Slides for public - REDACTED

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

2nd Appraisal Committee meeting

Additional analysis provided by company

Committee A

ERG: Kleijnen Systematic Reviews

NICE technical team: Thomas Walker, Rebecca Albrow

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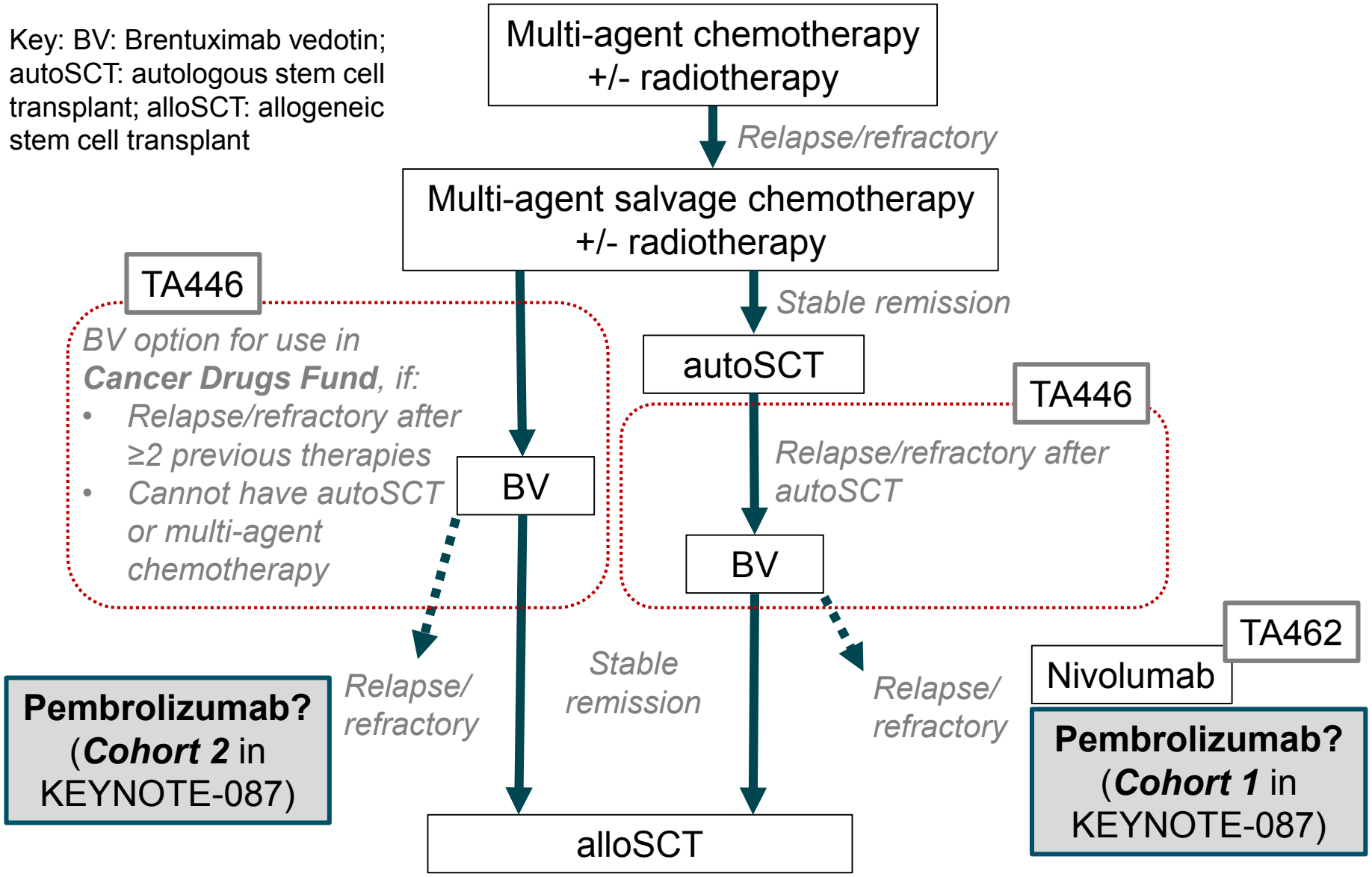
Issues for consideration

- What is the committee's view of the updated 12 week transplant model?
- What is the committee's view of the model using transplant at 24 weeks?
- Does the committee accept that modelling a later transplant improves the cost effectiveness estimates?
- The company has supplied scenario analyses for the 12 and 24 week transplant models which they say incorporate the ERG's preferences; does the committee accept that this is the case, if not what how would they differ?
- What is the committees view of the appropriate time to model transplant?
- Should a different trial be used to compare with pembrolizumab for cohort 2?

