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

For public – redacted

Technology appraisal committee A [07 November 2023]

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Company: Merck Sharp & Dohme (UK) Limited

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

- ✓ **Background**
- ❑ Clinical evidence and key clinical issues to consider
- ❑ Modelling and key cost effectiveness issues to consider
- ❑ Base case assumptions and cost-effectiveness results
- ❑ Other considerations: Equality, innovation, managed access and severity
- ❑ Summary

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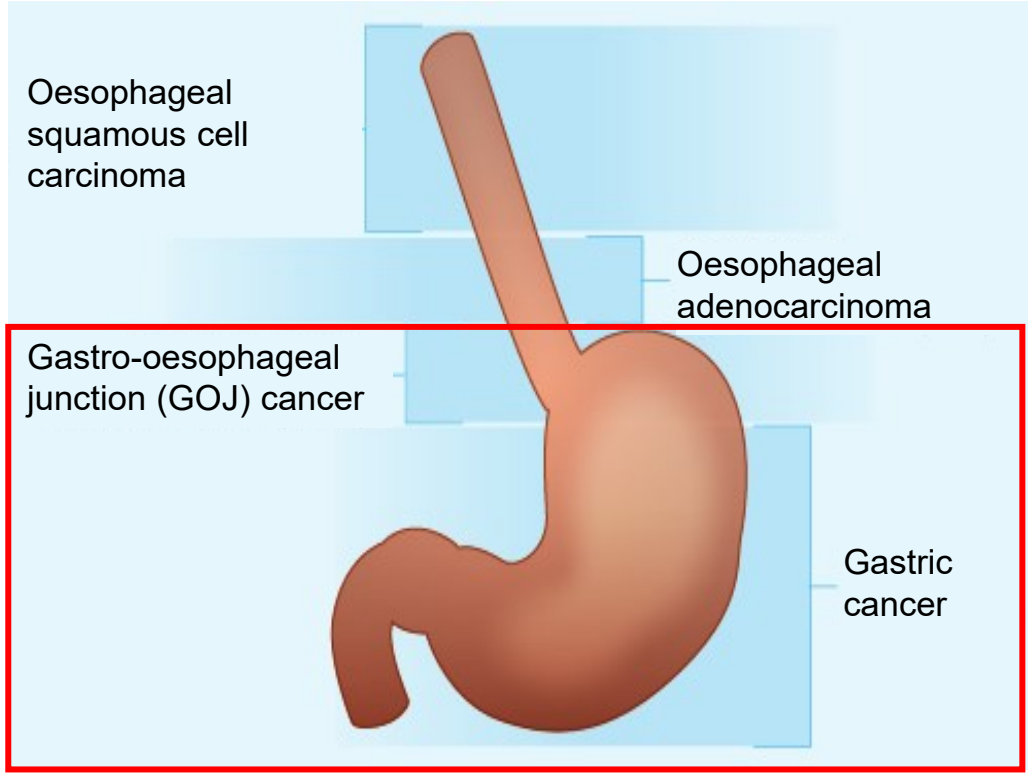
Background on gastric or gastro-oesophageal junction cancer



Causes

- Causes of gastric and gastro-oesophageal junction (GOJ) cancers are unknown
- Risk factors include diet, alcohol consumption, smoking, *H.pylori* infection and obesity

Epidemiology

- Gastric cancer is almost twice as common in men and approximately half of all new cases are diagnosed in people aged 75 years and over

Diagnosis and classification

- Gastric and GOJ cancer are often diagnosed at an advanced stage
    - 17% of gastric cancers were diagnosed at stage 3 (locally advanced), and 34% of gastric cancers were diagnosed at stage 4 (metastatic) in England in 2014

Symptoms and prognosis

- Initial symptoms are vague and similar to other stomach conditions, but for advanced stages may include lack of appetite, weight loss, fluid in the abdomen and blood in the stool
- 5-year survival for people with gastric cancer was 21.6% between 2013 and 2017

See slide 'Issues for discussion'

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 human epidermal growth factor receptor 2 (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

Question for clinical experts: Does the treatment pathway align with NHS clinical practice?

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

Patient perspectives

Oesophageal cancer has impact on physical, psychological, social and work life and affects the quality of life (QoL) of patients

Submissions from Guts UK Charity

- People are frequently diagnosed late (stage III or IV) due to no widely used screening tools and vague early symptoms ➔ Treatment options limited in these stages
- Symptoms have wider impact on QoL and affect physical, social and work life ➔ Nutritional status and ability to eat severely affected
- Psychological distress due to awareness of a poor prognosis and demanding treatment pathways
- Unmet need as only few effective treatments available, particularly in advanced disease, and no one treatment that fits all
    - Current treatments have physically debilitating symptoms and not always effective

"Patients with oesophageal cancer are putting their ordinary lives on hold and experiencing the meal as a battleground during treatment"

"Many patients are not able to communicate the extent of the side effects, some will just cope with them as know there is no other treatment and some will decide to just stop treatment as cannot cope."

Clinical perspectives

Survival remains very poor for people with HER2-positive gastric or GOJ cancer

Submissions from clinical expert

- Aim of treatment is to improve overall survival (OS) and progression-free survival (PFS)
- Treatment pathway is well defined
    - Variation in when the HER2 testing is done across the country (i.e. reflex versus on demand testing) ➔ Results in variations in when trastuzumab is added to chemotherapy regimen
- Introduction of pembrolizumab will require additional PD-L1 testing ➔ Require greater input from pathology departments
- Pembrolizumab plus SoC is considered a step change in treatment
- Addition of pembrolizumab to SoC did not significantly worsen toxicity profile compared to SoC
- Currently waiting for quality of life data for pembrolizumab plus SoC ➔ If quality of life maintained for longer than SoC, then may delay requirement for end-of-life treatment (e.g. hospice or hospital admissions)

"the survival still remains very poor (median survival less than 1.5 years)"

"For CPS PD-L1≥1, HER2-positive patients there is a clinical and statistically meaningful improvement in OS and PFS at the 3rd interim analysis [for pembrolizumab plus SoC versus SoC alone]"

Should the cost of PD-L1 testing be included in the model?

See slide 'Issues for discussion'

CPS: Combined positive score; GOJ: Gastro-oesophageal junction; HER2: Human epidermal growth factor receptor 2; PD-L1: Programmed death-ligand 1; SoC: Standard of care

See slide 'Issues for discussion'

Issues unresolved – for discussion at ACM1

Issue	ICER impact
Clinical effectiveness	
Post hoc analysis to define the non-Asia cohort • Non-Asia cohort – **Company base case** • Western Europe/Israel/North America/Australia region only – **EAG requested scenario**	Unknown impact 
Cost-effectiveness	
OS extrapolation • 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**	Large impact 
Utility analysis • Time-to-death approach (**company and EAG base case**) versus progression-based approach (**scenario presented**) • Descriptive analysis (**company base case**) versus mixed effect regression analysis (**EAG base case**)	Small impact 
PD-L1 testing	Unknown impact 

ACM1: Appraisal committee meeting 1; ICER: Incremental cost-effectiveness ratio; OS: Overall survival; PD-L1: Programmed death-ligand 1; SoC: Standard of care

Issues resolved prior to ACM1

Issue	ICER impact
Cost-effectiveness	
Severity modifier x1.2 QALY weighting applied by both company and EAG in all modelling	NA
Administration costs for trastuzumab • Complex chemotherapy cost for trastuzumab when given either with or without pembrolizumab (**company base case**) • Complex chemotherapy cost for trastuzumab when given with pembrolizumab but simple chemotherapy cost when given alone (**EAG base case**) • EAG scenario analysis with estimates from CDF clinical lead (**NICE tech team view**)	Small impact 
TTD for trastuzumab • Capped at 35 cycles (**company base case**) • No cap (**EAG base case, NICE tech team view**)	Small impact 

ACM1: Appraisal committee meeting 1; CDF: Cancer Drugs Fund; ICER: Incremental cost-effectiveness ratio; NA: Not applicable; QALY: Quality adjusted life years; TTD: Time-to-treatment discontinuation

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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*
Duration of follow up	Median = 15.4 months (range: 0.3 to 41.6 months)
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

* Trastuzumab and FP or CAPOX is referred to as SoC from now

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; SoC: Standard of care

KEYNOTE-811 Primary outcome results

Company uses PD-L1 positive with CPS ≥ 1 non-Asia subgroup for model base case, EAG requested scenario analyses for the Western Europe/Israel/North America/Australia region

- Non-Asia subgroup includes Western Europe/Israel/North America/Australia; and Rest of the World.
- Results from Rest of the World region more favourable for pembrolizumab plus SoC than the Western Europe/Israel/North America/Australia region

Table: KEYNOTE-811 primary outcome results – PD-L1 positive with CPS ≥ 1 (data cut off 25 May 2022)

