NICE National Institute for Health and Care Excellence

Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy

2nd Appraisal Committee meeting

25 August 2016

Pembrolizumab (Keytruda, MSD)

- Marketing authorisation (granted July 2016**)**
  - Keytruda is indicated for the treatment of locally advanced or metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received approved therapy for these mutations prior to receiving Keytruda
- SPC states: 'Patients should be treated until disease progression or unacceptable toxicity. Atypical responses (i.e. an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed'
- Administration:
  - 2 mg/kg every 3weeks (Q3W); intravenous (IV) infusion
- Cost:
  - List price: £1315.00 (50mg vial)
  - Revised simple discount PAS (commercial in confidence, approved July 2016)

Clinical effectiveness evidence summary

- **KEYNOTE-010**, a phase II/III head-to-head RCT that compared pembrolizumab with docetaxel

Results from KEYNOTE-010:

	Pembrolizumab	Docetaxel
	2 mg/kg Q3W n=344	75 mg/m2 Q3W n=343
Primary endpoints		
Overall survival – ITT population		
Median: months (95% CI)	10.4 (9.4, 11.9)	8.5 (7.5, 9.8)
Hazard ratio (95% CI)	HR 0.71 (95% CI 0.58, 0.88); p=0.00076	
12 month OS rate (%)	43%	35%
Progression-free survival – ITT population		
Median: months: (95% CI)	3.9 (3.1, 4.1)	4.0 (3.1, 4.2)
Hazard ratio (95% CI)	HR 0.88 (95% CI 0.73, 1.04); p=0.06758	
PFS rate at 12 months (%)	18%	9%

Cost effectiveness evidence summary

Company's deterministic base case ICERs with original PAS:

Scenario	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER
Base case 1: KEYNOTE 001 for extrapolation post 52 weeks					
Pembrolizumab	£41,509	1.30	£30,242	0.70	£43,351
Docetaxel	£11,267	0.60	-	-	-
Base case 2: KEYNOTE 010 for extrapolation post 52 weeks					
Pembrolizumab	£41,283	1.22	£30,016	0.61	£49,048
Docetaxel	£11,267	0.60	-	-	-
Source: Company submission, Table 96 (page 219)					

- Committee preferred the use of KEYNOTE 010 data in base-case-2 (probabilistic ICER of £48,667 per QALY gained). However, it recognised that with no treatment stopping rule the true ICER was likely to be higher
- Taking into account the uncertainties associated with the preferred ICER, the committee was minded to request further analyses and clarification from the company

Clinical effectiveness: committee's key considerations (I)

Clinical management	Pembrolizumab is an important treatment option for people with locally advanced or metastatic NSCLC. Pembrolizumab is better tolerated than docetaxel
Clinical trials/evidence base	KEYNOTE-010 evidence was the most applicable to the decision problem because the population was adults with PD-L1-positive locally advanced or metastatic NSCLC
Generalisability	Overall population in KEYNOTE-010 was generalisable to clinical practice in England
Treatment effect	Median overall survival gain from KEYNOTE-010 was **10.4 months** for pembrolizumab compared with **8.5 months** for docetaxel (statistically significant, ITT population)
Network meta-analysis	Not robust and limited because of the differences between the trial populations and the limited evidence base of only 2 trials
Treatment switching	Switching occurred in KEYNOTE-010 but the most appropriate method to adjust for treatment switching was unclear

Cost effectiveness: committee's key considerations (I)

Treatment duration	• Optimal treatment duration unknown, data immature • Model assumes that at 2 years all patients in the pre-progression state would stop treatment • SPC for pembrolizumab states treat until progression • No compelling evidence that a 2 year stopping rule would be applied in clinical practice
Time on treatment	• Uncertainty over how many additional weeks of therapy people had in KEYNOTE-010 • Additional weeks of therapy were needed to distinguish between true progression and pseudo-progression in KEYNOTE-010 • Costs of confirming true progression of disease should be included in the modelling • Uncertainty about time on treatment in KEYNOTE-010 and its impact on the cost-effectiveness estimates

Cost effectiveness: committee's key considerations (II)