Recap: Treatment pathway

Key: BV: Brentuximab vedotin; autoSCT: autologous stem cell transplant; alloSCT: allogeneic stem cell transplant



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 comparisons: **Objective response rate (ORR)**

Cohort	Comparison	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	Naïve	[redacted]	[redacted]
	MAIC	[redacted]	[redacted]
2	Naïve	[redacted]	[redacted]
	MAIC	[redacted]	[redacted]

MAIC: Matched adjusted indirect treatment comparison; SOC: Standard of care

- MAIC increases odds ratio (relative to naïve comparison)
- All results for ORR significantly favour pembrolizumab over SOC

Recap: Clinical evidence (3)

Indirect comparisons: **Progression-free survival**

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

MAIC: Matched adjusted indirect treatment comparison; SOC: Standard of care

- Hazard ratio for cohort 1 more favourable to pembrolizumab in the MAIC
- Almost all progression-free survival results show significant benefit for pembrolizumab versus SOC

Additional analysis requested (1)

What was asked for		Reason(s)
An updated model that:	Includes a progressive disease state after alloSCT	• The company's model of post-alloSCT population included only two states (alive and dead) and did not consider that disease could progress • The committee heard that the omission of a progressed disease state after allogeneic transplant is not clinically plausible
	Includes the possibility of having an alloSCT after 12 weeks	• In the original model all alloSCTs occurred at week 12 • The committee heard that this was unlikely to be the case in the NHS – therefore this structural assumption is inappropriate • Modelling in TA462 assumes all alloSCTs occur at 6 months

alloSCT: allogeneic stem cell transplant

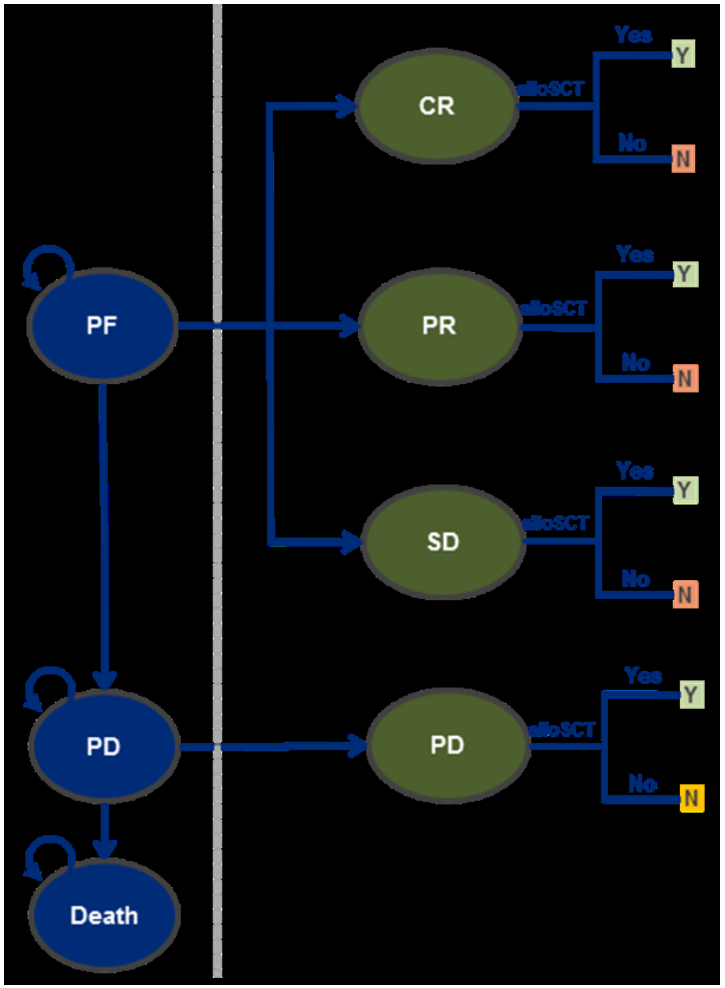
Additional analysis requested (2)