	Non-Asia subgroup (post hoc analysis)		Western Europe/Israel/North America/Australia		Rest of World	
	Pembrolizumab + SoC (N=202)	SoC (N=200)	Pembrolizumab + SoC (N=97)	SoC (N=96)	Pembrolizumab + SoC (N=105)	SoC (N=104)
Progression-free survival						
Events, n (%)	141 (69.8)	156 (78.0)	-	-	-	-
Median, months (95% CI)	9.9 (8.3, 11.3)	6.3 (5.6, 7.3)	-	-	-	-
Hazard ratio (95% CI, p-value)	**0.62 (0.49, 0.78; 0.0001)**		**0.69 (0.50, 0.97; NR)**		**0.56 (0.41, 0.78; NR)**	
Overall survival						
Events, n (%)	120 (59.4)	142 (71.0)	61 (62.9)	64 (66.7)	59 (56.2)	78 (75.0)
Median, months (95% CI)	18.8 (15.5, 24.3)	12.6 (11.1, 14.9)	18.8 (14.6, 24.2)	12.1 (10.4, 15.7)	20.3 (14.8, 27.9)	13.4 (10.4, 15.5)
Hazard ratio (95% CI, p-value)	**0.67 (0.52, 0.85; 0.0006)**		**0.81 (0.57, 1.15; 0.0317)**		**0.57 (0.40, 0.80; NR)**	

Company and EAG base case

EAG requested scenario analysis

See appendix for 'KEYNOTE-811 KM Curves of PFS and OS (CPS≥1, non-Asia)' and 'KEYNOTE-811 baseline characteristics'

CI: Confidence interval; CPS: Combined positive score; NR: Not reported; PD-L1; Programmed death-ligand 1; SoC: Standard of care

Unknown impact on ICER

Key issue: Post hoc analysis to define the non-Asia cohort

Company uses PD-L1 positive with CPS ≥ 1 non-Asia subgroup for model base case, EAG requested scenario analyses for the Western Europe/Israel/North America/Australia region

Background

- Company's cost-effectiveness analysis uses data from non-Asia cohort generated in a post hoc analysis combining data from Western Europe/Israel/North America/Australia and Rest of the World cohorts

EAG comments

- Hazard ratios from Rest of World cohort more favourable for pembrolizumab plus SoC arm for OS and PFS
- Scenario analysis for Western Europe/Israel/North America/Australia cohort only will be helpful

Company response

- All centres within Rest of World region provide care similar to that delivered in England and Wales
- Non-Asia cohort is very similar to the pre-specified subgroup analysis for “race” (Asian and non-Asian)

EAG critique

- Results on race and post-hoc non-Asia geographic region is not relevant to the issue of whether Western Europe/Israel/North America/Australia region alone is more appropriate
- Company have not explained the more favourable hazard ratios for the ‘Rest of World’ region

Should the clinical effectiveness data for the cost-effectiveness analyses be taken from:

- Non-Asia cohort (Western Europe/Israel/North America/Australia and Rest of World)
- Western Europe/Israel/North America/Australia cohort only

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See slide ‘Issues for discussion’

CPS; Combined positive score; OS: Overall survival; PD-L1: Progremmed death-ligand 1; PFS: Progression-free survival; SoC: Standard of care

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

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Large impact on ICER

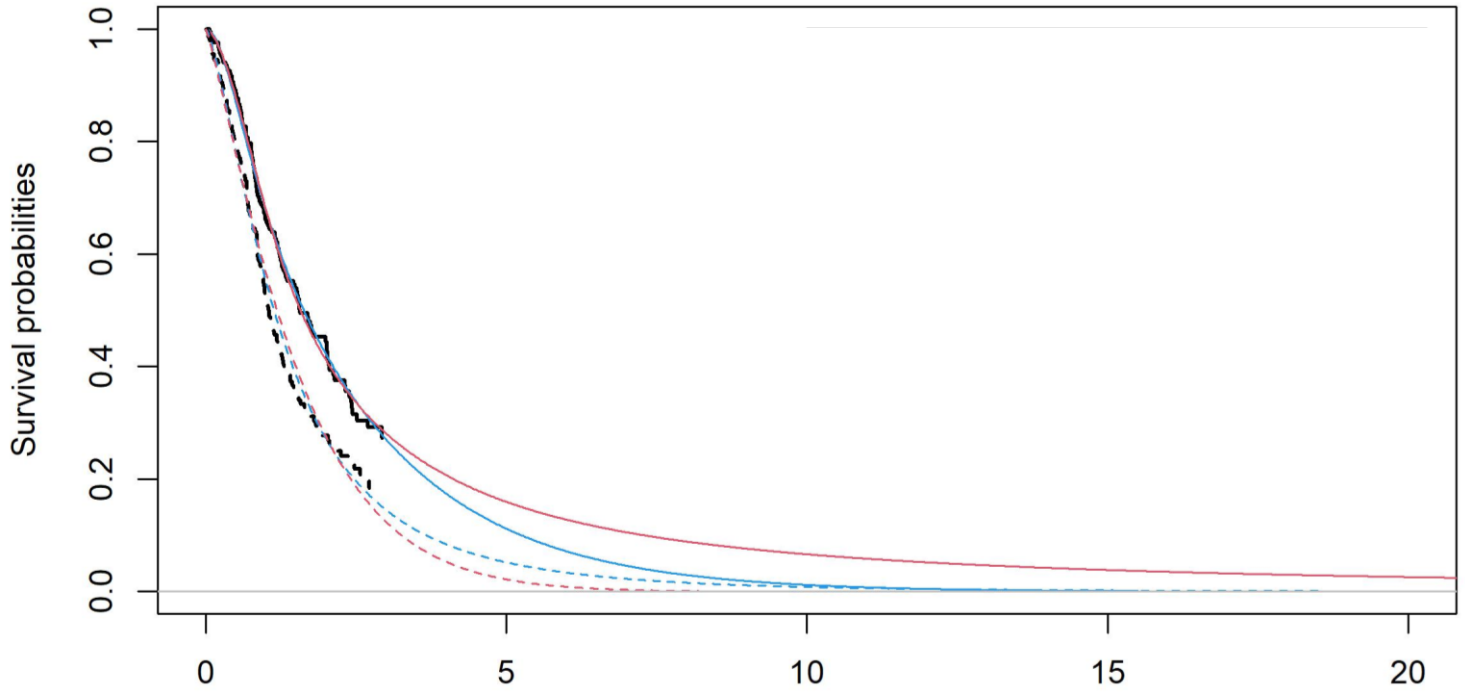
Key issue: OS extrapolations (1/4)

Company and EAG use independently fitted survivals curves to predict OS for pembrolizumab plus SoC arm and SoC arm

Background

- Post technical engagement, the company agrees with EAG to predict overall survival for pembrolizumab plus SoC and SoC arm using independently fitted parametric survivals curves and hazard spline models
  ➔ Avoids assuming either constant hazard ratio or constant acceleration factor for a life-time

Figure: Company and EAG's base case OS curves for pembrolizumab plus SoC arm and SoC arm



For pembrolizumab plus SoC arm:
- OS Kaplan-Meier (KM) curve from KEYNOTE-811 (non-Asia subgroup)
- **EAG:** 1-knot hazard spline model
- **Company:** 2-knot odds spline model

For SoC arm
- OS KM curve from KEYNOTE-811 (non-Asia subgroup)
- **EAG:** 1-knot normal spline model
- **Company:** Weibull

OS: Overall survival; SoC: Standard of care

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

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Large impact on ICER

Key issue: OS extrapolations (2/4)

EAG: Company's OS predictions for pembrolizumab plus SoC are highest and for SoC alone arm are lowest of all fitted parametric and spline models

Company comments

- Pembrolizumab plus SoC arm
  - 2-knot odds model overestimates survival at 1 year but underestimates survival at 2 years
  - Model predicts a 5-year survival of 16% → higher than one of the EAG clinical expert's opinion
  - Lack of immunotherapy precedent for this disease so experts may underestimate long-term survival benefit
- SoC arm
  - Weibull model reflects the KM OS rate at 2 years and is aligned with MSD and EAG clinical experts' opinion at 5 years

EAG critique

- Company has not provided enough evidence to support choice of 2-knot odds spline model for OS for the pembrolizumab plus SoC arm and the Weibull model for OS for the SoC arm
- Pembrolizumab plus SoC arm
  - Company choice associated with highest predictions of all fitted parametric and spline models and are much higher that EAG's clinical experts' opinions
  - Smoothed hazard function shows a unimodal shape, so log-normal, log-logistic, generalised gamma and all spline models may be appropriate

NICE See appendix for smoothed hazard function for OS for pembrolizumab plus SoC arm and slide 'Issues for discussion'

KM: Kaplan-Meier; OS: Overall survival; SoC: Standard of care

Large impact on ICER

Key issue: OS extrapolations (3/4)

EAG: Company's OS predictions for pembrolizumab plus SoC are highest and for SoC alone arm are lowest of all fitted parametric and spline models

EAG critique (continued)

- Pembrolizumab plus SoC arm (continued)
  - The 1-knot hazard spline model provides slightly higher 5-year survival probability than predicted by clinical experts, but 10-years survival probability was within the range provided
- SoC arm
  - Company's choice provides lowest predictions of all fitted parametric and spline models
  - Statistical goodness-of-fit and visual assessment suggests Weibull model does not fit the KM data well:
    - AIC and BIC score for the Weibull model are much higher than for other models
    - Visual assessment suggests poor fit, especially in the tail area
    - Weibull model is unable to capture unimodal shape shown in hazard plot
  - Smoothed hazard function shows a unimodal shape, so log-normal, log-logistic, generalised gamma and all spline models may be appropriate
  - Exponential, Weibull, Gompertz, generalised gamma, 1-knot hazard spline and 1-knot normal spline models provide 5 years and 10 years survival probabilities within the range provided by clinical experts

