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Chair's presentation

Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma (ID1062)

3rd Appraisal Committee meeting

Committee A

Lead team: Adrian Griffin, David Evans, Mohit Sharma

ERG: Kleijnen Systematic Reviews

NICE technical team: Thomas Walker, Rebecca Albrow, Janet Robertson

22 May 2018

Pembrolizumab (Keytruda)
Merck Sharp & Dohme Limited

Mechanism of action	Humanised monoclonal antibody that blocks PD-1 to promote anti-tumour response
Marketing authorisation	Indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autoSCT and BV, or who are transplant-ineligible and have failed BV
Administration and dose	Intravenous infusion • Induction dose: 200mg • 200mg every 3 weeks until disease progression or unacceptable toxicity
Cost	List price £2,630 (100mg vial) Company has agreed a commercial access agreement (CAA) with the Department of Health

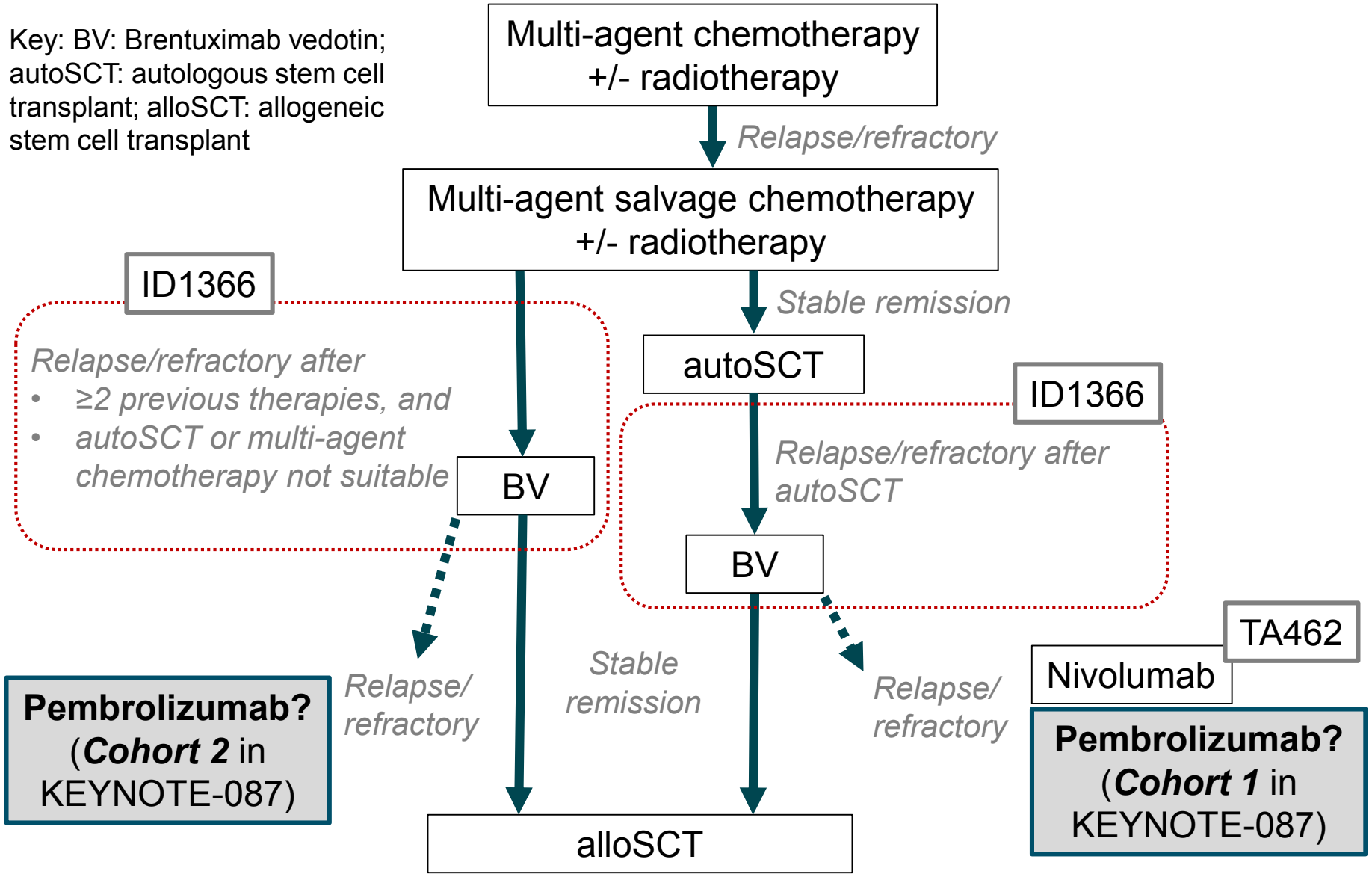
BV: Brentuximab vedotin; autoSCT: autologous stem cell transplant

