NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Talimogene laherparepvec for treating metastatic melanoma [ID508]

Response to clarification questions

Amgen Limited

Date: December 2015

File name	Version	Contains confidential information	Date
		Yes CIC: Highlighted in turquoise and underlined AIC: Highlighted in yellow and underlined	

Contents

A: Clarification on clinical-effectiveness data 5
B: Clarification on cost-effectiveness data 21
C: Textual clarifications, references and additional points 37
References 39
List of Appendices 40

List of tables

Table A-1 Calculation of weighted average of HRs for patients with stage M0 and M1a melanoma 7
Table A-2 Table corresponding to Figure 4-12 in Amgen submission: modified Korn adjusted mean and median OS for ipilimumab in patients with stage IIIB-IVM1a disease 7
Table A-3 Table corresponding to Figure 4-13 in Amgen submission: modified Korn adjusted mean and median PFS for ipilimumab in patients with stage IIIB-IVM1a disease ... 8
Table A-4 Table corresponding to Figure 4-14 in Amgen submission: 95% prediction interval around the modified Korn adjustment for Ipilmumab OS 8
Table A-5 Table corresponding to Figure 4-15 in Amgen submission: two-step Korn adjusted mean and median OS for ipilimumab in patients with stage IIIB-IVM1a disease 8
Table A-6 Table corresponding to Figure 4-16 in Amgen submission: two-step Korn adjusted mean and median PFS for ipilimumab in patients with stage IIIB-IVM1a disease ... 9
Table A-7 Two-step Korn adjusted mean and median OS for ipilimumab in patients with stage IIIB-IVM1a disease 10
Table A-8 Mean and median OS including or excluding KEYNOTE 006 using modified Korn adjustment 14
Table A-9 Mean and median PFS including or excluding KEYNOTE 006 using modified Korn adjustment 14
Table A-10 Outcomes prespecified to be assessed at each analysis 15
Table A-11 Treatment by subgroup interaction tests for DRR and OS in OPTiM (ITT population) 16
Table A-12 TTF per investigator assessment in patients with stage IIIB-IVM1a disease (final data cut) 17
Table A-13 Summary of the reasons for discontinuing treatment and discontinuing from the trial in the IIIB–IVM1a subgroup (primary analysis) 19
Table A-14 Summary of selected subsequent therapies given to patients following participation in the OPTiM study (final analysis) 20
Table B-1 T-VEC non-visceral subgroup (stage IIIB-IVM1A) – mean OS, PFS and PPS for original censoring versus re-censoring 23
Table B-2 T-VEC non-visceral subgroup (stage IIIB-IVM1A) – mean OS, PFS and PPS for original censoring versus re-censoring by stage 25
Table B-3 Summary of T-VEC PFS with or without assumptions of similarity of hazards 32
Table B-4 Impact on ICER with or without assumptions of similarity of hazards 33
Table B-5 Summary of time from initial diagnosis to randomisation in OPTiM (IIIB-IVM1a population) 33
Table B-6 T-VEC treatment: first cycle first dose (OPTiM) 34
Table B-7 T-VEC treatment: subsequent cycles (OPTiM) 34
Table B-8 Baseline weight in OPTiM (IIIB-IVM1a population) 36

List of figures

Figure A-1 Unadjusted and adjusted Kaplan-Meier curves for OS from MDX010-20 6
Figure A-2 Two-step Korn adjusted OS curve for ipilimumab in patients with stage IIIB-IVM1a disease 9
Figure A-3 OS curves for previously treated and previously untreated ipilimumab patients 12
Figure A-4 OS curves including KEYNOTE 006 trial using modified Korn adjustment 13
Figure A-5 PFS curves including KEYNOTE 006 trial using modified Korn adjustment 13
Figure A-6 Patient disposition during the OPTiM study in the IIIb-IVM1a population (primary analysis) 18
Figure B-1 T-VEC original versus re-censored OS (stage IIIB-IVM1A) 23
Figure B-2 T-VEC original versus re-censored PFS (stage IIIB-IVM1A) 24
Figure B-3 T-VEC original versus re-censored PPS (stage IIIB-IVM1A) 24
Figure B-4 T-VEC original versus re-censored OS (stage IIIB) 25
Figure B-5 T-VEC original versus re-censored OS (stage IIIC) 26
Figure B-6 T-VEC original versus re-censored OS (stage IVM1a) 26
Figure B-7 T-VEC original versus re-censored PFS (stage IIIB) 27
Figure B-8 T-VEC original versus re-censored PFS (stage IIIC) 27
Figure B-9 T-VEC original versus re-censored PFS (stage IVM1a) 28
Figure B-10 T-VEC original versus re-censored PPS (stage IIIB) 28
Figure B-11 T-VEC original versus re-censored PPS (stage IIIC) 29
Figure B-12 T-VEC original versus re-censored PPS (stage IVM1a) 29
Figure B-13 Modified Korn adjustment with no adjustment of T-VEC PFS 31
Figure B-14 Modified Korn adjustment with adjustment of T-VEC PFS 31
Figure B-15 Two-step Korn adjustment with no adjustment of T-VEC PFS 32
Figure B-16 Two-step Korn adjustment with adjustment of T-VEC PFS 32
Figure C-1 PRISMA flow diagram for non-RCT evidence 38

A: Clarification on clinical-effectiveness data

Korn adjustments conducted in order to provide evidence for clinical effectiveness:

<u>A1 (Priority question).</u> Please provide full details of the modified Korn and two-step Korn analyses conducted with references cited (and the accompanying relevant documents provided) and full details of calculations conducted (including how coefficients were derived), ideally in Microsoft Excel format

[redacted] and [redacted] include full details of calculations for the modified Korn and two-step Korn analyses in Microsoft Excel format. These appendices also cite the relevant references (Hodi et al, 2010; Robert et al, 2011; NICE TA319, 2014a).

<u>A2 (Priority question)</u>. In relation to tables 4-24 to 4-26:

a. **Please clarify that the data entered for patients with no visceral disease for patients previously untreated with ipilimumab in Table 4.24 is 0.17 and not 17 as stated**

   Yes, we confirm that the value should be 0.17.

b. **The formula for estimating the hazard ratio (HR) for T-VEC in Table 4-26 appears to be incomplete. Please clarify whether this is the case and if so, provide the correct formula**

   Yes this formula in Table 4-26 is incomplete. The complete formula is:

$$\log(\widehat{HR}) = -0.154X_{Gender=0.44} - 0.400X_{ECOG=0.74} - 0.285X_{Visceral=1} - 0.306X_{Brain=1} - 0.782X_{LDH=0.94}$$

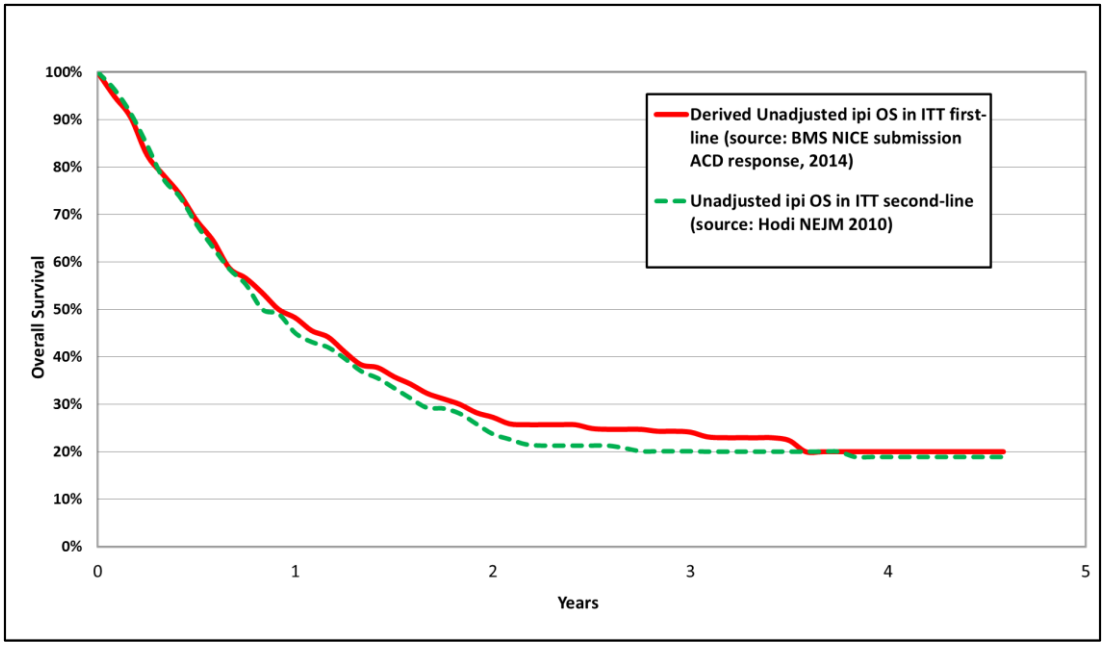
c. **For Table 4-24, please provide further details on the methodology used to derive the overall survival (OS) estimate for the monotherapy ipilimumab 3mg/kg group, as used in the company's submission in the NICE technology appraisal of ipilimumab for previously untreated (unresectable or metastatic) melanoma (TA319), using data from the trial of ipilimumab + dacarbazine.**

   The manufacturer of ipilimumab (BMS) adjusted the 3mg/kg ipilimumab monotherapy (licensed dose) OS data from the second-line trial (MDX010-20) to estimate the OS curve for ipilimumab 3mg/kg monotherapy in previously untreated patients, i.e. in the first-line setting. The worse prognosis of patients in second-line (MDX010-20) was adjusted to the baseline characteristics patients had in the first-line trial (CA184-024) which studied an unlicensed dose of ipilimumab 10mg/kg in combination with dacarbazine. The adjusted OS curve represented the expected OS of ipilimumab 3mg/kg monotherapy based on the prognostic characteristics of an untreated patient population (CA184-024). BMS present the detailed methodology and analysis of this adjustment in their Appraisal Consultation Document (ACD) response (pages 12-14) for the NICE appraisal of ipilimumab for previously untreated (unresectable or metastatic) melanoma (NICE TA319, 2014b). The NICE Appraisal Committee in the Final Guidance for TA319 accepted this analysis "*The Committee concluded that it is plausible that 3mg/kg*

ipilimumab could give the same treatment effect in both untreated and previously treated melanoma and that the use of the MDX010-20 trial data from the previous appraisal (TA268) provided more plausible estimates of the clinical effectiveness of 3 mg/kg ipilimumab in the first-line setting than those provided in the manufacturer's original submission." Figure A-1 illustrates the unadjusted and adjusted Kaplan-Meier curves for OS from MDX010-20 as presented in Figure 6, Page 14 of the BMS ACD response.

We digitised the adjusted Kaplan-Meier curves shown in Figure A-1 as reported in the manufacturer response to the ACD for the appraisal of ipilimumab for previously untreated advanced malignant melanoma (NICE TA319, 2014b). We estimated the adjustment factor to adjust the digitised OS curve for 3mg/kg ipilimumab in previously untreated patients to match T-VEC patient characteristics by adjusting the worse prognosis of patients in the CA184-024 trials to the baseline characteristics patients had in the T-VEC licensed population (non-visceral metastatic disease) in the OPTiM trial.

Figure A-1 Unadjusted and adjusted Kaplan-Meier curves for OS from MDX010-20



ACD, appraisal consultation document; ipi, ipilimumab; ITT, intent to treat; OS, overall survival.

d. In Table 4.25, there is reference to the weighted average of HRs for patients with stage M0 and M1a melanoma reported in Robert 2011. Please clarify how this weighted average was calculated and provide any relevant references for the method used.

The standard methodology of inverse-variance weighting was used to derive the weighted average of HRs for patients with stage M0 and M1a disease (Hartung et al, 2008). Details are shown in Table A-1.

Table A-1 Calculation of weighted average of HRs for patients with stage M0 and M1a melanoma

Group	OS Log HR (95% CI) from Robert 2011[a]	Log HR point estimate	L	U	Variance	Weight	Contribution
M0	−1.02 (−2.64, 0.60)	-1.02	-2.64	0.60	0.6832	1.4637	-1.4930
M1a	−0.09 (−0.63, 0.45)	-0.09	-0.63	0.45	0.0759	13.1742	-1.1857
Total						14.6379	-2.6787

[a] Source: (Robert et al, 2011).
CI, confidence interval; HR, hazard ratio; L, lower limit of 95% CI for log HR; OS, overall survival; U, upper limit of 95% CI for log HR.

Notes on calculation:

- Variance = $\left(\frac{U-L}{2\times 1.96}\right)^2$
- Weight=1/variance
- Contribution = point estimate * weight
- Combined log HR = total contribution / total weight =-0.1830
- Variance of combined log HR = 1 / total weight = 0.0683
- 95% CI = -0.1830 -/+ 1.96*sqrt(0.0683) = (-0.6953, 0.3293)
- Corresponding estimate of HR (95% CI) is 0.8328 (0.4990, 1.3900) as shown in Table 4-24 of our submission

<u>A3 (Priority question)</u>. For Figures 4.12 to 4.16, please provide a table providing the median and mean survival estimates (i.e. OS or progression-free survival [PFS], depending on the figure) for all presented curves in each figure.

Please find corresponding tables for Figures 4.12 to 4.16, providing the median and mean survival estimates (i.e. OS or PFS) for these curves (Table A-2 to Table A-6). The ipilimumab and T-VEC trials had different lengths of follow up which may have an impact on mean OS and PFS calculation. To ensure a fair comparison, the shorter follow up period was adopted to calculate AUC for mean OS and PFS.

Table A-2 Table corresponding to Figure 4-12 in Amgen submission: modified Korn adjusted mean and median OS for ipilimumab in patients with stage IIIB-IVM1a disease

	Unadjusted OS	Modified Korn
Median		
T-VEC	46.8	–
Ipilimumab pooled	10.9	21.3
Mean (AUC)[a]		
T-VEC	36.9	–
Ipilimumab pooled	19.5	29.2

[a] Calculated using the shorter available time period (55 months).
AUC, area under the curve; OS, overall survival; T-VEC, talimogene laherparepvec.

