Pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]

Redacted slides for the public

Technology appraisal committee A, 13 January 2026

Chair: Radha Todd

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Company: MSD

Pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer

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

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Background on high-risk locally advanced cervical cancer

Causes

More than 90% of cases caused by human papillomavirus (HPV)

Epidemiology

- Prevalence: 10,551 diagnosed in England in the last 5 years, or 36 per 100,000 (2022)
- 20% stage 3 or 4 (excluding unknown staging)
- Incidence rate rises sharply in the 15 to 19 age group, peaks at 30 to 34, and decreases in older age groups

Classification

Staged using FIGO system*:

- stage 3 – cancer on pelvic side wall or lower vagina involved
- stage 4A – cancer has spread beyond true pelvis or bladder mucosa or rectum (or both) involved, and has spread to nearby organs

Symptoms and prognosis

Survival related to stage at diagnosis: stage 3 – 44%, stage 4 – 18% (at 5 years)

*2014 FIGO staging system in marketing authorisation; abbreviations: FIGO, International Federation of Gynecology and Obstetrics

Patient perspectives

Company submitted evidence from survey by Jo's Cervical Trust (2016)

Survey of 35 women diagnosed with cervical cancer in the previous 2 years

Range of emotions after diagnosis: isolation in decision making, concerns about fertility, feeling trust in clinicians

Lots of information – mainly paper leaflets and patient group websites

Treatment challenges:

- chemotherapy – physical (nausea) and psychological (anxiety, loneliness) side effects
- radiotherapy – challenging

Impact on daily life: time for appointments and recovery, lifestyle changes

Family impact: disrupted routines, reduced energy for children, emotional closeness but reduced intimacy

