NICE National Institute for Health and Care Excellence

SLIDES FOR PUBLIC OBSERVER HANDOUTS

Pembrolizumab for treating recurrent or metastatic squamous cell head and neck cancer

Lead team presentation

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ERG: Liverpool Reviews and Implementation Group
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Company: Merck Sharp & Dohme
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Key issues

Treatment choice: Can clear subgroups be identified for treatment with monotherapy or combination therapy? (Issue 2)

Generalisability of KEYNOTE-048 results - Cetuximab as a comparator: Is the comparator appropriate for people whose cancer started in the oral cavity or outside the oral cavity? (Issue 3)

Clinical effectiveness of pembrolizumab: Is pembrolizumab differentially effective in people whose cancer started in the oral cavity vs those whose cancer started outside the oral cavity? (**New** - Issue 8)

Comparison of pembrolizumab with platinum plus 5-FU: Is the company's NMA or the ERG's approach using data from the cetuximab with platinum and 5-FU arm of KEYNOTE-048 the most appropriate approach for the comparison? (Issue 4)

Overall survival extrapolation: Which extrapolation of overall survival is most clinically plausible? (Issue 5)

Duration of treatment effect: What is the most plausible assumption of duration of treatment effect? (Issue 6)

End of life criteria: Does pembrolizumab meet NICE's end of life criteria? (Issue 7)

Pembrolizumab (Keytruda, Merck Sharp & Dohme)

Mechanism	• Monoclonal antibody that binds to the PD-1 receptor blocking the interaction with the receptor ligands, PD-L1 and PD-L2.
Marketing authorisation	• Keytruda, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS ≥ 1
Administration and dose	• Pembrolizumab monotherapy: 200mg every 3 weeks (Q3W) or 400mg every 6 weeks (Q6W) intravenously • Pembrolizumab in combination with platinum-based chemotherapy 200mg every 3 weeks (Q3W) intravenously
Indicative list price	• £2,630 per 100mg vial.

PD = programmed cell death, TPS = tumour proportion score

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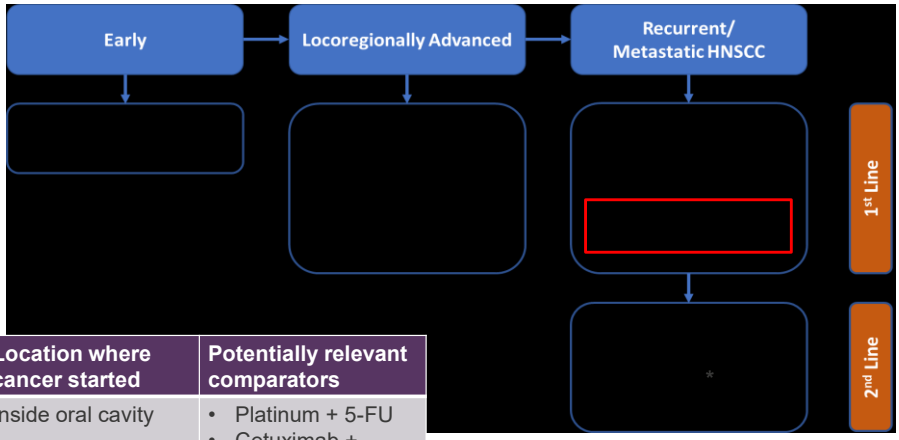
Treatment Pathway



Location where cancer started	Potentially relevant comparators
Inside oral cavity	• Platinum + 5-FU • Cetuximab + platinum + 5-FU
Outside oral cavity	• Platinum + 5-FU

***Note: Nivolumab (TA490) only available through the Cancer Drugs Fund**

HNSCC: head and neck squamous cell carcinoma
[1]Platinum-based chemotherapy regimens
[2]If the cancer started in the oral cavity

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Source: adapted from company submission

Patient perspectives

- Large impact on person, carer and family
- Hope to achieve complete response and or progression free long term
- Quality of Life must be considered in survivorship

Clinical expert statements

Aims of treatment
- Longer term survival gain, control progression and improve overall survival