Table A-3 Table corresponding to Figure 4-13 in Amgen submission: modified Korn adjusted mean and median PFS for ipilimumab in patients with stage IIIB-IVM1a disease

	Unadjusted PFS	Modified Korn
Median		
T-VEC	13.1	–
Ipilimumab pooled	2.8	5.3
Mean (AUC)[a]		
T-VEC	20.6	–
Ipilimumab pooled	8.0	15.2

[a] Calculated using the shorter available time period (43 months).
AUC, area under the curve; PFS, progression-free survival; T-VEC, talimogene laherparepvec.

Table A-4 Table corresponding to Figure 4-14 in Amgen submission: 95% prediction interval around the modified Korn adjustment for Ipilmumab OS

	Unadjusted OS	Modified Korn
Median		
T-VEC	46.8	–
Ipilimumab pooled	–	Not reached (upper limit) 14.6 (lower limit)
Mean (AUC)[a]		
T-VEC	36.9	–
Ipilimumab pooled	–	34.6 (upper limit) 23.8 (lower limit)

[a] Calculated using the shorter available time period (55 months).
AUC, area under the curve; OS, overall survival; T-VEC, talimogene laherparepvec.

Table A-5 Table corresponding to Figure 4-15 in Amgen submission: two-step Korn adjusted mean and median OS for ipilimumab in patients with stage IIIB-IVM1a disease

	Unadjusted OS	Two-step Korn
Median		
T-VEC	46.8	–
Ipilimumab pooled	10.9	Not reached
Mean (AUC)[a]		
T-VEC	33.5	–
Ipilimumab pooled	18.0	32.3

[a] Calculated using the shorter available time period (48 months).
AUC, area under the curve; OS, overall survival.

Table A-6 Table corresponding to Figure 4-16 in Amgen submission: two-step Korn adjusted mean and median PFS for ipilimumab in patients with stage IIIB-IVM1a disease

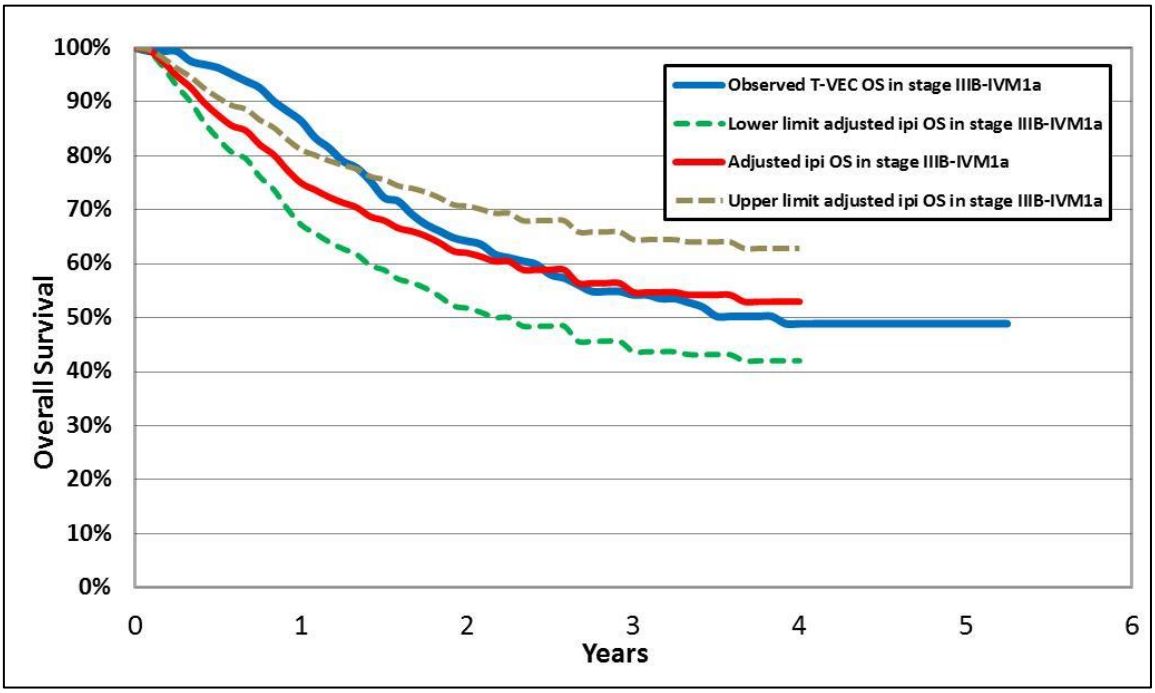
	Unadjusted PFS	Two-step Korn
Median		
T-VEC	13.1	–
Ipilimumab pooled	2.8	17.6
Mean (AUC)[a]		
T-VEC	18.2	–
Ipilimumab pooled	7.4	18.6

[a] Calculated using the shorter available time period (35 months).
AUC, area under the curve; PFS, progression-free survival; T-VEC, talimogene laherparepvec.

A4 (Priority question). The company's submission does not include a figure accounting for the 95% prediction intervals around the OS estimates. Please provide a new figure with 95% prediction intervals around the two-step Korn adjusted OS estimate for ipilimumab (and a corresponding table with median and mean OS estimates, as described in A3 above).

Figure A-2 includes the 95% prediction intervals around the two-step Korn adjusted OS estimate for ipilimumab. Table A-7 summarises the median and mean OS estimates from this analysis. The 95% prediction interval was constructed based on the estimated standard errors for coefficients in the modified Korn equation. The uncertainty associated with the hazard ratio of 0.47 was not incorporated.

Figure A-2 Two-step Korn adjusted OS curve for ipilimumab in patients with stage IIIB-IVM1a disease



Ipi, ipilimumab; OS, overall survival; T-VEC, talimogene laherparepvec.

Table A-7 Two-step Korn adjusted mean and median OS for ipilimumab in patients with stage IIIB-IVM1a disease

	Unadjusted OS	Two-step Korn
Median		
T-VEC	46.8	–
Ipilimumab pooled	–	Not reached (upper limit) 27.0 (lower limit)
Mean (AUC)[a]		
T-VEC	33.5	–
Ipilimumab pooled	–	35.8 (upper limit) 28.1 (lower limit)

[a] Calculated using the shorter available time period (48 months).
AUC, area under the curve; OS, overall survival; T-VEC, talimogene laherparepvec.

A5 (Priority question). Please clarify whether data from OPTiM used for the Korn adjustments for PFS is time to treatment failure (TTF) data.

The PFS data from OPTiM used for the Korn adjustment is time to treatment failure (TTF) data. TTF was defined as time from the first dose of study treatment until death or development of the first clinically significant progression per investigator for which no objective response was subsequently achieved. Clinically significant progressive disease was defined as a progressive disease that is associated with a decline in performance status and/or in the opinion of the investigator the patient requires alternative therapy.

Due to the mode of action of T-VEC, whereby responses could occur post-progression, simply measuring PFS would have been inappropriate. Treatment with T-VEC can lead to pseudoprogression (Fink et al, 2011; Wolchok et al, 2009), in which there is an increase in lesion size due to an inflammation/host immune response to the tumour rather than an actual tumour progression event. In the case of pseudoprogression, treatment continuation can result in a subsequent true partial response or complete response with regard to the traditional tumour assessment criteria. Under these circumstances, PFS was determined not to be a meaningful endpoint for the OPTiM study since the full effect of the immune response triggered by T-VEC may occur post-progression; in the OPTiM trial 54% of objective responses occurred post-progression. The modified PFS outcome, TTF, was accepted by the CHMP.

A6 (Priority question). Please provide further clarification on why the Hodi 2014 study, which compares ipilimumab monotherapy with ipilimumab + GM-CSF was excluded from the company's analyses using the Korn algorithm. The reason cited for the exclusion of this study (in the appendices to the company's submission) is that it does not include a relevant comparator. However, in the company's analyses, the company has used gp100 and dacarbazine as comparators. Please clarify why gp100 and dacarbazine are considered to be relevant comparators but ipilimumab + GM-CSF is not.

The study was excluded because it was a phase 2 study. The reason provided in our submission for its exclusion was incorrect.

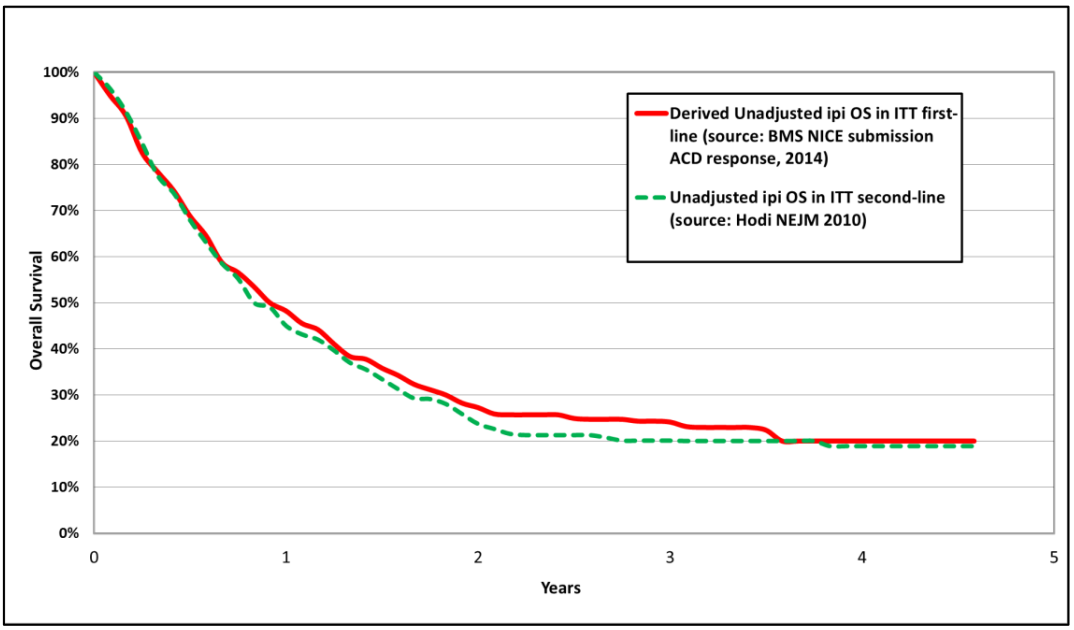
<u>A7 (Priority question).</u> Please justify why it is appropriate to pool data from both the ipilimumab monotherapy and ipilimumab + dacarbazine arms, and from trials of both previously treated and previously untreated patients. Please clarify whether the heterogeneity that may arise from these differences in the trials was considered/assessed and if so, how.

The NICE Appraisal Committee in their considerations around the appraisal of ipilimumab for previously untreated advanced malignant melanoma acknowledged the similarity of the previously treated and previously untreated sub-populations in the clinical studies and concluded that the shape of the Kaplan-Meier curves was similar in the first- and second-line settings. The final guidance also states that the CHMP commented in their licensing assessment report that "*there is no biological rationale to suspect a different activity for ipilimumab treatment in the first- or next-line setting"* (NICE TA319, 2014a). Indeed the OS curves for previously treated and previously untreated patients are very similar (Figure A-3).

It is noteworthy that the manufacturer of ipilimumab assumed that ipilimumab plus dacarbazine was equivalent to ipilimumab alone (NICE TA319, 2014a), stating that the CHMP granted marketing authorisation for ipilimumab monotherapy based primarily on the evidence for the ipilimumab plus dacarbazine regimen. To support this, the manufacturer of ipilimumab quote the EPAR in their ACD response for appraisal of ipilimumab for previously untreated advanced malignant melanoma, "*Furthermore, in previously untreated patients, the median and long-term OS from the 3mg/kg ipilimumab monotherapy and 10mg/kg ipilimumab + DTIC are similar*". Therefore we used the derived OS data that represents the expected OS for ipilimumab 3mg/kg monotherapy in previously untreated patients, taken from the NICE appraisal of ipilimumab for previously untreated metastatic melanoma (NICE TA319, Figure 6, Page 14 of the BMS ACD response), and not the observed OS data from 1st-line.

For these reasons it is appropriate to pool the adjusted OS data from the ipilimumab previously treated and previously untreated clinical trials. Given the similarity in the OS curves for ipilimumab in previously treated and untreated patients (Figure A-3) the heterogeneity is likely to be negligible, therefore no formal assessment of heterogeneity was conducted.

Figure A-3 OS curves for previously treated and previously untreated ipilimumab patients



ACD, appraisal consultation document; ipi, ipilimumab; ITT, intent to treat; OS, overall survival.

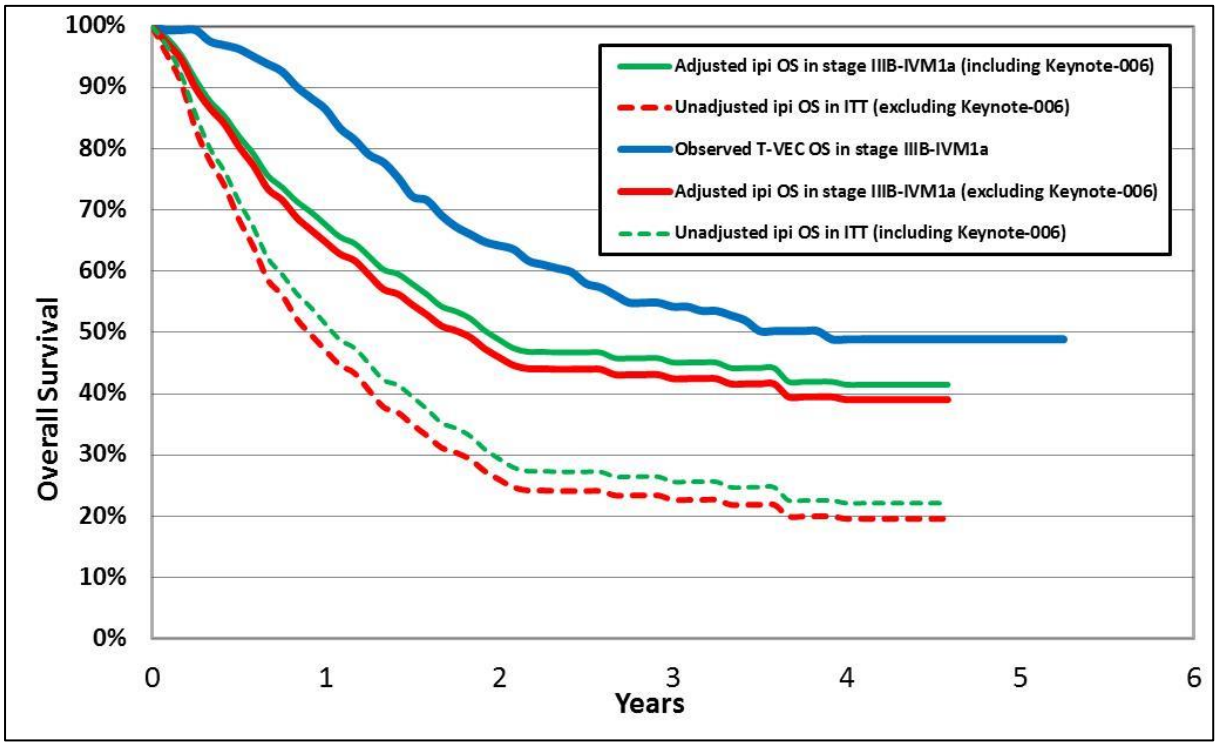
<u>A8 (Priority question).</u> Please clarify why the company did not include, in its analyses using the Korn algorithm, data from the CheckMate 067 and KEYNOTE 006 trials. If possible, please provide Korn adjusted OS and PFS estimates for ipilimumab (using both the modified and two-step methods) based on analyses that include data from the CheckMate 067 and KEYNOTE 006 trials.