Extrapolation methods for OS	• To estimate overall survival, the company used 52-week Kaplan–Meier data from KEYNOTE-010 • After 52 weeks, for docetaxel, the company fitted an exponential model to the KEYNOTE-010 data after a 2-stage crossover adjustment. For pembrolizumab, the company fitted an exponential model to the KEYNOTE-010 data (base case 2) • Committee preferred base case 2 as it was a better source of evidence and base case 1 had internal validity problems
Cut off points when switching to exponential model	• Cut-off point at which the Kaplan–Meier data switch to the exponential model is arbitrary • ERG approach of using individual patient data and re-estimating the exponential curve for each different cut-off point on the Kaplan–Meier curve was preferred • Would have liked to see analyses determining sensitivity of these cut-off points

Cost effectiveness: committee's key considerations (III)

Model structure	• No model parameter about how the treatment effect is varied over time. Would have liked to see an adjustment to the way the survival function is calculated at a particular point in time, by assuming that at trial end the hazard ratio is 1
Utility values	• The utility values used were incompatible with the partitioned survival model because the model cannot identify the health state in which people will die • The company base case ICER did not include a disutility for adverse events which was inappropriate • Would have liked to see further sensitivity analyses to explore the effect of a range of alternative utility values
Subgroups	• The comparison in the adenocarcinoma subgroup was too unreliable for decision-making
ICER	• Company's base-case-2 analysis using KEYNOTE 010 was preferred (probabilistic ICER of £48,667 per QALY gained) • With no stopping rule the true ICER was likely to be higher than this

End of life and cancer drugs fund: committee's key considerations (IV)

End of life	• Evidence presented showed that people with NSCLC have a life expectancy of less than 24 months • Significant uncertainty in the OS. Although reasonable that the benefit is likely to exceed 3 months, additional information was requested from the company • Pembrolizumab met the end-of-life criteria and can be considered a life-extending, end-of-life treatment
Cancer drugs fund	• Most plausible ICER for pembrolizumab was higher than the range usually considered a cost-effective use of NHS resources • Pembrolizumab did not have the potential to satisfy the criteria for routine use • Due to uncertainties in the evidence, collecting outcomes data from people in the NHS would not be enough to inform an update of the guidance • Company stated it did not intend to submit a case to include pembrolizumab in the Cancer Drugs Fund

Additional analyses requested from the company

A revised base-case 2 probabilistic cost-effectiveness analysis for pembrolizumab vs docetaxel:

- without the 2 year treatment duration assumption in the pre-progression state for pembrolizumab treatment

Scenario and sensitivity analyses applied to the revised base-case 2:

1. Impact of adjusting for treatment switching using the rank-preserving structural failure time method in a scenario analysis
2. Cut-off point after which the exponential model is fitted to those patients still at risk and applied in the cost-effectiveness analysis for extrapolation
3. Alternative approaches to estimating time on treatment using individual patient-level data and a gamma model to estimate duration
4. Time on treatment in the model when additional weeks of therapy are needed (to distinguish between true progression and pseudo-progression)
5. Use of a range of published post-progression utility values
6. Inclusion of adverse event disutilities
7. Impact when the hazard ratio is assumed to be 1 after the trial ends

Additional clarification requested from the company

- Number of people in KEYNOTE-010 still having pembrolizumab treatment after 2 years
- Proportion of people in KEYNOTE-010 who had confirmatory scans and the percentage who were confirmed to have disease progression. Of these, how many continued on treatment with pembrolizumab post-progression at clinician's discretion
- Summary of the hazard ratio for progression-free survival and overall survival calculated from the model results (that is, the hazard ratio based on the extrapolation)
- Why the rank-preserving structural failure time (RPSFT) method was disregarded and the two-stage adjustment method favoured instead
  - Clarification on why a formal analysis of a common treatment effect assumption using the RPSFT method was not carried out

Company's additional analyses: revised base case 2 analysis (without 2 year treatment assumption) (I)

- MSD explored the effect of varying the maximum duration of treatment after 2 years with 0%, 25%, 50%, 75% and 100% of patients remaining on treatment before disease progression
- Analyses reflects the additional costs related to drug and administration costs
- Efficacy (OS and PFS) has not been changed from the original base-case 2

Source: company additional analyses, table 1 (page 3)

Probabilistic cost-effectiveness results of base-case 2 (discounted, with revised PAS) - varying the maximum duration of treatment after 2 years