See appendix for smoothed hazard function for OS for SoC arm and slide 'Issues for discussion'

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; KM: Kaplan-Meier; OS: Overall survival; SoC: Standard of care

Large impact on ICER

Key issue: OS extrapolations (4/4)

EAG: Company's OS predictions for pembrolizumab plus SoC are highest and for SoC alone arm are lowest of all fitted parametric and spline models

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

	Expected survival probability					Predicted survival probability	
Timepoint	KEYNOTE-811	Company' expert 1	Company's expert 2	EAG's expert 1	EAG's expert 2	Company's TE base case	EAG's base case
Pembrolizumab plus SoC arm							
1 year	66%	NE	NE	NE	NE	68%	68%
2 years	44%	NE	NE	NE	NE	41%	42%
5 years	NA	NA	NA	5-10%	0%	16%	11%
10 years	NA	NA	NA	1%	0%	7%	1%
20 years	NA	NE	NE	NE	NE	3%	0%
SoC arm							
1 year	53%	NE	NE	NE	NE	57%	55%
2 years	28%	NE	NE	NE	NE	28%	27%
5 years	NA	5%	2-5%	≤5%	0%	2%	5%
10 years	NA	2%	0-1%	0%	0%	0%	1%
20 years	NA	NE	NE	NE	NE	0%	0%

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

NA: Not applicable; NE: Not evaluated; OS: Overall survival; SoC: Standard of care; TE: Technical engagement

Small impact on ICER

Key issue: Utility analysis (1/4)

EAG uncertain whether time-to-death or progression-based approach more appropriate

Background

- Company base case uses utility data based on the non-Asia (CPS≥1) cohort
- Utility values estimated based on a time-to-death approach with four categorical groups (<30 days; 30 to 179 days; 180 to 359 days, and ≥360 days). Scenario presented using progression-based approach

EAG comments

- Company should explore analysis using utility data from the Western Europe/Israel/North America/Australia (CPS ≥ 1) cohort
- Substantial uncertainty related to time-to-death approach being preferred to progression-based approach
- EAG's clinical advisers disagreed with time-to-death approach, as progression and AEs are key drivers for utility

Company response

- Censoring of patients with less than 360 days of survival (the “unknown” category) potentially underestimates the utility values for the time-to-death health states

See slide ‘Issues for discussion’

AEs; Adverse events; CPS: Combined positive score

Small impact on ICER

Key issue: Utility analysis (2/4)

Company uses descriptive analysis, EAG uses mixed effect regression analysis

Background

- Company base case uses utility values estimated using descriptive statistics, conducted scenario using linear mixed effect regression model
- **Descriptive statistics without adjustment for repeated measures:** utility measures weighted by number of measurements observed, so people with multiple measurements contribute more to the estimate of utility than those with a single measurement
- **Linear mixed effect regression with adjustment for repeated measures:** adjusts for repeated measures, and adjusts for covariates that may be important confounders
- Company adjusted for grade 3+ AEs and time-to-death or progression status for the time-to-death and progression-based regression models, respectively. Age and gender were assessed as potentially relevant covariates, but were not statistically significant so not included in model

EAG comments

- Using linear mixed effect regression model increased ICER for both time-to-death or progression-based approach
- Company's estimated utility values lack face validity ➔ Utility values for patients with a time-to-death of greater than 360 days are very similar to the age-adjusted utility values for the general population
- Mixed effect modelling approach accounts for the effect of covariates and correlations within a patient

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See slide 'Issues for discussion'

AEs: Adverse events; ICER: Incremental cost-effectiveness ratio

Small impact on ICER

Key issue: Utility analysis (3/4)

Company uses descriptive analysis, EAG uses mixed effect regression analysis

Company response

- Prefers approach without adjustment for repeated measures because:
  - Those who spend longest in a health state should contribute more to the estimate of utility for that health state
  - People with a single measurement are more likely to have died or transitioned to a worse health state shortly after that measurement, so likely to have lower utilities relative to other people in that health state
  - Repeated measures approaches are more helpful with smaller sample sizes

See slide 'Issues for discussion'

Small impact on ICER

Key issue: Utility analysis (4/4)

Table: Company and EAG preferred base case utility values (PD-L1 positive, CPS ≥ 1 non-Asia)

	Descriptive analysis	Mixed effect regression analysis (no grade 3+ AEs)
Time-to-death approach		
	Mean (SE)	**Mean (SE)**
<30	[redacted]	[redacted]
30 to 180	[redacted]	[redacted]
180 to 360	[redacted]	[redacted]
≥ 360	[redacted]	[redacted]
Progression-based approach*		
	Mean (SE)	**Mean (SE)**
Progression-free	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]

Company base case

EAG base case

Estimated general population utilities from the model: At [redacted] years: [redacted]. At [redacted] years: [redacted]

* Progression-based utility values are used in a scenario analysis

Which approach provides the most appropriate utility values to inform the economic model?
- Is time-to-death or progression-based approach more appropriate?
- Is use of descriptive analysis or mixed effect regression analysis more appropriate?

See slide 'Issues for discussion'

AEs: Adverse events; CPS: Combined positive score; PD-L1: Programmed death-ligand 1; SE: Standard error

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Differences between company and EAG base case assumptions post technical engagement

Parameter	Company	EAG	NICE tech team view
OS extrapolations	Curves fitted independently to both arms of non-Asia CPS ≥1 cohort **Pembrolizumab plus SoC:** 2-knot odds spline, **SoC:** Weibull	Curves fitted independently to both arms of non-Asia CPS ≥1 cohort **Pembrolizumab plus SoC:** 1-knot hazard spline, **SoC:** 1-knot normal spline	Key issue for discussion
Method used to estimate utilities for health states from KEYNOTE-811 data*	Time-to-death utilities estimated using descriptive statistics	Time-to-death utilities estimated using a linear mixed effects model*	Key issue for discussion
TTD of trastuzumab	Based on TTD curve from KENOTE-811, capped at 35 cycles	Based on TTD curve from KENOTE-811, with no cap	Resolved – Agree with EAG approach
Administration costs for trastuzumab when administered without pembrolizumab after doublet chemotherapy	Complex chemotherapy cost for trastuzumab when given either with or without pembrolizumab	Complex chemotherapy cost for trastuzumab when given with pembrolizumab but simple chemotherapy cost when given alone	Resolved – EAG scenario analysis with estimates from CDF clinical lead

NICE * Progression-based utility values are used in a scenario analysis

See appendix for 'Additional issues'

CDF: Cancer Drugs Fund; CPS: Combined positive score; OS: Overall survival; SoC: Standard of care; TTD: Time to treatment discontinuation

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

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

Treatment pathway – See slide 4

- Does the treatment pathway align with NHS clinical practice?

PD-L1 testing – See slide 6

- Is it appropriate to include PD-L1 testing and related resource use and costs?

Key issue: Post hoc analysis to define the non-Asia cohort – See slide 12

- Which OS and PFS estimates best reflect NHS clinical practice:
  - Western Europe/Israel/North America/Australia only
  - Non-Asia subgroup (Western Europe/Israel/North America/Australia **and** Rest of World)

Key issue: OS extrapolations – See slides 14-17

- 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**

Key issue: Utility values – See slides 18-21

- Which approach provides the most appropriate utility values to inform the economic model?
  - Is time-to-death or progression-based approach more appropriate?
  - Is use of descriptive analysis or mixed effect regression analysis more appropriate?

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

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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

Decision problem (1)

	Final scope	Company	EAG comments
Population	Adults with untreated locally advanced unresectable or metastatic HER2-positive gastric or GOJ adenocarcinoma	Scope population plus tumours expressing PD-L1 with a combined positive score (CPS) ≥ 1	PD-L1 positive subgroup of the KEYNOTE-811 trial, defined as those with a CPS ≥ 1 (85% of the global cohort) • Company submission (CS) highlights PD-L1 is routinely assessed in clinical practice
Intervention	Pembrolizumab with trastuzumab and chemotherapy	In line with final scope	Draft summary of product characteristics specifies pembrolizumab with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy

Comparators	• Chemotherapy only, which includes:
	  • doublet treatment with FP, FOLFOX, XP or CAPOX
	  • triplet treatment with ECF, EOF, ECX or EOX
	• Trastuzumab with CAPOX or FP
		Trastuzumab with CAPOX or FP	• Trastuzumab plus CAPOX or FP appropriate comparator
			• Appropriate to assume doublet chemo regimens are clinically equivalent
			• Trastuzumab plus CAPOX or FP used in people with metastatic or locally advanced disease in clinical practice (but note TA208 is restricted to HER2-positive metastatic disease)
			• Triplet chemo not used in this group

CAPOX: Capecitabine with oxaliplatin; ECF: Epirubicin, cisplatin and 5-fluorouracil; ECX: Epirubicin, cisplatin and capecitabine; EOF; Epirubicin, oxaliplatin and 5-fluorouracil; EOX; Epirubicin, oxaliplatin and capecitabine; FOLFOX: 5-fluorouracil with oxaliplatin; FP: 5-fluorouracil with cisplatin; GOJ: Gastro-oesophageal junction; HER2: Human epidermal growth factor receptor 2; PD-L1: Programmed death-ligand 1; TA: Technology Appraisal; XP: Cisplatin with capecitabine

