Pembrolizumab with trastuzumab and chemotherapy for untreated HER2-positive advanced gastric or gastro-oesophageal junction cancer (ID3742)

For zoom –
No ACIC

Technology appraisal committee A [13 February 2024]

Chair: Radha Todd

External assessment group: ScHARR

Technical team: Zain Hussain, Lizzie Walker, Ian Watson

Company: Merck Sharp & Dohme (UK) Limited

Pembrolizumab with trastuzumab and chemotherapy for untreated HER2-positive advanced gastric or gastro-oesophageal junction cancer (ID3742)

- ✓ ACM1 recap
  - Draft guidance recommendations
  - Issues from ACM1 and committee's key conclusions
- ❑ ACM2
  - Overview of MSD's consultation response and EAG critique
  - KEYNOTE-811 primary outcome results – Interim analysis 3 data
  - Issue: OS extrapolations
  - Issue: PD-L1 testing costs
  - Base case assumptions and cost-effectiveness results
  - Other considerations: Equality, innovation, managed access and severity
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Draft guidance (DG) recommendations

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

HER2: Human epidermal growth factor receptor 2; OS: PD-L1: Programmed death-ligand 1

Issues from ACM1 and committee's key conclusions

Issue	Committee's conclusion	DG section
Post hoc analysis to define the non-Asia cohort	Non-Asia cohort is generalisable to NHS clinical practice and is appropriate for decision-making	3.5
OS extrapolation	Unable to determine the most appropriate overall survival extrapolations ➔ Requested additional analyses using interim analysis 3 (IA3) of KEYNOTE-811	3.7
Utility analysis	Preferred approach to utility values was a time-to-death approach using linear mixed effect regression modelling	3.8
PD-L1 testing	PD-L1 testing costs should be included in the economic model	3.11
Trastuzumab administration costs	Costs for trastuzumab administration provided by the NHS England CDF lead is appropriate for decision-making	3.9
TTD for trastuzumab	Time-to-treatment discontinuation curve from KEYNOTE-811 with no cap applied is appropriate	3.10
Severity modifier	Severity weight of 1.2 applied to the QALYs was appropriate	3.12

***Consultation comments received from MSD only. No comments received from any other stakeholders**

Abbreviations: ACM1: Appraisal committee meeting 1; CDF: Cancer Drugs Fund; DG: Draft guidance; OS: Overall survival; PD-L1: Programmed death-ligand 1; QALYs: Quality-adjusted life years; TTD: Time-to-treatment discontinuation

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Overview of MSD's consultation response and EAG critique
Issues remaining for discussion post consultation

Company response	EAG critique summary	Resolved?	ICER impact
Updated OS extrapolation using IA3 • **Pembrolizumab plus SoC:** 2-knot odds spline • **SoC:** Weibull	Agrees with modelling approach but not model choices • **Pembrolizumab plus SoC:** 1-knot hazards spline • **SoC:** 1-knot normal spline	No – for discussion	Large
Prefers not to include PD-L1 testing costs in HER2 positive patients	Assume 100% sequential testing in its base case	No – for discussion	Small

See appendix for resolved issues

Consultation comments received from MSD only. No comments received from any other stakeholders

HER2: Human epidermal growth factor receptor 2; IA3: Interim analysis 3; ICER: Incremental cost-effectiveness ratio; OS: Overall survival; PD-L1; Programmed death-ligand 1; SoC: Standard of care

KEYNOTE-811 Primary outcome results: ITT population

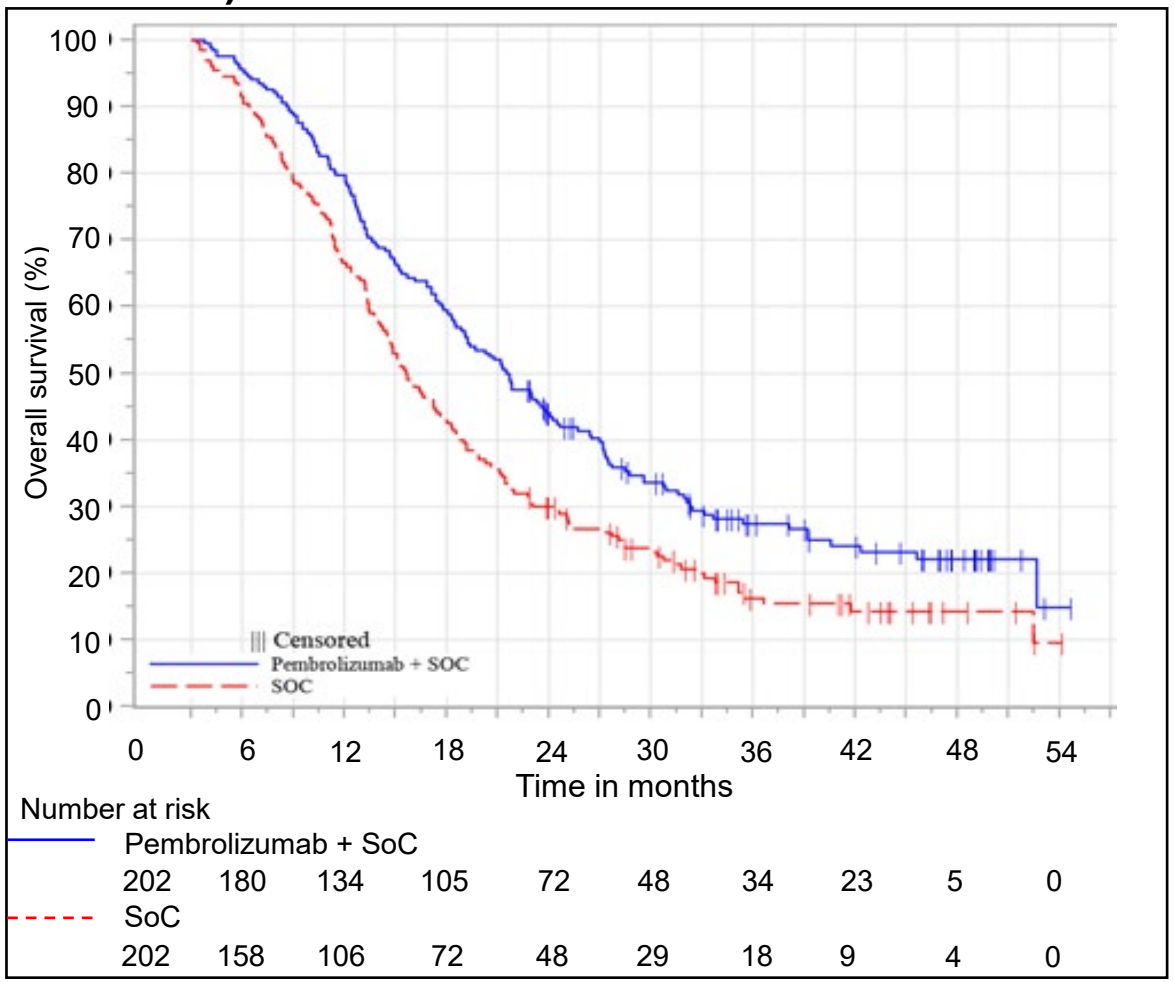
Updated using interim analysis 3 data (data cut off: 29 March 2023)