Employment: mix of sick leave and early retirement used

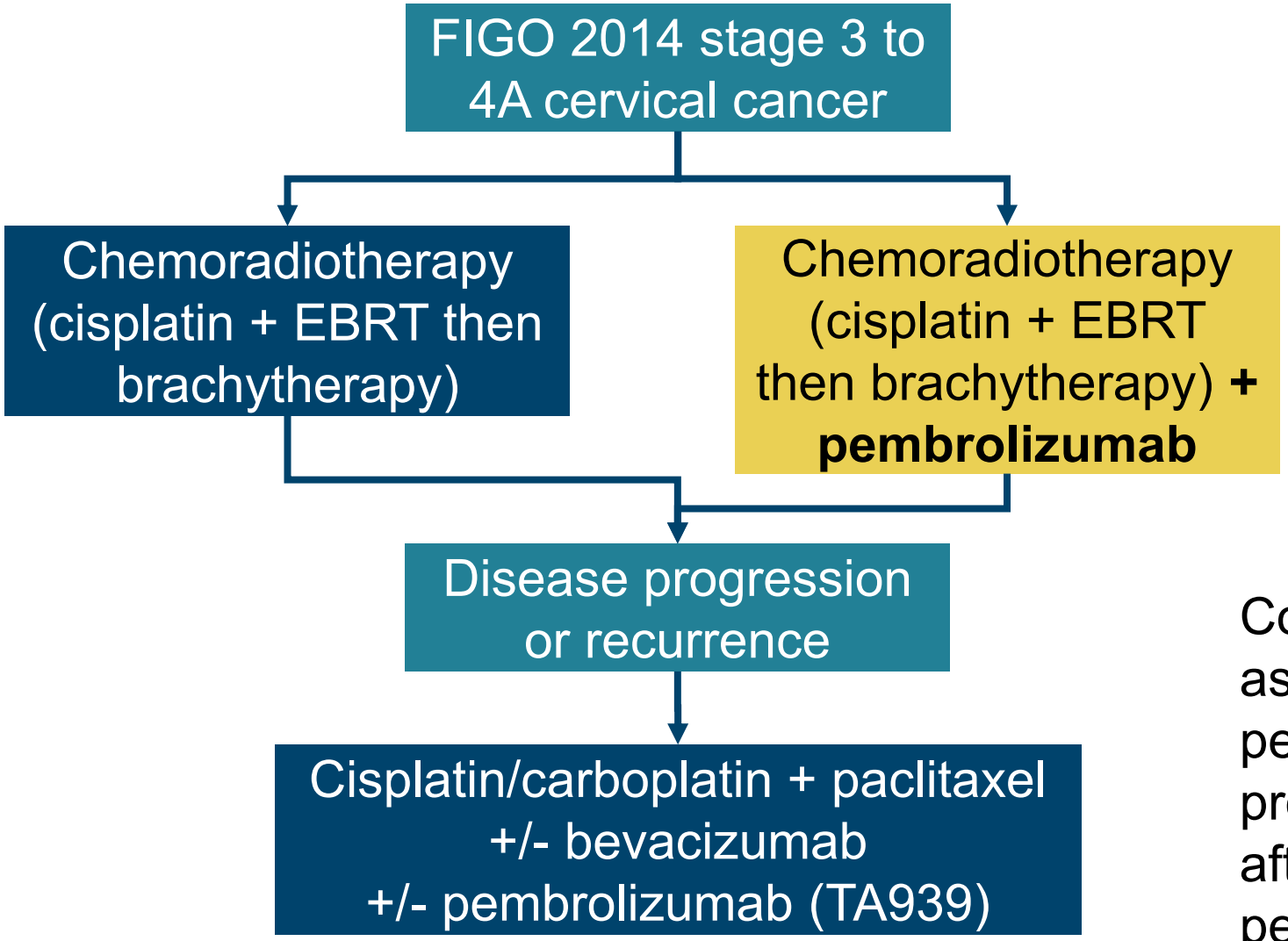
Clinical perspectives

Submissions from 2 clinical experts

- Main aim of treatment is cure
- Unmet need to improve survival rates in stage 3 to 4A cervical cancer
- One clinical expert notes that chance of cure <50% [at 5 years]); the other notes that about 20% to 25% in this cohort relapse or are not fully cured after primary treatment
- Local control leads to survival benefit
- Current NHS treatment: chemoradiation with EBRT, weekly cisplatin chemotherapy then intrauterine brachytherapy
- KEYNOTE-A18 consistent with NHS practice
- Adding pembrolizumab will increase number cured
- Most important outcomes: complete response, overall survival, progression-free survival
- More toxicity with pembrolizumab; prolonged nature of treatment (15 cycles every 6 weeks) will mean side effects continue or develop at later stages
- Implementation will be more challenging; many cycles of pembrolizumab with and after chemoradiotherapy mean a big commitment for patients

Abbreviations: EBRT, external beam radiotherapy

Treatment pathway



Company economic model assumes people can have pembrolizumab again if disease progresses at least 6 months after initial treatment with pembrolizumab

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Abbreviations: EBRT, external beam radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; TA, technology appraisal

Pembrolizumab (Keytruda, MSD)

Marketing authorisation	• Pembrolizumab, in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy), is indicated for the treatment of FIGO 2014 Stage 3 - 4A locally advanced cervical cancer in adults who have not received prior definitive therapy • UK marketing authorisation granted April 2025
Mechanism of action	Pembrolizumab is a checkpoint inhibitor targeting and blocking PD-1, which is responsible for dampening T-lymphocyte immune responses in the tumour microenvironment
Administration	200 mg every 3 weeks or 400 mg every 6 weeks as an intravenous infusion over 30 minutes until disease progression, unacceptable toxicity or up to 24 months; concurrent with chemoradiotherapy, then as monotherapy
Price	• List price per pack: £2,630 per 100 mg vial • List price for 12 months of treatment: around £91,000 per year • A confidential commercial arrangement applies

 Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; PD-1, programmed cell death 1

Key issues

No.	Issue	ICER impact
1	Uncertainty around long-term benefit • choice of survival model • cure assumption • treatment effect waning	Large
2	Poor overall survival model fit • use of calibration factors to adjust overall survival • competing risks approach • use of KEYNOTE-826 to inform post-progression modelling	Moderate

Abbreviations: ICER, incremental cost-effectiveness ratio

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Key clinical trials (1/2)

Both international, phase 3, double-blind, placebo-controlled RCTs

Feature	KEYNOTE-A18	KEYNOTE-826
Population	Adults with FIGO 2014 stage 3 to 4A untreated LACC (subgroup of trial relevant to evaluation)	Adults with recurrent, persistent or metastatic cervical cancer
Intervention	Pembrolizumab + CCRT	Pembrolizumab + chemotherapy +/- bevacizumab
Duration	Median follow up: [redacted] months for pembro + CCRT, [redacted] months for placebo + CCRT	Median follow up 39.1 months
1° outcome	OS, PFS (investigator assessed)	OS, PFS (investigator assessed)
2° outcomes	PFS (BICR assessed), CR rate, ORR (investigator and BICR assessed), HRQoL, AEs	PFS (BICR assessed), ORR, DoR, HRQoL, AEs
Used in model?	Yes	Yes – **for post-progression states only** (limited follow up in KEYNOTE-A18)

Abbreviations: 1°, primary; 2°, secondary; AE, adverse event; BICR, blinded independent central review; CR, complete response; CCRT, concurrent chemoradiotherapy; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HRQoL, health-related quality of life; LACC, locally advanced cervical cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; objective response rate

Key clinical trials (2/2)

KEYNOTE-A18: total radiation dose and FIGO staging different to NHS

Chemoradiotherapy

- KEYNOTE-A18 similar to UK practice (cisplatin, EBRT, brachytherapy)
- But total radiation dose lower than usual NHS clinical practice
- **EAG:** unclear if benefits of adding pembrolizumab would change with higher radiation dose

FIGO staging

- KEYNOTE-A18 (and marketing authorisation) used FIGO 2014 staging for stage 3 to 4A
- NHS now uses FIGO 2018, which upstages nodal involvement to stage 3C
- FIGO 2018 stage 3 includes patients with smaller tumours but nodal involvement – which may have been earlier than stage 3 under FIGO 2014
- **EAG clinical experts:** FIGO 2014 criteria can be mapped to FIGO 2018

