Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy

For public - redacted

Technology appraisal committee A [12 May 2026]

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Company: Regeneron

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy

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

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Background on recurrent or metastatic cervical cancer

Causes

- Develops when abnormal cells in lining of cervix grow in an uncontrolled way and form a tumour
- Infection with human papillomavirus (HPV) is associated with development of cervical cancer; HPV detected in 99.7% of cases

Epidemiology

- In UK, average of 3,256 people were diagnosed with cervical cancer each year from 2017 to 2019
- Company estimate that around 130 people each year would be eligible for cemiplimab[1]

Diagnosis and classification

- Cervical cancer is defined as recurrent when it has returned following treatment, persistent when it does not respond to treatment, and metastatic when it has spread beyond cervix to other places in body

Symptoms and prognosis

- Advanced cervical cancer symptoms: extreme tiredness, leg swelling or pain, lower back or abdominal pain, cough or problems urinating
- Survival for people having standard second-line chemotherapy is poor

Source: 1. Company's budget impact analysis

Patient perspectives

Patient expert feedback for this evaluation and for the evaluation of tisotumab vedotin [ID3753]

- For people with recurrent or metastatic cervical cancer, the prognosis is bleak
- Living with the condition is physically and emotionally exhausting
- Many people with the condition are young adults with caring responsibilities – having standard chemotherapy treatment makes it difficult to care for young children, because of:
  - The impact of side effects, such as fatigue, pain, nausea, and vomiting on quality of life
  - The time it takes to travel to hospital for treatment
- Fear of recurrence and uncertainty about the future can feel overwhelming
- For people who progress after first-line systemic treatment, there are limited treatment options available
- There is a sense that more needs to be done to expand later-line treatment options, giving people more time, hope, and choice

Most existing treatments involve regular hospital infusions, which can be exhausting and disruptive, especially when you're already unwell.

Side effects often build up over time – ongoing fatigue, nausea, nerve pain, lowered immunity, and emotional strain are common.

Clinical perspectives

Submissions from clinical experts

- Cervical cancer often affects young people with young families – there is a high symptom burden
- Second-line treatment is typically with single-agent chemotherapy, such as paclitaxel – but outcomes are very poor and there is an unmet need for additional, effective treatment options
- Cemiplimab has been shown to improve survival compared with chemotherapy – with some people in the trial surviving long-term
- It has also been shown to improve quality of life, with particular improvements in pain and functioning
- Much easier to deliver than weekly paclitaxel or gemcitabine, with fewer hospital visits for administration and blood tests
- Could be used in the same way as current care in NHS clinical practice
- Clinicians now have significant experience using immunotherapy treatments (such as cemiplimab) and managing potential toxicities

Patients who progress after first-line systemic therapy for metastatic cervical cancer have few good treatment options and often have a high symptom burden. This is a significant area of unmet need, especially in patients who are PD-L1 negative and cannot access immunotherapy

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Abbreviations: PD-L1, Programmed Death-Ligand 1.

Equality and health inequality considerations

- In deprived areas there are higher rates of cervical cancer and lower screening rates – people are more likely to have more advanced cancer at diagnosis
- Incidence is higher in non-white groups and immigrants from Africa, parts of Asia and Eastern Europe
- Cemiplimab is already recommended for second-line treatment of cervical cancer in Scotland[1]

EAG comments

- The company has not provided a specific analysis, such as a distributional cost-effectiveness analysis, demonstrating that recommending cemiplimab has the potential to reduce health inequalities
- These disparities are unlikely to be impacted by whether this technology is reimbursed for this indication as they are mostly associated with disease incidence or delayed diagnosis

Are there any equality or health inequality issues that need to be considered?

Sources: 1. SMC recommendation for cemiplimab

Cemiplimab (Libtayo, Regeneron)

Link to Summary of Product Characteristics

Marketing authorisation	• MHRA approval was granted in April 2023: 'for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy'
Mechanism of action	• Immunotherapy (an immune checkpoint inhibitor) • It is a fully human IgG4 monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2 ligands – this potentiates T cell responses
Administration	• The recommended dose is 350mg every 3 weeks administered as an intravenous infusion over 30 minutes • Treatment may be continued until disease progression or unacceptable toxicity
Price	• £4,650 per 350mg vial (BNF, April 2026) • Confidential patient access scheme in place

Abbreviations: BNF, British National Formulary; IgG4, immunoglobulin G4; MHRA, Medicines and Healthcare products Regulatory Agency; PD-1, Programmed cell death-1; PD-L1, Programmed Death-Ligand 1; PD-L2 Programmed Death-Ligand 2.

Key issues

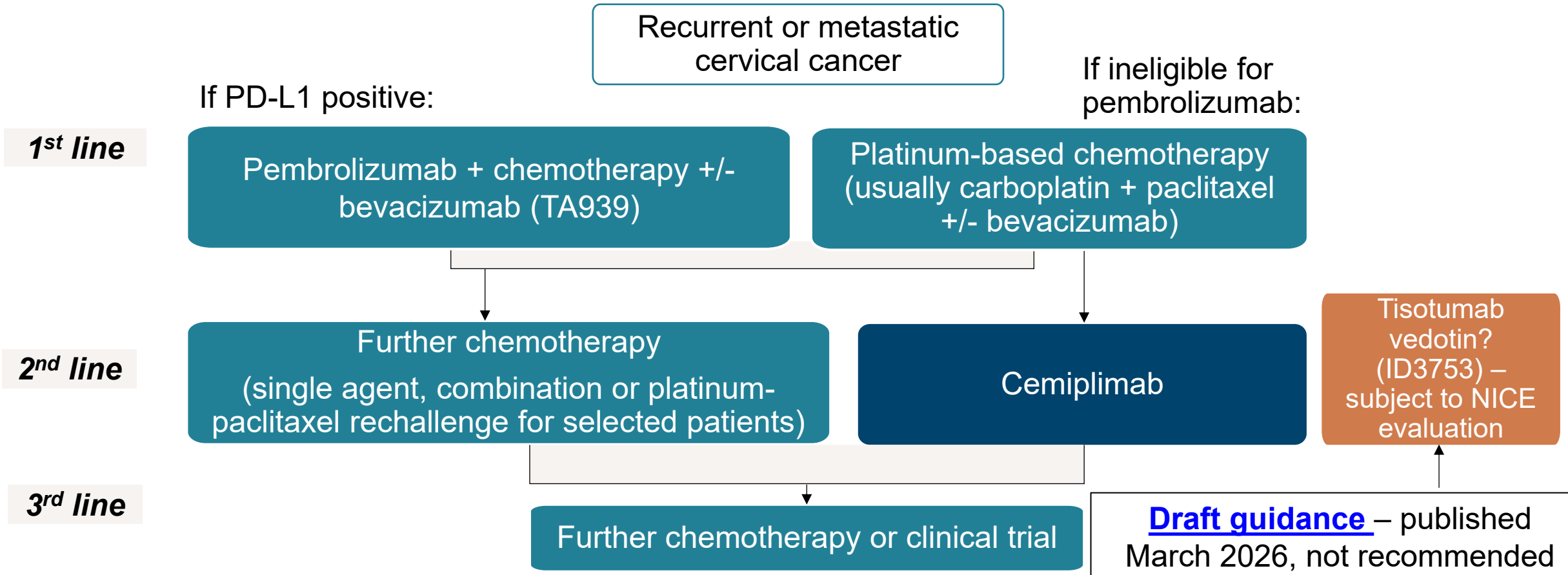
Issue	Resolved?	ICER impact
PD-L1 status • Subgroup analysis by PD-L1 status • PD-L1 status distribution in clinical practice • Curve selection for PD-L1 subgroups	No – for discussion	Moderate
Time on treatment • Choice of Kaplan-Meier data or parametric distribution • Time on treatment capping by progression-free survival (PFS) • Time on treatment in clinical practice for cemiplimab	No – for discussion	Small / Moderate
Treatment-dependent utilities • What are the appropriate utility values, particularly in the post-progression state?	No – for discussion	Small

