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

For public – redacted

Technology appraisal committee A, 10 March 2026

Chair: Radha Todd

External assessment group: Sheffield Centre for Health and Related Research (SCHARR)

Technical team: Emilene Coventry, Zoe Charles, Ian Watson

Company: MSD

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

- ✓ **Recap from first appraisal committee meeting**
- ❑ Consultation comments
- ❑ Company response and EAG critique
- ❑ Other considerations
- ❑ Summary

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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

Draft guidance recommendation

Pembrolizumab with chemoradiotherapy should not be used for untreated FIGO 2014 stage 3 to 4A locally advanced cervical cancer in adults

High level of uncertainty in the model, specifically:

- cure assumptions
- mismatch between observed trial overall survival and model-predicted overall survival, which needed the company to apply calibration factors to force a fit
- modelled assumptions about pembrolizumab retreatment

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics

Analyses requested by committee at the first appraisal committee meeting

- Mixture cure model based on observed progression-free and overall survival in KEYNOTE-A18
  - anticipated that using direct data from KEYNOTE-A18 rather than from KEYNOTE-826 for the pembrolizumab progressed disease states may help to reduce uncertainty
- Sensitivity analyses exploring different rates of retreatment, including no retreatment, and reduced efficacy with pembrolizumab when used as retreatment
- Preferred assumptions related to these analyses
  - cure assumption plausible
  - treatment effect waning should be applied for pembrolizumab

Equality considerations

No new equality considerations raised during consultation

Draft guidance conclusions:

Sex and age

- The company and clinical experts noted that cervical cancer primarily affects women, often of working age with caring responsibilities; younger people are frequently affected
- The committee agreed that these were not issues that could be addressed in a technology appraisal

Socioeconomic deprivation

- The committee recognised that cervical cancer, especially in the advanced stages, is concentrated in deprived groups and has poorer outcomes
- It concluded that there was a potential health inequalities benefit associated with pembrolizumab and it would take this into account when it agreed its preferred ICER threshold

Abbreviations: ICER, incremental cost-effectiveness ratio

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Consultation comments

Comments received from:

- 1 clinical expert
- Company (MSD)

Comments from clinical expert

Dr Alexandra Taylor – Royal Marsden NHS Foundation Trust

- Adding pembrolizumab to chemoradiation meaningfully increases cure potential in high-risk locally advanced cervical cancer, in which relapse is typically incurable
- FIGO 2014 stage 3 to 4A subgroup is a small cohort in UK – easily identified
- Although KEYNOTE-A18 permitted some lower radiotherapy doses (primarily for Japan cohort), median delivered doses comparable with UK practice; large T3 to T4A tumours often do not get adequate brachytherapy dosing – adding immunotherapy is especially important for these patients to improve outcomes

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; ICER, incremental cost effectiveness ratio

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Mixture cure modelling

Background

- Company included structural assumption of cure in both treatment arms of original economic model – probability of progression from progression-free state reduced by 0% at year 5, increasing to 95% at year 7
- Committee agreed cure assumption plausible but concluded uncertainty around modelling of cure
- Requested mixture cure model to estimate cure proportion based on KEYNOTE-A18 PFS and OS

Company draft guidance response

- MCMs (next slide) on PFS to validate existing assumptions – modelled cure assumptions unchanged
- Did not run OS MCM – OS in KEYNOTE-A18 too immature; structural link between PFS and OS suggests PFS benefits imply OS benefits
- Most MCM distributions showed higher cure proportions for pembrolizumab than CRT alone – supports modelled cure assumption; also supported by complete response results from trial and clinical advice
- Sensitivity analysis censoring all events after 200 weeks done to test robustness of MCM results – difference in cure fractions remained and was slightly higher

EAG critique

- MCMs useful and support modelled cure assumptions; agrees OS MCMs likely to be highly uncertain
- Company claim of structural link between PFS and OS broadly reasonable
- Company's modelled estimate of cure proportion (95% of progression-free patients at 7 years) may not be meaningful; in model **risk** of transitioning out of the progression-free state is reduced by 95% at 7 years – does not mean 95% of progression-free patients cured

