Slides for public – Redacted

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

1st Appraisal Committee meeting

Cost Effectiveness

Committee A

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Key issues: Cost effectiveness

Primary

- Is the structural assumption that all allogeneic stem cell transplants (alloSCTs) would occur at 12 weeks after starting treatment appropriate?
- Is the calculated utility for progressive disease more appropriate for use than the utility score for this state from KEYNOTE-087?

Secondary

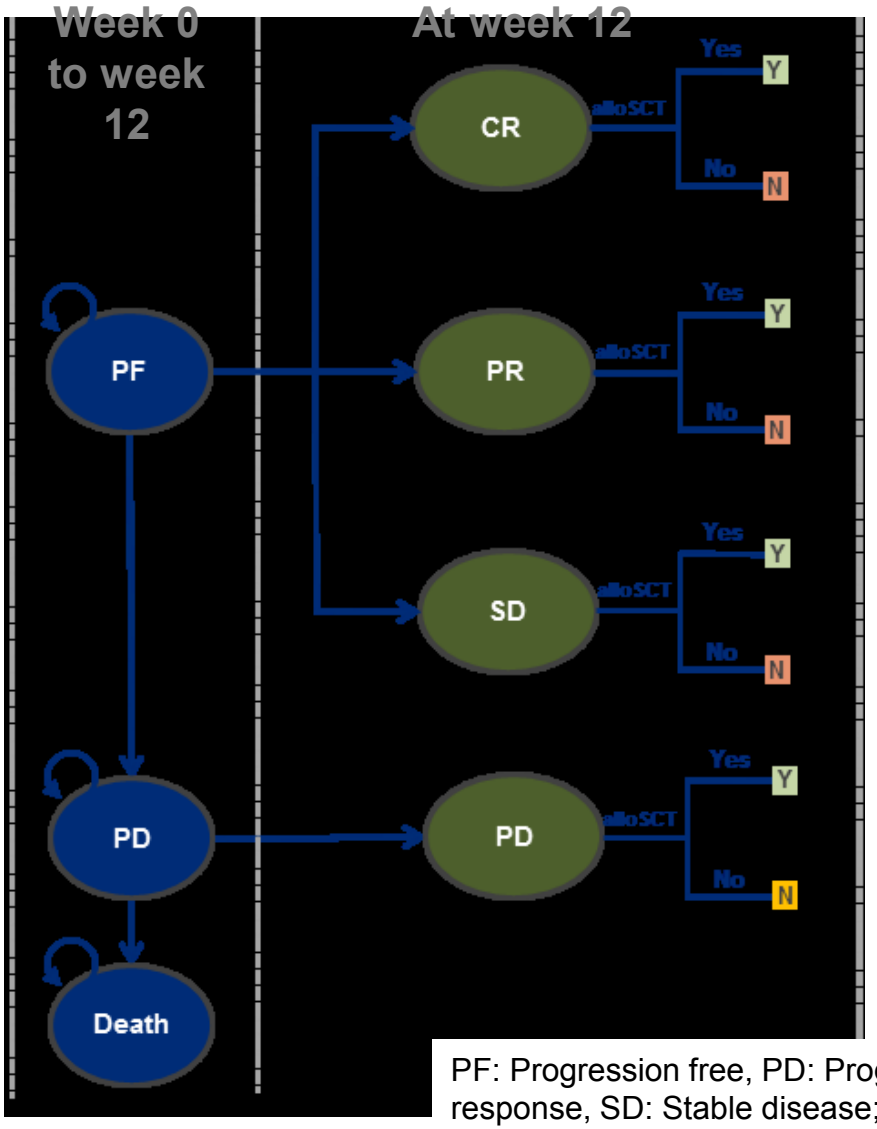
- Is the assumption that no patients with progressive disease would have alloSCT appropriate?
- Is it appropriate that best supportive care (BSC) was not considered as a comparator in the base-case analysis?
- Does pembrolizumab meet the criteria for a life-extending treatment at the end of life?
- Does pembrolizumab represent an innovative treatment?