Current treatment options
- Standard of care is chemotherapy with platinum plus 5-FU and cetuximab (oral cavity) and platinum plus 5-FU (non-oral cavity)
- Those with recurrent/metastatic head and neck squamous cell carcinoma - offered nivolumab through Cancer Drugs Fund (CDF) after progression within 6 months of platinum-based chemotherapy, otherwise second line palliative chemotherapy

Clinical need
- Pembrolizumab showed significantly improved longer term survival
- Toxicity compared with the current standard treatment is different, although the management is broadly equally complex

Additional
- Infrastructure is in place to deliver these treatments

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KEYNOTE-048

Trial design	Phase III, open label, randomised (1:1:1), multinational (n=37), multicentre (n=229)
Intervention	• Pembrolizumab (n=301) • Pembrolizumab + platinum + 5-fluorouracil (5-FU) (n=281)
Comparator	Cetuximab + platinum + 5-FU arm (n=300)
Population*	• Adults with confirmed recurrent or metastatic head and neck squamous cell carcinoma considered incurable by local therapies • ECOG Performance status of 0 or 1 • No prior systemic therapy administered in the recurrent or metastatic setting (with the exception of systemic therapy completed > 6 months prior if given as part of multimodal treatment for locally advanced disease)
Outcomes	• Primary outcomes: Overall survival (OS), Progression-free survival (PFS) • Secondary outcomes: Progression-free at 6 and 12 months, Objective response rate

*Company base-case population is a PD-L1 CPS ≥1 subgroup of KEYNOTE-048

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KEYNOTE-048 clinical results

Key results	All patients (overall survival) Monotherapy vs cetuximab + platinum + 5-FU: HR 0.71 (0.57 to 0.89) p=0.0027* Combination vs cetuximab + platinum + 5-FU: HR 0.62 (0.50 to 0.78) p=<0.0001* Cancer started inside the oral cavity (overall survival) Monotherapy vs cetuximab + platinum + 5-FU: HR [redacted] Combination vs cetuximab + platinum + 5-FU: HR [redacted]

*Adjusted for subsequent anti-PD-1 treatment using the simplified 2-stage method

Stratification in study design	Stratification by: 1. Tumour PD-L1 (Strongly positive = TPS≥50%, Not strongly positive = TPS<50%, or not able to be determined for any reason). 2. HPV status (positive or negative) – patients without oropharynx cancer (e.g. cancers of the oral cavity, hypopharynx and larynx) were considered HPV negative. 3. ECOG status (0 or 1)

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PD-L1 = programmed cell death ligand 1
TPS = tumour proportion score
HPV = Human papillomavirus
ECOG = Eastern Cooperative Oncology Group

Model assumptions

Partitioned survival model with 3 health states: progression-free, progressed disease, death	
Subsequent therapy	• No use of nivolumab as a subsequent therapy despite its use in KEYNOTE-048 (NICE position statement: exclusion as comparators or subsequent treatments, any drugs currently available in the Cancer Drugs Fund) • Cross-over adjustment conducted to remove its effect on overall survival curve - cost not included in economic model
Adverse events	• Incidence of AEs from KEYNOTE-048 and published trials assumed to reflect that observed in practice • Based on results of KEYNOTE-048 and published trials for platinum plus 5-FU
Utility values (collected in KEYNOTE-048 using EQ-5D-3L)	• Adjusted by UK general population utility where utility decreases with age - *Ara and Brazier* (2010). • Model assumed no difference between treatments in the pre- and post-progression states
Costs and resource use	• Assumed to be equal between pembrolizumab and cetuximab with platinum chemotherapy plus 5-fluorouracil / platinum plus 5-FU arms • Resource use assumed to be equal per treatment arm in the pre- and post- progression health states

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Issues resolved after technical engagement

	Summary	Technical team consideration	Stakeholder responses	Updated company base case?
1	• SPC for other indications → should receive pembrolizumab until disease progression or unacceptable toxicity • 2-year stopping rule was applied in trial & model	Consider a 2-year stopping rule to be appropriate for decision making (in line with previous pembrolizumab appraisals)	Clinical expert: 2-year stopping rule appropriate Company and NCRI-ACP-RCP-RCR agreed with technical team	Not applicable

