted]
Median age, years	[redacted]	[redacted]	[redacted]
Most recent ECOG PS at registry diagnosis (RWEQ) or study entry (GARNET), n (%)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
Not recorded	[redacted]	[redacted]	[redacted]
Histology at diagnosis, n (%)			
Endometrioid	[redacted]	[redacted]	[redacted]
Non-endometroid	[redacted]	[redacted]	[redacted]
Serous carcinoma	[redacted]	[redacted]	[redacted]
Unknown at diagnosis	[redacted]	[redacted]	[redacted]
Number of prior lines of therapy post advanced/recurrent diagnosis, n (%)			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
≥4	[redacted]	[redacted]	[redacted]

- Eastern Cooperative Oncology Group Performance Status (ECOG PS) not known for [redacted]% of UK real world equivalent (RWE) cohort.
- GARNET population had more prior lines of treatment than UK RWE population.
- **What are the most important prognostic factors? Which cohort is the better comparator?**

OS from the UK RWE study

- OS for patients (n=[redacted]) with recurrent or advanced EC that has progressed on or after platinum-based chemotherapy, receiving current clinical management.



Naïve OS comparison (UK RWE study v GARNET)

	UK RWE study (current clinical management) (N=[redacted])	GARNET ITT population (dostarlimab) (N=129)
Median OS (months) (95% CI)	[redacted]	[redacted]
OS distribution function (95% CI)		
Month 6	[redacted]	[redacted]
Month 9	[redacted]	[redacted]
Month 12	[redacted]	[redacted]
Month 18	[redacted]	[redacted]
Month 24	[redacted]	[redacted]

OS in the systematic literature review:

- Patients receiving doxorubicin monotherapy: the ZoptEC study had a median OS of **10.8** months (95% CI: 9.8, 12.6), with **23.0**% of patients alive at Month 24.
- Patients receiving paclitaxel or doxorubicin monotherapy: McMeekin et al. (2015) had a median OS of **12.3** months (95% CI: 10.7, 15.4), with **29.4**% of patients alive at Month 24.
- Patients receiving carboplatin plus paclitaxel: Mazgani et al. (2008) reported a median OS estimate of **15.0** months (95% CI: 9.1–30.4), with **35.5**% of patients alive at Month 24. Rubinstein et al. (2019) reported a median OS of **27.0** months (95% CI: 6.0, 117.0), with **59.5**% of patients alive at Month 24.

NICE

OS – overall survival; CI – confidence interval; RWE – real world equivalent; ITT – intention to treat

Summary of naïve PFS and OS results from GARNET ITT and RWE

	UK RWE	GARNETT (ITT)
Progression-free at 12 months (%)	[redacted]	[redacted]
Progression-free at 24 months (%)	[redacted]	[redacted]
Still alive at 24 months (%)	[redacted]	[redacted]

ERG comments on naïve comparison of GARNET and RWE:

UK RWE cohort broadly similar to the population in GARNET with some key differences:

- GARNET participants were required to have received no more than two lines of systemic anticancer therapy for advanced/recurrent disease vs. UK RWE study exactly one prior platinum doublet therapy.
- GARNET participants required to have histologically / cytologically proven recurrent solid tumour with measurable lesion(s) per RECIST v1.1 vs. UK RWE study probable recurrence.
- GARNET patients required to have dMMR/MSI-H EC vs. not stated in the eligibility criteria for the UK RWE study. dMMR/MSI-H is predominantly found within in Type I endometrioid tumours (28-40%), which tends to have better prognosis.
- Therefore, 2 MAIC approaches were used by the company (Scenario 1 and Scenario 2) to explore matching of different prognostic variables.

OS KM curves: MAIC for dostarlimab (GARNET) versus current management (UK RWE)

Two matching-adjusted indirect comparison (MAIC) scenarios were constructed:

- Prognostic variables identified by clinical expert opinion (Scenario 1), and
- Variables found to be statistically significant in regression analyses (Scenario 2).

	Prognostic variables	
Scenario 1	• Histology • Number of prior platinum-based therapies in the advanced/recurrent setting	
Scenario 2	• Race/ethnicity • Stage at diagnosis	• Histology • Prior surgery

[redacted]

Supporting MAICs for individual comparators

The company did an adjusted indirect comparison of OS between dostarlimab and doxorubicin monotherapy, using individual patient data from ZoptEC trial.

- People treated with dostarlimab were [redacted]% less likely to die at any given timepoint compared to those receiving doxorubicin monotherapy (HR: [redacted]; 95% CI: ([redacted], [redacted]); p<[redacted])

A total of five studies were included in alternative matching-adjusted indirect comparisons (MAICs) comparing dostarlimab to the individual chemotherapy comparators. McMeekin MAIC is the most robust.