History of the appraisal

- Pembrolizumab for treating adults with relapsed or refractory classical Hodgkin lymphoma in 2 populations:
  - **Population 1**: after autologous stem cell transplant (autoSCT) and brentuximab vedotin (BV)
  - **Population 2**: after BV if person is transplant ineligible
- Nivolumab is recommended for use in population 1 (TA462; July 2017)

- 1st committee meeting (December 2017)
  - No guidance document released
  - Company asked to do further analysis to address committee concerns about model structure
- 2nd committee meeting (February 2018)
  - Company submitted updated models
  - ACD:
    - 'minded no' for population 1; requested company provide cost comparison with nivolumab
    - population 2 not recommended

Recap: Treatment pathway



Recap: Clinical evidence (1)

Company's clinical evidence for pembrolizumab	**KEYNOTE-087**: Phase II single arm, open label trial • Pembrolizumab every 3 weeks until disease progression or unacceptable toxicity • Includes 2 cohorts corresponding to the marketing authorisation: Adults with RRcHL after: **Cohort 1:** autoSCT and BV (post-autoSCT) **Cohort 2:** Salvage chemotherapy and BV (no autoSCT)
Comparator data	No data providing direct comparison between pembrolizumab and SOC **Cheah et al. (2016)** – a retrospective observational study from the US – used to provide data for SOC for indirect comparison • Cheah et al. population is a mixture of cohorts 1 and 2; population most comparable to cohort 1 (~70%) • Committee for TA462 accepted Cheah et al. (2016) as appropriate comparator study

BV: Brentuximab vedotin; autoSCT: autologous stem cell transplant; RRcHL: Relapsed or refractory classical Hodgkin lymphoma; SOC: Standard of care

Recap: Clinical evidence (2)

Indirect naïve comparisons

Objective response rate

Population	Odds ratio (95% CI) Pembrolizumab (KEYNOTE-087) versus SOC (Cheah)	
	Response at week 12 (KEYNOTE-087) versus best overall response (Cheah et al.)	Best overall response
1	[redacted]	[redacted]
2	[redacted]	[redacted]