Other issues with small impact presented in Appendix.

Abbreviations: ICER, incremental cost-effectiveness ratio; PD-L1, Programmed Death-Ligand 1.

Treatment pathway, positioning and comparators

Company positioned cemiplimab as a second-line treatment after platinum-based chemotherapy in people who **have not had** first-line pembrolizumab



Draft guidance – published March 2026, not recommended
ACM2 – 14 April 2026
Final guidance – expected publication June 2026

Abbreviations: ACM2, second appraisal committee meeting; Programmed Death-Ligand 1

Treatment pathway, positioning and comparators

Clinical experts

- No defined 2L chemotherapy option, single agent chemotherapy used, most commonly weekly paclitaxel
- Tisotumab vedotin (referred to throughout slides as tisotumab) currently available on a named patient basis
- For people who **have** had immunotherapy, **tisotumab** would be the next line of therapy
- For people who **have not** had immunotherapy, **cemiplimab** would be the preferred option as it has less toxicity and a greater potential for prolonged responses [than tisotumab]
- **Expert 2:** Cemiplimab could be used as an alternative to weekly paclitaxel or as an option after weekly paclitaxel

ID3753 tisotumab – draft guidance

- Clinical experts at the first committee meeting for tisotumab explained that people usually have single-agent chemotherapy at 2L. Options include, but are not limited to, topotecan, vinorelbine, gemcitabine, irinotecan, pemetrexed and paclitaxel
- Very few people would be considered for retreatment with platinum doublet chemotherapy (e.g. platinum chemotherapy + paclitaxel) at 2L – **comparator: single-agent chemotherapy**

Clinical experts: Is the treatment pathway reflective of clinical practice? Would cemiplimab ever be used after previous immunotherapy?
Should the recommendation be restricted to people who have not had immunotherapy in line with the trial data and company positioning?

Abbreviations: 2L, second line.

Unknown impact

Key issue: Comparators

Final NICE scope

- Comparators include single agent chemotherapy, best supportive care (BSC) and tisotumab (subject to NICE evaluation ID3753) – expected publication date for final guidance 12 June 2026
- **Company submission user guide section 1.3.3 (updated recently):** "A potential comparator is one which has final guidance before the first committee meeting for the appraisal of the intervention in question"

Company

- Only comparator is single agent chemotherapy
- BSC not a comparator – if active treatment not suitable, cemiplimab also not suitable
- Tisotumab not a comparator – not established practice, cemiplimab and tisotumab may also be used in different populations in practice (no prior immunotherapy vs prior immunotherapy, respectively)

EAG comments

- EAG's clinical experts agreed that BSC is not a relevant comparator
- At time of writing EAG report, it was uncertain whether tisotumab would have final guidance at the time the committee makes its final decision on cemiplimab

Clinical expert

- Tisotumab is currently available on a named patient basis for recurrent cervical cancer after platinum chemotherapy

What is/are the appropriate comparator(s)? Should tisotumab be included as a comparator?

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy

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Key clinical trial – EMPOWER Cervical-1

Link to clinical trials.gov entry for EMPOWER Cervical-1

Clinical trial design and outcomes

	EMPOWER Cervical-1 (N=608)
Design	Phase 3, open label, randomised controlled trial.
Population	Adults with recurrent or metastatic cervical cancer whose disease progressed after platinum-containing chemotherapy
Intervention	Cemiplimab, intravenous (IV), 350 mg every 3 weeks for up to 96 weeks (n=304)
Comparator	Investigator's choice single-agent chemotherapy for up to 96 weeks. Options included pemetrexed, topotecan, irinotecan, gemcitabine and vinorelbine (n=304)
Duration	Median follow-up at final analysis – 47.3 months
Primary outcome	Overall survival (OS)
Key secondary outcomes	Progression-free survival (PFS), objective response rate (ORR)
Locations	Multicentre international trial conducted across 97 sites in 14 countries, including 6 UK sites
Used in model?	Yes

EAG comments on generalisability of EMPOWER Cervical-1

Feature	EAG comments on generalisability
Population	• Trial excluded people who had previously had immunotherapy (company also positioning in people who have not had immunotherapy) • Trial did not collect data on PD-L1 status routinely, and included a mix of PD-L1 positive and negative – population in clinical practice anticipated to be mainly PD-L1 negative (**key issue**) • Trial excluded people with ECOG performance status greater than 1, but licence does not include this restriction • Trial predominantly recruited people who had progressed within 6 months of completing platinum-based therapy – EAG concerned about the generalisability to people who have progressed after more than 6 months
Comparators	• Trial did not include paclitaxel as one of the single-agent chemotherapy regimens, when this is widely used in clinical practice
Treatment duration	• Cemiplimab – restricted to 96 weeks of treatment but no restriction in licence (**key issue**) • Chemotherapy – up to 96 weeks, but NHS treatment protocols for many options specify a maximum duration of 6 cycles, equivalent to 18 weeks