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Abbreviations: CRT, chemoradiotherapy; MCM, mixture cure model; PFS, progression-free survival; OS, overall survival; SMR, standardised mortality ratio

Mixture cure modelling results

Modelled cure proportions for the company and EAG base case

Treatment arm	5 year progression free (%)	7 year progression free (%)	95% of 7 years progression free (%)	Difference (%)
CRT	48.4	46.3	44.0	–
Pembrolizumab + CRT	58.7	55.8	53.0	9.0

MCM cure proportions on KEYNOTE-A18 PFS endpoint with (and without in brackets) SMR* adjustment

Distribution**	Pembrolizumab + CRT (%)	CRT (%)	Difference (%)
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]

Does the MCM analysis reduce uncertainty sufficiently around the company's modelled cure assumptions?

Abbreviations: CRT, chemoradiotherapy; EAG, external assessment group; MCM, mixture cure modelling; PFS, progression-free survival; SMR, standardised mortality ratio; *SMR 1.19 based on clinical advice that people who have had cancer typically have a higher mortality risk than the general population **Generalised gamma and Gompertz not shown because of implausible estimates

Survival modelling

Background

- Original company model used parameters including PPS data from KEYNOTE-826 (RCT in adults with recurrent persistent or metastatic cervical cancer) to estimate OS
- Modelled OS did not match observed OS in the KEYNOTE-A18 trial so company used calibration factors to force a fit
- Committee thought use of KEYNOTE-826 PPS likely main factor driving mismatch so anticipated that using direct data from KEYNOTE-A18 would help reduce uncertainty

Company draft guidance response

- New 3-state transition model using KEYNOTE-A18 PPS data (too immature to populate 4 disease states as for original company model structure)
- All parametric curves fit observed Kaplan-Meier PPS data well; log-logistic chosen based on visual fit and lowest AIC in CRT arm; same curve used for pembrolizumab + CRT (within 2 AIC points from best fit)
- PPS pembrolizumab waning: functionality included but not applied in updated company base case [but is included in subsequent treatment trade-off calculation]; post-progression outcomes depend more on prior pembrolizumab exposure than later treatment; minimal difference to ICER when waning applied in scenario

Abbreviations: AIC, Akaike Information Criterion; CRT, chemoradiotherapy; ICER, incremental cost-effectiveness ratio; PPS, post-progression survival; OS, overall survival; PPS, progression-free survival; RCT, randomised controlled trial

Should treatment effect waning be included for pembrolizumab post progression?

Post-progression survival modelling

Company

- After progression, observed survival in KEYNOTE-A18 very similar between treatment arms
- Substantially different from original modelling despite many more people in placebo arm of KEYNOTE-A18 having subsequent treatments (including immunotherapy) than on pembrolizumab – but PPS on CRT no better than on pembro
- Suggests benefit of pembrolizumab continues after progression regardless of subsequent treatment
- After relapse, people who have had first-line pembrolizumab are prognostically different to people who had placebo so PPS does not depend only on subsequent treatment (which was initially modelled)

Observed PPS from KEYNOTE-A18 and modelled PPS from KEYNOTE-A18 and KEYNOTE-826 (via PFS/TTP/PPS)

EAG: observed PPS similar between the progressed patients in both randomised groups of KEYNOTE-A18; substantially higher than PPS estimates derived from company's previous 4-state model; also notes that dashed lines reflect subsequent treatment mix in KEYNOTE-A18 (based on KEYNOTE-826 data)

Abbreviations: CRT, chemoradiotherapy; PFS, progression-free survival; PPS, post-progression survival; TTP, time to progression

