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

For public – redacted

Rapid Review of TA885

Technology appraisal committee A [3 October 2023]

Chair: Radha Todd

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

Technical team: Alex Sampson, Zoe Charles, Janet Robertson

Company: Merck Sharp & Dohme (MSD)

Appraisal history: Rapid review of TA885

Rapid review prompted by new data cut

ACM1 Sept 2022

Not recommended

- Adding pembrolizumab to standard care (chemo ± bevacizumab) extends PFS and OS, but OS data is immature (May 2021 data cut)
- EAG's extrapolation for PFS too pessimistic, company's too optimistic - neither suitable
- No plausible range of cost-effectiveness estimates
- Meets end of life criteria

ACM2 Dec 2022

Recommended in CDF

- Extrapolation of PFS and TTP a key uncertainty
- Uncertainty remains about duration and size of long-term benefit for the pembrolizumab group
- Most appropriate modelling approach may change when further data is available
- ICER should be "substantially below £50,000 per QALY gained"
- Plausible that pembrolizumab could be cost effective

Rapid Review Oct 2023

- Final data cut from KEYNOTE-826 now available (Oct 22), which initiated Rapid Review
- Additional 17 months of follow up data
- EAG has 'no substantive concerns' with implementation of FA data but outlines 3 key uncertainties

CDF = Cancer Drugs Fund; EAG = External Assessment Group; FA = final analysis; ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS = progression free survival; TTP = time to progression; QALY = quality adjusted life-year;

Recurrent, persistent or metastatic cervical cancer

People who do not receive a HPV vaccine or screening remain at risk

Causes

- Develops when abnormal cells in cervix lining grow in an uncontrolled way, forming a tumour
- Over 90% of all cervical cancers estimated to be caused by HPV

Epidemiology

- Incidence of new diagnoses of cervical cancer was 9.8 per 100,000 females in 2019
  - 2,735 new cervical cancer cases in England in 2019

Diagnosis and classification

- People with recurrent, persistent or metastatic cervical cancer have a median age of 51
- 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 the cervix to other places in the body

Prognosis

- Median OS with standard of care treatment is 13-17 months
- Aim of treatment is to relieve symptoms and improve quality of life, and to extend life if possible

HPV, human papillomavirus; OS, overall survival

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) • IV infusion over 30 minutes

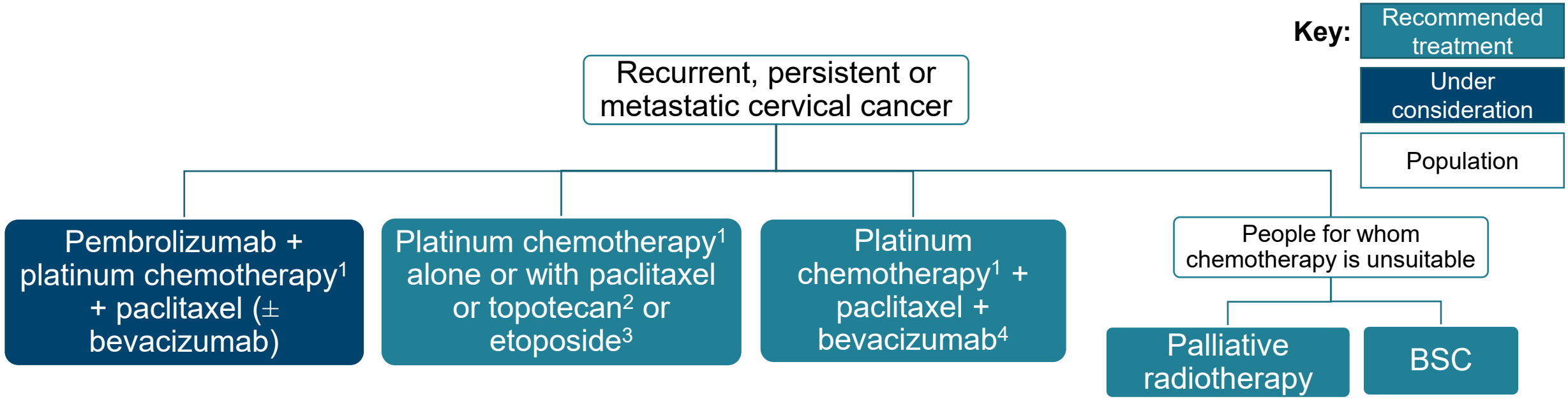
Price	• List price: £2,630 per 100 mg vial
	• Cost per administration (list price):
	  • 200 mg Q3W: £5,260
	  • 400 mg Q6W: £10,520
	• The price of pembrolizumab is subject to a confidential CAA with a simple discount

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

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.