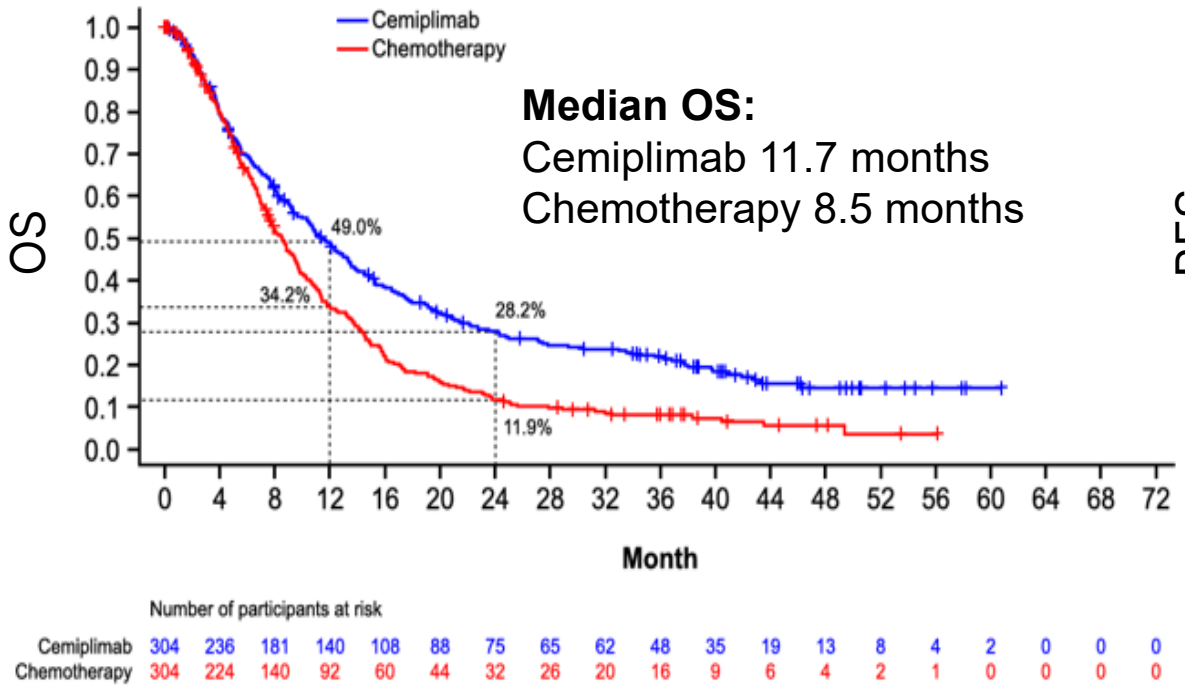
Is the EMPOWER trial generalisable to people expected to have cemiplimab in clinical practice?

Abbreviations: ECOG, Eastern Cooperative Oncology Group; Programmed Death-Ligand 1.

Key clinical trial results – EMPOWER Cervical-1

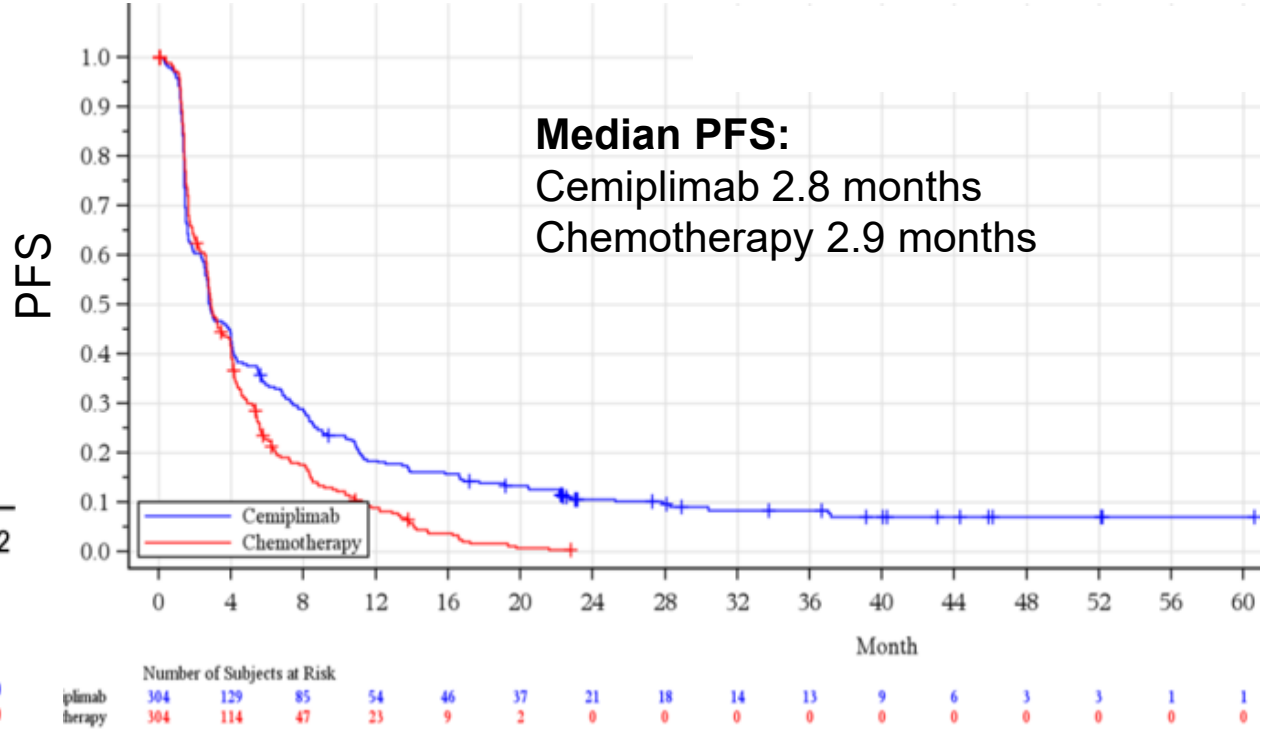
Cemiplimab improves OS and PFS compared with single-agent chemotherapy