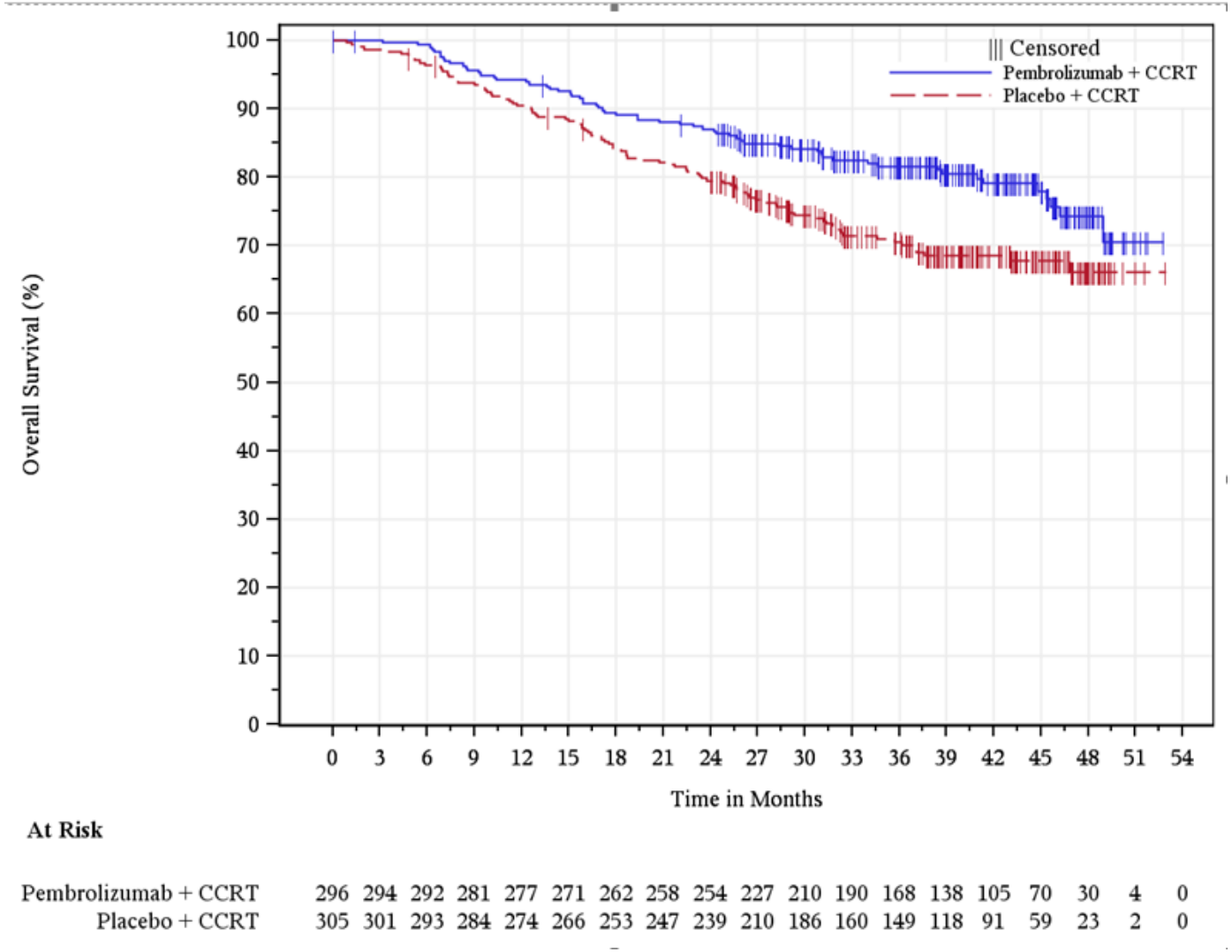
Subsequent oncological treatment: [redacted] in pembrolizumab + CCRT arm vs [redacted] in placebo + CCRT arm
(all participants as treated, final analysis)

Are the results of KEYNOTE-A18 applicable to the NHS?

Abbreviations: CCRT, concurrent chemoradiotherapy; EAG, external assessment group; EBRT, external beam radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; PFS, progression-free survival

KEYNOTE-A18: overall survival

Pembrolizumab improves overall survival compared with placebo



Final analysis, mITT population, FIGO stage 3 to 4A subgroup

Endpoint	Pembro + CCRT (n=296)	Placebo + CCRT (n=305)
OS events (n [%])	[redacted]	[redacted]
Median OS (months [95% CI])	[redacted]	[redacted]
OS rate at month 24 (% [95% CI])	[redacted]	[redacted]

HR: 0.64 (95% CI 0.46 to 0.88; p=0.0031)