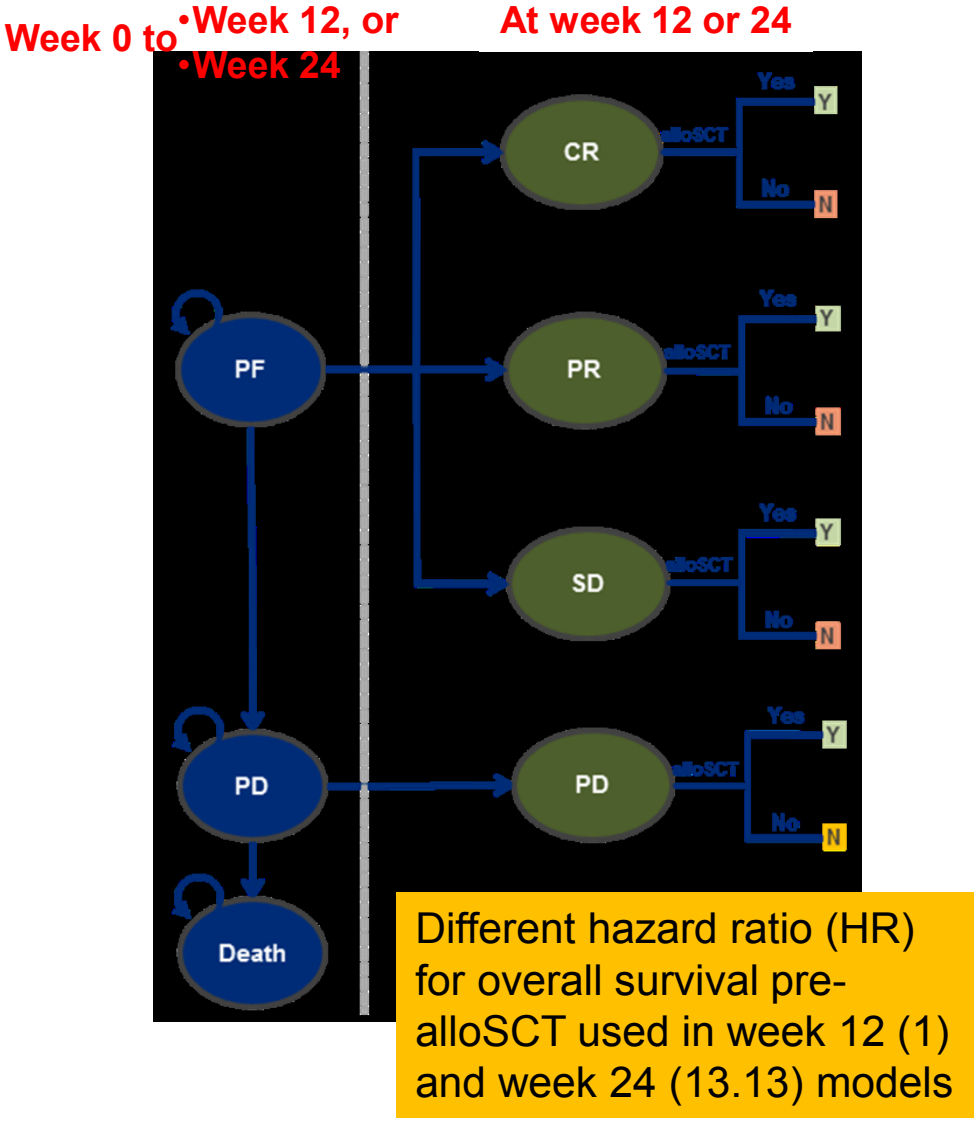
Progression-free survival

Population	Hazard ratio (95% CI) Pembrolizumab (KEYNOTE-087) versus SOC (Cheah)	
	From study initiation to week 12	From study initiation to most recent observation
1	[redacted]	[redacted]
2	[redacted]	[redacted]

SOC: Standard of care

Recap: Company's updated models

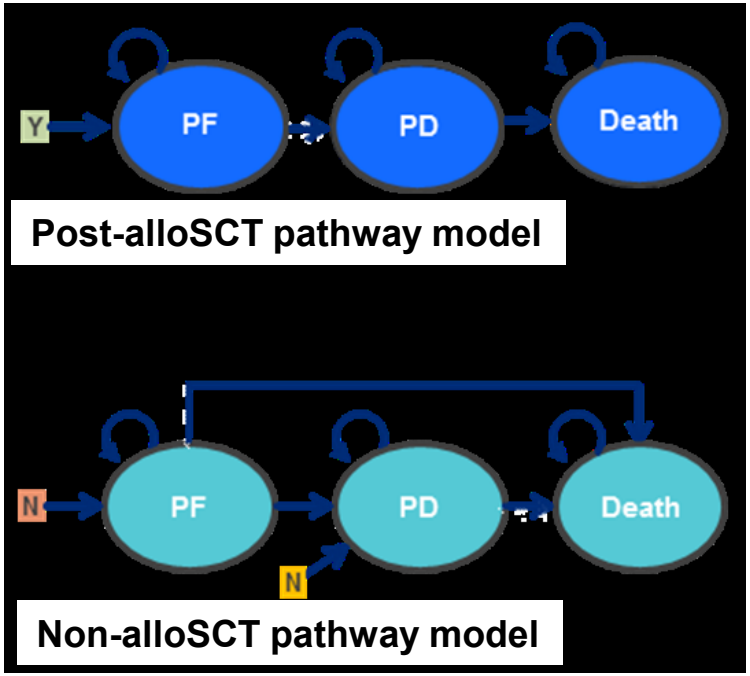
Updated models provided for February committee meeting