CheckMate 067 was excluded from the Korn analyses because OS data were not reported.

KEYNOTE 006 was excluded from the analysis using the Korn algorithm because the OS data reported was immature, coming from an interim analysis. Even if it had been included in the analyses, it could only have been used for the modified Korn analysis. The two-step Korn analysis required RCTs with a non-active control group (to represent best supportive care) for the first step of the adjustment. However, KEYNOTE compared ipilimumab against the active comparator pembrolizumab and therefore could not be included in the two-setp analysis.

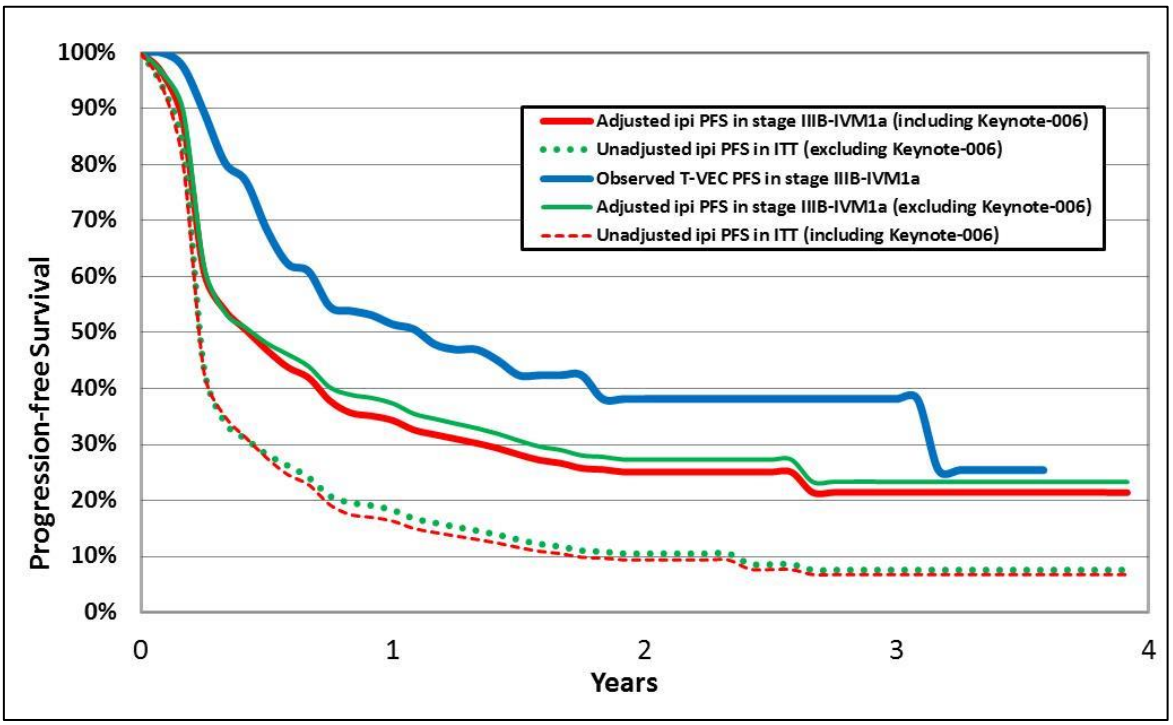
We provide below, the results from the modified Korn method when the KEYNOTE 006 trial data for ipilimumab is included (Figure A-4, Figure A-5, Table A-8 and Table A-9). The impact of including data from KEYNOTE 006 is small: the mean OS for ipilimumab is increased from 29.2 to 30.6 months, compared with 36.9 months for T-VEC. The mean PFS for ipilimumab is decreased from 15.2 to 14.4 months, compared with 20.6 months for T-VEC.

Figure A-4 OS curves including KEYNOTE 006 trial using modified Korn adjustment



ipi, ipilimumab; ITT, intent to treat; OS, overall survival.

Figure A-5 PFS curves including KEYNOTE 006 trial using modified Korn adjustment



ipi, ipilimumab; ITT, intent to treat; PFS, progression-free survival.

Table A-8 Mean and median OS including or excluding KEYNOTE 006 using modified Korn adjustment

	Ipilimumab				T-VEC
	Unadjusted OS (excluding KEYNOTE 006)	**Unadjusted OS (including KEYNOTE 006)**	**Modified Korn (excluding KEYNOTE 006)**	**Modified Korn (including KEYNOTE 006)**	**Unadjusted OS**
Median (months)	10.9	12.5	21.3	23.2	46.8
Mean (AUC)[a] (months)	19.5	21.2	29.2	30.6	36.9
[a] Calculated using the shorter available time period (55 months) AUC, area under the curve; OS, overall survival.					

Table A-9 Mean and median PFS including or excluding KEYNOTE 006 using modified Korn adjustment

	Ipilimumab				T-VEC
	Unadjusted PFS (excluding KEYNOTE 006)	**Unadjusted PFS (including KEYNOTE 006)**	**Modified Korn (excluding KEYNOTE 006)**	**Modified Korn (including KEYNOTE 006)**	**Unadjusted PFS**
Median (months)	2.8	2.8	5.3	5.1	13.1
Mean (AUC)[a] (months)	8.0	7.8	15.2	14.4	20.6
[a] Calculated using the shorter available time period (43 months). AUC, area under the curve; PFS, progression-free survival.					

OPTiM trial:

A9. Table 4-5 implies that response onset was assessed by investigator only. Table 4-17 provides data for "time to response per Endpoint Assessment Committee (EAC)". Please clarify if response onset was assessed by EAC.

There is an error in Table 4-5. Response onset was assessed by the EAC and by the investigator.

A10. On page 59, it is stated that "The null hypothesis was that there is no difference in durable response rate (DRR) between T-VEC and control at interim or final analysis." Please clarify whether the null hypothesis should actually refer to the primary analysis of DRR, rather than the interim or final analysis of DRR.

The null hypothesis should refer to the interim and primary analysis of DRR, not the final analysis.

A11. Primary and secondary outcomes are reported at both the primary and final data-cuts. Please clarify whether it was pre-specified that these outcomes would be reported at both the primary and final data-cuts.

The primary analyses of DRR and all other response-based outcomes per EAC were prespecified to be reported only at the primary data-cut (21 Dec 2012). These analysis were pre-specified to occur when no further patients had the possibility of meeting the criteria for durable response and therefore no change to these outcomes (per EAC) was possible in later data-cuts; these were presented in error for the final data-cut in Tables 4-13, 4-16 and 4-17 of our submission. A planned interim OS analysis also occurred at this the time of the primary analysis (21 Dec 2012). The primary OS analysis was performed when the required 290 death events had occurred (31 Mar 2014). The final analysis was performed when all subjects had been followed for at least 3 years after randomisation and is descriptive. Table A-10 clarifies which efficacy outcomes were prespecified to be assessed at each analysis.

Table A-10 Outcomes prespecified to be assessed at each analysis

Data-cut / analysis[a]	Data cut-off date	Efficacy outcomes assessed
Primary	21 Dec 2012	DRR, ORR and all response-based endpoints (per EAC and investigator). Time to treatment failure (per investigator). Planned interim analysis of OS and impact of response on OS overall. Quality of life.
Primary OS Prespecified to occur after 290 events	31 Mar 2014	OS (primary) Impact of Response on OS by treatment group Systemic effect endpoints (beyond local effects in injected lesions) of T-VEC treatment.
Final (descriptive) Prespecified to occur after all patients had been followed for at least 3 years after randomization	8 Aug 2014	OS DRR, ORR and all response-based endpoints (per investigator). Time to treatment failure (per investigator).

[a] Interim analyses prior to the primary analysis are not included.
DRR, durable response rate; EAC, Endpoint Assessment Committee; ORR, objective response rate; OS, overall survival.

A12. Please clarify the level of significance testing used for the analysis of DRR at the final data-cut as this final analysis is not mentioned in the Bonferroni alpha allocation described in the statistical analysis plan (SAP).

As explained in our response to A11 no change to DRR per EAC was possible after the primary data-cut and therefore no formal significance testing was planned for this endpoint at the final data-cut. Only descriptive analyses of DRR per investigator assessment were performed at the final data-cut.

A13. Please clarify which subgroup analyses were pre-planned for both DRR and OS analyses as they are not specified in the SAP or in the protocol. Please also provide the results for the tests of treatment interactions for the planned subgroup analyses.

The OPTiM SAP (amendment 4, dated 4 January 2013) states that 'DRR analysis will be presented for baseline characteristics and in clinically meaningful patient subgroups, such as site of first recurrence, time from diagnosis to first recurrence, disease stage, prior therapy, and disease burden'. The SAP also lists the following additional potentially important prognostic factors for DRR and OS: sex (male vs. female), age (<50 vs >50), geographic region (US vs rest of world) and presence of liver metastasis. In addition, the OPTiM protocol (amendment 5, dated 4 January 2013) refers to an 'exploratory analysis of treatment effects based on BRAF mutation status'.

The results of treatment by subgroup interaction tests that have been performed for DRR and OS are presented in Table A-11.

Table A-11 Treatment by subgroup interaction tests for DRR and OS in OPTiM (ITT population)

Subgroup	DRR - primary analysis (N=295 T-VEC, N=141 GM-CSF)		OS - final analysis (N=295 T-VEC, N=141 GM-CSF)	
	Quantitative interaction p-value[a]	Qualitative interaction p-value[a]	Quantitative interaction p-value[a]	Qualitative interaction p-value[a]
Disease stage (IVRS) (IIIb / IIIc, IVM1a / M1b, IV M1c)	<0.0001	0.7500	0.1907	0.7500
Disease stage (CRF) (IIIb / IIIc, IVM1a, IVM1b, IVM1c)	<0.0001	0.8204	0.0719	0.7331
Disease stage (CRF) (early [IIIb / IIIc / IVM1a], late [IVM1b / IVM1c])	<0.0001	0.5000	0.0101	0.3550
Site of first recurrence (visceral, in transit or distant skin, lymph node)	NE	NE	0.0034	0.1571
Presence of liver metastasis (yes, no)	0.5341	0.5000	0.5868	0.5000
Prior non-surgical melanoma treatment (prior treatment other than adjuvant therapy with recurrence > 1 year from primary diagnosis, prior treatment other than adjuvant therapy with recurrence <1 year from primary diagnosis, no prior treatment other than adjuvant therapy)	0.0006	0.7500	0.0059	0.4459
Line of therapy (first line, second line or greater)	0.0002	0.5000	0.0012	0.2318
LDH (≤ ULN, >ULN, unknown)	NE	NE	0.4038	0.5000
Visceral disease (CRF) (yes, no)	<0.0001	0.5000	0.0377	0.3793
ECOG (0, 1, unknown)	0.5485	0.5000	0.1472	0.5000
Sex (male, female)	0.9751	0.5000	0.9883	0.5000

Subgroup	DRR - primary analysis (N=295 T-VEC, N=141 GM-CSF)		OS - final analysis (N=295 T-VEC, N=141 GM-CSF)	
Age (<50, ≥50)	0.1997	0.5000	0.5088	0.5000
Geographic region (US, rest of world)	0.0012	0.5000	0.4228	0.4992
HSV-1 status at baseline (negative, positive, unknown)	0.9258	0.5000	0.7539	0.5000
BRAF status at baseline (mutation, wild-type, unknown)	0.5993	0.5000	0.3888	0.3872

[a] Gail and Simon test
BRAF, v-raf murine sarcoma viral oncogene homolog B; CRF, case report form; DRR, durable response rate, ECOG, Eastern Cooperative Oncology Group; GM-CSF, granulocyte macrophage colony-stimulating factor; HSV-1, herpes simplex virus type-1; IVRS, Interactive Voice Response System; LDH, Lactate dehydrogenase; NE, not estimable; OS, overall survival; T-VEC, talimogene laherparepvec; ULN, upper limit of normal.

A14. Table 4-18 provides an analysis for TTF for patients with stage IIIB-IVM1a disease at the time of the primary data-cut. If available, please also provide this analysis for the final data-cut.

This is provided in Table A-12.

Table A-12 TTF per investigator assessment in patients with stage IIIB-IVM1a disease (final data cut)

	T-VEC (N=163)	GM-CSF (N=86)	Treatment difference (T-VEC/GM-CSF)
TTF per investigator assessment (months)[a]			
Median	13.1	3.3	–
95% CI	(8.3, 21.3)	(2.8, 4.3)	–
Hazard ratio (T-VEC/GM-CSF)[b]	–	–	0.28
95% CI	–	–	(0.20, 0.40)
p-value	–	–	<0.0001

[a] TTF is calculated from randomisation until the first PDr where there is no response achieved after the PDr or death if no such PDr observed
[b] The hazard and hazard ratio estimates are obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a longer average time to treatment failure for T-VEC relative to GM-CSF. 95% CI Calculated from Cox regression model
CI, confidence interval; GM-CSF, granulocyte macrophage colony-stimulating factor; ITT, intent-to-treat; NE, not estimable; PDr, clinically relevant disease progression; TTF, time to treatment failure; T-VEC, talimogene laherparepvec

A15. Based on Figure 4-4 it appears that significantly more patients randomised to GM-CSF than to T-VEC withdrew from the study without having received any of the assigned treatment ([4/295] 1.4% T-VEC vs [14/141] 9.9% GM-CSF):

a. **if possible, please provide a similar patient disposition flow diagram to Figure 4-4 only including patients with non-visceral disease (at least for those who were randomly assigned treatment since such data are unlikely to be available for those not randomised)**

Please see Figure A-6 for the patient disposition flow diagram in the IIIb-IVM1a population.