- PFS: people treated with dostarlimab were more than five times less likely to experience disease progression or death (HR: [redacted]; 95% CI: [redacted], [redacted]; p<[redacted]) compared with doxorubicin monotherapy (MAIC v Makker et al. 2013).
- OS: people treated with dostarlimab were approximately three times less likely to die (HR: [redacted]; 95% CI: [redacted], [redacted]; p<[redacted]) compared with those receiving paclitaxel or doxorubicin (MAIC v McMeekin et al. 2015).

ERG comment:

- MAICs must be interpreted with considerable caution given limited data/small sample size and poorly reported patient characteristics and prognostic variables across the studies.
- In particular, lack of data on prior anti-cancer treatments is a key limitation as one of the most important prognostic variables based on clinical expert opinion.
- Analyses focusing on more homogeneous groups of patients, e.g. endometrioid disease only, would help to mitigate these concerns.
- Question what is the best comparator data for the GARNET trial?

Alternative endometrioid MAIC

At technical engagement

- A matching-adjusted indirect comparison (MAIC) between endometrioid-only populations from GARNET and UK RWE study was requested by ERG as more homogenous cohorts for comparison.
- Company notes that naive HR between dostarlimab and current clinical management in this cohort ([redacted]) was similar to the matching-adjusted HRs ([redacted] in both scenarios 1 & 2).
- Company suggest that there were only minor imbalances between the two endometrioid cohorts in the naïve comparison which result in a slight underestimation of the treatment effect associated with dostarlimab.

ERG

- Disagree with company's interpretation that similar HRs between naïve and adjusted analyses suggest only minor imbalances between the two endometrioid cohorts.
- Considers it more likely that the MAICs have not adequately adjusted for the important imbalances that remained between the two endometrioid cohorts due to lack of comparable data in RWE for some key prognostic factors.

Clinical issues

- How would these patents currently be treated in the NHS?
- What is the prognosis for this advanced disease?
- Given the single arm trial, what is the best comparator data?
- Which factors are most important in relation to prognosis? The company states the most important are number of lines of prior anti-cancer treatment, histology and ECOG PS. Is this reasonable?
- Is the subgroup of patients identified as GARNET-like from RWE as suitable comparator arm to represent current care?
- How robust is the OS MAIC analyses for efficacy of dostarlimab compared with current treatment (UK RWE study)?

Cost effectiveness

Cost issues

- Is the model design appropriate?
- What is the appropriate way to model OS for dostarlimab?
- A two-step elicitation process was used to inform model assumptions for survival, treatment discontinuation and treatment effect duration.
- Was the elicitation methodology appropriate to inform decision making?
- How should time on treatment be modelled?
- What should be assumed on the maintenance of treatment effect?

Company's model structure

- Partitioned survival, 3 health states (progression-free, post-progression, and death)
- 3 week cycle length to capture changes in costs and effects over time (and in line with the dostarlimab dose interval.

Factor	Chosen values
Time horizon	Lifetime horizon (40 years)
Mean age in model	[redacted] years
Clinical parameters	Dostarlimab (PFS and OS) from the GARNET study. Current clinical management (PFS and OS) from UK RWE study.
Cost of comparator treatments	Basket of treatments to represent current clinical management. ERG agree that choice of treatments in appropriate. Carboplatin plus pegylated liposomal doxorubicin (PLD) included but not in final scope.
Source of utilities	Health state utility values for the PFS and PPS health states were informed by EQ-5D-5L data collected in the GARNET study, cross-walked to the 3L scale using the Van Hout et al. algorithm.
Source of costs	NHS reference costs PSSRU BNF/eMIT

BNF: British National Formulary; eMIT: electronic market information tool; PSSRU: Personal Social Services Research Unit; RWE: real-world equivalent; PFS: progression-free survival; OS: overall survival

Company expert elicitation

Company elicited expert opinion on PFS, OS and TTD – used in the model

ERG's concerns

- OS and PFS elicitation were conducted prior to the discussions around treatment stopping rules and treatment waning.
  - Experts were not asked about the parameterised curves adjusted for dostarlimab treatment stopping rules.
- Experts asked to consider unadjusted curves for OS and PFS but results were applied to dostarlimab curves adjusted using an assumption of treatment waning
  - Expert responses likely biased and too high for curves adjusted for treatment withdrawal assumptions
- Company presented the number at risk and not the Kaplan Meier TTD curve.
  - Presenting the Kaplan Meier number remaining at risk, effectively treating data cut off as a discontinuation event, renders company elicitation exercise biased.
- TTD and stopping rules elicitation exercise was conducted after the OS and PFS
  - Unbiased OS and PFS estimates adjusted for the TTD and treatment stopping rules require prior consideration of the TTD and stopping rules.