Decision problem (2)

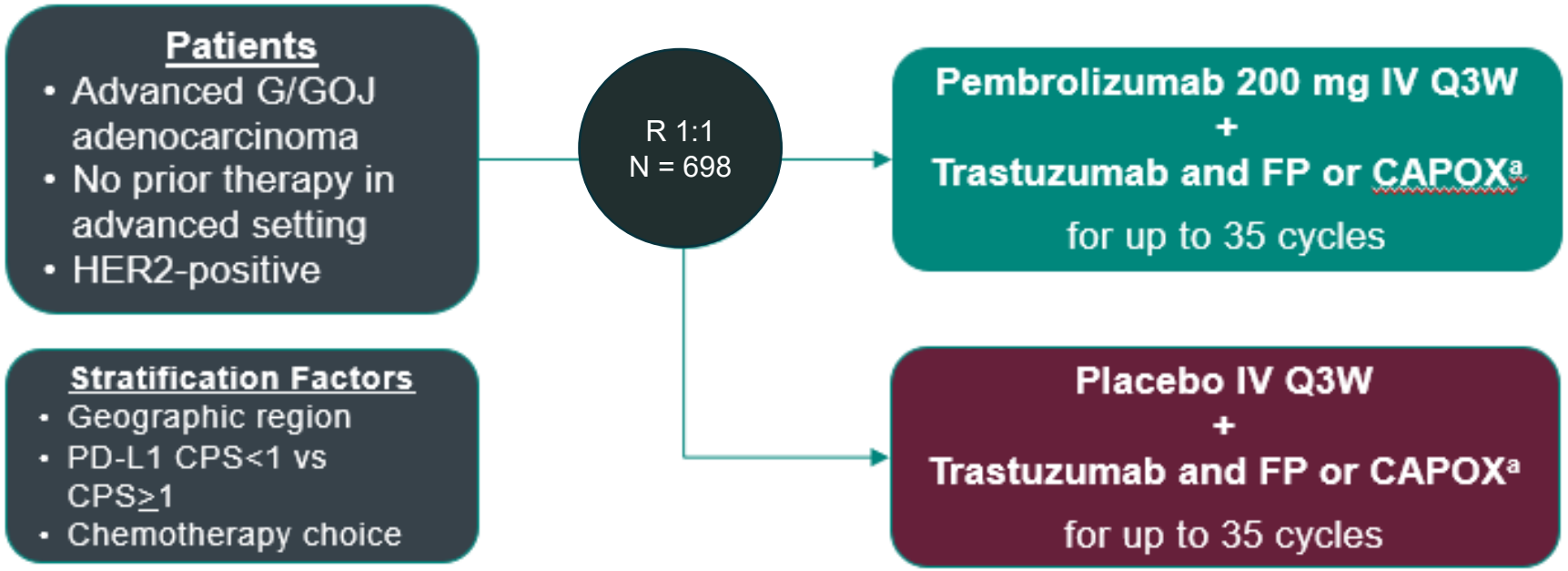
	Final scope	Company	EAG comments
Outcomes	OS, PFS, response rate, adverse events (AEs), health-related quality of life (HRQoL)	In line with final scope	• CS only summarises trial outcomes for the EQ-VAS but data were also collected for EORTC QLQ-C30 and EORTC QLQ-STO22 • Utilities by trial arm based on EQ-5D were provided during clarification
Subgroups	PD-L1 status, locally advanced unresectable, Metastatic	PD-L1 status	• Clinical advice to EAG suggests reasonable not to provide results for locally advanced unresectable and metastatic subgroup

CS: Company submission; OS: Overall survival; PD-L1: Programmed death-ligan 1; PFS: Progression-free survival

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

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 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)		17.0 (0.6 to 41.6)	13.9 (0.3 to 41.2)

See 'MSD response to CQs v4, table 13-15' for detailed baseline characteristics for non-Asia, Western Europe/Israel/North America/Australia and Rest of the World cohorts. See slide for 'KEYNOTE-811 Primary outcome results' for each cohort

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

KEYNOTE-811 KM Curves of PFS and OS (CPS≥1, non-Asia)

See slide for 'KEYNOTE-811 Primary outcome results'

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

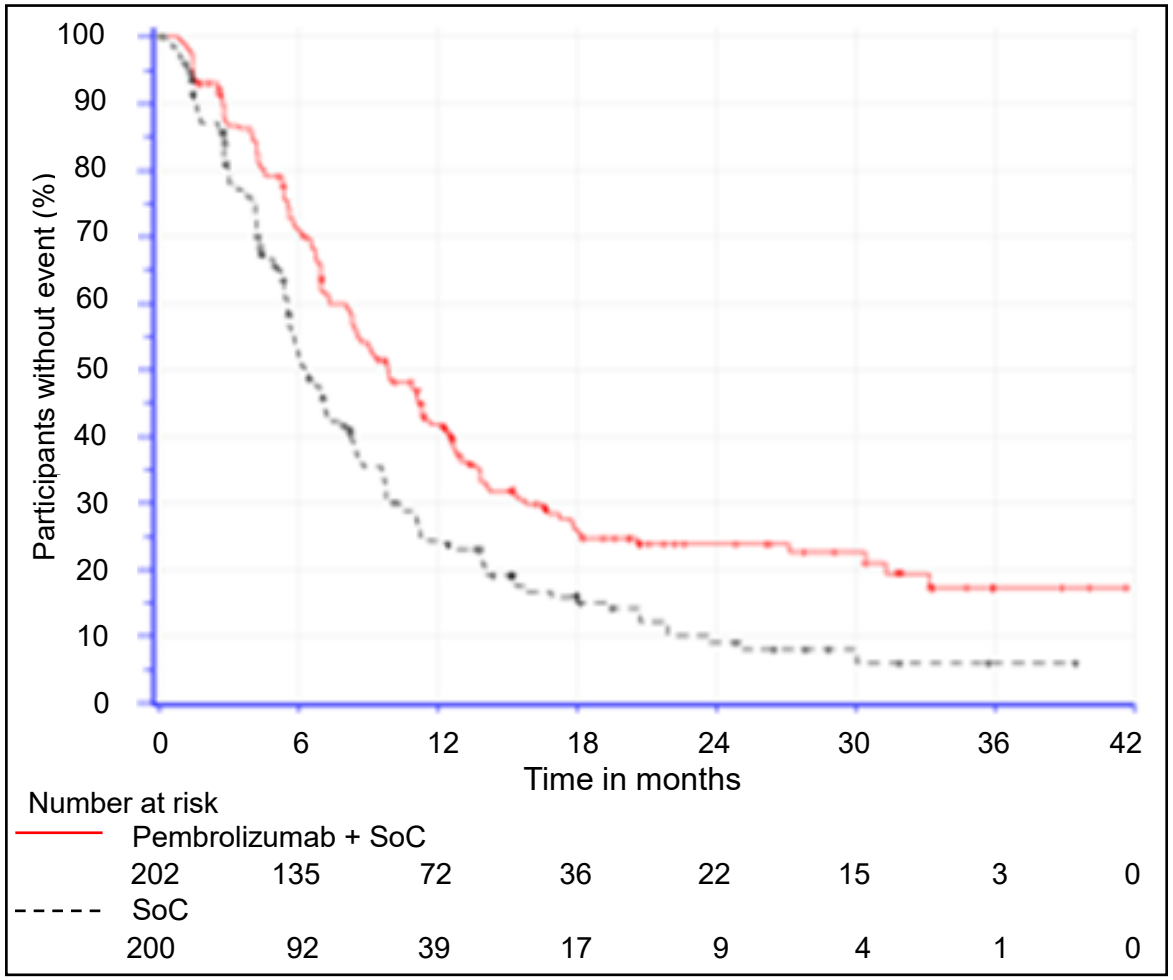
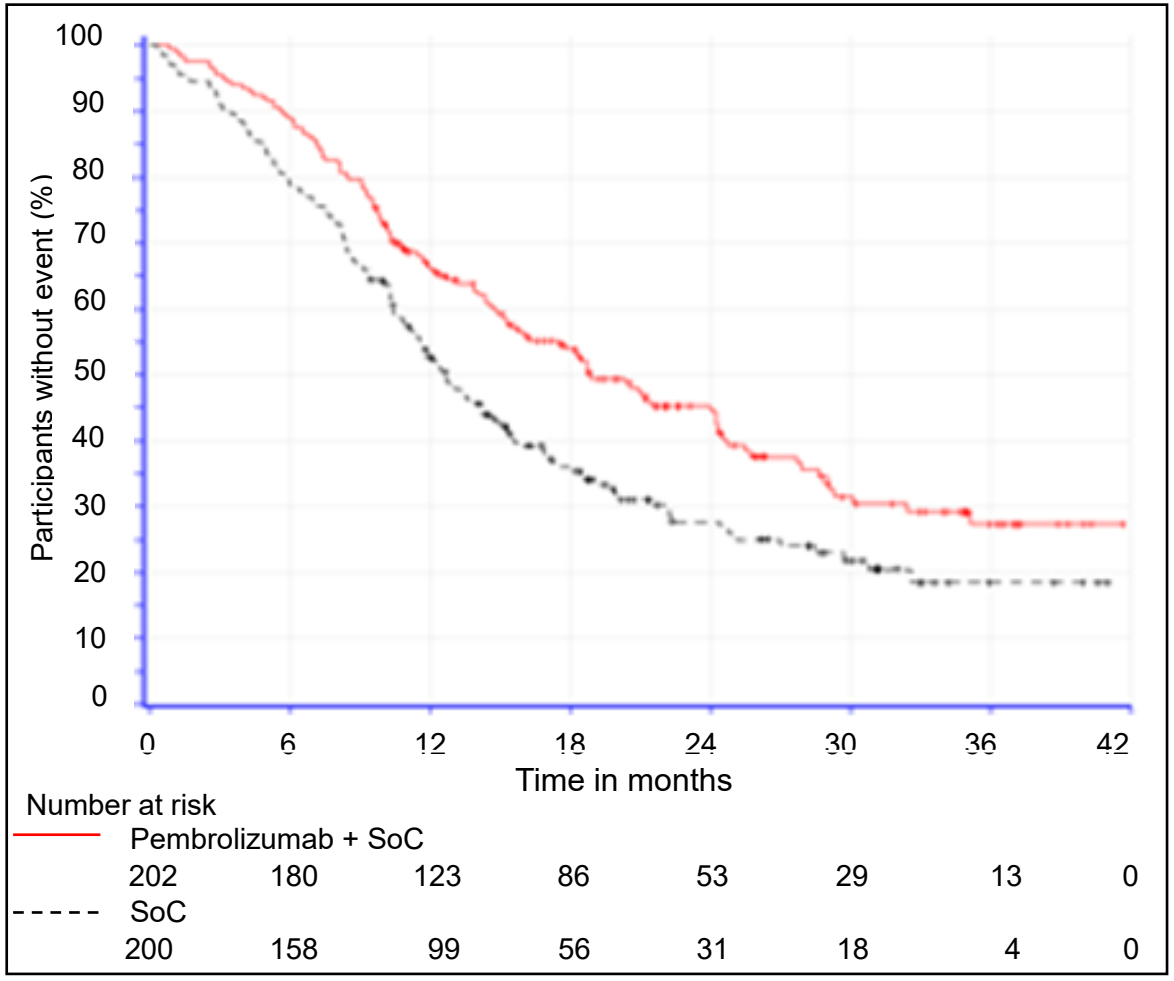