Table: KEYNOTE-811 primary outcome results – Non-Asia region PD-L1 positive with CPS ≥ 1

	Pembrolizumab + SoC (N=202)	SoC (N=200)
Progression-free survival		
Events, n (%)	155 (76.7)	161 (80.5)
Median, months (95% CI)	9.9 (8.3, 11.4)	6.4 (5.6, 7.4)
Hazard ratio (95% CI, p-value)	**0.64 (0.51, 0.80; <0.0001)**	
Overall survival		
Events, n (%)	149 (73.8)	165 (82.5)
Median, months (95% CI)	18.6 (15.5, 21.2)	12.6 (11.1, 14.9)
Hazard ratio (95% CI, p-value)	**0.70 (0.56, 0.87; 0.0007)**	

See appendix 'KEYNOTE-811 study design and baseline characteristics'

Figure: KEYNOTE-811 KM curve of OS (CPS ≥1, non-Asia)



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CI: Confidence interval; CPS: Combined positive score; ITT: Intention-to-treat; KM: Kaplan-Meier; OS: Overall survival; PD-L1; Programmed death-ligand 1; SoC: Standard of care

Large impact on ICER

Issue: OS extrapolations (1/5)

See appendix for alternative OS extrapolation and slide 'Issues for discussion'

Draft guidance committee conclusion:

- "Unable to determine the most appropriate overall survival extrapolations and requested additional analyses using interim analysis 3 of KEYNOTE-811. It also requested that the company provides clear justification for its choice of overall survival extrapolations, including validation with clinical experts"

Company's consultation response:

- Standard parametric survival models and flexible spline models independently fitted to each arm of the KEYNOTE-811 study using IA3 data cut:
- **For pembrolizumab plus SoC arm, company prefers the 2-knot odds spline model**
  - Higher OS estimates (15% at 5 years and 7% at 10 years) than seen in current clinical practice supported by step change in treatment paradigm with pembrolizumab plus SoC and established pattern of survival tails seen with pembrolizumab use in other cancers
  - In validation interviews with 11 clinical experts choosing between 2-knot odds spline model (company's updated base case) and 1-knot hazard spline model (EAG's base case at ACM1), 9 experts selected 2-knot odds spline model as more plausible, and 2 experts were uncertain
- **For the SoC arm, the company prefers the Weibull model**
  - Clinical advice suggests survival to 5 years is uncommon ➔ Weibull model more plausible
  - In validation interviews with 11 clinical experts choosing between Weibull model (company's updated base case) and 1-knot normal spline model (EAG's base case at ACM1), 9 experts selected Weibull curve, 1 expert selected 1-knot normal spline and 1 expert was indifferent

ACM1: Appraisal committee meeting 1; IA3: Interim analysis 3; ICER: Incremental cost-effectiveness ratio; OS: Overall survival; SoC: Standard of care

Large impact on ICER

Issue: OS extrapolations (2/5)

EAG critique of company's consultation response

- Agree with company's approach of independently fitted models to extrapolate OS, but disagree with model choice for both the pembrolizumab plus SoC arm and the SoC arm
- **For pembrolizumab plus SoC arm, EAG prefers the 1-knot hazard spline model fitted to IA3 data**
  - Company's preferred 2-knot odds spline predicts 3% survival at 20-years (80 years old in model) and 1% survival at 40-year (100 years old in model) → unclear if clinically plausible
  - In EAG base case, the risk of death greater in pembrolizumab plus SoC arm versus SoC arm at approximately 10 years, so capped the hazards in the pembrolizumab plus SoC arm so that they do not exceed hazards modelled in the SoC arm at any time point ➔ Minimal impact as only approximately 2% patients alive at 10 years
  - Acknowledges the plausibility of a long-term survival benefit at 5 and 10 years based on clinical advice
- **For SoC arm, EAG prefers the 1-knot normal spline model fitted to IA3 data**

See appendix for alternative OS extrapolation and slide 'Issues for discussion'

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IA3: Interim analysis 3; HR: Hazard ratio; ICER: Incremental cost-effectiveness ratio; OS: Overall survival; SoC: Standard of care

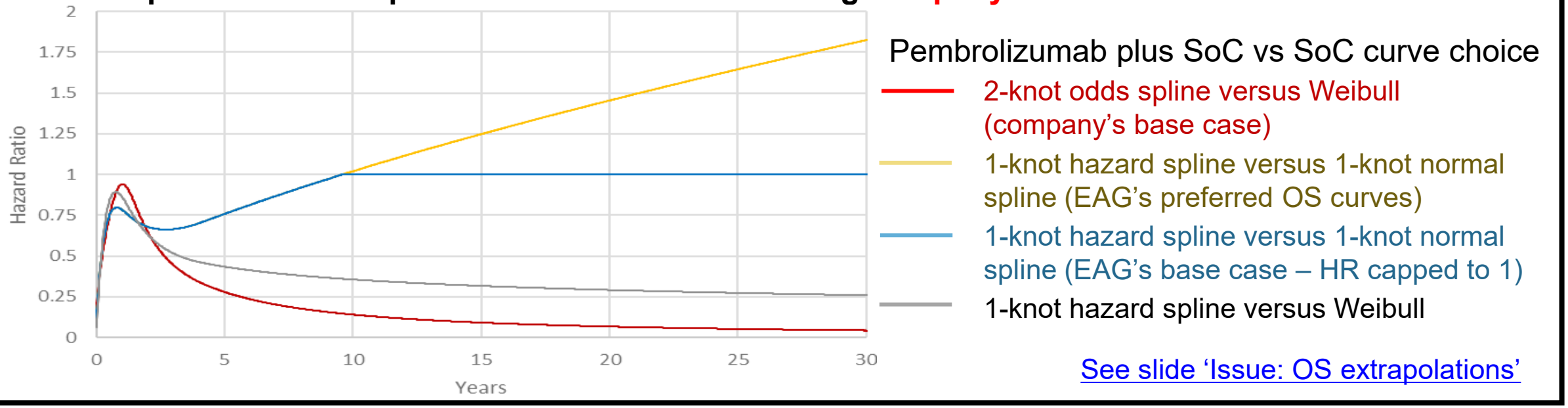
Large impact on ICER

Issue: OS extrapolations (3/5)

EAG critique of company's consultation response (continued)

- Company's base case (2-knot odds spline) for pembrolizumab plus SoC and Weibull for SoC leads to a continuously decreasing HR and pembrolizumab plus SoC becomes more effective in the longer term
- Most patients had progressed by year 4, but the HR continues to decline after this time → company's base case model choice for the 2 arms is not clinically plausible
- Similar trend of HR is also observed when using the EAG's base case for pembrolizumab plus SoC (1-knot hazard spline model) and the company's base case for SoC (Weibull model)

HRs for pembrolizumab plus SoC and SoC for OS using company's and EAG's model choice



See slide 'Issue: OS extrapolations'

For clinical experts: Is it plausible that: 1) pembrolizumab plus SoC would show a survival benefit over SoC 10 years after treatment initiation? 2) the relative benefit of pembrolizumab plus SoC over SoC would increase over time?