% of patients receiving treatment after 2 years	Technology	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
0%	Pembrolizumab	£38,640	1.219	-	-	-
	Docetaxel	£11,263	0.604	£27,377	0.614	£44,563
25%	Pembrolizumab	£39,493	1.217	-	-	-
	Docetaxel	£11,277	0.605	£28,216	0.612	£46,089
50%	Pembrolizumab	£40,439	1.216	-	-	-
	Docetaxel	£11,286	0.604	£29,154	0.612	£47,666
75%	Pembrolizumab	£41,099	1.215	-	-	-
	Docetaxel	£11,286	0.604	£29,814	0.611	£48,795
100%	Pembrolizumab	£42,069	1.219	-	-	-
	Docetaxel	£11,264	0.605	£30,805	0.614	£50,135

Source: company additional analyses, table 1 (page 3)

Company's additional analyses: adjusting for treatment switching

Median OS using two-stage and RPSFT methods (months, 95% CI)		
	ITT population cut-off (30SEP2015)	ITT population cut-off (31MAR2016)
Pembrolizumab 2 mg/kg Q3W	10.4 (9.4, 11.9)	10.5 (9.6, 12.4)
Docetaxel - unadjusted OS	8.5 (7.5, 9.8)	8.6 (7.9, 9.8)
Docetaxel - 2-stage adjusted OS	8.3 (7.4, 9.5)	8.1 (7.0, 9.2)
Docetaxel - RPSFT adjusted OS	8.4 (7.5;9.8)	8.3 (7.5, 9.6)

Cost-effectiveness results of base-case 2 (discounted, with PAS) using RPSFT method - varying the maximum duration of treatment after 2 years	
Assumption	Probabilistic ICER
0% of patients receiving treatment after 2 years	£48,480
25% of patients receiving treatment after 2 years	£50,184
50% of patients receiving treatment after 2 years	£51,679
75% of patients receiving treatment after 2 years	£52,834
100% of patients receiving treatment after 2 years	£54,826

Source: company additional analyses, tables 3 and 4 (page 6)

Company's additional analyses: exploring cut-off point used for extrapolation (I)

- 52 weeks used in company submission because:
  - supported by cumulative hazard and the log-cumulative hazard plots of OS for pembrolizumab and docetaxel based on KEYNOTE-010 data (shows hazard is not constant over time and presents a different slope before and after around 52 weeks)
  - resulted in a plausible visual fit
  - provided the most conservative estimate among the three alternative cut-off time points
- 82 week results considered unreliable as only 17 patients (5%) in the pembrolizumab arm and 3 patients in the docetaxel arm (1%) remained alive at that time, resulting in a flat extrapolation of the OS
- 42 week results considered unreliable because, when considering the cumulative hazard plot for OS in the pembrolizumab 2mg Q3W arm, there was a clear change in the slope happening at around week 52

Company's additional analyses: exploring extrapolation cut-off points (II)

Cost-effectiveness results of base-case 2 (discounted, with PAS) using 52, 42 and 82 week cut-off points - varying maximum duration of treatment after 2 years

Assumption	Probabilistic ICER		
	52 week	42 week	82 week
0% of patients receiving treatment after 2 years	£44,563	£83,127	£18,337
25% of patients receiving treatment after 2 years	£46,089	£86,303	£18,910
50% of patients receiving treatment after 2 years	£47,666	£88,197	£19,498
75% of patients receiving treatment after 2 years	£48,795	£91,354	£19,702
100% of patients receiving treatment after 2 years	£50,135	£93,884	£20,341
Source: company additional analysis, table 5 (page 9)			

Company's additional analyses: alternative approaches to time on treatment (I)

- The company stated:
  - fully parametric generalised gamma approach is not a close fit to the time on treatment KM curve for a large part of the curve, clearly overestimates treatment duration
  - a one piece parametric approach based on time on treatment was not found to be appropriate for estimate of time on treatment as they were not a close visual fit (see next slide)