Different hazard ratio (HR) for overall survival pre-alloSCT used in week 12 (1) and week 24 (13.13) models

2 versions of model, depending on when alloSCT done:

- at week 12
- at week 24



alloSCT: allogeneic stem cell transplant

Recap: Company base case results (deterministic)
From February 2018 committee meeting models (with CAA)

Updated week 12 model	ICER	
	Population 1	Population 2
Company's updated base-case	£45,033	£50,353
Company scenario analysis that incorporated 'ERG combined preferences' (scenario analysis 11)	£56,160	£64,353

- **ERG**: scenario analysis 11 not equivalent to their combined preferences
- ERG unable to implement entire base-case in the company's new model, but considered that this could possibly increase ICERs to ~£60,000 (population 1) and ~£71,000 (population 2)

Updated week 24 model	ICER	
	Population 1	Population 2
Company's updated base-case	£39,880	£39,714
Company scenario analysis that incorporated 'ERG combined preferences' (scenario analysis 11)	£41,021	£49,220

- **ERG:** ICER likely to be higher than for scenario 11 (£41,021) for **population 1**
- Difficult to assess for **population 2**

ACD: preliminary recommendations

‘Population 1’

1.1 The committee is minded not to recommend pembrolizumab as an option for treating relapsed or refractory classical Hodgkin lymphoma in adults who have had autologous stem cell transplant and brentuximab vedotin

1.2 The committee requests that the company provides a cost-comparison with nivolumab for treating relapsed or refractory classical Hodgkin lymphoma in adults who have had autologous stem cell transplant and brentuximab vedotin

‘Population 2’

1.3 Pembrolizumab is not recommended as an option for treating relapsed or refractory classical Hodgkin lymphoma in adults who cannot have autologous stem cell transplant and have had brentuximab vedotin

Committee's considerations (1)

Issue	Committee's conclusions
Comparator data	• Cheah study is best available evidence for standard care at the time of the company's submission • More appropriate data for population 2 (**Eyre et al**.) now available – committee would have preferred the additional analysis to explore use of data from this study
Survival pre-alloSCT	• Difference in **overall survival** between pembrolizumab and standard care is **overestimated** at week 24 (in week 24 model [HR 13.13]), compared to Cheah study data • Uncertainty in this parameter not adequately explored (e.g. validating against published data for standard care)
OS and PFS curves used to model the pre-alloSCT period	• Choice of models for PFS and OS in the pre-alloSCT period introduced considerable uncertainty, which was not fully investigated • Different parametric curves used in the 24 week-model, compared to the 12 week-model; use of Kaplan-Meier observed data would have been preferable

Committee's considerations (2)

Issue	Committee's conclusions
Uptake of alloSCT	• Company used results of clinician surveys to estimate uptake of alloSCT (expected rather than observed rates) – as used in TA462 • The uptake rate of allogeneic stem cell transplant is uncertain
Utility value for progressed disease	• Considerable uncertainty about the utility value for progressed disease • Actual value is likely to be between the company's and the ERG's base case values
Face validity of model results and end-of-life criteria	• There is a lack of face validity between modelled survival estimates for standard care and the clinical evidence, and the company's assertion that end-of-life criteria are met • More than 3 life-years were estimated for standard care in the company's models • The company should have provided further explanation and justification for this discrepancy

Committee's considerations (3)

Issue	Committee's conclusions
Time to alloSCT	• Time to alloSCT is a key driver of cost-effectiveness estimates • AlloSCTs likely to occur between weeks 12 and 24 • Most plausible ICER likely to fall between the values predicted by models using a fixed time of transplant of 12 and 24 weeks
Most plausible ICERs	• Cost effectiveness of pembrolizumab is highly uncertain, and a plausible ICER cannot be accurately estimated using the company's 12-week or 24-week model • A **cost-comparison** between pembrolizumab and nivolumab may help address uncertainties about pembrolizumab for **population 1**

