NICE National Institute for Health and Care Excellence

SLIDES FOR PROJECTOR

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

Chair's presentation

ERG: Liverpool Reviews and Implementation Group

Technical team: Ewa Rupniewska, Jamie Elvidge, Jasdeep Hayre

Company: Merck Sharp & Dohme

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ACD recommendations

- The committee is minded not to recommend pembrolizumab as an option for untreated metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a combined positive score (CPS) of 1 or more.
- The committee recommends that NICE requests further clarification and analyses from the company, which should be made available for the next appraisal meeting, including revised base case using:
  - Subgroup analyses for oral vs non-oral cavity populations, adjusted for imbalances in baseline characteristics
  - Alternative utility value for progressed disease (from literature)
  - Committee preferred assumptions: fully incremental analysis, 2-year stopping rule, 5-year duration of treatment effect and both company and ERG approaches for indirect comparison of pembrolizumab with platinum chemotherapy and 5-FU.

Key issues

Issue 1: Subgroup analyses (oral vs non-oral cavity origin): Is pembrolizumab differentially effective in people whose cancer started in the oral cavity vs those whose cancer started outside the oral cavity?

- Adjusting for baseline characteristics
- Overall survival analysis and extrapolation
- Appropriateness of using subgroup analyses for decision-making
- Cost-effectiveness analyses

Issue 2: Utility values: Which utility values are most appropriate for the post-progression disease state?

Issue 3: 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: End of life criteria: Does pembrolizumab meet NICE's end of life criteria?

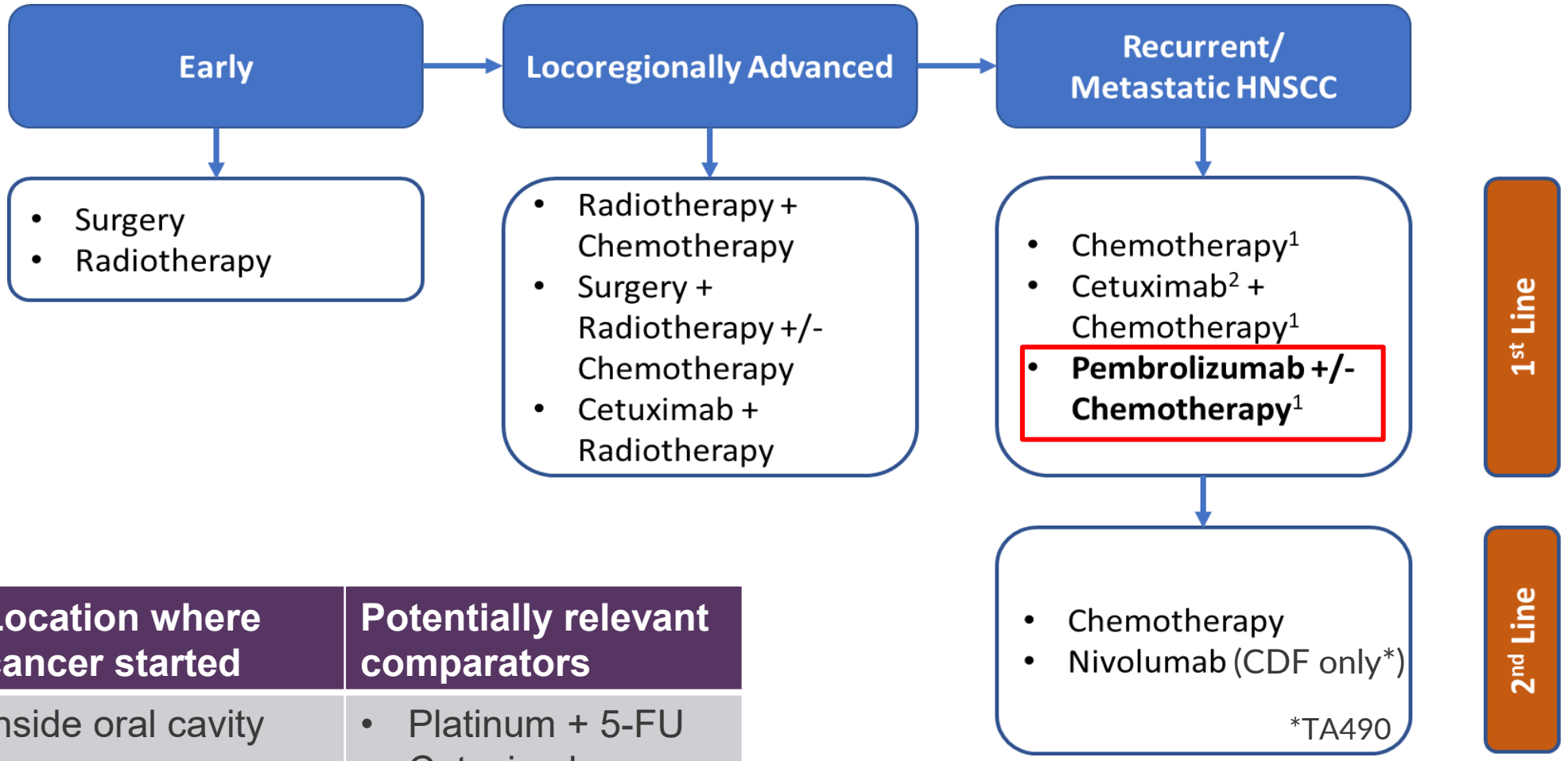
Issue 5: Fully incremental analysis: Should fully incremental analysis be used?