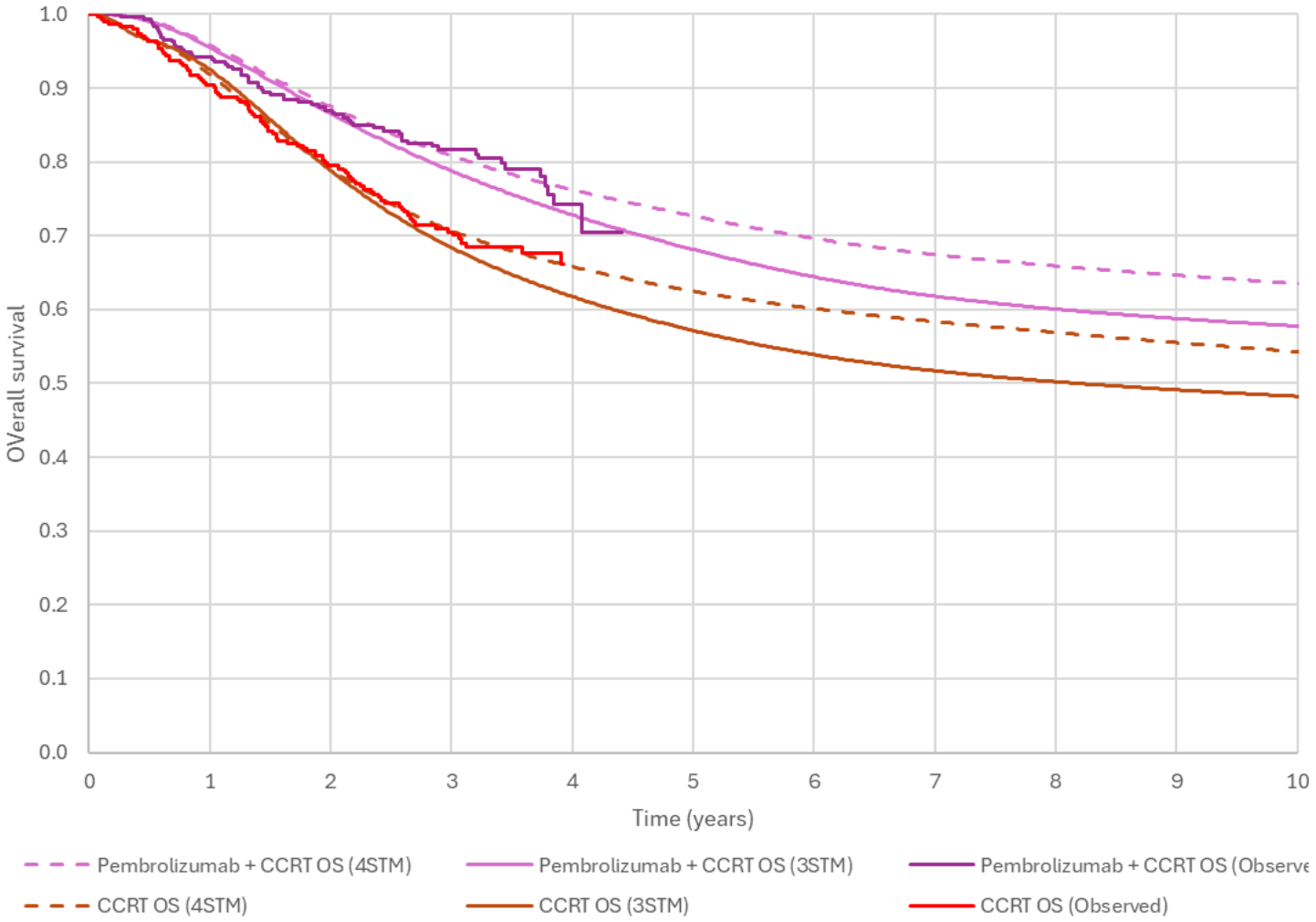
Overall survival modelling

Company

- Directly using KEYNOTE-A18 PPS data improved fit between trial and modelled OS
- But still underpredicts survival towards the end of the curve, particularly for pembrolizumab + CRT
- Suggests model is underestimating PPS life years for pembrolizumab + CRT more than for placebo + CRT so overestimating the ICER

Overall survival modelling with and without calibration

Modelled OS (3 and 4-state transition models) vs observed OS



Abbreviations: CRT, chemoradiotherapy; ICER, incremental cost-effectiveness ratio; PPS, post-progression survival; OS, overall survival

Subsequent treatments

Background

Company's original 4-state model used KEYNOTE-826 data to inform subsequent treatment (proportions, QALYs and costs) and PPS