Figure A-6 Patient disposition during the OPTiM study in the IIIb-IVM1a population (primary analysis)

[redacted]

[redacted]

b. if a flow diagram is not possible, please indicate how many of the early withdrawals in each trial arm were from the non-visceral subgroup.

See response to A15a.

A16. Table 4-7 provides data on the number of patients who withdrew from study treatment in the intention-to-treat (ITT) population and non-visceral subgroup. Please provide a summary of the reasons for (i) discontinuing treatment and (ii) discontinuing from the trial in each study arm in the non-visceral subgroup.

This is provided in Table A-13.

Table A-13 Summary of the reasons for discontinuing treatment and discontinuing from the trial in the IIIB–IVM1a subgroup (primary analysis)

[redacted]

A17. It is unclear whether the data for subsequent therapies reported in Table 4-10 are correct. Specifically, please clarify:

a. **that the data reported in the top row of Table 4-10 (i.e. ipilimumab, vemurafenib, dabrafenib, trametinib or anti-PD1 antibody) are a summation of all the data in the rows below**

   The data in the top row are not a summation of the rows below.

b. **that data in the rows below are mutually exclusive (and hence should not necessarily equal the data reported in the top row)**

   Patients may have received more than 1 subsequent therapy and hence the data in the rows below are not mutually exclusive.

c. **that the correct data have been input since the data reported for the ITT population do not appear to match the data reported in Table 14-8.1.7 of the clinical study report (CSR) and for the T-VEC group, a greater number of patients are reported to have received ipilimumab, dabrafenib and trametinib in the population in whom T-VEC is indicated (that is, non-visceral disease) than in the whole ITT population.**

   The data for the IIB-IVM1A population are correct. However, the data for the ITT population have been entered under the wrong treatment group in error. Please see the corrected data in Table A-14 which match Table 14-8.2.1 in the final analysis CSR. Note that the data referred to in Table 14-8.1.7 above come from the primary analysis as opposed to the final analysis.

Table A-14 Summary of selected subsequent therapies given to patients following participation in the OPTiM study (final analysis)

Treatment, n (%)	IIIB–IVM1a (T-VEC label population)		IIIB–M1c (ITT population)	
	T-VEC (N=163)	GM-CSF (N=86)	T-VEC (N=295)	GM-CSF (N=141)
Ipilimumab, vemurafenib, dabrafenib, trametinib or anti-PD1 antibody	67 (41.1)	43 (50.0)	119 (40.3)	63 (44.7)
Ipilimumab	61 (37.4)	32 (37.2)	106 (35.9)	49 (34.8)
Vemurafenib	15 (9.2)	13 (15.1)	27 (9.2)	21 (14.9)
Dabrafenib	6 (3.7)	2 (2.3)	7 (2.4)	2 (1.4)
Trametinib	3 (1.8)	0 (0.0)	3 (1.0)	0 (0.0)
Anti-PD1 antibody	2 (1.2)	4 (4.7)	5 (1.7)	4 (2.8)

Source: IIIB-IVM1A population:(Harrington et al, 2015); (Amgen (Data on file), 2015); ITT population: (Amgen (Data on file), 2015)

GM-CSF, granulocyte macrophage colony-stimulating factor; ITT, intent to treat; PD1, programmed cell death-1; T-VEC, talimogene laherparepvec.

<u>A18.</u> In relation to b, please clarify that where it is stated that "DR was associated with reduced risk of initiating subsequent systemic therapy" (company's submission, page 67), this analysis has been conducted with the correct data set for subsequent systemic therapy.

We can confirm that the analysis referenced in clarification question A18 has been conducted with the correct data set for subsequent systemic therapy and is not impacted by the transcription error noted in the response to question A17c. This analysis is based on the full ITT population and the final analysis data-cut (Kaufman et al, 2015).

B: Clarification on cost-effectiveness data

Kaplan-Meier analyses for OPTiM trial:

B1 (Priority question). The ERG has detected that the time-to-event results from the OPTiM trial are subject to substantial right-censoring especially in the T-VEC group and suspects that 'informative censoring' might have been introduced and therefore, the results poorly reflect the true profile of time-to-event hazards. The ERG wishes to investigate the extent to which this may be introducing bias and additional uncertainty into the model results. In addition, neither the published trial results nor the company's submission includes Kaplan-Meier results for PFS or Post-Progression Survival (PPS), so it is not possible for the ERG to verify that the partitioning of OS into PFS and PPS components is accurately reflected in the company's model.

Please provide the following Kaplan-Meier analyses (a, b and c below), to the following specification (using the final data-cut from OPTiM):

Population: OPTiM clinical trial non-visceral subgroup (stage IIIB/C and M1a) including all subgroup patients lost to follow-up or withdrawing from trial.

Censoring: Censor lost to follow-up and withdrawn patients at the date 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; i.e. not when last known to be alive (OS and PPS), and not at the date of last tumour assessment (PFS).

Analyses:

a. **Time to death from any cause (OS), stratified by treatment group (T-VEC vs GM-CSF) and stage of the disease (IIIB, IIIC and M1a).**
b. **Time to disease progression or death based on investigator assessment (PFS), stratified by treatment group (T-VEC vs GM-CSF) and stage of the disease (IIIB, IIIC and M1a).**
c. **Time from disease progression to death from any cause (PPS), stratified by treatment group (T-VEC vs GM-CSF) and stage of the disease (IIIB, IIIC and M1a).**

Please present analysis outputs using the following format:

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		……	……	……	…	…
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

As requested by the ERG, this further analysis on censoring of patients is based on patients in the non-visceral subgroup as aligned with the expected T-VEC license indication. Subjects were defined as “at risk”, if their primary reason for ending the study was not “lost to follow-up” or “consent withdrawn”. Out of 249 subjects, 112 subjects were censored for OS (T-VEC 83/163, GM-CSF 29/86) and, of these, 14 were not “at risk” by this definition (T-VEC 6/83, GM-CSF 8/29). For this analysis, those censored subjects “at risk” were re-censored at date of final analysis data-cut off (8 August 2014).

Figure B-1 to Figure B-3 show the Kaplan-Meier estimates for OS, PFS, and PPS for T-VEC patients with stage IIIB-IVM1a disease combined based on the two censoring approaches; original censoring versus re-censoring as requested by the ERG. The differences in mean survival between the two censoring approaches are presented in Table B-1.

For OS and PPS, there are no differences in the Kaplan-Meier estimates over time, although the number of patients “at risk” is higher with re-censoring (as expected) after month 36 since this is the minimum follow-up at the final analysis. Importantly, the median and mean OS and PPS (Figure B-1, Figure B-3 and Table B-1) do not change after re-censoring. The similarity in the Kaplan-Meier curves confirms that censoring was random as opposed to informative and addresses the concerns raised by the ERG with respect to substantial right-censoring and the possibility of informative censoring. Further, the OS and PPS results demonstrate that the original censoring reflects the true profile of the time-to-event hazards and are not likely to have introduced bias and additional uncertainty into the model results.

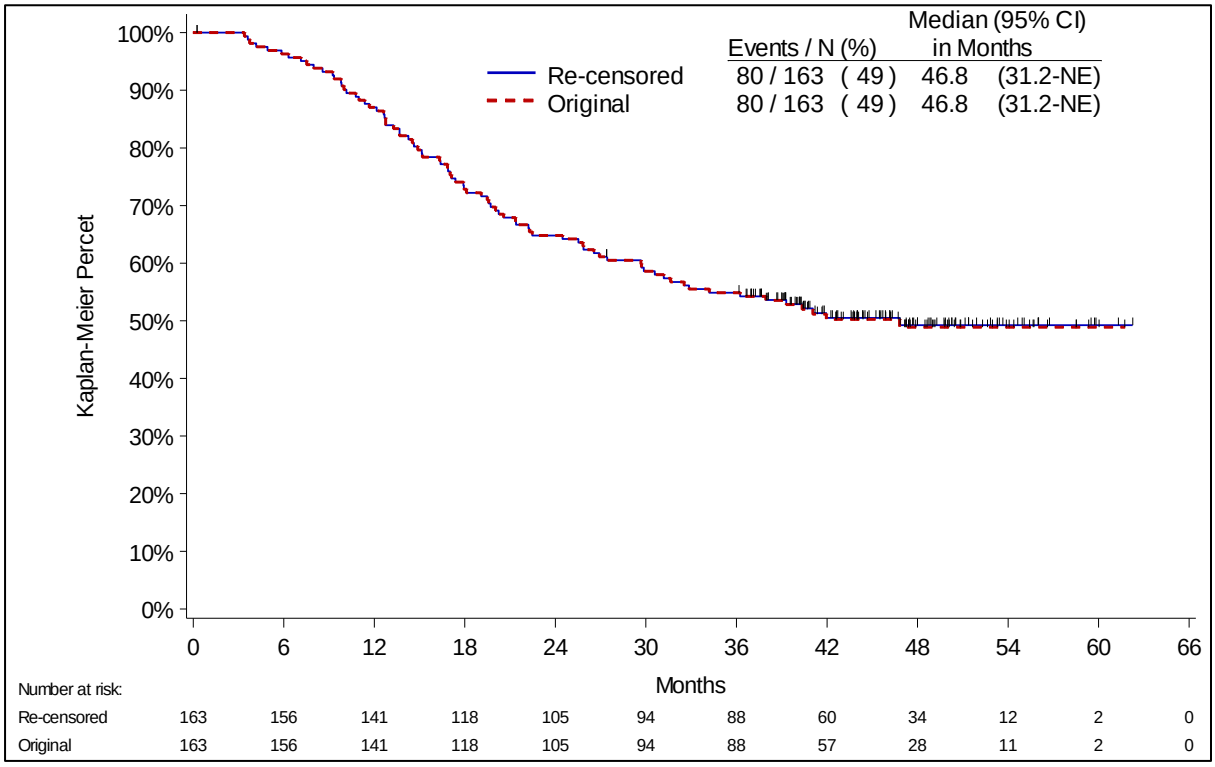
For PFS, the Kaplan-Meier estimates diverge after about 6 months with higher PFS rates after re-censoring (Figure B-2). However, the difference observed is mainly because the new censoring times were not allowed according to the original definition of the PFS endpoint. For the original analysis, censoring was imputed at the last tumour assessment if disease progression, or death in the absence of prior disease progression, occurred more than 70 days from the last tumour assessment or any time after initiation of subsequent anti-cancer therapy. Consequently, had more current survival follow-up been obtained in the original

analysis, censoring times would not necessarily have changed. The re-censoring of PFS data as per ERG request results in a different endpoint and consequently the PFS results between the original censoring and the re-censoring diverge.

Table B-1 T-VEC non-visceral subgroup (stage IIIB-IVM1A) – mean OS, PFS and PPS for original censoring versus re-censoring

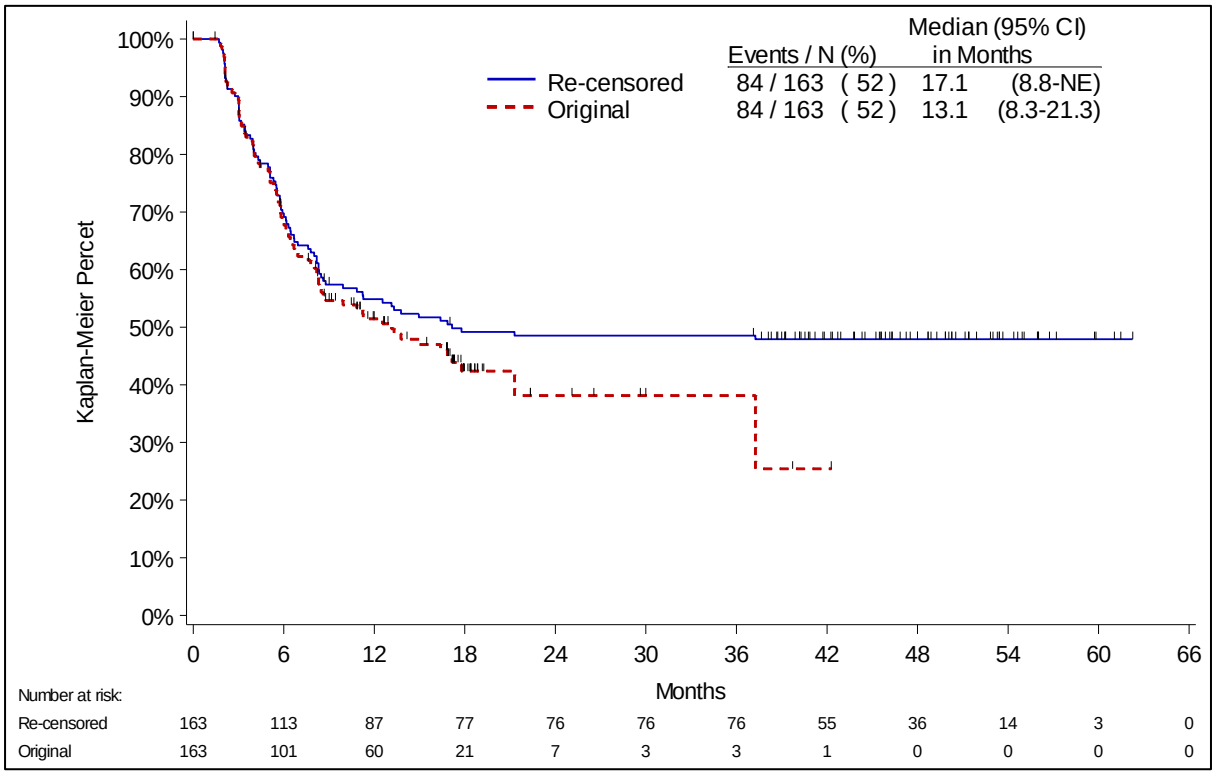
	Original censoring	Re-censoring as per ERG request
Mean OS (months)	33.1	33.1
Mean PFS (months)	19.0	21.4
Mean PPS (months)	18.3	18.3
ERG, Evidence Review Group; PFS, progression-free survival; PPS, post progression survival; OS, overall survival.		