Company's model

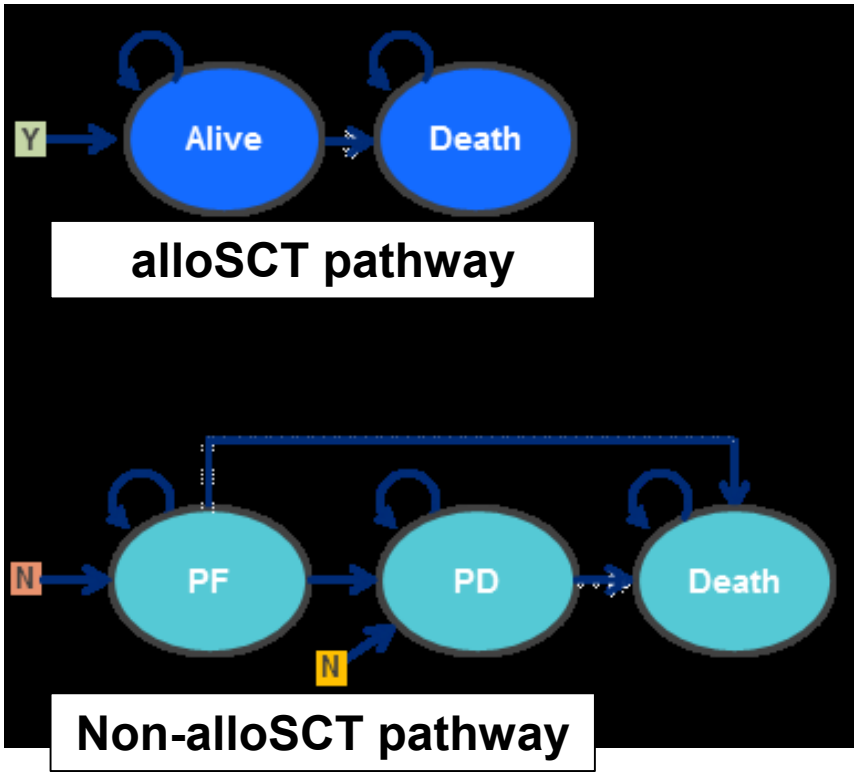
Model structure	• Two phase structure, unlike TA 462 • Short term model with decision tree element (first 12 weeks) • Markov models (from week 12)
Population	• People with RRcHL after autoSCT and BV have failed (Cohort 1) • People with RRcHL (who are autoSCT ineligible) after BV has failed (Cohort 2)
Comparator	• Standard of care (SOC) • Best supportive care (only in scenario analysis)
Time horizon	Lifetime (40 years)
Cycle length	1 week (with half-cycle correction)
Measure of health effects	QALY
Discounting of utilities and costs	3.5% per annum
Perspective	NHS/PSS

RRcHL: Relapsed or refractory classical Hodgkin lymphoma; autoSCT: Autologous stem cell transplant; BV: Brentuximab vedotin

Company's model
Structure



Week 12 to maximum lifetime horizon of 40 years



PF: Progression free, PD: Progressive disease, CR: Complete response, PR: Partial response, SD: Stable disease; alloSCT: Allogeneic Stem Cell Transplant

Company's model
Structure (cont.)

