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4th June 2015

Dear Janet,

Re. Pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab [ID760]

MSD welcomes the opportunity to answer the clarification questions. Our responses are provided below.

Should NICE or the ERG require any further clarification we would be more than happy to provide an answer to them.

Kind regards,

[redacted], Head of HTA and OR

Single Technology Appraisal (STA)

Pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab [ID760]

Dear [redacted],

The Evidence Review Group, Liverpool Reviews and Implementation Group (LR*i*G), and the technical team at NICE have now had an opportunity to take a look at the submission received on 23rd April 2015 by Merck Sharp & Dohme. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **10.00am on 4th June 2015** via NICE docs. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the checklist for in confidence information available via NICE docs.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Pilar Pinilla-Dominguez, Technical Lead . Any procedural questions should be addressed to Bijal Joshi, Project Manager in the first instance.

Yours sincerely

Janet Robertson
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1. **Priority question.** It is unclear why the crossover adjusted estimates of overall survival (OS) using the Rank-preserving structural failure time (RPSFT) method would fail to provide an accurate estimate of OS. Please provide a detailed justification of why the methods have been deemed to be unsuitable and why the results of the RPSFT analysis of KEYNOTE-002 OS have been rejected. Please also provide the code used to implement the RPSFT method and the full results of this analysis.

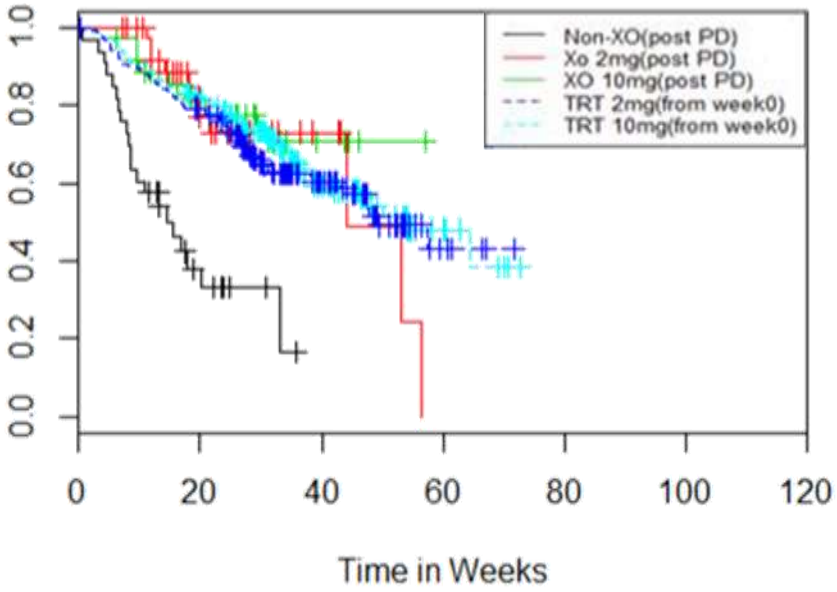
Details of why the RPSFT method was deemed unsuitable were presented in our submission (pages 150-152), and additional details are provided below:

- The validity of the RPSFT crossover adjustment relies on the assumption of a 'common treatment effect', which does not hold in practice. Patients who switch to the pembrolizumab arms experience a different treatment effect when they progress than that experienced by patients initially allocated to the pembrolizumab arms. This has been demonstrated by comparing the treatment effect for patients initially treated with pembrolizumab at 8, 12 and 20 weeks after baseline versus that at 8, 12 and 20 weeks post-progression among patients who crossed over to pembrolizumab 2 mg/kg after being treated with chemotherapy. For this comparison, the comparable non-crossover patients (matching all crossover criteria and survived "washout" period) were used as the comparison group. The treatment effect estimate at these various time points were determined by fitting a Cox Proportional Hazard model. The results of the corresponding hazard ratios (HRs) are summarized in Table 1 below. Based on these results, the treatment effect from the early part of the trial for the arm of patients initially treated with pembrolizumab 2mg is different from that experienced by patients initially treated with chemotherapy who subsequently crossed over to the pembrolizumab 2 mg/kg treatment arm. The treatment effect post-progression among patients who crossed over to pembrolizumab appears to be greater than that experienced by patients initially treated with pembrolizumab in the trial. These results do not support the assumption of a common treatment effect between patients initially treated and patients crossing over to pembrolizumab within the KEYNOTE-002 trial. This is also supported by the different shape of the OS post-baseline for patients initially treated with pembrolizumab vs. post-progression for patients in the control group that crossed over to pembrolizumab (see Figure 1 below).

Table 1. Hazard ratios for pembrolizumab versus control at 8, 12 and 20 weeks after baseline, and for patients crossing over from the control arm to the pembrolizumab 2mg arm at 8, 12 and 20 weeks after progression

Model from:	HR over 8 Weeks [95%CI]	HR over 12 Weeks [95%CI]	HR over 20 Weeks [95%CI]
Study Baseline	0.919 [0.668, 1.264]	0.904 [0.657, 1.244]	0.916 [0.666, 1.260]
PD	0.312 [0.150, 0.649]	0.313 [0.151, 0.650]	0.275 [0.132, 0.573]

Figure 1. OS from baseline for patients initially treated with pembrolizumab compared to post-progression OS for patients in the chemotherapy arm who crossed over to pembrolizumab



- Additionally, the validity of a crossover adjustment should be assessed against the outputs produced, as recommended by the NICE Decision Support Unit (DSU) for the adjustment of crossover in clinical trials.[1] As stated in page 152 of the submission, the adjusted OS for the chemotherapy arm estimated through the RPSFT adjustment was higher than what would be expected on the basis of the OS historically associated BSC/chemotherapy for the treatment of metastatic melanoma (11.1 months in the RPSFT-adjusted chemotherapy arm of the KEYNOTE-002 trial[2] versus between 6 and 9 months, respectively).[3-5]
- The RPSFT adjusted estimate also becomes less and less reliable in the long-term versus what would be expected in clinical practice; indicating that the full impact of immunotherapy from pembrolizumab is not being accounted for (see Figure 2 below). It is clinically unrealistic to expect previously treated patients who are refractory to ipilimumab receiving chemotherapy to have better survival than the overall population of chemotherapy treated patients.

- The results of the KEYNOTE-006 trial[6] provide additional evidence against the validity of the RPSFT approach to adjust adequately for crossover. In this Phase III, randomised, controlled trial, pembrolizumab was compared with ipilimumab in patients previously untreated with ipilimumab. A significant survival benefit associated with pembrolizumab over ipilimumab was demonstrated. Given that ipilimumab has demonstrated a significant improvement in survival (10.1 months vs. 6.4 months in the control arm),[7] it becomes evident that the RPSFT crossover adjustment fails to adjust for crossover since it does not reflect the survival benefit expected with pembrolizumab when compared to chemotherapy in the absence of crossover.

We compared the RPSFT-adjusted OS with the Korn adjusted data. As can be seen below, the OS for the RPSFT-adjusted control arm is higher than the adjusted OS for the Korn data.

Figure 2. Comparison of the adjusted OS using the RPSFT approach vs. the Korn data4 (adjusted to reflect the characteristics of KEYNOTE 002 patients)

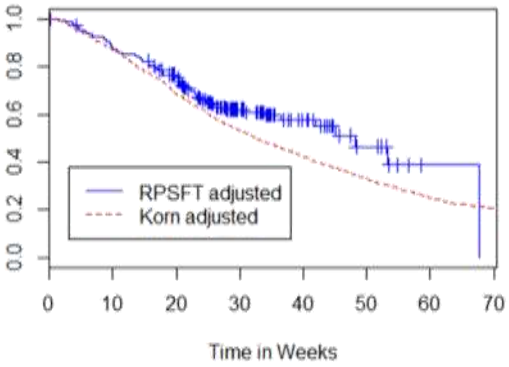
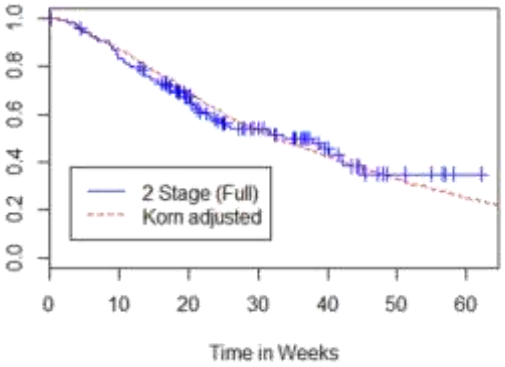


Figure 3: Comparison of the adjusted OS using the two-stage approach vs. the Korn data4 (adjusted to reflect the characteristics of KEYNOTE 002 patients)



The R code used for the RPSFT crossover adjustment has been shared with NICE on a CD as a supporting document.

This macro calls R functions within SAS to implement the RPSFT crossover adjustment. There are 3 main R functions called:

- rpsftm()
  This function uses the grid search to identify the estimate of the causal parameter (treatment effect) using a stratified log-rank statistics, the same statistic used in the ITT overall survival analysis. Re-censoring is implemented to remove potential dependent censoring on the potential outcomes between death times and censoring times.
- HRrpsftm()
  This function uses the point estimate computed from rpsftm() and calculates the potential observables for the control group. Then the hazard ratio is computed based on the observed data in the treatment arm and the corrected data in the control arm.
- Hr.boots()
  This function is used to implement the bootstrap that allows the estimation of the 95% CI and variance of the HR estimate.

A2. **Priority question.** Please provide a full breakdown, for each method (RPSFT, 2-stage simple, 2-stage all covariates, Inverse probability of censoring weighted [IPCW]) of how in KEYNOTE-002 crossover adjusted estimates of OS were calculated.

a. Please clarify whether all patients who crossed over (to either dose of pembrolizumab) were adjusted for in the analyses, or whether it was only patients who crossed over to the pembrolizumab 2mg/kg arm.
b. If only patients who crossed over to 2mg/kg were adjusted for, how were the patients who crossed over to the pembrolizumab 10 mg arm considered?

For the RPSFT crossover adjustment method, all patients who crossed over were adjusted for in the analysis (including patients crossing over to the 2 mg/kg and to the 10 mg/kg treatment arms).

For the two-stage (both simple and full models), and the IPCW crossover adjustment methods, only patients who crossed over to pembrolizumab 2mg/kg were adjusted. Those who crossed over to the 10 mg/kg treatment arm were excluded from the analysis and not adjusted. The reason to focus on adjusting the group of patients treated with the 2mg/kg dose was that this dose was the one anticipated in the licence. Additionally, there were no significant differences in outcomes between the two pembrolizumab doses (2 mg/kg vs. 10mg/kg arm; see Figure 1 above).

Table 2. Description of the patient groups that were adjusted as part of the different crossover adjustment methods

	Data used for crossover adjustment analysis

	Control without crossover	Crossover to pembrolizumab 2mg/kg	Crossover to pembrolizumab 10mg/kg
RPSFT	Yes	Yes	Yes
2-stage simple	Yes	Yes	No
2-stage all covariates	Yes	Yes	No
IPCW	Yes	Yes	No

A3. Table 21 of the company's submission presents KEYNOTE-002 progression free survival (PFS) rates at 3, 6, 9 and 12 months. Please provide hazard ratios and 95% confidence intervals for comparisons between pembrolizumab 2mg/kg and the control arm at each of these time points.

Please find below Table 3 detailing the requested hazard ratios and 95% confidence intervals for comparisons between pembrolizumab 2mg/kg and the control arm at each of these time points

Table 3: PFS at fixed time-points based on central (IRO) assessment per RECIST 1.1 (ITT population): Comparison of Pembrolizumab 2mg/kg Q3W versus Control - Hazard Ratios and 95% Confidence Intervals

Hazard Ratio (95% CI)			
Month 3	Month 6	Month 9	Month 12
0.64 (0.49, 0.85)	0.40 (0.24, 0.69)	0.65 (0.27, 1.60)	0.12 (0.01, 1.05)

† Obtained from piecewise proportional hazards model assuming constant hazard ratio in intervals 0-3, 3-6, 6-9 and >9. No stratification factor was included in the model because of small numbers at the later time intervals.

A4. For completeness, please provide the findings from the results of the first interim analyses conducted for KEYNOTE-002.

A report was not prepared for the first interim analysis (IA1) conducted for KEYNOTE-002. The first IA was performed after approximately 120 randomized patients had a minimum of 3 months follow-up. The primary objective of this analysis was to discontinue the 2 mg/kg or the 10 mg/kg from the study if one arm was clearly not as effective as the other arm. Only the overall response rate from the 2 mg/kg and 10 mg/kg arms were compared in this analysis. The analysis was performed by an external, unblinded statistician, and reviewed by the external data monitoring committee (DMC), who recommended on the basis of the data that the study continue as planned. Merck did not prepare a CSR or any other submission document based on the results of IA1.

A5. Please provide the p-values for interaction for all performed subgroup analyses as presented in Appendix 7 of the company's submission for KEYNOTE-002 and KEYNOTE-001 (part B2).

Please find below the requested p-values for interaction for all performed subgroup analyses as was presented in Appendix 7 of the submission document:

KEYNOTE-002:

The p-values for treatment-by-subgroup interaction from the KEYNOTE-002 subgroup analyses are available in the various tables for each of the pairwise treatment comparisons.

Table 4: ORR by IRO per RECIST (%) in PD-L1 subgroups

Treatment	PD-L1 subgroup		Treatment-by-subgroup † p-value
	PD-L1 positive	PD-L1 negative	
Control	4.1	8.1	
MK-3475 2 mg/kg Q3W	23.5	10.6	0.033
MK-3475 10 mg/kg Q3W	29.5	19.6	0.120

† Pairwise (MK-3475 dose group versus control) treatment-by-subgroup interaction based on observed proportions

Table 5: Analysis of Progression Free Survival at Interim Analysis 2 by PDL1 Status at Baseline (ITT Population)

Subgroup Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median† (Months) (95% CI)	Survival Rate at Month 3 in %† (95% CI)	Treatment vs. Control		
							Hazard Ratio‡ (95% CI)‡	p-Value§	p-Value‖
PD-L1 Positive									
Control	98	87 (88.8)	324.6	26.8	2.8 (2.6, 2.9)	38.7 (28.9, 48.4)	---	---	---
MK-3475 2 mg/kg Q3W	98	66 (67.3)	471.5	14.0	3.5 (2.9, 5.6)	53.6 (43.2, 62.9)	0.54 (0.39, 0.75)	0.0003	0.0002
MK-3475 10 mg/kg Q3W	95	63 (66.3)	462.7	13.6	4.0 (2.8, 6.0)	51.8 (41.2, 61.3)	0.49 (0.35, 0.69)	<0.0001	<0.0001
PD-L1 Negative									
Control	37	32 (86.5)	122.5	26.1	2.7 (2.0, 3.0)	29.7 (16.1, 44.6)	---	---	---
MK-3475 2 mg/kg Q3W	47	41 (87.2)	159.4	25.7	2.8 (2.7, 2.8)	26.4 (14.7, 39.6)	0.89 (0.53, 1.50)	0.6645	0.6972
MK-3475 10 mg/kg Q3W	46	35 (76.1)	233.4	15.0	2.8 (2.8, 5.6)	45.7 (31.0, 59.2)	0.41 (0.23, 0.72)	0.0020	0.0016
Treatment-by-subgroup interaction							p-Value based on Q-statistic		I^2 statistic (%)
MK-3475 2 mg/kg Q3W vs. Control							0.1105		60.74
MK-3475 10 mg/kg Q3W vs. Control							0.5834		0.00

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), LDH level (normal vs. elevated) and BRAF mutation (mutant vs. wild type).
§ Two-sided p-value based on Cox regression model.
‖ Two-sided p-value based on log-rank test.
(Database Cutoff Date: 12MAY2014).