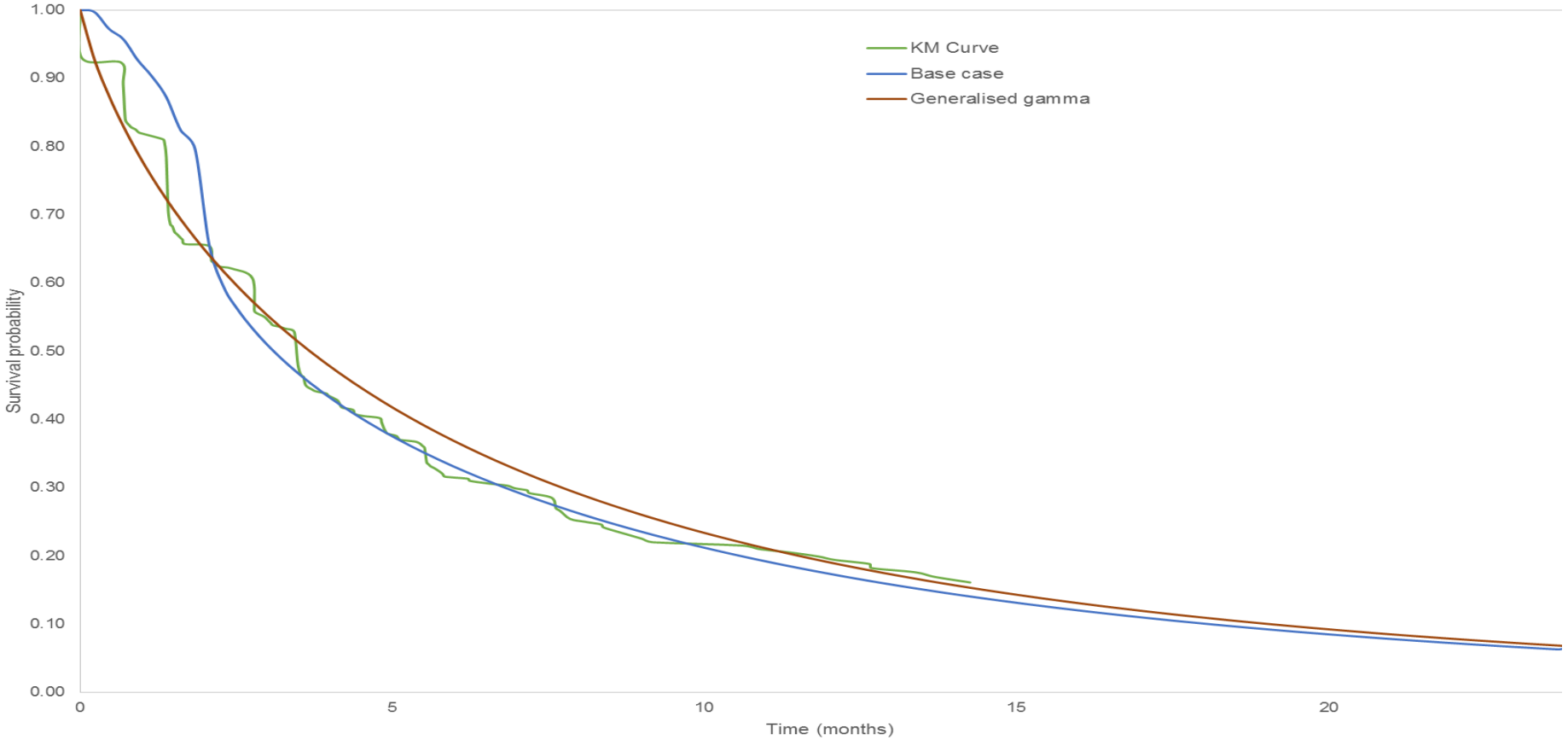
Cost-effectiveness results of base-case 2 (discounted, with PAS) using individual patient-level data and a gamma model - varying maximum duration of treatment after 2 years

Assumption	Probabilistic ICER
0% of patients receiving treatment after 2 years	£50,821
25% of patients receiving treatment after 2 years	£52,733
50% of patients receiving treatment after 2 years	£54,575
75% of patients receiving treatment after 2 years	£56,277
100% of patients receiving treatment after 2 years	£57,765

Source: company additional analyses, table 7 (page15)

Company's additional analyses: alternative approaches to time on treatment (II)

Figure 2. Estimation of the time on treatment (ToT) for patients treated with pembrolizumab, comparing the ToT KM data, the ToT as estimated in the base case (KM + exponential from week 9, adjusted with the HR of ToT vs. PFS), and a fully parametric generalised gamma



Source: company additional analyses, figure 2 (page 13)

Company's additional analyses: additional weeks of therapy (pseudo-progression)