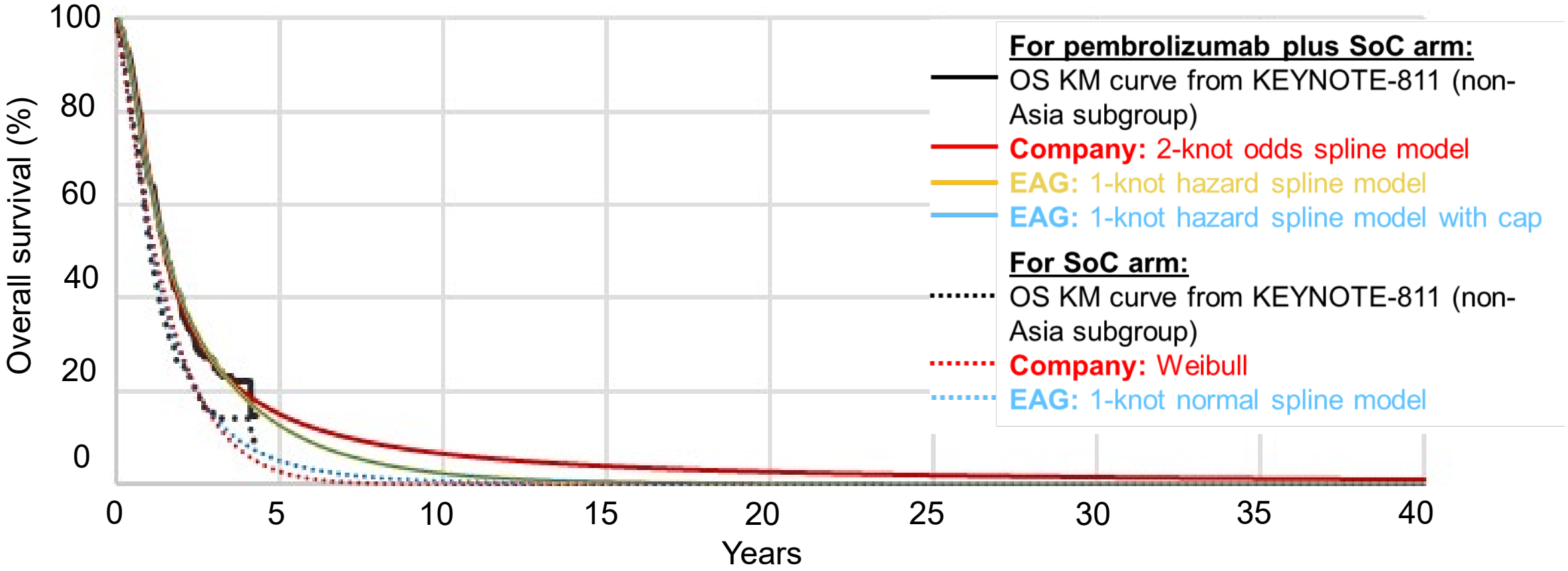
Large impact on ICER

Issue: OS extrapolations (4/5)

Company and EAG preferred OS curves same as ACM1

See appendix for alternative OS extrapolation and slide 'Issues for discussion'

Figure: Company and EAG's base case OS curves for pembrolizumab plus SoC arm and SoC arm (updated using IA3 data cut)



Note: Curves for EAG base case with cap (blue) and scenario without cap (yellow) for pembrolizumab plus SoC arm are overlapping, so curve appears green

IA3: Interim analysis 3; ICER: Incremental cost-effectiveness ratio; KM: Kaplan-Meier; OS: Overall survival; SoC: Standard of care

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Large impact on ICER

Issue: OS extrapolations (5/5)

At 5- and 10-year timepoints, company's predicted OS is higher for pembrolizumab plus SoC arm and lower for SoC arm compared with EAG's predictions

Table: OS estimates from KEYNOTE-811, clinical expert opinion and company and EAG base cases

	Expected survival probability					Predicted survival probability	
Timepoint	KEYNOTE-811 (updated IA3 data cut)	Company's expert 1	Company's expert 2	EAG's expert 1	EAG's expert 2	Company's ACM2 base case (2-knot odds spline)	EAG's ACM2 base case (1-knot hazard spline)
Pembrolizumab plus SoC arm							
1 year	66%	NE	NE	NE	NE	68%	68%
2 years	40%	NE	NE	NE	NE	41%	42%
5 years	NA	NA	NA	5-10%	0%	15%	13%
10 years	NA	NA	NA	1%	0%	7%	2%
SoC arm							
Timepoint	KEYNOTE-811 (updated IA3 data cut)	Company's expert 1	Company's expert 2	EAG's expert 1	EAG's expert 2	Company's ACM2 base case (Weibull)	EAG's ACM2 base case (1-knot normal spline)
1 year	53%	NE	NE	NE	NE	57%	55%
2 years	27%	NE	NE	NE	NE	29%	28%
5 years	NA	5%	2-5%	≤5%	0%	3%	5%
10 years	NA	2%	0-1%	0%	0%	0%	0.8%

See appendix for alternative OS extrapolation and slide 'Issues for discussion'

Which survival models provide the most plausible long-term OS extrapolations?
- 2-knot odds spline (pembrolizumab + SoC arm) and Weibull (SoC arm) **– Company base case**
- 1-knot hazard spline (pembrolizumab + SoC arm) and 1-knot normal spline (SoC arm) **– EAG base case**

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ACM2: Appraisal committee meeting 2; IA3: Interim analysis 3; NA: Not applicable; NE: Not evaluated; OS: Overall survival; SoC: Standard of care;

Small impact on ICER

Issue: PD-L1 testing costs

See slide 'Issues for discussion'

Draft guidance committee conclusion:

- "PD-L1 testing costs should be included in the economic model"

Company's consultation response:

- PD-L1 testing costs included in both arms in base case
- Clinical advice confirms that PD-L1 and HER2 testing usually occurs in parallel (PD-L1 and HER2 testing at same time), so PD-L1 testing already occurs in clinical practice so PD-L1 testing costs should not be included in economic model
  - Of 22 clinical experts with varying speciality across 21 clinical centres:
    - 77% did parallel testing
    - 22% did PD-L1 testing post-HER2 testing; 2 planned to move to parallel testing
  - Market research with 50 respondents across more than 27 UK centres found 92% did parallel testing
- Provided scenario analysis with PD-L1 testing costs for pembrolizumab plus SoC arm only

EAG critique of company's consultation response

- PD-L1 testing costs for pembrolizumab plus SoC arm only (so, PD-L1 testing not clinical practice currently)
- Provided a scenario analysis exploring company's position of vast majority of centres already testing for PD-L1 at same time as do HER2 testing
  - Scenario with 92% of centres already testing for PD-L1 ➔ Provides a lower limit for the incremental costs of PD-L1 testing

Has the committee seen any evidence to change its view at ACM1 that PD-L1 testing costs should be included in the model?

CPS: Combined positive score; DG: Draft guidance; GOJ: Gastro-oesophageal junction; HER2: Human epidermal growth factor receptor 2; PD-L1; Programmed death-ligand 1

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Differences between company and EAG base case assumptions at ACM2

Parameter	Company	EAG
OS extrapolations	**Pembrolizumab plus SoC:** 2-knot odds spline **SoC:** Weibull	**Pembrolizumab plus SoC:** 1-knot hazards spline **SoC:** 1-knot normal spline
PD-L1 testing	PD-L1 testing costs applied equally to both pembrolizumab plus SoC arm and SoC arm	PD-L1 testing costs applied only in the pembrolizumab plus SoC arm (100% sequential testing)
Administration costs for trastuzumab administered without pembrolizumab after doublet chemotherapy	Acknowledged committee preference for administration costs based on updated administration costs (provided by CDF Lead), but unable to replicate in model Applied 3-weekly pembrolizumab dosing	Applied administration costs based on updated administration costs (provided by CDF Lead) Applied 3-weekly pembrolizumab dosing, with scenario with 6-weekly pembrolizumab → CDF Lead advised that ~50% of NHS trusts would give pembrolizumab 6-weekly

ACM2: Appraisal committee meeting 2; CDF: Cancer Drugs Fund; OS: Overall survival; PD-L1: Programmed death-ligand 1; SoC: Standard of care

Cost-effectiveness results

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

Company and EAG base case ICERs are both above the range normally considered a cost-effective use of NHS resources

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Other considerations

During consultation, no comments were received from any stakeholders on equality considerations, innovation, potential for managed access and severity weighting

Equality considerations

- Patient experts noted that people from the most deprived areas are more likely to be diagnosed later and potential language barriers to share information with hard-to-reach community groups. Also potential for younger patients to be dismissed by GPs as only have vague symptoms

Innovation

- No new treatment options for patients with HER2-positive locally advanced unresectable or metastatic gastric cancer over a decade since NICE TA208 was recommended in 2010
- Pembrolizumab with trastuzumab and doublet chemotherapy offers the first immuno-oncology treatment option for patients with HER2-positive locally advanced unresectable or metastatic gastric or GOJ cancer, thereby broadening the available treatment options for clinicians to use for these patients

Potential for managed access

- Company willing to discuss options for managed access if needed to enable patient access
- Real-world evidence would potentially address representativeness of the non-Asia region data from KEYNOTE-811 for the population receiving the intervention in England and Wales

Severity weighting

- Company and EAG agree 1.2 QALY weighting is appropriate

See appendix for 'QALY weightings for severity'

GOJ: Gastro-oesophageal junction; GPs: General practitioners; HER2: Human epidermal growth factor receptor 2; QALY: Quality-adjusted life year; TA: Technology appraisal

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Issues for discussion

Key issue: OS extrapolations – See slides 8-12

- Is it plausible that:
    1) pembrolizumab plus SoC would show a survival benefit over SoC 10 years after treatment initiation?
    2) the relative benefit of pembrolizumab plus SoC over SoC would increase over time?
- Which survival models provide the most plausible long-term OS extrapolations?
    - 2-knot odds spline (pembrolizumab + SoC arm) and Weibull (SoC arm) – **Company base case**
    - 1-knot hazard spline (pembrolizumab + SoC arm) and 1-knot normal spline (SoC arm) – **EAG base case**

PD-L1 testing – See slide 13

- Has the committee seen any evidence to change its view at ACM1 that PD-L1 testing costs should be included in the model?

GOJ: Gastro-oesophageal junction; OS: Overall survival; PD-L1: Programmed death-ligand 1; PFS: Progression-free survival; TTD: Time to treatment discontinuation

Pembrolizumab with trastuzumab and chemotherapy for untreated HER2-positive advanced gastric or gastro-oesophageal junction cancer (ID3742)

Supplementary appendix

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Pembrolizumab (KEYTRUDA, MSD)

Marketing authorisation (MA)	'KEYTRUDA, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1'
Mechanism of action	Monoclonal antibody that binds to programmed cell death protein 1 (PD-1) receptor and blocks its interaction with programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2). PD-1 is a negative regulator of T-cell activity that controls T-cell immune responses
Administration	Pembrolizumab: 200 mg three weekly (Q3W) (up to a maximum of 35 cycles)
Price	List price is £2,630 per 100 mg vial Price per administration of 200 mg each Q3W cycle is £5,260 Pembrolizumab has a confidential commercial arrangement

CPS: Combined positive score; HER2: Human epidermal growth factor receptor 2

Treatment pathway

Proposed positioning of pembrolizumab in treatment pathway for locally advanced or metastatic gastric or GOJ cancer

1st line

NICE Guidelines (NG) 83:

- **Technology appraisal (TA) 208:** Trastuzumab, in combination with cisplatin and capecitabine or 5-fluorouracil for HER2-positive metastatic adenocarcinoma of the stomach or GOJ, who:
  - have not received prior treatment for their metastatic disease and
  - have tumours expressing high levels of HER2 as defined by a positive immunohistochemistry score of 3 (IHC3 positive)
- Offer palliative combination chemotherapy to people with a performance status of 0 to 2 and no significant comorbidities (doublet or triplet treatment, see **TA191**)

European Society of Medical Oncology (ESMO) guidelines: Trastuzumab plus platinum-fluoropyrimidine doublet chemotherapy for metastatic and advanced gastric cancer

Proposed indication: pembrolizumab with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy for untreated HER2-positive advanced gastric or GOJ cancer