Table 6: Analysis of Overall Survival at Interim Analysis 2 by PDL1 Status at Baseline (ITT Population)

Subgroup Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median† (Months) (95% CI)	Survival Rate at Month 3 in %† (95% CI)	Treatment vs. Control Hazard Ratio‡ (95% CI)‡	p-Value§	p-Value‖
PD-L1 Positive									
Control	98	38 (38.8)	663.8	5.7	16.3 (8.7, 16.3)	87.5 (79.1, 92.7)	---	---	---
MK-3475 2 mg/kg Q3W	98	37 (37.8)	714.6	5.2	Not Reached (10.2, .)	86.7 (78.3, 92.1)	0.93 (0.58, 1.49)	0.7669	0.7668
MK-3475 10 mg/kg Q3W	95	32 (33.7)	728.2	4.4	14.8 (8.9, .)	91.6 (83.9, 95.7)	0.73 (0.45, 1.19)	0.2071	0.2049
PD-L1 Negative									
Control	37	19 (51.4)	268.1	7.1	10.4 (5.4, .)	78.4 (61.4, 88.5)	---	---	---
MK-3475 2 mg/kg Q3W	47	25 (53.2)	326.9	7.6	8.9 (6.2, 13.2)	83.0 (68.8, 91.1)	1.19 (0.58, 2.46)	0.6376	0.6465
MK-3475 10 mg/kg Q3W	46	21 (45.7)	345.3	6.1	10.8 (4.6, .)	78.3 (63.4, 87.7)	0.60 (0.30, 1.18)	0.1389	0.1355

Treatment-by-subgroup interaction	p-Value based on Q-statistic	I^2 statistic (%)
MK-3475 2 mg/kg Q3W vs. Control	0.5779	0.00
MK-3475 10 mg/kg Q3W vs. Control	0.6363	0.00

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), LDH level (normal vs. elevated) and BRAF mutation (mutant vs. wild type).
§ Two-sided p-value based on Cox regression model.
‖ Two-sided p-value based on log-rank test.
(Database Cutoff Date: 12MAY2014).

Table 7: Analysis of Progression Free Survival at Interim Analysis 2 by Baseline Tumor Size (ITT Population)

Subgroup Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median† (Months) (95% CI)	Survival Rate at Month 3 in %† (95% CI)	Treatment vs. Control Hazard Ratio‡ (95% CI)‡	p-Value§	p-Value‖
Baseline tumour size measured by IRC < Median in overall population									
Control	81	65 (80.2)	283.3	22.9	2.8 (2.6, 3.1)	41.0 (29.9, 51.7)	---	---	---
MK-3475 2 mg/kg Q3W	85	55 (64.7)	401.9	13.7	3.3 (2.8, 5.6)	52.0 (40.8, 62.1)	0.58 (0.40, 0.85)	0.0054	0.0048

MK-3475 10 mg/kg Q3W	79	46 (58.2)	472.7	9.7	6.4 (3.6, 10.0)	64.6 (53.0, 74.0)	0.38 (0.26, 0.58)	<0.0001	<0.0001
Baseline tumour size measured by IRC >= Median in overall population									
Control	84	78 (92.9)	239.4	32.6	2.5 (2.2, 2.8)	26.7 (17.6, 36.7)	---	---	---
MK-3475 2 mg/kg Q3W	80	66 (82.5)	306.6	21.5	2.8 (2.7, 2.9)	37.5 (27.0, 47.9)	0.60 (0.42, 0.86)	0.0059	0.0048
MK-3475 10 mg/kg Q3W	84	69 (82.1)	307.3	22.5	2.8 (2.7, 2.9)	31.9 (22.2, 42.1)	0.59 (0.41, 0.84)	0.0039	0.0032
Treatment-by-subgroup interaction							p-Value based on Q-statistic		I^2 statistic (%)
MK-3475 2 mg/kg Q3W vs. Control							0.8930		0.00
MK-3475 10 mg/kg Q3W vs. Control							0.1187		58.93

Adverse experiences are reported from the first dose up to 30 following the last dose of study medication.
MedDRA preferred terms Neoplasm Progression Malignant Neoplasm Progression and Disease Progression not related to the drug are excluded.
† Peto-Odds Ratio instead of Relative Risk if incidence is ≤ 1 % or ≥ 99% in at least one cell. Note that a consistent summary statistic is used across all the subgroup values within a specific treatment comparison; that is either all Relative Risks or all Peto-Odds Ratios for a specific subgroup
‡ Unconditional exact test (CSZ method)
(Database Cutoff Date: 12MAY2014).

Table 8 : Analysis of Progression Free Survival at Interim Analysis 2 by Chemotherapy at Baseline ITT Population)

Subgroup Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median† (Months) (95% CI)	Survival Rate at Month 3 in %† (95% CI)	Treatment vs. Control Hazard Ratio‡ (95% CI)‡	p-Value§	p-Value‖
Carboplatin plus paclitaxel									
Control	42	31 (73.8)	133.9	23.2	2.9 (2.5, 3.9)	45.8 (29.3, 60.9)	---	---	---
MK-3475 2 mg/kg Q3W	41	30 (73.2)	173.3	17.3	3.0 (2.8, 5.4)	50.0 (33.8, 64.2)	0.68 (0.38, 1.20)	0.1841	0.1819
MK-3475 10 mg/kg Q3W	36	23 (63.9)	191.4	12.0	2.8 (2.6, 9.7)	47.2 (30.5, 62.3)	0.60 (0.32, 1.12)	0.1066	0.1041
Dacarbazine									
Control	48	44 (91.7)	143.0	30.8	2.5 (2.3, 2.7)	18.8 (9.3, 30.8)	---	---	---
MK-3475 2 mg/kg Q3W	45	30 (66.7)	196.7	15.2	2.9 (2.8, 6.9)	43.5 (28.7, 57.3)	0.44 (0.26, 0.75)	0.0024	0.0019
MK-3475 10 mg/kg Q3W	57	41 (71.9)	254.7	16.1	2.9 (2.8, 5.2)	48.5 (35.0, 60.7)	0.44 (0.27, 0.71)	0.0007	0.0006
Paclitaxel alone									
Control	32	26 (81.3)	130.8	19.9	3.1 (2.5, 4.1)	53.3 (34.3, 69.1)	---	---	---
MK-3475 2 mg/kg Q3W	38	30 (78.9)	159.2	18.8	2.9 (2.8, 5.4)	45.9 (29.6, 60.9)	0.77 (0.40, 1.45)	0.4163	0.4114
MK-3475 10 mg/kg Q3W	39	27 (69.2)	192.4	14.0	3.0 (2.8, 7.1)	48.7 (32.5, 63.2)	0.53 (0.29, 0.99)	0.0470	0.0446
Temozolomide									
Control	44	41 (93.2)	134.9	30.4	2.7 (2.2, 2.9)	30.2 (17.4, 44.1)	---	---	---
MK-3475 2 mg/kg Q3W	51	34 (66.7)	252.1	13.5	3.4 (2.8, 7.5)	51.0 (36.6, 63.6)	0.40 (0.24, 0.66)	0.0003	0.0002
MK-3475 10 mg/kg Q3W	42	29 (69.0)	199.9	14.5	3.1 (2.8, 6.8)	51.2 (35.1, 65.2)	0.49 (0.29, 0.83)	0.0076	0.0054
Treatment-by-subgroup interaction							p-Value based on Q-statistic		I^2 statistic (%)

MK-3475 2 mg/kg Q3W vs. Control	0.2945	19.13
MK-3475 10 mg/kg Q3W vs. Control	0.8807	0.00

Adverse experiences are reported from the first dose up to 30 following the last dose of study medication.
MedDRA preferred terms Neoplasm Progression Malignant Neoplasm Progression and Disease Progression not related to the drug are excluded.
† Peto-Odds Ratio instead of Relative Risk if incidence is ≤ 1 % or ≥ 99% in at least one cell. Note that a consistent summary statistic is used across all the subgroup values within a specific treatment comparison; that is either all Relative Risks or all Peto-Odds Ratios for a specific subgroup
‡ Unconditional exact test (CSZ method)
(Database Cutoff Date: 12MAY2014).

Table 9: Analysis of Progression Free Survival at Interim Analysis 2 by Region (ITT Population)

Subgroup Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median† (Months) (95% CI)	Survival Rate at Month 3 in %† (95% CI)	Treatment vs. Control Hazard Ratio‡ (95% CI)‡	p-Value§	p-Value‖
United States									
Control	97	84 (86.6)	333.3	25.2	2.8 (2.6, 2.9)	36.3 (26.7, 46.0)	---	---	---
MK-3475 2 mg/kg Q3W	88	56 (63.6)	449.1	12.5	3.6 (2.8, 7.0)	51.7 (40.8, 61.6)	0.47 (0.33, 0.68)	<0.0001	<0.0001
MK-3475 10 mg/kg Q3W	94	68 (72.3)	431.2	15.8	2.9 (2.8, 5.4)	49.5 (39.0, 59.1)	0.58 (0.41, 0.81)	0.0015	0.0012
Ex-United States									
Control	82	71 (86.6)	251.0	28.3	2.5 (2.2, 2.8)	33.5 (23.2, 44.1)	---	---	---
MK-3475 2 mg/kg Q3W	92	73 (79.3)	355.5	20.5	2.9 (2.8, 3.3)	43.5 (33.1, 53.4)	0.69 (0.49, 0.96)	0.0285	0.0264
MK-3475 10 mg/kg Q3W	87	58 (66.7)	449.9	12.9	3.0 (2.8, 6.4)	47.9 (37.0, 57.9)	0.48 (0.33, 0.69)	0.0001	<0.0001

Treatment-by-subgroup interaction	p-Value based on Q-statistic	I^2 statistic (%)
MK-3475 2 mg/kg Q3W vs. Control	0.1364	54.92
MK-3475 10 mg/kg Q3W vs. Control	0.4741	0.00

Adverse experiences are reported from the first dose up to 30 following the last dose of study medication.
MedDRA preferred terms Neoplasm Progression Malignant Neoplasm Progression and Disease Progression not related to the drug are excluded.
† Peto-Odds Ratio instead of Relative Risk if incidence is ≤ 1 % or ≥ 99% in at least one cell. Note that a consistent summary statistic is used across all the subgroup values within a specific treatment comparison; that is either all Relative Risks or all Peto-Odds Ratios for a specific subgroup
‡ Unconditional exact test (CSZ method)
(Database Cutoff Date: 12MAY2014).

Table 10: Analysis of Progression Free Survival at Interim Analysis 2 by Age Group (ITT Population)

Subgroup Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median† (Months) (95% CI)	Survival Rate at Month 3 in %† (95% CI)	Treatment vs. Control Hazard Ratio‡ (95% CI)‡	p-Value§	p-Value‖
<65									
Control	98	84 (85.7)	272.1	30.9	2.5 (2.3, 2.8)	27.6 (18.9, 36.9)	---	---	---
MK-3475 2 mg/kg Q3W	102	74 (72.5)	448.1	16.5	2.9 (2.8, 3.5)	45.5 (35.6, 54.9)	0.47 (0.34, 0.66)	<0.0001	<0.0001

MK-3475 10 mg/kg Q3W	106	74 (69.8)	486.5	15.2	2.9 (2.8, 4.3)	45.9 (36.2, 55.1)	0.42 (0.30, 0.59)	<0.0001	<0.0001
>=65									
Control	81	71 (87.7)	312.2	22.7	2.8 (2.6, 3.4)	43.8 (32.6, 54.4)	---	---	---
MK-3475 2 mg/kg Q3W	78	55 (70.5)	356.5	15.4	3.1 (2.9, 5.4)	50.1 (38.5, 60.7)	0.70 (0.48, 1.01)	0.0544	0.0508
MK-3475 10 mg/kg Q3W	75	52 (69.3)	394.6	13.2	3.6 (2.8, 6.0)	52.7 (40.8, 63.3)	0.60 (0.41, 0.88)	0.0083	0.0067
Treatment-by-subgroup interaction							p-Value based on Q-statistic		I^2 statistic (%)
MK-3475 2 mg/kg Q3W vs. Control							0.1298		56.43
MK-3475 10 mg/kg Q3W vs. Control							0.1792		44.57

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), LDH level (normal vs. elevated) and BRAF mutation (mutant vs. wild type).
§ Two-sided p-value based on Cox regression model.
‖ Two-sided p-value based on log-rank test.
(Database Cutoff Date: 12MAY2014).

Table 11: Analysis of Progression Free Survival at Interim Analysis 2 by Baseline Lactate Dehydrogenase (ITT Population)

Subgroup Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median† (Months) (95% CI)	Survival Rate at Month 3 in %† (95% CI)	Treatment vs. Control Hazard Ratio‡ (95% CI)‡	p-Value§	p-Value‖
Normal									
Control	107	90 (84.1)	387.1	23.2	2.8 (2.7, 3.1)	41.7 (32.0, 51.1)	---	---	---
MK-3475 2 mg/kg Q3W	99	60 (60.6)	515.9	11.6	4.5 (2.9, 7.5)	59.9 (49.5, 68.9)	0.50 (0.36, 0.70)	0.0001	<0.0001
MK-3475 10 mg/kg Q3W	105	64 (61.0)	605.5	10.6	5.7 (3.1, 8.3)	60.6 (50.5, 69.2)	0.43 (0.31, 0.61)	<0.0001	<0.0001
Elevated									
Control	68	62 (91.2)	188.7	32.9	2.3 (2.0, 2.6)	25.0 (15.3, 35.8)	---	---	---
MK-3475 2 mg/kg Q3W	77	67 (87.0)	275.4	24.3	2.8 (2.7, 2.9)	32.5 (22.4, 43.0)	0.65 (0.46, 0.93)	0.0186	0.0168
MK-3475 10 mg/kg Q3W	73	59 (80.8)	263.8	22.4	2.8 (2.7, 2.8)	30.9 (20.6, 41.6)	0.62 (0.43, 0.89)	0.0105	0.0087
Treatment-by-subgroup interaction							p-Value based on Q-statistic		I^2 statistic (%)
MK-3475 2 mg/kg Q3W vs. Control							0.2876		11.58
MK-3475 10 mg/kg Q3W vs. Control							0.1594		49.50

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), LDH level (normal vs. elevated) and BRAF mutation (mutant vs. wild type).
§ Two-sided p-value based on Cox regression model.
‖ Two-sided p-value based on log-rank test.
(Database Cutoff Date: 12MAY2014).

Table 12: Analysis of Progression Free Survival at Interim Analysis 2 by BRAF Mutation Type (ITT Population)

Subgroup Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median† (Months) (95% CI)	Survival Rate at Month 3 in %† (95% CI)	Treatment vs. Control Hazard Ratio‡ (95% CI)‡	p-Value§	p-Value‖
Mutant									
Control	41	36 (87.8)	101.2	35.6	2.4 (2.1, 2.8)	21.6 (10.2, 35.8)	---	---	---
MK-3475 2 mg/kg Q3W	44	40 (90.9)	130.8	30.6	2.8 (2.6, 2.9)	30.6 (17.7, 44.6)	0.74 (0.46, 1.18)	0.2073	0.1998
MK-3475 10 mg/kg Q3W	40	31 (77.5)	172.5	18.0	2.8 (2.7, 3.0)	33.8 (19.6, 48.5)	0.44 (0.26, 0.74)	0.0018	0.0012
Wild Type									
Control	138	119 (86.2)	483.1	24.6	2.8 (2.6, 2.9)	38.7 (30.5, 46.9)	---	---	---
MK-3475 2 mg/kg Q3W	136	89 (65.4)	673.8	13.2	4.1 (2.9, 6.2)	53.0 (44.2, 61.0)	0.51 (0.39, 0.67)	<0.0001	<0.0001
MK-3475 10 mg/kg Q3W	141	95 (67.4)	708.7	13.4	3.6 (2.8, 5.6)	52.9 (44.3, 60.7)	0.53 (0.40, 0.69)	<0.0001	<0.0001
Treatment-by-subgroup interaction							p-Value based on Q-statistic		I^2 statistic (%)
MK-3475 2 mg/kg Q3W vs. Control							0.1809		44.14
MK-3475 10 mg/kg Q3W vs. Control							0.5491		0.00

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), LDH level (normal vs. elevated) and BRAF mutation (mutant vs. wild type).
§ Two-sided p-value based on Cox regression model.
‖ Two-sided p-value based on log-rank test.
(Database Cutoff Date: 12MAY2014).

