For public and projector

NICE National Institute for Health and Care Excellence

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

3rd Appraisal Committee meeting

26 October 2016

Pembrolizumab (Keytruda, MSD)

- **Marketing authorisation (granted July 2016)**
  - for the treatment of locally advanced or metastatic 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 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)
  - PAS: Simple discount (commercial in confidence, approved July 2016)

Appraisal history

- ACM1 – 29th June 2016
  - Further information and analyses requested from company
  - Company presented updated value proposition
  - No ACD released
- ACM2 – 25th August 2016
  - Pembrolizumab not recommended
  - ACD released
  - Company requested to submit new evidence
- ACM3 – 26th October 2016
  - New data from KEYNOTE-010 (March 2016 data-cut)
  - Sensitivity analyses using different cut-offs points and treatment effect waning
  - The ERG was able to replicate the results and is satisfied the changes have been applied correctly

Committee conclusions in ACD (I)

Treatment switching	2-stage adjustment method was reasonable
Treatment continuation	Committee preferred case was that 100% of people would continue treatment after 2 years if their disease had not progressed
Utility values	KEYNOTE-010 utility data were the most appropriate to inform decision-making
Adverse events	Including a disutility for adverse events was appropriate
Company's base case	KEYNOTE-010 data used in base case 2 was more appropriate compared with the KEYNOTE-01 data used in base case 1

Committee conclusions in ACD (II)

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 • 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

Remaining uncertainties after ACM2

Time on treatment	• Company used time to progression with a constant hazard adjustment to estimate time to treatment discontinuation • Committee would have preferred to see time on treatment taken directly from KEYNOTE-010 • Committee noted that after a confirmatory scan some patients remained on treatment after disease progression • Concluded uncertainty about how many people continue treatment after disease progression and that these treatment and administration costs may not be appropriately captured.
Overall survival	• Company used 52-week Kaplan–Meier data then fitted an exponential model • No biological plausibility to using 52-week cut-off • ICERs highly sensitive to varying cut-off points • Concluded no evidence that the 52-week cut-off was the most appropriate and that that the choice of the 52-week cut-off point was overly optimistic
Long-term treatment effect	• Company's survival estimate includes no fading of treatment effect after the 52-week cut-off point irrespective of the time spent on treatment or disease progression • ICERs highly sensitive to modifying long-term treatment effect • Likely there would be some continued benefit after stopping treatment and in the progressed state, but the size of this effect and its duration is unknown for NSCLC • Concluded the company's additional analyses represented the most optimistic modelling scenario.

Comments on ACD consultation

Consultees

- ***Company:*** MSD (pembrolizumab)
- **Patient and professional:**
  - Roy Castle Lung Cancer Foundation
  - NCRI-ACP-RCP-RCR
  - British Thoracic Oncology Group
- **Other:** NHS England

Clinical & patient experts

- None

Comparators

- Bristol-Myers Squibb (nivolumab)

Web comments

- Public x1

Comments on the ACD: Patients, professional groups and public (1)

- Disappointed that the Appraisal Committee's preliminary decision not to recommend pembrolizumab – particularly as it is available in Scotland
- Emphasised that pembrolizumab would be a valuable treatment option for people with NSCLC
  - Treatment is innovative and novel
  - Clinically effective
  - Important unmet need – few other options available and short life expectancy
  - The tolerability and ease of administration of these compounds is a positive and meaningful outcome from a patient perspective.
- Noted the remaining uncertainty and sensitivity of the ICERs
  - Collection of information through the Cancer Drugs Fund in reducing the uncertainty?
  - encourage that the manufacturers look carefully at their pricing structure to improve cost effectiveness and urge NICE to push for this

Comments on the ACD: Patients, professional groups and public (2)

Committee's assumption that 100% would continue treatment at 2 years is an overestimate – but no consensus on figure:

- Company's assumption of 25% is more plausible – but clinical experience suggests this is still optimistic
- Patients whose disease is controlled may stop treatment for other reasons and this proportion will increase over time
- Some patients say that they would want to continue. Others would likely want a break, if no evidence for continuing
- Encourage Committee to have further discussion with clinical experts, who have experience with using this treatment

Comments on the ACD: Patients, professional groups and public (3)

No agreement with committee's assumption on stopping of treatment effect :