- Goal of alloSCT is cure; therefore model does not consider impact of post-alloSCT progressive disease (PD)
  - Omission of PD in post-alloSCT pathway simplifies calculation of post-alloSCT survival
  - Role of progression-free survival (PFS) in determining quality of life of patients who undergo alloSCT is unclear
- All alloSCTs assumed to occur at week 12, based on:
  - Mean number of administrations of pembrolizumab in the small number of people who have received alloSCT in KEYNOTE-087 ([redacted])
  - Time of first tumour assessment in KEYNOTE-087 was 12 weeks after treatment initiation
  - Clinician survey suggests median of 12 weeks of SOC prior to alloSCT

ERG's critique
Model structure

- **Patients can only have alloSCT at 12 weeks after starting treatment**
  - Main goal of pembrolizumab is to enable alloSCT – this should be represented as accurately as possible in the model
  - Model incorporating a continuous probability of having alloSCT was requested; not provided by company because:
    - alloSCT data from KEYNOTE-087 not considered to reflect UK practice
    - Time-to-alloSCT data from Cheah et al. not available
  - ERG uncertain about the impact of assuming no alloSCT after week 12 because:
    - Issue not appropriately explored by company
    - It is unclear how many cases of people responding to treatment and being considered for alloSCT after 12 weeks would occur for pembrolizumab and SOC
- **Assumption that alloSCT performed immediately after response**
  - Doesn't consider time taken to identify donor and schedule procedure
  - Procedure potentially performed at 12 to 24 weeks (in-line with assumption in TA462)

ERG's critique
Model structure (cont.)

- AlloSCT in model therefore carried out earlier than expected in clinical practice; consequently post-alloSCT benefits occur earlier
- Unlikely to be conservative assumption as more patients on pembrolizumab proceed to alloSCT (compared to SOC)

- **No progressed disease state in post-alloSCT pathway**
  - Disease progression not considered post-alloSCT despite Lafferty et al. (2017) reporting progression free survival at 1 year post-alloSCT of 54%
  - Post-alloSCT survival modelled independent of underlying disease state
- **Model structure compared with TA462**
  - Different model structure to the one used in TA462
  - Limitations/simplifications in current model not present in model presented for TA462
  - Impact of differences uncertain

Company's model
Treatment effectiveness

- Comparative data from naïve indirect comparison of data from KEYNOTE-087 cohorts 1 and 2 (pembrolizumab) and Cheah et al. (2016) (SOC) used in base-case
- Data from a matched adjusted indirect treatment comparison (MAIC) of pembrolizumab and SOC used in a scenario analysis
- No evidence identified on efficacy of BSC in this population
  - Scenario analysis for BSC as comparator uses SOC efficacy data

ERG general comments on treatment effectiveness:

- Use of naïve comparison data in base-case is appropriate
- BSC not included in base-case analysis – incomplete compared with NICE scope
- The model structure requires different survival curves to be fitted for pre- and post 12 weeks – this leads to loss of data and further uncertainty

Progression-free survival considerations

- **NOTE: 0 to 12 weeks** & **post-week 12** modelled separately

0 to 12 weeks:

- Models fitted to all available data from KEYNOTE-087; because only small number events occurred in first 12 weeks
- ERG: Fitted curves likely to have been influenced more by the post-12 week period
- SOC PFS estimated from naïve indirect comparison; applying HR to the pembrolizumab model (cohort 1 HR: [redacted]; cohort 2 HR: [redacted])

Post-week 12 (non-alloSCT pathway):

- Pembrolizumab modelled using parametric models fitted to KEYNOTE-087 data (post-week 12); SOC modelled assuming constant treatment effect pre- and post-12 weeks (cohort 1 HR: [redacted]; cohort 2 HR: [redacted])
- ERG: Use of constant HR lacks face validity; highlighted that different parametric models were used pre- and post-12 weeks

Company's model
PFS (from week 12) – **cohort 2**

Source: Figure 21 of the company submission

- Generalised gamma was best performing model according to AIC/BIC
- However final drops in KM curve (from month 11) stated to be associated with considerable uncertainty because of low patient numbers
- Exponential used in base-case

AIC: Akaike Information Criterion; BIC: Bayesian information criterion

ERG's comment

- Unconvinced there is sufficient justification to rule out generalised gamma distribution for cohort 2 – investigated use in ERG exploratory analysis