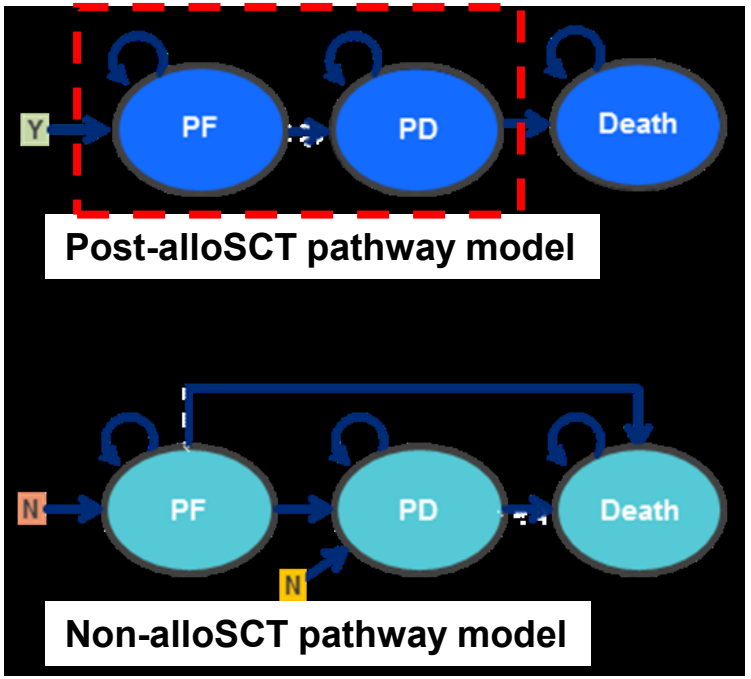
What was asked for	Reason(s)
Consideration of recently published UK data (Eyre et al. 2017) that is potentially relevant for SOC for cohort 2 (people who were unable to have a transplant and for who brentuximab vedotin has failed)	• Data for SOC in the company model is from a US study (Cheah et al.) • Committee heard from a clinical expert that a UK study has recently published that may be relevant for SOC for cohort 2 • Study was published after the company submission
Consideration of changes made to the model by the ERG	
SOC: Standard of care	

Company's additional analysis

Company's updated model: alloSCT at **week 12**

Week 0 to week 12 **At week 12**





Progressive disease state added after alloSCT

alloSCT: allogeneic stem cell transplant

Company's updated model: alloSCT at **week 12**
Base-case analysis

Company's base-case models		ICER	
		Deterministic	**Probabilistic**
Original company submission (alloSCT occurs at week 12)	Cohort 1	£43,511	£39,841
	Cohort 2	£48,571	£43,049
Updated model (alloSCT occurs at week **12**)	Cohort 1	£45,033	£49,588
	Cohort 2	£50,353	£54,704

alloSCT: allogeneic stem cell transplant

- Inclusion of a progressed disease health state post-alloSCT increases ICER by ~£2,000 per QALY
- At a maximum acceptable ICER of £50,000 per QALY, pembrolizumab has a probability of being cost effective of ~53% (cohort 1) and ~47% (cohort 2)

ERG's comments

- Model is similar enough to the original to assess the impact of introducing a progressed disease state post-alloSCT
- ERG believes that changes they made to the model for their base-case analysis should have been used by the company

Company's updated model: alloSCT at **week 12**
Scenario analyses (1)

Selected scenarios Updated week 12 model		ICER	
		Updated **week 12** model	
		Cohort 1	Cohort 2
-	Company's base-case	£45,033	£50,353
1	Uses utilities from mixed modelling from KEYNOTE-087	£51,319	£57,308
3	Use of MSD survey only (for uptake of alloSCT)	£49,987	£57,548
11	Combined scenarios 1 to 5	£56,160	£64,353