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	• As monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, 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: 200 mg every 3 weeks (Q3W) or 400 mg every 6 weeks (Q6W) intravenously • Pembrolizumab in combination with platinum-based chemotherapy: 200 mg every 3 weeks (Q3W) intravenously
Indicative list price	• £2,630 per 100 mg vial • PAS approved (simple discount; no change from ACM1)

PD-L1 = programmed cell death ligand 1

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

[1] Platinum-based chemotherapy regimens
[2] If the cancer started in the oral cavity
Source: adapted from company submission

Clinical effectiveness summary: KEYNOTE-048

KEYNOTE-048	
Trial design	Phase III, open label, randomised, multinational, multicentre
Intervention	• Pembrolizumab (n=301) • Pembrolizumab + platinum + 5-FU (n=281)
Comparator	• Cetuximab + platinum + 5-FU arm (n=300)
Population	• Adults with confirmed R/M HNSCC considered incurable by local therapies • ECOG Performance status of 0 or 1 • No prior systemic therapy administered in the recurrent or metastatic setting[1]
Stratification	• Tumour PD-L1 (based on TPS)[2] • HPV status (positive or negative)[3] • ECOG status (0 or 1)
Key results: overall survival	**Overall population** (PD-L1 CPS ≥1; adjusted for subsequent anti-PD-1 treatment)[4] • 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** (PD-L1 CPS ≥1; adjusted for subsequent anti-PD-1 treatment)[4] • Monotherapy vs cetuximab + platinum + 5-FU: HR [redacted] • Combination vs cetuximab + platinum + 5-FU: HR [redacted]

[1] With the exception of systemic therapy completed > 6 months prior if given as part of multimodal treatment for locally advanced disease; [2] Strongly positive = TPS≥50%, Not strongly positive = TPS<50%, or not able to be determined for any reason; [3] Patients without oropharynx cancer (e.g. cancers of the oral cavity, hypopharynx and larynx) were considered HPV negative; [4] using the simplified 2-stage method.
CPS: combined positive score; ECOG: Eastern Cooperative Oncology Group; HPV: Human papillomavirus; R/M HNSCC: recurrent or metastatic head and neck squamous cell carcinoma; TPS: tumour proportion score.