Figure B-1 T-VEC original versus re-censored OS (stage IIIB-IVM1A)



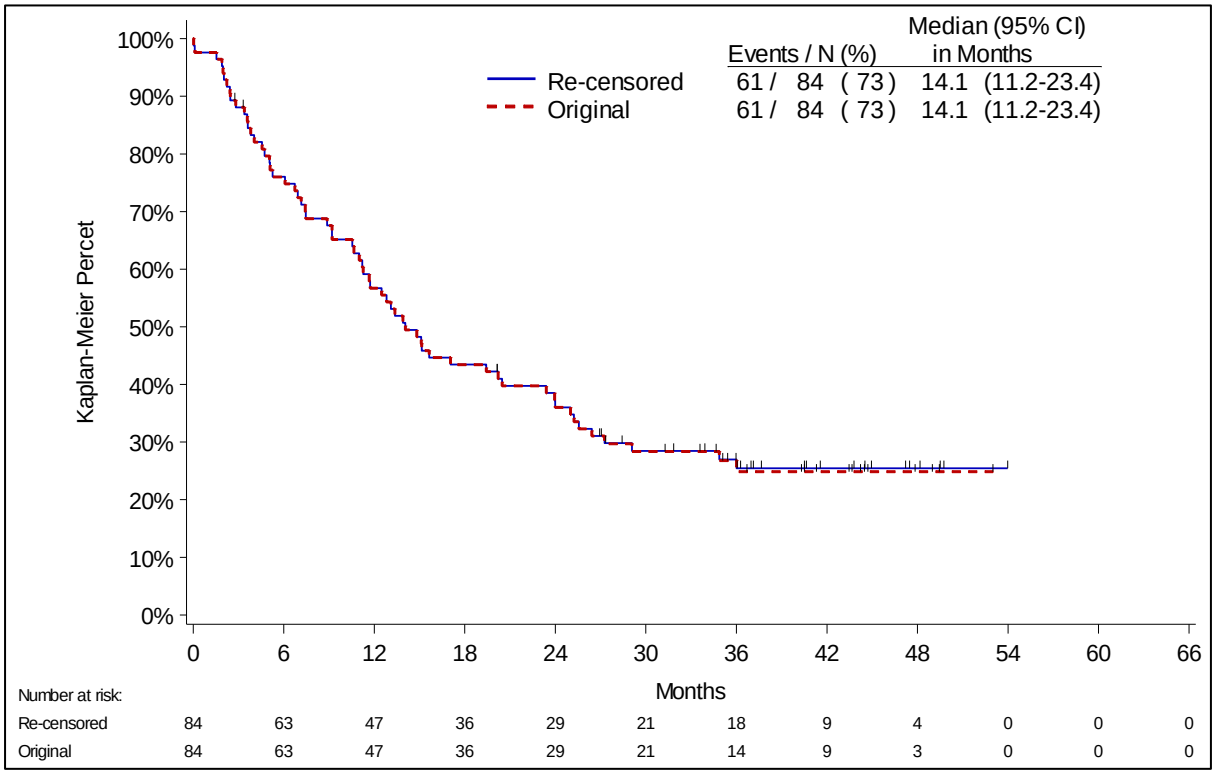
OS, overall, survival; T-VEC, talimogene laherparepvec.

Figure B-2 T-VEC original versus re-censored PFS (stage IIIB-IVM1A)



PFS, progression-free survival; T-VEC, talimogene laherparepvec.

Figure B-3 T-VEC original versus re-censored PPS (stage IIIB-IVM1A)



PPS, post progression survival; T-VEC, talimogene laherparepvec.

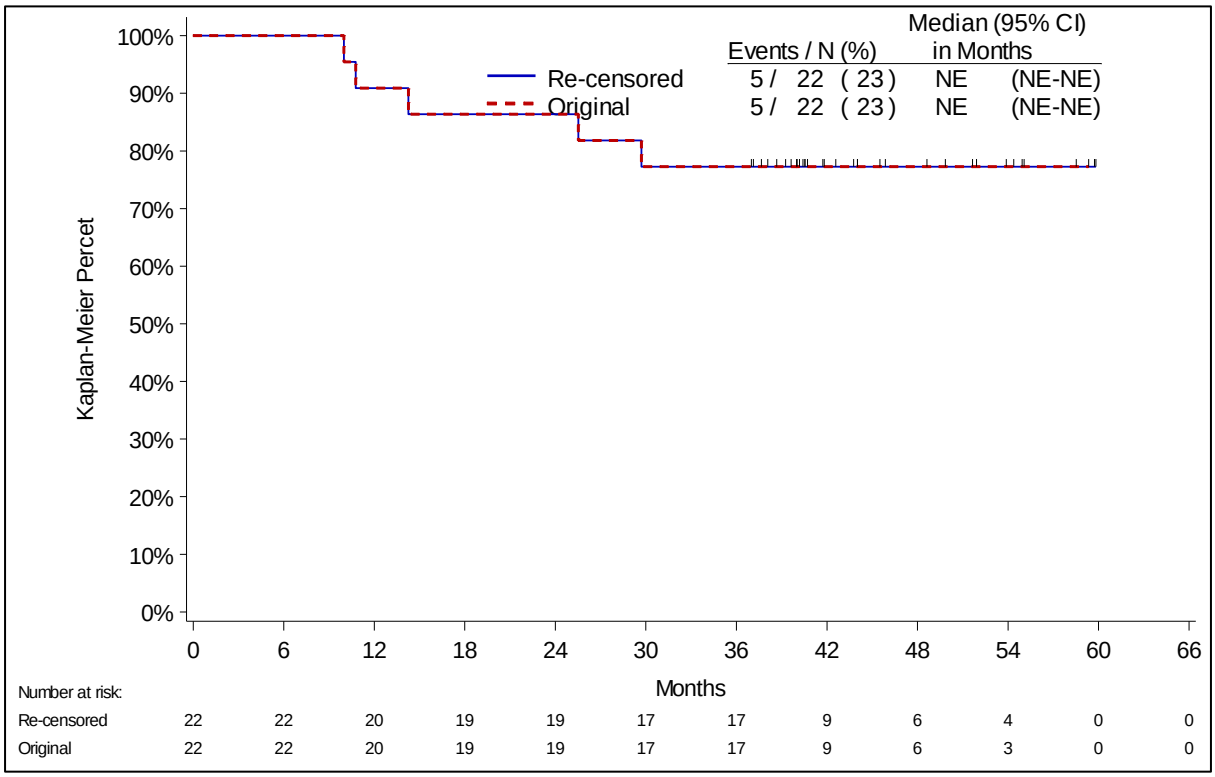
Similar analyses were performed stratified by disease stage and results were consistent with those for patients with stage IIIb-IVM1a combined. The differences in mean survival between the two censoring approaches are presented by stage in Table B-2. Kaplan-Meier estimates comparing the original censoring versus the requested re-censoring are shown by stage in Figure B-4 to Figure B-12.

Table B-2 T-VEC non-visceral subgroup (stage IIIB-IVM1A) – mean OS, PFS and PPS for original censoring versus re-censoring by stage

Stage	Endpoint	Original censoring	Re-censoring as per ERG request
IIIB	Mean OS (months)	27.1	27.1
	Mean PFS (months)	29.0	30.0
	Mean PPS (months)	15.7	15.7
IIIC	Mean OS (months)	34.7	34.7
	Mean PFS (months)	13.2	13.8
	Mean PPS (months)	20.6	20.7
IVM1a	Mean OS (months)	27.6	27.6
	Mean PFS (months)	10.1	10.5
	Mean PPS (months)	16.2	16.2

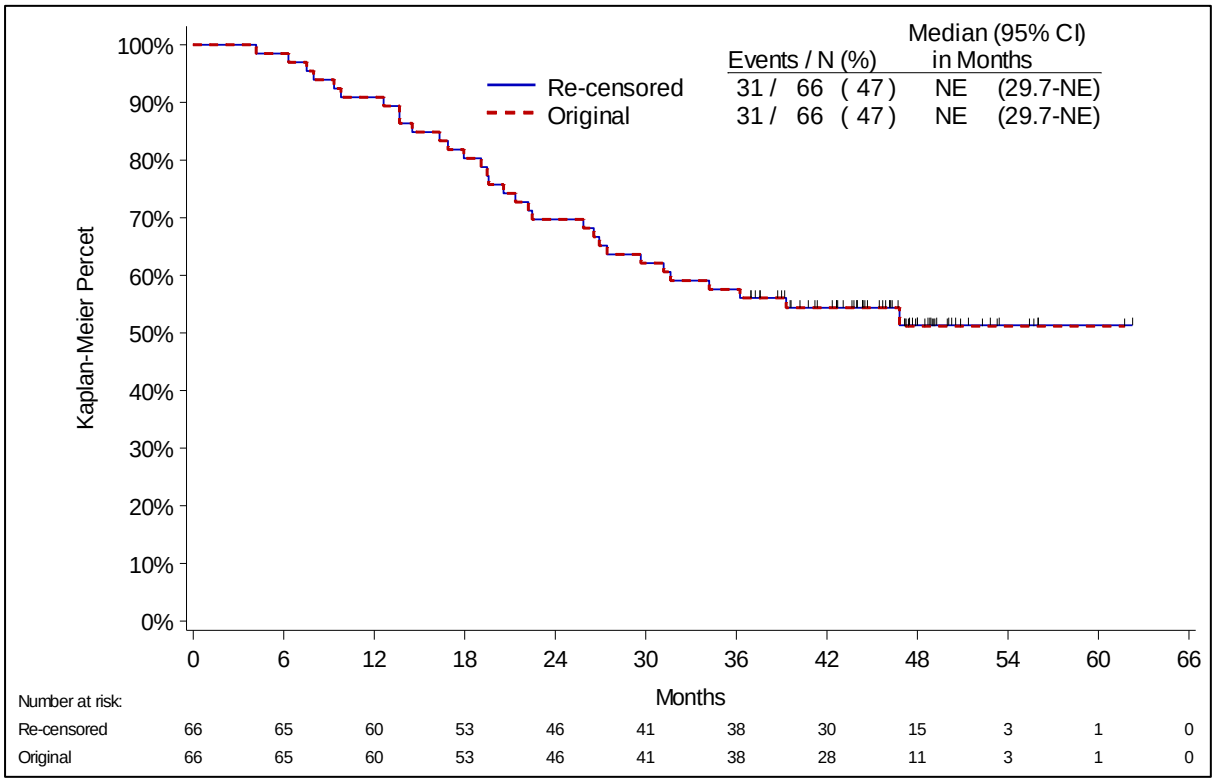
ERG, Evidence Review Group; PFS, progression-free survival; PPS, post progression survival; OS, overall survival.

Figure B-4 T-VEC original versus re-censored OS (stage IIIB)



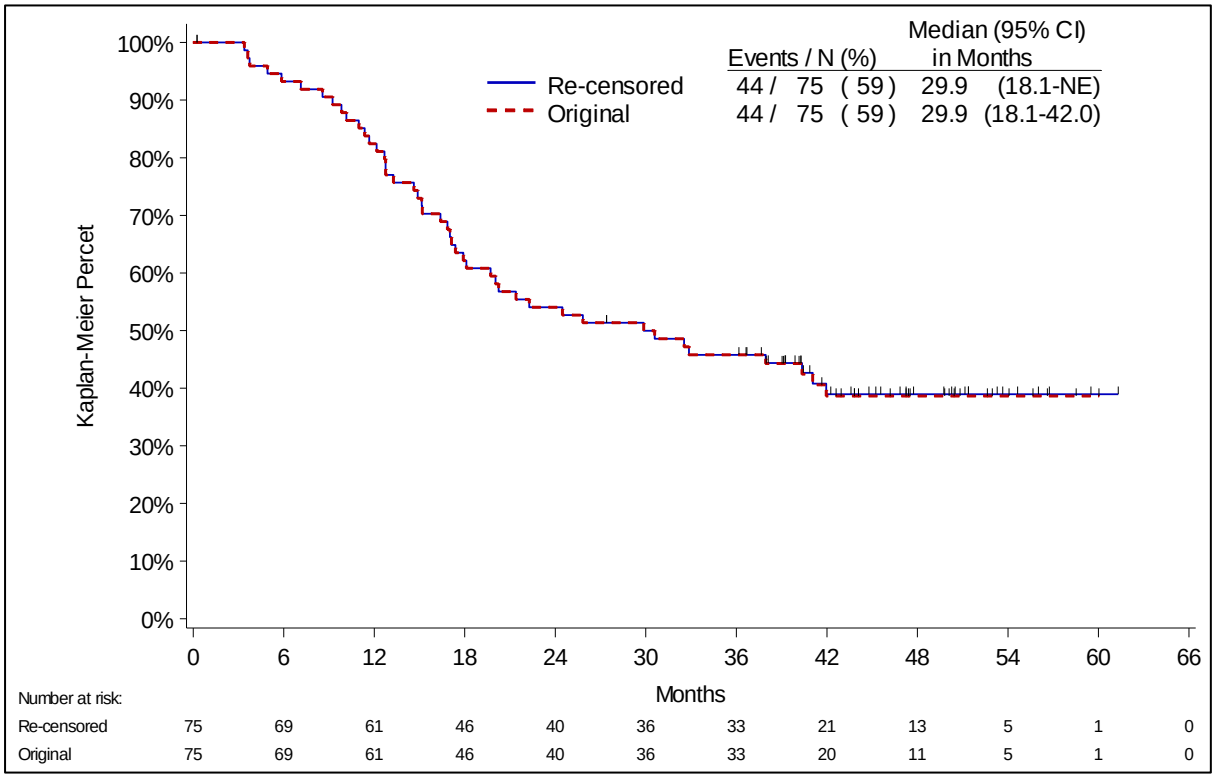
OS, overall, survival; T-VEC, talimogene laherparepvec.