- Company noted that duration of treatment was incorporated appropriately in the cost-effectiveness model (therefore no new analyses presented)
- Time on treatment was evaluated in the KEYNOTE-010 trial irrespective of disease progression and includes all weeks of treatment therapy
- Adjusted PFS was used as a proxy for time on treatment for the estimation of drug and administration costs in the model
- In the KEYNOTE-010 trial, RECIST 1.1 PFS would under-estimate the time on treatment considering that immune-related response criteria (irRC) generally occurs later than RECIST progression and patients could remain on treatment until confirmation of progression (4-9 weeks later).
- PFS and time on treatment curves are close with a HR of 0.96 with 95% CI: (0.81, 1.14) (no statistically significant difference between the two curves)
- Thus, PFS was adjusted with the HR to account for any difference between time on treatment and PFS, including discontinuation due to toxicities, and additional weeks of therapy

Company's additional analyses: using a range of utility values (I)

- In base case 2: method used to estimate QALYs considered time to death (TTD) and progression based utilities
- 6 studies were identified that included utility values for the post-progression health state. 5 were excluded leaving Chouaid et al (2013b).
- Company states it does appear to meet the NICE reference case but has concerns regarding the appropriateness of using post-progression utility values

	KEYNOTE-010 (All)		Chouaid et al, 2013b (only progressed disease used)	
Progression-free	**Mean**	**SE**	**Mean**	**SE**
>=30 days	0.763	0.006	0.74	0.18*
<30 days*	0.284	0.072		
Progressed	**Mean**	**SE**	**Mean**	**SE**
>=30 days	0.675	0.015	0.59	0.059
<30 days^	0.32	0.122		

*n=27 patients with EQ-5D score, ^n=12 patients with EQ-5D score; *SD instead of SE

Source: company additional analyses, table 8 (page 19)

Company's additional analyses: using a range of utility values (II)

Cost-effectiveness results of base-case 2 (discounted, with PAS) using post progression utilities from Chouaid et al. (2013b) - varying the maximum duration of treatment after 2 years	
Assumption	Probabilistic ICER
0% of patients receiving treatment after 2 years	£49,489
25% of patients receiving treatment after 2 years	£50,910
50% of patients receiving treatment after 2 years	£52,207
75% of patients receiving treatment after 2 years	£53,855
100% of patients receiving treatment after 2 years	£55,702
Source: company additional analyses, table 9 (page 19)	

Company's additional analyses: inclusion of adverse event related disutility

- Average disutility value was applied in this scenario as it was not possible to derive separate disutilities per AE from KEYNOTE-010

Cost-effectiveness results of base-case 2 (discounted, with PAS) after inclusion of disutilities derived from KEYNOTE-010 and published literature - varying the maximum duration of treatment after 2 years

	KEYNOTE-010	Published literature
0% of patients receiving treatment after 2 years	£42,416	£42,879
25% of patients receiving treatment after 2 years	£43,555	£43,693
50% of patients receiving treatment after 2 years	£44,926	£45,087
75% of patients receiving treatment after 2 years	£46,527	£46,748
100% of patients receiving treatment after 2 years	£47,404	£48,081

Source: company additional analyses, table 11 (page 21)

Company's additional analyses: varying hazard ratios at trial end (I)

Cost-effectiveness results of base-case 2 (discounted, with PAS) with varying hazard ratios - varying the maximum duration of treatment after 2 years

Assumption	Probabilistic ICER		
	HR=1.45	HR=1.2	HR=1.0
0% of patients receiving treatment after 2 years	£36,630	£63,311	£95,371
25% of patients receiving treatment after 2 years	£37,569	£65,299	£97,509
50% of patients receiving treatment after 2 years	£38,665	£67,100	£100,493
75% of patients receiving treatment after 2 years	£39,858	£69,824	£102,870
100% of patients receiving treatment after 2 years	£40,940	£71,596	£106,633

Source: company additional analyses, table 14 (page 26)

Company's additional analyses: varying hazard ratios at trial end (II)

Company stated:

- Evidence suggests patients in receipt of a checkpoint inhibitor that stop treatment before disease progression maintain clinical benefit
- No NICE HTA submission of a checkpoint inhibitor (TA268, TA319, TA357, STA366, TA384, TA400, ID900, ID811, ID853) has discussed or evaluated fading of treatment effect following discontinuation of drug
- [redacted]
  - [redacted]
  - [redacted]

Company's additional analyses: clarifications (I)