Company model: key inputs

Clinical efficacy: dostarlimab	
Progression-free survival	Lognormal
Overall survival	Generalised gamma
Time on treatment	Log-logistic
Percentage of patients who continue dostarlimab after [redacted], %	[redacted]
Percentage of patients who continue dostarlimab after [redacted], %	[redacted]
Timepoint for start of treatment waning applied to PFS and OS	[redacted]
Timepoint for end of treatment waning applied to PFS and OS	[redacted]
Clinical efficacy: current clinical management	
Progression-free survival	Log-logistic
Overall survival	Log-logistic
Time on treatment	Generalised gamma

- After technical engagement, company maintained assumptions that full treatment will be retained for [redacted] after cessation of dostarlimab. At this point, waning occurs over [redacted], so at [redacted] post treatment cessation the hazard of death is equal to that of the comparator.

PFS: progression-free survival; OS: overall survival.

Company model: key assumptions

Assumption	Description of assumption for the base case
Modelling of PFS and OS for dostarlimab	The GARNET ITT population is assumed to provide efficacy data for PFS and OS for patients treated with dostarlimab.
	The full treatment effect on PFS and OS for dostarlimab versus current clinical management is assumed to last for [redacted] after stopping dostarlimab, then linear waning for [redacted] until treatment effect lost.
Modelling of ToT for dostarlimab	[redacted]% of patients on dostarlimab will continue treatment beyond [redacted].
	There is a maximum treatment duration for patients treated with dostarlimab; [redacted] assumed to discontinue treatment at [redacted].
Modelling of PFS, OS and ToT for current clinical management	The UK RWE study provides efficacy data and ToT data for comparator treatments used as current clinical management in the UK.

ERG consider that the expert elicitation exercise for dostarlimab PFS, OS and TTD were flawed and likely to have resulted in bias.

Company base case

	ICER
Company base case	£48,608
Company scenario 5* (endometrioid cohort, represents company's conservative upper bound)	£55,626

* Further details on company scenarios presented on slides 36 & 37

Difference between company and ERG

	Company	ERG
Stopping Dostarlimab	[redacted]% continue beyond [redacted], [redacted].	[redacted]% continue beyond [redacted], [redacted].
Waning of Dostarlimab	[redacted] after stopping, then linear waning for [redacted]	Waning applied immediately after stopping Dostarlimab over [redacted]
Overall survival	Gen. gamma	Weibull
Time to treatment discontinuation	Lognormal	Gen. gamma

Time on Treatment

Company

- Base case assumes [redacted]% continue on dostarlimab beyond [redacted] ([redacted] assumed to discontinue treatment after [redacted]).
- Experts predicted that number of patients on treatment after [redacted] would be between [redacted]%–[redacted]%.

ERG

- Time on treatment elicitation exercise was poorly constructed, likely bias results - at best it provides a floor to the cessation percentage
- The company range of [redacted]% to [redacted]% is likely to be biased, a midpoint of [redacted]% would still be too low.
- ERG prefers [redacted]%.

Given the limitations of the company expert elicitation exercise, what are the most appropriate assumptions for time on treatment and treatment waning?

Treatment waning

Company

- Assume full treatment effect for [redacted] after stopping dostarlimab, then linear waning for [redacted] until treatment effect lost.
- Some patients continue to receive treatment up to [redacted] → conservative to apply treatment waning to all patients in the dostarlimab arm from the end of [redacted]
- Treatment waning from [redacted] consistent with other immunotherapy appraisals.
  - For example, TA490 and TA661 - full treatment effect was assumed to exist for 3 years after stopping treatment with the immunotherapy.
- Clinical feedback does not support the ERG's preferred assumption of treatment waning beginning immediately after treatment discontinuation: rather, it would likely start between [redacted] and between [redacted].

ERG

- More reasonable to assume that some, albeit small, treatment waning will start from treatment stopping.
- Prefer that [redacted]% remain on treatment at [redacted] which then falls due to waning effect over the next [redacted] with all patients stopping treatment by [redacted].
- Clinical consensus there is some retention of benefits from immunotherapy after stopping, but there is no good evidence.

NICE Substantial upwards impact on the ERG corrected base case ICER: increases from £49,341 per QALY to £60,509 per QALY.

Survival extrapolation & treatment waning

- In the base case cost-effectiveness analysis, treatment waning assumptions based on UK clinical expert feedback and previous appraisals of I-O therapies were applied to the dostarlimab OS extrapolations.
- Company used generalised gamma, ERG favours Weibull.