Table 13:Analysis of Progression Free Survival at Interim Analysis 2 by ECOG at Baseline (ITT Population)

Subgroup Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median† (Months) (95% CI)	Survival Rate at Month 3 in %† (95% CI)	Treatment vs. Control Hazard Ratio‡ (95% CI)‡	p-Value§	p-Value‖
0									
Control	99	85 (85.9)	359.4	23.6	2.8 (2.6, 2.9)	37.1 (27.5, 46.7)	---	---	---
MK-3475 2 mg/kg Q3W	98	68 (69.4)	476.2	14.3	3.7 (2.9, 5.6)	54.1 (43.7, 63.3)	0.55 (0.40, 0.76)	0.0003	0.0002
MK-3475 10 mg/kg Q3W	98	62 (63.3)	500.4	12.4	4.1 (2.9, 7.1)	54.6 (44.2, 63.9)	0.50 (0.35, 0.70)	0.0001	<0.0001
1									
Control	80	70 (87.5)	224.9	31.1	2.5 (2.0, 2.7)	32.3 (22.1, 43.0)	---	---	---
MK-3475 2 mg/kg Q3W	80	59 (73.8)	322.4	18.3	2.8 (2.7, 2.9)	39.2 (28.4, 49.9)	0.62 (0.43, 0.89)	0.0092	0.0075
MK-3475 10 mg/kg Q3W	83	64 (77.1)	380.7	16.8	2.8 (2.8, 3.6)	41.7 (31.0, 52.1)	0.54 (0.38, 0.77)	0.0007	0.0006
Treatment-by-subgroup interaction							p-Value based on Q-statistic		I^2 statistic (%)

MK-3475 2 mg/kg Q3W vs. Control	0.6409	0.00
MK-3475 10 mg/kg Q3W vs. Control	0.7242	0.00

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), LDH level (normal vs. elevated) and BRAF mutation (mutant vs. wild type).
§ Two-sided p-value based on Cox regression model.
‖ Two-sided p-value based on log-rank test.
(Database Cutoff Date: 12MAY2014).

Table 14: Analysis of Progression Free Survival at Interim Analysis 2 by Race White:Non-White (ITT Population)

Subgroup Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median† (Months) (95% CI)	Survival Rate at Month 3 in %† (95% CI)	Treatment vs. Control Hazard Ratio‡ (95% CI)‡	p-Value§	p-Value‖
White									
Control	172	148 (86.0)	569.2	26.0	2.7 (2.6, 2.8)	35.3 (28.0, 42.6)	---	---	---
MK-3475 2 mg/kg Q3W	176	125 (71.0)	796.0	15.7	2.9 (2.8, 4.2)	48.6 (41.0, 55.8)	0.58 (0.45, 0.73)	<0.0001	<0.0001
MK-3475 10 mg/kg Q3W	179	124 (69.3)	869.1	14.3	2.9 (2.8, 4.3)	48.1 (40.6, 55.2)	0.51 (0.40, 0.66)	<0.0001	<0.0001
Non white									
Control	6	6 (100.0)	13.0	46.1	1.8 (0.8, 3.9)	33.3 (4.6, 67.6)	---	---	---
MK-3475 2 mg/kg Q3W	4	4 (100.0)	8.6	46.3	2.7 (0.3, 2.9)	Not reached	1.35 (0.27, 6.81)	0.7184	0.7175
MK-3475 10 mg/kg Q3W	2	2 (100.0)	12.1	16.5	6.0 (., .)	100.0 (100.0, 100.0)	/ (/, /)	/	0.0969

Treatment-by-subgroup interaction	p-Value based on Q-statistic	I^2 statistic (%)
MK-3475 2 mg/kg Q3W vs. Control	0.3096	3.15
MK-3475 10 mg/kg Q3W vs. Control	.	0.00

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), LDH level (normal vs. elevated) and BRAF mutation (mutant vs. wild type).
§ Two-sided p-value based on Cox regression model.
‖ Two-sided p-value based on log-rank test.
(Database Cutoff Date: 12MAY2014).
/ Could not be estimated – Cox model did not converge. This subgroup value is not contributing to the calculation of treatment-by-subgroup p-value and I2 statistic

Table 15: Analysis of Progression Free Survival at Interim Analysis 2 by Gender at Baseline (ITT Population)

Subgroup Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median† (Months) (95% CI)	Survival Rate at Month 3 in %† (95% CI)	Treatment vs. Control Hazard Ratio‡ (95% CI)‡	p-Value§	p-Value‖
Male									
Control	114	100 (87.7)	369.6	27.1	2.8 (2.5, 2.8)	34.6 (25.8, 43.5)	---	---	---

MK-3475 2 mg/kg Q3W	104	74 (71.2)	493.1	15.0	3.3 (2.8, 5.6)	51.9 (41.9, 61.0)	0.54 (0.39, 0.74)	0.0001	0.0001
MK-3475 10 mg/kg Q3W	109	74 (67.9)	530.4	14.0	3.0 (2.8, 5.6)	48.8 (39.0, 57.8)	0.50 (0.36, 0.68)	<0.0001	<0.0001
Female									
Control	65	55 (84.6)	214.7	25.6	2.6 (2.4, 2.9)	35.8 (24.1, 47.6)	---	---	---
MK-3475 2 mg/kg Q3W	76	55 (72.4)	311.5	17.7	2.9 (2.8, 3.3)	41.4 (30.0, 52.3)	0.61 (0.41, 0.92)	0.0184	0.0169
MK-3475 10 mg/kg Q3W	72	52 (72.2)	350.8	14.8	2.9 (2.8, 5.5)	48.6 (36.7, 59.5)	0.52 (0.34, 0.78)	0.0017	0.0015

Treatment-by-subgroup interaction	p-Value based on Q-statistic	I^2 statistic (%)
MK-3475 2 mg/kg Q3W vs. Control	0.6474	0.00
MK-3475 10 mg/kg Q3W vs. Control	0.8931	0.00

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), LDH level (normal vs. elevated) and BRAF mutation (mutant vs. wild type).
§ Two-sided p-value based on Cox regression model.
‖ Two-sided p-value based on log-rank test.
(Database Cutoff Date: 12MAY2014).

KEYNOTE-001 (Part B2):

Please note the subgroup results from KEYNOTE-001 (Part B2) that were presented in our submission were based on information provided in the clinical study report (CSR) version 1 (data cut-off date Oct 2013). After our submission we were made aware of a CSR with a later data-cut that is now available (CSR version 2: data cut-off date April 2014) and is being provided with the response. The requested p-values for interaction for all performed subgroup analyses based on both the earlier and later data cuts (CSR v1 and CSR v2 respectively) are provided below.

Table 16: Summary of Best Overall Response (BOR) Based on IRO Assessment per RECIST 1.1 by Subgroups - Part B2 (APaT Population) – Data cut-off October 2013

	Best Overall Response Rate (N=173)				
	N	BOR n	(%)	95% CI (%)	P-Value
Overall	173	41	(23.7)	(17.6, 30.7)	.
Gender					
Male	105	24	(22.9)	(15.2, 32.1)	.
Female	68	17	(25.0)	(15.3, 37.0)	0.8550
Age					
< 65	111	28	(25.2)	(17.5, 34.4)	.
≥ 65	62	13	(21.0)	(11.7, 33.2)	0.5799
ECOG					
0	116	27	(23.3)	(15.9, 32.0)	.
1	57	14	(24.6)	(14.1, 37.8)	0.8512

LDH					
Normal	104	25	(24.0)	(16.2, 33.4)	.
Elevated	68	16	(23.5)	(14.1, 35.4)	1.0000
Brain Metastases					
Yes	15	4	(26.7)	(7.8, 55.1)	.
No	156	37	(23.7)	(17.3, 31.2)	0.7581
BRAF Mutation					
Mutant	31	5	(16.1)	(5.5, 33.7)	.
Wild Type	142	36	(25.4)	(18.4, 33.3)	0.3543
Metastasis Staging					
M0	24	7	(29.2)	(12.6, 51.1)	.
M1a	18	5	(27.8)	(9.7, 53.5)	.
M1b	27	8	(29.6)	(13.8, 50.2)	.
M1c	98	21	(21.4)	(13.8, 30.9)	0.6875
Number of Prior Therapies					
0	.	0	(0.0)	(0.0, .)	.
1	48	14	(29.2)	(17.0, 44.1)	.
2	65	13	(20.0)	(11.1, 31.8)	.
> 2	60	14	(23.3)	(13.4, 36.0)	0.5162
Prior Systemic Therapies					
Chemotherapy	80	18	(22.5)	(13.9, 33.2)	0.8579
Immunotherapy†	53	13	(24.5)	(13.8, 38.3)	0.8488
BRAF/MEK Inhibitor	34	5	(14.7)	(5.0, 31.1)	0.2595
Baseline Tumor Size (Sum of Longest Diameter)					
< median	94	23	(24.5)	(16.2, 34.4)	.
≥ median	79	18	(22.8)	(14.1, 33.6)	0.8586

Note: All treatment groups. Response only included confirmed complete or partial response.
P-value from Fishers Exact testing the difference between subgroups.
† Ipilimumab excluded.
Response only included confirmed complete response and confirmed partial response.
(Database Cutoff Date: 18Oct2013)

Table 17: Summary of Best Overall Response (BOR) Based on IRO Assessment per RECIST 1.1 by Subgroups Part B2: (APaT Population) – Data cut-off April 2014

	Best Overall Response Rate (N=173)				
	N	BOR n	(%)	95% CI (%)	P-Value
Overall	173	43	(24.9)	(18.6, 32.0)	.
Gender					
Male	104	27	(26.0)	(17.9, 35.5)	.
Female	69	16	(23.2)	(13.9, 34.9)	0.7224
Age					
< 65	111	27	(24.3)	(16.7, 33.4)	.
≥ 65	62	16	(25.8)	(15.5, 38.5)	0.8557

ECOG					
0	115	26	(22.6)	(15.3, 31.3)	.
1	58	17	(29.3)	(18.1, 42.7)	0.3557
LDH					
Normal	99	27	(27.3)	(18.8, 37.1)	.
Elevated	73	16	(21.9)	(13.1, 33.1)	0.4786
Brain Metastases					
Yes	15	4	(26.7)	(7.8, 55.1)	.
No	158	39	(24.7)	(18.2, 32.2)	1.0000
BRAF Mutation					
Mutant	30	4	(13.3)	(3.8, 30.7)	.
Wild Type	143	39	(27.3)	(20.2, 35.3)	0.1617
Metastasis Staging					
M0	1	0	(0.0)	(0.0, 97.5)	.
M1a	11	3	(27.3)	(6.0, 61.0)	.
M1b	20	6	(30.0)	(11.9, 54.3)	.
M1c	141	34	(24.1)	(17.3, 32.0)	0.8003
Number of Prior Therapies					
0	.	0	(0.0)	(0.0, .)	.
1	47	14	(29.8)	(17.3, 44.9)	.
2	65	13	(20.0)	(11.1, 31.8)	.
> 2	61	16	(26.2)	(15.8, 39.1)	0.4757
Prior Systemic Therapies					
Chemotherapy	81	21	(25.9)	(16.8, 36.9)	0.8604
Immunotherapy†	55	15	(27.3)	(16.1, 41.0)	0.7060
BRAF/MEK Inhibitor	34	4	(11.8)	(3.3, 27.5)	0.0745
Baseline Tumor Size (Sum of Longest Diameter)					
< median	95	24	(25.3)	(16.9, 35.2)	.
≥ median	78	19	(24.4)	(15.3, 35.4)	1.0000

Note: All treatment groups. Response only included confirmed complete or partial response.
P-value from Fishers Exact testing the difference between subgroups.
† Ipilimumab excluded.
Response only included confirmed complete response and confirmed partial response.
(Database Cutoff Date: 18APR2014)

A6. Please clarify which analysis population has been used for the KEYNOTE-001 (part B2) results presented in Table 32 of the company's submission.

Table 32 in page 90 of MSD original submission [ID760] document (provided again below as Table 18) was based on Table 2 from the following publication: Robert et al (2014) Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. The Lancet – please see the below red box below highlighting the source of this information.

Table 18: KEYNOTE-001 Part B2- Disease control rate and response duration

	RECIST 1.1, independent central review (IRO)	**irRC, investigator review**
	Pembrolizumab 2mg/kg	Pembrolizumab 2mg/kg
Disease control rate (95% CI)	51% (39 to 62)	62% (51 to 72)
Patients with response	n=21	n=24
Time to response (weeks): median (range)	12 (11 to 36)	12 (11 to 24)
Response duration (weeks): median (range)	NR (6–37¶)	NR (12–42¶)

NR=not reached; ¶Non-progressive disease or ongoing response at the last assessment. §Difference. Two-sided p values are provided for testing the null hypothesis that there is no difference in the response between groups versus there is a response difference

	RECIST, independent central review			Immune-related response criteria, investigator review		
	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	Estimated difference (95% CI)	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	Estimated difference (95% CI)
Best overall response*	n=81	n=76		n=89	n=84	
Complete response	1 (1%)	1 (1%)	–	3 (3%)	0 (0%)	–
Partial response	20 (25%)	19 (25%)	–	21 (24%)	27 (32%)	–
Stable disease	20 (25%)	18 (24%)	–	31 (35%)	27 (32%)	–
Progressive disease	27 (33%)	31 (41%)	–	24 (27%)	19 (23%)	–
Not evaluable†	13 (16%)	7 (9%)	–	–	–	–
No assessment‡	–	–	–	10 (11%)	11 (13%)	–
Overall response rate (95% CI)	26% (17 to 37)	26% (17 to 38)	0%§ (-14 to 13); p=0·96	27% (18 to 37)	32% (22 to 43)	-5%§ (-19 to 8); p=0·46
Disease control rate (95% CI)	51% (39 to 62)	50% (38 to 62)	1%§ (-15 to 16); p=0·94	62% (51 to 72)	64% (53 to 74)	-2%§ (-17 to 12); p=0·75
Patients with response	n=21	n=20	–	n=24	n=27	–
Time to response (weeks; median, range)	12 (11 to 36)	12 (7 to 17)	–	12 (11 to 24)	12 (7 to 39)	–
Response duration (weeks; median, range)	NR (6–37¶)	NR (8–37¶)	–	NR (12–42¶)	NR (4–37¶)	–
Progression-free survival	n=89	n=84	–	n=89	n=84	–
Median (weeks; 95% CI)	22 (12 to 36)	14 (12 to 24)	0·84‖ (0·57–1·23)	31 (22 to 48)	35 (24 to NR)	1·12‖ (0·73–1·72)
At 24 weeks (95% CI)	45% (34 to 55)	37% (27 to 48)	–	57% (46 to 67)	57% (45 to 67)	–

RECIST=Response Evaluation Criteria In Solid Tumors (version 1.1). NR=not reached. *Eight patients in each treatment group did not have measurable disease as per independent central review at baseline and were excluded from the analysis of best overall response as per RECIST by independent central review. †Patients who had no scans for response assessment or who had radiological images of non-diagnostic quality. ‡Patients who exited the study without post-baseline response assessment by the investigator. §Difference. ¶Non-progressive disease or ongoing response at the last assessment. ‖Hazard ratio. Two-sided p values are provided for testing the null hypothesis that there is no difference in the response between groups versus there is a response difference.

Table 2: **Antitumour activity of pembrolizumab at 2mg/kg and 10 mg/kg**

The primary efficacy analyses in KEYNOTE-001 Part B2 were based on the full analysis set (FAS) population, which is different for investigator assessment (n=89) and for central (IRO) assessment (n=81).

Patients with measurable disease at baseline (defined separately under investigator evaluation and central review), who received at least one dose of study treatment were included in the FAS population.

The following text included in the footnote which was provided under Table 31 in page 90 of MSD original submission [ID760] document (which was also based on Table 2 from the above mentioned publication) should have also been specified under Table 32. This footnote provides further clarification:

RECIST 1.1=Response Evaluation Criteria In Solid Tumours (version 1.1). *Eight patients in each treatment group did not have measurable disease as per independent central review at baseline and were excluded from the analysis of best overall response as per RECIST by independent central review.

Statistical methods employed in KEYNOTE-002:

A7. Please provide the level of power used for the sample size calculation for KEYNOTE-002.

The sample size calculation is based on the overall survival (OS) endpoint. Based on the following assumptions: 1) overall survival follows an exponential distribution with a median of 6 months in the control arm; 2) hazard ratio between pembrolizumab and control is 0.65, 3) an enrolment period of 15 months and a minimum of 9 months follow-up after enrolment completion, and 4) a dropout rate of 2% in 12 months, it was estimated that a total of 510 patients is required to randomise with 1:1:1 ratio into two pembrolizumab arms and one control arm and a total of 370 deaths are needed at the final analysis. Under the assumption that the hazard ratio is 0.65 in either pembrolizumab arm vs. the control arm, the study has approximately 88%- 94% power to have a positive OS result at the end of the study.

