# Pembrolizumab in combination with platinum-based chemotherapy for treating recurrent, persistent or metastatic cervical cancer

For public observers – ACIC information redacted

**Technology appraisal committee A [10 January 2023]:** 2nd appraisal meeting

**Chair:** Radha Todd

**Evidence assessment group:** Centre for Reviews and Dissemination and Centre for Health Economics – York

**Technical team:** Rachel Ramsden, Sally Doss, Janet Robertson

**Company:** Merck Sharp & Dohme (MSD)

# Recap from 1st meeting

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# Pembrolizumab (KEYTRUDA®, MSD)

| | |
|---|---|
| **Marketing authorisation (May 2022)** | • Treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1 |
| **Mechanism of action** | • Monoclonal antibody, which binds to the PD-1 receptor, increasing immune response to tumour cells |
| **Administration** | • 200 mg every 3 weeks (Q3W)* or 400mg every 6 weeks (Q6W)<br>• IV infusion over 30 minutes |
| **Price** | • List price: £2,630 per 100 mg vial<br>• Cost per administration (list price):<br>  • 200 mg Q3W: £5,260<br>  • 400 mg Q6W: £10,520<br>• The price of pembrolizumab is subject to a confidential CAA with a simple discount **(discount updated since ACM1)** |

Notes: *, KEYNOTE-826 only evaluated 200 mg Q3W dose



Abbreviations: Abbreviations: CAA, Commercial Access Arrangement; CPS, combined positive score; IV, intravenous; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; QxW, every x weeks.

# ACD recommendation: pembrolizumab plus chemotherapy with or without bevacizumab is not recommended

Cannot be recommended for routine use or for use in Cancer Drugs Fund

**Clinical effectiveness**

- OS data from KEYNOTE-826 is immature

**Cost effectiveness**

- When further data becomes available from KEYNOTE-826, most appropriate modelling approach may change
- Company's and ERG's approaches for extrapolating TTP and PFS are not reliable for decision making without further justification
- No plausible range of cost-effectiveness estimates. ICERs were above the range considered to be a cost-effective use of NHS resources when the end of life modifier was applied

**Cancer Drugs Fund**

- Uncertain if pembrolizumab with platinum-based chemotherapy has plausible potential to be cost effective



Abbreviations: ACD, appraisal consultation document; ERG, Evidence Review Group; ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

# Committee requests/preferred assumptions after ACM1

| Issue | Committee request/preferred assumption | Incorporated by company in response? |
|---|---|---|
| **Modelled outcomes** | Further justification of approaches for extrapolating TTP and PFS | Yes |
| | Company's approach for extrapolating PPS (1-piece generalised gamma model with a differential survival benefit across treatment arms) | Yes – original base case |
| **Duration of treatment effect** | Waning from 3 years to 5 years after stopping pembrolizumab treatment, with a 2-year stopping rule | Partially – 5-7 years post treatment |
| **Utilities** | Health state approach | Yes – with minor correction identified by company (small reduction to ICER) |

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Abbreviations: ACM1, first appraisal committee meeting; ICER, incremental cost effectiveness ratio; OS ,overall survival; PFS, progression-free survival; PPS, post-progression survival; TTP, time to progression.

# Consultation responses

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# ACD consultation responses

**Received from**

- **Company:** MSD
- **1 patient organisation**:
    - Jo's Cervical Cancer Trust
- **1 clinical expert**
- **Web comments (n=3)**



Abbreviations: ACD, appraisal consultation document.

# Patient organisation, web comments and clinical expert

## Unmet need and burden of disease

- "Very few new drugs become available which work for cervical cancer and this means women are left without options and hope. This drug being made widely available on the NHS would save the heartbreak and devastation suffered by their families."
- Patients often young and fit with dependants/young families → tolerate treatment well and any disease control and survival improvements lead to significant quality of life improvements
- Very limited treatment options despite fitness, often with enrolment in phase 1 trials etc.
- Patient group needs more options and this trial represents the biggest improvement in PFS

## Survival outcomes and link between PFS and OS

- Improvements in survival represent a massive step change for treatment outcomes
- The not yet reached median OS of estimated 2 years is ground breaking for this patient cohort
- A proportion of patients achieve a complete response - this is unprecedented in advanced cervical cancer
- Agree PFS benefit is highly indicative of a similar OS benefit

## ACD conclusion

- "I am very disheartened and concerned that the treatment I am able to deliver to this patient cohort is suboptimal if access to pembrolizumab is not possible despite the solid evidence"
- Decision is incorrect and does not take into account this is an aggressive cancer with limited options



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

Model driver  Unknown impact  Moderate impact

# Key issues to be resolved

| Key issue | Impact on ICER |
|---|---|
| **Uncertainty of modelled outcomes**<br>• Does the company's justification for the modelling approach taken to extrapolate TTP and PFS reduce the uncertainty? |  |
| • Are the long-term survival estimates from the model plausible? | N/A |
| • Does the company's response reduce the uncertainty in the OS gains from PFS gains? | N/A |
| **Duration of treatment effect**<br>• How appropriate are the company's assumptions for treatment effect waning? |  |
| **Other considerations** | **Impact on ICER** |
| **Uncaptured value**<br>• Is there uncaptured value in the company's economic model? |  |
| **Equality**<br>• How should the inequality issues raised by stakeholders be taken into account? | N/A |
| **Decision making threshold**<br>• What decision making threshold is appropriate? | N/A |

Abbreviations: ICER, incremental cost effectiveness ratio; N/A, not applicable; OS ,overall survival; PFS, progression-free survival; TTP, time to progression.