Company draft guidance response

- New 3-state model uses PPS data from KEYNOTE-A18, which had very different subsequent treatments from NHS clinical practice
- Company has adjusted subsequent treatment QALYs and costs based on KEYNOTE-826 to align with higher expected use in NHS practice – approach referred to as a 'subsequent treatment trade-off'
- Scenarios explore removing trade-off (company scenario with biggest effect on ICER) and using subsequent treatment proportions from KEYNOTE-A18

Subsequent treatment in KEYNOTE-A18

Treatment	Pembrolizumab + CRT (%)	CRT (%)
Immunotherapy + CT	[redacted]	[redacted]
CT	[redacted]	[redacted]
No treatment	[redacted]	[redacted]

Company-modelled subsequent treatment

Treatment	Pembrolizumab + CRT (early progressor; %)	Pembrolizumab + CRT (late progressor; %)	CRT (%)
Immunotherapy + CT	0.0	51.2 (64)	51.2 (64)
CT	80.0	28.8	28.8
No treatment	20.0	20.0	20.0

Abbreviations: CT, chemotherapy; CRT, chemoradiotherapy; ICER, incremental cost-effectiveness ratio; PPS, post-progression survival; QALY, quality-adjusted life year

EAG comments on updated base case model and scenario analyses (1/2)

EAG does not believe company's updated model is more suitable for decision-making than the previous base case model

Subsequent treatment trade-off approach

- Considers subsequent treatment trade-off approach to be inconsistent
  - combines data from KEYNOTE-A18 (PPS) and KEYNOTE-826 (QALY and costs pay-offs), which have populations with prognostic differences
  - adds extra QALYs (increased active treatment) without adjusting survival curves – modelled OS is therefore misleading
  - company's updated base-case model excludes treatment waning for subsequent pembrolizumab treatment but waning is included when calculating QALYs and costs using the trade-off method – so waning applies only to the difference in treatment distributions (but note that scenario including pembrolizumab subsequent treatment waning has minimal effect on ICER)
- Unlikely to solve inherent limitation that KEYNOTE-A18 does not reflect NHS subsequent treatment mix

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PPS, post-progression survival; QALY, quality-adjusted life year; TTP, time to progression

EAG comments on updated base case model and scenario analyses (2/2)

3-state model

- Considers that modelled OS still poor fit to observed OS; not clear why but may be because of not properly accounting for competing risks or misspecification of survival models used for transition probabilities that inform OS
- Company's updated 3-state model using PPS data from KEYNOTE-A18 provides worse fit to OS in KEYNOTE-A18 than the company's previous 4-state model; remains partially reliant on absolute costs and QALYs estimated using data from KEYNOTE-826 applied in the previous 4-state model – no more suitable for decision making
- Hazards of PPS in both KEYNOTE-A18 treatment groups almost flat so exponential model may be more appropriate than company's updated base case log-logistic model – however scenario shows ICER similar using either model

Scenarios

- Despite concerns about company's new model, scenario analyses done using company's updated model address other key concerns raised in draft guidance

Does committee agree with the company's approach to modelling subsequent treatments?

- Does using KEYNOTE-A18 data for PPS in model reduce enough uncertainty in the overall survival estimates?
- Is the company's updated 3-state model suitable for decision making or does committee prefer the 4-state model?

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Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PPS, post-progression survival

Retreatment with pembrolizumab

Background

- Company's model: pembrolizumab retreatment allowed 2.5 years after first pembrolizumab treatment (that is, if cancer progresses ≥6 months after initial pembrolizumab – late progressors)
- Subsequent treatment proportions for late progressors assumed to be:
  - 51% pembrolizumab + chemotherapy (+/- bevacizumab)
  - 29% chemotherapy (+/- bevacizumab)
  - 20% no treatment
- Committee heard retreatment with pembrolizumab uncertain; wanted to see sensitivity analyses on different rates of retreatment (including none) and reduced efficacy of pembrolizumab as retreatment

Company draft guidance response

- Scenarios: 0.7, 0.8, 0.9 efficacy multiplier; half as many patients having retreatment; 0% retreatment
- No evidence for reduced treatment efficacy for pembrolizumab as retreatment; if outcomes are worse, time on treatment and costs also likely to be lower – reduced efficacy does not automatically mean reduced cost effectiveness
- Biologically plausible that pembrolizumab could be more effective: patients who relapse after 2.5 years likely to have immunotherapy-sensitive/less aggressive disease
- Retreatment commissioned in NHS in other solid tumours after long PFS; NICE appraisals for them did not require reduced retreatment efficacy, no evidence suggesting cervical cancer different

Clinical expert: very small proportion of patients would be eligible for immunotherapy rechallenge at relapse; most recurrences are within 2 to 3 years of CRT; also discontinuations because of immune-related toxicity

Abbreviations: CRT, chemoradiotherapy; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival

Is it appropriate to include pembrolizumab retreatment?