- Other immune checkpoint inhibitors across multiple tumour types have a proportion of patients with a maintained effect even out to 5 years, which is expected to be the case in NSCLC too
- Company's estimate (with lifetime treatment effect) of 1-2% of patients being alive at 10 years would clinically seem reasonable
- Experts find the subtleties of the extrapolated survival and associated economic modelling complex and were unable to make any meaningful comments on these

Comments on the ACD: Bristol-Myers Squibb (nivolumab)

- As Pembrolizumab has a MA in adults whose tumours express PD-L1 a specific threshold of PD-L1 should be made clear in the recommendation
- For nivolumab the committee concluded that for the populations under consideration, the relevant comparators for this appraisal were nintedanib plus docetaxel, docetaxel monotherapy, and BSC
- nintedanib plus docetaxel should therefore be a comparator for pembrolizumab

Comments on the ACD: NHS England

Stopping of treatment effect

- A proportion of patients seeming to gain very much greater benefit with pembrolizumab i.e. plateauing of the PFS curve
- With further follow up, the HRs for OS and PFS are unchanged. There is therefore no current justification for assigning a HR of 1.0 for treatment effect beyond the end of the trial data

Patients continuing treatment at 2 years

- NHSE previously stated that stopping rules are difficult to implement in practice when primarily instituted for cost reasons alone
- Pembrolizumab for melanoma is continued until disease progression (with significant tails observed in both PFS and OS)
- EPAR included wording in the SPC to continue pembolizumab until disease progression