Question	Answer
How many people from KEYNOTE-010 are still having pembrolizumab treatment after 2 years?	• No patients from KEYNOTE-010 have continued treatment after 2 years (based on March 31 and 21 July 2016 data cut-off) • In line with KEYNOTE-010 protocol, patients discontinued treatment at 2 years of uninterrupted therapy (and no documented disease progression) or 35 treatment administrations, whichever occurred later
The proportion of people in KEYNOTE-010 who had confirmatory scans and the percentage who were confirmed to have disease progression. Of these, how many continued on treatment with pembrolizumab post-progression at the clinician's discretion?	• Disease progression was measured by RECIST 1.1 criteria for the purpose of evaluation of progression as one of the trial endpoints. This was measured centrally by an Independent Review Committee (IRC) • Results were not communicated to the local investigator and therefore had no role to play in treatment decisions

Company's additional analyses: clarifications (II)

Question	Answer
	The number of patients who had disease progression by RECIST (IRC) was [redacted] of ITT population = 344). • [redacted] patients had confirmatory scans • [redacted] patients continued on treatment with pembrolizumab post-progression • The number of patients who had disease progression by irRC was [redacted] of ITT population = 344). • [redacted] patients had confirmatory scans. • [redacted] patients continued on treatment with pembrolizumab post-progression by irRC). • ITT population (= 344 patients), • [redacted] had PD by both criteria, • [redacted] had no PD by both criteria, • [redacted] had PD by RECIST but not by irRC • [redacted] had PD by irRC and not by RECIST.

Company's additional analyses: clarifications (III)

Question	Answer
Please provide a summary of the hazard ratio for PFS and OS calculated from the model results (that is, the hazard ratio based on the extrapolation)	• OS HR = 0.46 • PFS HR = 0.68 • Hazard ratios are estimated assuming proportional hazards, and this assumption did not hold when evaluating the PFS and OS in the submission
Why the RPSFT method was disregarded and the two-stage adjustment method favoured instead. Please also clarify why a formal analysis of a common treatment effect assumption using the RPSFT method was not carried out.	• RPSFT method is assuming common treatment effect while the 2-stage method is assuming no unmeasured confounders • Evidence against the common treatment assumption • Two-stage adjustment appropriate due to clear secondary baseline (i.e. the time of progression), no relevant unmeasured confounders at the point of switch and method and results replicated advanced melanoma submission • No specific test for common treatment effect assumption using RPSFT

Company's updated value proposition & results of additional analyses

Company's probabilistic base case 2 ICERs with revised PAS using the following assumptions:

- 25% of patients remaining on pembrolizumab after 2 years of treatment in the original base-case 2 (i.e. 1.3% of patients who entered the model)
- 2-stage cross-over adjustment for the docetaxel arm
- 52-week cut-off data for the exponential parametric curves
- Time on treatment for pembrolizumab is based on HR
- Post progression utilities based on time to death (TTD) combined with progression-based utilities from KEYNOTE-010
- Inclusion of AE disutilities based on KEYNOTE-010
- No fading of treatment effect after the 52-week cut-off point

Scenario	Total cost	Total QALY	Inc cost	Inc QALY	ICER
Revised base case 2: KEYNOTE 010 for extrapolation post 52 weeks (discounted, with revised PAS)					
Pembrolizumab	£39,609	1.215	-	-	-
Docetaxel	£11,272	0.601	£28,337	0.614	£46,148
Source: company additional analyses (table 15, page 31)					

ERG critique - revised base case 2 analysis (without 2 year treatment assumption)

- Estimated costs in original base case 2 did correspond to drug use in the trial – all patients stopped treatment at 2 years
- Original base costs also appear to correspond to the effectiveness of the drug as estimated from the trial
- However, important to consider the potential effect of the termination of treatment at 2 years may not be evident in the extrapolation of overall survival based on the current cut of the trial data
- If termination of treatment at 2 years is enforced, original base case will reflect the cost of treatment in practice
- If termination of treatment at 2 years is not enforced, seems likely that at a least some patients will continue treatment beyond 2 years
- Due to the modelling approach used, the current sensitivity analysis provides information on the effect on costs of changes in treatment duration but not on outcomes
- Long term effects of terminating (or not) treatment at 2 years on long term survival remains uncertain

ERG critique – treatment switching assumption

Company view

- Compared with the original 2-stage adjustment, the RPSFT resulted in a smaller survival benefit (HR 0.71 compared with HR 0.69).
- ICER using RPSFT was £50,017
- ICER using two-part adjustment £45,987 (based on the assumption that 25% of pembrolizumab patients remain on treatment beyond 2 years).
- The company considered the RPSFT to be inappropriate due to the assumption of common treatment effect

ERG view

- Would have preferred the two stage adjustment for the effects of cross-over as the assumptions of the RPSFT analysis (that treatment would have been constant pre and post progression) are more restrictive and a prior unlikely
- If this assumption did hold the two analyses would on average give similar results (more uncertainty from the two part adjustment)

ERG critique - exploring cut-off point used for extrapolation (I)

- The ERG agrees with company that there appears to be an inflection in the survival curve at 52 weeks (less pronounced in the later 31 March 2016 data cut.