A8. It is stated in the methods section for KEYNOTE-002 in the company's submission that "the OS hypothesis will be tested at 2.0%, 2.25% and 2.5% respectively if none, exactly one, or both hypotheses are rejected at the second interim analysis" referring to the two PFS hypotheses. If both PFS hypotheses are rejected at the second interim analysis at the 0.25% significance level as pre-specified for KEYNOTE 002, this would take up 0.5% of the overall pre-specified 2.5% alpha allocation, whereas if no PFS hypotheses are rejected at the second interim analysis, this would take up 0.0% of the alpha allocation. Should this sentence therefore read "the OS hypothesis will be tested at 2.5%, 2.25% and 2.0% respectively if none, exactly one, or both hypotheses are rejected at the second interim analysis"?

The statement in the submission is correct. A gatekeeping testing procedure is used for the 0.5% allocated to PFS at IA2 and OS at the final analysis, i.e., if the PFS hypotheses at IA2 were rejected, the corresponding alpha would be rolled to the final analysis for OS, based on the gate keeping procedure. The more PFS hypotheses rejected at the IA2, the more alpha would be allocated at the OS final analysis.

A9. Please clarify, why 95% CIs are provided for the PFS and OS results of KEYNOTE- 002 at the second interim analysis when the level of testing is 0.5% for OS and 0.25% for PFS? These confidence intervals could be misinterpreted as significant results, whereas the significance depends on the p-value for the test.

For reporting purpose and comparison with other studies, we provided the 95% confidence interval for the hazard ratio (without adjusting to actual significance level). MSD agrees that the actual significance level at the second interim analysis would be reflected in the p- value only.

A10. For PFS, results are reported for both Central Assessment (IRO) and Investigator Assessment (INV) of disease progression. It is not clear why the company claims to have controlled the type 1 error strictly yet performed multiple analyses, seemingly without making adjustments for multiplicity. Please clarify if there were any adjustments for multiplicity.

Central assessment (IRO) is the primary analysis endpoint and the Investigator Assessment (INV) is a supportive analysis endpoint. Therefore, formal hypothesis testing only occurred for the central assessment (IRO) PFS analysis.

A11. For KEYNOTE-002, it is pre-specified that the full-analysis set population will be used for the analysis of objective response rate (see Table 11), but results for the intention-to-treat (ITT) population are presented. Please provide justification for this choice.

The FAS population was originally pre-specified as the analysis population for overall response rates (ORR), but in a subsequent protocol amendment (amendment 002) for

KEYNOTE-002 (latest protocol provided in response to clarification question C1), the protocol had been updated to include both FAS population (required measurable disease at baseline, which is different for investigator [INV] and central [IRO] analysis) and ITT population as the primary analysis populations for the objective response rate (ORR) analysis, based on regulatory agency feedback.

An updated version of Table 11 from page 58 of MSD original submission [ID760] document is provided below (Table 19), detailing the above mentioned change to the primary analysis population for ORR:

Table 19: Analysis strategy for key efficacy endpoints

Endpoint (description , time point)	Approach*	Statistical method	Analysis population
Primary			
PFS	P	Stratified Log-rank test Cox model with Efrons's tie handling method for estimation was used to assess the treatment difference in PFS(i.e., hazard ratio and its 95% confidence interval) Kaplan-Meier (KM) method for PFS curve estimation in each treatment group	ITT
OS	P	Stratified Log-rank test Cox model with Efrons's tie handling method for estimation. KM method for OS curve estimation in each treatment group	ITT
Secondary			
ORR	P	Stratified M&N[$] method	FAS and ITT
Response Duration	P	Summary statistics using KM method	All responders

** P= primary approach; [$] Miettinen & Nurminen method; ITT = intention-to-treat; FAS = full analysis set*

Table 27 in Section 4.7 of MSD submission document (provided again below as Table 20) detailed the results concerning ORR observed in KEYNOTE-002, based on the ITT population. Below we also provide results concerning ORR observed in KEYNOTE-002, based on the FAS population by IRC/IRO (Table 21).

Table 20: KEYNOTE-002 - Analysis of OR based on central (IRO) assessment - ITT population

Treatment	N	Number of Overall	Overall Response	Difference in % vs. Control

		Responses	Rate (%) (95% CI)	Estimate (95% CI) †	p-value ††
Control	179	8	4.5 (1.9,8.6)		
Pembrolizumab 2 mg/kg Q3W	180	38	21.1 (15.4,27.8)	12.8 (7.0,20.6)	<0.0001

Based on Miettinen & Nurminen method stratified by ECOG (0 vs. 1) and LDH level (normal vs. elevated) and BRAF mutation (mutant vs. wild type).
†† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.

Table 21: KEYNOTE-002 - Analysis of OR based on IRC assessment – (FAS population)

Treatment	N	Number of Overall Responses	Overall Response Rate (%) (95% CI)	Difference in % vs. Control	
				Estimate (95% CI) †	p-value ††
Control	165	8	4.8 (2.1,9.3)		
Pembrolizumab 2 mg/kg Q3W	165	35	21.2 (15.2,28.2)	12.4 (6.4,20.5)	<0.0001

IRC = Independent Review Committee
Responses are based on IRC global radiological assessments per RECIST 1.1 with confirmation.
† Based on Miettinen & Nurminen method stratified by ECOG (0 vs. 1) and LDH level (normal vs. elevated) and BRAF mutation (mutant vs. wild type).
†† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.

Response rates were generally similar between the ITT and FAS populations, but are slightly lower in the ITT population than the FAS population when using IRO assessment due to the inclusion of subjects who cannot achieve partial response (PR) by RECIST 1.1 definition. Therefore the ORR results presented based on the ITT population represent a conservative estimate compared to those based on the FAS population.

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** The ERG have detected indications in the KEYNOTE-002 data used in the model that informative censoring at data cut-off may be exaggerating hazards in both trial groups, and wish to examine the extent to which this may be introducing bias and additional uncertainty into the model results. Please provide the following Kaplan-Meier analyses (listed in a to h below) to the following specification:

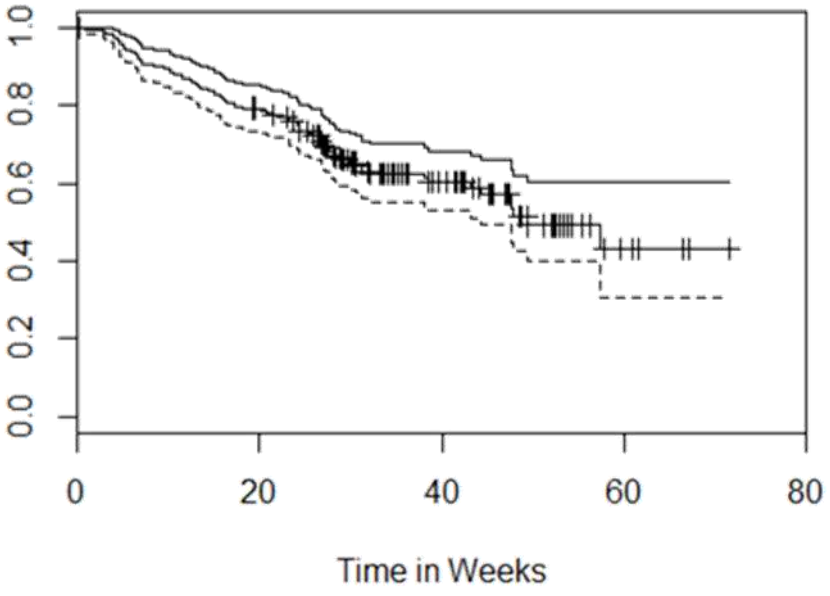
Population: Use the ITT population including all patients lost to follow-up or withdrawing from trial.

Censoring: Censor lost to follow-up and withdrawn patients at the time recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off, and not when last seen. Please use the format of the table provided below.

Trial data set: Keynote-002, latest data cut.

a. Time to death from any cause (OS) Kaplan-Meier analysis for the pembrolizumab 2mg/kg treatment group.

Figure 4. Time to death from any cause: OS KM analysis for the pembrolizumab 2mg/kg treatment group (as presented as part of the cost-effectiveness model in MSD's original submission [ID760])



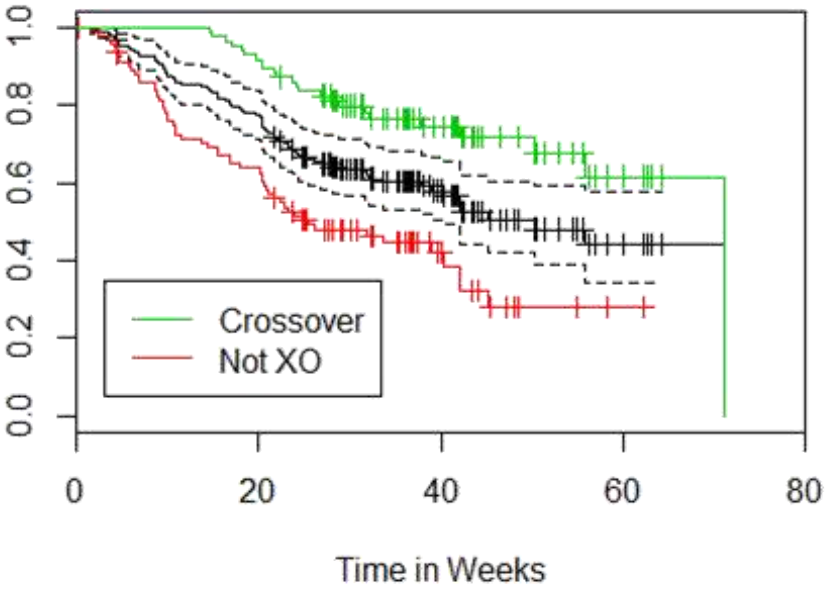
In the table below, to match SAS output, the first column time is "Time in Weeks"; the second one "n.risk" is "Number Left"; the third one "n.event" is "Number Failed" and the last one "std.err" is "Survival Standard Error". Probability of "Failure" can be obtained from taking 1-probability "survival".

Table 22. SAS output for time to death from any cause: OS KM analysis for the pembrolizumab 2mg/kg treatment group

[redacted]

c. Time to death from any cause (OS) Kaplan-Meier analysis for the comparator treatment group, without adjustment for crossover, stratified by those who did and those who did not crossover following disease progression.

Figure 5. Time to death from any cause: OS KM analysis for the chemotherapy treatment group



In the table below, to match SAS output, the first column time is "Time in Weeks"; the second one "n.risk" is "Number Left"; the third one "n.event" is "Number Failed" and the last one "std.err" is "Survival Standard Error". print(km.table).

Table 23. SAS output for time to death from any cause: OS KM analysis for the chemotherapy treatment group

[redacted]

Table 24. SAS output for time to death from any cause: OS KM analysis for the chemotherapy treatment subgroups (not crossover vs. crossover)

d. Time to death from any cause (OS) Kaplan-Meier analysis for the comparator treatment group, separately for each method of crossover adjustment (RPSFT, 2-stage simple, 2-stage all covariates, IPCW).

RPSFT crossover adjustment

Figure 6. Time to death from any cause: RPSFT-adjusted OS KM analysis for the chemotherapy treatment group

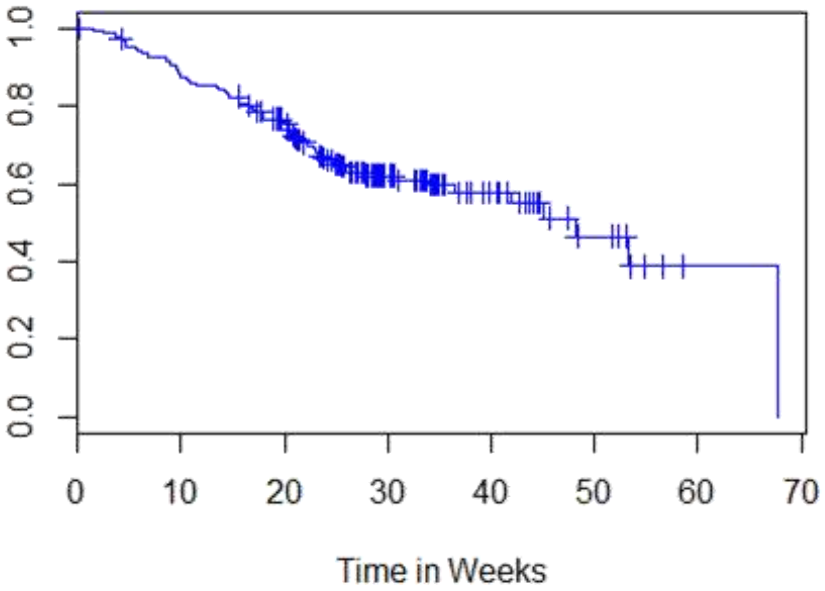


Table 25. SAS output for time to death from any cause: RPSFT-adjusted OS KM analysis for the chemotherapy treatment group

[redacted]

Two-stage crossover adjustment

Figure 7. Time to death from any cause: Two-stage-adjusted OS KM analysis for the chemotherapy treatment group using the full model (all covariates)

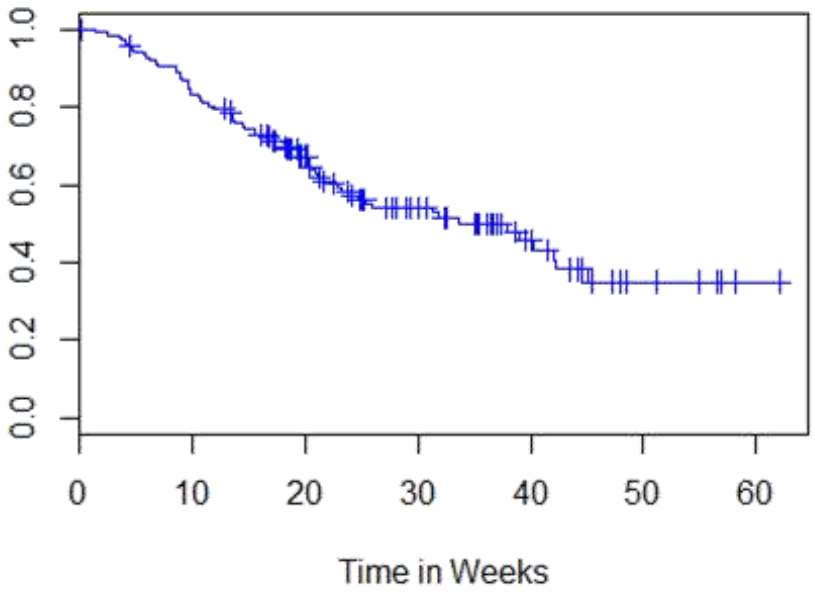


Table 26. SAS output for time to death from any cause: Two-stage -adjusted OS KM analysis for the chemotherapy treatment group using the full model (all covariates)

[redacted]

Figure 8. Time to death from any cause: Two-stage-adjusted OS KM analysis for the chemotherapy treatment group using the simple model

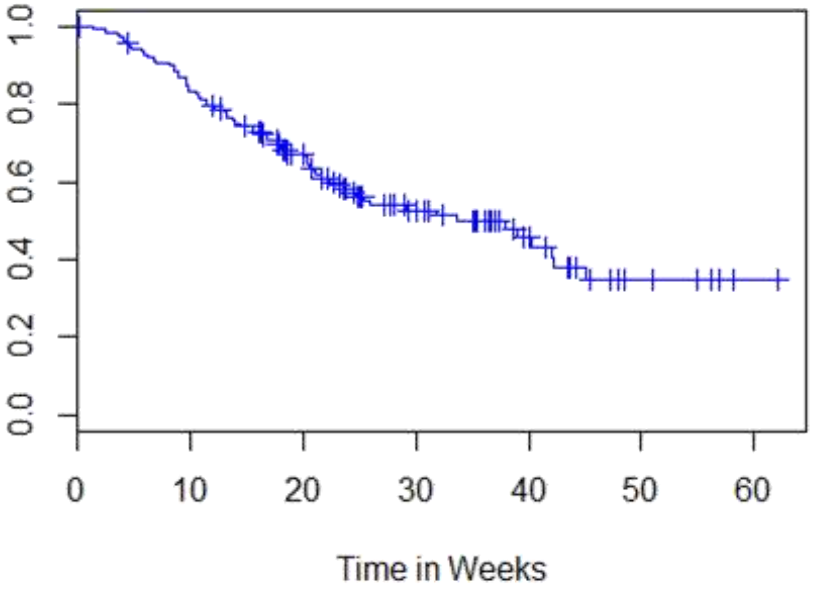


Table 27. SAS output for time to death from any cause Two-stage-adjusted OS KM analysis for the chemotherapy treatment group using the simple model

[redacted]

IPCW crossover adjustment

Please note that the KM analysis for the adjusted OS using the IPCW method cannot be provided. This method censors patients at the time of the treatment switch and therefore the adjustment is not done at the patient level; additionally, only the adjusted hazard ratio was estimated.

e. Time to disease progression or death (PFS) Kaplan-Meier analysis based on investigator assessment, stratified by treatment group.

