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

Technology appraisal committee A [13 February 2024]

For screen – CON redacted

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Company: Merck Sharp & Dohme

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

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

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Background on HER2 negative advanced gastric or gastro-oesophageal junction adenocarcinoma

Disease

- Gastric adenocarcinomas are cancers that originate in the cells of the stomach; GOJ adenocarcinomas are where the centre of the tumour is <5cm above or below where the oesophagus meets the stomach
- In the UK, GC accounts for 2% of all new cancer cases; 6,453 new cases reported each year (2016-2018)

Diagnosis and classification

- The most common method for diagnosing GC is via a specific type of endoscopy, called gastroscopy
- HER2 is a protein that helps cancer cells grow quickly; PD-L1 is a protein that can help tumour cells evade an attack by the immune system. The expression of these proteins are tested for because there are immunotherapies which specifically target them (trastuzumab, HER2; pembrolizumab and nivolumab, PD-L1)
- PD-L1 combined positive score is a measure of the number of PD-L1-expressing cells relative to all viable tumour cells

Symptoms and prognosis

- Symptoms include indigestion, poor appetite or early satiety, weight loss, and abdominal pain
- If symptoms are present at the time of diagnosis, the disease is often advanced and incurable

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

Patient perspectives

Submission from Together OG Support Group and patient expert

Living with advanced gastric or GOJ adenocarcinoma

- It is a difficult time for both patient and caregiver, as curative surgery is usually not an option
- Eating and swallowing difficulties can be an issue, often stents are used which are not always successful and some patients will need jejunostomy tube feeding as the condition progresses. Impaired swallowing can make oral treatments difficult

Current treatment options

- There is not a lot of choice with the current treatment options and patients are often enquiring about new technologies and potential clinical trials
- Current treatments are primarily palliative- side effects can affect quality of life to quite a large degree

Unmet need

- There is a particular unmet need for younger patients being diagnosed at a later stage of the condition

'This [technology] will certainly benefit younger patients as they will be fitter and healthier to be able to cope with the treatment'

'Patients and carers are looking for more than the current treatment to have a chance of longer survival and better QoL'

Abbreviations: GOJ, gastro-oesophageal junction; QoL, quality of life

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

Does the pathway represent UK clinical practice?

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

Pembrolizumab (Keytruda, Merck Sharp & 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; HER2, human epidermal growth factor receptor 2; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1

Key issues

Issue	ICER impact
Indirect treatment comparison of pembrolizumab + chemotherapy with nivolumab + chemotherapy	
Comparison with nivolumab + chemotherapy for people with PD-L1 CPS ≥5 • Is company's use of CPS ≥10 data to inform this comparison appropriate? • Is the treatment effect of pembrolizumab vs. nivolumab exchangeable between subgroups based on CPS?	N/A
• Proportional hazard assumptions – should the company use alternative methods in ITC?	Unknown
Uncertainty on long-term overall survival and the treatment effect	
• Would the treatment effect of pembrolizumab + chemotherapy vs chemotherapy be expected to decrease after stopping treatment? • Should the EAG's treatment waning assumption be applied?	Large
• People in trial could stay on chemotherapy for more than the NHS cap of 6 cycles. • Do the modelled overall survival estimates reflect what would be expected in the NHS?	Unknown
Severity modifier	
• Severity modifier – a 1.2 QALY weighting potentially applies for the CPS ≥1 population vs. chemotherapy, but not for CPS ≥ 5 assuming the comparator nivolumab. • N.B. Company apply 1.7 QALY weighting for comparison with chemotherapy in base case (outside of NICE methods)	Large

Abbreviations: CPS, combined positive score; ITC, indirect treatment comparison; QALY, quality-adjusted life year

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Key trials clinical trials

	KEYNOTE- 859 N= 1,579*	CHECKMATE- 649 N= 1,518*
Trial design	International double blind RCT	International open label RCT
Population	HER2 negative, previously untreated, unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma	Same as KEYNOTE-859 but also included people with unknown HER2 status and people with oesophageal adenocarcinoma (~14% trial population)
Subgroups^	CPS PD-L1≥1 n= 1,234 CPS PD-L1≥5 (post-hoc) [redacted] CPS PD-L1≥10 n=551	CPS PD-L1≥1 n=1,296 CPS PD-L1≥5 (pre-specified) n=955 CPS PD-L1≥10 n=768
Intervention	Pembrolizumab + CAPOX or FP	Nivolumab + XELOX (CAPOX) or FOLFOX
Comparator	Placebo + CAPOX or FP	Placebo + XELOX (CAPOX) or FOLFOX
Primary outcome	OS	PFS by BICR and OS in PD-L1 CPS ≥5 participants
Key secondary	PFS per RECIST 1.1 assessed by BICR ORR per RECIST 1.1 assessed by BICR	