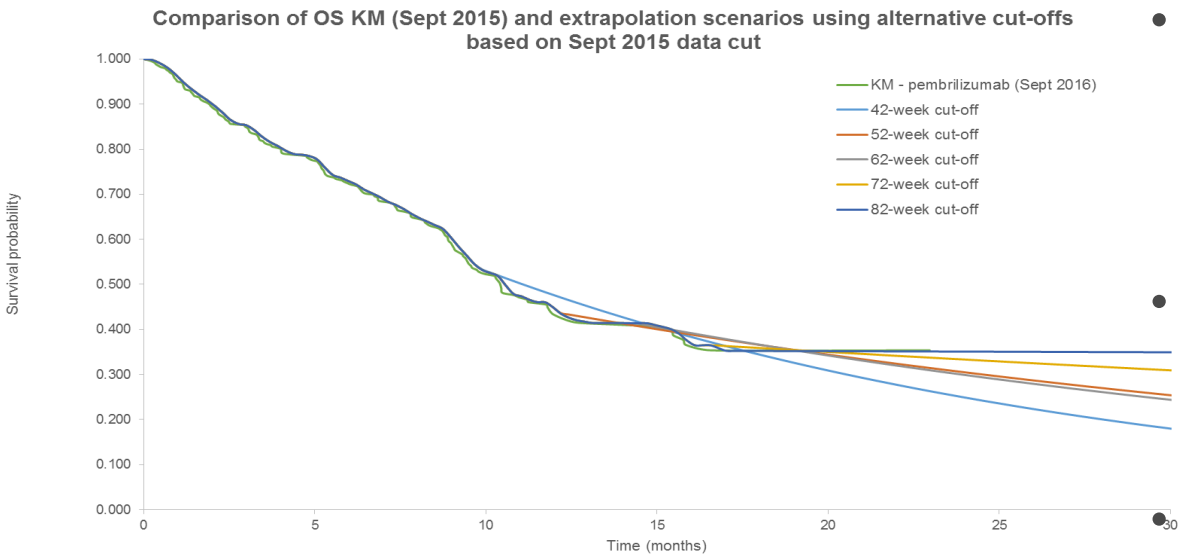
Comments on the ACD: NHS England

Patients continuing treatment at 2 years

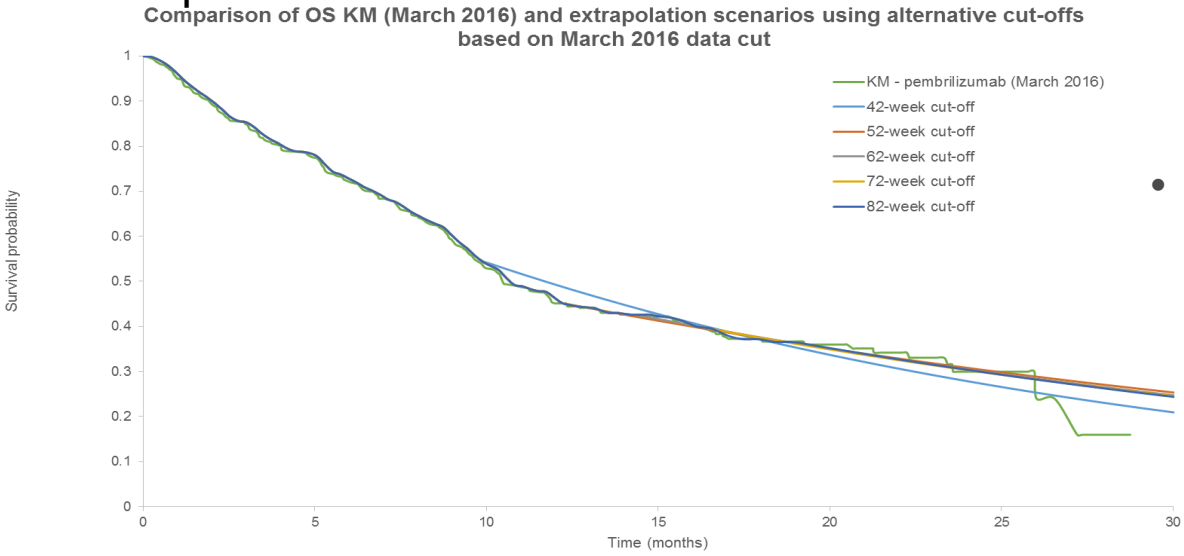
- Current clinical opinion is changing rapidly as to the assessment as to the optimal duration of treatment with checkpoint inhibitors in cancer
- Evidence from melanoma that patients who discontinue checkpoint inhibitors for reasons other than disease progression (mainly toxicity) derive the same OS benefit as those that continue on treatment until disease progression
- Current trial of randomised patients still on treatment at 1 year to continue on therapy with nivolumab or discontinue treatment at that stage. Results would be expected to be reported within the next 2 years
- NHSE is much more confident about an implementation of a 2 year stopping rule which would be acceptable to patients and clinicians
- NHSE suggests a recommendation which incorporates a 2 year stopping rule, but is re-appraised by NICE in 2 years time