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Company's updated model and base case assumptions ACM1 vs ACM2

Issue	ACM1 base case	ACM2 updated base case
Model structure	4-state transition model	3-state transition model
Cure assumption	Structural assumptions of cure	No change – but MCM carried out to support
Source of PPS data	KEYNOTE-826	KEYNOTE-A18
Treatment effect waning for pembrolizumab post progression	Applied	Not applied – explored in scenario (But applied in trade-off calculations)
Subsequent treatments	Informed by clinical advice and KEYNOTE-826	Intended to reflect same treatment pathways as original-base case model; includes cost and QALY trade-off estimates from KEYNOTE-826 to account for different subsequent treatment mix in KEYNOTE-A18 and previous model
Pembrolizumab retreatment	Allowed 2.5 years after initial treatment starts	No change Scenarios explore removing retreatment/reducing its efficacy

Abbreviations: ACM, appraisal committee meeting; MCM, mixture cure model; PPS, post-progression survival; QALY, quality-adjusted life year

Cost-effectiveness results

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

All company ICERs over £30,000

Greatest impact on ICER: removal of subsequent treatment trade-off
Other company analyses had a small impact on the ICER

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Thank you

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Supplementary appendix

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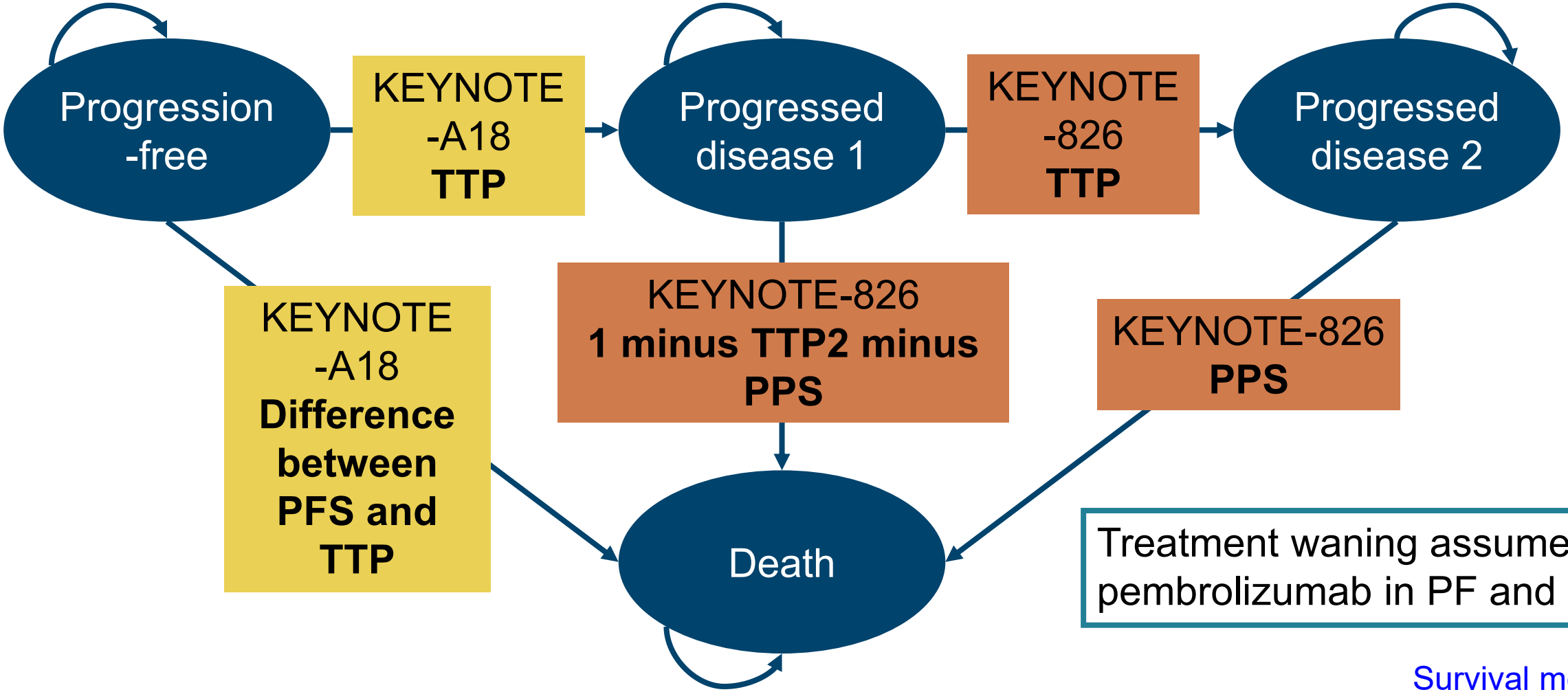
Original company model structure