Dostarlimab OS extrapolations up to five years (GARNET ITT, treatment waning applied)

Extrapolation of overall survival

Company

- Generalised gamma is the most appropriate and should be considered conservative
- Weibull (ERG's preferred) does not adequately meet the selection criterion:
  1) worst statistical fit to the GARNET data,
  2) concerns with clinical plausibility for immunotherapy
  3) underestimates survival compared to mean estimate elicited from clinical experts

ERG comments:

- Elicitation exercise used unadjusted curves → not good for selecting adjusted curves.
- Log-normal has similar AIC and superior BIC to the generalised gamma but company selected generalised gamma because the 'waned curve' closer to expert elictaion
- ERG prefers the company OS Weibull (considerably increases ERG corrected ICER)
- Following technical engagement, company method of adjustment for waning means that difference between models is reduced → illustrates waning method is driving the economic analysis.
- Generalised gamma model is still optimistic in extrapolation as modelling of OS is associated with substantial uncertainty - before and after adjustment for waning of treatment effect.

Given the limitations of the company expert elicitation exercise, is company generalised gamma or Weibull most appropriate for OS?

Extrapolation of time to treatment discontinuation (TTD)

Company

- Used updated GARNET intention to treat population TTD of dostarlimab
- Lognormal represents the most appropriate curve
- Generalised gamma extrapolation - clinically implausible:
  - extremely low rate of treatment discontinuation with dostarlimab after two years, which is unlikely to represent real world prescribing.

ERG

- TTD curve does not require much extrapolation - choice of curve → goodness of fit
- Generalised gamma provides the best statistical fit
- Does not understand argument for why generalised gamma is clinically implausible:
  - Parameterisation of the KM data is trying to best fit the GARNET trial data, not notional "real world prescribing"

- Company log-normal and generalised gamma TTD curves for dostarlimab correspond very closely with those of the ERG.

	AIC	BIC
generalised gamma (ERG	[redacted]	[redacted]
Log normal (company)	[redacted]	[redacted]

Is the company choice of lognormal time to treatment discontinuation (TTD) curve for dostarlimab appropriate? Is the ERG TTD generalized gamma a better choice?

Company base case & scenarios* (1)

		Incr. costs	Incr. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	£48,608
Scenario analyses based on the MAIC between GARNET and RWEQ				
1	RWEQ OS: Matching-adjusted HR ([redacted]) applied to independently extrapolated unmatched GARNET KM data – MAIC Scenario 1	[redacted]	[redacted]	£41,541
2	Dostarlimab OS: Independent extrapolation of matching-adjusted GARNET KM data (Generalised gamma) – MAIC Scenario 1	[redacted]	[redacted]	£43,977
Scenario analyses based on endometrioid cohorts of GARNET and the RWEQ				
3	• Dostarlimab PFS: Independent extrapolation of unmatched endometrioid GARNET KM data (Lognormal) • RWEQ PFS: Independent extrapolation of endometrioid RWEQ KM data (Log-logistic) • Dostarlimab OS: Independent extrapolation of unmatched endometrioid GARNET KM data (Generalised gamma) • RWEQ OS: Matching-adjusted HR ([redacted]) applied to independently extrapolated unmatched endometrioid GARNET KM data – **MAIC** Scenario 1	[redacted]	[redacted]	£48,614

* Post technical engagement, deterministic ICERs

Company base case & scenarios* (2)

		Incr. costs	Incr. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	£48,608
Scenario analyses based on the MAIC between GARNET and RWEQ				
4	• Dostarlimab PFS: Independent extrapolation of unmatched endometrioid GARNET KM data (Lognormal) • RWEQ PFS: Independent extrapolation of endometrioid RWEQ KM data (Log-logistic) • Dostarlimab OS: Independent extrapolation of matching-adjusted endometrioid GARNET KM data (Generalised gamma) – **MAIC Scenario 1** • RWEQ OS: Independent extrapolation of endometrioid RWEQ KM data (Log-logistic)	[redacted]	[redacted]	£53,437
5	• Dostarlimab PFS: Independent extrapolation of unmatched endometrioid GARNET KM data (Lognormal) • RWEQ PFS: Independent extrapolation of endometrioid RWEQ KM data (Log-logistic) • Dostarlimab OS: Independent extrapolation of unmatched endometrioid **GARNET KM data** (Generalised gamma) • RWEQ OS: Independent extrapolation of endometrioid **RWEQ KM data** (Log-logistic)	[redacted]	[redacted]	£55,626

Company consider these ICERs to be conservative, representing an upper bound.

* Post technical engagement

ERG preferred base case

- ERG01 to ERG06 represent the ERG's preferred model inputs for its base case. Each of these represents an independent impact on the company base case ICER.
- The final 2 lines represent different cumulative impacts on the company base case ICER.

Preferred assumption	ICER
ERG corrected company base-case*	£49,341
ERG01: Dostarlimab OS Weibull	£65,454
ERG02: Dostarlimab ERG ITT TTD GGAM	£52,709
ERG03: [redacted]% dostarlimab continuation	£53,755
ERG04: Waning from point of treatment cessation	£55,523
ERG05: Quality of life – no time to death coefficient	£49,513
ERG06: Ongoing resource use	£48,885
Cumulative effect: ERG02-ERG06	£64,006
Cumulative effect: ERG01-ERG06	£79,714

 * Uses company assumptions prior to technical engagement, but updated PAS price.