Figure: KEYNOTE-811 KM curve of OS (CPS ≥1, non-Asia)



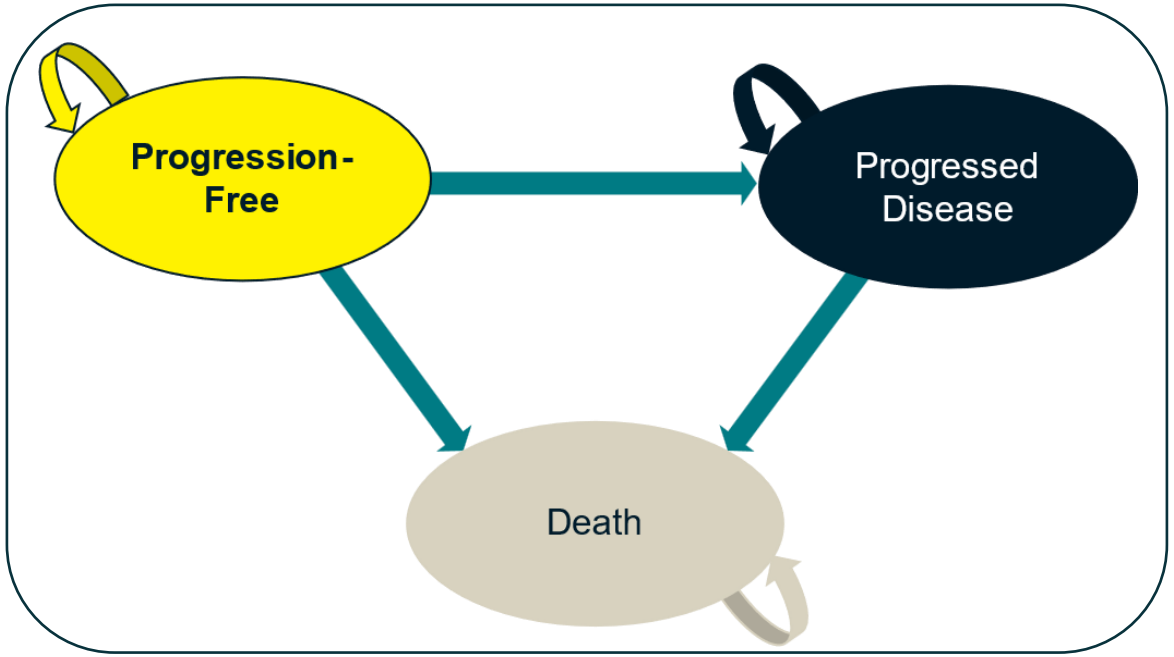
NICE

CPS: Combined positive score; ECOG: Eastern Cooperative Oncology Group; MA: Marketing Authorisation; OS: Overall survival; PD-L1; Programmed death-ligand 1; PFS: Progression-free survival; 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

How company incorporated evidence in the model (1/2)

Evidence source for model inputs and key assumptions

Input	Evidence source	Assumptions
Baseline characteristics	KEYNOTE-811 (PD-L1 CPS ≥1 from non-Asia region)	
OS	KEYNOTE-811 (PD-L1 CPS ≥1 from non-Asia region) – Curves fitted independently for pembrolizumab plus SoC arm and SoC arm	Progression free and progressed disease health state occupancy determined using pembrolizumab plus SoC arm and SoC arm OS and PFS distributions
PFS		
TTD	KEYNOTE-811 (non-Asia, CPS ≥1)	Treatment-specific TTD KM data
HRQoL	EQ-5D-5L data collected in KEYNOTE-811 (non-Asia, CPS ≥1) and mapped onto the 3L value set	HRQoL assumed to be independent of treatment received and determined by the patient's time to death, based on four categorical groups (<30 days; ≥30 to 180 days; ≥180 to 360 days, and ≥360 days) with utility declining as patients approach death

CPS: Combined positive score; HRQoL: Health-related quality of life; KM: Kaplan-Meier; OS: Overall survival; PD-L1: Programmed death-ligand 1; PFS: Progression-free survival; SoC: Standard of care; TTD: Time to treatment discontinuation

How company incorporated evidence in the model (2/2)

Evidence source for model inputs and key assumptions

Input	Evidence source	Assumptions
AEs	KEYNOTE-811 (non-Asia, CPS ≥1)	
Costs	Drug acquisition (eMIT and BNF), administration costs (National Schedule of NHS Costs 2021/22), management costs (TA208 and National Schedule of NHS Costs 2021/22), AEs (previous TA208, TA857, TA737 and National Schedule of NHS Costs 2021/22) and end of life (TA522 inflated to 2021/22)	Costs related to PD-L1 testing were not included as these “tests are administered to all patients in both treatment arms of the model”
Subsequent treatment	KEYNOTE-811 (non-Asia, CPS ≥1)	

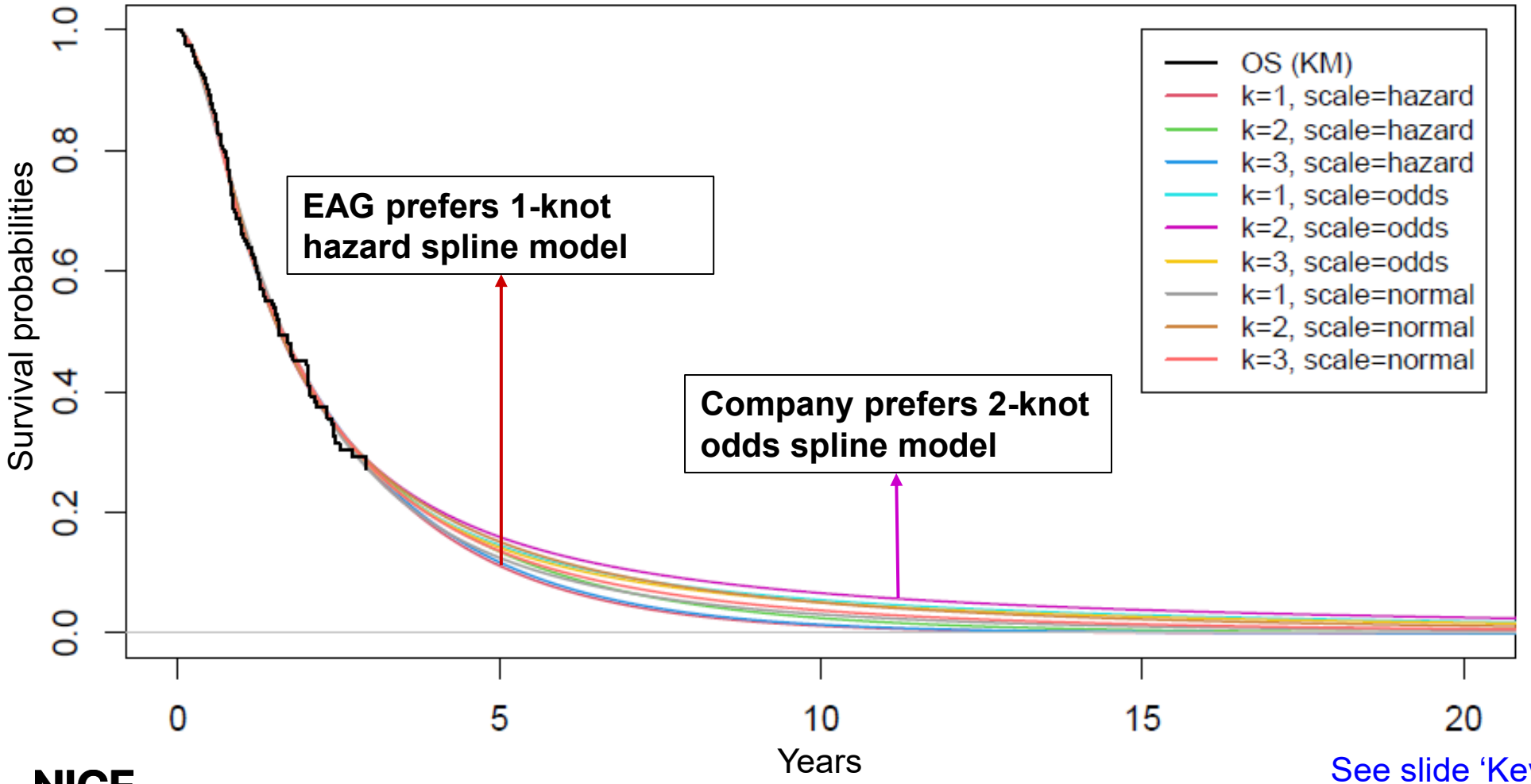
AEs: Adverse events; BNF: British National Formulary; CPS: Combined positive score; eMIT: Electronic market information tool; PD-L1; Programmed death-ligand 1; TA: Technology appraisal