2nd line

NG83: Palliative chemotherapy and best supportive care

NICE

GOJ: Gastro-oesophageal junction; HER2: Human epidermal growth factor receptor 2

Overview of MSD's consultation response and EAG critique
Issues resolved post consultation

Company response	EAG critique summary	Resolved?	ICER impact
Utility values updated using IA3 • Time-to-death approach with linear mixed effect regression modelling (aligned with committee preference)	Accept company's updated approach	Yes	Small
Trastuzumab administration costs • Unable to replicate these based on updated administration costs (provided by CDF Lead) ➔ EAG's model with these costs was not provided	Adapted company's model to include updated administration costs (provided by CDF Lead) ➔ Incorporated in EAGs base case	Yes	Small
Updated PFS extrapolation using IA3 • **Pembrolizumab plus SoC:** 2-knot odds spline • **SoC:** Weibull	Agree with the company's choice of curves for PFS using the updated data from IA3	Yes	Small

Consultation comments received from MSD only. No comments received from any other stakeholders

CDF: Cancer Drugs Fund; IA3: Interim analysis 3; ICER: Incremental cost-effectiveness ratio; PFS: Progression-free survival; SoC: Standard of care

Overview of MSD's consultation response and EAG critique
Issues resolved post consultation

Company response	EAG critique summary	Resolved?	ICER impact
Updated time on treatment (ToT) data using IA3 • Kaplan-Meier data used directly • ToT for trastuzumab is not capped at 35 cycles	Agree with company's approach	Yes	Small
Updated adverse events (AEs) using IA3	Data used to update AEs, RDIs and subsequent therapies to reflect the IA3 data cut or updated CSR were not provided • visually inspected the changes and accept these at face value • Minimal impact on ICER ➔ Consider no significant risk of bias	Yes	Small
Updated relative dose intensities (RDIs) using IA3		Yes	Small
Updated subsequent therapies using IA3		Yes	Small

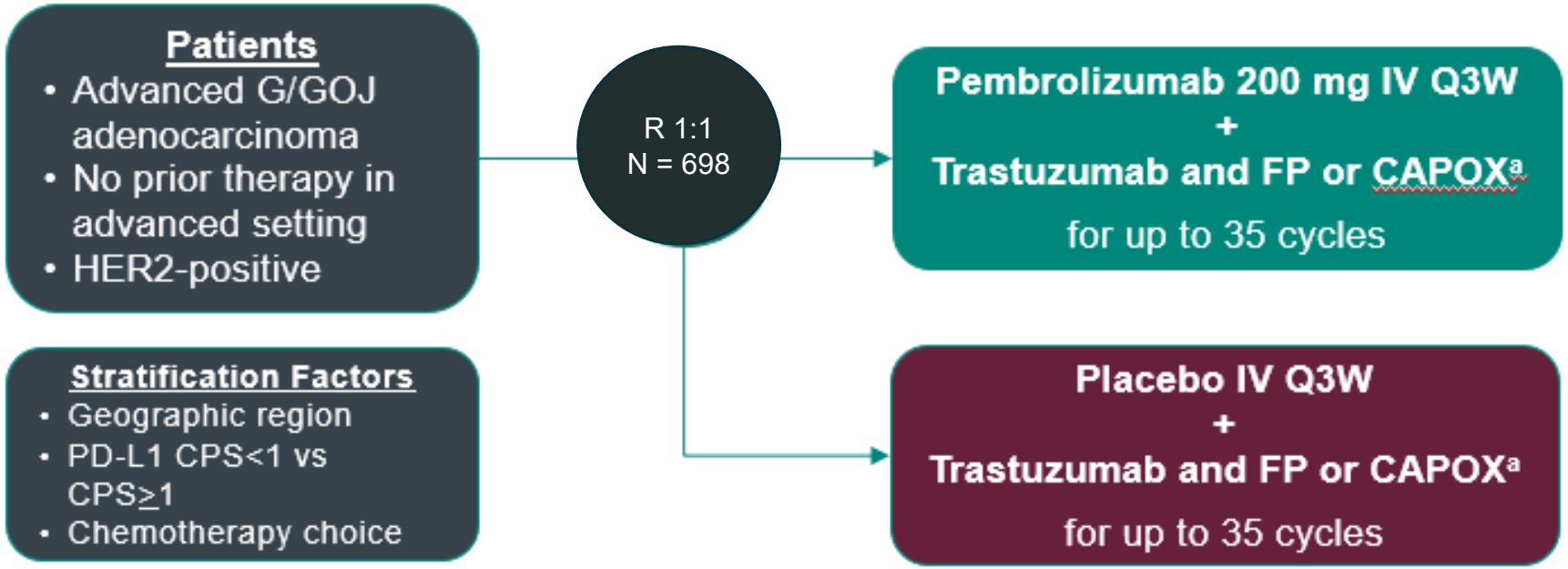
Consultation comments received from MSD only. No comments received from any other stakeholders

CSR: Clinical study report; IA3: Interim analysis 3; ICER: Incremental cost-effectiveness ratio; SoC: Standard of care

Key clinical trial: KEYNOTE-811 – study design

KEYNOTE-811 global cohort provides direct clinical evidence for pembrolizumab + trastuzumab + FP or CAPOX versus relevant comparator (trastuzumab + FP or CAPOX)

Figure: KEYNOTE-811 study design



- 2 cohorts: Global and Japan-specific S-1 + oxaliplatin (SOX) treated cohort
  - Only global cohort considered in the CS as SOX was not a comparator included in the NICE final scope ➔ EAG considered this was appropriate

See slide for 'KEYNOTE-811 Primary outcome results'

CAPOX: Capecitabine with oxaliplatin; CPS: Combined positive score; FP: 5-fluorouracil with cisplatin; G/GOJ: Gastric/Gastro-oesophageal junction; HER2: Human epidermal growth factor receptor 2; IV: Intravenous; PD-L1; Programmed death-ligand 1; Q3W: Three weekly

KEYNOTE-811 study design

Company only uses PD-L1 positive with CPS ≥ 1 subgroup for its analyses

Table: KEYNOTE-811 trial design and outcomes – Global cohort (intention-to-treat population)

KEYNOTE-811 (n=698)	
Design	Phase III randomised, double-blind, placebo-controlled trial
Population	Untreated locally advanced or unresectable HER2-positive gastric or GOJ adenocarcinoma
Intervention (n=350)	Pembrolizumab plus trastuzumab plus FP or CAPOX
Comparator(s) (n=348)	Placebo plus trastuzumab plus FP or CAPOX
Primary outcome	PFS and OS
Other outcomes	Overall response rate (ORR), Duration of response (DOR), Adverse events (AEs), HRQoL
Locations	Global – 192 centres from 19 countries (includes 29 subjects from 10 UK centres) • **Western Europe** (UK, France, Germany, Ireland, Italy, Spain)**/Israel/North America** (US)**/Australia** • **Asia** (China, Japan, South Korea) • **Rest of World** (Brazil, Chile, Guatemala, Poland, Russia, Turkey, Ukraine)
Used in model?	Yes – data from a post-hoc subgroup used