# Extrapolation of TTP and PFS: piecewise approach (original base case)

**Company:** re-presented preferred modelling approach (37-week piecewise) and justification

- One-piece models not a plausible set of analyses for decision-making
  - Very poor visual fit to PFS in PEM+SoC arm
  - Resulting OS inconsistent with 4-year data from GOG 240 in SoC arm
  - Resulting OS for PEM+SoC implies a drop between year 2 and 5 ([redacted])
    - Greater than observed in 5-year pembrolizumab trials to date
    - Inconsistent with relatively high levels of CR and PR in KEYNOTE-826
- Piecewise model with 37 week cut off
  - Survival estimates close to GOG 240 at 2 years in SoC arm (~15%) and appear plausible in PEM+SoC arm, given data from 5-year trials of pembrolizumab
  - Validated at advisory board of 8 UK clinicians. Estimates now more conservative given use of one-piece curve for SoC and treatment effect waning assumption
- Separate models per treatment arm
  - Pembrolizumab a different mechanism of action to SoC. PEM+SoC provides additional mechanism of action

**ERG:** continues to consider piecewise model to be overly optimistic

- Model predictions inconsistent with parametric extrapolations of OS, which are consistently more conservative
- Reiterates concerns about representativeness of patients treated in GOG 240
- Urges caution in applying different extrapolation approach across treatment arms



Abbreviations: CR, complete response; OS, overall survival; PEM, pembrolizumab; PFS, progression-free survival; PR, partial response; SoC, standard of care; TTP, time to progression.

# Extrapolation of TTP and PFS: spline based approach

**Company:** Explored spline functions modelled on odds, hazard and normal scales; based on 1, 2 or 3 knots

- Hazard scale function based on 2 knots (hazard, 2) best fitting for PFS and TTP for both arms
  - Plausible 4-year SoC OS against GOG 240 (13% vs. 15%)
  - 5-year pembrolizumab OS within range observed in published 5-year trials in metastatic solid tumours (e.g. 28.5% vs. 31.9% in KEYNOTE-024)
  - Central of available spline models rather than most optimistic or pessimistic
  - Long term PFS and OS may be considered optimistic but are tightly constrained by treatment effect waning

**ERG:** Good statistical and visual fit to observed data does not mean extrapolations are reliable

- More optimistic than company base case → unlikely to present more realistic long-term survival predictions
- Treatment effect waning is not a device that in itself reduces or increases uncertainty



Abbreviations: OS, overall survival; PFS, progression-free survival; SoC, standard of care; TTP, time to progression.

# Extrapolation of TTP and PFS: response based model

Response based model: survival curves extrapolated per responder category (CR, PR, SD, PD and NE/NA) and weighted average provided based on the proportions of people in each group in the trial

**Company:** RBM validates original base case approach (piecewise model)

- Single-piece parametric fits not suitable as PFS hazard function changes over time; initially dominated by events in PD and SD patients. As they progress, more comprised of CR and PR patients with slower event rates
- TTP, PFS and OS curves all similar to those used in/predicted by original piecewise approach

**ERG:** RBM increases flexibility but also uncertainty

- Structural uncertainties remain as retains assumption PFS is main driver of benefit
- Justification and clinical plausibility of company's assumed treatment-dependent relationship between response and TTP/PFS is unclear

Abbreviations: CR, complete responders; NE/NA, not evaluable/no assessment; OS, overall survival; PD, progressed disease; PFS, progression-free survival; PR, partial responders; RBM, response based model; SD, stable disease; TTP, time to progression.

# Extrapolation of PFS

Comparison of base case, RBM and spline PFS curves, and treatment effect waning

Abbreviations: PEM, pembrolizumab; PFS, progression-free survival; RBM, response based model; SoC, standard of care.

# Key issue: Extrapolation of TTP and PFS

**ACD**

- ERG's preferred one-piece log-logistic extrapolation may be too pessimistic for pembrolizumab. Company's preferred two-piece approach may be too optimistic.
- Both approaches not reliable for decision making without further justification

**Company response**

- Two-piece, spline and responder based models give consistent curves and converged on ICERs in range ~£34,000 to £55,000/QALY gained (treatment effect waning 5 to 7 years after end of treatment)
- Base case assumptions remain unchanged from ACM1

**ERG comments**

- While satisfied company have explored full range of realistic approaches to survival analysis, additional analyses do not address the fundamental limitations of the available data
- Full resolution of issue is not possible given current data limitations. Future data cuts will contribute to reducing associated uncertainty
- Base case assumptions remain unchanged from ACM1

**ACD responses (clinical expert):** Extrapolations of OS for SoC are in line with GOG 240. This would support the model used by the company and are in line with clinically observed outcomes from my experience

Has the additional analysis submitted by the company sufficiently resolved the uncertainties raised in ACM1?



Abbreviations: ACM1, first appraisal committee meeting; ERG, Evidence Review Group; ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression-free survival; SoC, standard of care; TTP, time to progression.