- The company's model:
  - Predicts long term overall survival solely based on the time to death observed during the trial. There is no link between time to progression or time on treatment.
  - Only considers those deaths that occur after 12 months for the long term extrapolation. The model treats the rate of death as both constant with time after 12 months (and by implication varying with time before 12 months) and different between the two treatments.
  - Assumes that at the 12 month time point the patients will be heterogeneous in terms of progression and treatment status.

- The choice of the 12 month is based purely on the form of the observed survival curve from the trial and is not clearly related to any underlying biological or clinical process.

ERG critique - exploring cut-off point used for extrapolation (II)

- The estimated ICER is sensitive to the selection of time points before 52 weeks.
- The assumption that the hazard of death for both treatments remains constant over the rest of the modelled time period as patients both progress and cease treatment is a strong assumption
- Given the structure of the model, the 52 week cut-point appears to represent the most sensible base case.
- Although considerable uncertainty remains, the overall survival (OS) curve based on the 31 March 2016 cut appears to supports the company's extrapolation based on the 52-week cut point

ERG critique – time on treatment

- ERG unable to replicate results of company model when fully parametric generalised gamma model was used to estimate treatment duration (ICER of £52,296 (assuming 25% of pembrolizumab patients remain on treatment beyond 2 years))

Deterministic incremental cost-effectiveness results of base-case 2, considering fully parametric generalised gamma model – company and ERG results (discounted, with PAS)

	0%	25%	50%	75%	100%
Company	£50,615	£52,296	£53,976	£55,657	£57,337
ERG	£46,105	£47,636	£49,166	£50,697	£52,227

- Company modelling was over-complicated (time to progression with a constant hazard adjustment to estimate time to treatment discontinuation)
- Evidence from the trial that some patients discontinued pembrolizumab before progression whilst others continued treatment beyond progression (although on average both curves appeared similar)
- More appropriate to use observed time to treatment discontinuation, rather than time to progression with its need for further adjustment
- More consistent with the overall model philosophy whereby other endpoints such as progression and death are modelled independently

ERG critique – pseudo-progression

- The company did not specifically adjust for pseudo-progression in their estimates of treatment costs.
- However, if patients did remain on treatment during pseudo-progression, the time on treatment (ToT) data would reflect this.
- Overall, the adjusted progression-free survival (PFS) curve appeared similar to the ToT curve
- The ERG is satisfied that the adjusted PFS approach did not introduce substantial bias
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- The company did not provide data on the proportion of scans confirming true disease progression.
- It is unclear whether the [redacted] who stopped treatment after between initial and second scan were due to true progression.

ERG critique – post-progression utility

- Only one study (Chouaid et al 2013) was considered appropriate for the scenario analysis
- Chouaid et al 2013 has limitations: population used to elicit utility values was sicker than KEYNOTE-010 (ECOG status 0 to 2, compared to 0 to 1) and pre and post-progression utilities derived from separate populations
- The ERG considers using KEYNOTE-010 data appropriate

ERG critique – adverse event disutilities

- ERG unable to duplicate results from the company's new model when using KEYNOTE-010 and using the other published data
  - but was able to duplicate results using KEYNOTE-010 disutilities in the company's previous model

Deterministic cost-effectiveness results of base-case 2, including the impact of AE-related disutilities from KEYNOTE-010 trial – company and ERG results (discounted, with PAS)

	0%	25%	50%	75%	100%
Company	£42,496	£43,741	£44,986	£46,231	£47,476
ERG	£44,678	£45,987	£47,296	£48,605	£49,914

Deterministic cost-effectiveness results of base-case 2, including the impact of AE-related disutilities from published literature – company and ERG results (discounted, with PAS)

	0%	25%	50%	75%	100%
Company	£42,496	£43,741	£44,986	£46,231	£47,476
ERG	£44,678	£45,987	£47,296	£48,605	£49,914

