Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Technology appraisal committee A [9 April 2024]

For Zoom – Redacted

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Company: Merck Sharp and Dohme

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ACM1 – Preliminary recommendation

Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy is not recommended, within its marketing authorisation, for untreated HER2-negative locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a combined positive score (CPS) of 1 or more.

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma

- ✓ **Background and recap of committee conclusions from 1st meeting**
- ❑ Consultation comments and updated cost effectiveness results

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Background: the condition and technology

- In the UK, GC accounts for 2% of all new cancer cases; 6,453 new cases reported each year (2016-2018)
- PD-L1 CPS is a measure of the number of PD-L1-expressing cells relative to all viable tumour cells
- If symptoms are present at the time of diagnosis, the disease is often advanced and incurable
- There is a particular unmet need for younger patients being diagnosed at a later stage of the condition

Technology details: pembrolizumab (Keytruda, Merck Sharp and Dohme)

Marketing authorisation	Pembrolizumab, in combination with fluoropyrimidine and platinum-containing containing chemotherapy for the first-line treatment of locally advanced unresectable or metastatic HER2 negative gastric or gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS≥1
Mechanism of action	Anti-programmed cell death 1 (PD-1) antibody; blocks interaction with PD-L1 and PD-L2 ligands and reactivates T-cell anti-tumour activity
Administration	Pembrolizumab 200 mg every three weeks or 400 mg every six weeks; intravenous infusion (up to a maximum 35 x 3-week cycles)
Price	There is a patient access scheme discount for pembrolizumab

Abbreviations: CPS, combined positive score; GC, gastric cancer; HER2, human epidermal growth factor receptor 2; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1

Treatment pathway.

1st line options are dependent on PD-L1 CPS

	HER2 negative advanced gastric or gastro-oesophageal junction adenocarcinoma PD-L1		
PD-L1 CPS	≥ 1	≥ 5	≥ 10
1st–line treatment options	Doublet chemotherapy (NG 83)		
		Nivolumab + doublet chemotherapy (TA 857)	
			Pembrolizumab + doublet chemotherapy (TA 737)*
	Pembrolizumab + doublet chemotherapy		
2nd–line treatment options	Chemotherapy options including irinotecan-based regimen, paclitaxel, capecitabine		
3rd–line+ treatment options	Chemotherapy options including irinotecan-based regimen, paclitaxel, capecitabine, trifluridine + tipiracil (TA 852)		

*Gastro-oesophageal junction cancer only

- All doublet chemotherapies in the pathway are platinum + fluoropyrimidine-based regimens
- Platinum-based chemotherapies: oxaliplatin and cisplatin; fluoropyrimidine-based chemotherapies: capecitabine and 5-fluorouracil

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Abbreviations: CPS, combined positive score; HER2, human epidermal growth factor receptor 2; PD-L1 programmed cell death ligand 1

Overlap between TA 737 and current appraisal for people with GOJ with CPS ≥10

- A previous appraisal (TA 737) recommends pembrolizumab plus doublet chemotherapy as an option for treating oesophageal or GOJ adenocarcinoma those with a CPS ≥10
- The indication in the MA for GOJ adenocarcinoma has changed since that guidance was published [it now includes people with a CPS≥ 1], so this evaluation will replace that guidance for those with GOJ adenocarcinoma.
- The timings of :
    - TA 737: pembrolizumab plus doublet chemotherapy for oesophageal or GOJ adenocarcinoma
    - TA 857: nivolumab plus doublet chemotherapy for gastric, GOJ or oesophageal adenocarcinoma

meant that pembrolizumab plus doublet chemotherapy and nivolumab plus doublet chemotherapy were not comparators for each other in those appraisals

Abbreviations: CPS, combined positive score; GOJ, gastro oesophageal junction; MA, marketing authorisation