ACD: Key points

Section	Committee decision
Clinical need (3.1-3.3)	• A new treatment option is needed for people with recurrent or metastatic HNSCC • The decision to use pembrolizumab monotherapy or combination therapy is made on a case-by-case basis • The comparators: cetuximab + platinum chemotherapy + 5-FU for cancer inside the oral cavity; platinum chemotherapy + 5-FU for cancer outside the oral cavity
Clinical effectiveness (3.4 to 3.7)	• People with PD-L1 positive CPS ≥1 HNSCC who have pembrolizumab live longer than people who have cetuximab with platinum chemotherapy and 5-FU • The KEYNOTE-48 trial is not wholly applicable to clinical practice in England • Clinical effectiveness in cancer starting inside vs outside the oral cavity is unclear • The most appropriate analysis for comparing pembrolizumab with platinum chemotherapy and 5-FU is not certain
Cost effectiveness (3.8 to 3.11)	• The company's modelling approach (with 2-year stopping rule) is appropriate for decision making; a 5-year treatment benefit for pembrolizumab is appropriate • Overall survival should be modelled for the 2 subgroups: cancer starting inside the oral cavity or outside • A lower utility value for progressed disease should be used, sourced from literature
Results (3.12 & 3.13)	• The company's base case is not suitable for decision making • The ERG base case is not suitable for decision making

ACD: Cost-effectiveness summary

Assumption	Company base case	ERG base case	Committee preferred base case
Efficacy inputs (OS, PFS, TTD)	Overall population (PD-L1 ≥CPS 1)	Overall population (PD-L1 ≥CPS 1)	Subgroups by cancer origin with adjustment for baseline characteristics
Treatment effect duration	20 years	5 years	5 years
OS extrapolation: pembrolizumab monotherapy	Log-logistic (overall pop'n)	Weibull (overall pop'n)	Fitted separately for each subgroup (by cancer origin)
OS extrapolation: pembrolizumab combination	Log-normal (overall pop'n)	Weibull (overall pop'n)	Fitted separately for each subgroup (by cancer origin)
Indirect comparison with platinum chemotherapy + 5-FU	Fractional polynomial network meta-analysis	Using data from the cetuximab + platinum + 5-FU arm of KEYNOTE-048	Both ERG and company approach considered
Post-progression utility value	0.71 (based on EQ-5D data from KEYNOTE-048)	0.71 (based on EQ-5D data from KEYNOTE-048)	Lower utility value (from published literature)

ACD consultation summary

Responses from 2 stakeholders:

- Merck Sharp & Dohme (new evidence submitted in response to the committee request)
- NCRI-ACP-RCP-RCR

ERG submitted a commentary on company responses, and an appendix with analyses using a confidential discount for cetuximab

Summary of new analyses submitted

Committee preferred base case assumptions	Company new analyses[1]	ERG new analyses[1]
Analyses based on subgroups by cancer origin with adjustment for baseline characteristics	Yes (without adjusting for baseline characteristics)[2]	Yes (without adjusting for baseline characteristics)[2]
Treatment effect duration of 5 years	Yes	Yes
OS extrapolation fitted separately for each subgroup (by cancer origin)	Yes – log-normal curve	Yes – Weibull curve
Both ERG and company approach considered for indirect comparison with platinum chemotherapy + 5-FU	ERG approach (NMA not possible for subgroups)	ERG approach
Lower post-progression utility value	Yes	Yes
Fully incremental	No	Yes

[1] Company and ERG preferred base cases remain as presented at ACM1.
[2] OS, PFS, TTD.

Issue 1: Oral and non-oral cavity subgroup analyses

ACD: Because current treatment options are different for cancer that started inside or outside the oral cavity, the committee would like to see all analyses by primary location