Figure 9. Time to disease progression or death: PFS KM analysis based on investigator assessment, stratified by treatment group

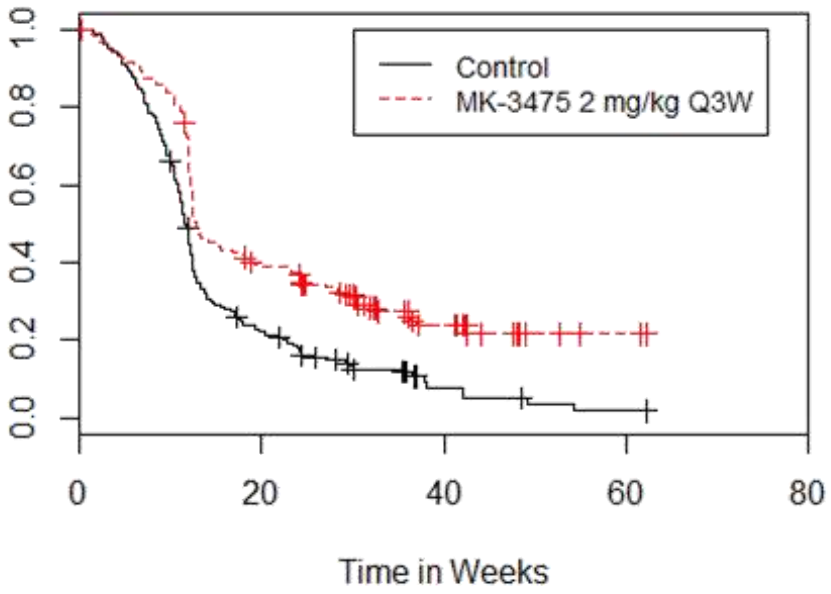


Table 28. SAS output for time to disease progression or death: PFS KM analysis based on investigator assessment, stratified by treatment group (chemotherapy/control vs. pembrolizumab 2mg/kg Q3W)

[redacted]

f. Time from disease progression by investigator assessment to death from any cause (PPS) Kaplan-Meier analysis for the pembrolizumab 2mg/kg treatment group.

Figure 10. Time to disease progression by investigator assessment to death from any cause: PPS KM analysis for the pembrolizumab 2mg/kg treatment group

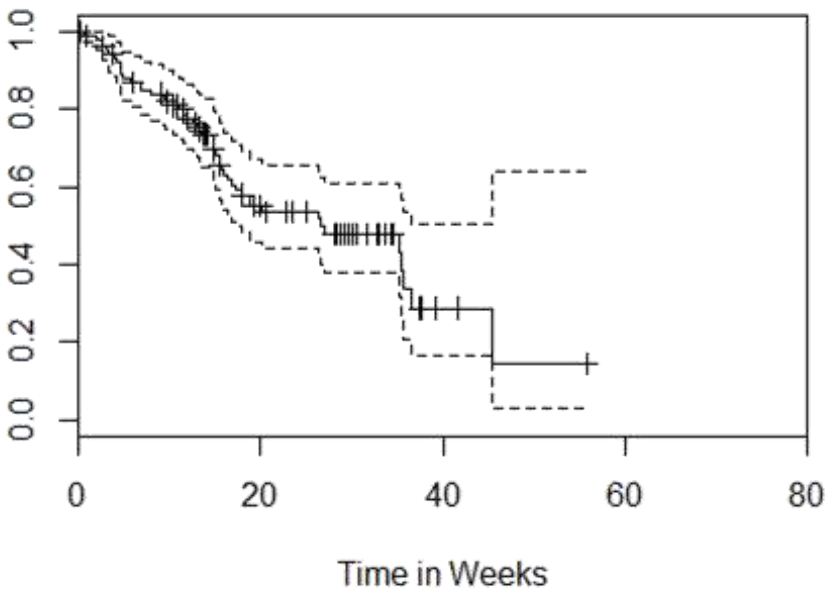


Table 29. SAS output for time to disease progression by investigator assessment to death from any cause: PPS KM analysis for the pembrolizumab 2mg/kg treatment group

[redacted]

g. Time from disease progression by investigator assessment to death from any cause (post-progression survival [PPS]) Kaplan-Meier analysis for the comparator group, without adjustment for crossover, stratified by those who did and those who did not crossover following disease progression.

Figure 11. Time to disease progression by investigator assessment to death from any cause: PPS KM analysis for the comparator group, without adjustment for crossover, stratified by those who did and those who did not crossover following disease progression

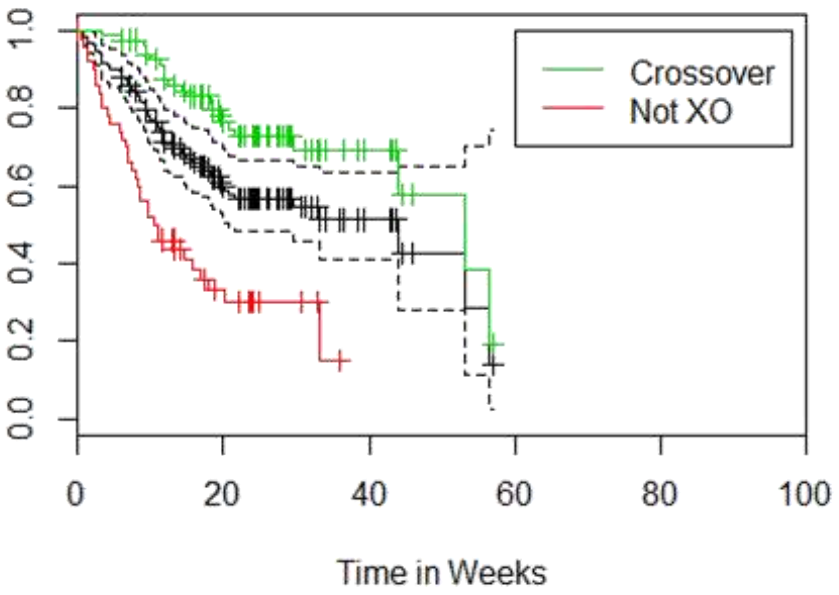


Table 30. SAS output for time to disease progression by investigator assessment to death from any cause: PPS KM analysis for the chemotherapy group

[redacted]

Table 31. SAS output for time to disease progression by investigator assessment to death from any cause: PPS KM analysis for the comparator group, without adjustment for crossover, stratified (not crossover vs. crossover)

g. Time from disease progression by investigator assessment to death from any cause (PPS) Kaplan-Meier analysis for the comparator group, separately for each method of crossover adjustment (RPSFT, 2-stage simple, 2-stage all covariates, IPCW).

RPSFT crossover adjustment

We cannot provide the “correct” KM analysis on PPS for the RPSFT method since the time to PD was not included as part of the RPSFT correction. Thus, if we want the adjusted PPS for RPSFT method, by taking the difference of simulated OS from RPSFT and real observed time-to-PD data, some PPS will be negative, preventing us being able to generate the “correct” KM analysis for PPS.

Two-stage crossover adjustment

Figure 12. Time to disease progression by investigator assessment to death from any cause: PPS KM analysis for the comparator group, adjusted using the two-stage crossover method (full model, all covariates adjusted)

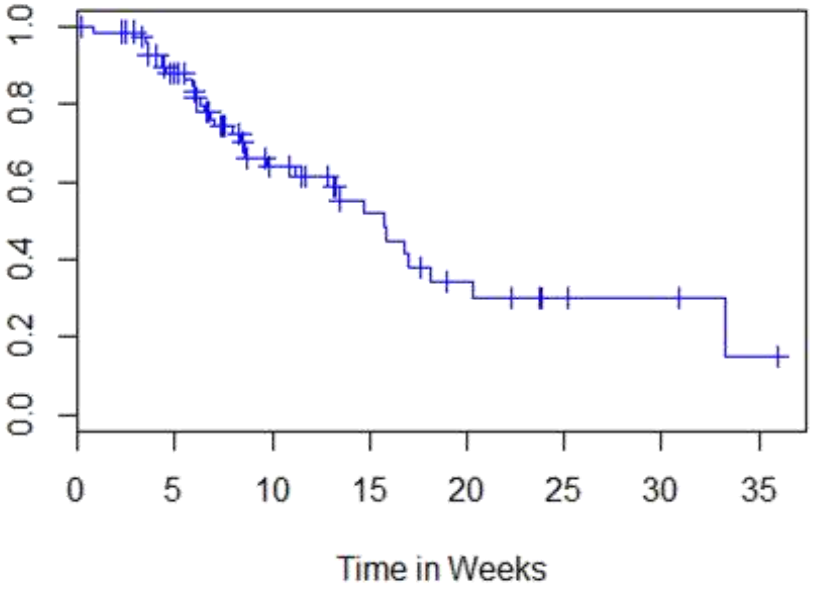


Table 32. SAS output for time to disease progression by investigator assessment to death from any cause: PPS KM analysis for the comparator group, adjusted using the two-stage crossover method (full model, all covariates adjusted)

[redacted]

Figure 13. Time to disease progression by investigator assessment to death from any cause: PPS KM analysis for the comparator group, adjusted using the two-stage crossover method (simple model)

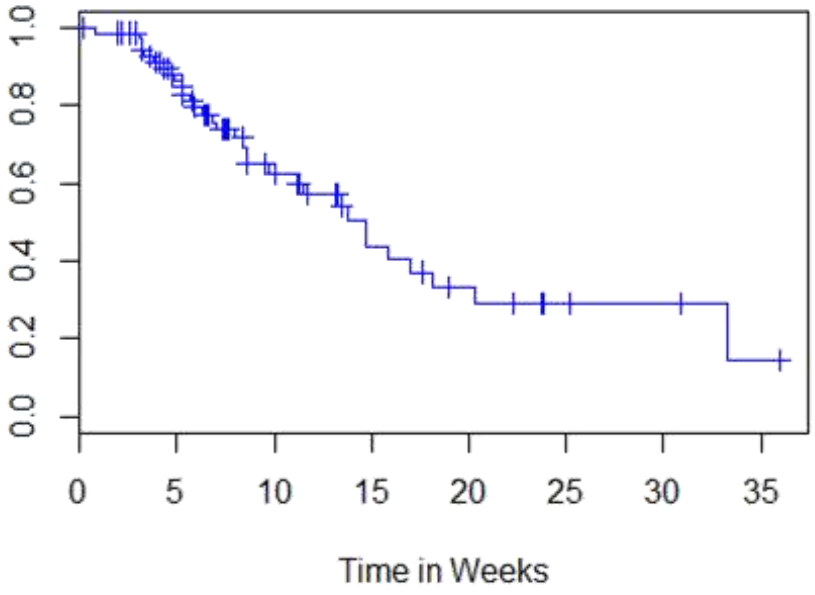


Table 33. SAS output for time to disease progression by investigator assessment to death from any cause: PPS KM analysis for the comparator group, adjusted using the two-stage crossover method (simple model)

[redacted]

IPCW crossover adjustment

Please note that the KM analysis for the adjusted PPS using the IPCW method cannot be provided. This method censors patients at the time of the treatment switch and therefore the adjustment is not done at the patient level; additionally, only the adjusted hazard ratio was estimated.

h. Time to treatment discontinuation Kaplan-Meier analysis.

Figure 14. Time to treatment discontinuation for the pembrolizumab 2mg/kg Q3W treatment arm

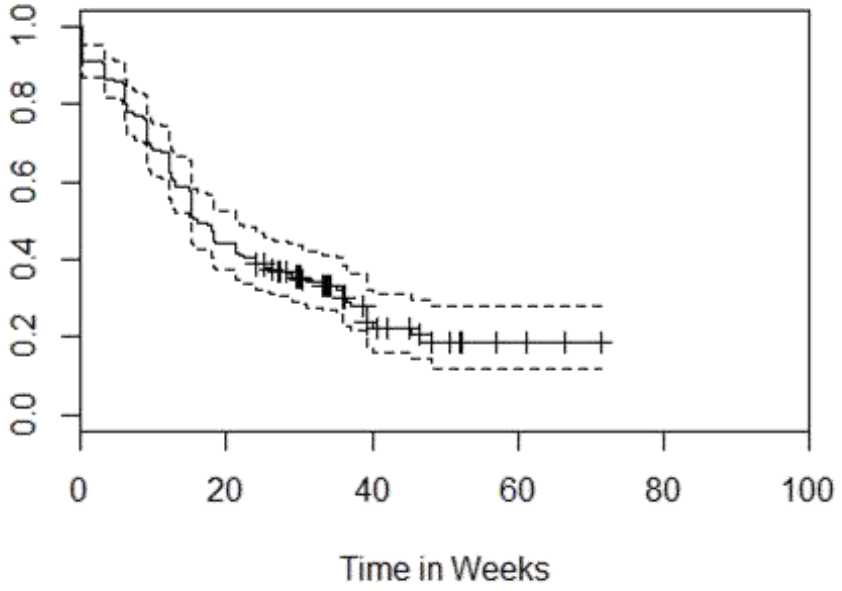


Table 34. SAS output for time to treatment discontinuation for the pembrolizumab 2mg/kg Q3W treatment arm

[redacted]

B2. **Priority question:** The use of secondary data sources for projection of short-term differences in survival to long-term gains requires compatibility between the trial and the secondary sources, in terms of those patient characteristics known to influence survival. In particular, the duration of diagnosed melanoma at baseline in the trial is important in assessing the validity of the manner in which secondary data sources are used to project survival beyond the trial period. Please provide a table summarising the baseline characteristics as shown in Table 16 of the company's submission, together with the time since initial diagnosis of malignant melanoma (mean and range) of patients in the KEYNOTE-002 trial for the 3 subgroups: 'pembrolizumab treated (2mg/kg)', 'comparator treated without crossover', 'comparator treated with crossover'.

Table 35. Baseline characteristics of patients in KEYNOTE-002 per treatment group, including the time since initial diagnosis of malignant melanoma

	Pembrolizumab 2mg/kg Q3W n = 180	Control without crossover n = 93	Control with crossover n = 86
Age, (years); mean (range)	59.5 (15.0-87.0)	60.5 (29.0-87.0)	60.5 (27.0-84.00)
Male	58%	67%	61%
ECOG			
0	54%	47%	64%
1	44%	53%	36%
Missing	1%	-	-
BRAF status			
Mutant	24%	25%	21%
Wild Type	76%	75%	79%
Prior Brain metastasis			
Yes	15.6%	28.0%	15.1%
LDH Level			
Normal	55%	53%	68%
Elevated	43%	46%	29%
Unknown	1%	1%	2%
Missing	1%	-	1%
Baseline tumour size*(mm); mean (range)	121.9 (10.0-428.0)	139.9 (11.0-568.0)	110.2 (17.0-428.0)
M stage			
M0	0.6%	0.0%	2.3%
M1a	5.0%	5.4%	11.6%
M1b	12.2%	7.5%	9.3%
M1c	82.2%	87.1%	76.7%
Prior line of therapies			
0	0.6%	0.0%	0.0%
1	22.2%	25.8%	26.7%
2	43.9%	40.9%	46.5%

3	17.8%	17.2%	18.6%
4	6.7%	8.6%	4.7%
≥5	8.9%	7.5%	3.5%
Previous therapy			
Immunotherapy, excluding IL-2 and IPI	13.9%	14.0%	11.6%
Chemotherapy	50.0%	49.5%	46.5%
BRAF Therapy	25.6%	28.0%	19.8%
Time (in days) since initial diagnosis of malignant melanoma; mean (range)	1422 (235-9765)	1275 (66-7088)	1536 (270-7094)

*Baseline tumour size was calculated as the sum of the longest diameters of all target lesions for patients with measurable disease by RECIST 1.1 criteria (version 1.1) by independent central review at baseline

B3. **Priority question:** The ERG wishes to assess whether there is clinical and analytical evidence of heterogeneity in the KEYNOTE-002 as it may prove important in establishing the appropriateness of the methods used to project survival in the model. Please provide a table summarising the same baseline characteristics of patients in the KEYNOTE-002 trial as in B2, but splitting each subgroup into 2 approximately equal sections (patients who progressed or died early versus patients who progressed or died later or who remained alive and progression-free at the time of data cut, that is a 50/50 split).