Figure B-5 T-VEC original versus re-censored OS (stage IIIC)



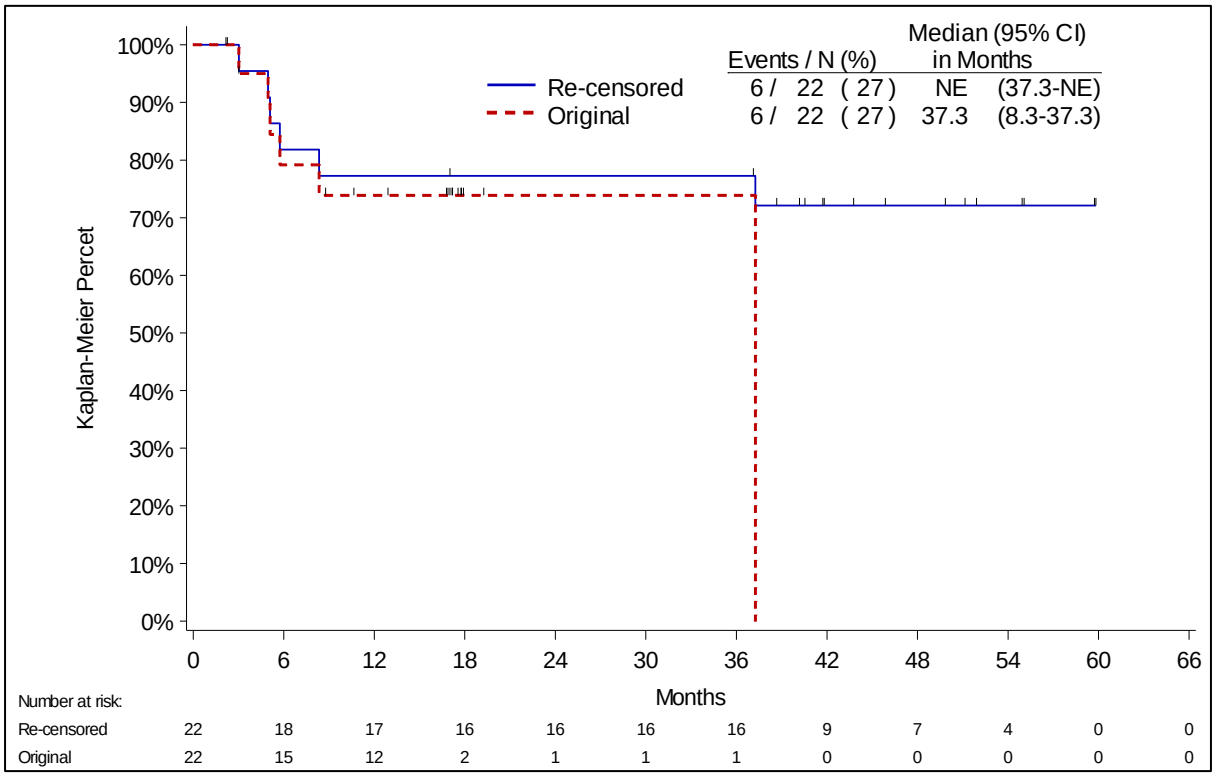
OS, overall, survival; T-VEC, talimogene laherparepvec.

Figure B-6 T-VEC original versus re-censored OS (stage IVM1a)



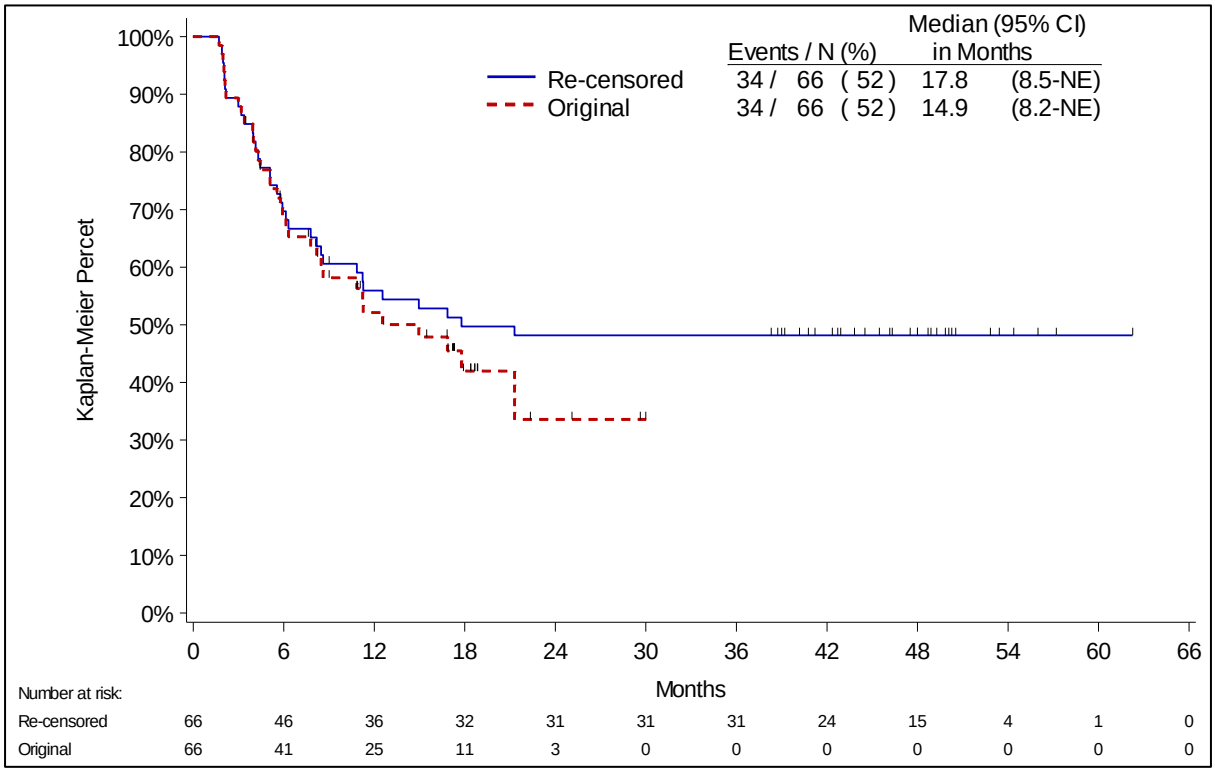
OS, overall, survival; T-VEC, talimogene laherparepvec.

Figure B-7 T-VEC original versus re-censored PFS (stage IIIB)



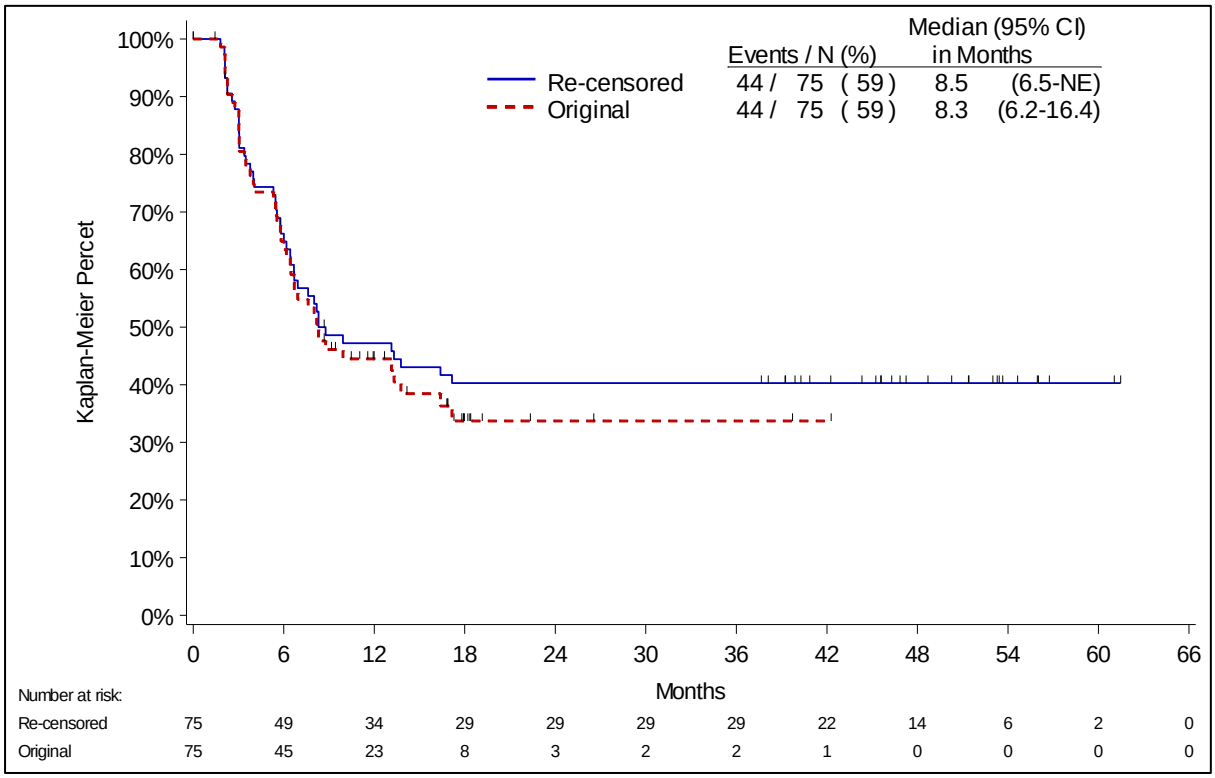
PFS, progression-free survival; T-VEC, talimogene laherparepvec.

Figure B-8 T-VEC original versus re-censored PFS (stage IIIC)



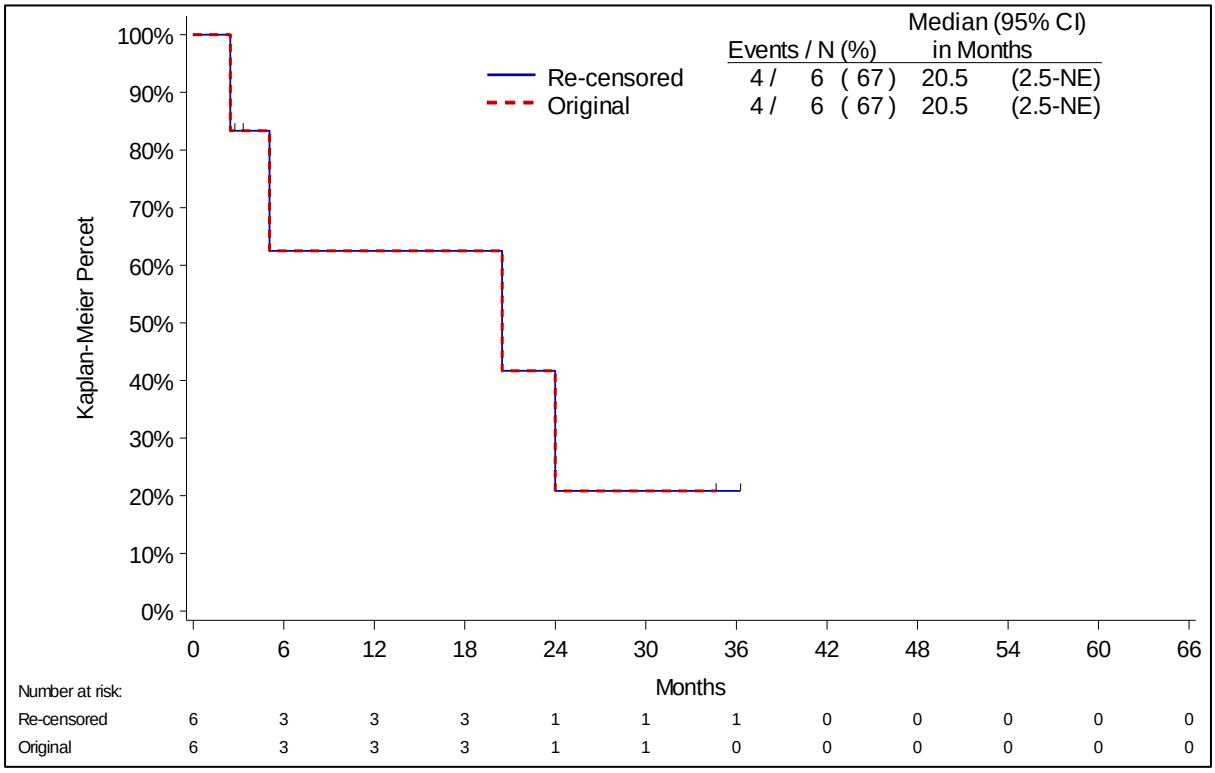
PFS, progression-free survival; T-VEC, talimogene laherparepvec.