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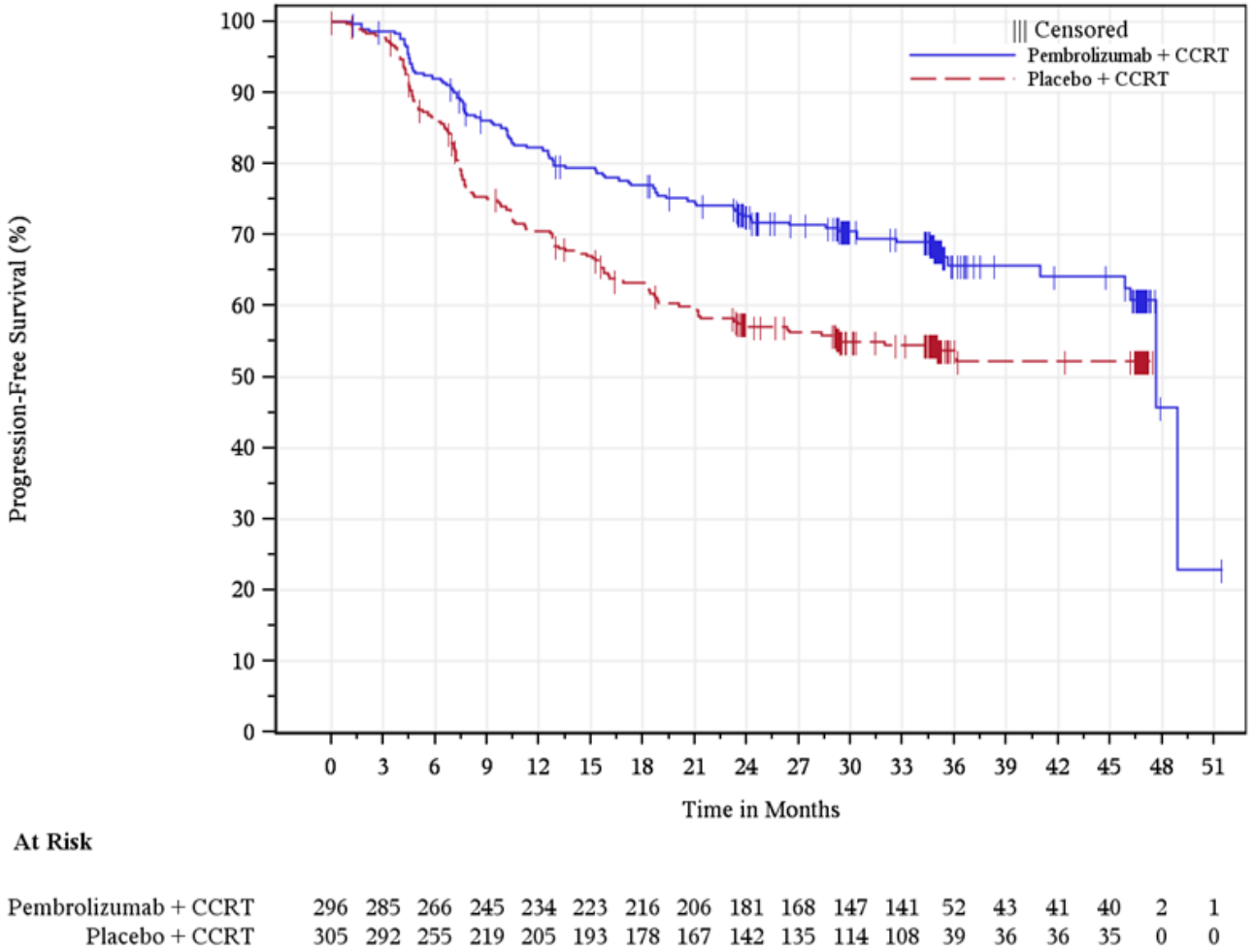
Abbreviations: CCRT, concurrent chemoradiotherapy; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; mITT, modified intent-to-treat; NR, not reached; OS, overall survival

KEYNOTE-A18: progression-free survival

Pembrolizumab improves progression-free survival compared with placebo



Final analysis, mITT population, FIGO stage 3 to 4A subgroup, investigator assessed

Endpoint	Pembro + CCRT (n=296)	Placebo + CCRT (n=305)
PFS events (n [%])	[redacted]	[redacted]
Median PFS (months [95% CI])	[redacted]	[redacted]
PFS rate at month 24 (% [95% CI])	[redacted]	[redacted]

HR: 0.63 (95% CI 0.48 to 0.82; p=0.0002)

Abbreviations: CCRT, concurrent chemoradiotherapy; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; mITT, modified intent-to-treat; NR, not reached; PFS, progression-free survival

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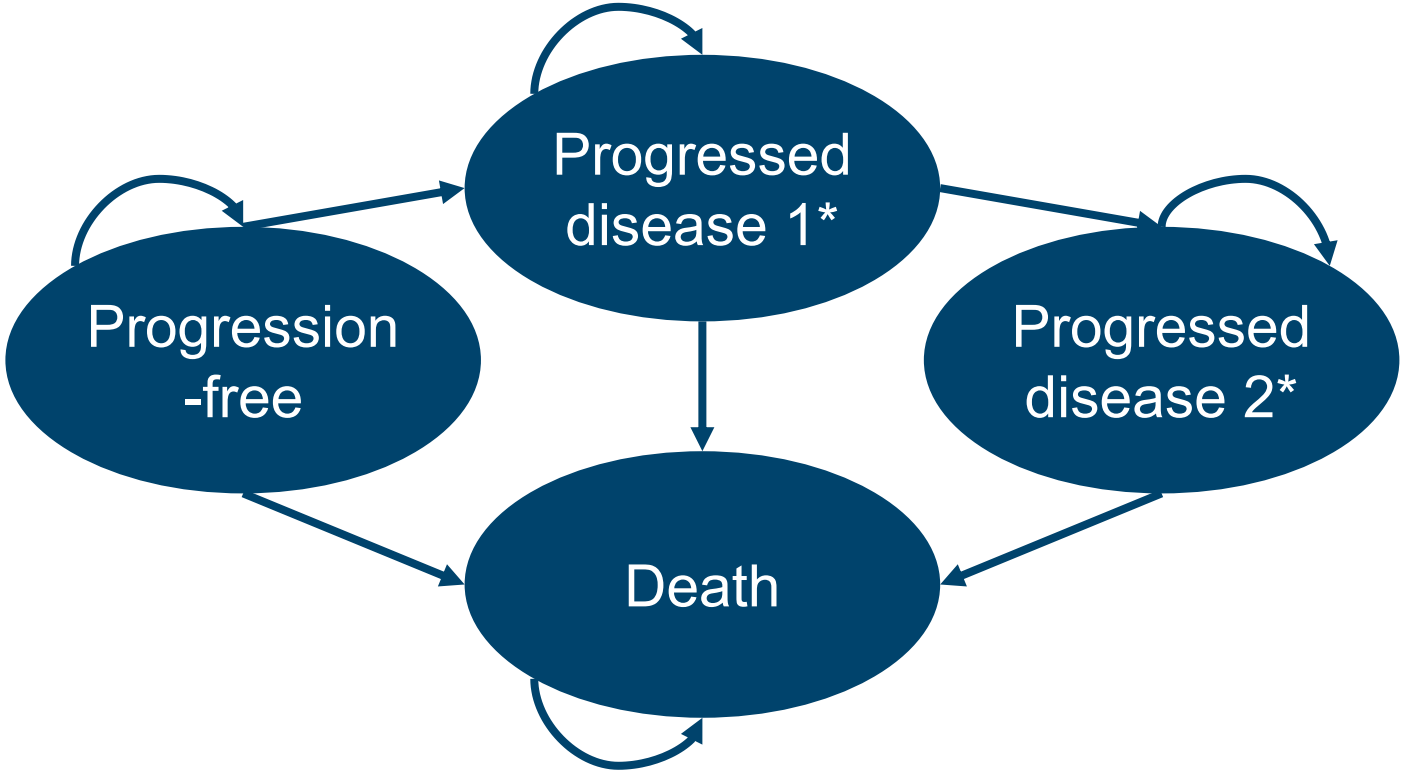
Overview of company's model