Overall Survival Considerations

Mortality post-week 12: **Non-alloSCT pathway**

- Company's model:
  - Pre-progression: General population rates (adjusted for age and sex) used; limited overall survival data available from KEYNOTE-087
  - Post-progression: Cheah et al. (2016) used (no post-progression survival benefit for Pembrolizumab assumed)
- ERG: Highlighted inconsistency in choice of data sources

Mortality post-week 12: **AlloSCT pathway**

- Company's model:
  - Lafferty et al. (2017) used to estimate overall survival after alloSCT
  - This study was used in economic model for NICE TA462
- ERG: Abstract - small retrospective UK case series (13 participants)
- ERG: Substantial uncertainty; assumptions about censoring may over-estimate survival which favours Pembrolizumab

Company's model

Response to treatment at week 12

- Odds ratios (pembrolizumab vs SOC) obtained from naïve comparison:

Response	Cohort 1	Cohort 2
	Mean (SE)	Mean (SE)
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]

Uptake of alloSCT at week 12 (conditional on response) - from clinician surveys:

Response	% people expected to receive alloSCT		
	MSD survey mean (n=16)	Alternative survey mean*	Overall mean
CR	56.79%	[redacted]	[redacted]
PR	43.93%	[redacted]	[redacted]
SD	18.36%	[redacted]	[redacted]

* alternative clinician survey completed by Bristol-Myers Squibb and presented for TA462

Key: CR: Complete response, PR: Partial response, SD: Stable disease; alloSCT: Allogeneic Stem Cell Transplant

Uptake of alloSCT at week 12
ERG's critique
(Both 1 and 2 important factors in cost effectiveness analysis)

1. People with progressive disease (PD) were assumed not to have alloSCT in the company's model

- Despite company survey suggesting that some patients with PD would have alloSCT
- Assumption was based on clinician feedback: not standard UK practice that people in PD state would get alloSCT
- ERG used the company's survey result to provide probability of having alloSCT for people in PD state in its base-case analysis

2. Combination of MSD and BMS clinician surveys on rates of transplant may introduce bias

- Possible that the surveys may include responses from the same clinicians
- ERG preferred to use MSD survey data only in base-case analysis

Uptake of alloSCT in company's and ERG's base-case analyses

		Company's base-case model		ERG's base-case model	
		Progressed disease at week 12	Entering alloSCT at week 12	Progressed disease at week 12	Entering alloSCT at week 12
Cohort 1	Pembrolizumab	4.1%	43.8%	4.4%	34.8%
	SOC	26.9%	30.7%	27.1%	27.2%
Cohort 2	Pembrolizumab	8.0%	40.1%	9.2%	32.1%
	SOC	28.7%	30.2%	29.9%	26.8%

Company's model
Time on treatment

- Progression-free survival (PFS) not considered a suitable proxy for time on treatment post-week 12 for pembrolizumab (people discontinue use before progression); use of PFS would overestimate pembrolizumab costs
- Time on treatment data from KEYNOTE-087 extrapolated to provide estimates for model (pembrolizumab post-week 12)
- PFS used as a proxy for time on treatment for SOC

ERG's comments

- Inconsistency in how time to treatment discontinuation estimated in pre-12 week period and post-week 12 for SOC (PFS used as proxy), and in post-12 week period for pembrolizumab (from extrapolated KEYNOTE-087 data)
- Assumption in model that pembrolizumab treatment capped at 24 months is not in line with marketing authorisation
  - Unclear if this would be the case in UK practice
  - Model may underestimate cost of pembrolizumab if treatment is continued after 24 months in clinical practice

Company's model: utility values
ERG's critique
(Important factor in cost effectiveness analysis)