Company submitted requested analyses – presented in the subsequent slides

Theme	Summary of company responses	ERG / other comments
Baseline characteristics	• Baseline characteristics were generally well balanced across treatment groups • No prognostic factors identified as meaningful • No adjustment for imbalances in the baseline characteristics applied in OS analysis	ERG: Agrees with the company - differences between subgroups/trial arms are not statistically significantly different for any of the baseline characteristics → no need to adjust
Extrapolating OS	• 5-year treatment effect duration applied • Oral cavity: log-normal for pembrolizumab (mono & combo); Weibull for comparator • Non-oral cavity: log-normal for pembrolizumab (mono & combo) and comparator	ERG: Company's approach is acceptable but leads to lower mortality hazard than the general population; Weibull preferred for all treatment arms in both subgroups
ICERs	• Presented for 2 subgroups, using 2 sets of utilities	ERG validated the ICERs (negligible differences)
Appropriateness of subgroup analyses	• Initial recommendation based on post-hoc subgroup analysis (TA172/473); not in agreement with the NICE methods guide and not supported by scientific evidence	ERG: agrees with the company NCRI-ACP-RCP-RCR: agrees with the company

Overall survival: oral cavity subgroup

Pembrolizumab monotherapy
vs. cetuximab + platinum +5-FU

Pembrolizumab combination therapy
vs. cetuximab + platinum +5-FU

OS extrapolation (with 5-year treatment effect duration):

Distribution	Pembrolizumab monotherapy (% survival)				Pembrolizumab combination therapy (% survival)				Cetuximab + Platinum + 5-FU (% survival)			
Years	1	2	5	10	1	2	5	10	1	2	5	10
Company: Log-normal	35.9	20.4	11.4	4.5	46.7	21.7	10.8	4.3	n/a – Weibull used			
ERG: Weibull	35.9	20.8	10.3	4.1	46.7	22.1	8.7	3.5	41.3	15.1	5.8	2.3

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Source: Company appendix Figures 5 and 9; Tables 28-31.

Overall survival: non-oral cavity subgroup

Pembrolizumab monotherapy vs. cetuximab + platinum +5-FU

Pembrolizumab combination therapy vs. cetuximab + platinum +5-FU

OS extrapolation (with 5-year treatment effect duration):

Distribution	Pembrolizumab monotherapy (% survival)				Pembrolizumab combination therapy (% survival)				Platinum + 5-FU (% survival)*			
Years	1	2	5	10	1	2	5	10	1	2	5	10
Company: Log-normal	55.8	32.3	17	2.5	57.5	36	22.9	3.4	42	14.2	1.5	0.2
ERG: Weibull	55.8	33.3	11.8	0	57.5	36.5	20.5	0	42	14.7	0.5	0

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* Assumed equal to cetuximab + platinum + 5-FU arm (NMA not possible for subgroups)

Source: Company appendix Figures 13 and 17; Tables 34-35.

Appropriateness of subgroup analyses

ACD: Because current treatment options are different for cancer that started inside or outside the oral cavity, the committee would like to see all clinical and cost-effectiveness analyses by primary location.

Company: No evidence to support differing clinical effectiveness of pembrolizumab regimens or the comparators by the site of tumour origin (oral vs non-oral cavity).

- TA172/TA473 recommendation based on underpowered statistically invalid subgroup analyses - a set of 40 independent subgroup analyses presented, testing at the 5% significance level (did not include patients whose tumour originated outside of the oral cavity as a distinct subgroup for analysis).
- High chance this was false-positive result: “When multiple subgroup analyses are performed, the probability of a false positive finding can be substantial. If the null hypothesis is true for each of 10 independent tests for interaction at 5% significance level, >40% chance of at least one false positive” (Wang et al. 2007)
- Against NICE methods guide:
  - “There should be a clear justification and, if appropriate, biological plausibility for the definition of the patient subgroup and the expectation of a differential effect. Post hoc data 'dredging' in search of subgroup effects is to be avoided and will be viewed sceptically.”
  - Types of subgroups that are not considered relevant are those based solely on the following factors: differential treatment costs for individuals according to their social characteristics.

ERG: agrees that the decision to treat patients in the NHS based on site of tumour origin is based on underpowered statistically invalid subgroup analyses presented as part of TA172/TA473.

Data from the overall population can be used to inform efficacy estimates for both models (by tumour origin)

NCRI-ACP-RCP-RCR: ACD recommendation is not a sound and suitable basis for guidance; the restriction on the use of cetuximab to the oral cavity subgroup was a health economic decision made by NICE; this restriction has not been adopted internationally.