- Cohort-level semi-Markov approach
- Lifetime time horizon
- 1-week cycle length
- Uses clinical data from KEYNOTE-A18 and KEYNOTE-826

Pembrolizumab is modelled to affect:

- **QALYs**
  –longer overall and progression-free survival, with more patients cured
  –slight drop in quality of life due to more side effects
- **costs**
  –higher overall costs of pembrolizumab
  –lower costs later – fewer treatments needed because of lower risk of disease progression
  –slight increase in disease and side effect management costs

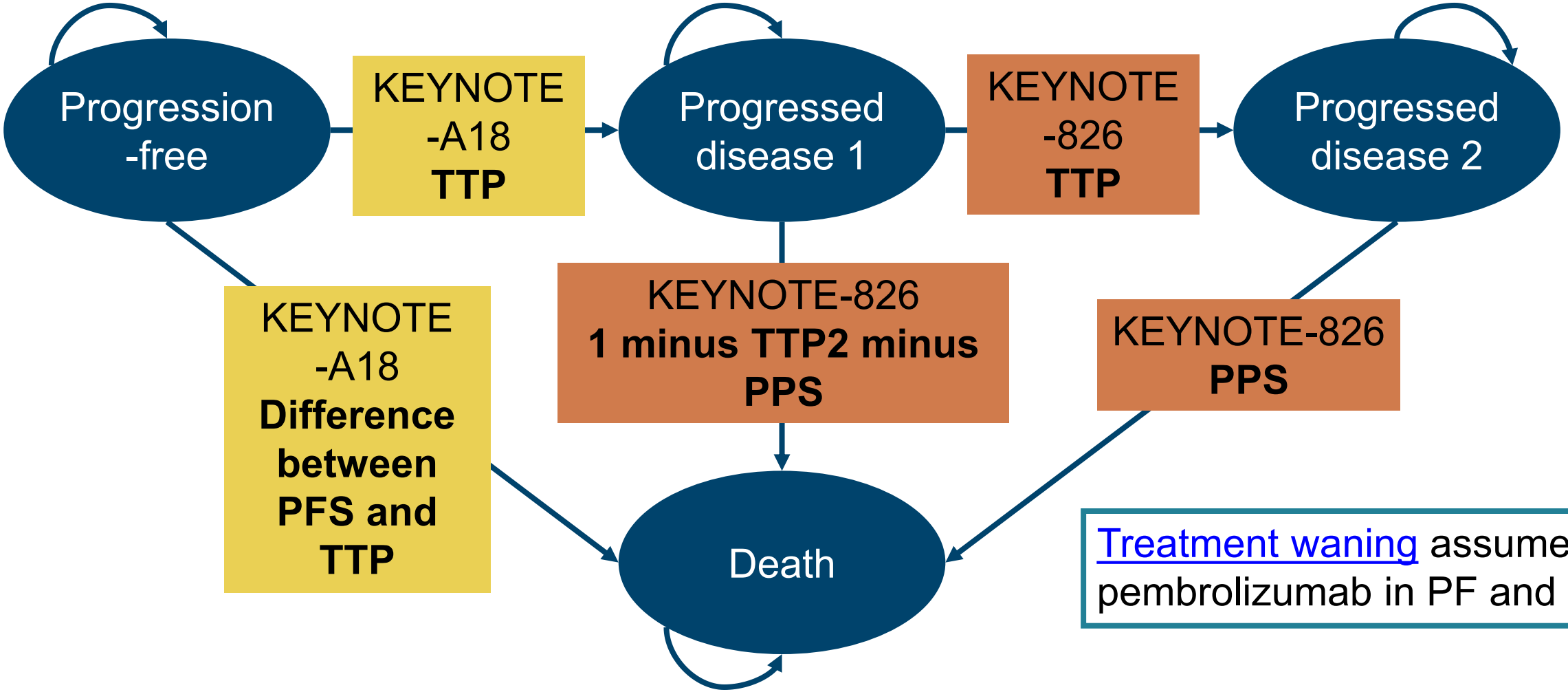
EAG: broadly satisfied; but need for calibration to fit overall survival + persistent uncertainty about long-term benefits and cure assumptions
= results highly uncertain

*Separate sub-models for PD1 and PD2 used to implement tunnel states to allow event risks to be conditional on time since state entry; in pembrolizumab plus CCRT group, separate PD1 and PD2 sub-models applied for early and late progressors; QALY, quality-adjusted life year

Note: model updated with final analysis from KEYNOTE-A18 at clarification stage

Transition probabilities

'Cure' assumed in both treatment arms: year 5 → year 7, cure rate increases in roughly straight line; from year 7+ transition probability PF → PD1 and PF → death reduced by 95%