- **Utility values in company base-case based on observations from week 12 in KEYNOTE-087 only**
  - Mixed effects model analysis incorporating all EQ-5D data from KEYNOTE-087 subsequently provided by company and preferred by ERG for their analysis
- **Estimated PD utility from KEYNOTE-087 not used in company base-case; decrement from Swinburn et el. (2015) used instead**
  - Company stated that week 12 utility observation may not capture longer-term disutility associated with progression
  - Company did not provide evidence showing long term impact of progression consistent with utility decrement from stable disease calculated from Swinburn et al. (2015)
  - Noted that ERG in TA462 considered utility results from Swinburn et al. (2015) as outliers which may not be realistic; and methodology in the paper deviates from NICE reference case
  - ERG preferred to use progressed disease utility from KEYNOTE-087 data (using provided mixed effects model analysis)

Utility values

Company's and ERG's base-case values

Health state		Company base-case	ERG base-case
Progression-free (first 12 weeks)	Pembrolizumab cohort 1	[redacted]	[redacted]
	Pembrolizumab cohort 2	[redacted]	[redacted]
	SOC	[redacted]	[redacted]
Progression-free (after first 12 weeks; no alloSCT)	Pembrolizumab cohort 1	[redacted]	[redacted]
	Pembrolizumab cohort 2	[redacted]	[redacted]
	SOC	[redacted]	[redacted]
Progressive disease		[redacted]	[redacted]
Post-alloSCT (first 100 days)		0.773	0.708
Post-alloSCT (post 100 days)		0.865	0.800

SOC: Standard of care, alloSCT: Allogeneic Stem Cell Transplant

Company's model
Resource use and costs

Treatment		Acquisition cost/per cycle	Administration cost/per cycle
Pembrolizumab		[redacted] with commercial access agreement. Cycle length of 21 days, to a maximum of 35 cycles (~2 years)	£236.19
SOC			
Chemotherapy (12 different regimens)	38.5%	Varies between regimens (from £63.32 to £2,183) Cycle length also varies between regimens (14 to 28 days) Maximum number cycles varies (2 to 6 cycles)	Varies between regimens (from £383.13 to £1,367.43)
Bendamustine	18.5%	£123.30 Cycle length of 28 days Maximum of 6 cycles	£383.13
Investigational agents	43.1%	Assumed to be £0	

Company's model: Resource use and costs
ERG's critique

- **All chemotherapy regimens assumed to contribute equally to SOC**
  - ERG cite previous report for TA462 which suggests lower price chemotherapy regimens are most commonly used in this population; and suggest that SOC costs are likely to be overestimated
- **One-off cost applied for alloSCT treatment**
  - ERG considered alloSCT costs to be under-estimated
  - In TA462, one-off cost was only applied in scenario analysis; monthly costs for subsequent treatment and monitoring were applied
  - ERG have applied monitoring costs over life time horizon in their base-case analysis

Company's base case results

Deterministic (with CAA)

Treatment		Total		Incremental		ICER
		Costs	QALYs	Costs	QALYs	
Cohort 1	SOC	£52,017	3.223	-	-	
	Pembrolizumab	£107,459	4.497	£55,442	1.274	**£43,511**
Cohort 2	SOC	£51,424	3.200	-	-	
	Pembrolizumab	£93,732	4.072	£42,308	0.871	**£48,571**

ERG's comments

- Main benefit of pembrolizumab from QALY gains after week 12 for people who have alloSCT
  - Accounts for 71% (cohort 1) and 78% (cohort 2) incremental QALYs
- Best supportive care (BSC) not included as comparator in base case; therefore pembrolizumab could not be compared to all relevant alternatives at the same time

Company's sensitivity analyses
Probabilistic and deterministic (with CAA)

Probabilistic sensitivity analysis

Treatment	ICER (versus SOC)	Probability of cost-effectiveness of pembrolizumab compared with SOC		
		Maximum acceptable ICER		
		£20,000/ QALY	£30,000/ QALY	£50,000/ QALY
Pembrolizumab – cohort 1	**£43,653**	1.1%	20.5%	60.1%
Pembrolizumab – cohort 2	**£50,894**	1.4%	16.1%	50.4%