QUESTIONS: Should subgroup analyses be used for decision-making? Should recommendation be considered separately for cancer that started inside or outside the oral cavity?

Issue 2: Post-progression utility value

ACD: A lower utility value for progressed disease should be used, sourced from published literature (utility value of 0.71 too high for people who are normally in very poor health – may be overestimated).

Company: 0.71 utility value estimated as per NICE reference case: UK tariff applied to EQ-5D data from KEYNOTE-048.

The model incorporates time to death utility decrements (+ age-related utility decrements): as patients get closer to death, utility decreases → addresses concerns that utility is too high.

An alternative value of 0.66 was identified though a systematic literature review (from cost-effectiveness analysis of nivolumab for recurrent or metastatic HNSCC).

- Nivolumab has a similar mode of action to pembrolizumab.
- 'Sicker' patients: Checkmate 141 **after** platinum chemotherapy, which is a later line of treatment.
- In Checkmate 141, the post-progression utility value for patients on standard therapy was 0.47
- Therefore treatment-independent utility values potentially underestimate the cost-effectiveness of pembrolizumab monotherapy and combination therapy.

ERG: Utility value from literature is arbitrary and not more robust that that from KEYNOTE-048. Applying time to death decrements leads to lower utility values – illustrated for Weibull OS extrapolation and 5-year treatment effect duration.

Days until death	Original company model	New company model
>180	[redacted]	[redacted]
90 to 180	[redacted]	[redacted]
30 to 90	[redacted]	[redacted]
<30	[redacted]	[redacted]

QUESTION: Which utility values are most appropriate for the post-progression disease state?

Issue 3: Comparison of pembrolizumab with platinum plus 5-FU

ACD: The most appropriate analysis for comparing pembrolizumab with platinum chemotherapy and 5-FU is not certain – so the committee considered both the company's and the ERG's approaches in its decision making

The ERG was concerned about the validity of the company's NMA, because it did not consider the plausibility of the hazard ratios estimated by the fractional polynomial model. The company did not say how the 2 categories of models were assessed.	The committee considered that the company's approach may overestimate the effectiveness of pembrolizumab (monotherapy and in combination), while the ERG's approach may overestimate the effectiveness of platinum and 5-FU chemotherapy.
Company: Technical engagement response described how the plausibility of the hazard ratios estimated by the fractional polynomial model were considered, and how the 2 categories of fractional polynomial models were assessed.	Company's approach that uses the fractional polynomial network meta-analysis is in fact more likely to underestimate the true effectiveness of pembrolizumab (mono and combo) vs platinum chemotherapy and 5-FU, as was explained.

ERG: Confirms that the methods described by the company during technical engagement are appropriate.

ERG maintains that the company's NMAs did not provide reliable evidence for the comparison of pembrolizumab (mono or combo) vs either of the relevant comparators, in either patient population (the trials were not restricted to people with PD-L1 ≥CPS 1, as in KEYNOTE-48; NMA was not stratified by cancer origin).

ERG prefers to use Kaplan–Meier data from the cetuximab + platinum chemotherapy + 5-FU arm of KEYNOTE-048 to represent people whose cancer started outside the oral cavity, but this may overestimate effectiveness of platinum chemotherapy + 5-FU.

QUESTION: Which approach is most appropriate for the comparison? (NMA not possible for subgroups)

Issue 4: End of life criteria

ACD: The committee accepted that, for the whole trial population, pembrolizumab meets both short life expectancy and life extension criteria. But it would like to see subgroup analyses (cancer starting inside or outside the oral cavity) to decide if the extension to life criteria are met for both subgroups.