Company model overview

Company

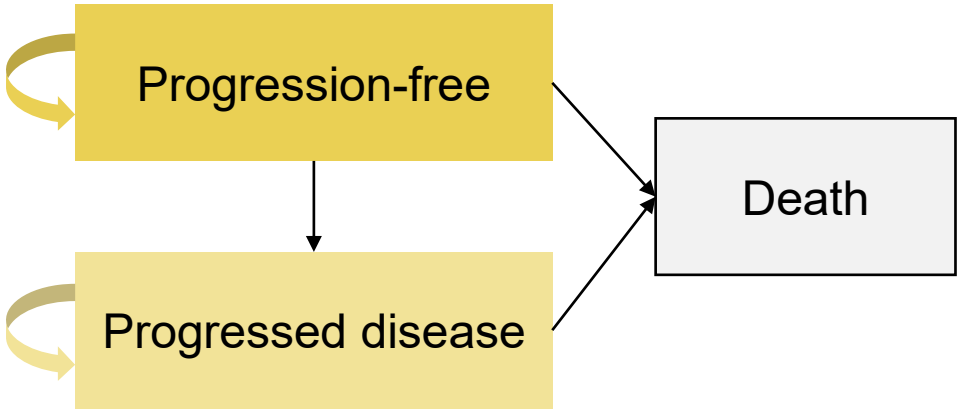
CPS ≥1 population

- Compared pembrolizumab + doublet chemotherapy with chemotherapy alone
- Extrapolated KM data (overall survival and progression free survival) from KEYNOTE-859.

CPS ≥5 population

- Indirectly compared pembrolizumab + doublet chemotherapy (KEYNOTE-859) with nivolumab + doublet chemotherapy (CHECKMATE-649).
- Company used data from CPS ≥10 subgroup as a proxy for CPS ≥ 5. Applied hazard ratios from NMA in model.

Model structure: partitioned survival



Time horizon: 30 years (lifetime)

EAG

- Used same methods to extrapolate trial data as company
- Included a treatment effect waning assumption in its exploratory base case
- Both company and EAG calculated that a 1.2 QALY weighting was appropriate for the CPS ≥1 population if doublet chemotherapy is the comparator

Abbreviations: CPS, combined positive score; KM Kaplan Meier; NMA, network meta-analysis; QALY, quality-adjusted life year

ACM1 committee conclusions

Company approach	Committee conclusion
Comparators	PD-L1 CPS 1-4: doublet chemotherapy PD-L1 CPS ≥5: nivolumab
Indirect comparison of pembrolizumab vs nivolumab in PDL1 CPS ≥5 population • Company used of CPS ≥10 subgroup data to inform comparison (relative treatment effect expected to be constant across subgroups by CPS) • Used constant hazard ratios	• Agreed treatment effect consistent across CPS subgroups. Data from pembrolizumab trial PDL1 CPS ≥5 post hoc subgroup also would be sufficiently powered for use in NMA • Time-varying hazard ratios preferred • Pembrolizumab and nivolumab are similarly effective + tolerated in this group • Cost minimisation approach appropriate for this subgroup
Assumed no treatment effect waning after stopping pembrolizumab in base case.	Appropriate to apply a treatment waning effect for pembrolizumab starting either 5 years or 7 years after starting treatment and reducing to the same as the comparator after 2 years
Costs for people having doublet chemotherapy capped at 6 cycles in the economic model	6-cycle cap was appropriate for modelling
Severity modifier – QALY weight (for CPS ≥1 population only)	x1.2 QALY weight should be applied in line with NICE methods

Abbreviations: CPS, combined positive score; NMA, network meta-analysis; PD-L1 programmed cell death ligand 1; QALY, quality-adjusted life year

Key issues for discussion today

Updated company survival model selection (CPS ≥1 population)	Are the company's chosen survival extrapolations appropriate?
Treatment effect waning	Is the company's approach to treatment effect waning appropriate?
CPS subgroup analysis for comparison with chemotherapy	Would the clinical and cost effectiveness of pembrolizumab + chemotherapy vs chemotherapy in the CPS ≥1 and <5 subgroup be expected to be the same as CPS ≥1 group?
Company has provided updated cost utility and new cost minimisation results for CPS ≥ 5 population	Which approach is the committee's preferred for its decision making- cost minimisation or cost utility?