Figure 1: Kaplan-Meier plot of OS



Median OS:
Cemiplimab 11.7 months
Chemotherapy 8.5 months

Figure 2: Kaplan-Meier plot of PFS



Median PFS:
Cemiplimab 2.8 months
Chemotherapy 2.9 months

OS HR (95% CI; p-value)	0.67 (0.56–0.80; p<0.00001)	PFS HR (95% CI; p-value)	0.741 (0.62–0.88); P=0.00031

EAG note: Although the HR is presented here, the company's assessment of the proportional hazards assumption suggested it may be violated. Therefore, the HR should be interpreted with caution. **Abbreviations:** CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Moderate impact

Key issue: PD-L1 status

Cemiplimab is likely to be used in a primarily PD-L1 negative population, but this was likely not captured in EMPOWER

Company

- Positioning cemiplimab as a 2L treatment in people who have **not had immunotherapy with pembrolizumab** at 1L

EAG comments

- This is a predominantly PD-L1 negative population – as people with PD-L1 positive status would have had pembrolizmab at 1L
- But licence is not restricted by PD-L1 status and EMPOWER recruited people irrespective of PD-L1 status
- Importantly, 39% of people in EMPOWER did not have PD-L1 status data and, for some people with PD-L1 status data, archival samples were used to determine PD-L1 status

Table: PD-L1 definitions used in committee papers / slides

Term	Definition
PD-L1 negative	PD-L1 combined positive score (CPS) below 1; PD-L1 < 1%
PD-L1 positive	PD-L1 combined positive score (CPS) at least 1; PD-L1 ≥ 1%

Clinical experts: Would PD-L1 status be expected to change over time? In clinical practice, would PD-L1 status ever be reassessed?

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Abbreviations: 1L, first line; 2L, second line; PD-L1, Programmed Death-Ligand 1.

Moderate impact

Key issue: PD-L1 status – subgroup analysis

Company: consistent benefit across PD-L1 subgroups

Company

- Subgroup analyses show a consistent benefit across PD-L1 positive and PD-L1 negative subgroups (**Table**)
- Effectiveness should be based on the whole trial (ITT) population (N=608) because the subgroup analyses are underpowered and the licence is not restricted by PD-L1 status

Table: Comparison of hazard ratios (HRs) for the PD-L1 subgroups (company clarification response A18)

Population	n (cemi)	n (chemo)	OS HR (95% CI)	OS interaction effect p-value	PFS HR (95% CI)	PFS interaction effect p-value
PD-L1 < 1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 ≥ 1%	[redacted]	[redacted]	[redacted]		[redacted]	

EAG: Subgroup analysis results not representative of all patients in the trial, only 371 out of 608 patients had tested samples – PD-L1 status was not obtained for 39% of people recruited.
In the cohort which did have PD-L1 status assessed, 36% were PD-L1 negative in both trial arms.

Kaplan-Meier curves for subgroup analyses presented in Appendix.

Abbreviations: 1L, first line; 2L, second line; cemi, cemiplimab; chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; PD-L1, Programmed Death-Ligand 1.

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Company's model

Partitioned survival model, including three mutually exclusive health states, state occupancy informed by OS and PFS curves from EMPOWER

Figure: Company's model structure

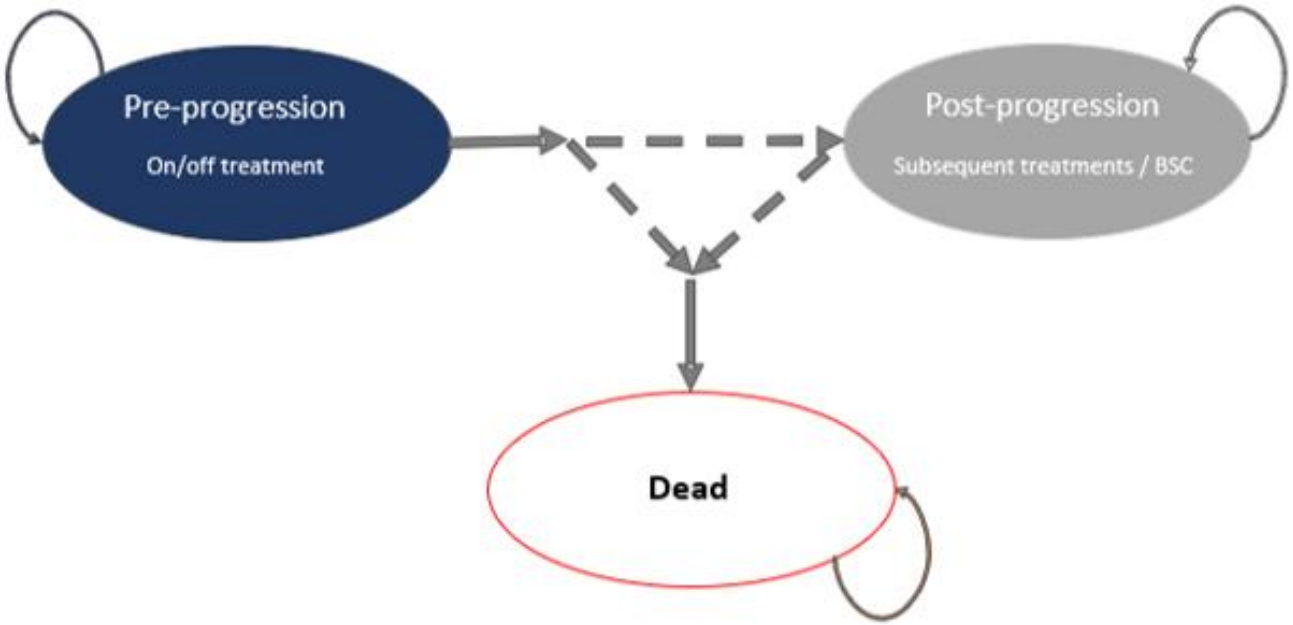

Table 21 in the EAG's report provides a summary of the evidence sources used to inform the model parameters for the company's base case

- Technology affects **costs** by:
  - Increasing drug acquisition costs
  - Moderately increasing health state management costs
  - Slightly increasing the downstream costs of subsequent treatments for progressed disease
  - Slightly reducing the management costs of treatment-emergent adverse events (TEAEs)

- Technology affects **QALYs** by:
  - Extending OS by increasing life-years gained in both the pre-progression and post-progression health states.
  - Providing a higher health-related quality of life (HRQoL) in both the pre-progression and post-progression health states.