Company comments - Sensitivity analysis on selection of extrapolation time-point

Cut-off points based on Sept 2015 data



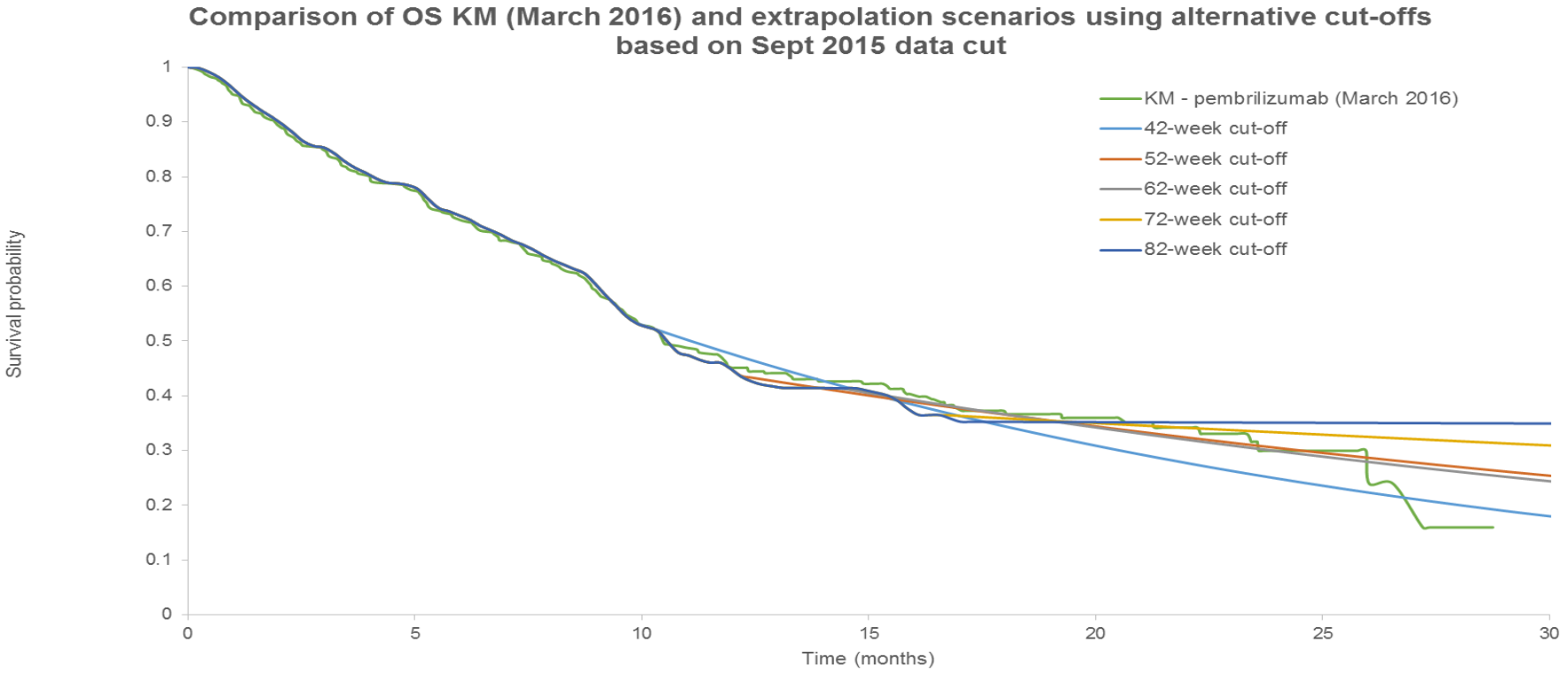
Cut-off points based on Mar 2016 data



- Several scenarios for switching between trial data and exponential curve
- Company used a 52-week cut-off for base-case
- New data from KEYNOTE-010 reduces the variation in the different scenarios
- Source: MSD ACD response 201016 – figure 1 (page 4) and figure 3 (page 6)

Company comments – selection of extrapolation time-point

- The 'inflection' in the KM curves for both September and March is related to the data and not the model
- Superimposed extrapolations show that the 42 week and 82 week cut-off points do not fit the new data cut-off



Source: MSD ACD response 201016 – figure 2 (page 5)

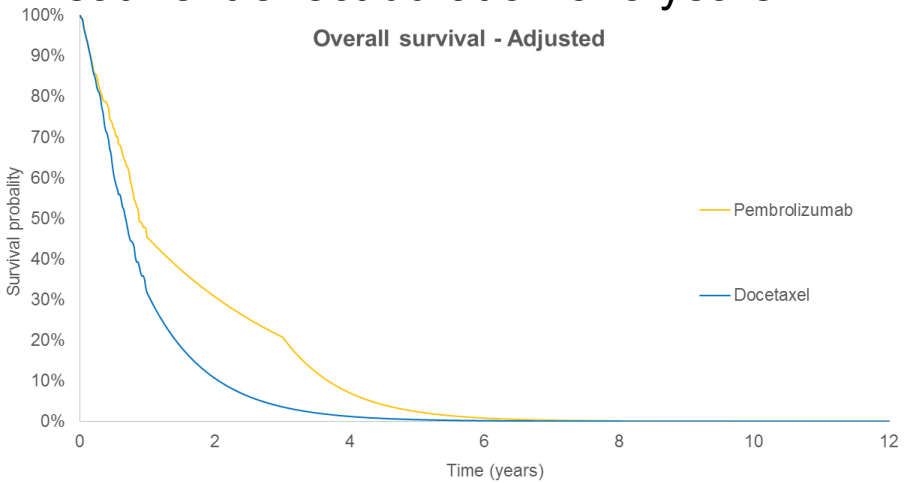
Company comments – treatment effect duration

- The ACD states *'…The committee recalled that the modelling projections used by the company suggested that 12% of patients in the pembrolizumab arm would be alive at 5 years and agreed with the experts that this was extremely optimistic, as was the assumption of no waning of treatment effect over 20 years.'*
  - The three, five and ten year estimates from our model, in base case 2, are 21.6%, 10.4% and 1.7% respectively
  - These estimates demonstrate that we already have a 'waning of treatment effect' reflected in our modelling of overall survival (OS).
  - Kaplan-Meier data and an exponential parametric extrapolation is in line with virtually every other recent NICE submission for oncology technologies and also the other PD-L1 inhibitor for NSCLC e.g nivolumab
  - Survey of clinicians - 10 answered estimates were reasonable, 2 answered pessimistic, and 2 answered optimistic. Of the 2 who answered optimistic, one specified that he believed the 10 year number to be reasonable.