Abbreviations:

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma

- ❑ Background and recap of committee conclusions from 1st meeting
- ✓ **Consultation comments**

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Consultation responses

Comments were received from:

MSD (pembrolizumab)

- Updated base case using later data cut for comparison with chemotherapy in CPS≥ 1 population. Includes assumption on treatment waning and 1.2 QALY weighting for severity
- New cost minimisation for comparison with nivolumab + chemotherapy in CPS ≥ 5 population. Used data from updated data cut and CPS ≥ 5 subgroup from KEYNOTE-859 trial
    - Also presented updated cost-utility analysis for this group informed by a time varying hazard ratio NMA, and constant hazard ratio NMA in a scenario analysis
- Other comments on the draft guidance

BMS (nivolumab)

Abbreviations: BMS, Bristol-Myers Squibb ; CPS, combined positive score; MSD, Merck Sharp and Dohme; QALY, quality-adjusted life year

Updated company clinical effectiveness data: KEYNOTE-859 longer-term follow-up

Additional 10 months follow-up data on OS and PFS available

- The company submitted longer term follow-up data from the KEYNOTE-859 study as part of their response to draft guidance consultation (DCO: 22 August 2023)
- Longer term follow-up data supports the committee's original conclusion that for the CPS ≥1 population, pembrolizumab plus doublet chemotherapy improves OS and PFS when compared with doublet chemotherapy alone
- Data from the 22 August datacut used for the CPS ≥ 5 subgroup from KEYNOTE-859 applied in cost minimisation and updated cost utility estimates for this group

Pembrolizumab vs chemotherapy	CPS ≥1 population
OS HR, 95% CI, p value	[redacted]
PFS HR, 95% CI, p value	[redacted]

Abbreviations: CPS, combined positive score; DCO, data cut-off; HR hazard ratio; OS, overall survival; PFS, progression-free survival

See appendix – Detailed results

Updated company survival model selection: CPS ≥1 population

New survival extrapolations were fitted based on longer term follow-up data

Company

- Survival extrapolation curves were fitted to OS and PFS longer term follow-up data
- The best statistically fitting spline curves resulted in PFS and OS crossing in both treatment arms.
- Therefore, 3k odds model was chosen for OS in both treatment arms and the 2k hazards model was chosen for PFS in both treatment arms because had minimal PFS and OS crossing and good visual and statistical fit

EAG comments

- EAG explored scenarios similar to those around spline models in the original submission
- Most relevant alternatives to company base case (3k odds) are using the 3-knot hazards spline, and the 2-knot hazard spline

Outcome	Treatment	Best statistical fit	Company base case
OS	Pembrolizumab + doublet chemotherapy	2k hazards	3k odds
	Doublet chemotherapy	3k odds	3k odds
PFS	Pembrolizumab + doublet chemotherapy	3k normal	2k hazards
	Doublet chemotherapy	3k odds	2k hazards

Abbreviations: CPS, combined positive score; OS, overall survival; PFS, progression-free survival 1

See appendix – Goodness-to-fit statistics

Updated company survival model selection: CPS ≥5 population

New survival extrapolations were fitted based on longer term follow-up data

Company

- For updated NMA, proportional hazards assumption did not hold for OS (based on KEYNOTE-859 Aug 23 datacut). Uncertainty whether PH met for PFS- company used same approach as OS for consistency. Time varying HR approach used for NMA.
- Best fitting fractional polynomial models for OS and PFS were used in the base case analysis
- Capped OS survival curve so probability of survival does not exceed general population

EAG comments

- Time-varying hazard ratio approach appropriate and showed no statistically significant differences in OS between pembrolizumab plus chemotherapy and nivolumab plus chemotherapy
- Impact of using time-dependant or constant PFS HR on cost effectiveness results minimal
- Presented scenarios using alternative functional forms for hazards (2nd and 3rd best fitting models)