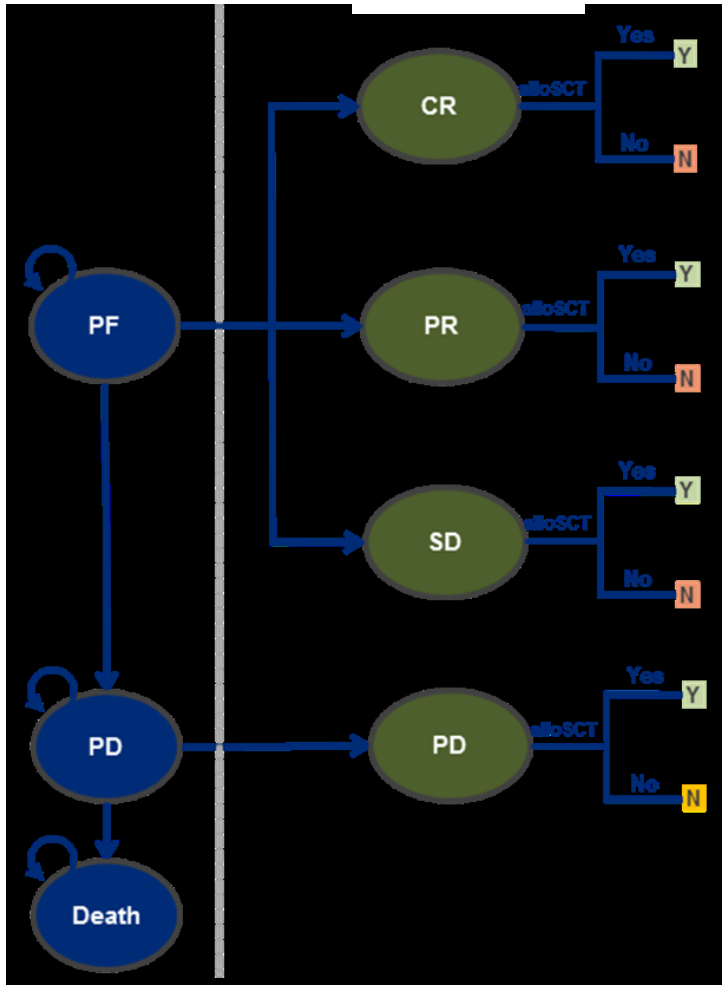
- Company state that several scenario analyses were done to reflect ERG comments – these are scenarios 1 to 5
- **Scenario 11** combines all adjustments made in scenarios 1 to 5; described by the company as the 'ERG combined preferences (1-5)'

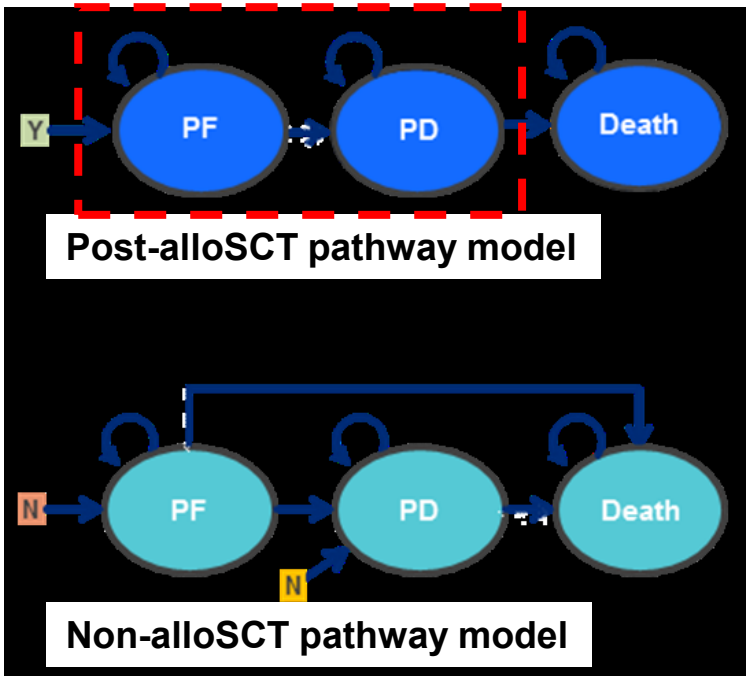
Company's updated model: alloSCT at **week 12**
ERG comments on scenario analyses

- Scenario 1 does not implement all the changes to the utilities made by the ERG for their base-case; for example raising the utility for progressed disease from the [redacted] used by the company (use of the ERG's preferred utilities increases ICERs by ~£2,000)
- ERG does not consider that the company's scenario 11 is equivalent to the ERG's combined preferences
- Although the ERG were unable to implement their entire base-case within the company's new models:
  - The ERG amendments increased the company's original base-case ICERs by £18,000 (cohort 1) and £25,000 (cohort 2) per QALY gained,
  - No evidence for the ERG amendments being substantially less influential in the company's newly submitted models
  - The ERG's amendments did include allowing people with disease progression to have a transplant which the clinical expert said did not happen in routine clinical practice. The company's original base-case ICER increases by less if this amendment is removed (by £14,000 for cohort 1 and £21,000 for cohort 2)