Treatment waning assumed for pembrolizumab in PF and PD1

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Abbreviations: PD1, first progressed disease state; PF, progression free; PFS, progression-free survival; PPS, post-progression survival; TTP, time to progression

Models fitted to progression-free survival data

KEYNOTE-A18, final analysis, investigator assessed (transitions out of progression-free state)

Pembrolizumab plus CCRT

Placebo plus CCRT

Company: 1-knot odds RCS models chosen for both arms: placebo + CCRT – best statistical fit (lowest AIC), good hazard fit; pembrolizumab + CCRT – same model for consistency; both similar to generalised gamma – considered plausible by clinical experts at interim analysis

Abbreviations: AIC, Akaike Information Criterion; BICR, blinded independent central review; CCRT, concurrent chemoradiotherapy; EAG, external assessment group; PF, progression-free; PFS, progression-free survival; RCS, restricted cubic spline

Models fitted to time to progression data

KEYNOTE-A18, final analysis, investigator assessed (transitions out of PF state)

Pembrolizumab plus CCRT

Placebo plus CCRT

Company: 1-knot odds RCS models chosen for both treatment arms for consistency with PFS

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Abbreviations: BICR, blinded independent central review; CCRT, concurrent chemoradiotherapy; EAG, external assessment group; PF, progression-free; PFS, progression-free survival; RCS, restricted cubic spline; TTP, time to progression

Key issue 1: uncertainty around long-term benefit (1/3)

Moderate impact on ICER

Choice of survival model

EAG

- Notes that company did not seek additional clinical input into plausibility of selected models for PFS and TTP after integrating final analysis of KEYNOTE-A18
- EAG clinical experts: predictions of 1-knot odds RCS reasonable but longer follow up needed to be confident benefits would be maintained long term
- Sensitivity analyses explore different 1- and 2-knot RCS models
- Model-predicted overall survival does not reflect observed overall survival from final results of KEYNOTE-A18 (see key issue 2)
- Further input from clinical experts about the plausibility of the company's modelled PFS and OS estimates would be valuable

Are the results for PFS and TTP using the 1-knot odds RCS model (company and EAG base case) clinically plausible?

Abbreviations: EAG, external assessment group; ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression-free survival; RCS, restricted cubic spline; TTP, time to progression

Key issue 1: uncertainty around long-term benefit (2/3)

Small impact on ICER

Cure assumption

Company

- Clinical advice: substantial proportion with LACC cured by chemoradiotherapy; routine follow up stops after ~5 years
- Model includes a cure period in both arms:
  –risk of progression or death predicted by parametric survival models reduced by 95% at year 7; reduction applied linearly from 0% to 95% during 5- to 7-year cure period (based on clinical expert input and UK practice); death risk cannot fall below background mortality
  –same cure assumption for both arms (no evidence to suggest differences)
- Cure proportion and time points uncertain – no epidemiological data; sensitivity analyses included

EAG

- Extent of cure uncertain
- Company could have attempted to estimate cure fraction using mixture cure models
- Instead structural assumption of cure applied which relies on arbitrary assumptions between years 5 and 7
- Sensitivity analysis removing cure 'warm up' period at 5 to 7 years

Are the company's cure assumptions acceptable and clinically appropriate?

Abbreviations: ICER, incremental cost effectiveness ratio; LACC, locally advanced cervical cancer; PF, progression-free; PD1, first progressed disease state

Key issue 1: uncertainty around long-term benefit (3/3)

Large impact on ICER

Treatment effect waning applied from 5 to 7 years after starting pembrolizumab

Company

- Disagrees with applying treatment waning for immunotherapies (no published evidence to support) but assumption in line with previous NICE appraisals (particularly TA939 pembrolizumab in cervical cancer)
- Any expected convergence of risks between arms addressed by cure assumption
- In model, pembrolizumab treatment effect wanes approx. linearly from year 5 – becomes same as control arm by year 7; includes assumptions of treatment effect waning for pembrolizumab in both the first- and second-line settings
- Scenario excluding treatment effect waning at first and second line increases ICER

EAG: longer follow-up of KEYNOTE-A18 needed to confirm this assumption; clinical advice that impact of treatment effect waning assumption is limited because baseline risk of progression for CCRT alone is close to 0 by year 7

Is it appropriate to include treatment effect waning for pembrolizumab in the model? Is the effect already addressed by the cure assumption?

Abbreviations: EAG, external assessment group; CCRT, concurrent chemoradiotherapy; ICER, incremental cost effectiveness ratio; TA, technology appraisal; OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival; TTP, time to progression

Key issue 2: poor overall survival model fit (1/4)

Comparison of observed and model-predicted overall survival

Based on investigator-assessed PFS (company primary base case)

Company: model substantially underpredicts OS for pembrolizumab plus CCRT after integrating final analysis from KEYNOTE-A18

[redacted]

Abbreviations: BICR, blinded independent central review; CCRT, concurrent chemoradiotherapy; FA, final analysis; KM, Kaplan–Meier OS, overall survival; PFS, progression-free survival

Key issue 2: poor overall survival model fit (2/4)

Moderate impact on ICER

Background

- In company economic model OS derived indirectly from:
  - –KEYNOTE-A18 PFS + TTP modelling
  - –KEYNOTE-826 PFS + TTP + PPS modelling
  - –structural assumptions around cure, waning, subsequent treatments
- Economic model curve does not fit well with observed OS from KEYNOTE-A18 so company applied calibration factors to TPs out of PD1 state to force fit to replicate trial outcomes [also applied in TA1037 pembrolizumab in NSCLC]; calibration reduces TPs in PD1 sub-model for 2 years [**note intended base case = 4 years** because 4 years of KM data available]

Is the use of calibration factors to adjust OS acceptable? Applied for 2 or 4 years?