SPC = summary of product characteristics

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Outstanding issues after technical engagement

Issue 2: Treatment choice (between monotherapy and combination)

Issue 3: Origin of tumour location

New issue (8): Clinical effectiveness of pembrolizumab

Issue 4: Network meta-analyses: comparing pembrolizumab (monotherapy or in combination) with platinum chemotherapy and 5-fluorouracil

Issue 5: Extrapolation of overall survival (OS)

Issue 6: Duration of treatment effect

Issue 7: End of life criteria

Issue 2: Treatment choice (identification of subgroups)

Company submission: choice of therapy made by clinician in consultation with patient. Combination better for people so unwell that unethical to give monotherapy as delayed response (3 to 6 months)

Company response from engagement:

Decision on therapy choice made on a case-by-case basis (benefit versus risk):

- Monotherapy - low burden of disease, disease progression, may not be fit to tolerate combination
- Combination therapy - heavy burden of disease, progressing rapidly, relapsed after chemotherapy

Summary of clinical expert responses from engagement:

Therapy	Indicators for choice of therapy
Pembrolizumab monotherapy	Good performance status, previous chemotherapy (neoadjuvant and/or high dose concurrent chemoradiotherapy) with residual chemotherapy induced toxicities
Pembrolizumab combination therapy	Good performance status, not heavily pre-treated with chemotherapy **or** have no residual chemotherapy induced toxicities (where a rapid response is needed). **Not** suitable for people with borderline/poor performance status. Preferred for rapid progressing disease.

ERG comment:

If people were so unwell that an immediate response to treatment was necessary, then they may also be too ill to tolerate the level of adverse events associated with pembrolizumab combination therapy.

KEY QUESTION: Can clear subgroups be identified for treatment with monotherapy or combination therapy?

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Issue 3: Origin of tumour location - treatment

Comparator in KEYNOTE-048 is cetuximab + platinum + 5-fluorouracil (5-FU) - given to all patients irrespective of where cancer started.

Company response from engagement:

- KEYNOTE-048 results generalisable to all patients with HNSCC.
- Not feasible to consider subgroups by cancer location because:-
  - KEYNOTE-048 not pre-specified to conduct subgroup analyses based on cancer location (not powered).
  - "not aware of biological reason for cetuximab to be more clinically effective in oral cavity" TA172
  - EMA decision for cetuximab not restricted to patients with cancer that starts in the oral cavity.

Summary of clinical experts response from engagement:

- KEYNOTE-048 results generalisable to all with HNSCC irrespective of primary tumour site.
- Subgroups by cancer location appropriate - variable prognoses (poorer prognosis for oral cavity).
- Primary tumour site as subgroups could be considered – may be biologically / clinically divergent.

Issue 3: Origin of tumour location - treatment

ERG pre-engagement comment:

- Cetuximab + platinum + 5-FU - NICE (TA473) option for HNSCC that started in the oral cavity.
- KEYNOTE-048: 31% had cancer that started in oral cavity, 69% received none standard NHS care.
- At clarification: company provided data from subgroup (cancer started in the oral cavity) in KEYNOTE-048. No evidence for subgroup whose cancer started outside the oral cavity.

ERG considerations on company engagement comments:

- Population recruited to KEYNOTE-048 trial only representative of the fittest patients in the NHS with R/M HNSCC, i.e. fit enough to receive cetuximab in combination with platinum chemotherapy and 5-FU.
- Clinical advice to ERG - in NHS practice, cetuximab in combination with platinum chemotherapy and 5-FU rarely used to treat cancer that started in the oral cavity because only a minority of people with this type of cancer are fit enough to tolerate the treatment.
- Cetuximab in combination with platinum chemotherapy and 5-FU only recommended for cancer that starts in the oral cavity. Treatment options for those with cancer that started in the oral cavity and those whose cancer started elsewhere are different and therefore these 2 populations need to be considered separately.