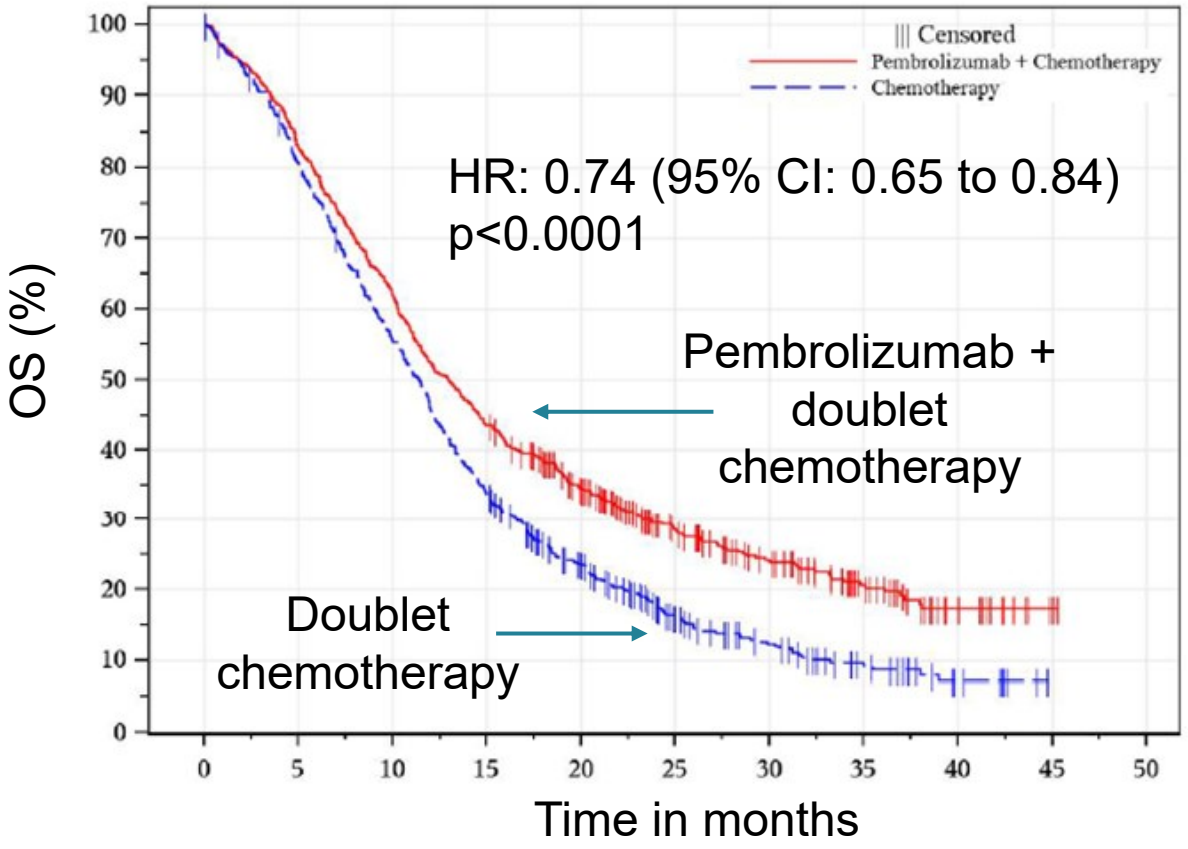
*Total trial population ^Participants can be part of more than one subgroup

Abbreviations: BICR, blinded independent central review; CAPOX/XELOX, capecitabine and oxaliplatin; CPS, combined positive score; FOLFOX,, folinic acid, fluorouracil and oxaliplatin; FP, cisplatin and 5-fluorouracil; HER2, human epidermal growth factor receptor 2; ORR, objective response rate; OS, overall survival; PD-L1 programmed cell death ligand 1; PFS, progression-free survival; RCT, randomised controlled trial; RECIST, response evaluation criteria in solid tumours

Key clinical trial results – KEYNOTE-859 CPS ≥1 Overall Survival

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

Overall survival



	Median OS (95% CI)
Pembrolizumab + chemotherapy	13.0 months (11.6 to 14.2)
chemotherapy	11.4 months (10.5 to 12.0)

At risk

Month	0	5	10	15	20	25	30	35	40	45	50
Pembrolizumab + chemotherapy	618	511	383	269	192	121	81	46	17	3	0
Chemotherapy	617	493	339	206	126	66	41	20	7	0	0

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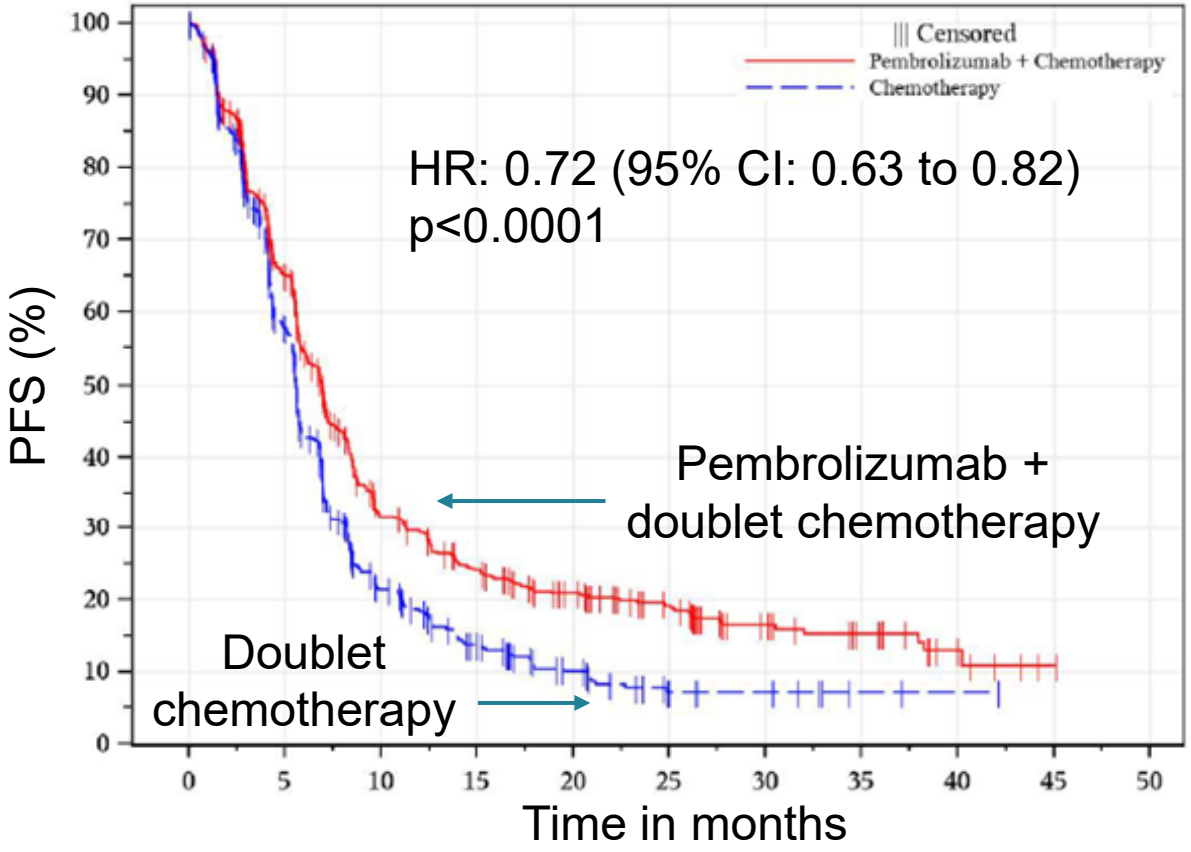
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival

*See appendix – Detailed results

Key clinical trial results – KEYNOTE-859 CPS ≥1 progression free survival

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

Progression free survival



	Median PFS (95% CI)
Pembrolizumab + chemotherapy	6.9 months (6.0 to 7.2)
chemotherapy	5.6 months (5.4 to 5.7)

At risk

Month	0	5	10	15	20	25	30	35	40	45	50
Pembrolizumab + chemotherapy	618	356	156	112	82	57	33	21	8	1	0
Chemotherapy	617	317	97	51	26	11	8	2	1	0	0

NICE

Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression free survival

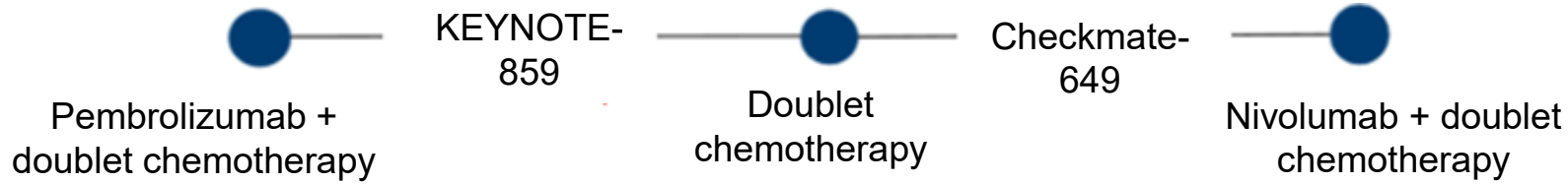
*See appendix – Detailed results

NMA methodology and results*

*See appendix – Post-hoc analysis

No statistically significant differences in key outcomes following indirect treatment comparison between pembrolizumab and nivolumab

- An NMA was required to compare pembrolizumab and nivolumab due to a lack of direct comparison data



- At time of original company submission, no data available for pembrolizumab for CPS ≥5 group. Company provided in response to clarification, but does not consider analysis in CPS ≥5 for pembrolizumab to be statistically valid as not pre-specified group in trial. Company used estimates from CPS ≥10 population in its model.
- NMA conducted using constant and time-varying HRs; used constant in base case, assumed proportional hazards; analyses for OS and PFS conducted using a fixed-effects model

Pembrolizumab vs nivolumab	CPS≥ 1	CPS≥ 5	CPS≥ 10
OS HR, 95% CrI	[redacted]	[redacted]	[redacted]
PFS HR, 95% CrI	[redacted]	[redacted]	PFS for this group not reported in CHECKMATE -649

Abbreviations: CPS, combined positive score; CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival

Key issue: Comparability of the two trials

Comparison of baseline characteristics between trials was not possible

Background

- Overall company considered KEYNOTE-859 and CHECKMATE-649 to be sufficiently similar to carry out NMA, assuming doublet chemotherapies used in the trial are equivalently clinically effective
- Company assumes treatment effect is consistent in all CPS subgroups, so CPS ≥10 can be used as a proxy for CPS ≥5
- No data for the comparison of baseline characteristics in people with PD-L1 CPS ≥1 and PD-L1 CPS ≥10 between the two trials (KEYNOTE-859 and CheckMate-649) were provided

Company

- Based on clinical opinion and ESMO guidelines, doublet chemotherapies were considered clinically equivalent across the two clinical trials
- No published data on baseline characteristics of CheckMate-649 for CPS ≥1 and CPS ≥10 CPS populations

EAG comments

- EAG were satisfied CPS ≥5 results were consistent with CPS ≥1 and CPS ≥10.
- It is unclear whether the baseline characteristics of people in the CPS subgroups between the two included trials are similar and therefore subgroup results are exchangeable for the purpose of the NMA
- Noted that KEYNOTE-859 double blind, CHECKMATE-649 open label

NICE Is company's use of CPS ≥10 data to inform pembrolizumab vs nivolumab comparison appropriate?

Abbreviations: CPS, combined positive score; ESMO, European Society for Medical Oncology; NMA, network meta-analysis; PD-L1, programmed cell death ligand 1

Key issue: Proportional hazard assumptions*

Uncertainty over appropriateness of using constant hazard ratios

Background

- Constant HRs for OS were used in the base-case indirect treatment comparison between pembrolizumab + chemotherapy and nivolumab + chemotherapy for people with PD-L1 CPS ≥1 and PD-L1 CPS ≥5 (using constant HRs assumes proportional hazards).
- Company submission inconsistent on what proportional hazard tests showed

Company

- 'Since the proportional hazard tests were consistent with the proportional hazards assumption… the NMA was conducted assuming constant HRs'
- 'PH assumption may not be valid for the OS outcome for the comparison of pembrolizumab plus doublet chemotherapy and doublet chemotherapy in people expressing CPS ≥1 during the trial period' KEYNOTE-859

EAG comments

- Tests demonstrated proportional hazards may not be valid for overall survival in CPS ≥1 and ≥5 groups for trial data from both arms in KEYNOTE-859
- This was inconsistent with the approach taken in company base case analysis of ITC (constant HR)
- Time-varying method may be more appropriate than using a constant HR

Should the proportional hazards assumption be accepted or rejected?