We have split the subgroups by considering the median PFS as the cut-off point to divide the groups, as this provided a balanced split in terms of number of patients within each treatment subgroup (pembrolizumab 2mg/kg Q3W, control without crossover and control with crossover) with a PFS shorter vs. longer than the median PFS. The results are presented below, in Table 36.

Table 36. Baseline characteristics per treatment subgroup, with categories generated according to duration of PFS (i.e. with PFS shorter vs. longer than the median PFS)

	Pembrolizumab 2mg/kg Q3W Median PFS = 88.2 days		**Control without crossover** Median PFS = 79.4 days		**Control with crossover** Median PFS = 83.6 days	
	PFS ≤ Median PFS within subgroup	**PFS > Median PFS within subgroup**	**PFS ≤ Median PFS within subgroup**	**PFS ≤ Median PFS within subgroup**	**PFS > Median PFS within subgroup**	**PFS ≤ Median PFS within subgroup**
Number of patients (N)	88	89	42	88	89	42
Age, (years, mean, range)	58.6 (15.0-84.0)	60.4 (23.0-87.0)	59.5 (31.0-69.0)	62.3 (29.0-72.5)	58.3 (27.0-84.0)	62.7 (43.0-84.0)
Male	55%	63%	69%	65%	55%	64%
ECOG						
0	47%	64%	36%	60%	55%	71%
1	53%	35%	64%	40%	45%	29%
Missing	1%	1%	-	-	-	-
BRAF status						

Mutant	32%	17%	26%	19%	25%	18%
Wild Type	68%	83%	74%	81%	75%	82%
Prior Brain metastasis						
Yes	16%	16%	29%	26%	23%	9%
LDH Level						
Normal	44%	65%	31%	70%	65%	71%
Elevated	53%	34%	69%	30%	33%	24%
Unknown	1%	0%	0%	0%	0%	4%
Missing	1%	1%	0%	0%	3%	0%
Baseline tumour size*(mm; mean, range)	143.8 (16.0-428.0)	99.9 (10.0-393.0)	187.4 (22.0-568.0)	99.4 (20.0-281.0)	115.3 (19.0-428.0)	104.1 (17.0-303.0)
M stage						
M0	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%
M1a	3.4%	6.7%	2.4%	7.0%	5.0%	17.8%
M1b	8.0%	14.6%	0.0%	14.0%	10.0%	8.9%
M1c	87.5%	78.7%	97.6%	79.1%	85.0%	68.9%
Prior line of therapies						
0	1.1%	0.0%	0.0%	0.0%	0.0%	0.0%
1	17.0%	28.1%	33.3%	20.9%	30.0%	24.4%
2	43.2%	44.9%	23.8%	55.8%	42.5%	51.1%
3	20.5%	13.5%	23.8%	11.6%	15.0%	20.0%
4	9.1%	4.5%	11.9%	4.7%	7.5%	2.2%
≥5	9.1%	9.0%	7.1%	7.0%	5.0%	2.2%
Previous therapy						
Immunotherapy, excluding IL-2 and IPI	14.8%	13.5%	14.3%	14.0%	12.5%	11.1%
Chemotherapy	50.0%	50.6%	45.2%	51.2%	47.5%	44.4%
BRAF Therapy	31.8%	19.1	28.6%	18.6%	25.0%	15.6%
The time (in days) since initial diagnosis of malignant melanoma	1359 (251-9765)	1458 (235-4780)	1160 (145-6449)	1423 (66-7088)	1400 (270-6191)	1656 (424-7094)
Number of patients with an observed PFS time < median PFS and with missing endpoint**	3		8		1	

*Baseline tumour size was calculated as the sum of the longest diameters of all target lesions for patients with measurable disease by RECIST 1.1 criteria (version 1.1) by independent central review at baseline

**Unclear whether the event happened before or after the median PFS time, that is, patients were censored prior to reaching the median PFS within the subgroup.

B4. **Priority question:** The company's model assumes that all patients enter the trial at a fixed age, and with fixed proportions of males and females. A detailed age/sex breakdown would allow the ERG to assess the magnitude of any bias introduced by this effect. Please provide a table showing the baseline age-sex distribution of patients in the KEYNOTE-002 trial in 5 year age bands (under 20, 20-24,25-29,etc.), for patients in the pembrolizumab 2mg/kg treated arm, and separately for comparator treated patients who did or who did not crossover on disease progression.

Table 37. Baseline distribution in the KEYNOTE-002 trial by age (in 5-year intervals), sex and treatment arm (pembrolizumab 2mg/kg Q3W, chemotherapy arm without crossover and chemotherapy arm with crossover)

Age	Pembrolizumab 2mg/kg Q3W		Control without crossover		Control with crossover	
	Female	Male	Female	Male	Female	Male
<20	0	1	0	0	0	0
20-24	3	1	0	0	0	0
25-29	1	1	1	0	1	0
30-34	2	4	1	1	0	1
35-39	3	2	0	3	0	0
40-44	5	6	3	4	3	4
45-49	5	10	4	5	3	6
50-54	10	7	2	3	2	9
55-59	4	17	6	6	7	3
60-64	9	11	1	12	2	5
65-69	6	16	4	8	7	11
70-74	14	11	6	11	6	8
75-79	7	15	3	5	1	3
80-84	7	2	0	4	2	2

B5. **Priority question:** Although the KEYNOTE-002 utility results have been calculated using the UK tariff of social values, a substantial proportion of EQ-5D responders are from US residents. The ERG considers it important to consider any uncertainty introduced into the cost-effectiveness results from including data from US responders. Please provide results for EQ-5D scores in the KEYNOTE-002 trial split between US and non-US patients for Appendix 20 Tables 3, 5, 7 and 9.

In light of the ERG request MSD has undertaken further analyses on the EQ-5D scores in the KEYNOTE-002 trial by splitting the results between US and non-US patients for the aforementioned Appendix 20 tables 3, 5, 7, and 9 of the original MSD submission [ID760].

Please note that the aforementioned table 7 and table 9 of the Appendix 20 of the MSD submission [ID760] are relative to INV assessment while we consistently used IRO assessment results in the economic model (see MSD answer to question B6). Of note, progression-based utilities, by IRO assessment, were implemented in sensitivity analyses. For consistency, we have also provided the progression-based utilities tables for US and non-US patients by IRO assessment as well as the EQ-5D health utility scores in progression-free state: with and without grade 3-5 AEs tables for US and non-US patients by IRO assessment.

Please find below the requested tables (see Table 38, Table 39, Table 40, Table 41, Table 42, Table 43, Table 46, Table 47, Table 46, Table 47, Table 48 and Table 49):

a) Baseline utilities

Table 38: Baseline utilities by treatment group, UK algorithm, US population

	MK3475 2 mg					Chemotherapy					MK3475 2 mg + Chemotherapy				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
Baseline	81	81	0.80	0.02	(0.76, 0.84)	86	86	0.78	0.02	(0.74, 0.82)	167	167	0.79	0.01	(0.76, 0.82)

† n=Number of patient with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score
EQ-5D index score during crossover is not included

Table 39: Baseline utilities by treatment group, UK algorithm, non-US population

	MK3475 2 mg					Chemotherapy					MK3475 2 mg + Chemotherapy				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
Baseline	85	85	0.70	0.03	(0.65, 0.76)	69	69	0.70	0.03	(0.64, 0.76)	154	154	0.70	0.02	(0.66, 0.74)

† n=Number of patient with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score
EQ-5D index score during crossover is not included

b) EQ-5D health utility scores analysis by time to death

Table 40: EQ-5D health utility scores analysis by time to death – UK algorithm, US population

Time to Death (days)	MK3475 2 mg					Chemotherapy					MK3475 2 mg + Chemotherapy				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
≥180*	49	128	0.81	0.02	(0.78, 0.84)	42	102	0.78	0.02	(0.74, 0.83)	91	230	0.80	0.01	(0.77, 0.83)
[90, 180)	17	30	0.63	0.05	(0.54, 0.72)	12	24	0.75	0.02	(0.70, 0.79)	29	54	0.68	0.03	(0.62, 0.74)
[30, 90)	14	18	0.59	0.06	(0.45, 0.72)	15	22	0.60	0.07	(0.46, 0.74)	29	40	0.60	0.05	(0.50, 0.69)
<30	5	5	0.52	0.19	(-.00, 1.03)	8	8	0.50	0.06	(0.36, 0.65)	13	13	0.51	0.08	(0.34, 0.67)

† n=Number of patient with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score
EQ-5D index score during baseline and crossover is not included
* This group also includes patients whose death dates were censored and report EQ5D during this time.

Table 41: EQ-5D health utility scores analysis by time to death – UK algorithm, non-US population

Time to Death (days)	MK3475 2 mg					Chemotherapy					MK3475 2 mg + Chemotherapy				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
≥180*	48	116	0.75	0.03	(0.70, 0.80)	40	79	0.71	0.03	(0.66, 0.76)	88	195	0.73	0.02	(0.70, 0.77)
[90, 180)	18	32	0.57	0.06	(0.45, 0.70)	18	30	0.55	0.05	(0.44, 0.65)	36	62	0.56	0.04	(0.48, 0.64)
[30, 90)	18	24	0.43	0.07	(0.29, 0.57)	17	20	0.46	0.06	(0.34, 0.58)	35	44	0.44	0.04	(0.36, 0.53)
<30	9	10	0.30	0.13	(0.01, 0.60)	3	3	0.40	0.26	(-.71, 1.50)	12	13	0.33	0.11	(0.08, 0.57)

† n=Number of patient with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score
EQ-5D index score during baseline and crossover is not included
* This group also includes patients whose death dates were censored and report EQ5D during this time.

c) EQ-5D health utility score analysis based on progression from KEYNOTE-002 trial (by INV assessment)

Table 42: EQ-5D health utility scores (progression by INV assessment) – UK algorithm, US population

	MK3475 2 mg					Chemotherapy					MK3475 2 mg + Chemotherapy				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
Progression-Free	81	237	0.80	0.01	(0.77, 0.83)	85	182	0.77	0.02	(0.74, 0.80)	166	419	0.78	0.01	(0.76, 0.81)
On treatment	80	236	0.80	0.01	(0.78, 0.83)	81	170	0.78	0.02	(0.75, 0.81)	161	406	0.79	0.01	(0.77, 0.81)
Off treatment	1	1	-0.07	.	NA	11	12	0.62	0.04	(0.52, 0.71)	12	13	0.56	0.07	(0.42, 0.71)
Progressive	40	54	0.74	0.03	(0.67, 0.81)	56	73	0.71	0.03	(0.64, 0.77)	96	127	0.72	0.02	(0.67, 0.76)

† n=Number of patient with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score
EQ-5D index score during baseline and crossover is not included

Table 43: EQ-5D health utility scores (progression by INV assessment) – UK algorithm, non-US population

	MK3475 2 mg					Chemotherapy					MK3475 2 mg + Chemotherapy				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
Progression-Free	84	220	0.71	0.02	(0.67, 0.74)	61	118	0.67	0.02	(0.62, 0.72)	145	338	0.69	0.02	(0.66, 0.72)
On treatment	81	215	0.71	0.02	(0.68, 0.75)	56	108	0.69	0.02	(0.64, 0.74)	137	323	0.71	0.02	(0.68, 0.74)
Off treatment	4	5	0.31	0.13	(-0.06, 0.68)	10	10	0.45	0.11	(0.21, 0.69)	14	15	0.40	0.08	(0.23, 0.58)
Progressive	35	52	0.58	0.06	(0.47, 0.70)	46	63	0.65	0.03	(0.58, 0.71)	81	115	0.62	0.03	(0.56, 0.68)

† n=Number of patient with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score
EQ-5D index score during baseline and crossover is not included

d) EQ-5D health utility score analysis based on progression from KEYNOTE-002 trial (by IRO assessment)

Table 44: EQ-5D health utility scores (progression by IRO assessment) – UK algorithm, US population

	MK3475 2 mg					Chemotherapy					MK3475 2 mg + Chemotherapy				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
Progression-Free	80	224	0.80	0.01	(0.78, 0.83)	86	178	0.77	0.02	(0.74, 0.80)	166	402	0.79	0.01	(0.77, 0.81)
On treatment	79	221	0.81	0.01	(0.78, 0.83)	81	161	0.78	0.02	(0.74, 0.81)	160	382	0.79	0.01	(0.77, 0.82)
Off treatment	3	3	0.53	0.32	(-0.84, 1.89)	16	17	0.68	0.05	(0.58, 0.78)	19	20	0.66	0.06	(0.53, 0.78)
Progressive	46	67	0.73	0.03	(0.67, 0.79)	56	77	0.71	0.03	(0.65, 0.77)	102	144	0.72	0.02	(0.68, 0.76)

† n=Number of patient with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score
EQ-5D index score during baseline and crossover is not included

Table 45: EQ-5D health utility scores (progression by IRO assessment) – UK algorithm, non-US population

	MK3475 2 mg					Chemotherapy					MK3475 2 mg + Chemotherapy				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
Progression-Free	84	212	0.70	0.02	(0.65, 0.74)	61	119	0.68	0.02	(0.63, 0.72)	145	331	0.69	0.02	(0.66, 0.72)
On treatment	81	207	0.71	0.02	(0.67, 0.75)	56	108	0.69	0.02	(0.64, 0.74)	137	315	0.70	0.02	(0.67, 0.73)
Off treatment	4	5	0.27	0.16	(-0.17, 0.72)	10	11	0.57	0.08	(0.39, 0.75)	14	16	0.48	0.08	(0.31, 0.64)
Progressive	39	60	0.63	0.05	(0.54, 0.73)	46	62	0.64	0.04	(0.56, 0.71)	85	122	0.63	0.03	(0.58, 0.69)

† n=Number of patient with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score
EQ-5D index score during baseline and crossover is not included

e) EQ-5D health utility scores in progression-free state: with and without Grade 3-5 AEs (progression by INV assessment)

Table 46: EQ-5D health utility scores in progression-free state: with and without grade 3-5 AEs (progression by INV assessment), UK algorithm, US population

	MK3475 2 mg					Chemotherapy					MK3475 2 mg + Chemotherapy				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
During Grade3-5 AEs	16	38	0.59	0.05	(0.50, 0.69)	24	51	0.65	0.04	(0.57, 0.73)	40	89	0.63	0.03	(0.56, 0.69)
Other w/o Grade3-5 AEs	73	213	0.82	0.01	(0.79, 0.84)	75	143	0.78	0.02	(0.75, 0.81)	148	356	0.80	0.01	(0.78, 0.82)

† n=Number of patient with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score
EQ-5D index score during baseline and crossover is not included

Table 47: EQ-5D health utility scores in progression-free state: with and without grade 3-5 AEs (progression by INV assessment), UK algorithm, non-US population

	MK3475 2 mg					Chemotherapy					MK3475 2 mg + Chemotherapy				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
During Grade3-5 AEs	25	49	0.49	0.05	(0.39, 0.59)	15	25	0.55	0.06	(0.42, 0.67)	40	74	0.51	0.04	(0.43, 0.59)
Other w/o Grade3-5 AEs	68	183	0.75	0.02	(0.71, 0.79)	50	95	0.70	0.03	(0.64, 0.75)	118	278	0.73	0.02	(0.70, 0.76)

† n=Number of patient with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score
EQ-5D index score during baseline and crossover is not included

f) EQ-5D health utility scores in progression-free state: with and without Grade 3-5 AEs (progression by IRO assessment)

Table 48: EQ-5D health utility scores in progression-free state: with and without grade 3-5 AEs (progression by INV assessment), UK algorithm, US population

	MK3475 2 mg					Chemotherapy					MK3475 2 mg + Chemotherapy				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
During Grade3-5 AEs	14	31	0.62	0.05	(0.53, 0.72)	23	48	0.65	0.04	(0.56, 0.73)	37	79	0.64	0.03	(0.57, 0.70)
Other w/o Grade3-5 AEs	73	204	0.82	0.01	(0.79, 0.85)	75	142	0.78	0.02	(0.74, 0.81)	148	346	0.80	0.01	(0.78, 0.82)

† n=Number of patient with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score
EQ-5D index score during baseline and crossover is not included

Table 49: EQ-5D health utility scores in progression-free state: with and without grade 3-5 AEs (progression by INV assessment), UK algorithm, non-US population

	MK3475 2 mg					Chemotherapy					MK3475 2 mg + Chemotherapy				
	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI	n†	n‡	Mean	SE	95% CI
During Grade3-5 AEs	24	48	0.46	0.05	(0.36, 0.57)	15	25	0.55	0.06	(0.42, 0.67)	39	73	0.49	0.04	(0.41, 0.57)
Other w/o Grade3-5 AEs	68	174	0.75	0.02	(0.71, 0.79)	51	96	0.70	0.02	(0.66, 0.75)	119	270	0.73	0.02	(0.70, 0.76)

† n=Number of patient with non-missing EQ-5D index score
‡ n=Number of records with non-missing EQ-5D index score
EQ-5D index score during baseline and crossover is not included

Please note that the utilities presented in Table 38 to Table 49 are lower in the non-US population compared to US population except for Table 42. For the latter (i.e. US population), only 1 patient is reported in progression-free health state off-treatment which could explain why the mean value is lower than for the non-US population.