KEY QUESTIONS: Is the comparator appropriate for people whose cancer started in the oral cavity and outside the oral cavity?

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Issue 8 (New): Clinical effectiveness of pembrolizumab

Median overall survival results from KEYNOTE-048 (All PD-L1 CPS≥1 patients)

Pembrolizumab monotherapy vs cetuximab + platinum + 5-FU = **12.3 months** (95% CI: 10.8 to 14.3)* vs **10.1 months** (95% CI: 9.0 to 11.5)* respectively

Pembrolizumab combination therapy vs cetuximab + platinum + 5-FU = **13.6 months** (95% CI: 10.7 to 15.5)* vs **10.3 months** (95% CI: 9.0 to 11.5)* respectively

Hazard ratios - All PD-L1 CPS≥1 patients (overall survival)

Monotherapy vs cetuximab + platinum + 5-FU: HR 0.71 (0.57 to 0.89) p=0.0027*
Combination vs cetuximab + platinum + 5-FU: HR 0.62 (0.50 to 0.78) p=<0.0001*

*Adjusted for subsequent anti-PD-1 treatment using the simplified 2-stage method

Hazard ratios - cancer started inside the oral cavity (overall survival)

Pembrolizumab monotherapy vs cetuximab + platinum + 5-FU: HR [redacted]
Combination therapy vs cetuximab + platinum + 5-FU: HR [redacted]

*Adjusted for subsequent anti-PD-1 treatment using the simplified 2-stage method

- No statistically significant difference between pembrolizumab treatments in people whose cancer started in the oral cavity
- No evidence provided for people whose cancer started outside the oral cavity

KEY QUESTION: Is pembrolizumab differentially effective in people whose cancer started in the oral cavity vs those whose cancer started outside the oral cavity?

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Issue 4: NMA: pembrolizumab vs platinum + 5-FU

Company approach	ERG approach
Network meta-analysis	**Use K-M data from cetuximab + platinum + 5-FU arm of KEYNOTE-048 to represent those whose cancer did not start in the oral cavity**
• Accounts for study-observed differences • Results likely to reflect true relative effectiveness • PD-L1 unlikely to be a treatment effect modifier • Only fractional polynomial models with treatment effects scale and first shape parameter used	• Simple, transparent and based on data from high-quality trial
ERG concerns with company approach • No assessments of plausibility for hazard ratios estimated by the fractional polynomial models • No information provided on how 2 categories of fractional polynomial models assessed • Used data from the PD-L1 CPS≥1 subgroup vs overall trial populations in other trials – likely introduced heterogeneity • Not stratified by primary tumour location • If effectiveness differs by origin of cancer (as suggested by OS differences subgroups in EXTREME study) – NMA results compromised	**Company concerns with ERG approach** • May overestimate effectiveness of platinum + 5-FU - underestimate relative treatment effect • Assumes OS K-M curves for cetuximab + platinum + 5-FU in KEYNOTE-048 same as in EXTREME study

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Issue 4: NMA: pembrolizumab vs platinum + 5-FU

Overall survival NMA results for pembrolizumab monotherapy (all PD-L1 CPS≥1 subgroup patients):

Comparator	Time after starting treatment	Hazard Ratio
Cetuximab + platinum + 5-FU	Month 6	[redacted]
	Month 36	[redacted]
Platinum + 5-FU	Month 6	[redacted]
	Month 36	[redacted]

Overall survival NMA results for pembrolizumab combination therapy (all PD-L1 CPS≥1 subgroup patients):

Comparator	Time after starting treatment	Hazard Ratio
Cetuximab + platinum + 5-FU	Month 9	[redacted]
	Month 36	[redacted]
Platinum + 5-FU	Month 6	[redacted]
	Month 36	[redacted]

*Adjusted for subsequent anti-PD-1 treatment using the simplified 2-stage method

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Issue 4: NMA: pembrolizumab vs platinum + 5-FU

ERG approach: K-M data from cetuximab + platinum + 5-FU arm of KEYNOTE-048 to represent those whose cancer did not start in the oral cavity results in the following hazard ratios

Monotherapy vs platinum + 5-FU: HR 0.71 (0.57 to 0.89) p=0.0027*
Combination vs platinum + 5-FU: HR 0.62 (0.50 to 0.78) p=<0.0001*

*Adjusted for subsequent anti-PD-1 treatment using the simplified 2-stage method

Response from engagement:

Clinical expert: Agree with the ERG's approach.