ACD consultation responses

- Consultee comments from:
  - Merck Sharp & Dohme
  - NCRI-RCP-ACP

- Web comments from:
  - 2 patients

Comments from NCRI-ACP-RCP

- Concerned that pembrolizumab is not recommended for patients who can’t have a stem cell transplant (population 2)
- “Our experts believe that it does not matter to patients and clinicians if pembrolizumab is funded post- (ASCT) and post-BV, as nivolumab is already funded for this indication”
- Pembrolizumab can bridge to curative therapy, for a group of mainly young patients
- Potential equity issue; a negative decision will lead to disparity for people who can’t afford to self-fund treatment or crowd fund

Comments from patients

- Both patients had not been able to have a stem cell transplant and highlighted how limited treatment options are for this group
- Only way to get access to nivolumab is to have a stem cell transplant - which would be likely to fail
  - Questioned the ethics of this and noted waste of resources
- Both patients self-fund nivolumab treatment, but cannot afford to do so indefinitely and are worried about not having a good enough response to have a stem cell transplant when they can no longer afford treatment
- Commented that they have had improvements in quality of life since starting nivolumab
  - Highlighted reduction in side effects compared to chemotherapy
- Both patients have young children and highlighted the challenges of child care while having ongoing chemotherapy or radiotherapy
- Patient commented that a matched donor is available if they are able to get into remission and have a transplant

- NCRI-ACP-RCP and patient comments in support of pembrolizumab refer to population 2

Comments from the company

Population 1

- There is a lack of consistency in committee decision making for population 1 between this appraisal and TA462 (nivolumab)

> ***Note***: Committee in TA462 concluded that the most plausible ICER for nivolumab was likely to be around £30,000 per QALY gained

- Company are reluctant to respond to the committee's request for a cost comparison with nivolumab
  - This may limit further options in the NICE process
  - At the time of the company submission, TA462 was within the 90 day implementation period
  - Clinical/economic case for pembrolizumab has been demonstrated against the same historical control (Cheah et al.) as in TA462
  - Single arm trial data is available for pembrolizumab and nivolumab and the only potential link is through Cheah et al. It is unclear what additional certainty this additional analysis would provide

Additional analysis from the company

- Company's base case ICERs in the new analysis **differ** from those presented in previous analysis (for the February 2018 meeting)

		Company's base case ICERs	
		February 2018	**May 2018**
Week **12** model	Population 1	£45,033	£49,058
	Population 2	£50,353	£55,628
Week **24** model	Population 1	£39,880	£42,123
	Population 2	£39,714	£36,950

Changes to models used to produce base case ICERs:

- New CAA price
- Changes to some of the parametric distributions used

Additional analysis from the company
Eyre et al. for population 2 SOC data (1)

- Company highlighted differences between KEYNOTE-087 and Eyre et al. populations; commented that Cheah et al. is most comparable population
- Individual patient data for Eyre et al. not available; naïve indirect comparisons done using digitised Kaplan-Meier curves:

	KEYNOTE-087 (population 2) versus Eyre et al.	KEYNOTE-087 (all population) versus Cheah et al.
		June 2016 data cut
Overall survival	[redacted]	0.076 (0.02 to 0.33)
Progression-free survival	[redacted]	0.18 (0.12 to 0.27)

- Hazard ratio for overall survival from naïve indirect comparison between KEYNOTE-087 (population 2) and Eyre data ([redacted]) similar to hazard ratio used in economic model (0.076; [13.13 when inverted])
- Company provided scenario analysis (for population 2) that used hazard ratios calibrated to match Eyre et al. data
  - Week 12 model: ICER reduced from £55,628 to £42,724 per QALY gained
  - Week 24 model: ICER reduced from £36,950 to £36,483 per QALY gained

Additional analysis from the company
Eyre et al. for population 2 SOC data (2)