*See appendix – Proportional hazard assumptions analysis

Abbreviations: CPS, combined positive score; HR, hazard ratio; ITC, indirect treatment comparison, NMA, network meta-analysis; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival

Treatment-specific adverse events affecting >3% (included in model)

	Pembrolizumab + chemotherapy (n=785)		Doublet chemotherapy + placebo (n=787)		Nivolumab + chemotherapy (n=782)	
Doublet chemotherapy in trial	85.5% CAPOX, 14.5% FP				51% FOLFOX, 49% CAPOX	
	Events	Incidence	Events	Incidence	Events	Incidence
Anaemia	69	8.8%	59	7.5%	47	6.0%
Neutropenia	82	10.4%	78	9.9%	118	15.1%
Diarrhoea	51	6.5%	40	5.1%	35	4.5%
Vomiting	39	5.0%	34	4.3%	17	2.2%
Fatigue	29	3.7%	34	4.3%	30	3.8%
Nausea	28	3.6%	31	3.9%	20	2.6%
Hypokalaemia	30	3.8%	24	3.0%	0	0.0%
Palmar-plantar erythrodysaesthesia syndrome	25	3.2%	14	1.8%	11	1.4%
Neuropathy peripheral	10	1.3%	25	3.2%	31	4.0%

EAG comments on rates in the pembrolizumab vs. nivolumab comparison

- Company suggest observed difference in pembrolizumab and nivolumab AE profiles explained by difference in backbone chemotherapy and includes a scenario assuming AEs equal pembrolizumab vs nivolumab. EAG does not exclude possibility AE profile difference caused by pembrolizumab or nivolumab themselves. Area of uncertainty for this comparison.

Are pembrolizumab and nivolumab similarly tolerable?

Abbreviations: AE, adverse event; CAPOX, capecitabine and oxaliplatin; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; FP, cisplatin and 5-fluorouracil

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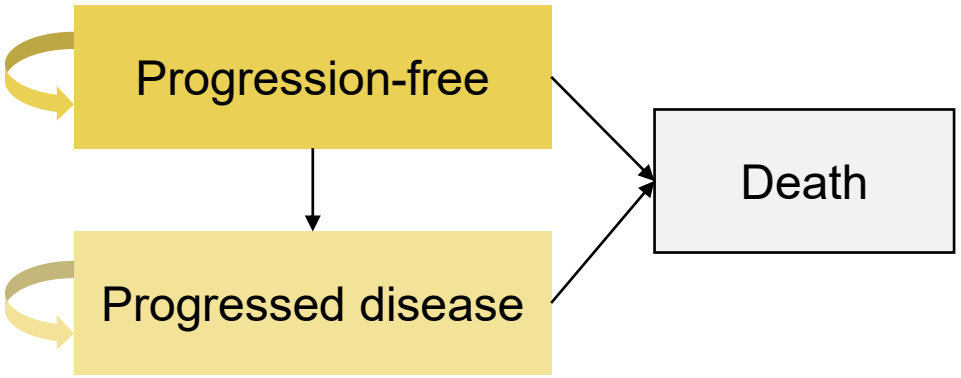
Company's model overview

Model structure: partitioned survival



Baseline patient characteristics included in the model

Baseline patient characteristic	CPS ≥1	CPS≥10 (used for ≥ 5)
Age, years	60.1	60.7
Proportion of females	29.6%	27.8%
Weight, kg	66.3	66.7

Time horizon: 30 years (lifetime)

	CPS≥1		CPS ≥5	
	Pembrolizumab + chemotherapy	Chemotherapy	Pembrolizumab + chemotherapy	Nivolumab + chemotherapy
PFS	KEYNOTE-859 with extrapolation		CPS ≥10 from KEYNOTE-859 with extrapolation	Applied HR for OS (from CPS ≥10 ITC) to pembrolizumab PFS curve
OS	KEYNOTE-859 with extrapolation		CPS ≥10 from KEYNOTE-859 with extrapolation	Applied HR for OS (from CPS ≥10) ITC to pembrolizumab OS curve
ToT	Kaplan Meier from KEYNOTE-859 costs of chemotherapy capped at 6 treatment cycles			Assumed same as pembrolizumab in absence of data

Abbreviations: CPS, combined positive score; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; QoL, quality of life; ToT, time on treatment

Key issue: Treatment effect waning*

Company and EAG disagree on treatment waning assumption

Background

- Company assume there is no treatment effect waning in the base-case analysis
- Provided a scenario analysis that applied gradual treatment waning effect 7 years after treatment initiation

Company

- No clear evidence to indicate a treatment effect waning based on the independent estimation of survival curves for the intervention and comparator arms
- Clinical experts concluded that the expected long-term shape of the pembrolizumab + chemotherapy OS curves relative to the doubled chemotherapy OS curve would diverge over time
- Absent from the base-case analysis in TA857 - no evidence of treatment waning effect in CheckMate-649

EAG comments

- Reasonable to assume that the treatment effect will remain for a certain period after treatment with pembrolizumab has stopped, but not lifetime
- Decision making ICER in TA857 included treatment effect waning assumption for nivolumab + chemotherapy
- Scenario analysis explored by the company is conservative, prefers scenario when waning starts at 5 years rather than after 7 years and treatment effect reduces to same as chemotherapy over 2 years

Is it appropriate to apply a treatment waning effect?