Large impact on ICER

Key issue: OS extrapolation

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



See slide 'Key issue: OS extrapolations'

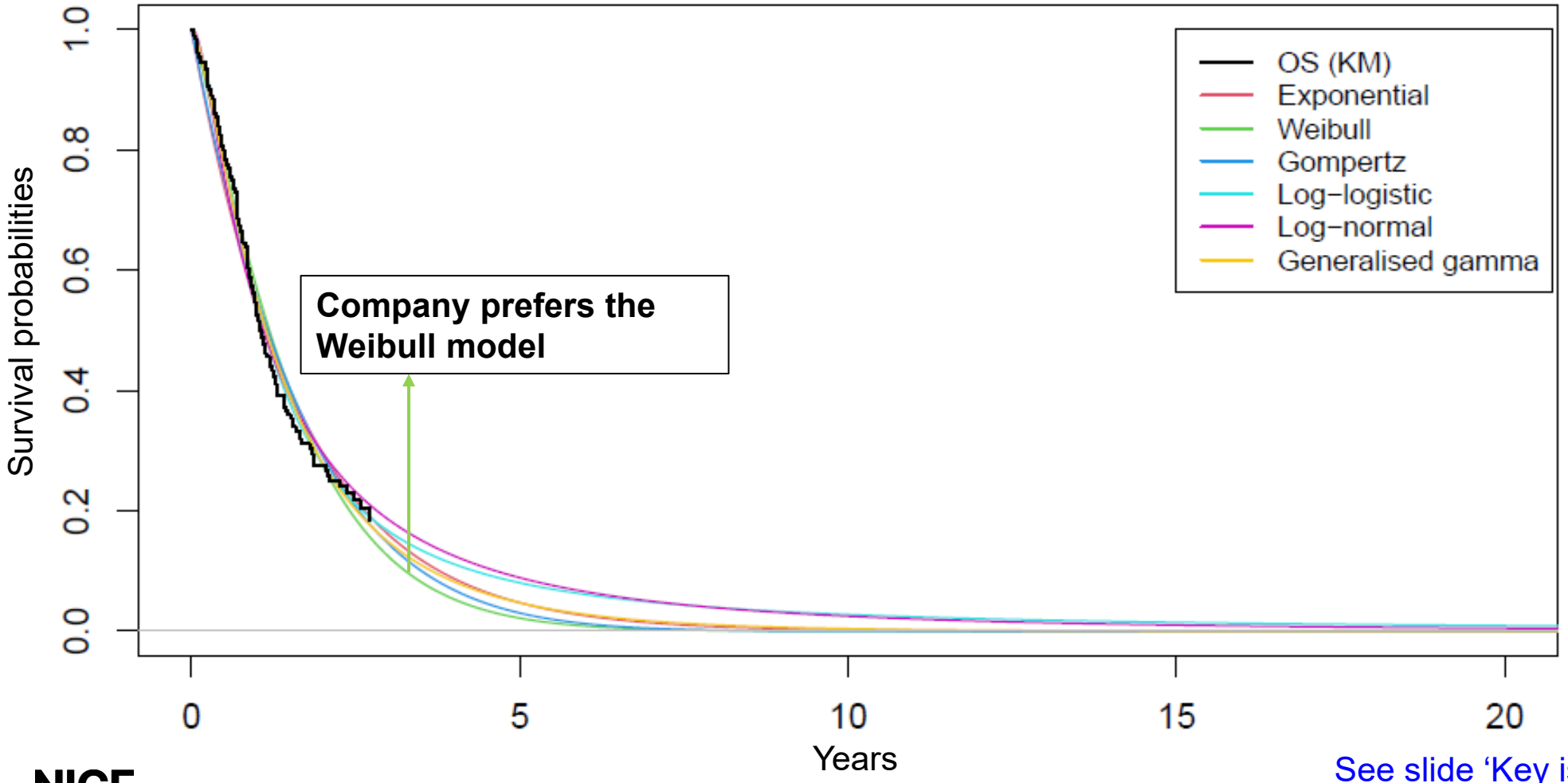
KM: Kaplan-Meier; OS: Overall survival; SoC: Standard of care

Large impact on ICER

Key issue: OS extrapolation

For SoC arm, company prefers the Weibull model

OS for the SoC arm, independently fitted standard parametric models



See slide 'Key issue: OS extrapolations'

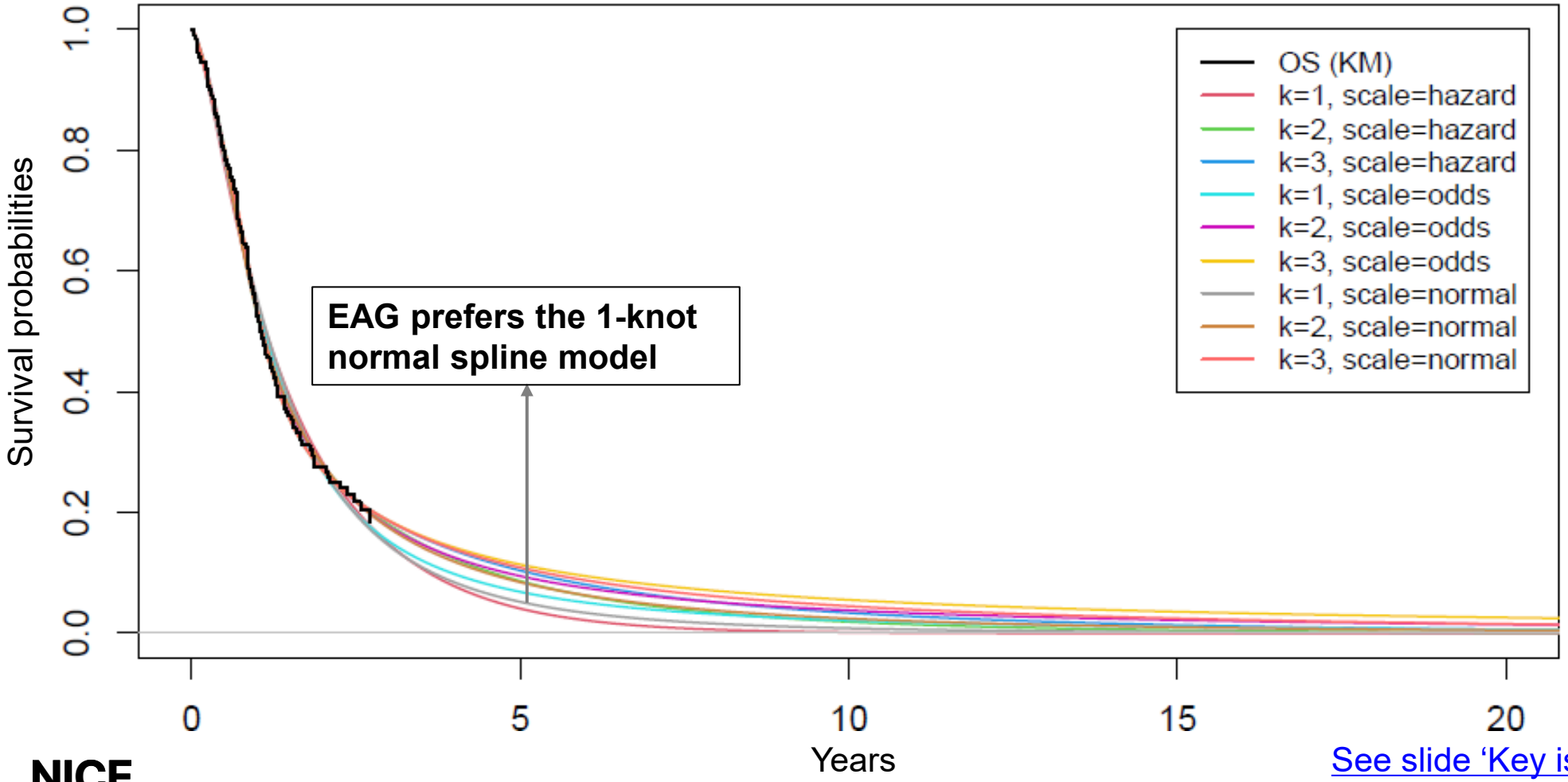
KM: Kaplan-Meier; OS: Overall survival; SoC: Standard of care