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

Survival modelling

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

KEYNOTE-A18 complete response results

KEYNOTE-A18 complete response (based on investigator assessment per RECIST 1.1 – people with measurable disease at baseline)

Measure	Pembrolizumab + CRT	Placebo + CRT
Total patients	292	300
Complete response (n [%])	[redacted]	[redacted]
Complete response without progression or pre-progression death event at maximum follow up (n [%])	[redacted]	[redacted]

Mixture cure modelling

Abbreviations: CRT, chemoradiotherapy; MCM, mixture cure modelling; RECIST, Response Evaluation Criteria in Solid Tumours

Mixture cure modelling results – 200-week scenario analysis

Company draft guidance response

- Company provided a scenario analysis censoring all events after an arbitrary 200 weeks to test robustness of MCM
- Explores how small number of late events might affect cure proportion
- 2 late events in the pembrolizumab arm were censored: 1 late progression and 1 late death

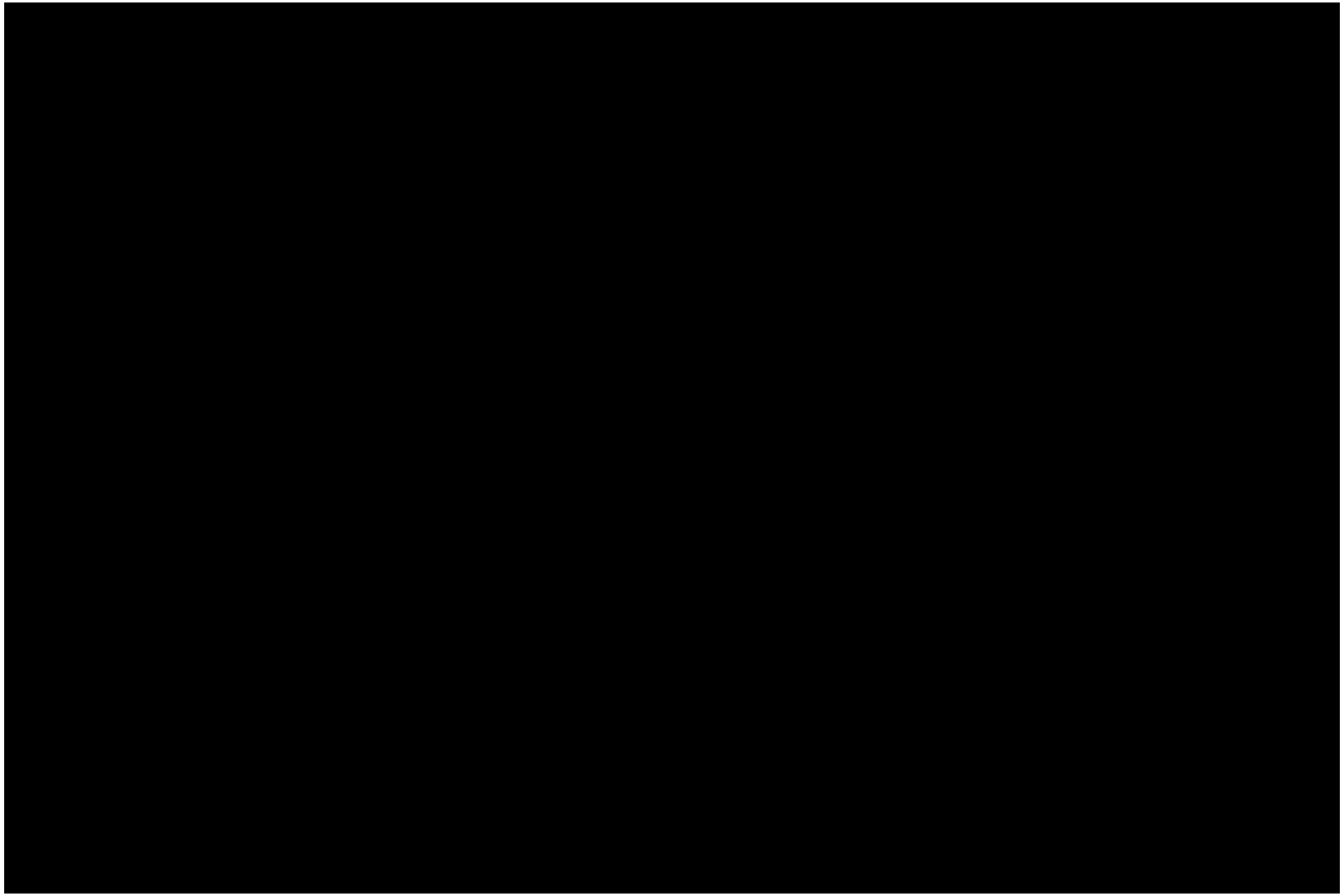
MCM cure proportions on KEYNOTE-A18 PFS endpoint with (and without in brackets) SMR adjustment: 200-week scenario analysis