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival

* See appendix – Recent NICE appraisals

Treatment waning assumptions from previous appraisals

Treatment effect waning assumptions were considered in a related appraisal

Technology appraisal	Company preferred assumption	EAG preferred assumption
ID4030 (current appraisal)	No treatment effect waning in base-case analysis. Scenario: treatment waning starts at 7 years after treatment initiation then treatment effect gradually reduces to same as the comparator arm over the next 2 years	Treatment waning starts at 5 years after treatment initiation then treatment effect gradually reduces to same as the comparator arm over the next 2 years
TA857*	Treatment waning starts 6.5 years after treatment initiation, at this point the hazard of dying becomes the same as the comparator arm	Treatment waning starts 5 years after treatment initiation, at this point the hazard of dying becomes the same as the comparator arm

*Nivolumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma (January 2023)

Key issue: Time on treatment – doublet chemotherapy*

Chemotherapy cycle cap may not have been applied in KEYNOTE-859

Background

- In the company base-case, a cap of 6 cycles was added for all patients receiving doublet chemotherapy

Company

- In NHS clinical practice, cisplatin and oxaliplatin are capped at 6 cycles
- In the KEYNOTE-859 trial, cisplatin or oxaliplatin treatment may be capped at 6 cycles per local standard
- All doublet chemotherapy regimens in the model are capped at 6 cycles in the base case, without adjustment for efficacy

EAG comments

- In KEYNOTE-859, local policy was followed for the maximum number of doublet chemotherapy cycles
- For some of these treatments the number of cycles far exceeded the NHS limit of 6 treatment cycles
- Capping regimens at 6 cycles does not account for the fact the observed OS and PFS in both treatment arms of the KEYNOTE-859 trial were based on patients receiving chemotherapy for much longer
- OS and PFS curves from KEYNOTE-859 may be higher than what would be observed in clinical practice
- Unable to assess if and how exactly this bias will affect the comparative effectiveness evidence presented

Do the modelled overall survival estimates reflect what would be expected in the NHS?

Is a chemotherapy cycle cap applied in NHS practice?

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

* See appendix – Time on treatment – KEYNOTE-859

QALY weightings for severity

- For the CPS ≥1 population, both the company and EAG calculated a QALY severity weight of 1.2 was applicable in accordance with NICE methods. This assumed people with the condition had doublet chemotherapy as current care.
- However, the company applied a 1.7 QALY weight to their base-case analysis for the CPS ≥1 population, but provided a scenario where a 1.2 QALY weight was used.
- The EAG applied a 1.2 QALY weight to their exploratory base-case for the CPS ≥1 population.
- For the CPS ≥10 population (company proxy for CPS ≥5 population) both the company and EAG determined a QALY weighting was not applicable. This assumed that people with the condition had nivolumab plus doublet chemotherapy as current care.

* See appendix – QALY weightings

Abbreviations: CPS, combined positive score; QALY, quality-adjusted life year

Summary of company and EAG base case assumptions*

Different assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Treatment waning	No treatment waning	Initiation of waning effect after 5 years, completion after 2 subsequent years
QALY severity weight (for CPS ≥1 population only)	QALY weight of 1.7	QALY weight of 1.2

- EAG had concerns about the following company assumptions, but not changed in its exploratory base case
  - Exchangeability of treatment effectiveness across CPS populations. EAG base case used company model for comparison with nivolumab which applied hazard ratios derived from CPS ≥10 NMA
  - Methods for indirect comparison of pembrolizumab + doublet chemotherapy with nivolumab + doublet chemotherapy
  - The EAG also commented that the duration of chemotherapy in the trials may not be generalisable to NHS clinical practice so the estimated overall survival estimates may be overestimated.
- EAG noted some uncertainty regarding applying a one-off cost at disease progression subsequent treatment costs and the modelled different rates of modelled adverse events with pembrolizumab and nivolumab

* See appendix – QALY weightings and Subsequent treatment costs

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Abbreviations: CPS, combined positive score; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; QALY, quality-adjusted life year

Summary of cost-effectiveness results

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

CPS ≥1 population

- When using a x1.2 QALY modifier, company ICER increases to over £30,000 per QALY gained, both with and without comparator discounts
- EAG exploratory base case is also over £30,000 per QALY gained and higher than company's

CPS ≥10 population (company uses as a proxy for CPS >5)

- Both the company and EAG base case ICERs are over £30,000 per QALY gained for the comparison between pembrolizumab + chemotherapy vs. nivolumab + chemotherapy. The total costs of pembrolizumab + chemotherapy are higher than the total costs of nivolumab + chemotherapy

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

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Thank you.

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

Supplementary appendix

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Equality considerations

- **No equality issues were raised by the company, EAG or stakeholders during the appraisal process**

Recent NICE appraisals for HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma

Recent NICE appraisals

Technology appraisal	Drug	Recommendation
Nivolumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma, NICE TA857 (January 2023)	Nivolumab	Nivolumab with platinum- and fluoropyrimidine-based chemotherapy is recommended, within its marketing authorisation, as an option for untreated HER2-negative, advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma in adults whose tumours express PD-L1 with a combined positive score (CPS) of 5 or more.

Assumptions in previous appraisals

Assumption	Nivolumab (TA857)
Treatment waning	5- and 6.5-year treatment waning assumptions are potentially plausible, but uncertain. No evidence underpinning either the 5- or 6.5-year treatment waning assumption or a lifetime treatment effect.
Willingness-to-pay threshold	An ICER well below £50,000 per QALY gained is needed for this technology to be considered cost effective

Abbreviations: HER2, human epidermal growth factor receptor 2; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Link to – Key issue: Treatment waning and Key issue: QALY weight