Abbreviations: BSC, best supportive care; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year.

Moderate impact

Key issue: PD-L1 status – subgroup analysis

Company and EAG base cases are based on ITT data from EMPOWER, scenarios provided which explore weighting PD-L1 subgroups

Background

- Company and EAG base case OS and PFS curves are based on ITT population of EMPOWER – independent generalised gamma models used (non-proportional hazards)

Company

- Provided scenario analysis where:
  - PD-L1 subgroups were analysed separately and separate curves fit for each subgroup
  - Generalised gamma distributions were selected (consistent with the ITT population) as these provide one of the best fits for the PD-L1 subgroups
  - Costs and QALYs were re-weighted assuming 96% PD-L1 negative – ICERs slightly reduced

EAG comments

- Noted that the company's generalised gamma distributions had the most optimistic projections
- So the EAG explored the log-normal, which provided a good visual* and statistical fit* to the data but with lower projected OS and PFS
- EAG presented scenarios assuming 96% and 100% were PD-L1 negative, applying EAG's preferred distributions – both scenarios moderately increase the ICER

***EAG note:** the hazard plots provided by the company were not informative, so the EAG relied on the visual and statistical assessments of fits provided by the company, and the analysis of their reconstructed IPD. **Abbreviations:** PD-L1, Programmed Death-Ligand 1; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival.

Moderate impact

Key issue: PD-L1 status – subgroup analysis

Table: Company's selected curves and EAG's proposed alternative curves in the ITT population and PD-L1 subgroups (EAG's alternative curves highlighted in red*)

Population / subgroup	Company selected curve	EAG alternative
ITT population (company and EAG base case)	OS and PFS for both arms: generalised gamma	Same as company
PD-L1 negative (used in scenario analyses)	OS and PFS for both arms: generalised gamma (same as ITT population)	OS cemi: log-normal* OS chemo: gen. gam. PFS cemi: gen. gam. PFS chemo: log-normal*
PD-L1 positive (used in scenario analyses)	OS and PFS for both arms: generalised gamma (same as ITT population)	OS cemi: gen. gam. OS chemo: gen. gam. PFS cemi: gen. gam. PFS chemo: log-normal*

EAG's exploration of alternative curves presented in Appendix

Abbreviations: cemi, cemiplimab; chemo, chemotherapy; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; PD-L1, Programmed Death-Ligand 1.

Moderate impact

Key issue: PD-L1 status

Questions for committee

- Are the intention-to-treat (ITT) data from the EMPOWER generalisable to the population likely to have treatment in clinical practice?
- Should the ITT population of EMPOWER be used in the modelling? Or should the PD-L1 re-weighted analysis be used?

If the re-weighted analysis is more appropriate:

- What proportion of people having cemiplimab would be PD-L1 negative? Is the company's estimate of 96% appropriate?
- What are the most appropriate curves for each PD-L1 subgroup?

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Abbreviations: ITT, intention-to-treat; PD-L1, Programmed Death-Ligand 1.

Small impact

Key issue: Time on treatment – company and EAG base case model assumptions

Company and EAG use different approaches for modelling ToT in the base case

Company

- Used log normal models for both arms
- ToT capped by PFS – assumes treatment stopped on progression

EAG comments

- Prefers to use KM data directly for both arms – company's approach of using parametric model unnecessary as data mature
- Also introduces uncertainty and inaccuracy
- Not appropriate to cap ToT by PFS as some people in the cemiplimab arm of EMPOWER (n = 70) were treated beyond progression events – these were deemed by investigators as being pseudo-progressions
- Prefers to remove capping in base case

Figure 1: Observed and model-predicted ToT, cemiplimab

Figure 2: Observed and model-predicted ToT, single agent chemotherapy

Abbreviations: KM, Kaplan–Meier; PFS, progression-free survival; ToT, time on treatment.

Key issue: Time on treatment – company and EAG base case model assumptions

Questions for experts:

- Do clinical experts observe pseudo-progression on immunotherapies in clinical practice?
- Would cemiplimab be continued after progression if pseudo-progression is suspected?

Questions for committee:

- Is the company's log-normal model or EAG's KM approach more appropriate for modelling ToT?
- Is it appropriate to cap ToT by PFS (company) or should capping be removed (EAG)?

Abbreviations: KM, Kaplan–Meier; PFS, progression-free survival; ToT, time on treatment.

Moderate impact

Key issue : Time on treatment for cemiplimab – scenario analysis exploring treatment beyond 96 weeks

In EMPOWER, people had cemiplimab for up to 96 weeks, but licence permits treatment beyond this

Background

- EMPOWER restricted people to 16 six-week cycles of cemiplimab (equivalent to 96 weeks of treatment when given without delays or interruptions)
- Summary of Product Characteristics (SmPC) states that cemiplimab may be continued until disease progression or unacceptable toxicity

EAG comments

- EAG's clinical experts – reluctant to stop treatment if no progression and treatment still tolerated
- EAG is therefore concerned that in clinical practice, the cost of treatment could be substantially higher than estimated by the company based on EMPOWER data
- Acknowledges that extending treatment duration has the potential to provide further OS and PFS benefits
- But the size of these potential benefits are unknown, meaning the impact on the ICER is uncertain
- Requested scenarios from company to explore potential impact of this

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival.

Moderate impact

Key issue: Time on treatment for cemiplimab – scenario analysis exploring treatment beyond 96 weeks

Company provided scenario analysis exploring impact of treatment beyond 96 weeks. **EAG:** Scenario analysis demonstrates sensitivity to this uncertainty

Company

- Provided scenario where ToT data were re-censored at 96 weeks and curves fitted to the re-censored data to extrapolate ToT beyond 96 weeks (see Appendix)
- Approach provides a "worst-case scenario" because it includes the additional cost of treatment beyond 96 weeks without adjusting the OS and PFS estimates to allow for any potential benefit
- Log normal curve selected – second best fitting after generalised gamma

EAG comments

- Notes company's scenario analysis showed a slight increase in the ICER when using log normal curve, but a larger increase when using alternative generalised gamma curve (see Appendix)
- Demonstrates sensitivity of cost-effectiveness estimates to uncertainty regarding duration of treatment
- But notes that these scenarios should not be considered a plausible alternative to EAG's base case –
  - This is due to the lack of adjustment to OS and PFS and the high uncertainty regarding whether the tail of the 96-week censored ToT KM predicts future cemiplimab use in clinical practice
  - Although the EAG notes the latter is somewhat mitigated by the capping of ToT by PFS

Abbreviations: ICER, incremental cost-effectiveness ratio; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival; ToT, time on treatment.