NCRI-ACP-RCP-RCR: ERG's approach seems reasonable.

Technical report:

Technical team prefer a treatment comparison using the ERG's approach

KEY QUESTION: Is company's NMA or the ERG's approach using data from cetuximab with platinum and 5-FU arm of KEYNOTE-048 the best to compare pembrolizumab with platinum plus 5-FU?

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Issue 5: Overall survival extrapolation

Company choice of distribution curve	ERG choice of distribution curve
log-logistic for monotherapy **log-normal** for combination therapy	**Weibull** for both monotherapy and combination therapy
• Good predictors for OS (clinician input) • Best AIC/BIC test fit • 5-year follow up of EXTREME study - 2.9% of patients alive at 5-years – company extrapolation for KEYNOTE-048 is 2.4%	• Gave most clinically plausible results
ERG concerns with company choice • Very long tails and hazard ratios that decrease over time = suggest clinically implausible • Mortality hazard rate falls below that of general population after approx.18 years = lower probability of dying than the general population	**Company concerns with ERG approach** • Weibull curve gives worst goodness-of-fit • underestimates OS of both comparator arms in EXTREME study 5-year follow up

Summary of clinical experts responses from engagement:

- Company's data plausible for up to 5 years.
- ERG modelled data seems most plausible for monotherapy and combination therapy survival.
- Company and ERG seem clinically plausible for cetuximab + platinum + 5-FU or platinum + 5-FU

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Issue 5: Overall survival extrapolation

EXTREME (5-year follow up) vs KEYNOTE-048 (extrapolated survival estimates)

Treatment arm	% people alive at approx. 5-years				
	EXTREME (Actual results)	Monotherapy (KEYNOTE-048)		Combination therapy (KEYNOTE-048)	
		Company	ERG	Company	ERG
Cetuximab + platinum + 5-FU	2.9	3.3	2.1	2.4	0.9
Platinum + 5-FU	1.7	2.3	1.6	0.7	0.3

Note: EXTREME study = Cetuximab + platinum + 5-FU vs Platinum + 5-FU

Technical report:

- Uncertainty with the extrapolation of survival estimates.
- Both company and ERG extrapolations provided clinically plausible results 5 years after starting treatment.
- Technical team accepts ERG's argument that distributions preferred by the company have very long tails and clinical expert feedback that indicated that the 10-year survival estimates are clinically less plausible.
- Technical team prefer a piecewise model (K-M data from KEYNOTE-048 up to 80 weeks) followed by a Weibull distribution.

KEY QUESTION: Which extrapolation of overall survival is most clinically plausible?

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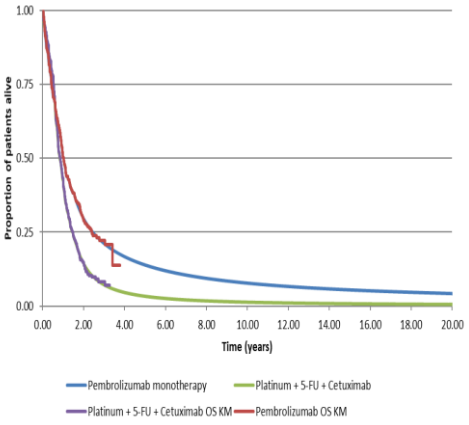
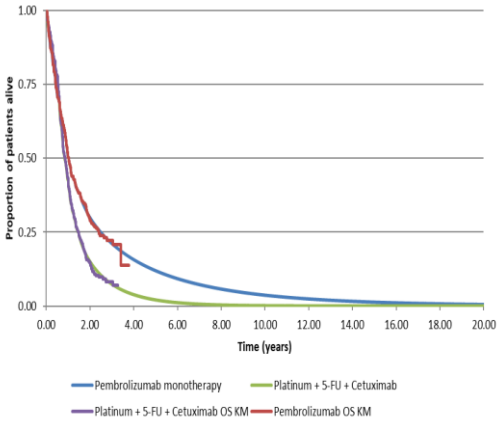
Issue 5: Overall survival extrapolation - preference