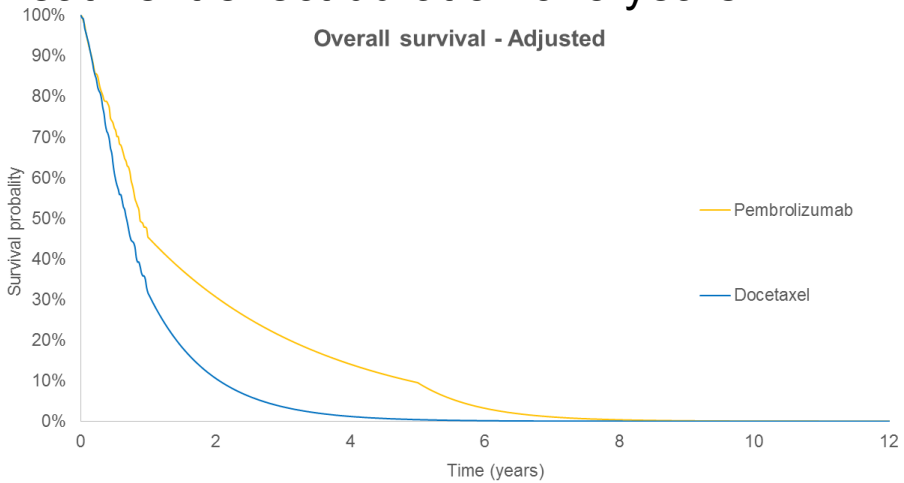
Company comments - sensitivity analysis on treatment effect duration

- Company scenarios based on reduced treatment effect after treatment stop
- Company base-case is there is no 'artificial' adjustment of treatment effect