Deterministic sensitivity analysis

- Most influential model inputs: discount rate applied to outcomes, odds ratios applied to CR and PR at week 12
- In most scenarios ICER for pembrolizumab versus SOC was below £50,000/QALY

Company's scenario analyses (with CAA)

Scenario		ICER	
		Pembrolizumab versus SOC	
		Cohort 1	Cohort 2
1	BSC as comparator	£44,161	£49,387
2a	100% people with CR, PR or SD response at week 12 have alloSCT	£23,564	£24,492
2b	Proportion of people with partial response at week 12 who have alloSCT taken from MSD survey	£47,957	£56,677
3	MAIC instead of naïve comparison	£36,423	£41,087
4a	Weibull model used for PFS (weeks 0 to 12) in cohort 2	-	£47,410
4b	Gompertz model used for PFS (week 12 onwards) in cohort 2	-	£52,562
4c	Lognormal model fitted to post-alloSCT survival data from Lafferty et al.	£42,075	£46,812
5	Time horizon of 50 years	£42,651	£47,516

ERG's comments: Model validation

- Patients with no evaluated response were assumed to have stable disease; this probably leads to an overestimation of patients in this state
- No cross validation of model assumptions, structure or outcomes compared to TA462 was carried out
  - Different model structure used in TA462: 3 heath states (progression-free, progressed, dead) in a semi-Markov model
  - Progression post-alloSCT is incorporated in modelling in TA462 (this is not allowed in the current assessment model)
  - In TA462 modelling patients may receive alloSCT after 6 months
- Higher total QALYs (almost doubled) and costs (more than doubled) generated by modelling for SOC (cohort 1) in this assessment compared to TA462

ERG's base-case

Adjustments made to company's base-case model

8 adjustments made to the company's base-case:

Fixing errors

- Corrected errors in the calculation of AE disutilities (1)
- Patient characteristics were excluded from the probabilistic sensitivity analysis (2)

Fixing violations

- Only the MSD clinician survey used for the probabilities of alloSCT depending on response to treatment (rather than combined MSD and BMS survey results) (3)
- Time horizon of 50 years used (rather than 40 years) (4)
- Post-alloSCT long-term monitoring costs included (consistent with committee preference in TA462) (5)

ERG's base-case

Adjustments made to company's base-case model (cont.)

Matters of judgement

- Alternative utility values used (6):
  - Mixed model utilities (using all available utility data time points) rather than utility data from week 12 only
  - Kurosawa et al. used to calculate alternative utilities post-alloSCT
- Alternative distributions used for pre-week 12 overall survival (7)
  - Exponential used for cohort 1
  - Lognormal used for cohort 2
- Company's clinician survey used to inform the proportion of people with progressive disease at week 12 who would receive alloSCT (rather than assuming this would be 0%) (8)

- **All adjustments (1) to (8) made to form ERG base-case model**

ERG's base-case - deterministic (with CAA)
Effects of ERG's adjustments

Adjustment	ICER (pembrolizumab versus SOC)	
	Cohort 1	Cohort 2
Company's base-case	***£43,511***	***£48,571***
Fixing errors **(1) and (2)**	£43,262	£48,178
MSD survey only used for alloSCT probabilities **(3)***	£48,363	£55,478
50 year time horizon **(4)***	£42,412	£47,141
Monitoring costs included post-alloSCT **(5)***	£43,927	£48,908
Alternative utility values **(6)***	£52,705	£59,223
Alternative pre-week 12 OS distributions **(7)***	£43,262	£48,236
Proportion of alloSCT in PD state taken from MSD survey **(8)***	£46,841	£53,508

* Conditional on fixing errors (1) and (2)

ERG's base-case results (with CAA)

ERG base-case (deterministic) – combines adjustments (1) to (8)

Treatment		Total		Incremental		ICER
		Costs	QALYs	Costs	QALYs	
Cohort 1	SOC	£50,913	3.535	-	-	
	Pembrolizumab	£107,998	4.460	£57,085	0.925	**£61,705**
Cohort 2	SOC	£50,609	3.541	-	-	
	Pembrolizumab	£93,095	4.118	£42,486	0.577	**£73,594**