ERG critique – long term treatment effect (I)

- Strong assumptions:
  - Assumption that hazard of death for both treatments remains constant over the rest of the study period
  - difference in the hazards of death between treatments is maintained as patients both progress and cease treatment is a strong assumption
- Clear uncertainty in both whether the differential effect of treatment on the hazard of death will be maintained as treatment is discontinued and the overall rate of death
- Company supplied analysis where the incremental treatment effect was reduced by various degrees beyond the “trial” period (taken as 2 years)
- ERG also conducted analyses where there was assumed to be no incremental treatment effect beyond various time points
- The ERG was unable to duplicate these results from the company’s model for the 1.45 hazard ratio

ERG critique – long term treatment effect (II)

- Exploratory analysis on the duration of treatment effect undertaken
- Model adapted to enable the duration of treatment effect to be varied
  - Used the pembrolizumab OS curve (KM + exponential) to the time point that treatment effect stopped and then continuing with the docetaxel OS curve following this time point
- Based on the assumption that 25% of patients remain on treatment beyond 2 years, the ICERs were estimated for treatment effect being maintained to 3 years, 5 years, 10 years, 15 years and lifetime
- Evidence from other disease settings for sustained reduction in mortality and that relative treatment effect continues beyond the discontinuation of treatment (and therefore disease progression)
- Schadendorf (2015) meta-analysis pooled study data from studies of ipilimumab for the treatment of unresectable or metastatic melanoma
  - Appears to show a plateauing survival curve from 3 years (possibly continuing to 10 years although small numbers of at risk patients)

ERG critique – long term treatment effect (III)

- Although published analysis is for different treatment and different disease area, equivalent data directly relevant to the current appraisal will not be available for at least 5 years
- Schadendorf (2015) might be regarded as providing relevant information for the current analysis
  - Company presents evidence of persistent treatment effect of pembrolizumab in KEYNOTE-001 for melanoma patients, this evidence shows treatment effect up to and beyond 3 years
- ERG suggests 3 years treatment effect duration might be reasonable taking into account Schadendorf (2015) where patients showed treatment effect duration to 3 years and some to 10 years on ipilimumab – results in an ICER of £70,441
- ERG results show that treatment effect duration would need to last at least 10 years for the ICER to be cost-effective

ERG critique – long term treatment effect (IV)

Cost-effectiveness results of base-case 2 assuming 25% of patients remain on treatment beyond 2 years and varying treatment effect duration (discounted, with PAS)

Treatment effect duration (years)	ICER
3 years	£70,441
5 years	£54,269
10 years	£46,914
15 years	£46,092
Lifetime	£45,987

ERG critique – ICERs

Worst case scenario	Preferred scenario
25% of the patients remain on pembrolizumab after 2 years of treatment in the original base-case 2	25% of the patients remain on pembrolizumab after 2 years of treatment in the original base-case 2
RPSFT for treatment switching	Applying a 2-stage cross-over adjustment for treatment switching
52 week cut-off (ERG considers this a sensible base-case)	Using a 52 weeks cut-off for the exponential parametric curves
Gamma model for time to treatment	ToT based on PFS and hazard ratio adjustment
Chouaid et al post-progression utilities	Post-progression utilities based on TTD combined with progression-based utilities from KEYNOTE-010
Inclusion of AE disutilities from KEYNOTE-010	Inclusion of AE disutilities from KEYNOTE-010
Hazard ratio of 1 for duration of treatment effect	Treatment effect duration of 3 years
ICER incorporating all the above is **£118,417 per QALY** gained (ERG considers this ICER to be unlikely)	ICER incorporating all the above is **£65,200 per QALY** gained (ERG preferred ICER)

Key issues for consideration

- The impact of the following changes to the revised base case 2 cost effectiveness model:
  - 2 year treatment duration assumption
  - Treatment switching
  - Sensitivity of cut-off points when extrapolation of OS
  - Alternative approaches to estimating time to treatment
  - Additional weeks of therapy added to the model
  - Alternative utility values used in the model
  - Inclusion of adverse event related disutilities
  - Changing of the hazard ratio to 1 after the trial has ended (fading of the treatment effect)
- End of life considerations
- Innovation: any health-related benefits not captured in the QALY?
- Any potential equality issues?
- Is there a case to recommend for use in the CDF?