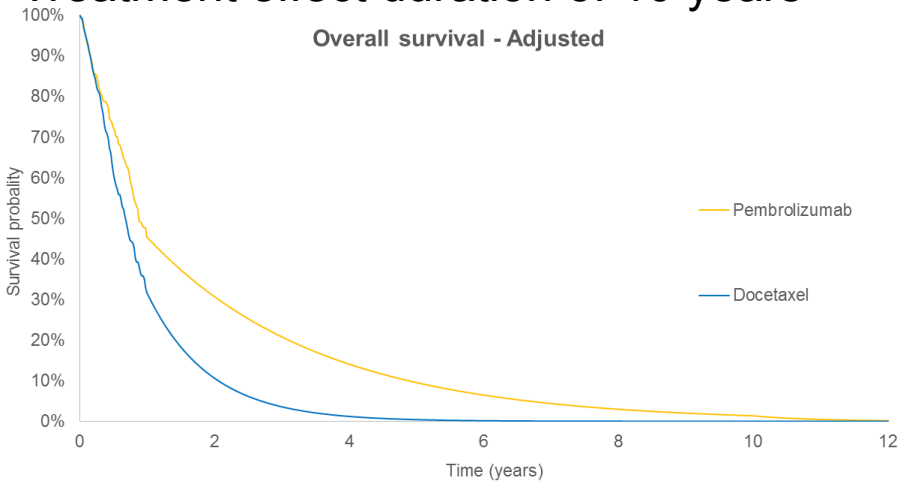
Treatment effect duration of 3 years



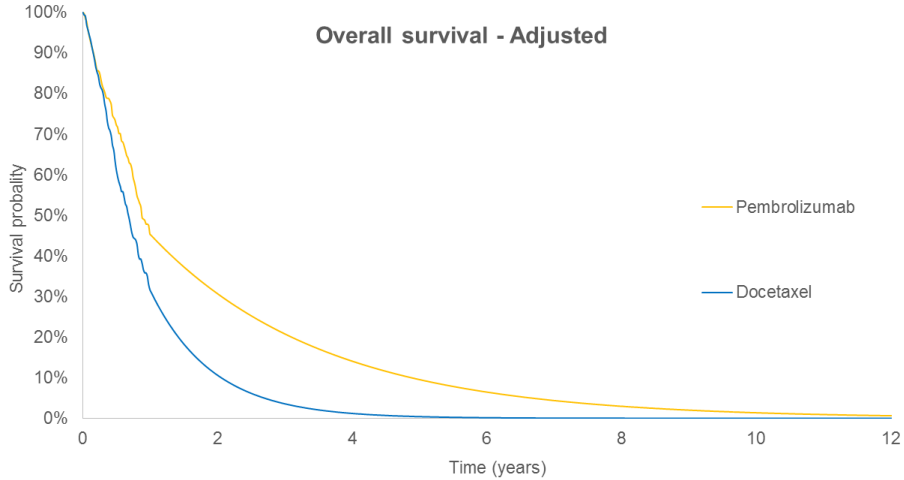
Treatment effect duration of 5 years



Treatment effect duration of 10 years



Lifetime treatment effect



Source: March 2016 data-cut – company additional analyses 18102016 (figures 6-8; pages 9-11)

Company additional evidence

	ACM2 –base case 2 probabilistic ICER	Company additional evidence submitted during consultation
Data	KEYNOTE-010 (September 2015 cut-off)	KEYNOTE-010 (March 2016 cut-off)
PAS	Simple patient access scheme of [redacted] (July 2016)	Simple patient access scheme [redacted] (Not yet approved)
Treatment continuation	25% of patients still treated at 2 years would continue*	25% or 100% of patients still on treatment at 2 years would continue
Time on treatment	time to progression with a constant hazard adjustment	time to progression with a constant hazard adjustment
Overall survival	KEYNOTE-010 data until 52-weeks, then exponential model	Sensitivity analysis – cut-off points for extrapolation at weeks 42, 62, 72, and 82
Long-term effect	no stop of treatment effect after treatment is stopped	Sensitivity analysis – stop in treatment effect at 3, 5 and 10 years after treatment stop

*The committee considered 100% of patients would continue after 2 years if they benefited from treatment, and estimated this would increase the ICER by around £4,000

Company additional clinical effectiveness evidence

	Primary endpoints	Pembrolizumab	Docetaxel
		2 mg/kg Q3W n=344	75 mg/m2 Q3W n=343
Overall survival – ITT population			
September 2015	Median: months (95% CI)	10.4 (9.4, 11.9)	8.5 (7.5, 9.8)
	Undiscounted life years	1.918	0.890
	Hazard ratio (95% CI)	HR 0.71 (0.58, 0.88); p=0.00076	
March 2016	Median: months	10.5	8.6
	Undiscounted life years	1.884	0.931
	Hazard ratio (95% CI)	HR 0.72 (0.60, 0.87); p=0.0003	
Progression-free survival – ITT population			
September 2015	Median: months: (95% CI)	3.9 (3.1, 4.1)	4.0 (3.1, 4.2)
	Undiscounted life years	0.629	0.426
	Hazard ratio (95% CI)	HR 0.88 (0.73, 1.04); p=0.06758	
March 2016	Median: months	3.8	4.1
	Undiscounted life years	0.697	0.472
	Hazard ratio (95% CI)	HR 0.87 (0.74, 0.1.03); p=0.06758	

Company additional cost effectiveness evidence

Scenario	Total cost	Total QALY	Inc cost	Inc QALY	ICER
ACM2 probabilistic ICER – Sept 2015 data; 52-week cut-off; 25% patients continue treatment after 2 years*; life-time treatment effect; discounted, with old PAS					
Pembrolizumab	£39,609	1.215	-	-	-
Docetaxel	£11,272	0.601	£28,337	0.614	**£46,148 + ~ £4,000***
Source: company additional analyses (table 15, page 31)					
Company additional evidence – March 2016 data; 52-week cut-off; 100% patient continue after 2 years; life-time treatment effect; discounted, with new PAS					
Pembrolizumab	£41,136	1.203	-	-	-
Docetaxel	£11,416	0.597	£29,720	0.606	**£49,063**
Source: company additional analyses 25102016 (table 2, page 4)					

*The committee considered 100% of patients would continue after 2 years if they benefited from treatment, and estimated this would increase the ICER by around £4,000