Moderate impact

Key issue: Time on treatment for cemiplimab – scenario analysis exploring treatment beyond 96 weeks

In clinical practice, would cemiplimab be stopped at 96 weeks in line with the trial? Or would clinicians continue to use cemiplimab beyond 96 weeks in line with the licence? What impact would this would have on the OS and PFS estimates?
Is a stopping rule appropriate/acceptable?

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

Small impact

Key issue: Treatment dependent utilities

Company

- EMPOWER EORTC QLQ-C30 responses were mapped to EQ-5D-3L utility values
- Pre-progression utilities **estimated separately for each treatment arm** based on EMPOWER:
  - Statistically significant differences between treatment arms
  - Approach consistent with clinical expectations of poorer quality of life for people having chemotherapy
- Post-progression utility **for cemiplimab based on pooled data for both arms** of EMPOWER:
  - Fewer data points available post-progression to model treatment differences
- Post-progression utility **for chemotherapy based on assumptions**:
  - Using the pooled post-progression utility of 0.613 for chemotherapy lacks face validity as it is close to chemotherapy pre-progression estimate of 0.622
  - Assumed that utility decrement due to progression on chemo would be the same as for cemi (17%)
  - Some chemotherapy AEs, such as peripheral neuropathy, have a persistent impact on HRQoL after stopping
- Alternative scenarios based on literature and clinical input presented (See company submission Table 30)
- TEAE-related QALY losses were not included in the base case model to avoid double counting

Health state / treatment arm	Company mean utility	Source
Pre-prog – cemiplimab	0.735	EMPOWER (cemiplimab arm)
Pre-prog – chemotherapy	0.622	EMPOWER (chemo arm)
Post-prog – cemiplimab	0.613	EMPOWER (pooled arms)
Post-prog– chemotherapy	0.519	Assumption ([redacted]% relative reduction on progression)

Abbreviations: AE, adverse event; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-3L, EuroQoL 5 dimensions 3 level; HRQoL, health-related quality of life; QALY, quality-adjusted life year; TEAE, treatment-emergent AE.

Small impact

Key issue: Treatment dependent utilities

EAG comments

- Reasonably satisfied with the company's decision to use treatment-dependent utilities pre-progression
- But considers that it may be incorrect to assume the same proportionate decrement ([redacted] associated with progression in both arms
- The utility difference between arms may not persist post-progression
  - This is because the lower pre-progression utility for chemotherapy versus cemiplimab may be due to AEs that do not persist once chemotherapy is stopped (at progression)
- Acknowledges that some chemotherapy related AEs may not be reversible, for example, peripheral neuropathy, but this was infrequently reported in EMPOWER
- EAG base case uses pooled post-progression utility from EMPOWER for both arms, maintaining separate pre-progression utilities
- EAG presents a scenario which also uses the pooled pre-progression utility value (treatment independent utilities)

Abbreviations: AE, adverse event.

Small impact

Key issue: Treatment dependent utilities

Health state / treatment arm	Company base case, mean utility	Source	EAG base case, mean utility	Source	EAG scenario, mean utility	Source
Pre-prog – cemiplimab	0.735	EMPOWER (cemi arm)	0.735	EMPOWER (cemi arm)	0.678	EMPOWER (pooled arms)
Pre-prog – chemo	0.622	EMPOWER (chemo arm)	0.622	EMPOWER (chemo arm)		EMPOWER (pooled arms)
Post-prog – cemiplimab	0.613	EMPOWER (pooled arms)	0.613	EMPOWER (pooled arms)	0.613	EMPOWER (pooled arms)
Post-prog – chemo	0.519	Assumed same % reduction on progression as cemi ([redacted])		EMPOWER (pooled arms)		EMPOWER (pooled arms)

What are the most appropriate utility values?
Should treatment-dependent utilities be used for the post-progression state?
Should treatment-dependent utilities be used for the pre-progression state?

Differences between company and EAG base cases

Assumption	Company base case	EAG base case
EA1 Correction of minor programming errors	No	Yes
EA2 Time on treatment (key issue)	Log-normal models ToT capped by PFS	KM data ToT **not** capped by PFS
EA3 Utility values (key issue)	Pre-progression: Treatment-dependent Post-progression: Treatment-dependent	Pre-progression: Treatment-dependent Post-progression: **Treatment-independent**
EA4 Adjustment of PFS to account for fatal events, when calculating subsequent treatment costs	No	Yes
EA5 Resource use in post-progression health state	Different for cemiplimab and chemotherapy	Same for both treatment arms
EA6 Immune-related TEAE	Not included	Included

None of the EAG's alternative base case assumptions had a significant impact on the ICER, but note that not all key issues reflected in EAG base case ICER

Abbreviations: ICER, incremental cost-effectiveness ratio; KM, Kaplan–Meier; PFS, progression-free survival; TEAE, treatment-emergent adverse event; ToT, time on treatment.

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Uncaptured benefits

Uncaptured benefits in company's submission

- Cemiplimab provides a step change for the management of this condition
- Allows young women to continue in employment, education or provide ongoing care to young dependants and elderly family members
  - **EAG:** considers these as productivity benefits, which fall outside of the NICE reference case. No specific description of how the treatment would provide QALY gains for carers
- 3-weekly dosing for cemiplimab is a particular advantage over weekly paclitaxel – reducing the burden on people with the condition and their families
- The administration process for cemiplimab is also simpler and shorter than for paclitaxel
- These benefits reduce demand, freeing up staff time and chair capacity, reducing waiting times and delays
  - **EAG:** weekly paclitaxel is not one of the comparator regimens included in the company's base case and even in the company's scenario analysis implementing a mix of comparator regimens based on clinical advice, weekly paclitaxel is assumed to be used only 46% of the time*

Are there any uncaptured benefits?