Detailed clinical trial results – KEYNOTE-859

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

Outcome: Overall survival (CPS ≥1 population)	Pembrolizumab + doublet chemotherapy (n=618)	Doublet chemotherapy + placebo (n=617)
Median OS (95% CI)	13.0 months	11.4 months
OS – 6 months (95% CI)	79.0% (75.5 to 82.0)	75.7% (72.1 to 78.9)
OS – 18 months (95% CI)	38.4% (34.6 to 42.3)	26.6% (23.2 to 30.2)
OS – 30 months (95% CI)	23.9% (20.3 to 27.6)	12.3% (9.6 to 15.4)
HR (95% CI; p-value)	0.74 (0.65 to 0.84), p < 0.0001	
Outcome: Progression-free survival (CPS ≥1 population)	**Pembrolizumab + doublet chemotherapy (n=618)**	**Doublet chemotherapy + placebo (n=617)**
Median PFS (95% CI)	6.9 months (6.0 to 7.2)	5.6 months (5.4 to 5.7)
PFS – 6 months (95% CI)	54.4% (50.1 to 58.4)	43.4% (39.3 to 47.5)
PFS – 18 months (95% CI)	21.2% (17.7 to 24.9)	10.4% (7.7 to 13.6)
PFS – 30 months (95% CI)	16.6% (13.2 to 20.3)	7.3% (4.7 to 10.5)
HR (95% CI; p-value)	0.72 (0.63 to 0.82), p < 0.0001	

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

Link to – Key clinical trial results

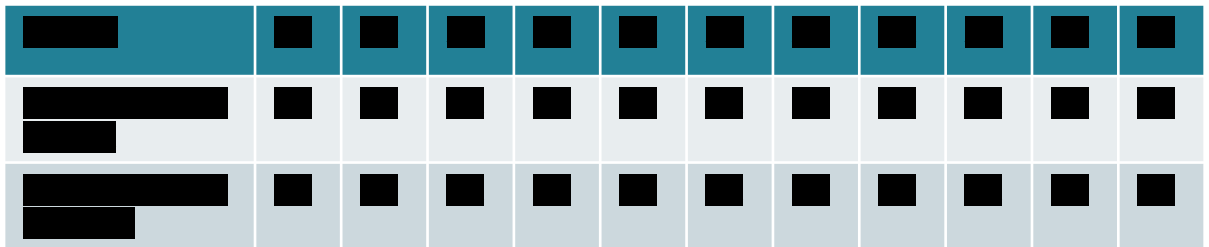
KEYNOTE-859 CPS≥5 post-hoc analysis

Pembrolizumab + doublet chemotherapy (n=379) improves OS and PFS compared to placebo + doublet chemotherapy (n=388)

Overall survival

At risk

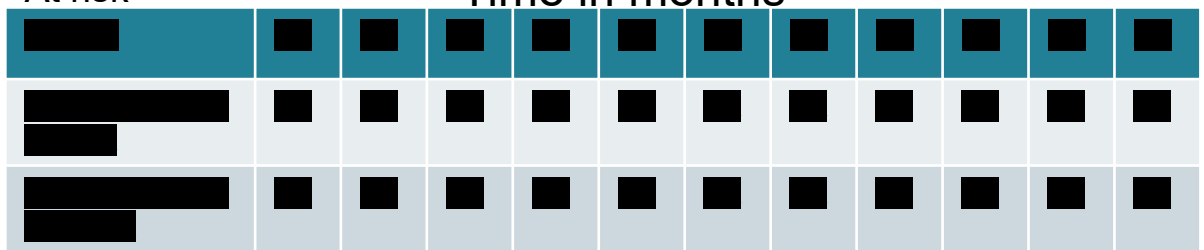
Time in months



Progression free survival

At risk

Time in months



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

Link to – NMA methods

Proportional hazard assumptions analysis

Analysis indicates proportional hazards assumption may not be valid for OS

OS CPS≥1 cumulative hazard plot and log-log plot

[redacted]

Company

- Evidence that hazards may not be proportional at the start of the trial as the curves overlap
- Flattening of the curves between weeks 150 and 200 suggests a change in the hazard, but this is likely due to the small number of patients left at risk in the trial

Abbreviations: CPS, combined positive score; OS, overall survival

Link to – Key issue: Proportional hazard assumptions

Proportional hazard assumptions analysis

Analysis indicates proportional hazards assumption may not be valid for OS

OS CPS≥1 Schoenfeld Residuals plot

Company

- There is some divergence from zero during the latter part of the curve.
- The test was found to be significant (p=0.0248)
- This provides additional evidence that the proportional hazard assumption may not be valid

Abbreviations: CPS, combined positive score; OS, overall survival

Link to – Key issue: Proportional hazard assumptions

How company incorporated evidence into model

Input and evidence sources

Input	Assumption and evidence source
Baseline characteristics	KEYNOTE-859 trial
Intervention efficacy	OS – KEYNOTE-859 pembrolizumab + doublet chemotherapy arm PFS – KEYNOTE-859 pembrolizumab + doublet chemotherapy arm
Comparator efficacy	Chemotherapy OS – KEYNOTE-859 doublet chemotherapy + placebo arm Chemotherapy PFS – KEYNOTE-859 doublet chemotherapy + placebo arm Nivolumab OS – Hazard ratio from NMA of nivolumab and doublet chemotherapy compared to pembrolizumab + doublet chemotherapy Nivolumab PFS – Hazard ratio from NMA of nivolumab and doublet chemotherapy compared to pembrolizumab + doublet chemotherapy
Utilities	EQ-5D-5L data collected from patients in the KEYNOTE-859 trial mapped onto the 3L value set
Costs	National Schedule of NHS Costs, Unit Costs of Health and Social Care, BNF, eMIT
Resource use	Informed by the literature, previous NICE appraisals such as TA857, or clinical expert opinion

Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival

Model extrapolation: company explored fitting standard parametric distributions and 1- 2- or 3-knot spline

	Model used	EAG comments
OS CPS ≥ 1	**Independent 2 knot hazard spline**. Proportional hazards does not hold so separate model fitted to each arm. • Pembrolizumab + chemotherapy: 2-knot hazard spline lowest AIC and strong fit to the observed KM data • Chemotherapy: Although odds spline model had a low AIC, 2-knot hazard preferred on visual fit	2-knot hazard spline reasonable EAG considered use of 3 knot-spline
PFS CPS ≥ 1	**Independent 1 knot hazard spline** (company stated proportional hazard assumption held but still fitted separate model)	Does not agree 1-knot model has best fit - prefers 2- or 3-knot, but accepted that company chose to1-knot model to stop PFS and OS curves crossing
OS CPS ≥ 10	Independent 2 knot hazard spline (pembrolizumab)	
PFS CPS ≥ 10	Independent 1 knot hazard spline (pembrolizumab)	