Overall survival curves (Pembrolizumab monotherapy)

COMPANY: Piecewise K-M (80 weeks) + log-logistic



ERG: Piecewise K-M (80 weeks) + Weibull



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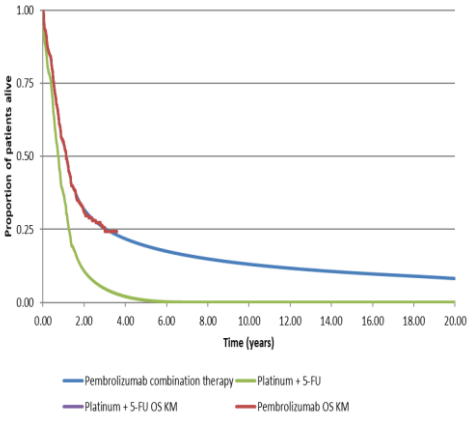
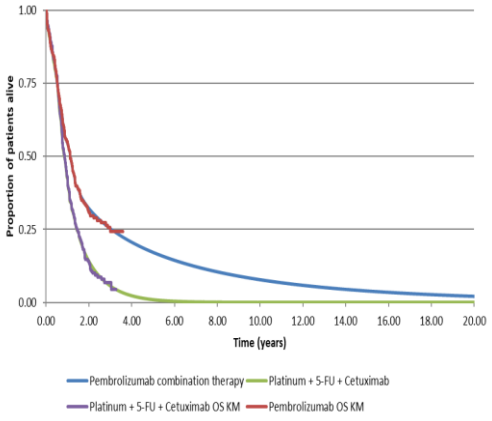
Issue 5: Overall survival extrapolation - preference

Overall survival curves (Pembrolizumab combination)

COMPANY: Piecewise K-M (80 weeks) + log-normal



ERG: Piecewise K-M (80 weeks) + Weibull



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Issue 6: Duration of treatment effect (time from starting treatment)

- Company original base-case assumes 20-year duration of treatment effect (that is, treatment effect continues up to 20 years from starting therapy)
- Technical team preference for 5-year duration of treatment effect
- **Note: all patients in KEYNOTE-048 stopped treatment with pembrolizumab (monotherapy or in combination) 2 years after starting**

Company response from engagement:

5-year duration of treatment effect inappropriate because:-

- Long-term treatment effect of pembrolizumab in other tumours: 5-year follow up data in advanced NSCLC - continued to respond with pembrolizumab (plateau phase at month 40 through to year 5
- Pembrolizumab vs ipilimumab in advanced melanoma - plateau phase from 35 months
- Overall survival in KEYNOTE-048 CPS ≥ 1 subgroup for monotherapy and combination therapy - plateau phase has begun at roughly 35 months in both intervention arms
- Clinical expert (TA490) believed patients who enter plateau will enjoy health benefits (including out to 5 to 10 years)
- NICE clinical expert (for this appraisal) responses: “duration of treatment effect with pembrolizumab or other immuno-oncology (IO) agents are likely to be 5 years or more, but unlikely to be 10 years” **and** all treatment effect beyond 5 years is by definition due to the pembrolizumab as almost zero survivors without pembrolizumab beyond 5 years

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Issue 6: Duration of treatment effect (time from starting treatment)

ERG pre-engagement comment:

- No substantial clinical evidence presented to support 20-year duration of treatment effect.
- Previous appraisals of immunotherapies, e.g. atezolizumab for treating NSCLC after chemotherapy (TA520), explored scenarios where mortality rates for immunotherapies become the same as those for comparator therapies 3 and 5 years after starting treatment.

ERG considerations on company engagement comments:

- In the absence of evidence this is a matter of conjecture.