# Key issue: Uncertain level of OS benefit for pembrolizumab

**ACD:** Likely that improvements in PFS are associated with an OS benefit but, given the immaturity of OS data, level of benefit is uncertain

**Company response:** Only uncertain to extent that gains in PFS are uncertain

- Committee accepted PPS longer for PEM+SoC; mean PFS gain → at least same mean OS gain
- ACM1 clinical experts: benefits of pembrolizumab might persist beyond progression, and depth of response is greater in PEM+SoC in KEYNOTE-826
- Observed KEYNOTE-826 PPS data relatively mature and in line with GOG 240
- ACM1 clinical experts confirmed PFS-OS phenomenon observed in cervical cancer before (GOG 240)
- No confounding of efficacy due to subsequent treatment in KEYNOTE-826 or clinical practice
- Patient population relatively young → non-cancer mortality does not influence survival
- Similar KEYNOTE-826 OS and PFS HRs (~0.6 in the CPS of at least 1 population)

**ERG:** Company correct PFS is principal uncertainty but, given structural relationship between PFS and OS, equally accurate to characterise this as uncertainty about magnitude of OS benefits

- Plausible that PFS gains result in OS gains but relationship subject to uncertainty
  - PFS is not a validated surrogate for OS in this indication
- Cervical cancer also affects older women. For a proportion of patients, non-cancer mortality will be relevant

**ACD responses (clinical expert):** Significant improvement in PFS is highly indicative of similar OS benefit

Has the response submitted by the company sufficiently resolved the uncertainties raised in ACM1?

Abbreviations: ACD, appraisal consultation document; ACM1, first appraisal committee meeting; CPS, combined positive score; ERG, Evidence Review Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PEM, pembrolizumab; PFS, progression-free survival; PPS, post progression survival; SoC, standard of care.

# Key issue: Treatment effect waning

**ACD:** Committee concluded treatment effect waning from 3 to 5 years after stopping treatment with a 2 year stopping rule was reasonable for pembrolizumab

## Company response

- No more empirical evidence for committee's preferred 3-5 year assumption, than 5-7 year or no waning
- No evidence of waning in multiple 5-year trials of pembrolizumab → 3-5 years is most conservative assumption
- Propose company preferred 5-7 years post treatment cessation could be considered a middle ground

## ERG comments

- Accepts biological plausibility of a durable treatment effect after stopping pembrolizumab
  - Duration is highly uncertain
  - No indication-specific evidence to support a sustained treatment effect
- In absence of evidence, 3 to 5-year waning period plausible and consistent with previous NICE appraisals

## ACD responses (clinical expert)

- "I have not observed a waning effect to extent being considered here. i.e. patients who respond and are long term responders do not relapse subsequently"

Are the company's treatment effect waning assumptions appropriate?

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Abbreviations: ACD, appraisal consultation document; ERG, Evidence Review Group.

# Other considerations: Uncaptured value

**ACD:** All relevant benefits of the technology were captured in the QALY calculations

## Company response

- Benefit of prolonged response (particularly CR) would add QALYs to both patients' carers and children/dependents, which are not included in the model
- Likely significant increase in quality of life and incremental QALYs for patients remaining progression free after 2-years in KEYNOTE-826, above what has been captured in the model

## ERG comments

- Correct that eligible cervical cancer patients will include many working-age women with dependent children
  - Plausible additional HRQoL benefits associated with younger population, but evidence provided insufficient to conclude provision of pembrolizumab will generate additional benefits
  - Lack of precedent for including additional carer benefits in cancer appraisals
  - Also affects many older women (55% of patients KEYNOTE-826 were over 50 and 16.2% were over 65) and provision of HPV vaccine means age of patients likely to increase over time
- Agrees it plausible there are additional benefits in patients surviving beyond two years as not in receipt of treatment or subject to associated AE burden
  - Magnitude of benefit likely to be very small and inconsequential for ICER (AE disutility in pembrolizumab arm sums to just -0.013 QALYs over entire time horizon)

Is there uncaptured value in the company's economic model?

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Abbreviations: ACD, appraisal consultation document; AE, adverse event; CR, complete response; ERG, Evidence Review Group; HPV, human papillomavirus vaccine; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year.

# Other considerations: Equality

**Recap from ACM1:** No equality considerations relating to use of pembrolizumab identified or anticipated except that condition is relatively more prevalent in lower socioeconomic and ethnic minority groups. Improving outcomes for these groups is in line with NICE's "Principle 9. Aim to reduce health inequalities".

**ACD:** Potential equality issues raised during the appraisal could not be addressed through NICE technology appraisal guidance → committee concluded that there were no relevant equality issues

**Company response:** Metastatic cervical cancer more common among most deprived communities in society as well as ethnic minority groups and migrants who have low engagement with vaccination and screening programmes. A recommendation will work towards reducing health inequalities (NICE Principle 9)

**ACD responses (patient organisation)**

- Patients do not want it known by others if they accessed this line of treatment due to inequality that exists
  - Awareness some patients offered pembrolizumab, depending on their cancer centre location
  - Some patients may access via private healthcare
- "…sometimes feels that as a 'woman's illness' further stigmatised by the mention of HPV, things just have not moved on for decades"

**ERG comments:** Differences in incidence cannot be addressed by this technology appraisal

- No suggestion any recommendation for pembrolizumab would differentially impact individuals protected by equalities legislation

How should the equality issues raised be taken into account?

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Abbreviations: ACD, appraisal consultation document; ACM1, first appraisal committee meeting; CR, Complete Response; HPV, human papillomavirus; QALY, quality-adjusted life year.

# Other considerations: Decision making threshold

**ACD:** Pembrolizumab combination meets end of life criteria

- Because of the uncertainty, an acceptable ICER would be very comfortably below £50,000
- Pembrolizumab combination cannot currently be recommended for use in the CDF

**Company response:** Decision threshold should be £50,000/QALY gained

- Certainty in appropriateness of model structure and clinical benefit
- Range of plausible ICERs, all close to or below the threshold → low risk of decision error
- Uncaptured benefit would reduce base case ICER
- Pembrolizumab represents a badly needed innovation in advanced cervical cancer
- Potential to reduce health inequalities

**ERG comments:**

- Does not agree with assertion that decision uncertainty is small. There is a high risk of decision error
- KEYNOTE 826 follow up is limited → much of the modelled incremental benefit associated with pembrolizumab is in extrapolated portion of survival curve
- While ERG agrees there is high unmet need and there would be substantive clinical benefits associated with a positive recommendation for pembrolizumab, these benefits are already captured by the model

**Other considerations:** Company did not include a response to the committee's consideration of CDF

What decision making threshold is appropriate? Can pembrolizumab be recommended for routine commissioning or through the CDF?