End of life

- End of life criteria are that the treatment should extend life by more than 3 months compared with current clinical management, and that current clinical management survival is less than 24 months.
- OS was immature in GARNET but has been modelled by the company and ERG.
- Company and ERG agree that dostarlimab appears to meet these criteria for patients with recurrent or advanced EC that has progressed on or after platinum-based chemotherapy.
- The company model estimates the following undiscounted life years:

	RWEQ	DOST	Net
Company base case	[redacted]	[redacted]	[redacted]
ERG corrected company base case	[redacted]	[redacted]	[redacted]
ERG base case	[redacted]	[redacted]	[redacted]

- However, there may be some concerns around whether the values for the comparator arm are underestimates given how the company elicited the experts' opinions.
- There is uncertainty around the survival estimates as GARNET's data is immature and there are many issues surrounding data for comparators and longer-term outcomes beyond two years.

Equalities and Innovation

Are there any equalities issues or innovation the committee should consider?

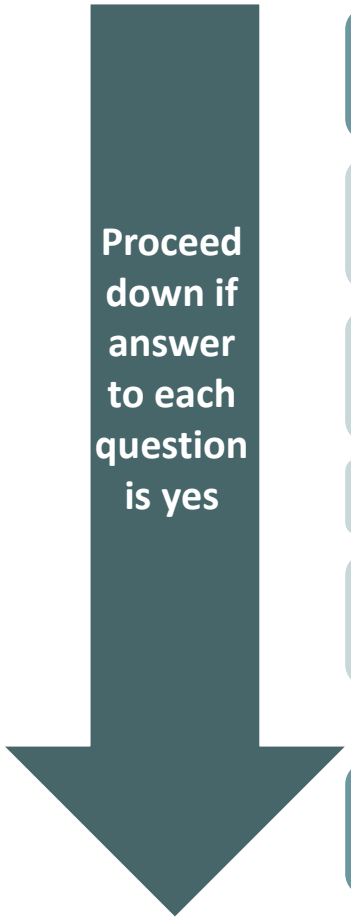
Equalities:

- No equality issues identified.

Innovation:

- Dostarlimab is the first immuno-oncology (I-O) therapy to receive a licence in this indication. Like other I-O therapies, the mechanism of action of dostarlimab enables a patient's own immune system to mount an anti-tumour response. This novel mechanism of action has allowed other I-O therapies to revolutionise the management of other cancers. Most notably, I-O therapies have been shown to result in extended treatment benefits and long-term remission even after treatment discontinuation.

Cancer Drugs Fund Recommendation Criteria



Starting point: drug not recommended for routine use due to **clinical uncertainty**

1. Is the model structurally robust for decision making? (omitting the clinical uncertainty)

2. Does the drug have plausible potential to be cost-effective at the offered price, taking into account end of life criteria?

3. Could further data collection reduce uncertainty?

4. Will ongoing studies provide useful data?

and

5. Is CDF data collection via SACT relevant and feasible?

Consider recommending entry into CDF (invite company to submit CDF proposal)

Define the nature and level of clinical uncertainty. Indicate the research question, analyses required , and number of patients in NHS in England needed to collect data.

Company's ongoing trials:

- The GARNET trial is still ongoing, with the next data cut expected in early 2022.
- Dostarlimab is also currently being investigated as a 1st-line treatment in combination with carboplatin plus paclitaxel for patients with recurrent or advanced EC in the Phase III randomised RUBY trial. Estimated primary completion date: October 11, 2021.

Backup slides

High priority Lower priority Resolved

Summary of issues in the ERG report (1)

Issue	Impact	Technical team
1: The patient population specified in marketing authorisation and addressed in the company submission (CS) is narrower that what is specified in the final scope		No committee discussion required. Company submission highlighted difference and ERG critiqued and interpreted the submitted evidence accordingly.
2: Patients with advanced disease and with recurrent disease are potentially two distinct populations, but they were identified in different ways between the GARNET trial for dostarlimab and the GARNET-like Real World Equivalent (RWE) cohort		Clinical advice at technical engagement suggests that the patient cohorts are not sufficiently different and outcomes will be very similar.
3: Overall the GARNET trial data were fairly immature and may not be sufficient to provide reliable effectiveness and cost-effectiveness estimates		Additional trial data will not be available within the timeframe of this appraisal. ERG suggest Possible CDF?
4: There are uncertainties over the magnitude of the benefit of dostarlimab relative to comparators due to the single-arm design of the GARNET trial and lack of suitable data for comparator treatments		Inevitable limitations in the data. No plans for any head-to-head trials for dostarlimab.