Company's additional analysis

Company's updated model: alloSCT at **week 24**





24 week model
Several parameters updated to change the time at which alloSCT occurs in the model from 12 to 24 weeks

Company's updated model: alloSCT at week 24
Amended parameters in the week 24 model (1)

Overall survival (week 0 to 24) – Pembrolizumab

- In the 12 week model, pembrolizumab and standard of care assumed to have equivalent overall survival in weeks 0 to 12 (hazard ratio of 1)
- Company state that this would overestimate the number of people alive on SOC in the week 24 model
- The company pooled data for cohorts 1 and 2 from an earlier KEYNOTE-087 study data cut point (June 2016) to estimate a hazard ratio of **13.13** (95% CI 3.07-56.04) for relative treatment effect

ERG's comments

- The hazard ratio could not be reproduced as data were not provided
- Use is questionable because the hazard ratio was generated using a mixed population (cohorts 1 and 2)
- Model predicts lower survival for people on SOC compared to data from Cheah et al.
  - 78% (cohort 1) and 72% (cohort 2) alive at 24 weeks in the model versus approximately 85% alive at 26 weeks in Cheah

Company's updated model: alloSCT at week 24

Amended parameters in the week 24 model (2)

Progression-free survival (week 0 to 24) – Cohort 1

Company's updated model: alloSCT at week 24

Amended parameters in the week 24 model (3)

Progression-free survival (week 0 to 24) – Cohort 2

Company's updated model: alloSCT at week 24
Amended parameters in the week 24 model (4)

ERG's comments: Progression-free survival (week 0 to 24)

- The original distributions for progression-free survival were fitted to the entire KEYNOTE-087 data and a change of distributions should therefore be obsolete
- Company has used the model with the worst statistical fit for both cohort 1 and 2 rather than the best fitting model
- This is not in accordance with NICE DSU guidance

Company's updated model: alloSCT at week 24
Amended parameters in the week 24 model (5)

- New distributions were also used for **progression free survival (post-24 weeks)** and **time to treatment discontinuation (post-24 weeks)** in the updated week 24 model
- **ERG comment:** Distributions with the best statistical fit were not always used in the base-case and were not considered in further analysis

Health state utility values

- Utility values from KEYNOTE-087 at week 24 (rather than week 12) were used
- **ERG comment:** ERG preferred the use of all available utility data by using a mixed model - and also used different assumptions to generate utilities for their original base-case analysis

Response rates at week 24

- Response to treatment was updated to use week 24 data from the KEYNOTE-087 trial (rather than week 12)

Company's updated model: alloSCT at **week 24**
Base-case analysis (1)

Company's base-case models		ICER	
		Deterministic	Probabilistic
Original company submission (alloSCT occurs at week 12)	Cohort 1	£43,511	£39,841
	Cohort 2	£48,571	£43,049
Updated model (alloSCT occurs at week **12**)	Cohort 1	£45,033	£49,588
	Cohort 2	£50,353	£54,704
Updated model (alloSCT occurs at week **24**)	Cohort 1	£39,880	£37,682
	Cohort 2	£39,714	£39,828

alloSCT: allogeneic stem cell transplant

- ICERs are lower than for the original and updated week 12 model
- Company state that the lower ICER is largely because people on SOC progress more quickly; therefore at week 24 less have alloSCT
- Company state that true average time to transplant likely to be between 12 and 24 weeks

Company's updated model: alloSCT at **week 24**
Base-case analysis (2)

ERG's comments

- Company have disregarded most amendments made to the model for the ERG's base-case – some of which significantly increased ICERs
  - Company state that the ERG's preferred model amendments were separately explored in scenario analyses (later slides)
- ERG questioned the change of distributions used to model progression-free survival (week 0 to 24) from those used in the week 12 models
- ERG implemented previously used distributions in the week 24 model:

Updated week 24 model		**ICERs**	
		Cohort 1	Cohort 2
Company's base-case		£39,880	£39,714
ERG' analysis: Alternative distributions used for progression-free survival (week 0 to 24)	**Cohort 1:** Log-logistic	£43,724	N/A
	Cohort 2: Generalised gamma	N/A	£38,845

Company's updated model: alloSCT at **week 24**
Scenario analyses (1)