Abbreviations: ACD, appraisal consultation document; CDF, Cancer Drugs Fund; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

# Summary of company and ERG base case assumptions

## Company revised base case assumptions include committee preferred utility values, ERG base case assumptions unchanged from ACM1

Post ACM1 assumptions in company and ERG base case

| Assumption | Committee preferred | Company base case | ERG base case |
|---|---|---|---|
| **TTP/PFS: PEM+SoC** | None - requested further justification | Two-piece (KM to 37 weeks plus log-logistic) | One-piece (log-logistic) |
| **TTP/PFS: SoC** | | One-piece (log-logistic) | |
| **Treatment effect waning** | From 3-5 years after end of treatment | From 5-7 years after end of treatment | From 2-5 years after end of treatment |
| **Utility** | Health state approach | Health state approach with minor correction | |
| **PPS** | One-piece (generalised gamma) | One-piece (generalised gamma) | Pooled (generalised gamma) |

Abbreviations: ACM1, first appraisal committee meeting; ERG, Evidence Review Group; KM, Kaplan-Meier; PEM, pembrolizumab; PFS, progression-free survival; PPS, post-progression survival; SoC, standard of care; TTP, time to progression.

# Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator and subsequent treatment discounts

**Summary**

- Company's base case is **lower** than what would **usually** be considered a cost-effective use of NHS resources when the end of life criteria are met
- ERG's base case is **higher** than what would **usually** be considered cost-effective use of NHS resources, when the end of life criteria are met

ACD 3.12: "The committee also agreed that the end of life criteria applied to pembrolizumab, which allows it to consider ICERs of up to £50,000 per QALY gained, but given the level of uncertainty the ICER would have to be very comfortably below this to be accepted for routine commissioning."

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Abbreviations: ERG, Evidence Review Group; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year.

# Cost-effectiveness results and scenarios

Scenarios applied to company base case:

| PFS/TTP extrapolation | | Impact on ICER |
|---|---|---|
| PEM | SoC | |
| Piecewise (lognorm) | One piece | ↓ |
| Piecewise (average. Loglog/Weibull) | One piece | ↑↑ |
| Piecewise (loglog) | Piecewise | ↑ |
| RBM 1 | | ↑↑ |
| RBM 2 | | ↑↑ |
| RBM 3 | | ↑↑ |
| Spline (2 knot) | | ↓↓ |
| Spline (3 knot) | | ↓↓ |

| Treatment effect waning | Impact on ICER |
|---|---|
| 3-5 years after treatment | ↑↑ |
| None | ↓↓ |

Scenarios applied to ERG base case:

| Scenario | Impact on ICER |
|---|---|
| PEM TTP/PFS extrapolation: One-piece (log-logistic) | ↑↑↑ |
| Pooled survival curve for PPS | ↑ |
| GP/nurse visits, blood counts, and thyroid function tests costs | ↑ |
| All AEs of special interest occurring in more than 5% of patients modelled | ↑ |

Impact on ICER: ↑ = small; ↑↑ = moderate; ↑↑↑ large

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Abbreviations: AE, adverse event; ICER, incremental cost effectiveness ratio; PEM, pembrolizumab; PFS, progression-free survival; PPS, post-progression survival; RBM, response based model; SoC, standard of care; TTP, time to progression

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# Thank you.

# Back up slides

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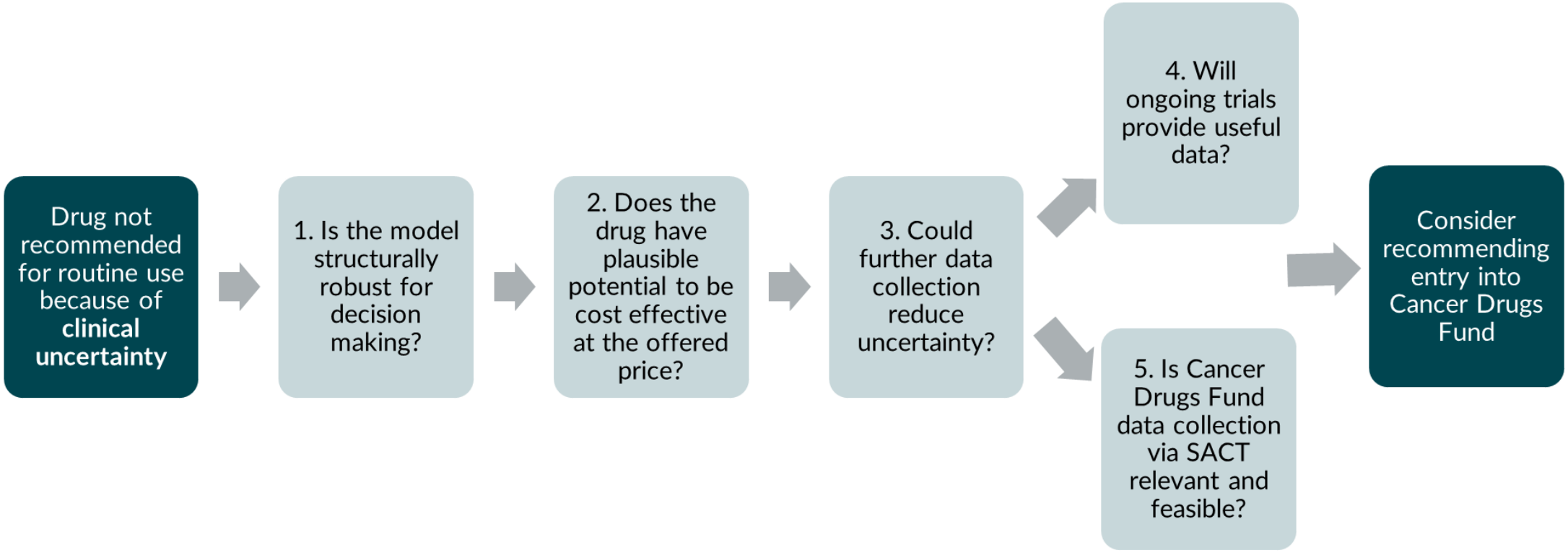
# Cancer Drugs Fund