See slide for 'KEYNOTE-811 Primary outcome results'

CAPOX: Capecitabine plus oxaliplatin; CPS: Combined positive score; FP: 5-fluorouracil plus cisplatin; GOJ: Gastro-oesophageal junction; HER2: Human epidermal growth factor receptor 2; HRQoL: Health-related quality of life; OS: Overall survival; PD-L1; Programmed death-ligand 1; PFS: Progression-free survival

KEYNOTE-811 baseline characteristics

MA is for a subgroup of KEYNOTE-811 – PD-L1 positive with CPS ≥ 1

Company presented analyses for the non-Asia subgroup (Western Europe/Israel/North America/Australia; and Rest of the World including South America) considered to be more generalisable to patients in England

Table: KEYNOTE-811 baseline characteristics – PD-L1 positive with CPS ≥ 1, non-Asia subgroup (post-hoc analyses)

Characteristic		Pembrolizumab + SoC (n=202)	SoC (n=200)
Age	Mean (years)	59.7	60.6
Sex, n (%)	Male	160 (79.2)	158 (79)
Disease status. n (%)	Locally advanced	8 (4)	5 (2.5)
	Metastatic	194 (96)	196 (97.5)
Geographic region (enrolment), n (%)	Western Europe/Israel/North America/Australia	97 (48)	96 (48)
	Rest of the World	105 (52)	104 (52)
ECOG, n (%)	0	91 (45)	79 (39.5)
	1	111 (55)	120 (60)
Follow up (months), median (range), IA3 data cut		20 (0.6 to 51.7)	18.2 (0.3 to 51.7)

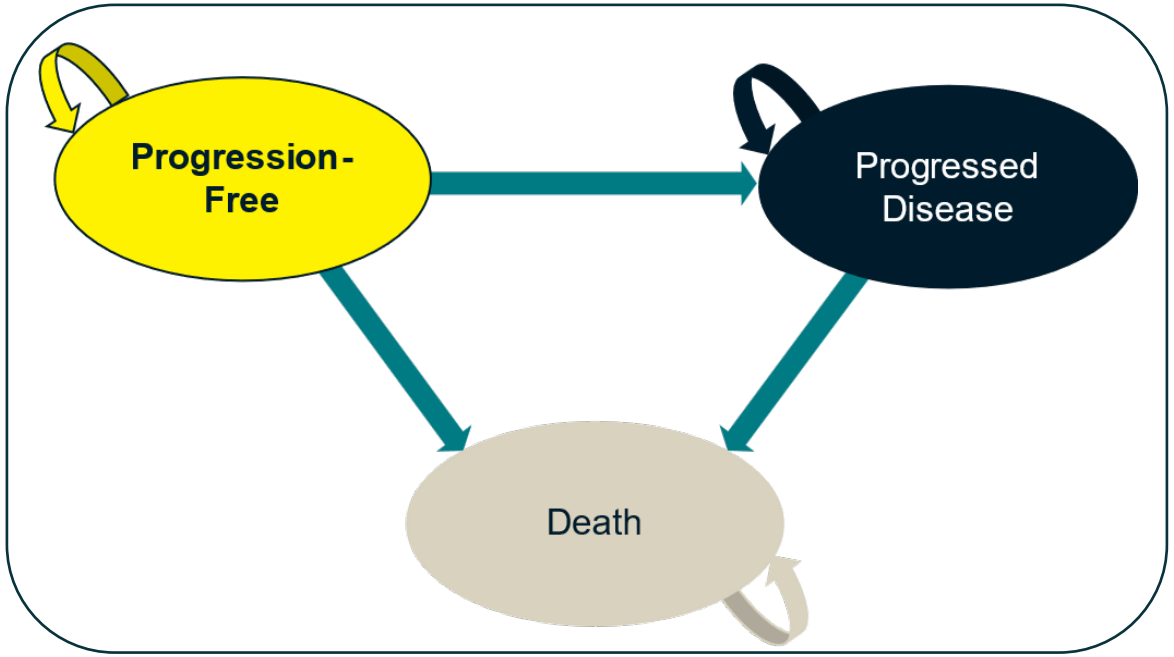
See 'MSD response to CQs v4, table 13' for detailed baseline characteristics for non-Asia subgroup. See slide for 'KEYNOTE-811 Primary outcome results'

CPS: Combined positive score; IA3: Interim analysis 3; MA: Marketing Authorisation; PD-L1; Programmed death-ligand 1; SoC: Standard of care

Company's model overview

- A *de novo* partition survival cohort simulation model
- Life-time horizon of 40 years using 1-week cycles

Figure: Model structure



- Pembrolizumab plus SoC affects **costs** by:
  - Drug acquisition costs
  - Administration costs
  - AE costs
- Pembrolizumab plus SoC affects **QALYs** by:
  - Improved OS
  - AE disutility
- Assumptions with greatest ICER effect:
  - Choice of long-term OS extrapolations for pembrolizumab plus SoC and SoC alone