Positioning

Platinum based therapy is standard care 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

BSC = best supportive care.

Recap of TA885

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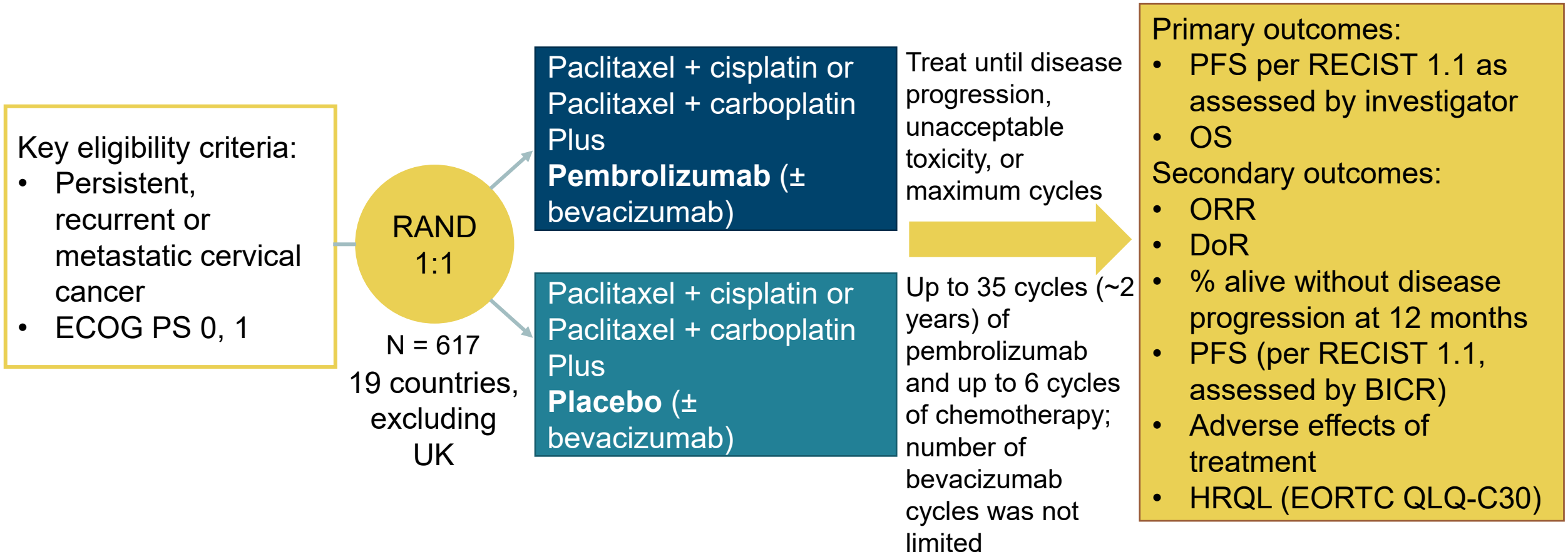
KEYNOTE-826 (NCT03635567) study design

Phase III, randomised, double-blind, placebo-controlled trial



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; RAN = randomised; RECIST 1.1, Response Evaluation Criteria in Solid Tumours Version 1.1.