Abbreviations: AIC, Akaike information criterion; CPS, combined positive score; KM, Kaplan–Meier; OS, overall survival; PFS, progression free survival

Modelled OS in company base case - CPS ≥1 population

[redacted]

Year	Expert A	Expert B	Expert C
2	≤ 20%	<20%	15%
5	<5 %	3 to 4%	<1%
10	0%	0%	0%

Company clinical expert expectations of survival on doublet chemotherapy

Abbreviations: CPS, combined positive score; KM, Kaplan–Meier; OS, overall survival

Modelled OS curves in company base case CPS ≥ 10 population

Abbreviations: CPS, combined positive score; KM, Kaplan–Meier; OS, overall survival

Time-varying HR NMA results - CPS ≥1 population

Modelled overall survival curves with 95% CI

*Statistically significant at the 0.05 significance level

^Results at 48 months estimated based on model extrapolations

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

Key issue: Uncertainty on long-term OS and treatment effect

Only interim analysis from KEYNOTE-859 was available at company submission

Background

- Data cut for the interim analysis of the KEYNOTE-859 trial was 3 October 2022
- More mature data from the KEYNOTE-859 trial was not available at the time of company submission

EAG comments

- Survival data and other efficacy outcomes from the CS are not relatively mature
- During the clarification stage, the EAG requested more mature data from the KEYNOTE-859 trial for all outcomes reported
- The company stated that more mature data from the KEYNOTE-859 trial is not available

Company

- Pembrolizumab plus chemotherapy was associated with a statistically significant improvement in OS when compared with chemotherapy alone: HR 0.74 (95% CI: 0.65 to 0.84; p<0.0001)
- Additional longer term follow-up data has become available following the clarification stage

Is there enough certainty on long-term OS for the committee to make a preferred assumption?

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

Time on treatment – KEYNOTE-859

Length of some doublet chemotherapy treatments exceeded 6 cycles

ToT pembrolizumab + doublet chemotherapy CPS ≥1

ToT doublet chemotherapy CPS ≥1

EAG comments

- It is clear from the curves that for some of these treatments the number of cycles far exceeded the NHS limit of 6 treatment cycles (12-18 weeks)

Abbreviations: 5-FU, 5-fluorouracil; CAPOX, capecitabine and oxaliplatin; CPS, combined positive score; FP, cisplatin and 5-fluorouracil; KM Kaplan Meier; ToT, time on treatment

*Link to – Key issue: Time on treatment

Subsequent treatment costs

How one-off cost of subsequent treatments per treatment arm used in the economic model

Treatment arm	NHS practice (base-case)		Trial data (scenario analysis)	
	List prices	Including CAA price for pembrolizumab	List prices	Including CAA price for pembrolizumab
Pembrolizumab + doublet chemotherapy*	£16,779	£16,779^	£48,060	[redacted]
Doublet chemotherapy + placebo	£35,203	[redacted]	£58,281	[redacted]

*For nivolumab plus doublet chemotherapy, subsequent treatment costs were assumed equal to pembrolizumab plus doublet chemotherapy subsequent treatment costs
^No subsequent usage of pembrolizumab is assumed in NHS practice according to clinical experts

Company

- To cost the overall survival benefits of subsequent treatment lines in the trial, the economic model applied a one-off cost upon progression as a simplifying assumption. The costs included treatments used in the NHS.

EAG comments

- Assumption may be too simplistic to capture impact of subsequent treatments on costs and health gains

Abbreviations: AEs, adverse events; CAA, commercial access agreement SD, standard deviation

*Link to – Base case assumptions

Utility values – time-to-death vs health state approach

Average utility for each approach to include utility in model (CPS ≥1)

Treatment arm	Time to death	Health State	General population (60.1 years)
Pembrolizumab + doublet chemotherapy	[redacted]	[redacted]	0.8434
Doublet chemotherapy	[redacted]	[redacted]	

Company

- Due to the limited collection of assessments with PD, health state utilities from the KEYNOTE-859 trial data may only reflect QoL in proximity to the progression event rather than the entirety of progressed disease
- [redacted] compared to those identified in literature (0.577 to 0.600) and are informed by relatively fewer records and patients than PF utility values
- Time-to-death approach used in the base case analysis rather than health state approach

EAG comments

- Little difference in terms of economic outcomes between two approaches
- Agreed that time-to-death approach may be better in capturing the QoL for progressed patients

NICE

Abbreviations: AE, adverse event; CPS, combined positive score; PD, progressive disease; PF, progression free, QoL, quality of life

Utility values used in company base case – CPS ≥1 population

Treatment arm	Time to death	Utility value	Justification
Pembrolizumab + doublet chemotherapy	≥360 days to death	[redacted]	• Time-to-death method addresses the issue with the data collection schedule (small number of PD assessments) • AE disutility values are applied as a one-off QALY loss in the first model cycle to account for different AE profiles. • Time-to-death utility values and AE disutility values are obtained from the KEYNOTE-859 trial to reduce heterogeneity.
	180 to 359 days to death	[redacted]	
	30 to 179 days to death	[redacted]	
	<30 days to death	[redacted]	
	One-off QALYs loss	[redacted]	
Doublet chemotherapy	≥360 days to death	[redacted]	
	180 to 359 days to death	[redacted]	
	30 to 179 days to death	[redacted]	
	<30 days to death	[redacted]	
	One-off QALYs loss	[redacted]	

Background

- Time-to-death approach estimates utilities using time intervals that describe life expectancy rather than progression status
- Death events can arise from both PF and PD health states
- Time intervals shown pre-specified time intervals used as a standard approach in the company's trials