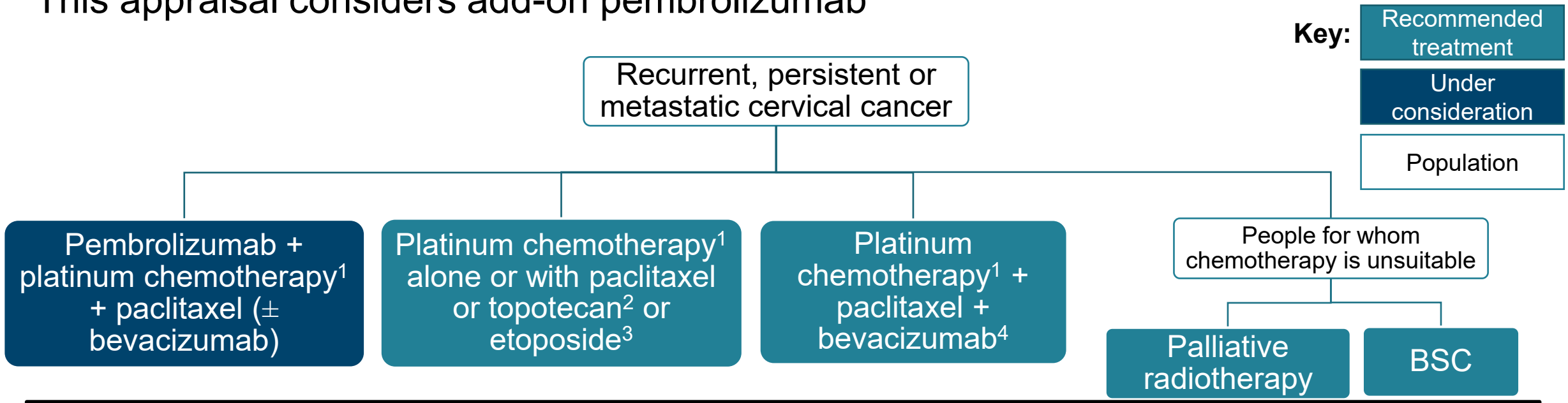

Define the nature and level of clinical uncertainty. Indicate the research question, analyses needed, and number of patients in the NHS in England needed to collect data.



Abbreviations: SACT, Systemic Anti-Cancer Therapy

# Treatment pathway

Platinum based therapy reflects clinical practice for majority of UK patients.
This appraisal considers add-on pembrolizumab




[1]Cisplatin or carboplatin

[2]NICE recommends topotecan with cisplatin as an option for treating recurrent or stage 4B cervical cancer in people who have not previously received cisplatin (TA183)

[3]Source: Cancer Research UK and NHS chemotherapy protocol (indicated for small cell gynaecological cancers including those affecting the cervix, endometrium and ovaries)

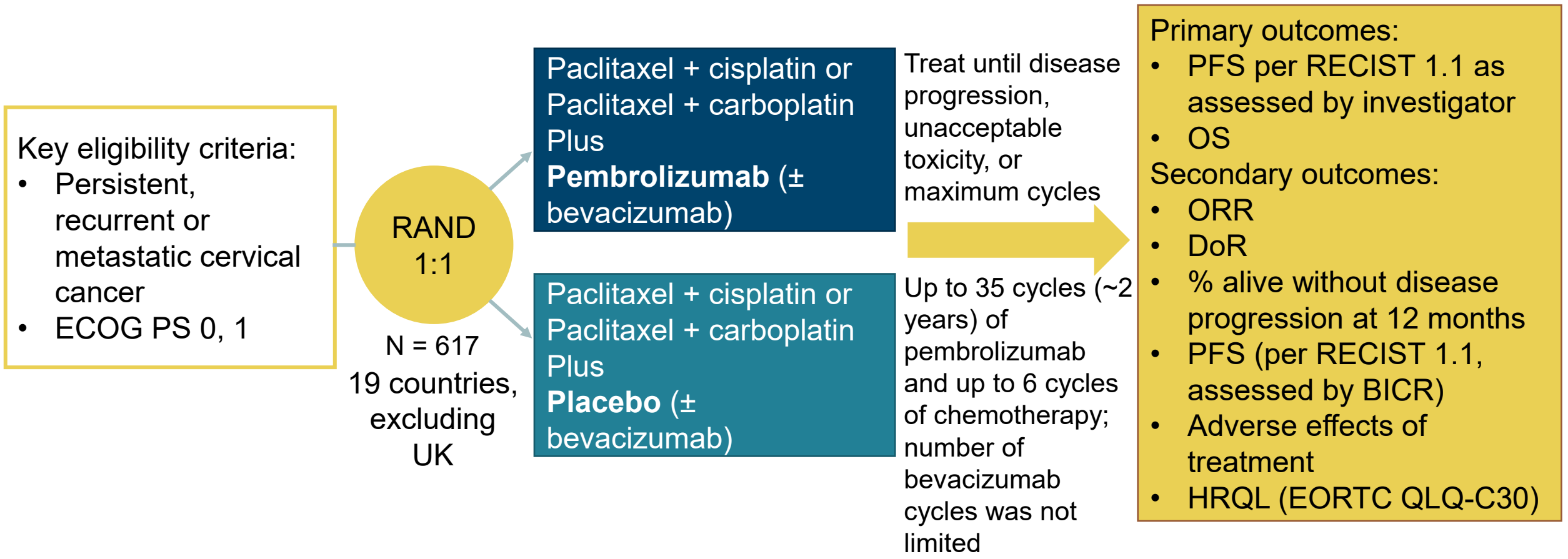
[4]Bevacizumab with paclitaxel and platinum chemotherapy[1] available in routine commissioning for untreated recurrent or metastatic cervical cancer