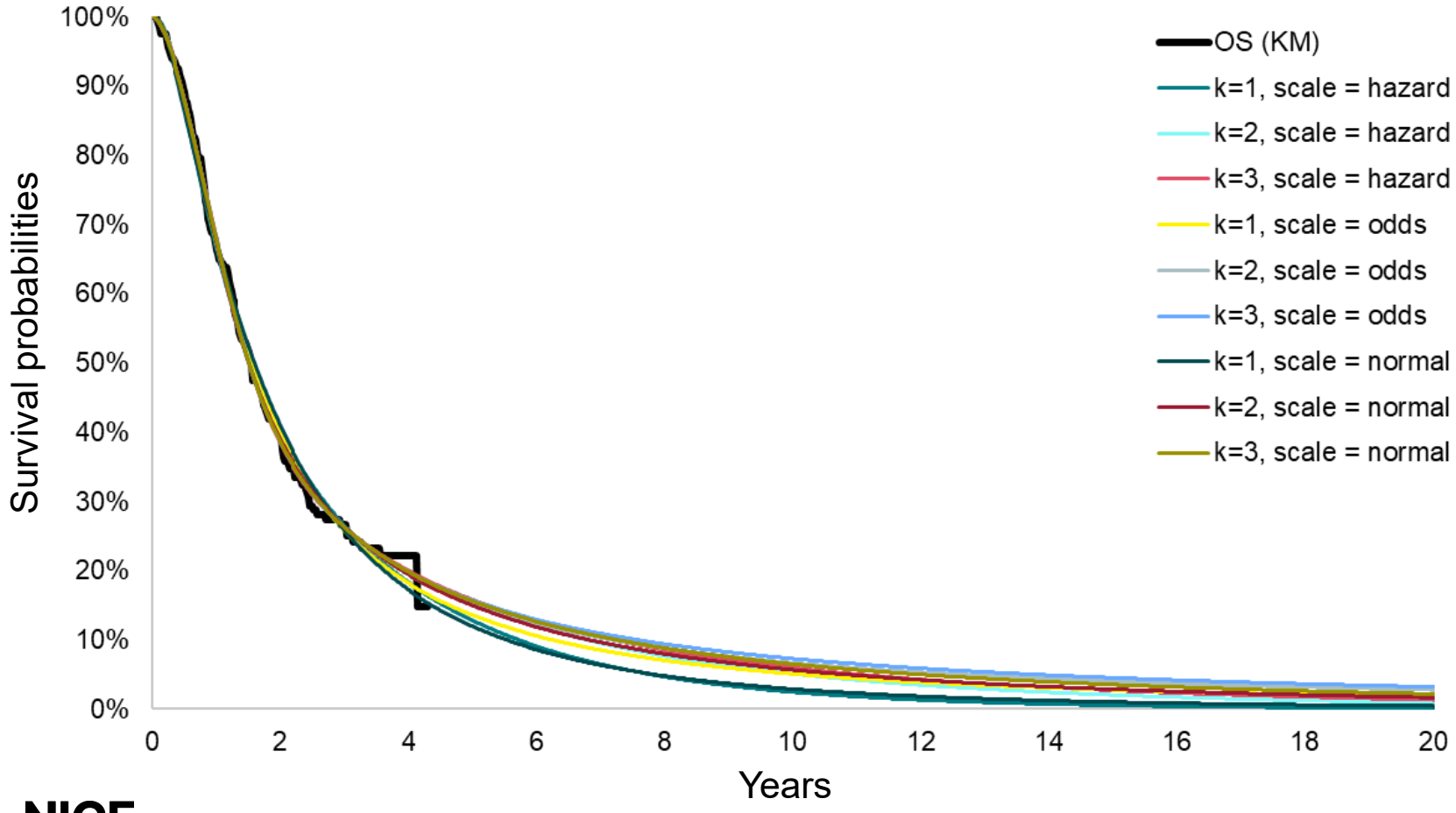
AE: Adverse event; ICER: Incremental cost-effectiveness ratio; OS: Overall survival; QALYs: Quality-adjusted life years; SoC: Standard of care

Large impact on ICER

Issue: OS extrapolations (1/3)

For pembrolizumab plus SoC arm, company prefers 2-knot odds spline model and EAG prefers the 1-knot hazard spline model

OS for the pembrolizumab plus SoC arm, independently fitted spline models (updated using KEYNOTE-811 IA3 data cut)



See slide 'Issue: OS extrapolations'

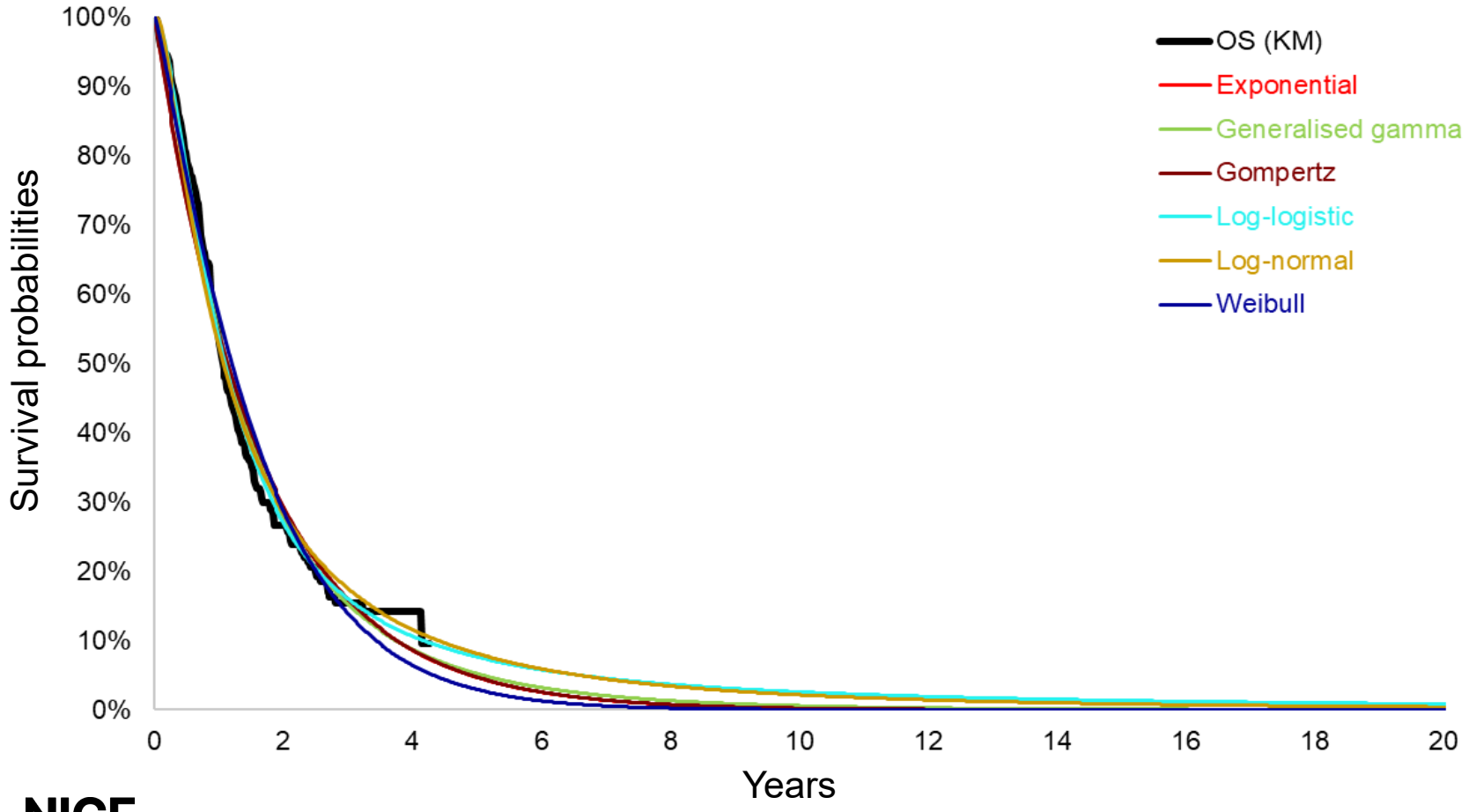
IA3: Interim analysis 3; KM: Kaplan-Meier; OS: Overall survival; SoC: Standard of care