Large impact on ICER

Key issue: OS extrapolation

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

OS for the SoC arm, independently fitted spline models



See slide 'Key issue: OS extrapolations'

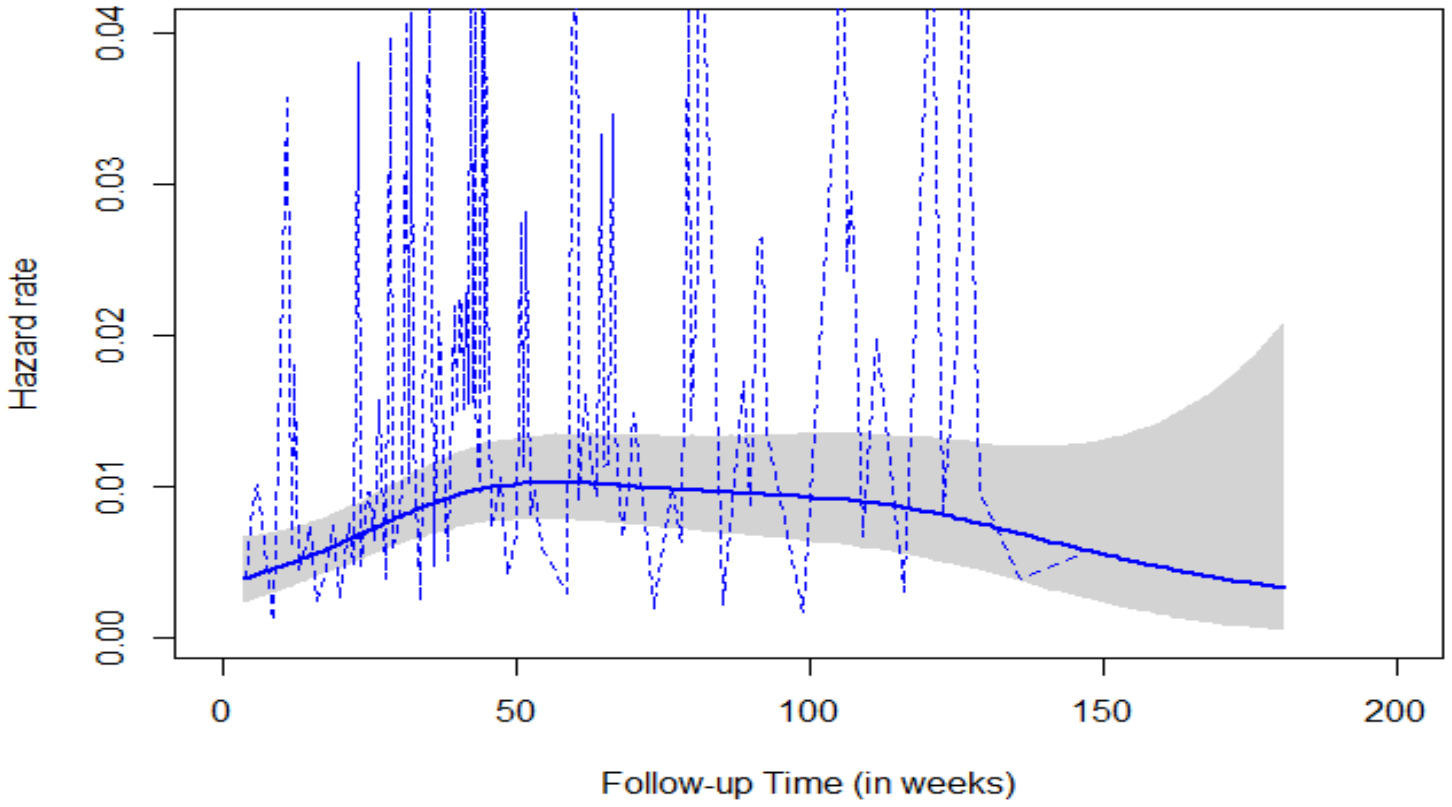
KM: Kaplan-Meier; OS: Overall survival; SoC: Standard of care

Large impact on ICER

Key issue: OS extrapolation

For pembrolizumab plus SoC arm, the smoothed hazard function shows a unimodal shape, which indicates that the log-normal, log-logistic, generalised gamma and all spline models may be appropriate

Figure: Unsmoothed hazards versus smoothed hazards for OS for pembrolizumab plus SoC arm



See slide 'Key issue: OS extrapolations'

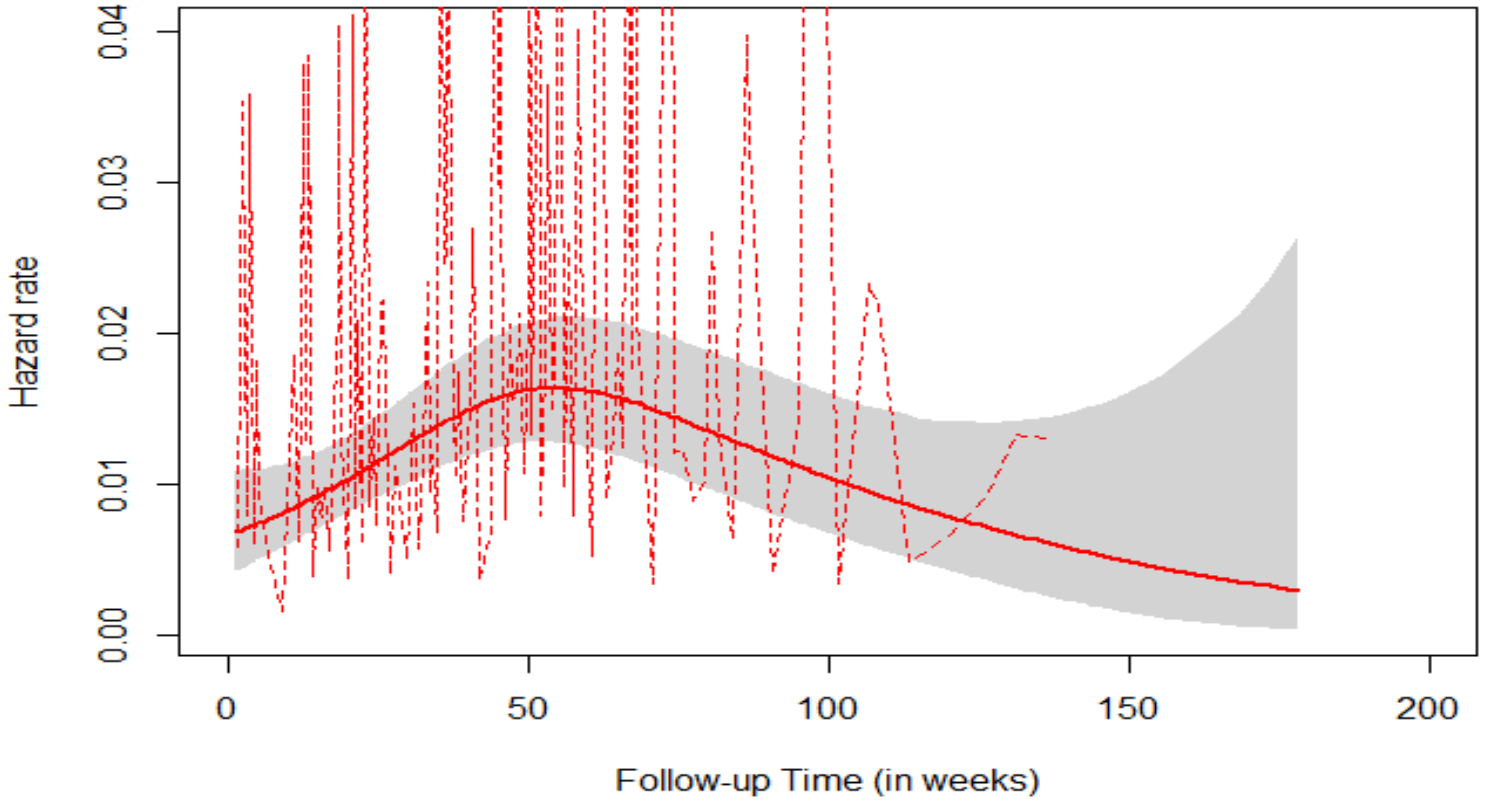
OS: Overall survival; SoC: Standard of care

Large impact on ICER

Key issue: OS extrapolation

For SoC arm, the smoothed hazard function shows a unimodal shape, which indicates that the log-normal, log-logistic, generalised gamma and all spline models may be appropriate

Figure: Unsmoothed hazards versus smoothed hazards for OS for SoC arm



See slide 'Key issue: OS extrapolations'