Abbreviations: BSC, best supportive care.

# KEYNOTE-826 (NCT03635567) study design

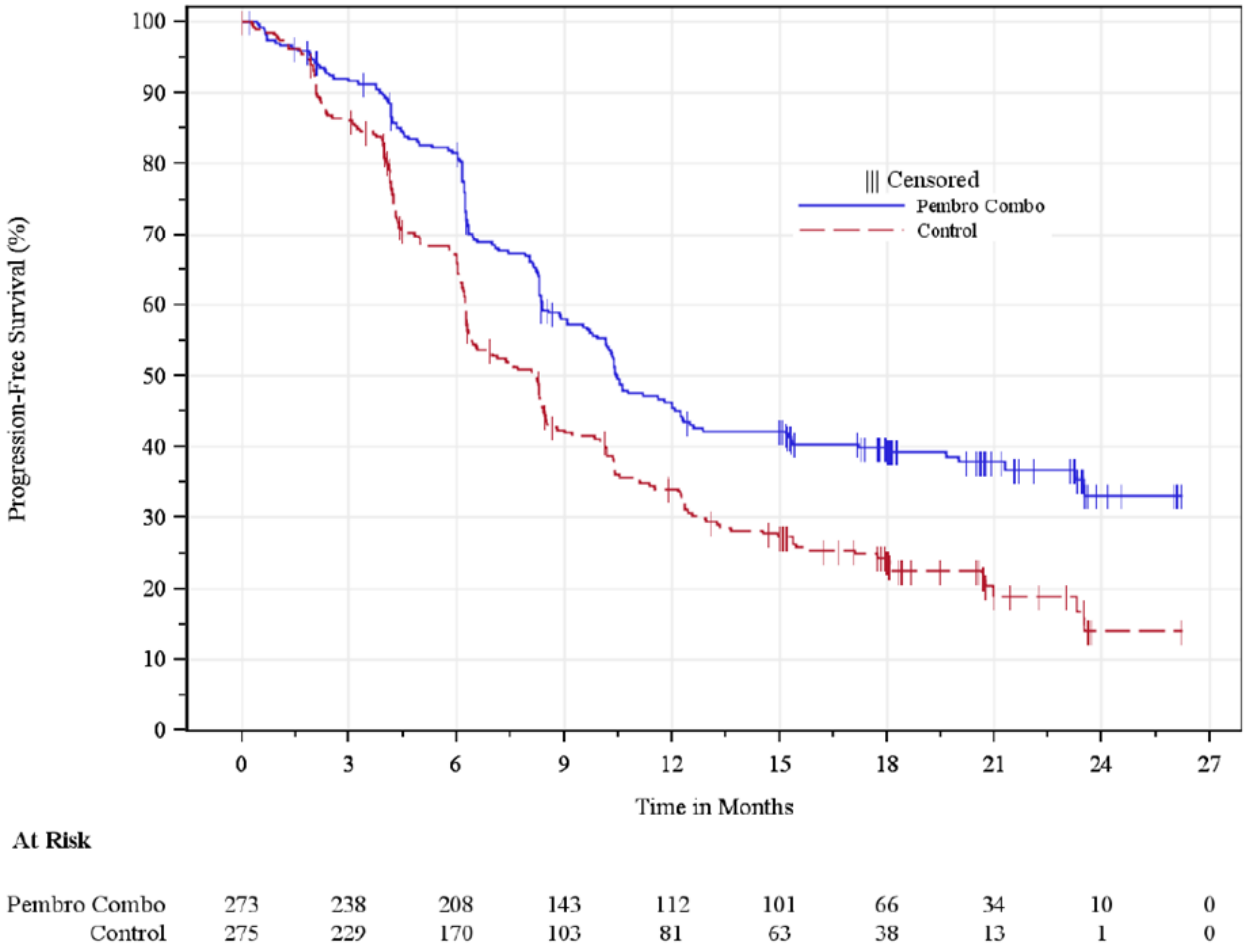
## Phase III, randomized, double-blind, placebo-controlled trial




Abbreviations: BICR, blinded independent central review; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC, European Organisation for Research and Treatment of Cancer; HRQL, health-related quality of life; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QLQ-C30, Quality of Life questionnaire C30; PFS, progression-free survival; RAND, randomised; RECIST 1.1, Response Evaluation Criteria in Solid Tumours Version 1.1.