Figure B-9 T-VEC original versus re-censored PFS (stage IVM1a)



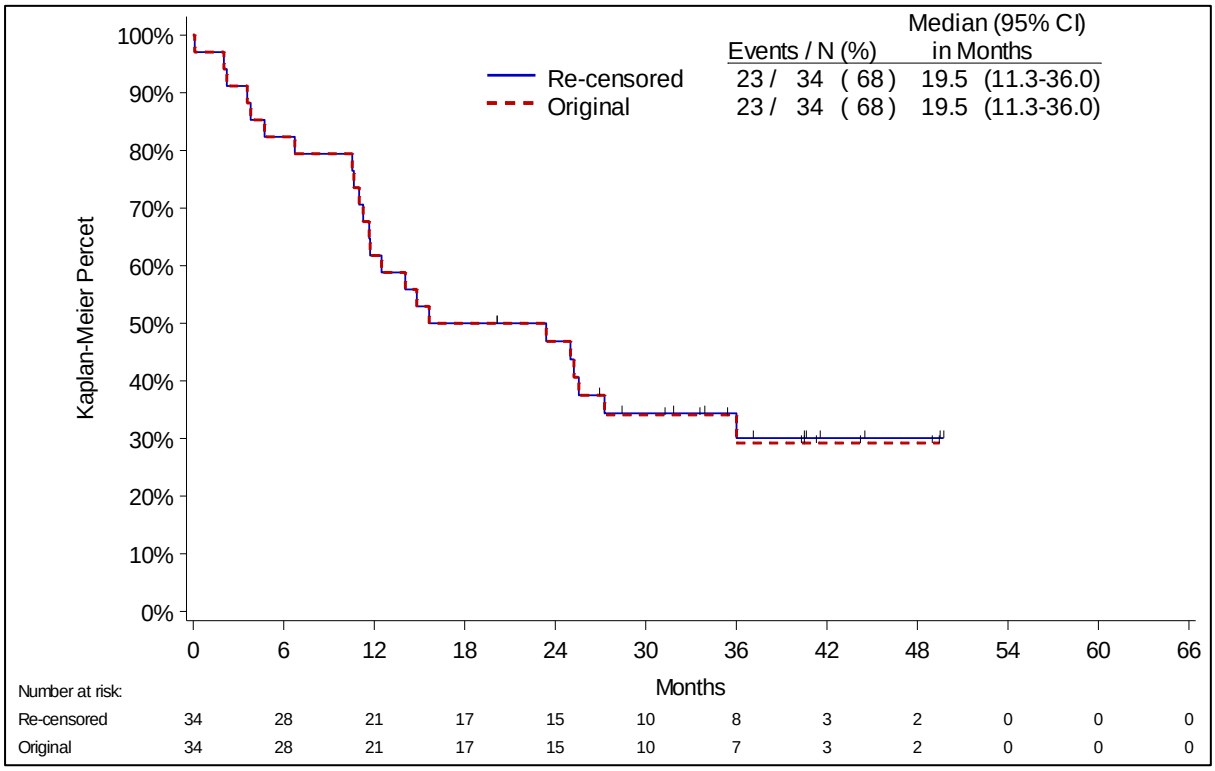
PFS, progression-free survival; T-VEC, talimogene laherparepvec.

Figure B-10 T-VEC original versus re-censored PPS (stage IIIB)



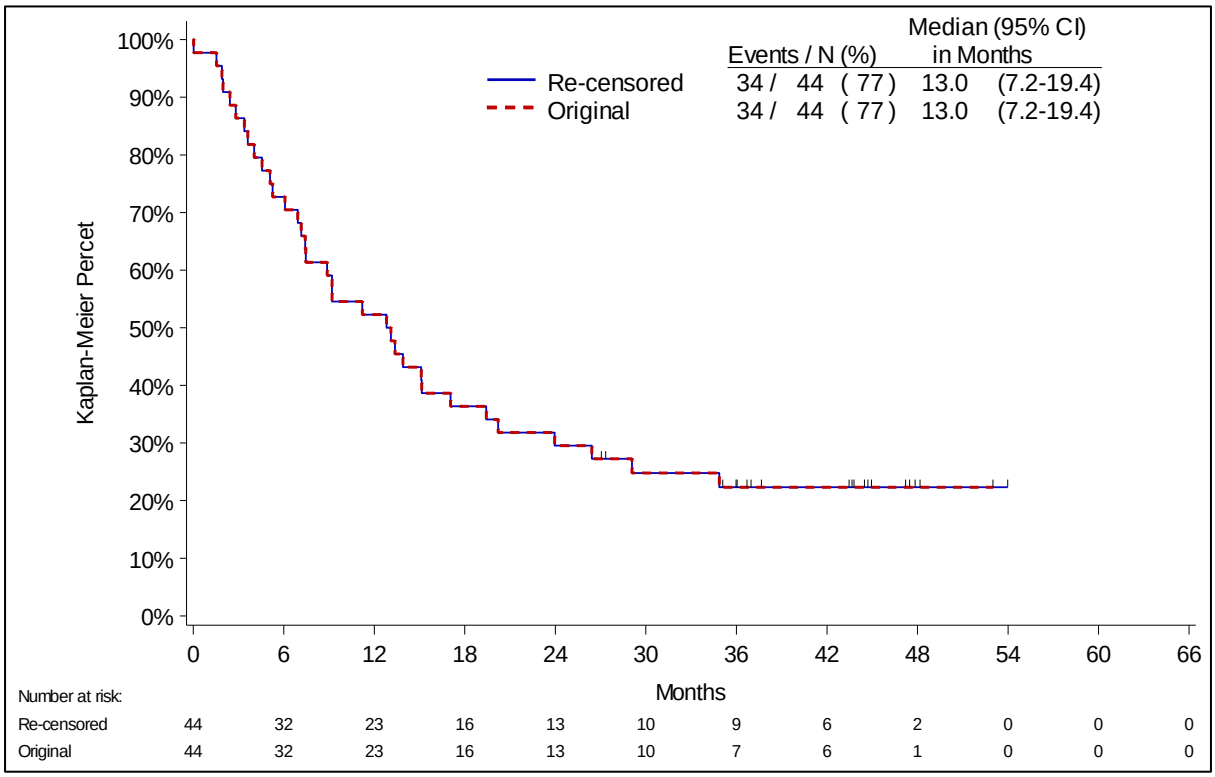
PPS, post progression survival; T-VEC, talimogene laherparepvec.

Figure B-11 T-VEC original versus re-censored PPS (stage IIIC)



PPS, post progression survival; T-VEC, talimogene laherparepvec.

Figure B-12 T-VEC original versus re-censored PPS (stage IVM1a)



PPS, post progression survival; T-VEC, talimogene laherparepvec.

Outputs in the format requested are attached as [redacted] (stage IIIB-IVM1a combined) and [redacted] (stage IIIB, stage IIIC, stage IVM1a).

Korn adjustments conducted in order to provide evidence for cost effectiveness:

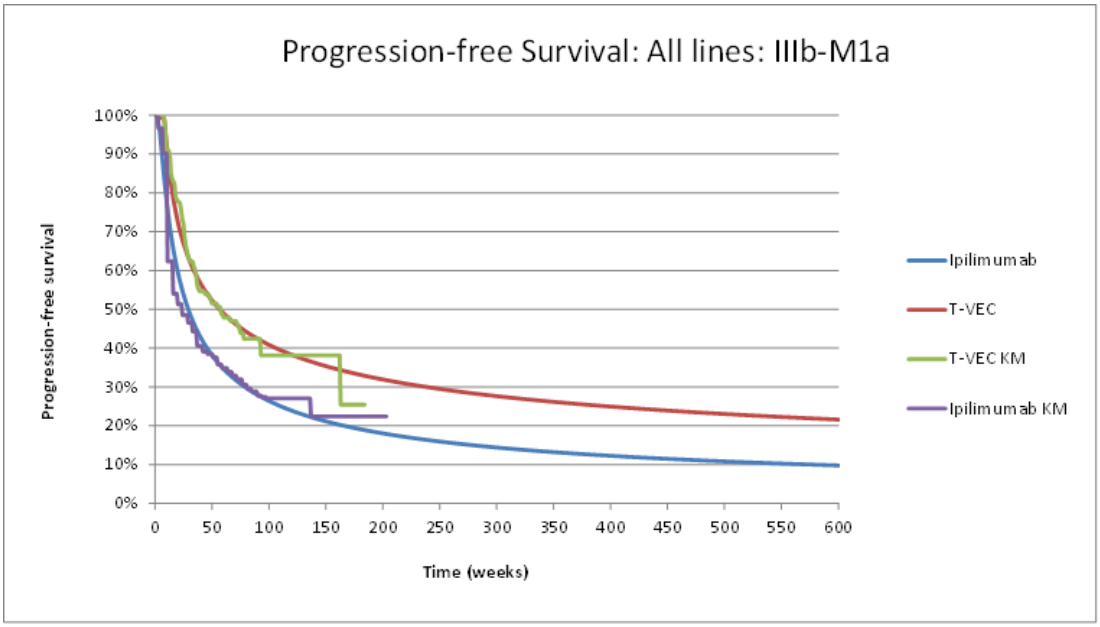
<u>B2 (Priority question</u>). Application of Korn adjustments: Figures 5-30 and 5-32 indicate that in the T-VEC group the PFS estimates (and hence also the PPS estimates) are altered by the Korn adjustments, whereas OS is unaffected when either of the Korn adjustments are applied to the model. The ERG considers this to be incorrect because the role of the Korn adjustments should only be to generate OS and PFS estimates for the comparators from the pooled data for ipilimumab and therefore, the OPTiM trial-based information should not be affected. Please clarify how the company considers the model should be amended to remove this error, indicating how the reported model results are altered.

The changes in T-VEC PFS are not an error, and the PFS estimates have not been altered by the Korn adjustments given that the Korn adjustments were only applied to ipilimumab. Instead 'altered PFS estimates' are due to assumptions we have made regarding the post-trial data collection (i.e., after the Kaplan-Meier period) for T-VEC PFS compared with ipilimumab. In the model base-case, it is assumed that the hazards for PFS are similar between T-VEC and ipilimumab after the Kaplan-Meier period. Thus, when PFS data for ipilimumab change, PFS data for T-VEC correspondingly change. This assumption was made for the following reasons:

- To be consistent with the hazard assumptions for OS, the base-case OS assumption is that long-term survival follows the registry data, which means that the OS hazards are similar between T-VEC and ipilimumab.
- The base-case best-fit curve for T-VEC PFS was the generalized gamma. While the generalized gamma fits the observed data well, the long tail of the curve was considered to be not clinically valid. Therefore by assuming T-VEC hazards are similar to ipilimumab the T-VEC tail is more clinically valid.
- Importantly, assuming that T-VEC PFS hazards are similar to ipilimumab is a conservative assumption of PFS efficacy for T-VEC.

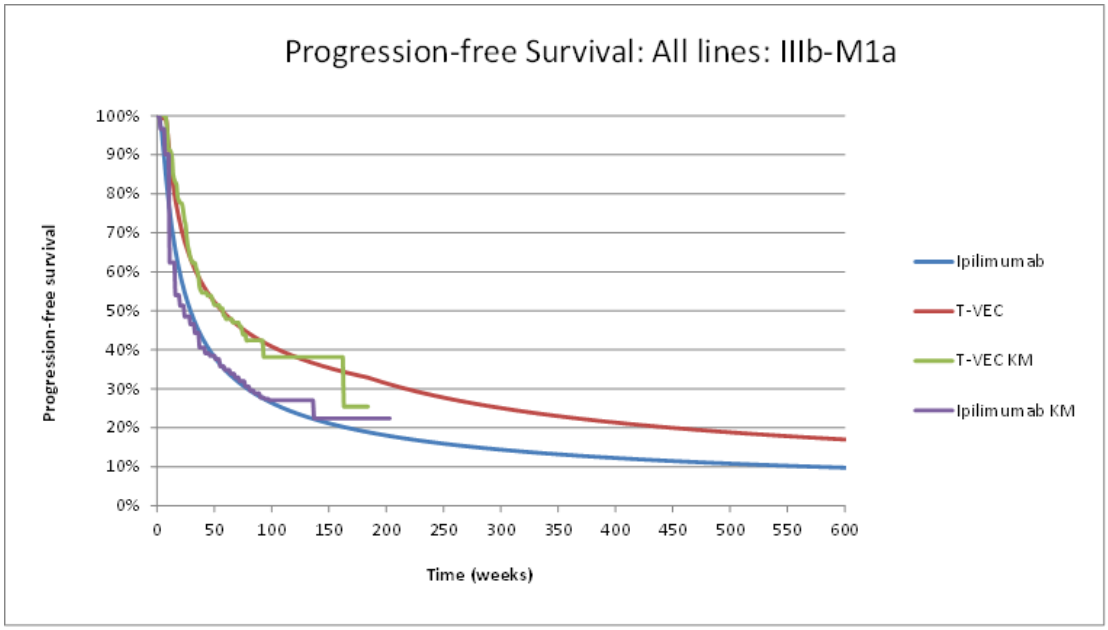
The impact of these assumptions on PFS is presented in Figure B-13 to Figure B-16 and Table B-3; results show that PFS estimates for T-VEC do not change when the assumption of similar hazards is not applied. Importantly the effect of the PFS adjustment on the incremental cost-effectiveness ratio (ICER) was negligible; with ICERs slightly more favourable for T-VEC when the PFS adjustment is not applied (Table B-4).

Figure B-13 Modified Korn adjustment with no adjustment of T-VEC PFS



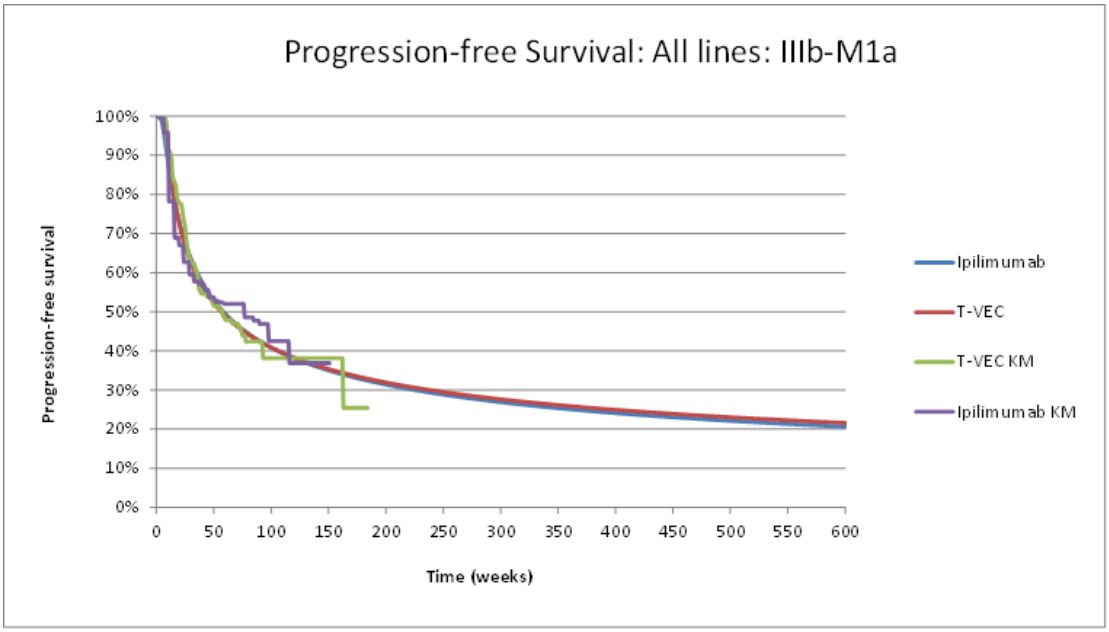
KM, Kaplan-Meier; PFS, progression-free survival; T-VEC, talimogene laherparepvec.