ERG base-case (probabilistic)

Treatment	ICER (versus SOC)	Probability of cost-effectiveness of pembrolizumab compared with SOC	
		Maximum acceptable ICER	
		£30,000/ QALY	£50,000/ QALY
Pembrolizumab – cohort 1	**£64,186**	18%	42%
Pembrolizumab – cohort 2	**£78,696**	21%	40%

ERG's base-case model
Selected further exploratory analysis (deterministic)

Exploratory analysis		ICER	
		Pembrolizumab versus SOC	
		Cohort 1	Cohort 2
-	***ERG's base-case***	***£61,705***	***£73,594***
1b	Cohort 2: Generalised gamma used for post-week 12 PFS	-	£90,152
2	MAIC used instead of naïve indirect comparison	£54,466	£60,372
3	Removal of 24 months cap on time to treatment discontinuation for pembrolizumab	£78,992	£79,284
5	Use of alternative assumptions to extrapolate post-alloSCT OS from Lafferty et al. (2017)	£78,204	£95,712

- None of the ERG's alternative scenarios resulted in an ICER below £50,000 per QALY gained
- Use of the MAIC rather than naïve indirect comparison was the only factor that reduced the ERG's ICER

ERG's conclusions: Cost-effectiveness

- Company's economic model meets NICE reference case, except (1) time horizon (40 years) is too short, and (2) BSC – a comparator included in the scope – was excluded from the base-case
- Major limitation is model structure: implausible assumption that people could only be eligible for, and receive, alloSCT 12 weeks after starting treatment
- Impact of limitations due to model structure on outcomes is unknown
- Lifting the assumed capping of pembrolizumab at 24 months significantly increased ICERs, as did the use of alternative assumptions when extrapolating post-alloSCT overall survival data from Lafferty et al. (2017)
- Use of alternative models to extrapolate PFS post-week 12 also had a large effect on ICERs
- Use of MAIC rather than naïve indirect comparison decreased ICERs
- Uncertainty about the cost effectiveness of pembrolizumab remains substantial

End of life

Criterion	Company's submission	ERG comments
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Estimates from literature suggest OS for people with RRcHL between 17.1 and 19 months	Considerable uncertainty that criterion met TA462: criterion for short life expectancy not 'unequivocally met'; but committee considered it plausible that the criterion could apply
Sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	KEYNOTE-087 (at March 2017): [redacted] Estimated OS rate at 15 months [redacted] (cohort 1) and [redacted] (cohort 2).	Company's base case model predicts increased survival of 21 months (cohort 1) and 15 months (cohort 2) for pembrolizumab versus SOC Second criterion more likely to be met

RRcHL: Relapsed or refractory classical Hodgkin lymphoma; OS: Overall survival

Innovation

- Limited treatment options at this later line of therapy – substantial level of unmet need
- March 2017: FDA accelerated approval for the treatment of adult and pediatric patients with refractory classical Hodgkin Lymphoma, or those who have relapsed after three or more prior lines of therapy
- FDA Breakthrough Therapy Designation (BTD) and MHRA's Early Access to Medicines Scheme (EAMS) for other indications

Equality considerations

- No equality issues raised in scoping process
- No equality issues raised by company
- No equality issues raised by ERG

Key issues: Cost effectiveness

Primary

- Is the structural assumption that all alloSCTs would occur 12 weeks after starting treatment appropriate?
- Is the calculated utility for progressive disease more appropriate for use than the utility score for this state from KEYNOTE-087?

Secondary

- Is the assumption that no patients with progressive disease would have alloSCT appropriate?
- Is it appropriate that best supportive care (BSC) was not considered as a comparator in the base-case analysis?
- Does pembrolizumab meet the criteria for a life-extending treatment at the end of life?
- Does pembrolizumab represent an innovative treatment?