Summary of FAD – TA885

Model structure may need to change when OS data is mature

- Pembrolizumab is more effective than placebo, but duration and size of long-term OS benefit is uncertain
- Interim OS largely informed by people whose disease had not responded to treatment - not enough overall survival data for people whose disease responded
- So, state transition model used instead of a partitioned survival model, which relies on direct extrapolation of observed overall survival data
- State transition model uses structural link between PFS & OS, so OS depends heavily on PFS extrapolation
- When further data available from KEYNOTE-826, most appropriate modelling approach may change
- Extrapolation of PFS and TTP a key uncertainty (despite further justification of company approach)
- Reasonable to assume a differential survival benefit across treatment arms, with people whose disease progresses on pembrolizumab assumed to have longer post-progression survival than standard care
- 2 year stopping rule and treatment effect waning 3 years to 5 years after stopping is reasonable
- End of life is met; survival is normally < 24 months for people having standard care

FAD = final appraisal document; OS = overall survival; PFS = progression free survival; TTP = time to progression

Updated clinical data

NICE National Institute for Health and Care Excellence

KEYNOTE-826 Final Analysis

Longer term follow-up shows continuation of trends seen in interim results

Company:

- Additional 17 months of follow-up data – median OS now reached
- Trends observed in interim analysis have continued - plateau observed in pembrolizumab PFS and OS
- Observed PFS data consistent with company's base case extrapolation
- Range of appropriate extrapolation curves for PFS, TTP and PPS has been narrowed
- Utility values, adverse events and use of subsequent treatments updated based on Final data cut

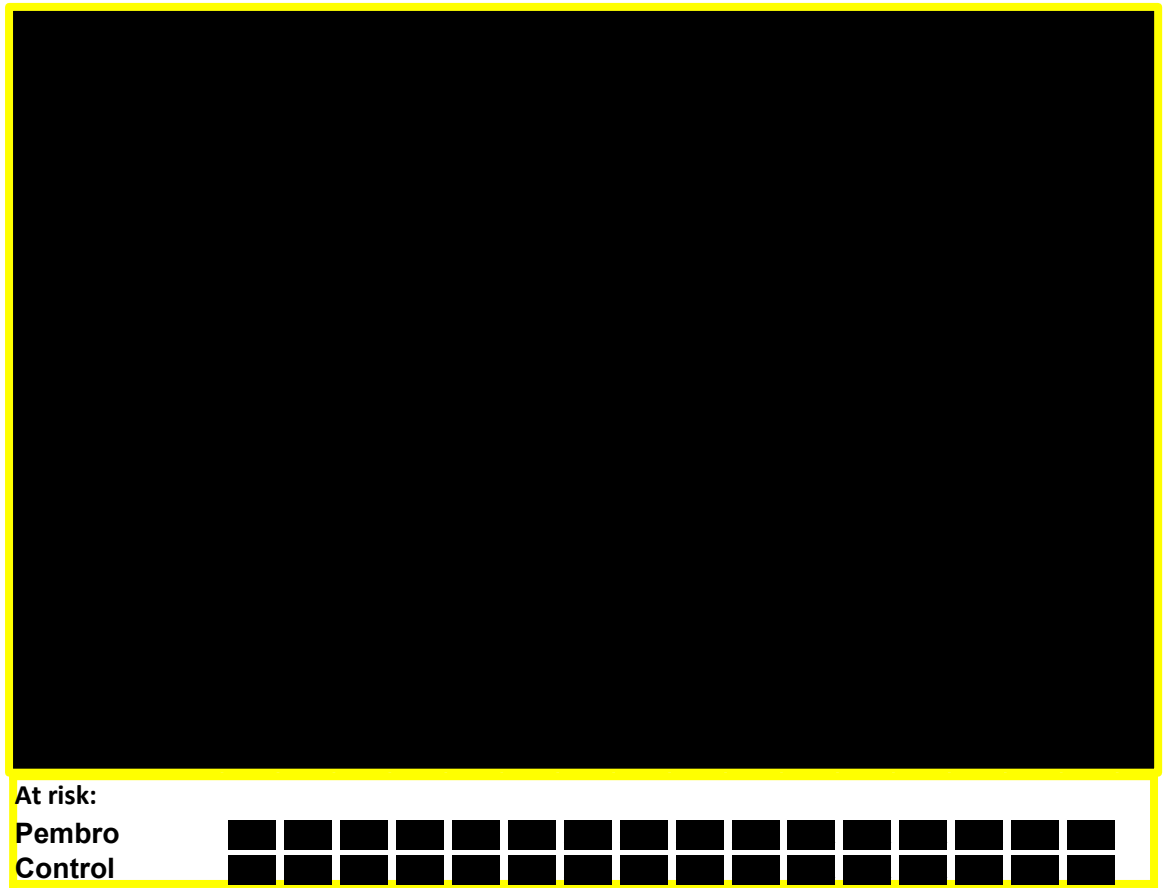
EAG critique:

- All reported endpoints from the final analyses were similar to the interim analyses
- Effect sizes were generally similar in magnitude with greater precision due to the additional observed events
- Much of pembro benefit remains within the extrapolated portion of survival curves, and so remains uncertain

OS = overall survival; PFS = progression free survival; PPS = post-progression survival; TTP = time to progression

Pembrolizumab extends PFS and OS vs SoC

Progression free survival (CPS ≥ 1 population, ITT)



Overall survival (CPS ≥ 1 population, ITT)

Company:

- Plateau observed in the pembro PFS arm has extended
- Plateau in pembro OS arm 'continuing to emerge'

 CPS = combined positive score; OS = overall survival; PFS = progression free survival; SoC = standard of care;

Comparison of key outcomes from IA1 to FA

Hazard ratios have improved slightly in final analysis

		IA1		FA	
		Pembro	**SoC**	**Pembro**	**SoC**
PFS	Median PFS, months (95% CI)	10.4 (9.7 to 12.3)	8.2 (6.3 to 8.5)	10.5 (9.7, 12.3)	8.2 (6.3, 8.5)
	PFS Hazard ratio (95% CI)	0.62 (0.50, 0.77)		0.58 (0.47, 0.71)	
		Pembro	**SoC**	**Pembro**	**SoC**
OS	Median OS, months (95% CI)	NR ([redacted])	16.3 ([redacted])	28.6 (22.1, 38.0)	16.5 (14.5, 20.0)
	OS Hazard ratio (95% CI)	0.64 (0.50, 0.81)		0.60 (0.49, 0.74)	
		Pembro	**SoC**	**Pembro**	**SoC**
Response rate	ORR, % (95% CI)	68.1 (62.2, 73.6)	50.2 (44.1, 56.2)	[redacted] (NR)	[redacted] (NR)

- All reported endpoints are similar between the interim and the final analyses, with slight improvement for OS and PFS hazard ratios
- Pembrolizumab significantly favoured over SoC

NICE

FA = final analysis; IA1 = interim analysis 1; ORR = overall response rate; OS = overall survival; PFS = progression free survival; SoC = standard of care;

Cost effectiveness

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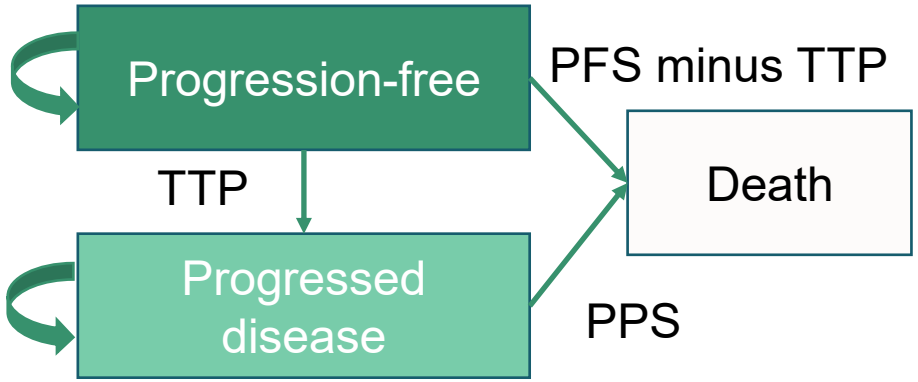
Company's model overview

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 FA (CPS≥1) with extrapolation
Utilities	KN-826 FA 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	Waning from 3-5years, with 2 year stopping rule
PD-L1 testing	KN-826 (% patients); NHS reference costs
Subsequent treatment composition	UK advisory board (composition); KN-826 (duration)

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.