Outcome	Model used to inform base case analysis for the CPS ≥5 population
OS	First-order fractional polynomial (P1=1, P2=0.5, scale and 2nd shape)
PFS	Second-order fractional polynomial (P1=0, P2=0.5, scale and 2nd shape)

Abbreviations: NMA, network meta analysis; PH, proportional hazards CPS, combined positive score; OS, overall survival; PFS, progression-free survival

Updated company base case: Treatment effect waning

Company included treatment effect waning assumption in updated base case

Company

- No clear evidence to indicate treatment waning effect, as the KM curves for PFS and OS separated early and remained separated throughout the evaluation period
- [Hazard ratio over the trial period] suggests that the long-term benefits of pembrolizumab are stable after approximately [redacted] of treatment
- Acknowledging committee preferences in CPS ≥1 population waning applied 7 years after initiation (5 years after stopping pembrolizumab) in [redacted]% patients (excludes proportion of people from KEYNOTE-859 who had complete response)
- Company quotes clinical expert statement at first meeting *"for the 10 to 15% of people who have a complete response, treatment effect waning would not be expected"* draft guidance section 3.7
- Also provides scenarios in which waning applied 6 and 5 year after treatment initiation

EAG comments

- EAG presented scenarios with no treatment waning, and waning at 5 or 7 years for 100% of people (not just those without a complete response to treatment)
- Impact of assuming waning only for patients without a complete response is very small

Is the company's approach to treatment effect waning appropriate?

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Abbreviations: CPS, combined positive score; KM Kaplan Meier; OS, overall survival; PFS, progression-free survival

Company's new cost-minimisation analysis – CPS ≥5 population

- Uses most recent data cut for CPS ≥5 subgroup and QALYs are made equal in both arms by assuming pembrolizumab and nivolumab have the same PFS, OS and adverse events
- Time on treatment is from Kaplan Meier data from KEYNOTE-859 . Assumed same in pembrolizumab and nivolumab modelled treatment arms
- Costs for disease management, adverse events, progression, subsequent treatments and end of life care were equivalent for both pembrolizumab and nivolumab
- Administration costs were higher for pembrolizumab because of different infusion times and administration costs for the different doublet chemotherapy regimens used in KEYNOTE-859 (pembrolizumab) and CHECKMATE-649 (nivolumab)
- Company notes that 3 weekly administration of pembrolizumab used in economic analyses, 6 weekly administration is permitted which would reduce administration costs

Abbreviations: CPS, combined positive score; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year

MSD other comments

- "…in the event that NICE is unable to make a positive recommendation in line with the full population covered by the decision problem in ID4030, **it would not be necessary or appropriate for any change to be made to the existing TA737 recommendation".**
- "Clinical and cost-effectiveness has already been demonstrated in the GOJ CPS ≥10 population [in] TA737. Removal of the GOJ population from the current TA737 recommendation would effectively represent removing a treatment option which has been demonstrated to be a cost-effective use of NHS resources. The KEYNOTE-590 data which informed the appraisal which led to publication of TA737 remains valid".
- "The change in the oesophageal carcinoma indication statement in the pembrolizumab SmPC was proposed to avoid duplicating reference to the GOJ population in both oesophageal and gastric indication statements in the SmPC (i.e. overlapping indication statements). … not caused by new safety or efficacy data from the KEYNOTE-590 trial data… there is no change to the evidence base, clinical pathway or economic case that could lead to a material effect on the recommendation".