 Unknown impact

 Small impact

 Model driver

High priority Lower priority Resolved

Summary of issues in the ERG report (2)

Issue	Impact	Technical team
5: GARNET trial population and RWEQ cohort may have fundamental differences that cannot be easily adjusted statistically		Some uncertainty in the extent and direction of potential bias.
6: The model contain a number of errors, in particular the waning of the dostarlimab treatment effect after cessation of treatment.		Collectively these model errors have a big upwards impact on the ICER. Corrected by the company at technical engagement.
7: Is the company elicitation exercise for dostarlimab overall survival (OS) mainly relevant to the unadjusted curves for treatment waning? What does this imply for the choice of the adjusted OS curve?		Choice of OS curve for dostarlimab has a big impact on the ICER.
8: Company elicitation exercise for current treatment OS suggest that the RWEQ OS data and curves are too pessimistic		No plausible alternative approaches that could be used to fit a parametric extrapolation to OS data.
9: Company elicitation exercise for dostarlimab treatment discontinuation and waning of treatment effect biased, and if so what does this imply for the values that should be applied?		ERG preferred assumptions have a big upwards impact on the ICER.

High priority Lower priority Resolved

Summary of issues in the ERG report (3)

Issue	Impact	Technical team
10: For dostarlimab treatment discontinuation (TTD) is the company choice (lognormal) Would the Gompertz, or the ERG estimated intention to treat (ITT) generalized gamma most appropriate?		Choice of TTD extrapolation has a modest impact on the ICER.
11: GARNET had a lot more censoring (mostly early censoring) than RWEQ. Might poorly performing patients have dropped out of GARNET early and if they did how might this have affected results?		Comparison of censoring between GARNET and RWEQ study must take account of the different study settings.
12: For the ICERs for dostarlimab compared to individual treatments, does the difference in effect when using RWEQ data compared to when using values within the literature raise questions about the reliability of using the RWEQ data?		Unknown whether differences in ICERs are due to differences in the patient populations, or scenario analysis methodology.

Survival extrapolation & treatment waning (1)

- In the base case cost-effectiveness analysis, treatment waning assumptions based on UK clinical expert feedback and previous appraisals of I-O therapies were applied to the dostarlimab PFS and OS extrapolations.

Dostarlimab PFS extrapolations up to five years (GARNET ITT, treatment waning applied)

Issue 2:

Advanced disease and recurrent disease are potentially two distinct populations identified in different ways for dostarlimab (GARNET) and GARNET-like Real World EQuivalent (RWEQ) cohort

ERG comments:

- Tumour and prognosis, may differ between advanced disease and recurrent disease.
- They also have different treatment histories, which may affect response to treatment.
- Company didn't produce data stratified by advanced vs recurrent disease for both the GARNET and the RWEQ cohorts, because of inconsistencies in the way that patient cohorts are defined between the two studies.
- Although recurrent and advanced diseases were not separately recorded in the GARNET trial, it should be possible to adopt the same definition of advanced disease being FIGO stage III & IV at diagnosis (or at treatment initiation) and then classify remaining patient groups as recurrent.

Company response:

- Disagrees that patients with advanced disease and patients with recurrent disease represent two potentially distinct populations.
- Unanimous feedback from company's clinical experts that both populations are treated the same in clinical practice and both lack effective treatment options. All have progressed on platinum treatment.
- Previous NICE appraisals in different disease areas have appraised recurrent and advanced populations together.

Issue 2 (cont.):

Company response (cont.):

- ERG's proposed resolution (the use of FIGO stage III or IV for advanced disease, with all other patients assumed to have recurrent disease) is a substantial over-simplification.
- This would result in the incorrect classification of patients, given the limitations associated with the GARNET trial data collection, and the nature of staging in endometrial cancer.
- Also, recurrent and advanced disease are not mutually exclusive disease states.

Clinical expert:

- The majority of endometrial cancer trials include both recurrent and advanced disease and to date, have not always separated these groups out.
- Women with advanced endometrial cancer have incurable disease and similar prognosis to women with recurrent disease.
- Given the criteria in the GARNET trial and company submission for prior platinum, the potential differences in outcome between two populations likely not substantial.

Issue 3:

Overall the GARNET trial data were fairly immature and may not be sufficient to provide reliable effectiveness and cost-effectiveness estimates

ERG comments:

- Dostarlimab were immature (median duration of follow up of [redacted] months and median overall survival not yet reached). Longer-term effectiveness unknown.
- The substantial uncertainties in longer-term effectiveness directly contribute to substantial uncertainties in cos-effectiveness estimates

Company response:

- Although data from GARNET are not fully mature, the evidence is associated with sufficient levels of certainty to be considered for routine commissioning.
- Planned future data analysis of GARNET trial not be available during the appraisal.