ERG: Additional analyses:

End of life estimates for oral subgroup

Treatment	Pembro OS model	Mean months	Pembro gain
Cetux+Plat+5FU	Log-normal (company)	[redacted]	
Pembro mono		[redacted]	[redacted]
Pembro combo		[redacted]	[redacted]
Cetux+Plat+5FU	Weibull (ERG)	[redacted]	
Pembro mono		[redacted]	[redacted]
Pembro combo		[redacted]	[redacted]

End of life estimates for non-oral subgroup

Treatment	Pembro OS model	Mean months	Pembro gain
Platinum+5FU	Log-normal (company)	[redacted]	
Pembro mono		[redacted]	[redacted]
Pembro combo		[redacted]	[redacted]
Platinum+5FU	Weibull (ERG)	[redacted]	
Pembro mono		[redacted]	[redacted]
Pembro combo		[redacted]	[redacted]

QUESTION: Does pembrolizumab meet NICE's end of life criteria in either or both subgroups?

Issue 5: Fully incremental analysis

ACD: A fully incremental analysis should be used because the populations who would be offered pembrolizumab monotherapy over combination therapy are not distinct patient populations.

Company: Fully incremental analysis is not appropriate. Neither pembrolizumab monotherapy nor combination therapy is established practice or recommended by NICE. As stated in the NICE methods guide, only treatments that are part of established practice should be considered comparators:

- "the Committee will normally be guided by established practice in the NHS when identifying appropriate comparator(s)".
- "the Committee's overall decision on whether it is a valid comparator will be guided by whether it is recommended in extant NICE guidance, and/or whether its use is so embedded in clinical practice that its use will continue unless and until it is replaced by a new technology"

Technical team: The methods guide states "Standard decision rules should be followed when combining costs and QALYs. When appropriate, these should reflect when dominance or extended dominance exists, presented thorough incremental cost–utility analysis. Incremental cost-effectiveness ratios (ICERs) reported must be the ratio of expected additional total cost to expected additional QALYs compared with alternative treatment(s)."

- Note: alternative treatment(s) may refer to all relevant comparators and interventions.

QUESTION: Should fully incremental analysis be used?

ERG's fully incremental ICERs: both subgroups

(2-year stopping rule, 5-year treatment effect duration, Weibull OS extrapolation; non-oral subgroup: efficacy of platinum+5-FU assumed equal to the efficacy of cetuximab + platinum +5-FU; NMA not possible for subgroup analysis[a])

		Total costs £	Total QALYs	Incr. costs £	Incr. QALYs	ICER £/QALY
Oral cavity subgroup						
Lower post-progression utility value	Pembrolizumab monotherapy	41,134	1.14			
	Pembrolizumab combination	55,769	1.18	14,635	0.03	430,441[b]
	Cetuximab + Plat + 5-FU	60,193	0.99	4,424	-0.19	Dominated
Trial-based utility value	Pembrolizumab monotherapy	41,134	1.19			
	Pembrolizumab combination	55,769	1.22	14,578	0.03	497,543[b]
	Cetuximab + Plat + 5-FU	60,193	1.02	4,481	-0.20	Dominated
Non-oral cavity subgroup						
Lower post-progression utility value	Platinum + 5-FU	21,758	0.77			
	Pembrolizumab monotherapy	48,166	1.27	26,408	0.50	52,307
	Pembrolizumab combination	61,100	1.45	12,934	0.18	73,073[b]
Trial-based utility value	Platinum + 5-FU	21,758	0.79			
	Pembrolizumab monotherapy	48,166	1.32	26,408	0.53	50,291
	Pembrolizumab combination	61,100	1.50	12,934	0.19	68,761[b]

[a] EXTREME trial data not available for non-oral subgroup; [b] Calculated by the ERG, not from the model.

Key issues

Issue 1: Subgroup analyses (oral vs non-oral cavity origin): Is pembrolizumab differentially effective in people whose cancer started in the oral cavity vs those whose cancer started outside the oral cavity?

- Adjusting for baseline characteristics
- Overall survival analysis and extrapolation
- Appropriateness of using subgroup analyses for decision-making
- Cost-effectiveness analyses

Issue 2: Utility values: Which utility values are most appropriate for the post-progression disease state?

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Issue 4: End of life criteria: Does pembrolizumab meet NICE's end of life criteria?

Issue 5: Fully incremental analysis: Should fully incremental analysis be used?