# KEYNOTE-826 results: PFS as assessed per RECIST 1.1 by investigator assessment (CPS ≥ 1 population)

Pembrolizumab combination improves progression free survival




| PFS | Pembrolizumab (n=273) | Placebo (n=275) |
|---|---|---|
| N patients with event (%) | 157 (58) | 198 (72) |
| Median, months (95% CI) | 10.4 (9.7 to 12.3) | 8.2 (6.3 to 8.5) |
| HR (95% CI) | 0.62 (0.50 to 0.77); p < 0.0001 | |

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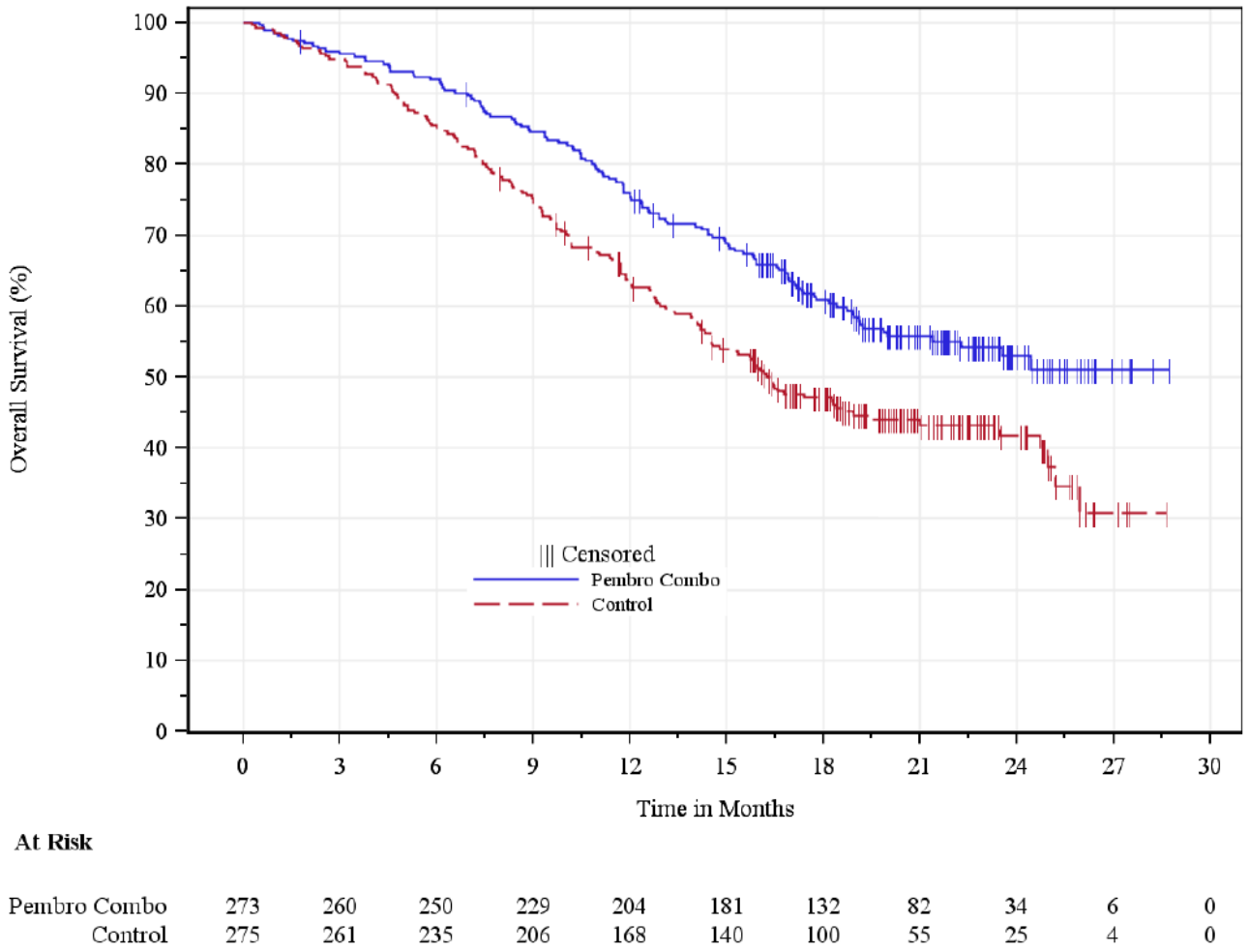
Abbreviations: CI, confidence interval; CPS, combined positive score; HR, hazard ratio; PFS, progression-free survival; RECIST 1.1, Response Evaluation criteria in solid tumours version 1.1.

# KEYNOTE-826 results: OS (CPS ≥ 1 population)

Pembrolizumab combination improves OS, but data immature (median OS estimate not reached in pembrolizumab arm)




| OS | Pembrolizumab (n=273) | Placebo (n=275) |
|---|---|---|
| N patients with event (%) | 118 (43) | 154 (56) |
| Median, months (95% CI) | NR (19.8 to NR) | 16.3 (14.5 to 19.4) |
| HR (95% CI) | 0.64; (0.50 to 0.81); p < 0.0001 | |

[redacted]

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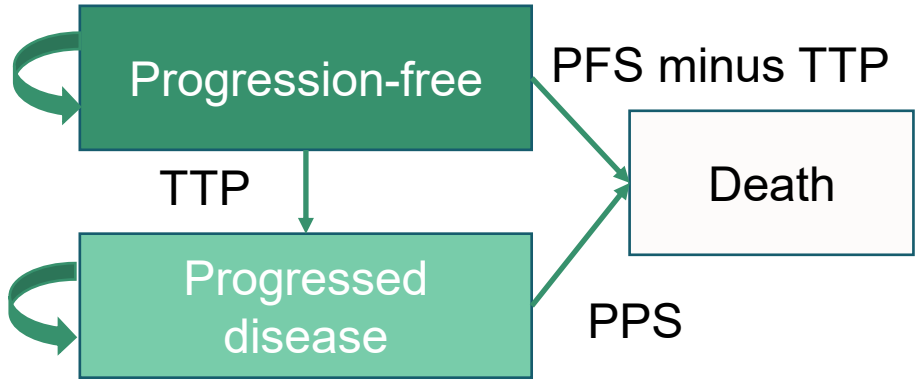
Abbreviations: CI, confidence interval; CPS, combined positive score; HR, hazard ratio; NR, not reached OS, overall survival.