***Note:** Dosing regimens for all chemotherapy drugs is presented in company submission Table 32.
Abbreviations: QALY, quality-adjusted life year.

Severity modifier

Company and EAG agree that a severity modifier of 1.7 is appropriate

Table: Results of company's and EAG's base-case QALY shortfall analyses and preferred QALY weighting

	Expected total QALYs for the general population (discounted)	Expected total QALYs for people living with a condition on current treatment (discounted)	Absolute QALY shortfall	Proportional QALY shortfall	Preferred QALY weight
Company's base case	15.78	0.57	15.21	0.96	1.7
EAG's base case	15.78	0.62	15.15	0.96	1.7

Does committee agree it is appropriate to apply a 1.7x QALY weighting for severity?

Table: QALY weightings for severity

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Abbreviations: QALY, quality-adjusted life year

Managed access

- Company has not submitted managed access proposal

Cost-effectiveness results

- All ICERs reported in PART 2 slides because they include confidential discounts
- Company and EAG base cases both below £25,000 per QALY gained

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Cemiplimab for treating recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy

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

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Key issues

Issue	Resolved?	ICER impact
PD-L1 status • Subgroup analysis by PD-L1 status • PD-L1 status distribution in clinical practice • Curve selection for PD-L1 subgroups	No – for discussion	Moderate
Time on treatment • Choice of Kaplan-Meier data or parametric distribution • Time on treatment capping by progression-free survival (PFS) • Time on treatment in clinical practice for cemiplimab	No – for discussion	Small / Moderate
Treatment-dependent utilities • What are the appropriate utility values, particularly in the post-progression state?	No – for discussion	Small

Other issues with small impact presented in Appendix.

Abbreviations: ICER, incremental cost-effectiveness ratio; PD-L1, Programmed Death-Ligand 1.

Appendix

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Final NICE scope

Decision problem

Table: EAG comments on decision problem

	Final scope	Company	EAG comments
Population	Adults with r/m CC that has progressed on or after having platinum-based chemotherapy	Adults with r/m CC that has progressed on or after having platinum-based chemotherapy who have not had immunotherapy	Population addressed in the CS is narrower than in the scope – people having cemiplimab in practice likely PD-L1 negative. Noted other issues with trial generalisability - ECOG performance status and time of progression after completing platinum-based therapy.
Comparators	Single-agent chemotherapy Best supportive care Tisotumab vedotin monotherapy (subject to NICE evaluation)	Basket of single agent chemotherapy regimens only BSC not a comparator – if active treatment not suitable, cemiplimab also not suitable Tisotumab vedotin not currently established clinical practice	EAG clinical experts agree that BSC not a relevant comparator, but EAG would have liked to see a comparison with tisotumab vedotin (key issue)

Abbreviations: BSC, best supportive care; CS, company submission; ECOG, Eastern Cooperative Oncology Group; PD-L1, Programmed Death-Ligand 1; r/m CC, recurrent or metastatic cervical cancer.

Other issues

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Issue	Company	EAG comments	ICER impact
Types of 2L single-agent chemotherapy treatments used	EMPOWER	EMPOWER may not be reflective of treatments used in clinical practice (for example, paclitaxel not used in trial)	Unknown but likely small
ToT for chemotherapy	EMPOWER – 96 weeks max.	NHS treatment protocols specify max duration of 6 cycles (18 weeks)	Small
Resource use following disease progression	Different for each arm	Prefers to assume the same resource use post-progression	Small
Uncertainty regarding OS extrapolation	Base case uses generalised gamma	Base case aligned with company – but the ICER is still sensitive to choice of extrapolation	Small to moderate
Approach to calculating subsequent treatment costs	Applied one-off subs. treatment cost at time of disease progression based on PFS	Applied an adjustment to account for the proportion of PFS events which were deaths, as company's approach could overestimate costs	Small
Immune-related TEAE	Not included	Included	Small

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Key issue: PD-L1 status – subgroup analysis