PFS and TTP extrapolation

EAG satisfied with extrapolation approaches, but uncertainties remain about underlying data

- PFS extrapolation a key uncertainty in TA885
- As in TA885, company explored one-piece, two-piece, spline-based models and an exploratory response-based model (due to complex shape of the hazard function, due to heterogeneous hazard rates experienced by patients in different response categories)
- 3-knot hazard model selected (similar estimates to those previously used and was the middle option).
- 1-knot and 2-knot models examined as sensitivity analysis

EAG:

- 'Generally satisfied' with company's extrapolation approach - good visual and statistical fit to data
- Predictions are sensitive to changes in waning assumptions and are based on an optimised trial population which may overestimate outcomes compared to NHS practice

EAG = External Assessment Group; PFS = progression free survival; TTP = time to progression;

Key issue: Ongoing immaturity of OS data in KEYNOTE-826

EAG says full extent of pembrolizumab benefit is still uncertain

Background

- In TA885, a PSM wasn't suitable due to immaturity of OS. Company continues to use STM in rapid review.
- At EAG's request, company has provided a PSM using final OS data (as scenario, not base case)

Company

- Median OS now reached in pembro arm; trends seen in IA1 have continued; clinical certainty strengthened
- Additional data has narrowed the range of credible extrapolation of PFS, TTP and PPS
- PSM gives implausible extrapolations, as the OS data doesn't yet fully reflect the survival benefit for people who responded well to treatment (seen in the PFS plateau).
- Almost 90% of inc. QALYs in company base case are obtained within PFS health state

EAG comments

- Agree that OS data is still too immature to give plausible long-term extrapolations (using PSM)
- Cost-effectiveness results produced under PSM remain relatively robust and are unlikely to be a key driver of uncertainty in this appraisal
- Much of the pembro benefit remains within the extrapolated portion of survival curves, so is uncertain

Is the data from the final analysis of KEYNOTE-826 suitable for decision making, despite remaining uncertainty?

EAG = External Assessment Group; OS = overall survival; PFS = progression free survival; PPS = post-progression survival; PSM = partitioned survival model; STM = state transition model; TTP = time to progression; QALY = quality-adjusted life year

Key issue: Generalisability of KEYNOTE-826 outcomes

EAG says trial outcomes better than in NHS practice, exaggerating cost-effectiveness of pembro

Background

- In TA885, clinical experts acknowledged that people in clinical trials tend to be fitter than in clinical practice

Company

- Base case model produces OS estimates confirmed as plausible by clinical experts at ACM1 and by separate recent discussion with two UK clinicians

EAG comments

- PFS and OS in SoC arm are longer than expected in practice
- Suggests trial population is fitter with higher likelihood of durable response, and therefore may overestimate the benefit of treatment in both arms (SoC and pembro)
- Also, [redacted] patients in SoC arm and [redacted] in the pembro arm had subsequent immunotherapies (not available in NHS), so likely to overestimate outcomes, particularly post-progression survival in the SoC arm.
- → likely to overestimate the cost-effectiveness of pembrolizumab (as long-term, post-waning, PFS hazards are based on those achieved on SoC)

Are cost effectiveness results generalisable to NHS practice?

ACM1 = 1st appraisal committee meeting; OS = overall survival; PFS = progression free survival; SoC = standard of care;

End of life criteria

EAG questions whether EoL criteria are still met, as mean SoC OS in model exceeds 2yrs

		IA1	FA
Life expectancy normally <24 months	SoC OS: median	KEYNOTE: 16.3 months (95% CI [redacted]) GOG 240*: 13.3 to 16.8 months	KEYNOTE: 16.5 mths (95% CI: 14.5, 20.0)
	SoC OS: mean	Estimate from model: 2.06 years (company) to 2.08 years (ERG)	2.65 years
	% SoC died by 24 months	KEYNOTE: 58.3%	KEYNOTE: 60.6%
Intervention extends life by ≥3 months	Undiscounted LYG vs SoC: Mean		2.68 years (company base case)

Company:

- Committee agreed that end of life criteria were met in TA885, and 'little has changed' since
- Mean can be heavily skewed by a small number of people with good response, median more informative
- [redacted]% control arm had subsequent immunotherapy (not available on NHS), which likely overestimates OS
- Clinical experts gave survival estimates of 3-15 months for people on SoC (varies by age, health status etc)
- In the appeal for TA788, the end of life appeal point was upheld on similar LY data.