EAG: calibration pragmatic but not ideal; possible reasons for poor fit:

- Misspecification of 1 or more parametric survival models used to estimate any of the transition probabilities that inform OS
- Company did not properly account for competing risks in deriving progression and death risks
- Use of KEYNOTE-826 may not fully represent progressed population in KEYNOTE-A18

Need for calibration to force OS fit = unresolvable uncertainty; EAG preferred analysis very similar to company's (with correction of minor errors)

Abbreviations: KM, Kaplan–Meier; NSCLC, non-small-cell-lung-cancer; OS, overall survival; PD1, first progressed disease state; PFS, progression-free survival; PPS, post-progression survival; TTP, time to progression; TP, transition probability

Key issue 2: poor overall survival model fit (3/4)

Unknown impact on ICER

EAG: competing risks approach more appropriate for PFS but may not be sole issue

EAG

- PFS comprises 2 events: progression and death before progression – most appropriate approach to derive transition probabilities is competing risks approach
- To use competing risks, company would need to reprocess PFS data into 2 separate datasets: 1 for progression (censoring deaths) 1 for death before progression (censoring progression)
- Calculate the proportion of the joint hazard attributable to each cause-specific hazard

Company

- Using full competing risks approach would mean censoring all progression events and only counting deaths as events
- But very few deaths before progression in this young population – would make estimates highly uncertain (shown by how close PFS and TTP curves are and very small hazards for progression-free to death transitions)
- PFS/TTP approach accepted in TA939; data from that appraisal used in model

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; TA, technology appraisal; TTP, time to progression

Key issue 2: poor overall survival model fit (4/4)

Unknown impact on ICER

KEYNOTE-826 CPS ≥1 with prior CRT subgroup used for post-PD1 states

Background: PFS and TTP data from KEYNOTE-826 CPS ≥1 with prior CRT subgroup used to inform post-PD1 states to align with model population after progression

EAG

- KEYNOTE-826 CPS ≥1 with prior CRT subgroup broadly comparable to population in KEYNOTE-A18 at progression; using subgroup KEYNOTE-826 data reasonable
  - over [redacted]% in KEYNOTE-A18 had a CPS of ≥1
  - prior CRT subgroup appropriate given use of CCRT in KEYNOTE-A18
- But unmeasured prognostic differences leave uncertainty:
  –KEYNOTE-826 patients completed CRT before Nov 2018
  –KEYNOTE-A18 patients started CCRT from May 2020
  Clinical advice that CCRT dose and delivery mode may influence OS (no data available on radiotherapy regimens used in KEYNOTE-826)
- Prior treatment not a randomisation stratification factor in KEYNOTE-826 so restricting the data set to patients who had prior CRT may compromise randomisation
- Issue of poor OS fit remains when CPS ≥1 subgroup (not restricted by prior CRT) used

CPS, combined positive score; CRT, chemoradiotherapy; CCRT, concurrent CRT; OS, overall survival; PD1, first progressed disease state

Is the KEYNOTE-826 CPS ≥1 with prior CRT subgroup appropriate to inform the post-progression modelling?

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Equality considerations (1/3)

Company

Sex and age: primarily affects working age women, often with caring responsibilities
Deprived groups: most deprived groups have a higher rate of cervical cancer, and a poorer prognosis, than the least deprived; see distributional cost-effectiveness analysis

Clinical expert

Age: often affects younger people
Ethnicity: in London majority of cases in people born outside the UK, where HPV vaccination and cervical screening may not be routine; language barrier can be a challenge
Extended treatment schedule: other barriers to treatment – caring responsibilities, work

- many may struggle to commit to nearly 2 years of treatment (vs current 6-week standard)
- pembrolizumab is an infusional immunotherapy – needs face-to-face review before each cycle, adding further appointments
- for people from more deprived socioeconomic backgrounds (common in this group) cost and time associated with frequent hospital visits may be prohibitive
- younger age and competing responsibilities may further limit ability to adhere to treatment

Do these or any other equality issues need to be addressed in the guidance?

Abbreviations: HPV, human papillomavirus

Equality considerations (2/3)

Company says there are marked health inequalities in LACC

Company

- Substantial health inequalities in LACC, mostly because people in more deprived groups are less likely to take part in NHS cervical screening
- People from more deprived socioeconomic groups, with low health literacy, migrants and people whose first language is not English all disproportionately represented in LACC

Cervical cancer (all stages) in most and least deprived groups in England (2022)

Parameter	Most deprived	Least deprived
Diagnosis rate per 100,000	12.1	7.3
Mortality rate per 100,000	4.1	1.8
5-year survival (%)	56.2	65.7