ERG comments

- ERG agreed with company's assessment that there is substantial uncertainty associated with the indirect relative effectiveness estimates from Eyre et al. because:
  - Analysis was based on a small sample (n=38)
  - Estimates are from digitised published figures
  - Comparability of baseline characteristics unknown
- Scenario analysis based on Eyre et al. uses HRs that are calibrated to match the observed Eyre et al. data
- ERG cautioned against use of this analysis to validate the use of a HR of 13.13 in the company's model
  - If pembrolizumab is more effective in population 2 than population 1, a HR produced by comparing the total population (1 and 2) with standard care (0.076 [13.13 inverted]) should have been higher than a HR produced by comparing only population 2 with standard care ([redacted] inverted])

Additional analysis from the company
Difference in overall survival (OS) at week 24 (1)

- ACD: The difference in OS between pembrolizumab and standard care is overestimated at week 24
- Hazard ratio 13.13 for pre-alloSCT OS was used in the 24 week model
  - Scenario analysis was also provided using a hazard ratio of 1
- Company provided analyses using a hazard ratio (HR) for weeks 0 to 24 to match OS at week 24 in Cheah et al. (8.01 for population 1; 5.18 for population 2)
  - **ERG**: Updated OS estimates from models approximately in-line with Cheah data

Scenario	ICER (£ per QALY) Pembrolizumab versus SOC	
	Population 1	Population 2
Base-case week 24 model	£42,123 (HR 13.13)	£36,950 (HR 13.13)
Base-case week 24 model – **with updated hazard ratios for OS (weeks 0 to 24)**	£44,057 (HR 8.01)	£41,208 (HR 5.18)

Additional analysis from the company
Difference in overall survival (OS) at week 24 (2)

ERG comments

- Agreed with company that this method of deriving HRs is not an evidence-based approach
- Method doesn't allow for estimation of uncertainty
- Despite this, ERG has slight preference for using these estimates of HRs [8.01 for population 1 and 5.18 for population 2], because:
  - They appear superior in terms of external validity
  - Data was not provided to validate HR of 13.13 and the use of a HR of 1 lacks face validity
- Because of this uncertainty, the 24 week-model results should be interpreted with caution, and should only be considered as a scenario analysis

⊙ *What is the committee's preferred HR(s) for OS in weeks 0 to 24?*
- *13.13*
- *8.01 (population 1) / 5.18 (population 2)*
- *1*

Additional analysis from the company
Alternative utility value for progressed disease (PD)

- ACD: Committee considered that the actual utility value for PD is likely to be between the company's and the ERG's base-case values
- Company presented a scenario analyses with an average utility PD ([redacted]):

		ICER Pembrolizumab versus SOC	
		Population 1	**Population 2**
Week **12** model	Base case	£49,058	£55,628
	Base case – with **average PD utility**	£48,382	£54,516
Week **24** model	Base case	£42,123	£36,950
	Base case (updated OS HRs weeks 0-24)	£44,057	£41,208
	Base case (updated OS HRs weeks 0-24) • **average PD utility**	£42,254	£38,998

ERG comment

- An arbitrary, and not evidence-based, approach
  - Results should only be used to illustrate direction of the changes to the ICERs

Additional analysis from the company
Implementing ERG's preferred assumptions

- Company provided models with **ERG's preferred assumptions**
- ERG noted minor deviations in how company had implemented ERG preferences for utilities and post-alloSCT monitoring

		ICER Pembrolizumab versus SOC	
		Population 1	**Population 2**
Week **12** model	Company base case	£49,058	£55,628
	Company base case + ERG preferences	£54,431	£62,503
	ERG base case	£54,325	£62,527
Week **24** model	Company base case	£42,123	£36,950
	Company base case + ERG preferences	£46,122	£42,950
	ERG base case	£45,829	£42,501

Further ERG analysis

- ERG highlighted that company's additional analyses presented in their ACD response were done in the company's, rather than ERG's, base-case
- ERG therefore repeated some of the company's scenario analyses in its own base case:

		Week 12 model		Week 24 model	
		Population 1	Population 2	Population 1	Population 2
ERG base case		£54,325	£62,527	£45,829	£42,501
Scenarios	Lower PD utility	£54,877	£63,549	£47,673	£44,969
	Parameters derived from Eyre et al.	NA	£54,085	NA	£36,177

ERG comments

- Company has explored some of the identified uncertainties
- Still substantial uncertainty associated with relative effectiveness and model predictions of OS and PFS
  - Particularly in population 2 and in the week 24 model (both populations)