NICE

Abbreviations: AE, adverse event; CPS, combined positive score; PD, progressive disease; PF, progression free; QALY, quality-adjusted life year

Utility values used in company base case – CPS ≥10 population

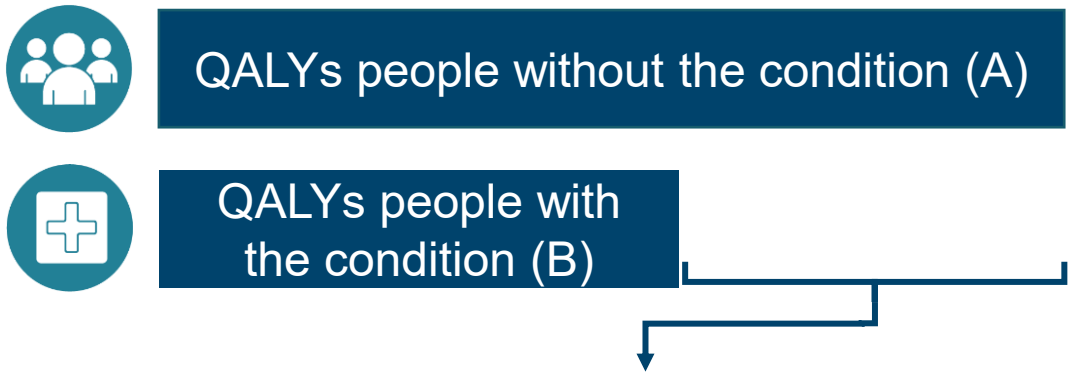
Treatment arm	Time to death	Utility value	Justification
Pembrolizumab + doublet chemotherapy	≥360 days to death	[redacted]	• Time-to-death method addresses the issue with the data collection schedule (small number of PD assessments) • AE disutility values are applied as a one-off QALY loss in the first model cycle to account for different AE profiles. • Time-to-death utility values and AE disutility values are obtained from the KEYNOTE-859 trial to reduce heterogeneity.
	180 to 359 days to death	[redacted]	
	30 to 179 days to death	[redacted]	
	<30 days to death	[redacted]	
	One-off QALYs loss	[redacted]	
Nivolumab + doublet chemotherapy	≥360 days to death	[redacted]	
	180 to 359 days to death	[redacted]	
	30 to 179 days to death	[redacted]	
	<30 days to death	[redacted]	
	One-off QALYs loss	[redacted]	

*Nivolumab plus doublet chemotherapy utility assumed to equal pembrolizumab plus doublet chemotherapy

Abbreviations: AE, adverse event; CPS, combined positive score; PD, progressive disease; QALY, quality-adjusted life year

QALY weightings for severity (1/2)

Severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Abbreviations: QALY, quality-adjusted life year

Link to – QALY weightings for severity

QALY weightings for severity (2/2)

Shortfall measurement meeting QALY weight criteria

Background

- Total lifetime QALYs associated with only doublet chemotherapy treatment were obtained from the model results of the base-case analysis
- Estimated total QALYs for the general population reflected the baseline characteristics of the KEYNOTE-859 trial and the economic analyses
- 29.6% female and 60.1 years for people with CPS ≥1; 27.8% female and 60.7 years for patients with CPS ≥10

	Current treatment	QALYs of people without condition	QALYs with the condition on current treatment	**Absolute QALY shortfall**	**Proportional QALY shortfall**	**QALY weight**
Company CPS ≥ 1 population	Doublet chemo	12.40	[redacted]	[redacted]	[redacted]	1.2
Company CPS ≥ 10 population	Nivolumab + doublet chemo	12.40	[redacted]	[redacted]	[redacted]	1.0
EAG CPS ≥ 1 population	Doublet chemo	12.40	[redacted]	[redacted]	[redacted]	1.2
EAG CPS ≥ 10 population	Nivolumab + doublet chemo	12.40	[redacted]	[redacted]	[redacted]	1.0

Abbreviations: CPS, combined positive score; QALY, quality-adjusted life year

Link to – QALY weightings for severity

Company uses an alternative QALY weighting for severity in the CPS≥ 1 group outside of NICE methods in base case

Background

- Severity modifier methods has replaced previous end of life criteria in NICE methods manual 2022
- Previous methods allowed application of a 1.7 QALY weighting if life expectancy of population < 24 months and new treatment extended life by 3 months

Company

- Current appraisal would have met the previous end-of-life criteria (based on NMA results and a visual inspection of the naïve curves from CheckMate-649 and KEYNOTE-859)
- In TA857 nivolumab + chemotherapy met end of life criteria [in the PD-L1 CPS ≥ 5 group]
- Despite the results of the QALY shortfall analysis, a QALY weight of 1.7 should be used in people expressing CPS ≥1 (used for company base case analysis)

EAG comments

- Up-to-date NICE methods should be applied in the current appraisal
- A QALY weight of 1.2 should be used in people expressing CPS ≥1 (used for EAG base case analysis)

Link to – QALY weightings for severity

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

QALY weightings for severity – company and EAG differences

EAG comments

- QALY shortfall results were validated with the Institute for Medical Technology Assessment Disease Burden Calculator
- Results presented by the EAG are broadly in line with those presented by the company in for both people expressing CPS ≥1 and CPS ≥10 (as a proxy for CPS ≥5)
- Minor differences observed are likely due to:
  - Using different utility sources and/or life tables to estimate expected QALYs for the total population
  - Using the PSA results from company model to estimate the QALYs under doublet chemotherapy for CPS ≥1 population and nivolumab plus doublet chemotherapy for CPS ≥10
- Regarding uncertainty around QALY weights:
  - CPS ≥1 population – severity modifier of 1.2 would apply in 100.0% of simulations (no uncertainty)
  - CPS ≥10 population – severity modifier of 1.0 would apply in 97.2% of the simulations

Link to – QALY weightings for severity

Abbreviations: CPS, combined positive score; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year