Technical report:

- More evidence needed to support the longer duration of treatment effect of 20 years.
- Clinical expert advice indicated that treatment effect duration of up to 5 years is plausible.
- Previous appraisals (including nivolumab for treating head and neck cancer after platinum-based chemotherapy [TA490]) assumed 5-year duration of treatment effect.
- Preferable to model a more conservative duration of 5 years.

KEY QUESTION: What is the likely duration of treatment effect for pembrolizumab?

Issue 7: End of life – overall population approach

Short life expectancy: KEYNOTE-048

Median OS for people having cetuximab + platinum + 5-FU = **10.3 months** (95% CI: 9.0 to 11.5)

Extension to life (median) - all PD-L1 CPS≥1 subgroup patients

- Base case company model: compared with cetuximab + platinum + 5-FU and platinum + 5-FU, treatment with pembrolizumab monotherapy offers life extensions of **1.06** and **1.44** years respectively
- Base case company model: compared with treatment with cetuximab + platinum + 5-FU and platinum + 5-FU, treatment with pembrolizumab combination therapy offers life extensions of **1.19** and **1.61** years respectively

Population	End of life criteria met?	
	Short life expectancy	Extension to life
KEYNOTE-048 PD-L1 CPS≥1 subgroup - all patients	YES	YES
KEYNOTE-048 PD-L1 CPS≥1 subgroup whose cancer started inside the oral cavity	YES	YES
KEYNOTE-048 PD-L1 CPS≥1 subgroup whose cancer started outside the oral cavity	YES	YES

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Issue 7: End of life – subgroup population approach

Short life expectancy: KEYNOTE-048

Median OS for people having cetuximab + platinum + 5-FU = **10.3 months** (95% CI: 9.0 to 11.5)

Hazard ratios - cancer started inside the oral cavity (overall survival)

Pembrolizumab monotherapy vs cetuximab + platinum + 5-FU: HR [redacted]
Combination therapy vs cetuximab + platinum + 5-FU: HR [redacted]

*Adjusted for subsequent anti-PD-1 treatment using the simplified 2-stage method

- No statistically significant difference between pembrolizumab treatments in people whose cancer started in the oral cavity
- No evidence provided for people whose cancer started outside the oral cavity

Population	End of life criteria met?	
	Short life expectancy	Extension to life
KEYNOTE-048 PD-L1 CPS≥1 subgroup - all patients	YES	YES
KEYNOTE-048 PD-L1 CPS≥1 subgroup whose cancer started inside the oral cavity	YES	NO
KEYNOTE-048 PD-L1 CPS≥1 subgroup whose cancer started outside the oral cavity	YES	UNKNOWN (no evidence)

KEY QUESTION: Does pembrolizumab meet NICE's end of life criteria for all subgroups?

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Additional areas of uncertainty

Issue	Why issue is important	Impact on ICER
Relative effectiveness of pembrolizumab compared with cetuximab in combination with platinum chemotherapy and 5-FU or platinum plus 5-FU chemotherapy	• No head-to-head trial. • Relative effectiveness has to be estimated that adds uncertainty in the assessment of clinical effectiveness.	Unknown
Standard care in KEYNOTE-048 only included people with ECOG Performance Status of 0 or 1	• Increased uncertainty in the true relative clinical effectiveness of the treatments because in clinical practice this population may have a poorer prognosis than those in the trial and in the economic model.	Unknown

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Cost-effectiveness results – company base-case (1)

Key assumptions:

- 20-year duration of treatment effect
- Log-logistic piecewise approach for monotherapy
- Log-normal piecewise approach for combination therapy
- Confidential discount applied for pembrolizumab and list price for all other drugs (first line and subsequent treatment)

Cancer started inside the oral cavity

	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
Monotherapy	£48,945	1.688	-£2,886	0.777	**Dominant**
Cetuximab + platinum + 5-FU	£51,832	0.912			

	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
Combination therapy	£64,414	2.122	£11,817	1.277	**£9,255**
Cetuximab + platinum + 5-FU	£52,597	0.845			

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Note: Analysis with confidential discounts for all other drugs (first line and subsequent treatment) will be considered in PART 2