Clinical expert:

- It is a balance of waiting for long term follow-up for outcomes such as survival and access to the latest treatments in a population with a significant unmet need.
- The efficacy reported in GARNET is consistent with the scientific rationale of immunotherapy approaches in dMMR/MSI-H tumours (seen in other tumour types).

Issue 4:

There are uncertainties over the magnitude of the benefit of dostarlimab relative to comparators due to the single-arm design of the GARNET trial and lack of suitable data for comparator treatments

ERG comments:

- GARNET was a single arm, phase I trial - relative effectiveness estimated through unanchored indirect comparison.
- Company identified different sources of comparator evidence and undertook a series of matching adjusted indirect comparisons (MAICs) in support of the RWEQ data, **but** all MAICs were susceptible to bias due to limitations in available data.
- Suggested improving MAICs may reduce potential bias but may not eliminate residual confounding, the direction and magnitude of which is difficult to estimate.

Company response:

- Recognise the limitations associated with the single-arm design of the GARNET trial and have made substantial efforts to identify different sources of comparative efficacy that provide sufficiently robust evidence for decision-making.
- No plan to undertake a randomised controlled trial of dostarlimab in this indication. This is due to a number of reasons that render the development of a Phase III randomised controlled trial in this indication challenging (e.g. small population)

Issue 4 (cont.):

Clinical expert:

- Prospective trials specifically in dMMR endometrial cancer are limited. The best example is the Phase 3, randomised trial study309/MK-775 of Lenvatinib plus pembrolizumab vs standard of care (Makker et al 2021).
- Patients had advanced/metastatic or recurrent endometrial cancer and prior platinum-based therapy.
- The response rate, duration of response, PFS and OS to date seen in GARNET is greater than seen in the comparator arm of the above study.

Issue 5:

GARNET trial population and RWEQ cohort may have fundamental differences that cannot be easily adjusted statistically

ERG comments:

- Major differences in setting, patient characteristics and case definitions for GARNET vs. population of the RWEQ cohort (company's main base case comparator).
- The MAIC conducted by the company for GARNET vs RWEQ did not take into account some important prognostic factors and had many methodological issues.
- In order to characterise the differences between GARNET and RWEQ cohort and to identify potentially more comparable patients between the cohorts, data stratified by advanced versus recurrent diseases, and by endometrioid versus other diseases for both cohorts may be valuable.

Company response:

- Whilst it is not possible to adjust for dMMR/MSI-H status between the GARNET and RWEQ populations, substantial effort has been made to adjust for endometrioid disease status. A matching-adjusted indirect comparison (MAIC) has been conducted between the endometrioid cohorts of GARNET and the RWEQ may help to indicate the upper bound of the Company's base case ICER.

Issue 5 (cont.):

Company response (cont.):

- Reasonable to conclude that a naive comparison between the endometrioid cohorts in GARNET and the RWEQ provide a ceiling to the upper limit of uncertainty for the treatment effect between dostarlimab and current clinical management.
- Given the outstanding imbalances between the two populations, including age (the RWEQ endometrioid cohort is younger than the GARNET endometrioid cohort), and prior treatments ([redacted]% of the GARNET endometrioid population received two or more prior treatments, compared to [redacted]% in the RWEQ endometrioid cohort), the naive treatment effect observed in the endometroid subgroup analysis is likely to be conservative (slight bias in favour of current clinical management).

Clinical expert:

- Most notable difference is that the RWEQ will include patients that are biomarker positive and negative (i.e. dMMR and pMMR).
- But given that MMR testing is relatively recent in practice, it will be a challenge to have robust, comprehensive retrospective data on standard of care according to MMR status.

Issue 6:

Model errors (in particular waning of the dostarlimab treatment after treatment stops)

ERG comments:

- There appear to be modelling errors, particularly for the waning of treatment effect.
- Company applies hazard ratios. But the RWE curves of the base case are based upon the RWE parameterised curves. Equalising the risk of events between the arms requires that the risk of events in the RWE arm be used.
- There are a number of other more minor modelling errors.
- Collectively there is a big upwards impact on the ICER, from a company base case ICER of £50,221 per QALY to £68,376 per QALY.

Company response:

- Company used revised version of ERG's preferred treatment waning methodology (and majority of ERG assumptions) in base case cost-effectiveness analysis.
- Company disagrees with the ERG's preference to include the costs of cisplatin plus doxorubicin in the base case cost-effectiveness analysis (it is not a modelling error).
- Company continues to use time to death utilities in base case cost-effectiveness.

Clinical expert:

- Clinically reasonable assumption that treatment effect from dostarlimab is maintained for progression-free patients when treatment waning is assumed to end.

Issue 8:

Does the company elicitation exercise for current treatment OS suggest that the RWE OS data and curves are too pessimistic?