Large impact on ICER

Issue: OS extrapolations (2/3)

For SoC arm, company prefers the Weibull model

OS for the SoC arm, independently fitted standard parametric models (updated using KEYNOTE-811 IA3 data cut)



See slide 'Issue: OS extrapolations'

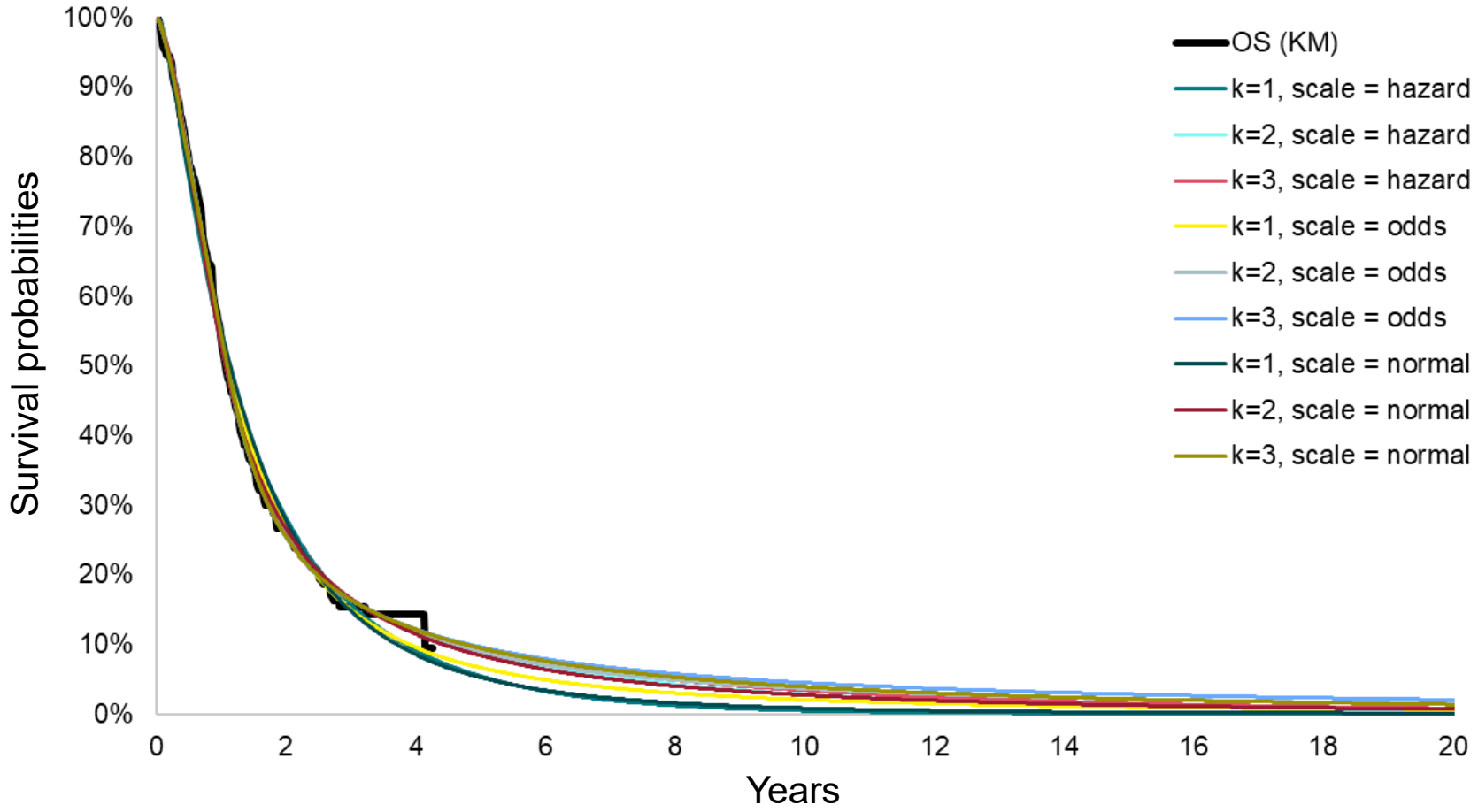
IA3: Interim analysis 3; KM: Kaplan-Meier; OS: Overall survival; SoC: Standard of care

Large impact on ICER

Issue: OS extrapolations (3/3)

For SoC arm, EAG prefers the 1-knot normal spline model

OS for the SoC arm, independently fitted spline models (updated using KEYNOTE-811 IA3 data cut)

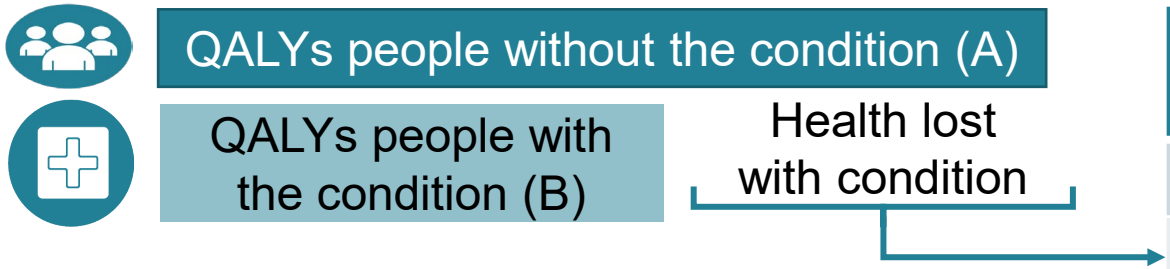


See slide 'Issue: OS extrapolations'

IA3: Interim analysis 3; KM: Kaplan-Meier; OS: Overall survival; SoC: Standard of care

QALY weightings for severity

New severity modifier calculations and components:



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

- EAG argued that if the OS and PFS data from the Asia (CPS≥1) region are not considered generalisable to England, then the company should use data from the non-Asia (CPS≥1) region to estimate OS and PFS under SoC to inform the QALYs ➔ This approach used by EAG supported a QALY multiplier of 1.2x
- In response to technical engagement, company's preferred assumptions resulted in a proportional QALY shortfall of 0.908, supporting a 1.2x QALY weighting ➔ Agree with the EAG's assessment that a QALY weight of 1.2 is justified based on its updated survival modelling using parametric survival curves for OS fitted separately to the non-Asia cohort for both trial arms.

See slide for 'Other considerations'

CPS: Combined positive score; OS: Overall survival; PFS: Progression-free survival; QALY: Quality-adjusted life year; SoC: Standard of care

Thank you

NICE