Selected scenarios Updated week 24 model		ICER	
		Updated **week 24** model	
		Cohort 1	Cohort 2
-	Company's base-case	£39,880	£39,714
10	Hazard ratio of 1 used for overall survival (weeks 0 to 24) rather than 13.13	£45,048	£48,523
11	Combined scenarios 1 to 5	£41,021	£49,220

Updated week 24 model

- All scenario analyses have ICERs under £50,000 per QALY
  - This includes scenario analysis 11 which considers all ERG assumptions together

Company's updated model: alloSCT at **week 24**
Scenario analyses (2)

ERG's comments

- As for the updated week 12 model, not all of the changes made by the ERG in their base-case were implemented by the company
  - Scenario 1 does not correspond to all changes made to utilities in the ERG's base-case adjustments and if the ERG's preferred utilities are used in the updated week 24 model the ICER is ~£650 ***higher*** for cohort 1 and ~£4,500 ***lower*** for cohort 2 (compared to scenario 1)
- The main reason for the reduction in the ICERs for pembrolizumab in the week 24 model appears to be the newly applied **hazard ratio for overall survival** in weeks 0 to 24 (hazard ratio of 13.13; compared to hazard ratio of 1 used in week 12 models)
  - If the hazard ratio is set back to 1 in the model, the resulting ICER is very close to the original company's ICER for cohort 2 at £48,524 per QALY gained
  - ERG acknowledges that this is an extreme scenario

Company's updated model: alloSCT at **week 24**
Scenario analyses (3)

ERG's comments (continued)

- The ERG were unable to implement all of their base-case amendments in the company's new models
- If the ERG's base-case amendments have the same effect as in the original model, applying them to the updated week 24 model would increase the ICERs to £53,000 (cohort 1) and £57,000 (cohort 2) per QALY gained
- However, due to the significant changes to the structure and parameters of the model, it is not clear if the ERG's preferences would have the same effect as for the original model
- ERG considers that the ICER for this model with the ERG preferences incorporated is:
  - Likely to be higher than the company's ICER for scenario 11 (£41,021) for **cohort 1**
  - Difficult to assess for **cohort 2** given the substantial uncertainties in this group

Summary (deterministic)

Selected scenarios Updated week 12 model		ICER	
		Updated **week 12** model	
		Cohort 1	Cohort 2
-	Company's base-case	£45,033	£50,353
11	'ERG combined preferences'	£56,160	£64,353

- ERG's preferred assumptions – including higher utility for progressed disease - possibly add £18,000 (cohort 1) and £25,000 (cohort 2): **~£64k and ~£75k**
  - Or if no transplant for progressive disease: **~£60k and ~£71k**

Selected scenarios Updated week 24 model		ICER	
		Updated **week 24** model	
		Cohort 1	Cohort 2
-	Company's base-case	£39,880	£39,714
11	'ERG combined preferences'	£41,021	£49,220

- **ERG:** ICER is likely to be higher than the company's for scenario 11 (£41,021) for **cohort 1**
- Difficult to assess for **cohort 2**

Company's additional analysis
Additional published data – Eyre et al. for cohort 2

- There are differences in the Eyre et al. and KEYNOTE-087 (cohort 2) populations; KEYNOTE-087 population may be more heavily treated and further advanced in their disease course
- Only a subset (~30%) of patients from Eyre et al. – who did not proceed to have a stem cell transplant - are potentially relevant to the decision problem. For consideration further detail would be needed on this group:
  - Information on subsequent treatment received
  - Outcome data and baseline characteristics for this subgroup alone which was not presented in the paper
- It is not feasible to consider this evidence in cost-effectiveness modelling

ERG's comments

- ERG were unconvinced that data reported in Eyre et al. could not be used to provide better estimates for cohort 2 than Cheah et al.
- The company used a naïve indirect comparison; therefore the lack of patient characteristics in this subgroup may not prevent use of data
- Lack of data reported for the relevant subpopulation is a limitation

Issues for consideration

- What is the committee's view of the updated 12 week transplant model?
- What is the committee's view of the model using transplant at 24 weeks?
- Does the committee accept that modelling a later transplant improves the cost effectiveness estimates?
- The company has supplied scenario analyses for the 12 and 24 week transplant models which they say incorporate the ERG's preferences; does the committee accept that this is the case, if not what how would they differ?
- What is the committees view of the appropriate time to model transplant?
- Should a different trial be used to compare with pembrolizumab for cohort 2?