In addition to the ERG request MSD has re-run the base case scenario only taking into account the non-US patients time to death utilities (see Table 41) to measure their impact on the base-case ICER results.

As per the methodology employed in the original submission, we have re-run the base-case scenario taking into account the above (Table 41) pooled utilities (i.e. MK3475 2 mg + chemotherapy). We obtain the below ICERs (see Table 50).

Table 50: Incremental analysis taking into account utilities derived from non-US patients only; results discounted with PAS

	Total Costs	Total LYs	Total QALYs	Incremental costs	Incremental QALYs	Incremental LYS	ICER
BSC	£15,960	1.51	0.99	£50,995	1.109	1.592	£45,968
Pembrolizumab	£66,955	3.10	2.10				

The lower utility-results obtained in the non-US patients slightly impact the total number of quality-adjusted life years (QALYs). Table 50 presents lower QALYs (0.99 for BSC and 2.10 for pembrolizumab) compared to the base case presented in the submission (1.07 for BSC and 2.26 for pembrolizumab) (see table 82 page 195 of the original MSD submission [ID760]).

These lower QALYs result in a slightly higher ICER (i.e. £45,968) compared to the original submission (i.e. £42,923).

B6. Neither the company's submission nor the submitted model state which definition of assessment was selected when analysing KEYNOTE-002 trial data for inclusion in the model. Please clarify whether model PFS projections are based on IRO or INV of disease progression.

We have consistently used the IRO disease progression estimates to model PFS projections. The reason for this is that, as described in the KEYNOTE-002 clinical study report,[2] the primary method of analysis for PFS is by IRO assessments in the ITT population based on RECIST 1.1. Whereas PFS based on the Investigator (INV) assessment and the independent radiologists plus an adjudicator if needed (i.e., IRC assessment without the oncology assessment) were conducted as supportive analyses to evaluate the robustness of the PFS results.

B7. Please explain why on page 155 you consider the two-stage crossover model which included all the covariates to be the most conservative.

Both the full and the simple models used to adjust for crossover using the two-stage adjustment resulted in statistically significant differences between pembrolizumab 2mg/kg and the chemotherapy adjusted arm. However, the two-stage full covariate adjustment model was considered to be the more conservative of the two models applied because the crossover-adjusted median OS estimated for the chemotherapy arm was higher and the hazard ratio for OS for the treatment effect of pembrolizumab 2mg/kg Q3W versus the chemotherapy comparator adjusted for crossover was lower than those estimated with the simple model, , leading to a smaller estimated treatment effect for pembrolizumab, as presented in Table 51 below.

Table 51. Median OS and hazard ratio OS results for the full and simple models obtained with the two-stage crossover adjustment using progressive disease as the secondary baseline

Model (full or simple)	Median OS for Control (weeks)	95% CI	Hazard Ratio (Treatment vs. Control) p value	95% CI
Full	34.43	(23.48, 42.09)	0.6328 p=0.007*	(0.4525, 0.8843)
Simple	33.91	(23.28, 42.07)	0.6272 p=0.006*	(0.4488, 0.8766)

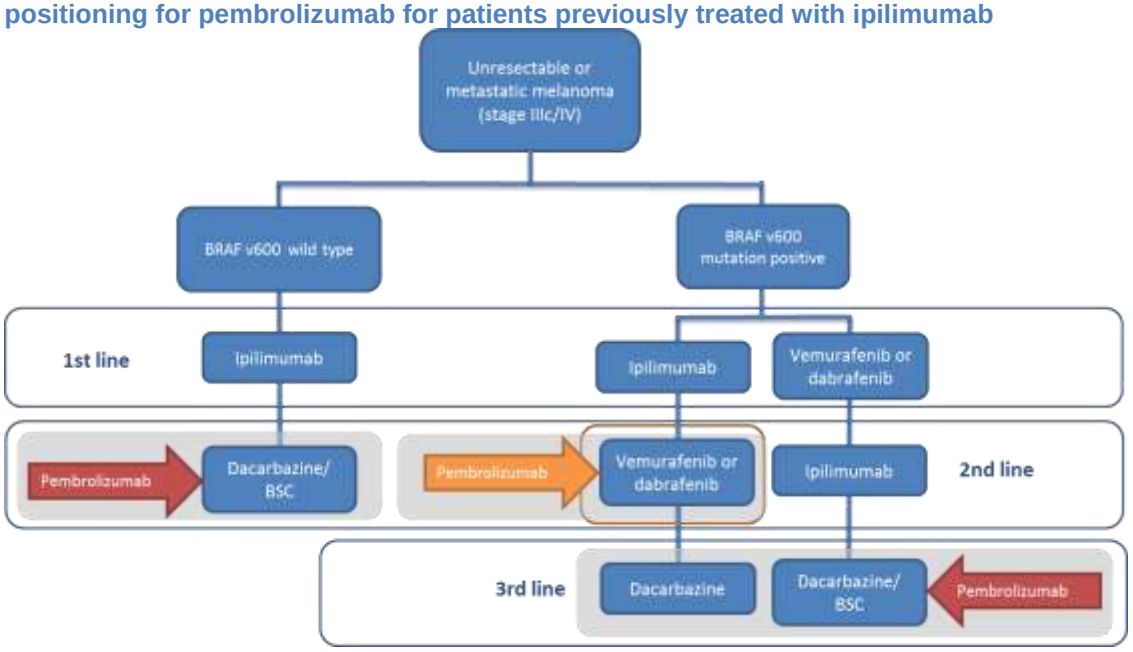
B8. Please clarify the following inconsistency. On page 32 of the company's submission, it is claimed that "Therefore, pembrolizumab is expected to displace the use of BSC (including dacarbazine) to further subsequent lines of treatment for patients experiencing disease progression" and on page 136 it is restated that "it is expected that pembrolizumab would be used prior to chemotherapy treatment where possible". However your economic model did not include post progression therapy (including dacarbazine) after progression with pembrolizumab. Clinical advice to the ERG also suggested that there might be situations where clinicians may also prefer to use BRAF inhibitors after treatment with pembrolizumab, as opposed to prior to this. Therefore, please clarify whether Figure 3 in the company's submission may need adapting and these 2 scenarios considered.

Within our submission, our population of interest focused on "Adults with unresectable or metastatic melanoma who have progressed after being previously treated with ipilimumab and, if BRAFV600 mutation positive, a BRAF or MEK inhibitor", to reflect the population of interest covered by the key clinical trial supporting this submission (KEYYNOTE-002). This was also consistent with what we had previously believed would be our initial licence. As communicated to NICE

on 5th May 2015, on the day of submission we received a 'provisional draft' SmPC, which stated a broader indication "Treatment of adults with unresectable or metastatic melanoma", without specifying any requirement that patients who are BRAF mutation positive must have received prior treatment with a BRAF inhibitor before being eligible to receive pembrolizumab (this document had been included as Appendix 1 of the submission).

On 21st May 2015 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for pembrolizumab for the treatment of advanced (unresectable or metastatic) melanoma in adults. Consequently, at this moment our licence indication is not expected to include a requirement for patients with BRAF positive mutations to have received prior treatment with a BRAF inhibitor. In this situation, we agree that BRAF inhibitors could be administered after the use of pembrolizumab, as stated in the updated treatment pathway presented in Figure 15 below.

Figure 15. Updated treatment algorithm for unresectable or metastatic melanoma with proposed positioning for pembrolizumab for patients previously treated with ipilimumab



It is important to note that the KEYNOTE-002 trial required all patients who were BRAFV600 positive to have received prior treatment with a BRAF/MEK inhibitor as an inclusion criterion. Therefore, no data could have been drawn from our KEYNOTE-002 trial to inform comparisons of pembrolizumab versus BRAF inhibitors in BRAFV600 mutation positive patients previously treated with ipilimumab. Additionally, from the non-randomised Part B1 of the Phase 1 KEYNOTE-001 trial the only available data was from a total of 5 patients who were BRAF positive but who had not received a BRAF inhibitor. Given the very

small patient numbers, it would have been inappropriate to use this data as an evidence base from which to draw any meaningful conclusions.

Consequently, when considering the population of patients previously treated with ipilimumab we are aware that there is a small subgroup of patients that have not been covered by the initial submission, but who would be eligible to receive pembrolizumab based on the wording of the proposed licence indication – namely those patients who are BRAF mutation positive, but who receive ipilimumab first line rather than a BRAF inhibitor. Considering the group of advanced melanoma patients, we have estimated this proportion of patients to be around 16.3% (see question C4 below).

The economic model did not include post-progression chemotherapy (including dacarbazine) after progression with either pembrolizumab or best supportive care as such therapy would most likely be used on both arms of the model, has not demonstrated any impact on OS in melanoma and is of relatively low cost.

Section C: Textual clarifications, references and additional points

C1. The ERG appreciates the company providing the clinical study reports for KEYNOTE-002 and KEYNOTE-001 (part B2) which include the statistical analysis plans. In addition, please provide the study protocols for these 2 trials.

As requested, please find enclosed the study protocols for KEYNOTE-002 and KEYNOTE-001 (covering part B2).

C2. The ERG notes that although not statistically significant, compared with patients receiving 2mg/kg, OS appears to be improved in patients receiving 10mg/kg in both KEYNOTE-001 (part B2) and KEYNOTE-002 whereas response rates in KEYNOTE-
001 (part B1) also appear to be improved with the higher dose (particularly when administered fortnightly). Please provide more context as to why the 2mg/kg dose is preferred over the 10mg/kg dose.

Our positive CHMP opinion indicates that our 2mg/kg dose will be the licensed dose. In the population covered by this submission, no clinically or statistically significant difference in efficacy or safety has been observed between the two pembrolizumab Q3W doses (2 mg/kg and 10 mg/kg). In addition, please note that the latest draft version of the European summary of product characteristics (see updated draft of pembrolizumab SmPC attached) stipulates that the "recommended dose of KEYTRUDA is 2 mg/kg administered intravenously over 30 minutes every 3 weeks. Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity".

In response to the request, a summary is provided below based on the different clinical trial outcome endpoints that strongly support the regulators agreement that the 2 mg/kg Q3W dose is the appropriate one.

As the ERG notes, there are no statistically significant (or clinically significant) differences in efficacy observed among the two pembrolizumab Q3W doses (2 mg/kg and 10 mg/kg). This is most evident from data in studies with direct comparisons between these two doses. KEYNOTE-002 included 361 subjects randomised to pembrolizumab at 2 mg/kg or 10 mg/kg Q3W, and the primary efficacy endpoint outcomes for the 2 mg/kg and 10 mg/kg Q3W doses were essentially the same with overlapping PFS KM curves (Figure 1 in Appendix 6 of MSD submission document, provided again below as Figure 16) with a hazard ratio for the comparison of the two doses of 0.91 (95% CI 0.71, 1.16, p = 0.43898), and 6-month PFS rates of 34% and 38%, respectively (Table 3 in Appendix 6 of

MSD submission document, provided again below as Table 52).

Figure 16: Appendix 6 of submission document: KEYNOTE-002 - KM of PFS based on central (IRO) assessment (primary censoring rule) – ITT population

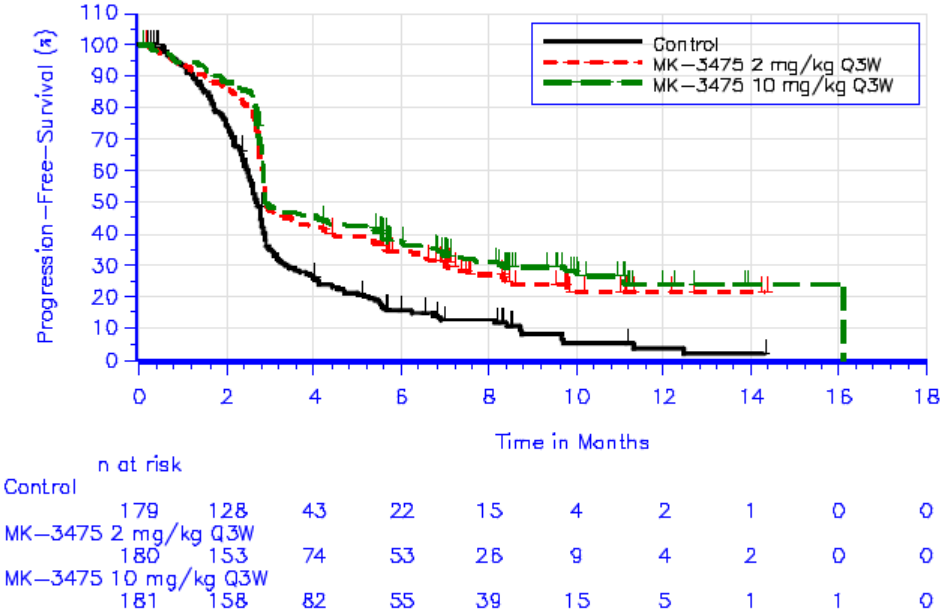


Table 52: Appendix 6 of submission document: KEYNOTE-002 - Analysis of PFS based on central review (IRO assessment) - primary censoring rule - (ITT population)

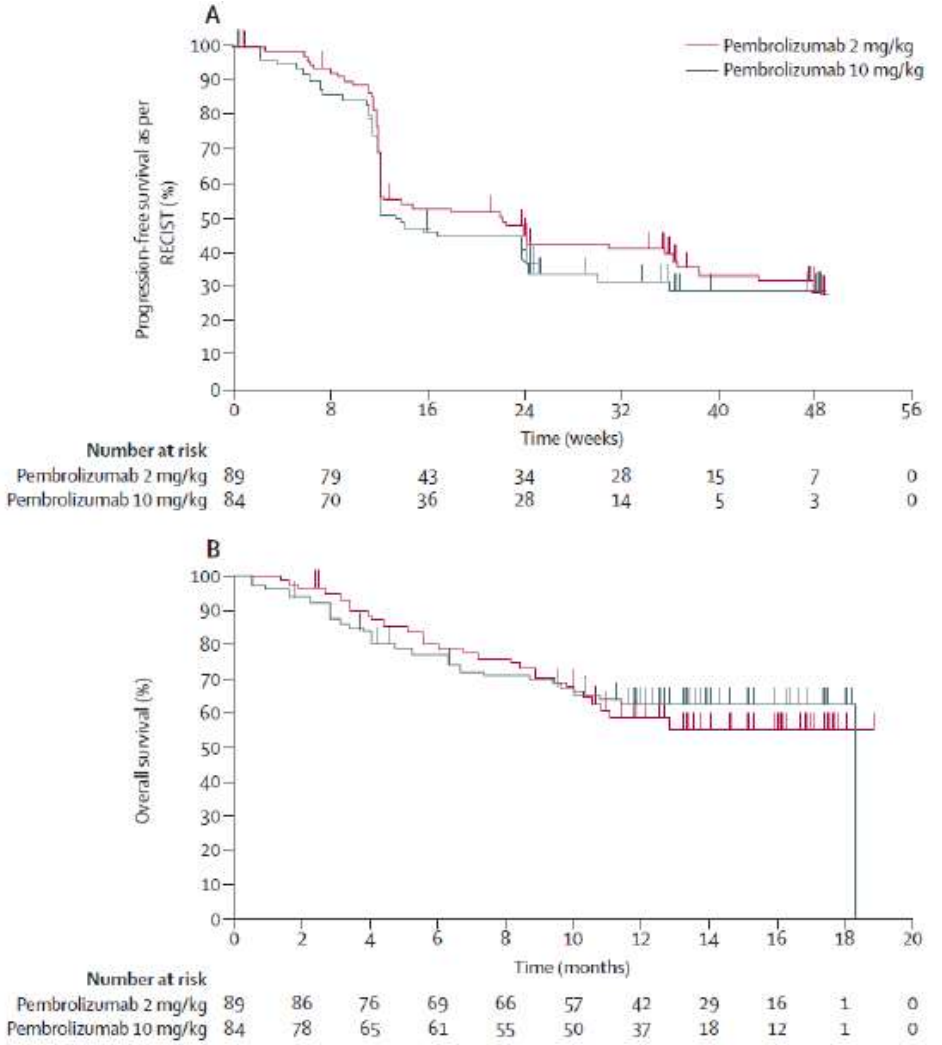
Treatment	N	Number of Events (%)	Person-Months	Event Rate/100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS rate at 6 Months in %† (95% CI)	Treatment vs. control	
							Hazard Ratio‡ (95% CI)‡	p-value§
Control	179	155 (86.6)	584.3	26.5	2.7 (2.5, 2.8)	15.6 (10.5, 21.5)		
Pembrolizumab 2 mg/kg Q3W	180	129 (71.1)	804.6	16.0	2.9 (2.8, 3.8)	34.3 (27.4, 41.3)	0.57 (0.45, 0.73)	<0.0001
Pembrolizumab 10 mg/kg Q3W	181	126 (69.6)	881.1	14.3	2.9 (2.8, 4.7)	37.7 (30.6, 44.8)	0.50 (0.39, 0.64)	<0.0001
Pairwise Comparison							**Hazard Ratio‡ (95% CI)‡**	**p-Value‖**
Pembrolizumab 10 mg/kg Q3W vs. Pembrolizumab 2 mg/kg Q3W							0.91 (0.71, 1.16)	0.4390

† From product-limit (KM) method for censored data.