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Cost-effectiveness results – company base-case (2)

Key assumptions:

- 20-year duration of treatment effect
- Log-logistic piecewise approach for monotherapy
- Log-normal piecewise approach for combination therapy
- Confidential discount applied for pembrolizumab and list price for all other drugs (first line and subsequent treatment)

Cancer started outside the oral cavity

	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
Monotherapy	£48,945	1.688	£28,329	0.908	**£31,212**
Platinum + 5-FU	£20,616	0.781			

	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
Combination therapy	£64,414	2.122	£44,762	1.441	**£31,070**
Platinum + 5-FU	£19,652	0.681			

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Cost-effectiveness results – technical report (1)

Key assumptions:

- 5-year duration of treatment effect
- Weibull piecewise approach for monotherapy and combination therapy
- Confidential discount is applied for pembrolizumab and list price for all other drugs (first line and subsequent treatment)

Cancer started inside the oral cavity

	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
Monotherapy	£46,907	1.282	-£3,118	0.443	**Dominant**
Cetuximab + platinum + 5-FU	£50,025	0.839			

	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
Combination therapy	£59,129	1.389	£9,104	0.550	**£16,553**
Cetuximab + platinum + 5-FU	£50,025	0.839			

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Note: Analysis with confidential discounts for all other drugs (first line and subsequent treatment) will be considered in PART 2

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Cost-effectiveness results – technical report (2)

Key assumptions:

- 5-year duration of treatment effect
- Weibull piecewise approach for monotherapy and combination therapy
- Confidential discount is applied for pembrolizumab and list price for all other drugs (first line and subsequent treatment)

Cancer started outside the oral cavity

	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
Monotherapy	£46,907	1.282	£24,832	£0.443	**£56,085**
Platinum + 5-FU	£22,076	0.839			

	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
Combination therapy	£59,129	1.389	£37,053	0.550	**£67,386**
Platinum + 5-FU	£22,076	0.839			

Incremental analyses – cancer started outside the oral cavity

Key assumptions:

- Using all patients from the cetuximab + platinum + 5-FU arm of KEYNOTE-048 trial to model OS, PFS and TTD for oral cavity patients receiving cetuximab + platinum + 5-FU
- Weibull piecewise approach for monotherapy and combination therapy

1. No duration of treatment effect applied

Treatment	Total costs	Total QALYS	Incremental costs	Incremental QALYs	ICER per QALY gained
Platinum plus 5-FU	£22,076	0.839	-	-	-
Pembrolizumab monotherapy	£47,644	1.422	£25,568	0.583	extendedly dominated
Pembrolizumab combination	£61,956	1.771	£14,312	0.349	**£42,790**

2. 5-year duration of treatment effect applied

Treatment	Total costs	Total QALYS	Incremental costs	Incremental QALYs	ICER per QALY gained
Platinum plus 5-FU	£22,076	0.839	-	-	-
Pembrolizumab monotherapy	£46,907	1.282	£24,831	0.443	**£56,052**
Pembrolizumab combination	£59,129	1.389	£12,222	0.107	**£114,224**

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Key issues

Treatment choice: Can clear subgroups be identified for treatment with monotherapy or combination therapy? (Issue 2)

Generalisability of KEYNOTE-048 results - Cetuximab as a comparator: Is the comparator appropriate for people whose cancer started in the oral cavity or outside the oral cavity? (Issue 3)

Clinical effectiveness of pembrolizumab: Is pembrolizumab differentially effective in people whose cancer started in the oral cavity vs those whose cancer started outside the oral cavity? (**New** - Issue 8)

Comparison of pembrolizumab with platinum plus 5-FU: Is the company's NMA or the ERG's approach using data from the cetuximab with platinum and 5-FU arm of KEYNOTE-048 the most appropriate approach for the comparison? (Issue 4)

Overall survival extrapolation: Which extrapolation of overall survival is most clinically plausible? (Issue 5)

Duration of treatment effect: What is the most plausible assumption of duration of treatment effect? (Issue 6)

End of life criteria: Does pembrolizumab meet NICE's end of life criteria? (Issue 7)