Figure 1: OS Kaplan–Meier curves for cemiplimab and chemotherapy PD-L1 subgroups

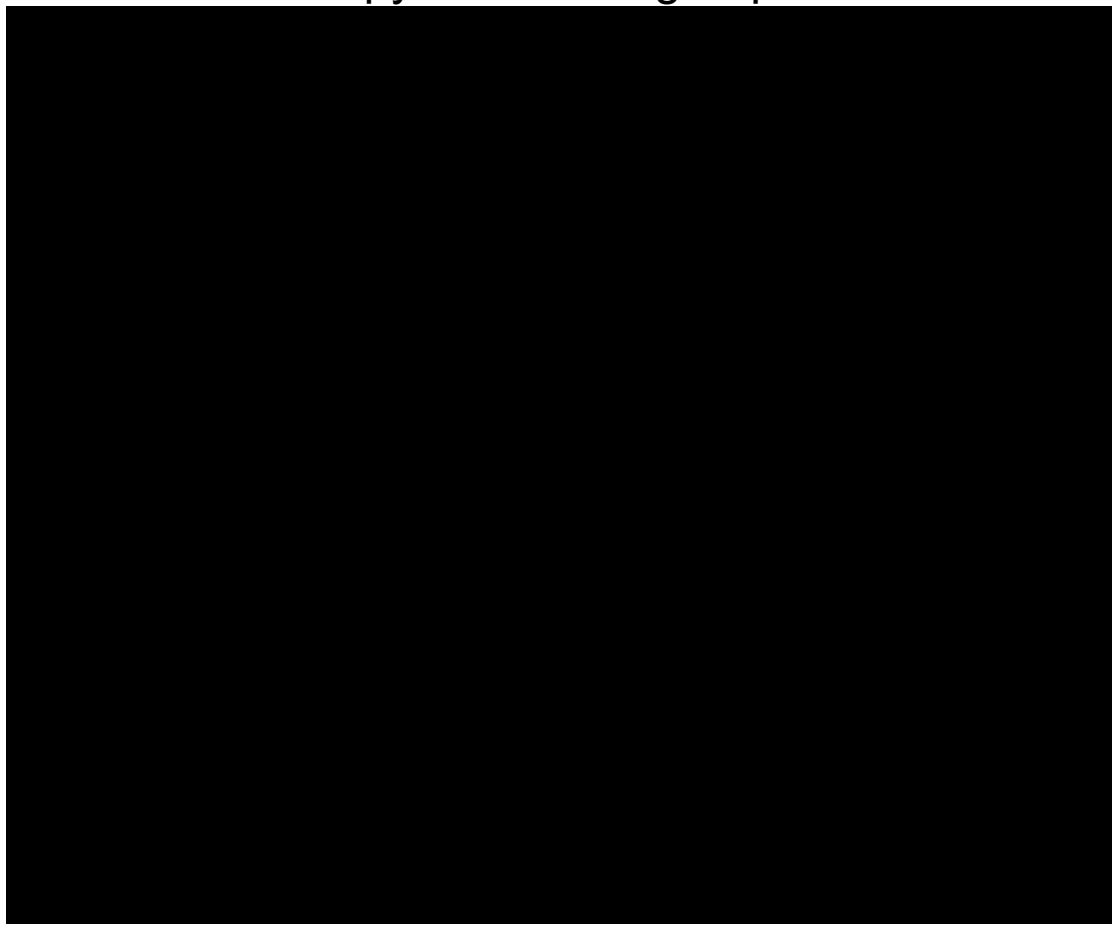

Figure 2: PFS Kaplan–Meier curves for cemiplimab and chemotherapy PD-L1 subgroups

Abbreviations: OS, overall survival; PFS, progression-free survival; PD-L1, Programmed Death-Ligand 1.

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Key issue: PD-L1 status – curve selection

Company: Prefers generalised gamma, EAG: prefers log-normal for **OS in PD-L1 negative** subgroup for **cemiplimab**

Figure: Observed and model-predicted OS in PD-L1 < 1% subgroup, cemiplimab

Table: AIC/BIC statistics, company preferred gen. gamma (green) and EAG preferred log-normal (purple)

Distribution	Cemiplimab (PD-L1 < 1%)	
	AIC (rank)	BIC (rank)
Exponential	421.1 (5)	423.3 (4)
Weibull	422.8 (6)	427.2 (6)
Log-normal	414.1 (2)	418.5 (1)
Generalised gamma	**412.7 (1)**	**419.3 (2)**
Gompertz	423.1 (7)	427.5 (7)
Log-logistic	420.9 (4)	425.3 (5)
Gamma	417.3 (3)	421.7 (3)

Note: Corresponding hazard plots were not decipherable and could not be relied on to help inform the model choice further.

Abbreviations: OS, overall survival; PD-L1, Programmed Death-Ligand 1.

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Key issue: PD-L1 status – curve selection

Company: Prefers generalised gamma, EAG: prefers log-normal for **PFS in PD-L1 negative** subgroup for **chemotherapy**

Figure: Observed and model-predicted PFS in PD-L1 < 1% subgroup, chemotherapy

Table: AIC/BIC statistics, company preferred gen. gamma (green) and EAG preferred log-normal (purple)

Distribution	Single-agent chemotherapy (PD-L1<1%)	
	AIC (rank)	BIC (rank)
Exponential	344.1 (5)	346.3 (4)
Weibull	344.4 (6)	348.9 (6)
Log-normal	333 (1)	337.4 (1)
Generalised gamma	**334.5 (2)**	**341.2 (3)**
Gompertz	342.3 (4)	346.8 (5)
Log-logistic	346.1 (7)	350.5 (7)
Gamma	335.1 (3)	339.5 (2)

Note: Corresponding hazard plots were not decipherable and could not be relied on to help inform the model choice further.
Abbreviations: PFS, progression-free survival; PD-L1, Programmed Death-Ligand 1.

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Key issue: PD-L1 status – curve selection

Company: Prefers generalised gamma, EAG: prefers log-normal for **PFS in PD-L1 positive** subgroup for **chemotherapy**

Figure: Observed and model-predicted PFS in PD-L1 >=1% subgroup, chemotherapy

Table: AIC/BIC statistics, company preferred gen. gamma (green) and EAG preferred log-normal (purple)

Distribution	Single-agent chemotherapy (PD-L1 ≥ 1%)	
	AIC (rank)	BIC (rank)
Exponential	577.6 (6)	580.4 (6)
Weibull	574.4 (5)	580 (5)
Log-normal	553.6 (1)	559.2 (1)
Generalised gamma	**553.9 (2)**	**562.3 (2)**
Gompertz	569.7 (4)	575.3 (4)
Log-logistic	579.5 (7)	585.1 (7)
Gamma	558.9 (3)	564.5 (3)

Note: Corresponding hazard plots were not decipherable and could not be relied on to help inform the model choice further.
Abbreviations: PFS, progression-free survival; PD-L1, Programmed Death-Ligand 1.

Moderate impact

Key issue: Time on treatment for cemiplimab – scenario analysis exploring treatment beyond 96 weeks

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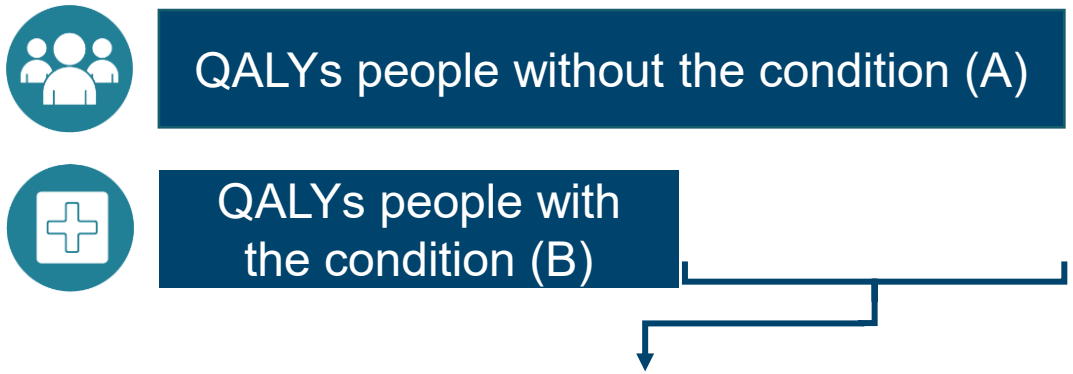
Figure: Parametric curves fit to cemiplimab ToT data censored at 96 weeks

Abbreviations: ICER, incremental cost-effectiveness ratio; ToT, time on treatment.

QALY weightings for severity

Severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Abbreviations: QALY, quality-adjusted life year