Additional analysis from the company
Comparison with model results in TA462

- Company suggest difference in costs generated for SOC by original model (December 2017) and TA462 model is because of lower cost for alloSCT used in the TA462 model
- If the models for this appraisal are run using this lower cost they produce similar total costs for SOC to the original submission TA462 model (in a scenario analysis with alloSCT)
- Company also commented that a higher proportion of people have alloSCT in the TA462 model; when this proportion was applied in the company's models it reduced the ICER (analyses not provided)

ERG comments

- Committee's and ERG's preferred analysis in TA462 used the higher alloSCT costs; as used in this appraisal
- ERG believes that the alternative costs should not be considered for decision-making

Comments from the company
End of life criteria (1)

- End of life criteria were accepted for TA462 (corresponding to population 1) and the committee accepted uncertainty based on using the model outputs; for consistency the same criteria should apply here
- The modelled overall survival (in this appraisal and in TA462) for standard care is overestimated by models
  - ICERs are therefore conservative; generated from comparison with superior SOC resulting in lower incremental gain than expected in UK clinical practice
- Standard care survival data is from Cheah et al. (only aggregate data available) which includes people who had alloSCT (~20%) and increases overall survival estimates
- When alloSCT is not included in models:
  - 2.933 life years were generated in the TA462 nivolumab model for standard of care
  - 2.946 life years are generated by the current model for standard of care

Comments from the company
End of life criteria (2)

- The FAD for TA462 states that:
  - "…*Committee noted that the company's modelling predicted a mean overall survival in the comparator treatment arm of more than 24 months. However, the Committee also considered the data from the Haematological Malignancy Research Network provided by the company in response to consultation, which showed shorter survival and suggested that the Cheah study may have been optimistic. The Committee acknowledged that nivolumab did not unequivocally meet the criterion for short life expectancy but that it was plausible that the criterion could apply*."
  - Committee in TA462 agreed that nivolumab met the criterion for short life expectancy
- Eyre et al. (2017) reports a median overall survival of 12.2 months (95% CI 8.1 to 18.3 months) for people who have not had a stem cell transplant (population 2)

Comments from the company
Consideration of **CDF** for population 2

Population 2

- Insufficient consideration of access opportunities given unmet need
- Company have no further data collection plans to support this submission
- Uncertainty could be addressed by recommending population 2 in the CDF
- Following data suggested as feasible for collection in the CDF:
  - Timing of stem cell transplant
  - Duration of pembrolizumab treatment before stem cell transplant
  - Proportion of patients treated with pembrolizumab who have subsequent stem cell transplant
  - Long term follow-up of people treated with pembrolizumab (with or with subsequent stem cell transplant)

Summary
Base case ICERs from current analysis

- ACD: Most plausible ICER likely to fall between the values predicted by models using a fixed time of transplant of 12 and 24 weeks

		Week 24	Week 12
Population 1	Company base case	£42,123 →	£49,058
	ERG base case	£45,829 →	£54,325
Population 2	Company base case	£36,950 →	£55,628
	ERG base case	£42,501 →	£62,527

- Company commented that committee for TA462 was able to reach decision based on single alloSCT time point of 6 months
- ERG highlighted substantial uncertainty associated with model results remains
  - Particularly for population 2 and the 24 week-model (both populations)

Key issues for consideration

Key issues	
Cost comparison	No cost comparison with nivolumab for population 1 provided
Overall survival (OS) pre-alloSCT in week 24 model	Considerable uncertainty about the most appropriate HR(s) to use for OS pre-alloSCT in the week 24 model • What is the committee's preferred HR(s) for OS in weeks 0 to 24?
Consistency with TA462	Company claim that there is a lack of consistency in committee decision making between TA462 (nivolumab) and population 1 (in this appraisal)
Plausible ICERs	Given the further analysis provided, can plausible ICERs be determined using the company's models?
End of life	Are the criteria for end of life met?
Population 2 and the CDF	Is population 2 suitable for use in the CDF?
	Are the models considered suitable for use in decision-making if updated with further data collected in the CDF?