*GOG 240: phase III trial of paclitaxel + cisplatin or topotecan, +/- bevacizumab in people with persistent, recurrent or metastatic cervical cancer

OS = overall survival; LY = life year; LYG = life years gained; SoC = standard of care;

End of life criteria

EAG questions whether EoL criteria are still met, as mean SoC OS in model exceeds 2yrs

EAG:

- Mean OS for SoC arm (2.65yrs) is well above usual EoL criteria
- However, this is longer than expected in practice (based on clinical opinion)
- If we accept that trial population isn't generalisable to NHS (i.e. because is overestimates OS in the SoC arm), it follows that the cost effectiveness results are not generalisable either. This is because long-term (i.e. post-waning) PFS hazards are based on those achieved on SoC.

Tech team considerations:

Appeal judgement from TA788 stated:

- Totality of the data and analysis (inc. mean, the median, and clinical opinion) have to be looked at when considering if life expectancy is "normally less than 24 months".
- No general rule that median is preferable to mean or vice versa.

Appeal judgement from TA883 stated:

- Despite mean OS > 2 years, median OS is consistently less than 2 years and significant majority of patients (~65%) have died before 2 years
- Committee's conclusion that EoL isn't met 'does not adequately reflect how NICE's stakeholders would reasonably interpret and apply this criterion'

Does committee accept that life expectancy for SoC is 'normally <24 months'?
Are the end of life criteria still met?

OS = overall survival; PFS = progression free survival; SoC = standard of care;

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Backup

Model structure

PSM provided, but gives clinically implausible crossing of curves

Background:

- In TA885 an STM was used due to the comparative maturity of PFS data relative to OS, but committee said STM may no longer be appropriate when final data available

Company:

- Have provided PSM, but maintain that STM is most appropriate
- Clinician opinion and data from GOG240 support the link between PFS and OS
- STM shows positive PPS benefit for pembrolizumab (accepted by committee in TA885)
- Almost 90% of incremental QALYs in company base case are obtained within PFS health state (and PFS is modelled in the same way in both models)
- Most logical PSM extrapolations will result in an unrealistic crossing of OS and PFS curves (as OS data is too immature to capture plateau trend seen in PFS curve).
- When the PSM is used, in the event of crossing curves, both outcomes should be modelled based on PFS. OS trend is still driven by higher event rates in patients who haven't responded well to immunotherapy (time lag)
- Having zero patients in the PD health state (when PFS=OS due to crossing curves), is highly unrealistic

EAG:

- All reasonable extrapolations of PFS and OS data result in the crossing of curves
- PSM analysis is likely unable to capture post-progression survival outcomes
- Cost-effectiveness results from PSM remain relatively robust and are unlikely to be a key driver of uncertainty

EAG = External Assessment Group; OS = overall survival; PD = progressed disease; PFS = progression free survival; PSM = partitioned survival model; STM = state transition model

PPS extrapolation

- Selected the independently fitted generalised gamma curves as had among the lowest AIC and best visual fit to the data
- Mean PPS was longer in the pembrolizumab arm than SoC, and the curves did not cross
- Consistent with committee's preference in TA885 (also independently fitted generalised gamma models with slightly longer PPS in the pembro arm).

PPS = post-progression survival; SoC = standard of care;

OS extrapolation – used in PSM model only

EAG satisfied with extrapolation approaches, but uncertainties remain about underlying data

EAG:

- OS extrapolation offers good visual and statistical fit to the observed data
- Extrapolations are based on optimised trial population which may overestimate survival compared to NHS
- Much of pembro benefit is within extrapolated part of curves and as such remains uncertain

EAG = External Assessment Group; = overall survival; PSM = partitioned survival model; SoC = standard of care;