# Company's model overview

## Three-state Markov state transition model

- OS data from trial not used in model
- Company based model OS on PFS and PPS
- There are 2 ways to transition to death health state




| Input | Assumption/ evidence source |
|---|---|
| **Baseline characteristics** | KN-826 (CPS≥1) |
| **Clinical effectiveness: PFS, TTP and PPS** | KN-826 (CPS≥1) with extrapolation |
| **Utilities** | KN-826 EQ-5D-5L mapped to 3L (van Hout et al.) |
| **Costs/resource use** | NHS reference costs and PSSRU/ UK clinician input |
| **Treatment effect waning assumption** | Company included preferred waning from 5-7 years after end of treatment (years 7-9 in the model) |
| **PD-L1 testing** | KN-826 (% patients); NHS reference costs |
| **Subsequent treatment composition** | UK advisory board (composition); KN-826 (duration) |

Abbreviations: CPS, combined positive score; EQ-5D, EuroQol five-dimension scale; KN-826, KEYNOTE-826; OS, overall survival; PD-L1, Programmed death-ligand 1; PFS, progression-free survival; PPS, post-progression survival; PSSRU, Personal Social Services Research Unit; TTP, time-to-progression.

# KEYNOTE-826 results: OS and PFS by response status

OS (top) and PFS (bottom) Kaplan-Meier data by response status categories for PEM+SoC (left) and SoC (right) (CPS ≥1 population)

~90% of complete responders still alive at 2 years and make up [redacted] of pembrolizumab cohort

Abbreviations: CPS, combined positive score; CR, complete response; NE, not evaluable; OS, overall survival; PD, progressive disease; PEM, pembrolizumab; PFS, progression-free survival; PR, partial response; SD, stable disease; SoC, standard of care

# Extrapolation of TTP and PFS: OS scenarios per approach

| Scenario | Waning* | OS | | | | | |
|---|---|---|---|---|---|---|---|
| | | 2y | 3y | 5y | 10y | 15y | 20y |
| **Pembrolizumab+SoC** | KN-826: 53% | | | | | | |
| Piecewise | None | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| RBM | None | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Spline | None | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Piecewise (base case)** | **5-7** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| RBM | 5-7 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| RBM2 | 5-7 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Spline | 5-7 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Piecewise | 3-5 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| RBM | 3-5 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| RBM2 | 3-5 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Spline | 3-5 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **SoC** | KN-826: 42% | | | | | | |
| Piecewise | - | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **One Piece (base case)** | **-** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| RBM | - | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| RBM2 | - | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Spline | - | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

OS estimates: spline > base case > RBM

Treatment effect waning scenarios → 15y+ OS is similar

Fairly consistent

NICE

Notes: *, waning is vs. corresponding SoC model e.g. spline vs. spline; RBM2, assumed TTP curves for NE/NA group = PR group.
Abbreviations: KN, KEYNOTE; OS, overall survival; SoC, standard of care; RBM, response based model; y, years.

# Plausibility of PFS and OS

**Company:** Base case piecewise model is within range of other trials for PFS and conservative for OS

- One-piece curve leads to OS and PFS decreasing at a rate greater than observed in long term trials of pembrolizumab → very surprising given response data in KEYNOTE-826
- One-piece model produces pessimistic results with OS and PFS being roughly ¼ of their 2-year value by 5 years

**ERG:** evidence presented broadly supportive of company's position but not conclusive that this pattern of declining hazards will occur across all indications

- Differences in disease biology, population, and subsequent treatment availability may impact hazard trends
- Company ratio of 2 to 5 year PFS being amongst highest is consistent with relative optimism of PFS extrapolations

Table: 2 year and 5 year PFS and OS in pembrolizumab arms of advanced solid tumour trials

| | PFS | | | OS | | |
|---|---|---|---|---|---|---|
| | 2 years | 5 years | Ratio | 2 years | 5 years | Ratio |
| KEYNOTE-024 | 29% | 12.8% | 0.44 | 50.0% | 31.9% | 0.64 |
| KEYNOTE-010 TPS ≥50% | 30% | 18.2% | 0.61 | 34.5% | 25.0% | 0.72 |
| KEYNOTE-010 TPS ≥1% | 19% | 9.4% | 0.49 | 22.9% | 15.6% | 0.68 |
| KEYNOTE-006+ | 35% | 21.5% | 0.61 | 60.0% | 45.0% | 0.75 |
| KEYNOTE-189* | 23.1% | 7.5% | 0.32 | 45.7% | 19.4% | 0.42 |
| KEYNOTE-407* | 20.7% | 10.8% | 0.52 | 36.0% | 18.4% | 0.51 |
| Company - KN826 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| One-piece model - KN826 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Notes: + projected from 26% at 4 years to 21.5% at 5; *, included approximately 1/3 PDL1 negative patients.
Abbreviations: KN, KEYNOTE; OS, overall survival; PFS, progression-free survival; TPS,