Abbreviations: CPS, combined positive score; GOJ, gastro oesophageal junction; OS, overall survival; PFS, progression-free survival; SmPC, summary of product characteristics

Consultation response – Bristol-Myers Squibb

- No analysis comparing pembrolizumab against chemotherapy in people with tumours with PD-L1 CPS ≥1 and <5 (for whom chemotherapy is a comparator). Using CPS ≥1 data may overestimate treatment effect because includes people with CPS ≥5 who are likely to have greater benefits from immunotherapies
- Not appropriate to use data from the PD-L1 CPS ≥10 subgroup as a proxy to inform the PD-L1 CPS ≥5 subgroup because absolute outcomes will vary substantially for immunotherapies between CPS subgroups*
- Agree with the committee conclusion that pembrolizumab plus doublet chemotherapy and nivolumab plus doublet chemotherapy were similarly effective and tolerated
- Treatment effect waning assumptions should be based on plausibility of long-term outcomes and be applied at 5 years to ensure transparency and comparability between previous appraisals (TA 857). Notes drop to chemotherapy mortality hazard at 5 and 6.5 years considered plausible but uncertain by committee [in TA857].

Potential equality issues

- Different CPS tests used for nivolumab and pembrolizumab. Not all centres have both assays or can do parallel testing. Access to nivolumab and pembrolizumab may be impacted by clinical judgement, test availability and/or timing
- Agree symptoms of gastric or GOJ cancer can have a considerable impact on quality of life and that life expectancy with the condition is poor. Particularly the case for younger adults

Would the clinical and cost effectiveness of pembrolizumab + chemotherapy vs chemotherapy in the CPS ≥1 and <5 subgroup be expected to be the same as CPS ≥1 group?

*See appendix – KEYNOTE-859 OS by CPS subgroup

Summary of cost-effectiveness results – CPS ≥1 population

Exact results are reported in part 2

- Cost-effectiveness results are confidential because nivolumab and trifluridine-tipiracil (a modelled follow-on treatment) have confidential patient access schemes

Key assumptions in revised company base case

- Longer-term follow-up data is used to inform OS, PFS and ToT
- A gradual treatment effect waning is applied 7 years after initiation of pembrolizumab treatment
- A severity weighting of 1.2 is applied to QALYs

Results

- The revised company base case ICER is between £20,000 and £30,000 per QALY gained for the comparison between pembrolizumab plus doublet chemotherapy vs. doublet chemotherapy
- Using updated data cut has reduced the ICER compared with 1st meeting. Using alternative models to extrapolate overall survival from trial data increases the ICER
- Treatment effect waning assumptions and decreasing time before waning starts increase the ICER but scenarios with a 5-year treatment waning assumption still below £30,000 per QALY gained

Abbreviations: CPS, combined positive score; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; ToT, time on treatment

Summary of cost-effectiveness results – CPS ≥5 population

Cost-minimisation analysis results (committee preference from 1st meeting)

- Acquisition costs were higher for pembrolizumab compared with nivolumab
- Total costs were higher for pembrolizumab compared with nivolumab

Cost-utility analysis- key assumptions

- Longer-term follow-up data is used to inform OS, PFS and ToT from CPS ≥5 in KEYNOTE-859
- Time-varying HRs are used for OS and PFS
- No treatment effect waning applied
- No severity weighting is applied to QALYs

Cost-utility analysis results

- The revised company base case ICER is above £30,000 per QALY gained for the comparison between pembrolizumab plus doublet chemotherapy vs. nivolumab plus doublet chemotherapy. All scenarios around modelling of OS and PFS ICER remains above £30,000 per QALY gained

Abbreviations: CPS, combined positive score; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

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Supplementary appendix

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KEYNOTE-859: CPS ≥1 OS – longer-term follow-up data

Pembrolizumab + doublet chemotherapy (n=618) improves OS compared to placebo + doublet chemotherapy (n=617)

Overall survival

	Median OS (95% CI)
Pembrolizumab + chemotherapy	[redacted]
chemotherapy	[redacted]

At risk

Month	0	5	10	15	20	25	30	35	40	45	50	55	60
Pembrolizumab + chemotherapy	[redacted]												
Chemotherapy	[redacted]												

Abbreviations: CPS, combined positive score; CI, confidence interval; HR, hazard ratio; OS, overall survival

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Link to – Clinical effectiveness data