‡ Based on Cox regression model with treatment as a covariate stratified by ECOG (0 vs. 1), LDH level (normal vs. elevated) and BRAF mutation (mutant vs. wild type).
§ One-sided p-value based on stratified log-rank test.
‖ Two-sided p-value based on stratified log-rank test

An additional direct comparison of the two doses in ipilimumab-refractory melanoma was performed in KEYNOTE-001 - Part B2 (n=173), which randomly assigned subjects to the two dose levels (2 mg/kg and 10 mg/kg given Q3W). Study results demonstrated that the ORR for the 2 mg/kg and 10 mg/kg Q3W doses were essentially identical in ipilimumab-refractory melanoma subjects in KEYNOTE-001 – Part B2 (at 25% in each arm of the study) as well as similar efficacy on secondary endpoints of PFS and OS (see Figure 17 below).

Figure 17: KM estimates of PFS and OS for KEYNOTE-001 Part B2



Data source: Robert 2014 Fig. 3, pg.1114.

Finally, a comparison of all key efficacy endpoints in KEYNOTE-001 - Part B2 and

KEYNOTE-002 (each concerning ipilimumab-refractory melanoma patients, comparing 2 mg/kg Q3W to 10 mg/kg Q3W) as shown in the Table 53 below, does not indicate differences between the doses despite a 5X difference in dose. Please note that overall survival data from KEYNOTE-002 was immature at the time of IA2 and only a small number of subjects were at risk at 12 months; therefore, the median OS for KEYNOTE-002 should be interpreted with caution.

Table 53: Cross study comparison of key efficacy endpoints by dose level in KEYNOTE-001(Part B2) and KEYNOTE 002

	KEYNOTE-001 – Part B2*		KEYNOTE-002	
	2 mg/kg Q3W	10 mg/kg Q3W	2 mg/kg Q3W	10 mg/kg Q3W
ORR (%)	25	25	21	25
PFS (median, mo)	4.9	3.2	2.9	2.9
6-month PFS rate (%)	43	35	34	38
OS (median, mo)	Not reached	18.3	11.4	12.5
6 month OS rate (%)	79	77	72	76

**Data based on KEYNOTE-001 CSRv.2 (data-cut18-April-2014)*

C3. Please provide a reference (and if not already provided, accompanying document) for the methods used to control the overall type 1 error rate in KEYNOTE-002 (as mentioned on pages 57 to 58 of the company's submission.

In this study, the type I error used Bonferroni, Hochberg step-up and Gatekeeping procedure between PFS and OS at different analyses. The relevant references are listed below:

- Hochberg, Y. (1988). A sharper Bonferroni procedure for multiple tests of significance. Biometrika 75, 800-803
- Wiens, B.L. (2003) A fixed-sequence Bonferroni procedure for testing multiple endpoints. Pharmaceutical Statistics 2:211-215

C4. The number of patients estimated to be eligible for treatment with pembrolizumab by the company is cited to be 628. However, following the text and tables in section 6.2 of the company's submission, the ERG has been unable to replicate these numbers. Specifically, from following the text in section 6.2 and numbers cited in Tables 94 to 96 of the company's submission, the ERG calculates the numbers as follows:

Parameters	Proportion	Source	Number
Total population - England		Table 94: ONS Mid-2013 UK population estimates	53,865,800
Estimate of incident melanoma population	0.02%	Table 94: Calculated (average of male and female) from ONS cancer registration 2012 (released June 2014	11,366

Proportion of patient with stage IIIc or IV disease	10.00%	Table 94: Vemurafenib NICE costing report (NICE costing template TA269)	1,137
Proportion of patients who are BRAF^{V600} mutation-positive	48.00%	Table 94: Long et al	546
Proportion of patients who are BRAF^{V600} mutation-negative	52.00%	Table 94	591
Patients who are BRAF^{V600} mutation-positive			
- Treated first line with BRAF inhibitor and/or MEK inhibitor	43.20%	Table 95	236
- Treated first line with ipilimumab	16.30%	Table 95	89
- Treated second-line following treatment with BRAF inhibitor and/or MEK inhibitor*	65.00%	Table 95: Merck Sharp & Dohme. Data on file. 2015. Ref Type: Data File (Table 95)	153
- Treated second-line following treatment with ipilimumab*	75.00%	Table 95: Merck Sharp & Dohme. Data on file. 2015. Ref Type: Data File (Table 95)	67
Patients who are BRAF^{V600} mutation-negative			
- Treated first line with ipilimumab	75.00%	Table 96	443
- Treated second-line following treatment with ipilimumab*	75.00%	Table 96: Merck Sharp & Dohme. Data on file. 2015. Ref Type: Data File (Table 96)	332
All patients treated second-line			
Patients eligible for treatment with pembrolizumab		Calculated (sum of BRAF^{V600} mutation positive + BRAF^{V600} mutation negative)	552

* The proportion of patients treated first-line minus those who withdrew treatment as a result of death, performance status, contraindication or adverse event.

Please clarify how the estimate of 628 patients is derived, noting if any errors have occurred in the ERG's calculations above. In particular, the ERG queries whether the proportion of patients who are BRAF^{V600} mutation-positive and treated first line with ipilimumab (16.3% as reported in Table 95) may be an underestimate?

MSD has built on the table (see Table 54) developed by the ERG to summarise the information used to estimate the number of patients eligible for treatment with pembrolizumab in the original MSD submission [ID760].

The first difference noticed between the ERG calculation and MSD's was relative to the number patients who are BRAFV600 mutation-positive and BRAFV600 mutation-negative. The estimates used by the ERG vary slightly from MSD's ones. Although, the same proportion of patients BRAFV600 mutation-positive (i.e. 48%) and BRAFV600 mutation-negative (i.e. 52%) was implemented, the starting number of patients was different (ERG: 546 and 591 respectively; MSD: 605 and 655 respectively).

The figures reported by the ERG (i.e. 546 for BRAFV600 mutation-positive and

591 for BRAFV600 mutation-negative in 2015) are the ones MSD estimated for 2012 given that the estimate of incident melanoma population was based on the 2012 ONS figures. As per ipilimumab 1st line NICE STA submission[8] (see section C – Implementation, table 81 page 210), we applied a 3.5% yearly increase in incidence to estimate a number of patients BRAFV600 mutation-negative and BRAFV600 mutation-positive of respectively 605 and 655 in 2015 (i.e. year 1 of the budget impact assessment).

We also noticed some inconsistencies while comparing the proportions used by the ERG (see Table 10, column (2)) to the ones used by MSD (see Table 54, column (3)). To estimate the number of $BRAF^{V600}$ mutation-positive patients, the proportions taken into account varied slightly as described below:

- Proportion of patients treated in 2nd line following treatment with a BRAF inhibitor and/or a MEK inhibitor: ERG: 65%; MSD: 67.5%
- Proportion of patients treated in 2nd line following treatment with ipilimumab: ERG: 75%; MSD: 76.5%

For $BRAF^{V600}$ mutation-negative patients, the proportion of patients treated in 2nd line following treatment with ipilimumab was slightly different: ERG: 75%; MSD: 76.5%.

The above proportions that MSD used in the budget impact assessment calculation are based on clinical opinion.

In column (6) (see Table 54) we have adjusted the number of patients who are $BRAF^{V600}$ mutation-negative and $BRAF^{V600}$ mutation-positive to reflect the figures we originally based our calculation on and applied the percentages obtained from clinical opinion. From this calculation we derived the figures that were presented in section C of the original MSD submission [ID760].

Please accept our apologies as we have noticed a typo in Table 99 page 219 of the original MSD submission [ID760]. For year 2017, the total number of patients stage IIIc and IV treated with PD-1 class for 2nd or 3rd line should read 201 rather than 208. The budget impact was correctly estimated for every year but the figure was inadvertently wrongly reported for year 2017.

Table 54 seeks to validate the estimates MSD reported in section C of the original submission [ID760].

Table 54: estimates of incident population

Parameters (1)	% ERG (2)	% MSD (3)	Source (4)	Numbers ERG (5)	Numbers MSD (6)
Total population - England			MSD [ID760] - Table 94: ONS Mid-2013 UK population estimates	53,865,800	
Estimate of incident melanoma population	0.0211%	0.0211%	MSD [ID760] - Table 94: Calculated (average of male and female) from ONS cancer registration 2012 (released June 2014	11,366	
Proportion of patient with stage IIIc or IV disease	10%	10%	MSD [ID760] - Table 94: Vemurafenib NICE costing report (NICE costing template TA269)	1,137	
Proportion of patients who are BRAFV600 mutation-positive	48%	48%	MSD [ID760] - Table 94: Long et al	546	605
Proportion of patients who are BRAFV600 mutation-negative	52%	52%	MSD [ID760] - Table 94	591	655
Patients who are BRAFV600 mutation-positive					
- Treated first line with BRAF inhibitor and/or MEK inhibitor	43.2%	43.2%	MSD [ID760] - Table 95	236	261
- Treated first line with ipilimumab	16.3%	16.3%	MSD [ID760] - Table 95	89	99
- Treated second-line following treatment with BRAF inhibitor and/or' MEK inhibitor	65%	67.5%	MSD [ID760] - Table 95: Merck Sharp & Dohme. Data on file. 2015. Ref Type: Data File (Table 95)	153	176
- Treated second-line following treatment with ipilimumab	75.00%	76.5%	MSD [ID760] - Table 95: Merck Sharp & Dohme. Data on file. 2015. Ref Type: Data File (Table 95)	67	75
Patients who are BRAFV600 mutation-negative					
- Treated first line with ipilimumab	75%	75.0%	MSD [ID760] - Table 96	443	491
- Treated second-line following treatment with ipilimumab*	75%	76.5%	MSD [ID760] - Table 96: Merck Sharp & Dohme. Data on file. 2015. Ref Type: Data File (Table 96)	332	376
All patients treated second-line					
Patients eligible for treatment with pembrolizumab			MSD [ID760] - Calculated (sum of BRAFV600 mutation positive + BRAFV600 mutation negative)	552	628

Please note that the proportion of patients who are BRAFV600 mutation-positive (i.e. 16.30% in 2015) is derived from internal MSD forecasting.

Please note that we have provided the excel document entitled “Clarification questions C - Ref 88 MSD Data on file.xlsx” supporting the budget impact analysis calculation.

Report of error in original submission

We are taking this opportunity to point out that we have mistakenly used £2,680 as administration cost for pembrolizumab instead of £245.17. Please find in Table 55 the right figures.

Table 55: estimated budget impact over 5 years (revised estimates)

	2015	2016	2017	2018	2019	2020
Total stage IIIc and IV patients treated with pembrolizumab for 2L or 3L	**188**	**186**	**201**	**211**	**218**	**226**
Total costs for pembrolizumab	**£27,061**	**£27,061**	**£27,061**	**£27,061**	**£27,061**	**£27,061**
Total treatment costs	£25,290	£25,290	£25,290	£25,290	£25,290	£25,290
Total administration costs	£1,682	£1,682	£1,682	£1,682	£1,682	£1,682
Total adverse event costs	£89	£89	£89	£89	£89	£89
Total budget impact with pembrolizumab	**£5,096,337**	**£5,029,875**	**£5,448,606**	**£5,699,455**	**£5,899,762**	**£6,106,254**

C5. Please clarify if the source for all data reported in Table 95 is reference 88: Merck Sharp & Dohme. Data on file. 2015. Please also provide a copy of this document.

This is correct. The source for all data reported in Table 95 is “reference 88: Merck Sharp & Dohme. Data on file. 2015”.

We have provided the excel document entitled “Clarification questions C - Ref 88 MSD Data on file.xlsx” supporting the budget impact analysis calculation.

C6. Please clarify if the source for all data reported in Table 96 is reference 88: Merck Sharp & Dohme. Data on file. 2015.

This is correct. The source for all data reported in Table 96 is “reference 88: Merck Sharp & Dohme. Data on file. 2015”.

We have provided the excel document entitled “Clarification questions C - Ref 88 MSD Data on file.xlsx” supporting the budget impact analysis calculation.

C7. Please clarify whether in Table 96, “% treated with BRAFi* +/- MEKi in 1L” should in fact read “% treated with ipilimumab in 1L”.

Please accept our apologies for this typo. We have provided the document as part of the excel document entitled “Clarification questions C - Ref 88 MSD Data on file.xlsx” supporting the budget impact analysis calculation.

C8. One key exclusion criterion for entry into KEYNOTE-002 is listed on page 46 of the company's submission as "Disease progression within 24 weeks of last dose of ipilimumab." However "Disease progression within 24 weeks of last dose of ipilimumab" is also used to define a patient who is refractory, a key inclusion criterion (page 43 of the company's submission). Please clarify whether "Disease progression within 24 weeks of last dose of ipilimumab" is an inclusion or exclusion criterion.

Please accept our apologies for this error. "Disease progression within 24 weeks of last dose of ipilimumab" should not have been listed as a key exclusion criterion. It is correct that this is in fact one of the criteria used to defining ipilimumab refractory patients (a key inclusion criterion).

References

(1) Latimer NR, Abrams KR. NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching. http://www nicedsu org uk/TSD16_Treatment_Switching pdf [Accessed on: 10/01/2015] [2014

(2) Merck Sharp & Dohme. Clinical Study report P002V01 - KEYNOTE-002: Second interim analysis of MK-3475 Phase II advanced melanoma study. 6-2-2015.

(3) Balch CM, Buzaid AC FAU, Soong SJ FAU, Atkins MB FAU, Cascinelli NF, Coit DG FAU et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol* 2001; 19(16):3635-3648.

(4) Korn EL, Liu PY, Lee SJ, Chapman JA, Niedzwiecki D, Suman VJ et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. *J Clin Oncol* 2008; 26(4):527-534.

(5) Thirlwell C, Nathan P. Melanoma--part 2: management. *BMJ* 2008; 337:a2488.

(6) Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N Engl J Med* 2015.

(7) Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010; 363(8):711-723.

(8) National Institute for Health and Care Excellence (NICE). Single Technology Appraisal for ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma (TA319). https://www nice org uk/guidance/ta319 [Accessed on: 10/02/2015] [2013