ERG comments:

- Company expert advice on OS at 5, 10 and 15 years under current therapy was that the curves fitted to the RWE data extrapolate too low an OS at 5, 10 and 15 years.
- The RWE data may be poorly aligned with the GARNET population.
- The OS for the individual treatments within the RWE are also hugely different from one another with combination therapies performing much better than monotherapies.
- Aggregating the RWE patients into a single treatment groups may not be sensible.
- If the RWE OS underestimates what OS is with current therapy the ICER is biased in favour of dostarlimab.

Company response:

- Company's preferred log-logistic extrapolation for RWE OS represents the best statistically fitting curve, as well as the most optimistic curve with regard to the predicted long-term survival estimates for current clinical management.
- Agrees with ERG that there are no plausible alternative approaches that could be used to fit a parametric extrapolation to the RWE OS data.

Issue 11:

A lot of the censoring in GARNET was early on and there was much less censoring in the RWE data. Could this be explained by poor efficacy of dostarlimab?

ERG comments:

- Quite a lot of patients in GARNET were censored early in the trial.
- If the much higher censoring in GARNET than in the RWE data was observed in a two-arm trial it would be a major concern.
- Those who did not respond well during GARNET may have dropped out of the trial/ been censored vs those with a better response continue (informative censoring).

Company response:

- Company does not believe that a comparison between censoring in GARNET and censoring in the RWE study is appropriate, and therefore this issue should not be considered a major source of uncertainty.
- People in the RWE study are not subject to the same strict trials protocols of GARNET, and it is not possible for these patients to “remove themselves” from the RWE study (i.e. real-life current clinical practice) in the same way as it is in GARNET.

Issue 12:

The ICERs for dostarlimab differ by the comparator treatment and source of evidence. How reliable are cost effectiveness estimates using the RWE data ?

ERG comments:

- ERG exploratory analyses fitted curves to RWE individual treatment KM data.
- Marked differences in overall survival by treatment within the RWE dataset.
- Combination therapies had better survival and monotherapies worse survival.
- This could be partially accounted for by marked differences in the patient baseline characteristics (e.g. fewer younger patients and higher unknown ECOG status for platinum doublet monotherapy and carboplatin monotherapy).
- If GARNET recruited fitter patients or patients whose disease had a better prognosis than the RWE patients or if there is a trial or placebo effect within GARNET the analyses will be biased in favour of dostarlimab.
- Differences in the ICER for dostarlimab vs doxorubicin based on the RWE and the matched adjusted indirect comparison with the ZoptEC study suggest RWE data may be unreliable.

Company response:

- Differences noted by the ERG between the scenario analysis versus doxorubicin (in ZoptEC) and versus doxorubicin (in the RWE) are substantially influenced by methodological differences between the two scenario analyses, and may not be due to differences in the patient populations.

Issue 12 (cont.):

Company response (cont.):

- Modelling comparator efficacy by applying a HR to the corresponding dostarlimab OS/PFS curves is associated with substantial uncertainty.
- Company believes that independently fitting extrapolations to PFS and OS for both dostarlimab and the comparators represents the most robust approach, where possible.

Changes to company model after TE (1)

Key issue	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the Company's base-case ICER
NA	[redacted]	[redacted]	[redacted]
Key Issue 6	It was assumed that all patients discontinued treatment at the first cessation point, and therefore applied treatment waning to all patients, even those who remained on treatment.	The Company has incorporated an adapted version of the ERG's revised treatment waning methodology, whereby treatment waning is only applied to patients once they discontinue treatment.	[redacted]
Key Issue 6	The ERG identified that there was an error in the calculation of the percentage of patients who continue to receive dostarlimab beyond the first cessation point.	Company have incorporated the ERG's correction to the calculation of the [redacted] cessation percentage into the revised base case cost-effectiveness analysis.	[redacted]

Changes to company model after TE (2)

Key Issue 6	Patients were assumed to receive 0.5 doses of dostarlimab once every three weeks from the 5th administration onwards.	The Company have incorporated the ERG's revised methodology: patients receive 1 dose of dostarlimab every six weeks from the 5th administration onwards.	[redacted]
Key Issue 6	The resource use assumptions detailed in the CS, Document B, Section B.3.5, were used in the cost-effectiveness analysis.	The ERG's preferred resource use assumptions have been incorporated into the base case cost-effectiveness analysis.	[redacted]
Key Issue 10	TOT for the ITT population had been implemented incorrectly in the cost-effectiveness analysis. A log-logistic curve was previously selected to model TOT prior to adjustment for anticipated real-world prescribing.	The lognormal curve is now selected to model TOT prior to adjustment for anticipated real-world prescribing. This adjustment is still applied, meaning that [redacted]% of patients continue to receive treatment with dostarlimab following [redacted].	[redacted]
New base case following TE	Incremental costs: £[redacted]	Incremental QALYs: [redacted]	ICER: £48,608