KEYNOTE-859: CPS ≥1 PFS – longer term follow-up

Pembrolizumab + doublet chemotherapy (n=618) improves PFS compared to placebo + doublet chemotherapy (n=617)

Progression free survival

	Median PFS (95% CI)
Pembrolizumab + chemotherapy	
chemotherapy	

At risk

Month	0	5	10	15	20	25	30	35	40	45	50	55	60
Pembrolizumab + chemotherapy													
Chemotherapy													

Abbreviations: CPS, combined positive score; CI, confidence interval; HR, hazard ratio; OS, overall survival

Link to – Clinical effectiveness data

Goodness-of-fit statistics for OS using longer term follow-up data – CPS ≥1 population

Model	Pembrolizumab + doublet chemotherapy (AIC)	Doublet chemotherapy (AIC)
1k hazards	5,517.1	5,712.3
2k hazards	5,495.3	5,690.3
3k hazards	5,497.6	5,675.0
1k odds	5,507.3	5,683.8
2k odds	5,495.9	5,679.4
3k odds	5,498.1	5,674.8
1k normal	5,520.6	5,701.1
2k normal	5,497.2	5,685.6
3k normal	5,498.7	5,675.9

Company

- 3k odds chosen for pembrolizumab + doublet chemotherapy over best fitting 2k hazards because a difference in the AIC of less than 3 is considered negligible: 5,495.3 for 2k hazards versus 5,498.1 for 3k odds
- Curves of the same type are preferred for both treatment arms when possible

Abbreviations: AIC, Akaike information criterion; CPS, combined positive score; OS, overall survival

Link to – Base case curves

Goodness-of-fit statistics for PFS using longer term follow-up data – CPS ≥1 population

Model	Pembrolizumab + doublet chemotherapy (AIC)	Doublet chemotherapy (AIC)
1k hazards	4437.4	4400.5
2k hazards	4421.2	4360.6
3k hazards	4421.5	4353.2
1k odds	4442.2	4381.2
2k odds	4425.1	4369.0
3k odds	4418.4	4351.0
1k normal	4461.9	4407.7
2k normal	4424.2	4372.4
3k normal	4417.5	4351.6

Company

- 2k hazards model chosen over best fitting 3k normal (for pembrolizumab arm) and 3k odds (for doublet chemotherapy arm because 3k spline models result in more OS crossing than the 2k and 1k spline models
- 2k hazards model had the best statistical fit of 2k and 1k splines in both treatment arms

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Abbreviations: AIC, Akaike information criterion; CPS, combined positive score; OS, overall survival