NHS Digital Cancer Registration Statistics

Abbreviations: LACC, locally advanced cervical cancer

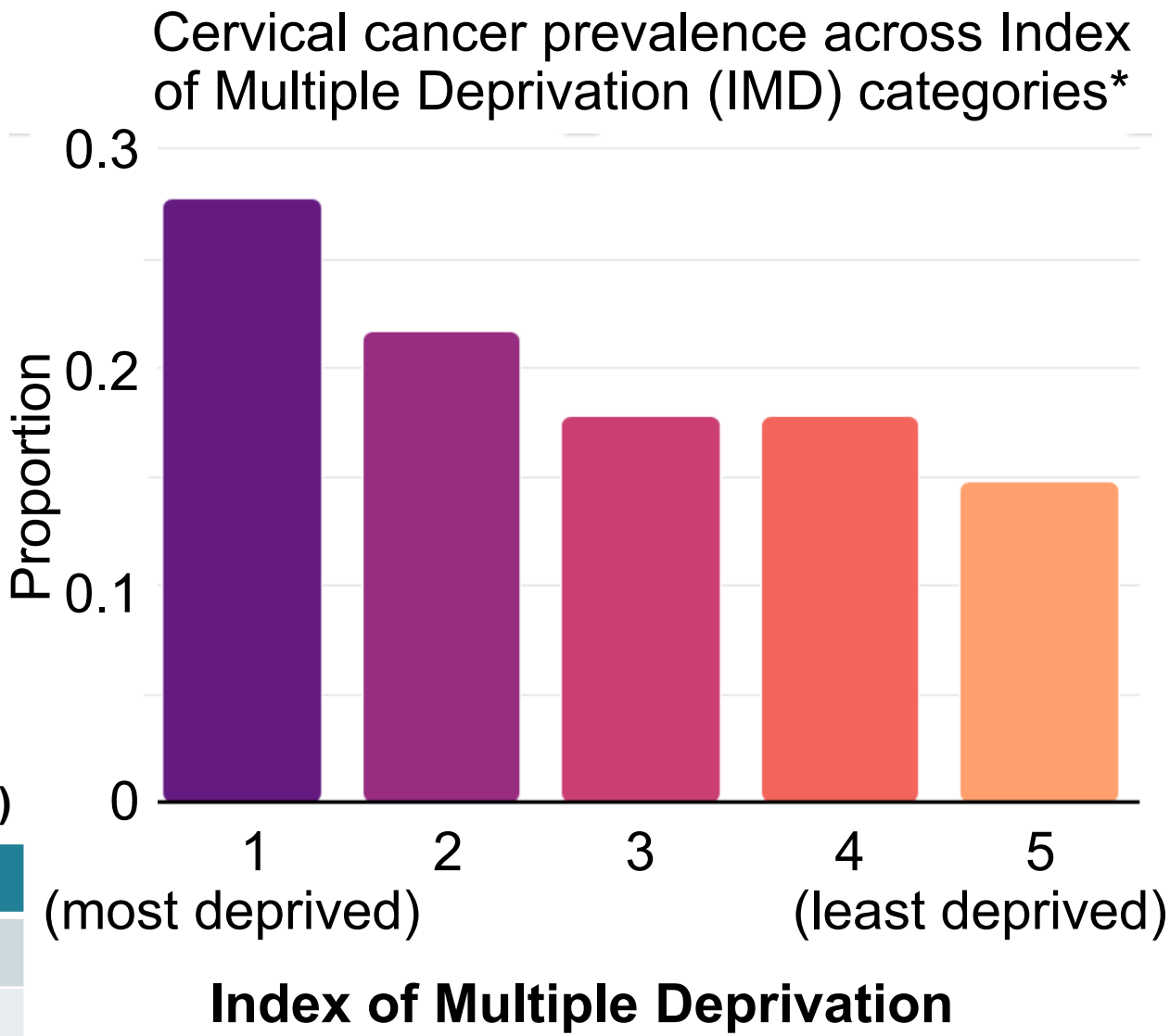
Equality considerations (3/3)

Company

- DCEA based on economic model outputs and using University of York's health equity impact calculator
- Used ICD10 code C53 (all malignant neoplasm of the cervix uteri)
- Substantial gradient in incidence across deprivation groups; likely even steeper for stage 3 to 4A cervical cancer

DCEA results for pembrolizumab (EAG-calculated, using company base case, no cPAS included, £30,000 threshold)

Opportunity cost gradient	NHIB (QALYs)
Flat**	59
Moderate	21
Steep	-18



cPAS, comparator patient access scheme; DCEA, distributional cost-effectiveness analysis; ICD10, International Classification of Diseases Version 10; NHIB, net health inequality benefit (population-level net QALY gap between most and least deprived IMD groups); WTP, willingness to pay; *York Health Equity Impact calculator code C53 neoplasms of the cervix; **opportunity cost equally distributed across social groups

Other issues

Family and carers – potential uncaptured benefit suggested by company:

- important to take account of effect on family members and dependants
- evidence suggests pembrolizumab will mean more people with locally advanced cervical cancer are cured and so can return to normal life, improving quality of life of family members and carers and enabling them to return to work

Managed access

No managed access proposal – no more data cuts due

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Cost-effectiveness results

ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

All company and EAG ICERs over £30,000

Key drivers of the ICER:

- choice of parametric survival model for PFS and TTP data (informing transition probabilities out of the PF health state)
- use of calibration factors to adjust transition probabilities out of PD1
- assumptions about cure and treatment effect waning
- investigator vs BICR-assessed PFS and TTP

Abbreviations: EAG, external assessment group; BICR, blinded independent central review; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; PD1, first progressed disease state; PF, progression-free; PFS, progression-free survival; TA, technology appraisal; TTP, time to progression

Key issues

No.	Issue	ICER impact
1	Uncertainty around long-term benefit • choice of survival model • cure assumption • treatment effect waning	Large
2	Poor overall survival model fit • use of calibration factors to adjust overall survival • competing risks approach • use of KEYNOTE-826 to inform post-progression modelling	Moderate