OS: Overall survival; SoC: Standard of care

EAG's and company's preferred base case PFS extrapolations

Company agreed post technical engagement with EAG's choice of log-normal curves fitted independently to both arms of non-Asia CPS ≥1 cohort

Figure: PFS for pembrolizumab plus SoC arm, independently fitted standard parametric models

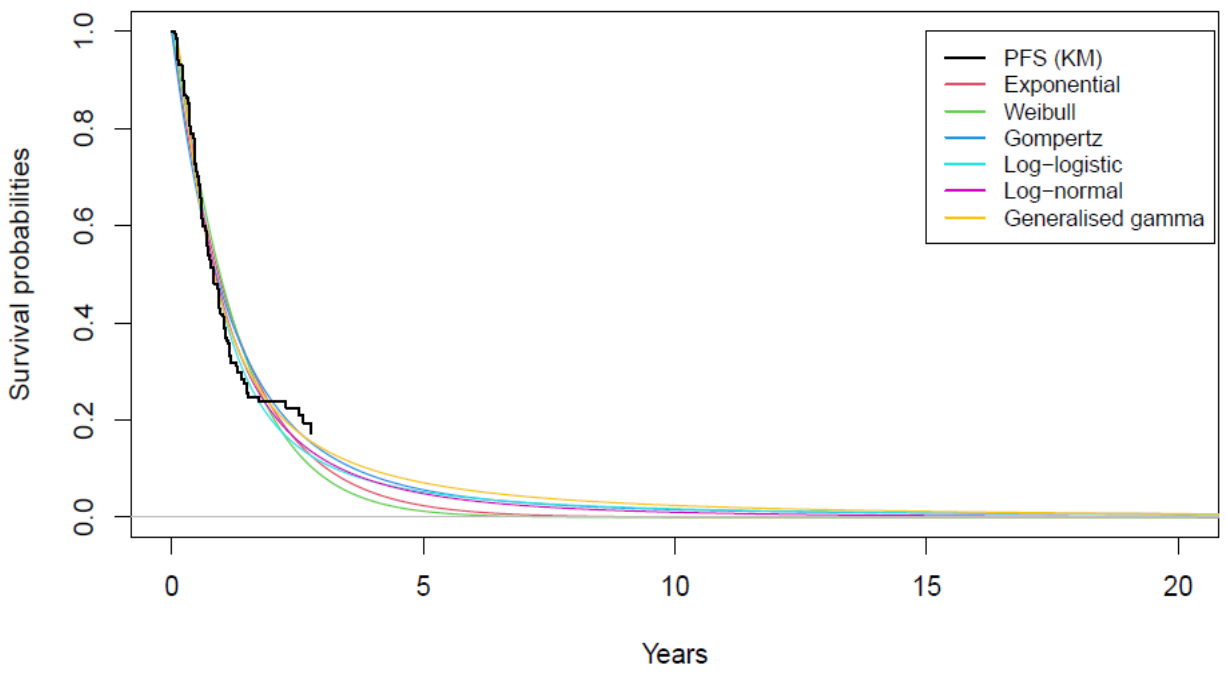
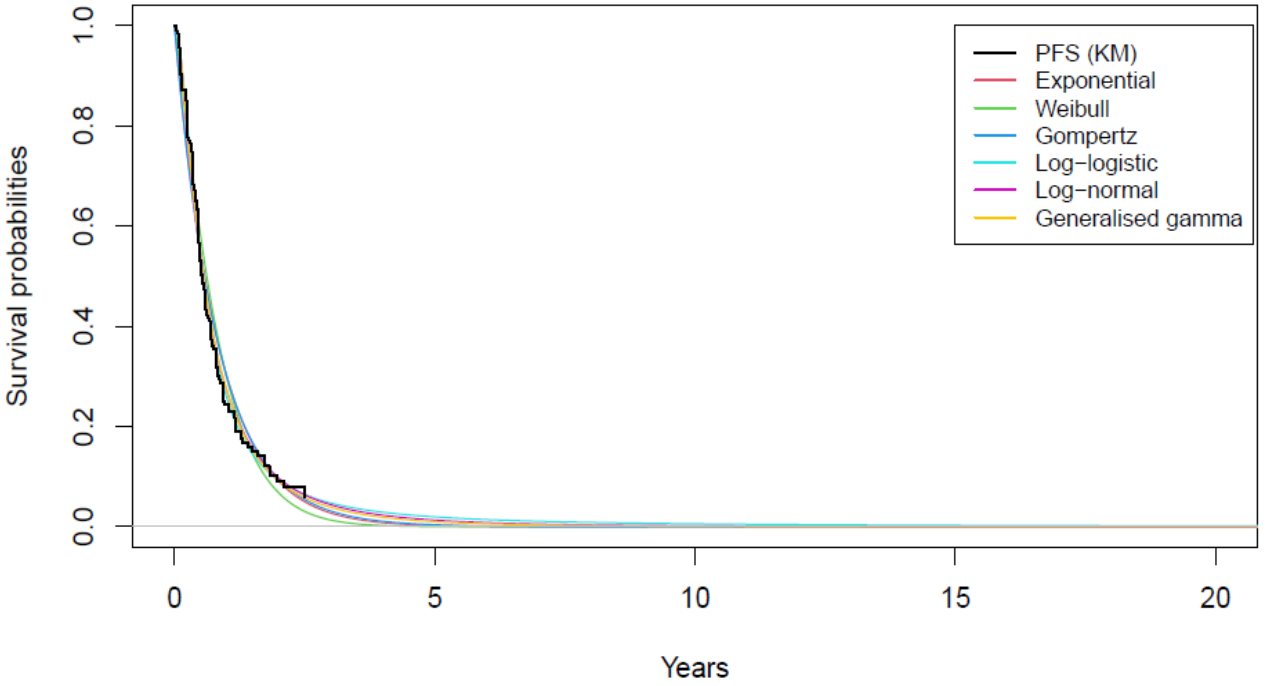


Figure: PFS for SoC arm, independently fitted standard parametric models



CPS: Combined positive score; PFS: Progression-free survival; SoC: Standard of care

Small impact on ICER

Additional issue 1 – Trastuzumab administration costs

Remaining additional issues have a very small impact on cost-effectiveness results

Additional issue	Company's base case	EAG base case	NICE tech team comments
Administration costs for trastuzumab when administered without pembrolizumab after doublet chemotherapy	• Applies reference cost for HRG code SB13Z (complex delivery) to trastuzumab whether given alone or with pembrolizumab after completion of CAPOX/XP • Considers addition of pembrolizumab will not change the administration cost	• Considers that there should be some difference in administration costs for trastuzumab given alone (simple delivery – HRG code SB12Z) versus trastuzumab given in combination with pembrolizumab (complex delivery – HRG code SB13Z) • Additional administration time required to deliver two treatments versus one should be reflected in the model	CDF clinical lead: • Trastuzumab monotherapy after chemotherapy: £127 (SB12Z) • Pembrolizumab with trastuzumab after chemotherapy: £320 (SB17Z) • Add cost of Medical Oncology Review NICE tech team view: • EAG scenario analysis with estimates from CDF clinical lead

See slide for 'Differences between company and EAG base case assumptions post technical engagement'

CAPOX: Capecitabine with oxaliplatin; CDF: Cancer Drugs Fund; HRG: Healthcare resource group; Cisplatin with capecitabine

Small impact on ICER

Additional issue 2 – Trastuzumab TTD

Remaining additional issues have a very small impact on cost-effectiveness results

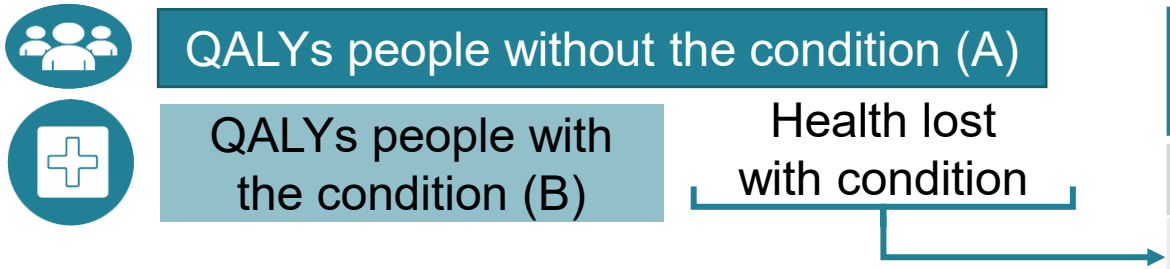
Additional issue	Company's base case	EAG base case	NICE tech team comments
Removing the cap for TTD of trastuzumab	• Caps the maximum number of treatment cycles of trastuzumab at 35 • Notes that only a small proportion of patients had more than this number of cycles in KEYNOTE-811 [redacted] for pembrolizumab plus SoC; [redacted] for SoC)	• Clinical advice suggests trastuzumab not restricted to 35 treatment cycles in clinical practice • Higher proportion of people on trastuzumab after 35 cycles in the pembrolizumab plus SoC arm could be related to improvements in PFS relative to SoC arm	• Clinical experts state trastuzumab should continue to disease progression • Recommend no cap (EAG base case) – NICE tech team agrees with EAG's approach

See slide for 'Differences between company and EAG base case assumptions post technical engagement'

PFS: Progression-free survival; SoC: Standard of care; TTD: Time to treatment discontinuation

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