Link to – Base case curves

Longer term follow-up base case curves – CPS ≥1 population

Pembrolizumab + doublet chemotherapy

Doublet chemotherapy

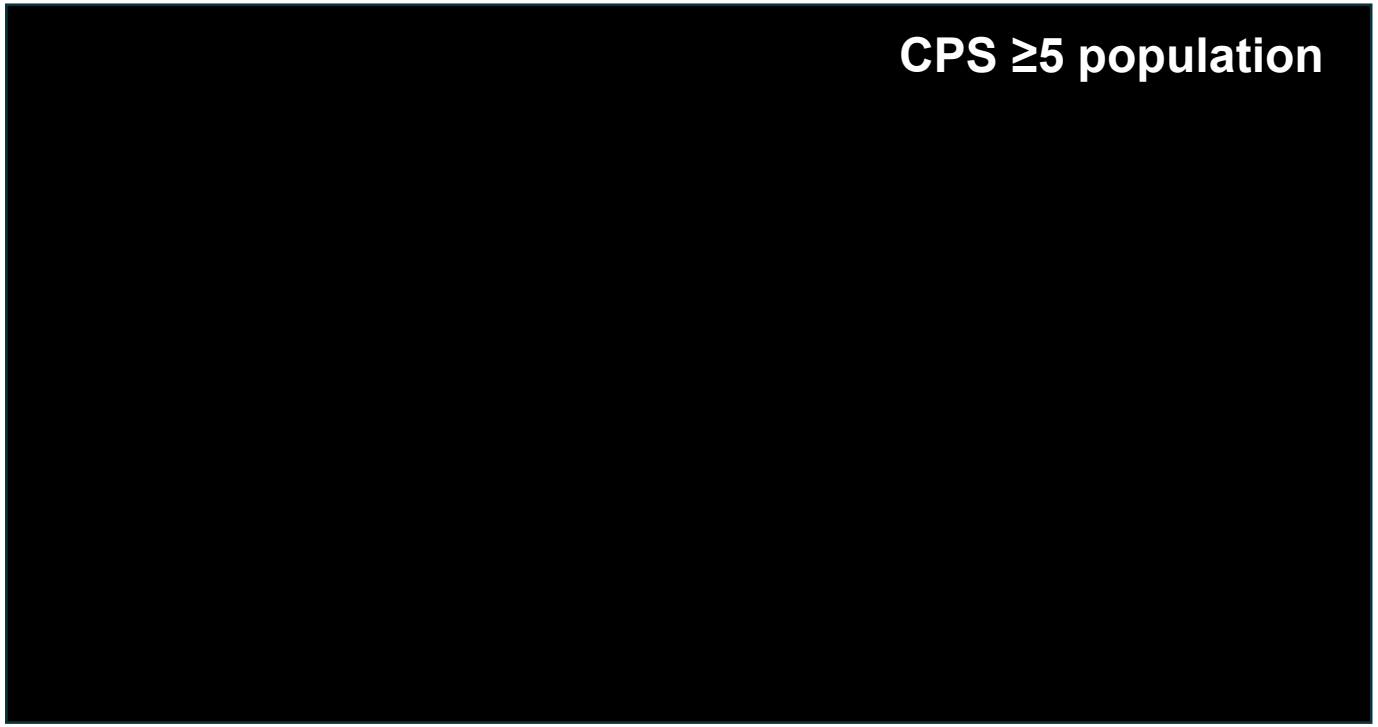
Are the company's chosen survival extrapolations appropriate?

Abbreviations: CPS, combined positive score; OS, overall survival; PFS, progression-free survival

See appendix – Goodness-to-fit statistics

Time-varying hazards ITC results - longer term follow-up

Modelled overall survival curves with 95% CI



Background

- Following ACM1, both the company and EAG agreed that time-varying method was more appropriate than using a constant HR when conducting the ITC for both the PD-L1 CPS ≥1 and CPS ≥5 populations

According to the model selection process, the best fitting model was the first-order fractional polynomial (P1=1, P2=0.5, scale and 2nd shape)

*Statistically significant at the 0.05 significance level

Time-varying HRs (95% CrI) from fixed effect fractional polynomial NMA for OS

Pembrolizumab + chemo vs.	6 months	12 months	24 months	48 months
Chemo	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + chemo	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CPS, combined positive score; CrI, credible interval; NMA, network-meta analysis; OS, overall survival

Longer term follow-up base case curves – CPS ≥5 population

Best fitting FP extrapolations – pembrolizumab + doublet chemotherapy

Abbreviations: CPS, combined positive score; OS, overall survival; PFS, progression-free survival

KEYNOTE-859: Overall survival by CPS subgroup

	CPS ≥5		CPS ≥10	
Outcome	**Pembrolizumab + doublet chemotherapy**	**Doublet chemotherapy**	**Pembrolizumab + doublet chemotherapy**	**Doublet chemotherapy**
N	379	388	279	272
Number of events (%)	269 (71.0)	325 (83.8)	188 (67.4)	226 (83.1)
Median OS (95% CI), months	14.0 (12.1 to 15.4)	11.5 (10.3 to12.5)	15.7 (13.8 to19.3)	11.8 (10.3 to 12.7)
HR (95% CI)	0.70 (0.60 to 0.82)		0.65 (0.53 to 0.79)	
p-value	<0.0001		<0.0001	

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival

Link to – BMS Consultation response