Company's preferred scenarios

- 25% of patients will continue treatment
- Removal of 42-week and 82-week cut-offs
- Lifetime treatment effect

Scenario	ICER: originally submitted cut-off data (September, 2015)	ICER: updated cut-off data (March, 2016)
52 week cut-off	£40,685	£44,490
62 week cut-off	£42,611	£46,324
72 week cut-off	£22,040	£46,655

ERG critique – Selection of extrapolation timepoint

- In the original data cut there was a high level of censoring at 72 and 82 weeks leading to high levels of uncertainty at these cut-off points. However, there is more consistency using the new data cut which supports the exponential curve extrapolation

- The company's preferred cut-off point was 52 weeks. From 52 weeks onwards the exponential curve gives a reasonable visual fit to the new data cut, suggesting a reasonable basis for extrapolation at this cut-off

- However, there is no evidence to support a definitive selection of the cut-off point for switching from trial survival data to exponential model.

ERG critique – treatment effect duration

- Company's preferred assumption of an incremental treatment effect that continues for a lifetime is implausible
- Due to the limited trial follow-up period, there is no evidential basis for a definitive judgement
- The ERG has previously considered that 3 years to be a reasonable estimate of treatment effect duration. We have not been presented with evidence to contradict this assumption.

Company comments – continuation of treatment

- Company believes that, given the acknowledged uncertainty in the ACD, using one extreme is inappropriate
- Acknowledging the uncertainty expressed by one of the clinicians, revised our base case from 0% to 25% to reflect the proportion of patients remaining progression free and on treatment at two years, carrying on treatment with pembrolizumab
- Surveyed 14 practicing UK oncologists
  - no-one was prepared to provide an answer either way
  - a number reflected that in two years' time, when faced with making a decision, they would expect to be in possession of sufficient new information to enable them to be confident about the right duration of therapy
  - Two of the clinicians who have been involved in KEYNOTE-010 and KEYNOTE-024 expressed the view that the proportion continuing would be lower rather than higher

ERG critique – remaining uncertainties

- In modelling the long-term OS, there is uncertainty regarding the use of an exponential curve to model long term survival
- In estimating the appropriate long-term treatment effect of pembrolizumab, there is no evidence to conclude on the duration of incremental treatment effect

ERG preferred ICER

- The ERG's preferred assumptions are:
  - 25% of the patients remaining on pembrolizumab after 2 years of treatment in the original base-case 2
  - Using a 52 weeks cut-off for the exponential parametric curves
  - Treatment effect duration of 3 years
  - March 2016 data
- The company has not provided evidence to suggest that these assumptions are not reasonable

Scenario	Total cost	Total QALY	Inc cost	Inc QALY	ICER
ERG preferred base case (discounted, with PAS)					
Pembrolizumab	£37,893	1.024			
Docetaxel	£11,416	0.597	£26,477	0.427	**£61,954**
Source: company additional analyses 25102016 (table 6, page 8)					

Sensitivity analysis – Long term treatment effect

March 2016 data; 100% (25%) of patients continue treatment; 52 week cut-off

Treatment effect duration	Incremental costs	Incremental QALY	ICER
3 years	£29,246 £26,477)	0.427	**£68,433** **(£61,954)**
5 years	£29,518 (£26,748)	0.530	**£55,661** **(£50,438)**
10 years	£29,697 (£26,927)	0.597	**£49,740** **(£45,100)**
Lifetime (company base case)	£29,720 (£26,950)	0.606	**£49,063** **(£44,490)**

Source: company additional analyses 25102016 (table 6, page 8)

Key issues for consideration

- Is it appropriate to use the new March 2016 KEYNOTE-010 data in decision making?
- Are there any changes in committee's preferred assumptions from ACM2?
  - Is it still appropriate to assume that 100% of people would continue treatment after 2 years if their disease had not progressed?
- What are the committee's preferred assumptions on:
  - The cut-off for switching from trial survival data to the exponential model?
  - The modifying of treatment effect after a number of years?
- Impact of a positive recommendation on the PAS for advanced melanoma (TA357)?
- Innovation: any health-related benefits not captured in the QALY?
- End of life considerations?
- Any potential equality issues?
- Is there a case to recommend for use in the CDF?