Figure B-14 Modified Korn adjustment with adjustment of T-VEC PFS



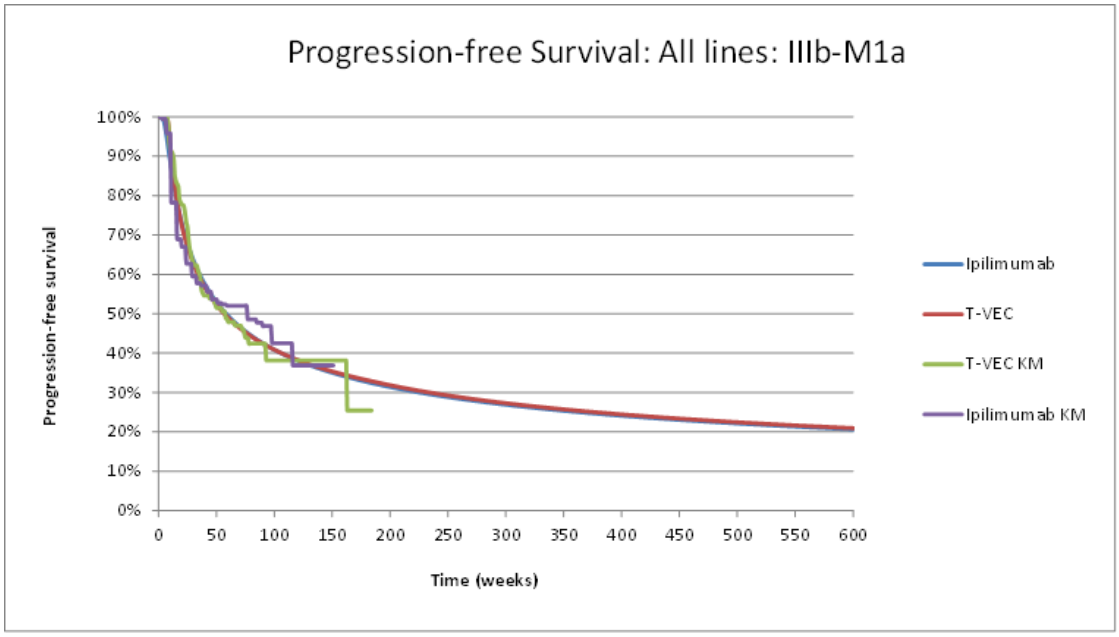
KM, Kaplan-Meier; PFS, progression-free survival; T-VEC, talimogene laherparepvec.

Figure B-15 Two-step Korn adjustment with no adjustment of T-VEC PFS



KM, Kaplan-Meier; PFS, progression-free survival; T-VEC, talimogene laherparepvec.

Figure B-16 Two-step Korn adjustment with adjustment of T-VEC PFS



KM, Kaplan-Meier; PFS, progression-free survival; T-VEC, talimogene laherparepvec.

Table B-3 Summary of T-VEC PFS with or without assumptions of similarity of hazards

	PFS adjustment	
	Yes (base case)	**No**
Modified Korn	4.22	4.76
Two-step Korn	4.69	4.76

	PFS adjustment	
	Yes (base case)	**No**
Difference	0.47	0.00
PFS, progression-free survival.		

Table B-4 Impact on ICER with or without assumptions of similarity of hazards

	PFS adjustment	
	Yes (base case)	**No**
Modified Korn	[redacted]	[redacted]
Two-step Korn	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; PFS, progression-free survival.		

B3 (Priority question). Korn adjusted ipilimumab OS and PFS estimates: The ERG wishes to validate the accuracy of the figures on which the cost-effectiveness estimates are based. Please provide Kaplan-Meier estimates for OS and PFS before and after Korn adjustments in the same format as indicated above for B1.

Please see [redacted] for this information.

OPTiM trial data required for cost-effectiveness analyses:
B4 (Priority question). Time from diagnosis: Please provide the mean, standard deviation and standard error of the mean for the time from initial diagnosis to date of randomisation for each treatment group of the OPTiM clinical trial.

This is provided in Table B-5.

Table B-5 Summary of time from initial diagnosis to randomisation in OPTiM (IIIB-IVM1a population)

	T-VEC (N=163)	GM-CSF (N=86)
Time from initial diagnosis to randomisation (years)		
n[a]	151	69
Mean	3.2	2.8
Standard deviation	3.57	2.51
Standard error of mean	0.30	0.30
[a] number of patients with complete diagnosis dates GM-CSF, granulocyte macrophage colony-stimulating factor; T-VEC, talimogene laherparepvec.		

B5. T-VEC treatment – first cycle: Please provide the number of patients randomised to T-VEC who required 0, 1, 2, 3, … vials for their first treatment in the OPTiM trial.

Table B-6 details the number of T-VEC patients on 0, 1, 2, 3 or 4 vials for the first dose (also known as the priming dose) in the OPTiM trial.

Table B-6 T-VEC treatment: first cycle first dose (OPTiM)

Number of vials (first treatment)	Number of patients
0	[redacted]
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
Total number of patients	[redacted]
Total number of vials	[redacted]
Vials per patient	[redacted]
T-VEC, talimogene laherparepvec.	

B6. T-VEC treatment – subsequent cycles: Please complete the following table for all subsequent treatment cycles with T-VEC in the OPTiM trial:

Please see Table B-7. Note that treatment cycle 1 (Day 22) is defined as the first dose taken at Day 22 at a concentration of 10^8 PFU/mL following the priming dose. The 'patients still on treatment' is the number of patients who had at least one treatment in the cycle. The 'number of treatments' is the number of treatments that these patients had in the cycle. The number of treatments counts each occasion on which T-VEC was used.

As explained in the submission (Section 5.2, Page 126), accelerated dosing not provided as part of routine treatment was not included in the base case. Accelerated dosing is not recommended in the anticipated license for T-VEC (EMA, 2015). Further patients who received accelerated doses in the trial had poor survival outcomes compared to patients who did not receive accelerated dosing. In the OPTiM trial patients who had successfully completed treatment were eligible to enter into an extension study. As a conservative measure, the base case analysis includes the doses that patients took in the extension study. It is noteworthy that all patients completed the extension phase in the final analysis. This provides complete information on T-VEC dosing and reduces the uncertainty regarding treatment duration.

Table B-7 T-VEC treatment: subsequent cycles (OPTiM)

Treatment cycle	Patients still on treatment	Number of treatments	Total vials used in cycle
OPTiM trial			
1 (Day 22)	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]

Treatment cycle	Patients still on treatment	Number of treatments	Total vials used in cycle
10	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]
Total (OPTiM)		[redacted]	[redacted]
Extension phase[a]			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]
Total (Extension phase)		[redacted]	[redacted]
Overall total		[redacted]	[redacted]
Vials per patient		[redacted]	[redacted]

[a] There is no “cycle 1” in the Extension phase given that there was no priming dose for this phase.

T-VEC, talimogene laherparepvec.

B7. Body weight: Please provide the mean and standard deviation of body weight separately for males and females randomised to treatment with T-VEC in the OPTiM trial.

Please see Table B-8.

Table B-8 Baseline weight in OPTiM (IIIB-IVM1a population)

	T-VEC (N=163)		GM-CSF (N=86)	
	Males (N=92)	**Females (N=71)**	**Males (N=47)**	**Females (N=39)**
Weight at baseline (kg)				
n	92	70	43	35
Mean	93.67	80.79	85.5	77.74
Standard deviation	19.64	22.49	13.45	21.76

GM-CSF, granulocyte macrophage colony-stimulating factor; T-VEC, talimogene laherparepvec.

C: Textual clarifications, references and additional points

C1 (Priority question). Please provide a published paper describing the modified Korn method. The company notes this was used in the appraisal of ipilimumab for previously untreated (unresectable or metastatic) melanoma (TA319) but the only reference that appears to be cited in TA319 (Bristol-Myers Squibb Company. Meta-analysis of overall survival from literature publications and study MDX010-20) is unavailable to the ERG.

A predictive model for survival was developed by Korn et al (Korn et al, 2008) using pooled data from 2,100 patients with metastatic melanoma treated with variety of regimens from 42 trials conducted between 1975 and 2005. The Korn model demonstrated that four factors are associated with OS: gender, ECOG performance status, presence of visceral metastases, and presence of brain metastases. In 2014, a five-factor model was used in the NICE technology appraisal of ipilimumab for previously untreated advanced melanoma (NICE TA319, 2014a) in which the original Korn model was modified to include LDH level as the fifth factor. The details of this five-factor model are explained in Pages 12-14 of the manufacturer response to the ACD for this appraisal (NICE TA319, 2014b). In that response, the manufacturer of ipilimumab (BMS) adjusted for the differences in patient baseline characteristics between the first line (CA184-024) and second line (MDX010-20) trials by means of a Cox proportional hazards model with five baseline prognostic factors. Four out of five of these baseline prognostic variables were found to be important covariates in the original Korn model. The five-factor model was accepted by NICE.

We call this model the modified Korn model given that the manufacturer of ipilimumab modified the original Korn model to include the presence of elevated LDH levels as a fifth factor in their response to the NICE ACD. The manufacturer response to the ACD for this appraisal of ipilimumab for previously untreated advanced melanoma is the only reference around the modified Korn model.

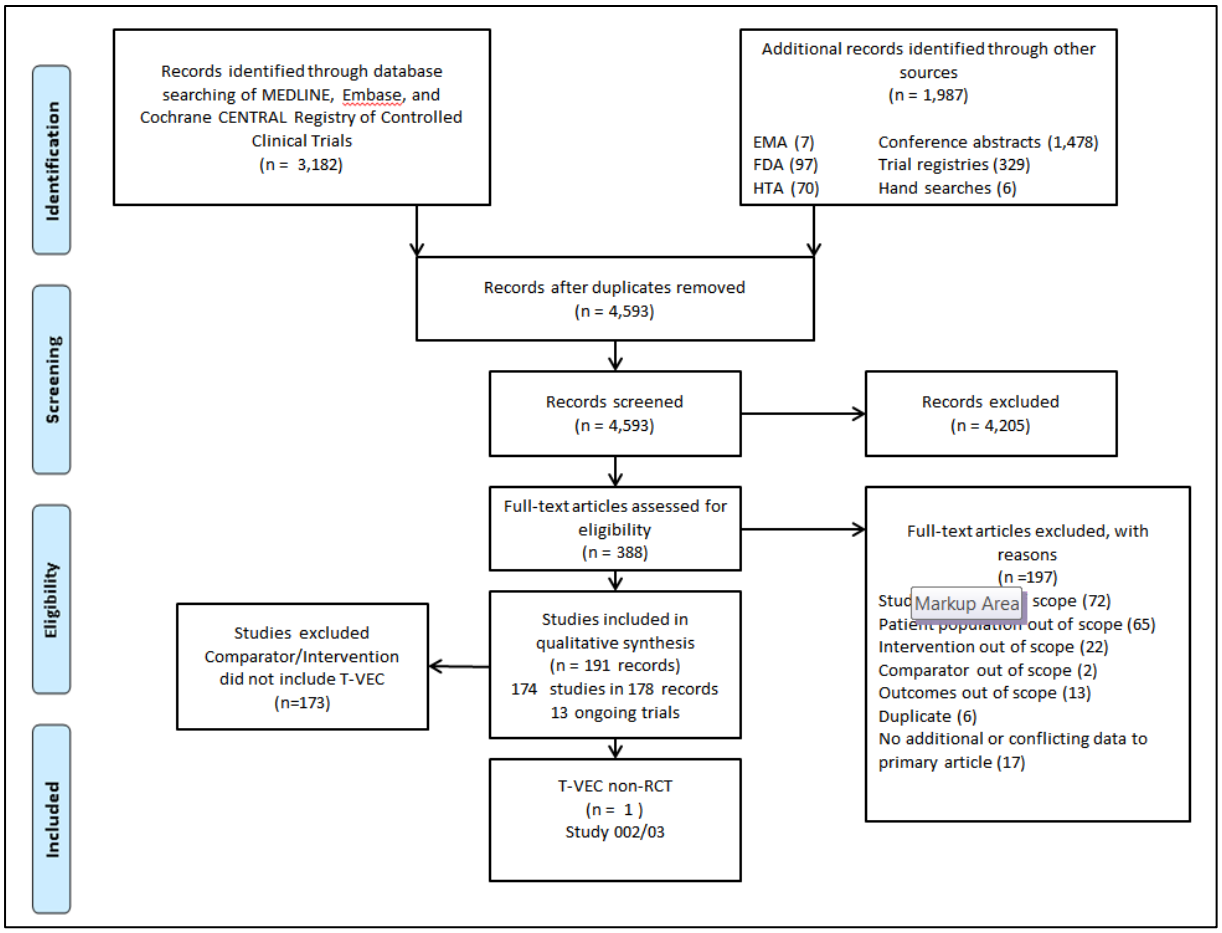
C2. Figure 3-1 includes a treatment pathway option for patients with BRAF V600 mutation positive disease starting with pembrolizumab followed by ipilimumab as a second-line option which is absent from Figure 3-2. Please clarify whether the company believes a treatment pathway starting with pembrolizumab and followed by T-VEC for patients with BRAF V600 mutation positive disease would be appropriate.

Pembrolizumab is not within the scope of this appraisal although it has recently been approved by NICE, and was included in the treatment pathway diagram to describe current treatments in the UK. For this appraisal, T-VEC is proposed as an alternative treatment to ipilimumab, wherever ipilimumab is used. Therefore, given that a treatment pathway starting with pembrolizumab followed by ipilimumab would be reasonable for patients with BRAF V600 mutation positive disease, a treatment pathway starting with pembrolizumab and followed by T-VEC would also be appropriate.

C3. Figure 4-2 (PRISMA flow diagram for non-RCT evidence) seems to be identical to Figure 4-1 (PRISMA flow diagram for RCT evidence). Please provide the correct figure for Figure 4-2.

This is provided in Figure C-1.

Figure C-1 PRISMA flow diagram for non-RCT evidence



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List of Appendices

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