Distribution*	Pembrolizumab + CRT (%)	CRT (%)	Difference (%)
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]

EAG critique: interpret higher cure fractions in sensitivity analyses with caution because ignores 2 late events in pembrolizumab + CRT arm of model

Abbreviations: CRT, chemoradiotherapy; MCM, mixture cure modelling; PFS, progression-free survival; SMR, standardised mortality ratio
*Generalised gamma and Gompertz not shown because of implausible estimates

Overall survival modelling with and without calibration



Observed OS in KEYNOTE-A18 and modelled OS based on the company's original base-case model at ACM1 with and without calibration and the company's updated base case model after draft guidance consultation

Overall survival modelling

Abbreviations: ACM, appraisal committee meeting; OS, overall survival

Subsequent treatment trade-off

Company 'bolted on' additional QALY and cost payoffs to expected outcomes in 3 state model to adjust for higher than expected use of active subsequent treatment (including pembrolizumab)

Step 1: calculate net discounted QALY and cost payoffs using 4-state model

- Based on company's 4-state model, model rerun – everyone starts in PD1 state and has pembrolizumab plus chemotherapy, chemotherapy alone, or no treatment
- Total QALYs and costs estimated for each subsequent treatment option
- In PD1 only non-treatment costs included (treatment costs already accounted for by model); in PD2 all costs included
- Differences in proportions having each subsequent treatment between KEYNOTE-A18 and company's 4-state model calculated for both treatment groups – for example subsequent pembrolizumab + chemotherapy in CRT arm: 4-state model 51.20%, KEYNOTE-A18 13.68%; so extra 37.52% expected to have pembrolizumab + chemotherapy as subsequent treatment in CRT arm
- Net discounted QALY and cost payoffs associated with additional/lower use of 3 subsequent treatment options estimated for both treatment groups

Step 2: apply net discounted QALY and cost payoffs in company's 3-state model

- Net QALY and cost payoffs applied to new progressors entering PD1 state in each model cycle in new 3-state model
- Total expected QALY and cost payoffs then calculated over lifetime horizon then added to total QALYs and costs accrued in PD1 state of 3-state model

Abbreviations: CRT, chemoradiotherapy; QALY, quality-adjusted life year; PD, progressed disease